National Institute for Health and Clinical Excellence

Issue date: March 2011

Diabetic foot problems

Inpatient management of diabetic foot problems

NICE clinical guideline 119
Developed by the Centre for Clinical Practice at NICE

NICE clinical guideline 119
Inpatient management of diabetic foot problems

Ordering information
You can download the following documents from
www.nice.org.uk/guidance/CG119

- A quick reference guide – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – a summary for patients and carers.
- The full guideline – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N2467 (quick reference guide)
- N2468 ('Understanding NICE guidance').

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London WC1V 6NA

www.nice.org.uk

Contents

Introduction 4
Topic 4
Who this guideline is for 5
Patient-centred care 6
1 Recommendations 7
1.1 Key priorities for implementation 7
1.2 List of all recommendations 10
2 Care pathway 18
3 Evidence review and recommendations 19
3.1 Key components and organisations of hospital care 20
3.2 Assessment, investigation and diagnosis of diabetic foot problems 27
3.3 Debridement, wound dressings and off-loading 63
3.4 Antibiotics for diabetic foot infections 82
3.5 Adjunctive treatments for diabetic foot problems 101
3.6 Timing for surgical management to prevent amputation 130
4 Notes on the scope of the guideline 132
5 Implementation 132
6 Other versions of this guideline 132
6.1 Quick reference guide 132
6.2 'Understanding NICE guidance' 132
7 Related NICE guidance 133
8 Updating the guideline 134
9 Contributors 135

Introduction

Topic

Diabetes is one of the biggest health challenges facing the UK today. In 2010, 2.3 million people in the UK were registered as having diabetes, while the number of people estimated as having either type 1 or type 2 diabetes was 3.1 million. By 2030 it is estimated that more than 4.6 million people will have diabetes (Diabetes UK, 2010).

As the longevity of the population increases, the incidence of diabetes-related complications also increases (Anderson and Roukis, 2007). Among the complications of diabetes are foot problems, the most common cause of non-traumatic limb amputation (Boulton et al, 2005). The feet of people with diabetes can be affected by neuropathy, peripheral arterial disease, foot deformity, infections, ulcers and gangrene.

Diabetic foot problems have a significant financial impact on the NHS through outpatient costs, increased bed occupancy and prolonged stays in hospital. In addition, diabetic foot problems have a significant impact on patients' quality of life; for example, reduced mobility that may lead to loss of employment, depression and damage to or loss of limbs. Diabetic foot problems require urgent attention. A delay in diagnosis and management increases morbidity and mortality and contributes to a higher amputation rate (Reiber et al, 1999).

The common clinical features of diabetic foot problems include infection, osteomyelitis, neuropathy, peripheral arterial disease and Charcot arthropathy.

Laboratory evaluations include blood tests, different imaging techniques, microbiological and histological investigations, but currently there is no guidance on which tests are the most accurate and cost effective.

The primary objective in managing diabetic foot problems is to promote mobilisation. This involves managing both medical and surgical problems and involving a range of medical experts in related fields (Bridges et al, 1994).

Despite the publication of strategies on commissioning specialist services for the management and prevention of diabetic foot problems in hospital ('Putting feet first', Diabetes UK 2009; 'Improving emergency and inpatient care for people with diabetes', Department of Health 2008), there is variation in practice in the inpatient management of diabetic foot problems. This variation is due to a range of factors, including differences in the organisation of care between patients' admission to an acute care setting and discharge. This variability depends on geography, individual trusts, individual specialties (such as whether the service is managed by vascular surgery, general surgery, orthopaedics, diabetologists or general physicians) and the availability of podiatrists with expertise in diabetic foot disease.

This short clinical guideline aims to provide guidance on the key components of inpatient care of people with diabetic foot problems from hospital admission onwards.

Who this guideline is for

This document is intended to be relevant to hospital staff who care for patients with diabetic foot problems.

Patient-centred care

This guideline offers best practice advice on the hospital-based care of people with diabetic foot problems.

Treatment and care should take into account patients' needs and preferences. People with diabetic foot problems should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

1 Recommendations

1.1 Key priorities for implementation

The following recommendations have been identified as key priorities for implementation.

Multidisciplinary foot care team

- Each hospital should have a care pathway for patients with diabetic foot problems who require inpatient care[1].
- The multidisciplinary foot care team should consist of healthcare professionals with the specialist skills and competencies necessary to deliver inpatient care for patients with diabetic foot problems.
- The multidisciplinary foot care team should normally include a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, and the team should have access to other specialist services required to deliver the care outlined in this guideline.
- The multidisciplinary foot care team should:
  - assess and treat the patient's diabetes, which should include interventions to minimise the patient's risk of cardiovascular events, and any interventions for pre-existing chronic kidney disease or anaemia (please refer to 'Chronic kidney disease' [NICE clinical guideline 73] and 'Anaemia management in people with chronic kidney disease' [NICE clinical guideline 114])
  - assess, review and evaluate the patient's response to initial medical, surgical and diabetes management
  - assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
  - assess the patient's pain and determine the need for treatment and

[1] The term 'diabetic foot problems requiring inpatient care' refers to people with diabetes who have i) an ulcer, blister or break in the skin of the foot; ii) inflammation or swelling of any part of the foot, or any sign of infection; iii) unexplained pain in the foot; iv) fracture or dislocation in the foot with no preceding history of significant trauma; v) gangrene of all or part of the foot. Diabetes UK (2009): 'Putting feet first: commissioning specialist services for the management and prevention of diabetic foot disease in hospitals'.

access to specialist pain services
  - perform a vascular assessment to determine the need for further interventions
  - review the treatment of any infection
  - determine the need for interventions to prevent the deterioration and development of Achilles tendon contractures and other foot deformities
  - perform an orthotic assessment and treat to prevent recurrent disease of the foot
  - have access to physiotherapy
  - arrange discharge planning, which should include making arrangements for the patient to be assessed and their care managed in primary and/or community care, and followed up by specialist teams. Please refer to 'Type 2 diabetes: prevention and management of foot problems' (NICE clinical guideline 10).

Patient information and support

- The patient should have a named contact[2] to follow the inpatient care pathway and be responsible for:
  - offering patients information about their diagnosis and treatment, and the care and support that they can expect
  - communicating relevant clinical information, including documentation prior to discharge, within and between hospitals and to primary and/or community care.

Initial examination and assessment

- Remove the patient's shoes, socks, bandages and dressings and examine their feet for evidence of:
  - neuropathy
  - ischaemia
  - ulceration
  - inflammation and/or infection

[2] This may be a member of the multidisciplinary foot care team or someone with a specific role as an inpatient pathway coordinator.

  - deformity
  - Charcot arthropathy.

  Document any identified new and/or existing diabetic foot problems.
- Obtain urgent advice from an appropriate specialist if any of the following are present:
  - Fever or any other signs or symptoms of systemic sepsis.
  - Clinical concern that there is a deep-seated infection (for example palpable gas).
  - Limb ischaemia.

Care: within 24 hours of a patient with diabetic foot problems being admitted to hospital, or the detection of diabetic foot problems (if the patient is already in hospital)

- Refer the patient to the multidisciplinary foot care team within 24 hours of the initial examination of the patient's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.

Investigation of suspected diabetic foot infection

- If osteomyelitis is suspected and initial X-ray does not confirm the presence of osteomyelitis, use magnetic resonance imaging (MRI). If MRI is contraindicated, white blood cell (WBC) scanning may be performed instead.

Management of diabetic foot infection

- Each hospital should have antibiotic guidelines for the management of diabetic foot infections.

Management of diabetic foot ulcers

- When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

1.2 List of all recommendations

Multidisciplinary foot care team

1.2.1 Each hospital should have a care pathway for patients with diabetic foot problems who require inpatient care[3].

1.2.2 A multidisciplinary foot care team should manage the care pathway of patients with diabetic foot problems who require inpatient care.

1.2.3 The multidisciplinary foot care team should consist of healthcare professionals with the specialist skills and competencies necessary to deliver inpatient care for patients with diabetic foot problems.

1.2.4 The multidisciplinary foot care team should normally include a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, and the team should have access to other specialist services required to deliver the care outlined in this guideline.

1.2.5 The multidisciplinary foot care team should:

- assess and treat the patient's diabetes, which should include interventions to minimise the patient's risk of cardiovascular events, and any interventions for pre-existing chronic kidney disease or anaemia (please refer to 'Chronic kidney disease' [NICE clinical guideline 73] and 'Anaemia management in people with chronic kidney disease' [NICE clinical guideline 114]
- assess, review and evaluate the patient's response to initial medical, surgical and diabetes management

[3] The term 'diabetic foot problems requiring inpatient care' refers to people with diabetes who have i) an ulcer, blister or break in the skin of the foot; ii) inflammation or swelling of any part of the foot, or any sign of infection; iii) unexplained pain in the foot; iv) fracture or dislocation in the foot with no preceding history of significant trauma; v) gangrene of all or part of the foot. Diabetes UK (2009): 'Putting feet first: commissioning specialist services for the management and prevention of diabetic foot disease in hospitals'.

- assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
- assess the patient's pain and determine the need for treatment and access to specialist pain services
- perform a vascular assessment to determine the need for further interventions
- review the treatment of any infection
- determine the need for interventions to prevent the deterioration and development of Achilles tendon contractures and other foot deformities
- perform an orthotic assessment and treat to prevent recurrent disease of the foot
- have access to physiotherapy
- arrange discharge planning, which should include making arrangements for the patient to be assessed and their care managed in primary and/or community care, and followed up by specialist teams. Please refer to 'Type 2 diabetes: prevention and management of foot problems' (NICE clinical guideline 10).

Patient information and support

1.2.6 Offer patients consistent, relevant information and clear explanations that support informed decision making, and provide opportunities for them to discuss issues and ask questions.

1.2.7 The patient should have a named contact[4] to follow the inpatient care pathway and be responsible for:

- offering patients information about their diagnosis and treatment, and the care and support that they can expect

[4] This may be a member of the multidisciplinary foot care team or someone with a specific role as an inpatient pathway coordinator.

- communicating relevant clinical information, including documentation prior to discharge, within and between hospitals and to primary and/or community care.

Care: within 24 hours of a patient with diabetic foot problems being admitted to hospital, or the detection of diabetic foot problems (if the patient is already in hospital)

1.2.8 A named consultant should be accountable for the overall care of the patient and for ensuring that healthcare professionals provide timely care.

1.2.9 Refer the patient to the multidisciplinary foot care team within 24 hours of the initial examination of the patient's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.

1.2.10 The named consultant and the healthcare professionals from the existing team remain accountable for the care of the patient unless their care is transferred to the multidisciplinary foot care team.

Initial examination and assessment

1.2.11 Remove the patient's shoes, socks, bandages and dressings and examine their feet for evidence of:

- neuropathy
- ischaemia
- ulceration
- inflammation and/or infection
- deformity
- Charcot arthropathy.

Document any identified new and/or existing diabetic foot problems.

1.2.12 Consider a diagnosis of Charcot arthropathy if there is deformity, redness or warmth. Refer to an appropriate specialist to confirm the diagnosis.

1.2.13 Examine the patient for signs and symptoms of systemic sepsis (such as fever, tachycardia, hypotension, reduced consciousness or altered cognitive state).

1.2.14 X-ray the patient's affected foot (or feet) to determine the extent of the foot problem.

1.2.15 If the patient has a diabetic foot ulcer, assess and document:

- deformity
- gangrene
- ischaemia
- neuropathy
- signs of infection
- the size and depth of the ulcer.

1.2.16 Obtain urgent advice from an appropriate specialist if any of the following are present:

- Fever or any other signs or symptoms of systemic sepsis.
- Clinical concern that there is a deep-seated infection (for example palpable gas).
- Limb ischaemia.

1.2.17 Use pressure-relieving support surfaces and strategies in line with 'Pressure ulcers' (NICE clinical guideline 29) to minimise the risk of pressure ulcers developing.

Investigation of suspected diabetic foot infection

1.2.18 If a moderate to severe soft tissue infection is suspected and a wound is present, send a soft tissue sample from the base of the debrided wound for microbiological examination. If this cannot be

obtained, a superficial swab may provide useful information on the choice of antibiotic therapy.

1.2.19 If osteomyelitis is suspected and initial X-ray does not confirm the presence of osteomyelitis, use magnetic resonance imaging (MRI). If MRI is contraindicated, white blood cell (WBC) scanning may be performed instead.

1.2.20 Do not exclude osteomyelitis on the basis of X-rays alone. X-rays should be used for alternative diagnoses, such as Charcot arthropathy.

1.2.21 Do not exclude osteomyelitis on the basis of probe-to-bone testing.

1.2.22 Do not use the following bone scans to diagnose osteomyelitis: 99mTc-MDP-labelled scintigraphy, 99mTc-HMPAO-labelled scintigraphy, antigranulocyte Fab' fragment antibody scintigraphy or 99mTc-labelled monoclonal antigranulocyte antibody scintigraphy.

Management of diabetic foot infection

1.2.23 Each hospital should have antibiotic guidelines for the management of diabetic foot infections.

1.2.24 Do not delay starting antibiotic therapy for suspected osteomyelitis pending the results of the MRI scan.

1.2.25 Start empirical antibiotic therapy based on the severity of the infection, using the antibiotic appropriate for the clinical situation and the severity of the infection, and with the lowest acquisition cost.

1.2.26 For mild infections, offer oral antibiotics with activity against Gram-positive organisms.

1.2.27 For moderate and severe infections, offer antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria. The route of administration is as follows:

- Moderate infection: oral or intravenous antibiotics, based on the clinical situation and the choice of antibiotic (see recommendation 1.2.23).
- Severe infection: start with intravenous antibiotics then reassess, based on the clinical situation (see recommendation 1.2.23)

1.2.28 The definitive antibiotic regimen and the duration of treatment should be informed by both the results of the microbiological examination and the clinical response to empiric antibiotic therapy.

1.2.29 Do not use prolonged antibiotic therapy for mild soft tissue infections.

1.2.30 Treat infections with MRSA in line with local and national guidance.

Management of diabetic foot ulcers

Debridement, dressings and off-loading

1.2.31 Debridement should only be done by healthcare professionals from the multidisciplinary foot care team, using the technique that best matches their specialist expertise, clinical experience, patient preference, and the site of the ulcer.

1.2.32 When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

1.2.33 Offer off-loading for patients with diabetic foot ulcers. Healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use the technique with the lowest acquisition cost.

1.2.34 Use pressure-relieving support surfaces and strategies in line with ‘Pressure ulcers’ (NICE clinical guideline 29) to minimise the risk of pressure ulcers developing.

Adjunctive treatments

1.2.35 Negative pressure wound therapy should not be routinely used to treat diabetic foot problems, but may be considered in the context of a clinical trial or as rescue therapy (when the only other option is amputation).

1.2.36 Do not offer the following treatments for the inpatient management of diabetic foot problems, unless as part of a clinical trial:

- Dermal or skin substitutes.
- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and deltaparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy.

Assessment of suspected limb ischaemia

Limb ischaemia with redness and pain can be misdiagnosed as soft tissue infection. The new onset of gangrene of a digit or of the forefoot is often precipitated by soft tissue infection, even though the signs of inflammation may be attenuated by coincidental peripheral arterial disease.

1.2.37 If limb ischaemia is suspected, obtain a history of any previous cardiovascular events and symptoms, including previous treatments and/or procedures.

1.2.38 Inspect the limb for the following:

- Colour and temperature.
- Presence of gangrene or tissue loss.
- Presence or absence of a peripheral pulse.

1.2.39 Measure and document the ankle–brachial pressure where clinically possible, ensuring careful interpretation of the results.

1.2.40 Arrange prompt specialist assessment of patients with risk factors, symptoms and signs of limb ischaemia.

Care pathway

Multidisciplinary foot care team:

- Each hospital should have an inpatient care pathway, managed by a multidisciplinary foot care team.
- The team should consist of healthcare professionals with the specialist skills to deliver inpatient care, including a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, and the team should have access to other specialist services needed to deliver the care outlined in the guideline.
- The multidisciplinary foot care team should:
  - assess and treat the patient's diabetes, which includes minimising the risk of cardiovascular events, and interventions for pre-existing chronic kidney disease or anaemia
  - assess, review and evaluate the patient's response to initial medical, surgical and diabetes management
  - assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
  - assess the patient's pain and determine the need for treatment and access to specialist pain services
  - perform a vascular assessment to determine the need for further interventions
  - review the treatment of any infection
  - assess the need for interventions to prevent the deterioration and development of foot deformities
  - perform an orthotic assessment and treat to prevent recurrent disease of the foot
  - have access to physiotherapy
  - arrange discharge planning.

Patient information and support:

- Offer patients consistent, relevant information and clear explanations that support informed decision making, and provide opportunities for them to discuss issues and ask questions.
- Patients should have a named contact to provide information and to liaise between secondary and primary and/or community care.

Within 24 hours of the patient being admitted or a foot problem being detected (if the patient is already in hospital)

- A named consultant should be accountable for the care of the patient and for ensuring that healthcare professionals provide timely care.
- Refer the patient to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor.

Initial examination and assessment

- Examine the feet and record details of new and/or existing foot problems.
- Examine the patient for signs and symptoms of systemic sepsis.
- X-ray the affected foot (or feet).
- Use pressure-relieving support surfaces and strategies in line with 'Pressure ulcers' (NICE clinical guideline 29).

If you suspect the following, obtain advice from an appropriate specialist:

- Charcot arthropathy
- a deep-seated infection
- systemic sepsis
- limb ischaemia.

Diabetic foot ulcers

Investigation

Record the size and depth of the ulcer. Assess and record any signs of infection, ischaemia, neuropathy, gangrene or deformity.

Management

Debridement should only be done by healthcare professionals from the multidisciplinary foot care team using the technique that best matches their expertise, clinical experience, patient preference and site of the ulcer.

When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

Offer off-loading. Healthcare professionals from the multidisciplinary foot care team should take into account the wound, patient preference and the clinical circumstances, and should use the technique with the lowest acquisition cost.

Use pressure-relieving support surfaces and strategies in line with NICE clinical guideline 29.

Interventions not recommended

Negative pressure wound therapy, unless in the context of a clinical trial or as rescue therapy (when the only other option is amputation).

Dermal or skin substitutes, electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices, deltaparin, growth factors, hyperbaric oxygen therapy, unless in the context of a clinical trial.

Diabetic foot infection

Investigation

Send a deep soft tissue sample (or a superficial swab) for microbiological examination.

If you suspect osteomyelitis but the initial X-ray was not diagnostic, carry out magnetic resonance imaging (MRI) or white blood cell scanning if MRI is contraindicated.

Management

Start antibiotic therapy based on infection severity, using the antibiotic with the lowest acquisition cost appropriate for the clinical situation. Take into account local antibiotic guidelines as well as the microbiology results.

Do not delay starting therapy for suspected osteomyelitis pending MRI results.

For mild infections, offer oral antibiotics with activity against Gram-positive organisms.

For moderate and severe infections, offer antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria. For moderate infections use oral or intravenous; for severe infections start with intravenous and then reassess.

Interventions not recommended

- ***Investigation***
  X-rays or probe-to-bone testing to exclude osteomyelitis.
  Bone scans to diagnose osteomyelitis.
- ***Management***
  Prolonged antibiotic therapy for mild soft tissue infections.

Suspected limb ischaemia

Obtain a history of any previous cardiovascular events and symptoms, including treatments and/or procedures.

Inspect the limb for colour and temperature, gangrene or tissue loss and presence or absence of a peripheral pulse.

Measure and document the ankle–brachial pressure where clinically possible and interpret the results carefully.

Arrange prompt specialist assessment.

3 Evidence review and recommendations

'Inpatient management of diabetic foot problems' (NICE clinical guideline 119) is a NICE short clinical guideline. For details of how this guideline was developed see appendix B.

Introduction

The guideline is structured into six sections based on the review questions. Evidence in each section is presented in the summary of GRADE (Grading of Recommendations Assessment, Development and Evaluation) profiles and relevant evidence statements (which are cross-referred to individual summaries of GRADE profiles). Additional information, such as the full GRADE evidence profiles and outputs of different analyses, such as meta-analyses, summaries of receiver–operator–characteristics (ROC) and others, are available in the appendices. References of all included studies are also available in appendix C.

Section	Guideline section number	Number of studies included
Key components and organisations of hospital care	3.1	5
Assessment, investigation and diagnosis of diabetic foot problems	3.2	35
Debridement, wound dressings and off-loading	3.3	14
Antibiotics for diabetic foot infections	3.4	13
Adjunctive treatments for diabetic foot problems	3.5	37
Timing for surgical management to prevent amputation	3.6	0
Total		104

Health economic modelling

Examination of the existing literature and the quality of the evidence available suggested that an economic analysis would not be possible for the majority of this guideline. However, the Guideline Development Group (GDG) considered that analyses would be required in two areas to help inform decision making. Firstly, does magnetic resonance imaging (MRI) for the diagnosis of osteomyelitis represent a cost-effective use of resources? Secondly, are hyperbaric oxygen therapy (HBOT) and negative pressure wound therapy

cost-effective treatments for diabetic foot problems? These areas are considered in sections 3.2.4 and 3.5.4. Given the low quality of the evidence these analyses should be considered as exploratory. No other areas were considered for health economic modelling.

3.1 Key components and organisations of hospital care

3.1.1 Review question

What are the key components and organisations of hospital care to ensure optimal management of people with diabetic foot problems?

3.1.2 Evidence review

The systematic search retrieved 9817 studies. Of these, five studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles.
- Full GRADE evidence profiles (see appendix D).
- Evidence statements.

Table 1: Characteristics of included studies

Study	Key components (specific organised/multidisciplinary care)	Outcome of interest
Crane et al. (1999)	Critical pathway approach to diabetic foot infections compared with non-pathway standard care. The pathway was initiated in the Emergency Department utilising committee-approved standing physician's orders and clinical progress records to facilitate transitions between departments.	Length of stay Major amputations Readmission
Dargis et al. (1999)	Multidisciplinary approach compared with standard care. The multidisciplinary team was staffed by a diabetologist, a rehabilitation physician, a podiatrist, orthopaedic surgeons and shoemakers.	Ulcer recurrence Amputations
Larsson et al. (1995)	Multidisciplinary foot care team approach compared with standard care. The team consisted of a diabetologist and an orthopaedic surgeon assisted by a diabetes nurse, a podiatrist and an orthotist, working in close cooperation with the Department of Vascular Surgery and the Department of Infectious Diseases. A programme for patient and staff education was also started.	Amputations
Canavan et al. (2008)	Organised diabetes foot care compared with standard care.	Lower extremity amputations
Driver et al. (2005)	Multidisciplinary foot care (limb preservation service model) compared with standard care. Services included prevention and education, wound care, infection management, surgical and hospital management, research and grant development, community and regional education, and the creation of orthotics, prosthetics and shoes.	Lower extremity amputations

Summary of GRADE profile 1: Key components of care (specific organised/multidisciplinary care)

No. of studies	Design	Intervention	Control	Summary of results	GRADE quality
Outcome: Amputation					
1 [Cr]	Cohort	60	25	Percentage of major amputation: Intervention = 7%, control = 29%, p = 0.02	Very low
1 [D]	Cohort	56	89	Percentage of amputation (major and minor): Intervention = 7%, control = 13.7%	Very low
1 [L]	Cohort	294	NK[1]	The incidence of major amputations decreased by 78% from 16.1 to 3.6/100 000 (p < 0.001).	Very low
1 [Ca]	Cohort	223	NK[2]	LEA rates decreased from 564.3/100,000 persons in the first year to 176.0/100,000 persons in the fifth year.	Very low
1 [Dr]	Cohort	223	NK[2]	LEA rates decreased from 9.9/1000 persons in the first year to 1.8/1000 persons in the fifth year.	Very low
Outcome: Hospital length of stay					
1 [Cr]	Cohort	60	25	Mean hospital length of stay (days): [year 1995]: Intervention = 5.4, control = 7.8, p < 0.05 [year 1996]: Intervention = 3.6, control = 8.7, p < 0.05	Very low
Outcome: Hospital readmission					
1 [Cr]	Cohort	60	25	Percentage of hospital readmission: [year 1995]: Intervention = 7%, control = 18% [year 1996]: Intervention = 15%, control = 15%	Very low
Outcome: Ulcer recurrence					
1 [D]	Cohort	56	89	Percentage of ulcer recurrence: Intervention = 30.4%, control = 58.4%	Very low

[Ca] = Canavan et al. (2008)

[Cr] = Crane et al. (1999)

[D] = Dargis et al. (1999)

[Dr] = Driver et al. (2005)

[L] = Larsson et al. (1995)

LEA = lower extremity amputation; NK = not known

[1] Actual number unknown, only reported participants treated prior to 1983.

[2] Actual number unknown, not reported.

3.1.3 Evidence statement

Key components and organisations of hospital care (see Summary of GRADE profile 1)

3.1.3.1 *Five observational studies suggested that organised care or multidisciplinary care improved outcomes of patients with diabetic foot problems compared with standard care. However, there was inconclusive evidence on the specific elements and composition of both the organised and multidisciplinary care. (Very low quality)*

3.1.4 Evidence to recommendations

Quality of the evidence

The GDG agreed that there was very limited evidence and the evidence was of very low quality. Nevertheless, this limited, very low quality evidence suggested that some form of organised care or multidisciplinary care improved outcomes of patients with diabetic foot problems. However, evidence on the specific elements and composition of organised or multidisciplinary care was inconclusive. The GDG also noted the existence of skills and competency frameworks, such as the the National Minimum Skills Framework for the Commissioning of Foot Care Services for People with Diabetes (www.diabetes.org.uk/Professionals/Education_and_skills/Competencies_-_Feet/).

Other considerations

As the limited evidence showed that organised care or multidisciplinary care improved patients outcomes, the GDG further discussed this particular component of care. Based on the GDG's expertise, knowledge, experience, and the Diabetes UK document 'Putting feet first' (2009), the GDG reached consensus on the following:

- There should be a care pathway, managed by a multidisciplinary foot care team, for inpatients with diabetic foot problems.

- The overall care pathway should consist of providing care within 24 hours of admission or detection of a foot problem, and further investigation and management of specific diabetic foot problems.
- The multidisciplinary foot care team should consist of healthcare professionals who:
  - have the resources and specialist skills
  - are competent to deliver the key components of inpatient care.
- The multidisciplinary foot care team should normally include a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems,, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, together with access to other specialist services required.
- A named consultant should be accountable for the overall care of the patient and referral to the multidisciplinary foot care team within 24 hours.
- The responsibility of care should be transferred to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.
- Relevant information and clear explanations that support informed decision making, and a named contact person as a coordinator, should be offered to patients.

3.1.5 Recommendations and research recommendations for key components and organisations of hospital care

Recommendations for key components and organisations of hospital care

Multidisciplinary foot care team

Recommendation 1.2.1

Each hospital should have a care pathway for patients with diabetic foot problems who require inpatient care[5].

Recommendation 1.2.2

A multidisciplinary foot care team should manage the care pathway of patients with diabetic foot problems who require inpatient care.

Recommendation 1.2.3

The multidisciplinary foot care team should consist of healthcare professionals with the specialist skills and competencies necessary to deliver inpatient care for patients with diabetic foot problems.

Recommendation 1.2.4

The multidisciplinary foot care team should normally include a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, and the team should have access to other specialist services required to deliver the care outlined in this guideline.

Patient information and support

Recommendation 1.2.6

Offer patients consistent, relevant information and clear explanations that support informed decision making, and provide opportunities for them to discuss issues and ask questions.

[5] The term 'diabetic foot problems requiring inpatient care' refers to people with diabetes who have i) an ulcer, blister or break in the skin of the foot; ii) inflammation or swelling of any part of the foot, or any sign of infection; iii) unexplained pain in the foot; iv) fracture or dislocation in the foot with no preceding history of significant trauma; v) gangrene of all or part of the foot. Diabetes UK (2009): 'Putting feet first: commissioning specialist services for the management and prevention of diabetic foot disease in hospitals'.

Recommendation 1.2.7

The patient should have a named contact[6] to follow the inpatient care pathway and be responsible for:

- offering patients information about their diagnosis and treatment, and the care and support that they can expect
- communicating relevant clinical information, including documentation prior to discharge, within and between hospitals and to primary and/or community care.

Care: within 24 hours of a patient with diabetic foot problems being admitted to hospital, or the detection of diabetic foot problems (if the patient is already in hospital)

Recommendation 1.2.8

A named consultant should be accountable for the overall care of the patient and for ensuring that healthcare professionals provide timely care.

Recommendation 1.2.9

Refer the patient to the multidisciplinary foot care team within 24 hours of the initial examination of the patient's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.

Recommendation 1.2.10

The named consultant and the healthcare professionals from the existing team remain accountable for the care of the patient unless their care is transferred to the multidisciplinary foot care team.

[6] This may be a member of the multidisciplinary foot care team or someone with a specific role as an inpatient pathway coordinator.

Research recommendations for key components and organisations of care

No research recommendations have been made for this review question. See appendix A for full details of research recommendations.

3.2 Assessment, investigation and diagnosis of diabetic foot problems

3.2.1 Review question

What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?

3.2.2 Evidence review

The systematic search retrieved 9817 studies. Of these, 35 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). All the evidence was grouped and synthesised by individual tests and/or assessments rather than individual studies. Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles with Youden index, where appropriate (with common cut-off > 0.5 as a 'good test').
- Results of individual studies (see appendix E).
- Full GRADE evidence profiles (see appendix D).
- Forest plots (where appropriate) (see appendix F).
- Summary of ROC (where appropriate) (see appendix F).
- Van der Bruel plots (where appropriate) (see appendix G).
- Evidence statements.

The decision not to conduct a meta-analysis for this review question (that is, to not produce a 'point summary' across the studies) was made because of the following methodological reasons.

- Not all studies used the same single definitive reference standard (please see table 2).
- Variability of pre-test probabilities among studies (please see the ranges in the full GRADE evidence profiles, appendix D).
- Variability in the quality of the included studies (please see QUADAS [Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews] methodological quality graph, appendix E).
- High risk of heterogeneity (please see confidence intervals of the forest plots, and the summary ROC, appendix F).

Although a 'point summary' (or pooled estimate) was not produced for this review question, a summary of ROC (without pooled estimates) was provided where appropriate as a visual guide to aid discussion, but not as a sole decision tool for recommendations. Other factors were discussed in order to draw conclusions for recommendations, such as:

- assessing the 'width' of the range of results in GRADE profiles
- assessing the confidence intervals in a forest plot
- assessing the clinical utility (Smart 2006) of individual tests, for example:
  - appropriateness: effectiveness and accuracies, relevance to practice
  - accessibility: resource implications and procurement
  - practicality: functionality, suitability, training and knowledge
  - acceptability: whether acceptable to healthcare professionals, patients and carers, society (public or stakeholder groups)
- health economic evaluation.

Table 2: Characteristics of included studies

Study	Index test	Reference standard
Al-Khawari et al. (2005)	• MRI	Culture growth or characteristic histological findings in diagnosing osteomyelitis
Beckert et al. (2006)	• DUSS	Wound-based clinical scoring system
Beltran et al. (1990)	• MRI	Aspiration, pathological examination, and plain radiographs in detecting osteomyelitis
Boyko et al. (1997)	• Medical history information • Physical examination findings • Clinical tests	AAI ≤0.5 in diagnosing severe peripheral vascular disease
Croll et al. (1996)	• MRI • 99mTc bone scan • In-WBC • Plain radiographs	Pathological specimen, or bone culture in diagnosing osteomyelitis
Devillers et al. (1998)	• 3 -phase 99mTc-MDP-labelled bone scintigraphy • 99mTc-HMPAO-labelled leukocyte scintigraphy	Radiographic and/or bacteriological or histological results or clinical follow up in diagnosis of diabetic foot infection
Ertugrul et al. (2009)	• ESR • Wound sizes	Histopathology, microbiology and MRI with conventional spin echo in diagnosing osteomyelitis
Ertugrul et al. (2006)	• Microbiological processing • MRI • 99mTc-MDP-labelled leukocyte scan	Histopathological findings in diagnosing osteomyelitis
Gardner et al. (2009)	• Classical signs: – Increasing pain – Erythema – Oedema – Heat – Purulent exudate	High microbial load in detecting infections

	• Signs specific to secondary wounds: – Serous exudate – Sanguineous exudate – Delayed healing – Discoloured granulation – Friable granulation – Pocketing – Foul odour – Wound breakdown	
Grayson et al. (1995)	• Probe-to-bone	Histological tests in detecting osteomyelitis
Harvey et al. (1997)	• 99mTc-HMPAO-labelled leukocyte scintigraphy • 99mTc-MDP-labelled bone scintigraphy	Histology, bone cultures and radiographic results in diagnosing osteomyelitis
Harwood et al. (1999)	• Sulesomab • In-WBC and 99m-Tc bone scan	Histology and/or microbiological cultures in detecting osteomyelitis
Kaleta et al. (2001)	• ESR	Histological examination (pathological reports) in diagnosing osteomyelitis
Keenan et al. (1989)	• 3-phase 99mTc-MDP bone scintigraphy • In-WBC	Culture and/or histological examination in diagnosing osteomyelitis
Kreitner et al. (2000)	• Three-dimensional contrast-enhanced MRA	DSA evaluating arteries of the distal calf and foot
Lapeyre et al. (2005)	• MRA	DSA detecting critical limb ischaemia
Larcos et al. (1991)	• 111-In-WBC • 99mTc-MDP-labelled bone scintigraphy • Radiographs	Surgery (bone culture or biopsy) and clinical follow-up in diagnosing osteomyelitis
Levine et al.	• MRI	Pathological and histological determination, surgical observation and clinical

(1994)	• Plain-film roentgenography • 111-In-WBC scintigraphy • 99mTc bone scan	resolution in diagnosing osteomyelitis
Malabu et al. (2007)	• ESR • Haematocrit • Haemoglobin • Platelet count • Red cell distribution width • White cell count	Bone scan, MRI, radiographs or the ability to probe an open wound to bone in detecting osteomyelitis
Morrison et al. (1995)	• MRI	Histological analysis of biopsy specimens OR Clinical and radiographic demonstration of progression in detecting osteomyelitis
Newman et al. (1991)	• Roentgenography • 111-In-WBC (4 h and 24 h) • Bone scans	Bone biopsy and culture in diagnosing osteomyelitis
Newman et al. (1992)	• MRI • Leukocyte scanning	Bone specimens for histology and culture in diagnosing osteomyelitis
Oyibo et al. (2001)	• Wagner wound classification system • University of Texas diabetic wound classification system	Comparing the utility of two wound scores
Palestro et al. (2003)	• 99mTc-labelled monoclonal antibody • In-WBC • 3-phase (99mTc-MDP-labelled bone scintigraphy)	Bone biopsy examination and culture in diagnosing osteomyelitis
Poirier et al. (2002)	• 99mTc-MDP bone scintigraphy • 99mTc-HMPAO-labelled leukocyte scan	Radiological examination, bacteriological and histological studies in diagnosing osteomyelitis
Remedios et al. (1998)	• 99m-Tc nanocolloid • MRI	Histological and microbiology tests in detecting osteomyelitis
Rozzanigo et al. (2009)	• MRI	Bacteriological and/or histological tests in detecting osteomyelitis
Rubello et al.	• LeukoScan (4 h and 18–24 h)	Microbiological findings or other laboratory and imaging techniques in detecting

(2004)		bone infection
Shaw et al. (2007)	• The Visitrak system • A digital photography and image processing system • An elliptical measurement method using the standard formula	Wound measurement in diabetic foot wounds
Shone et al. (2006)	• Probe-to-bone	Clinical signs of osteomyelitis, supported by MRI and microbiological analysis of deep tissue samples
Slater et al. (2004)	• Swab cultures	Deep tissue biopsy to accurately identify bacterial pathogens in diabetic foot wounds
Strauss et al. (2005)	• Wagner (1979), US • Forrest and Gamborg-Neilsen (1984), Sweden • Knighton et al. (1986), US • Pecoraro and Reiber (1990), US • Lavery et al. (1996), US • MacFarlane and Jeffcoate (1999), UK • Foster and Edmunds (2000), UK	The new wound score (clinical utility)
Wang et al. (1990)	• MRI • Plain radiographs	Histological examination in detecting osteomyelitis
Weinstein et al. (1993)	• MRI • Plain radiographs • 99mTc/Ga scan	Histological examination in diagnosing osteomyelitis
Yuh et al. (1989)	• MRI • Bone scans • Plain radiographs	Pathological tests detecting osteomyelitis

99m-Tc = technetium-99m; AAI = ankle–arm index; DSA = digital subtraction angiography; DUSS = diabetic ulcer severity score; ESR = erythrocyte sedimentation rate; Ga = gallium; HMPAO = hexamethylpropylamine oxine; In-WBC = indium leukocyte scanning; MDP = methylene diphosphonate; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging.

The clinical utility of different diabetic ulcer/wound scores

There are numerous wound scores available that are used by healthcare professionals in the field. However, most scores have not been validated in different data sets or study populations. There is a lack of evidence that assesses the clinical utility of these wound scores. From the systematic searches, only three studies were identified that met the inclusion/exclusion criteria (Beckert et al. 2006; Strauss et al. 2005; Oyibo et al. 2001). These three studies were of low quality and therefore needed cautious interpretation. The evidence was presented in the summary of GRADE profiles and evidence statements (which were cross-referred to the relevant summary of GRADE profiles) (also see results of individual studies in appendix E; full GRADE evidence profiles in appendix D).

Summary of GRADE profile 2:
Clinical utility of different diabetic ulcer/ wound scores

<table>
<tr><th colspan="3">Study characteristics</th><th colspan="2">Summary of findings</th></tr>
<tr><td>No. of studies</td><td>No. of patients</td><td>Clinical parameters/evaluation criteria</td><td>Summary of findings</td><td>GRADE quality</td></tr>
<tr><td colspan="5">DUSS</td></tr>
<tr><td>1
[B]</td><td>1000</td><td>Palpable pedal pulses
Probing to bone
Ulcer location
Multiple ulcerations</td><td>Multivariate analysis: an increase of 1 point reduced the chance for healing by 35% (at the end of follow-up).</td><td>Low</td></tr>
<tr><td>1
[B]</td><td>1000</td><td>Palpable pedal pulses
Probing to bone
Ulcer location
Multiple ulcerations</td><td>
<table>
<tr><th>Score</th><th>Wound duration (days) (median range)</th><th>Surgery (%)</th></tr>
<tr><td>0</td><td>29 (2 to 597)</td><td>9</td></tr>
<tr><td>1</td><td>26.5 (1 to 2922)</td><td>17</td></tr>
<tr><td>2</td><td>31 (1 to 4018)</td><td>27</td></tr>
<tr><td>3</td><td>42 (1 to 18708)</td><td>37</td></tr>
<tr><td>4</td><td>61 (3 to 1516)</td><td>50</td></tr>
</table>
</td><td>Low</td></tr>
<tr><td colspan="5">Comparison of Wagner wound score and UT wound scores</td></tr>
<tr><td>1
[O]</td><td>194</td><td>Wagner wound classification system (grade 0 to 5)
UT diabetic wound classification system (stage A to D, each stage has grade 1 to 3)</td><td>Positive trend with increased number of amputations
Wagner grade: χ^2 trend = 21.0, $p < 0.0001$
UT grade and stage: χ^2 trend = 23.7, $p < 0.0001$ and χ^2 trend = 15.1, $p = 0.0001$

Cox regression analysis
Only the UT stage had a predictive effect on healing time ($\chi^2 = 10.3$, df = 3, $p < 0.05$). The higher the stage at presentation, the less likely it was for that ulcer to heal within the study period (hazard ratio = 0.8, 95% CI: 0.67 to 0.98, $p < 0.05$).</td><td>Low</td></tr>
<tr><td colspan="5">Evaluation of diabetic foot wound scores</td></tr>
<tr><td>1
[S]</td><td>N/A
Qualitative evaluation</td><td>Number of criteria
Objectivity of findings to evaluate each criterion
Scoring permutations
Versatility
Guide to seriousness
Integration with wound information
Integration with patient information
Documentation of progress
Validity
Reliability</td><td>Assessment scores:
<table>
<tr><th>Test</th><th>Total</th></tr>
<tr><td>WAG[1]</td><td>7</td></tr>
<tr><td>FOR[2]</td><td>4</td></tr>
<tr><td>KNI[3]</td><td>4</td></tr>
<tr><td>PEC[4]</td><td>3</td></tr>
<tr><td>LAV[5]</td><td>10</td></tr>
<tr><td>JEF[6]</td><td>11</td></tr>
<tr><td>FOS[7]</td><td>8</td></tr>
</table>
</td><td></td></tr>
</table>

[B] = Beckert et al. (2006)

[S] = Strauss et al. (2005)

[O] = Oyibo et al. (2001)

[1] Wagner (1979), US

[2] Forrest and Gamborg-Neilsen (1984), Sweden

[3] Knighton et al. (1986), US
[4] Pecoraro and Reiber (1990), US
[5] Lavery et al. (1996), US
[6] MacFarlane and Jeffcoate (1999), UK
[7] Foster and Edmunds (2000), UK
CI = confidence interval; df = degrees of freedom, DUSS = diabetes ulcer severity score, UT = University of Texas

The clinical utility of assessment, investigative or diagnostic tools for diabetic foot infections

From the systematic searches, only two studies were identified that met the inclusion/exclusion criteria. Both studies needed cautious interpretation as both were subjected to a high risk of bias. The evidence was presented in the summary of GRADE profiles and evidence statements (which were cross-referred to the relevant summary of GRADE profiles) (also see results of individual studies in appendix E; full GRADE evidence profiles in appendix D).

Summary of GRADE profile 3: Clinical signs of diabetic foot infections

Study characteristics			Summary of findings					
No. of studies	No. of patients	Clinical signs	Pre-test probability	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Post-test probability (+ve)	Post-test probability (despite [-ve])	GRADE quality
Clinical signs of diabetic foot infection (reference standard: high microbial loads > 1 million organisms per gram of tissue)								
1 [G]	64	Increasing pain	0.39	12 (26 to 32)	100 (90 to 100)	1.00	0.37	Very low
1 [G]	64	Erythema	0.39	32 (15 to 53)	77 (60 to 89)	0.47	0.53	Very low
1 [G]	64	Oedema	0.39	20 (6 to 41)	77 (60 to 89)	0.36	0.40	Very low
1 [G]	64	Heat	0.39	12 (2 to 31)	84 (69 to 94)	0.33	0.40	Very low
1 [G]	64	Purulent exudate	0.39	28 (12 to 49)	64 (47 to 79)	0.33	0.42	Very low
1 [G]	64	Serous exudate	0.39	88 (69 to 97)	73 (64 to 81)	0.42	0.04	Very low
1 [G]	64	Sanguineous exudate	0.39	84 (64 to 95)	90 (76 to 97)	0.84	0.11	Very low
1 [G]	64	Delayed healing	0.39	48 (23 to 69	54 (37 to 70)	0.40	0.39	Very low
1 [G]	64	Discoloured granulation	0.39	28 (12 to 49)	85 (69 to 94)	0.54	0.36	Very low
1 [G]	64	Friable granulation	0.39	0 (0 to 14)	77 (61 to 89)	0.00	0.46	Very low
1 [G]	64	Pocketing	0.39	40 (21 to 61	59 (42 to 74)	0.38	0.40	Very low
1 [G]	64	Foul odour	0.39	20 (6 to 41)	87 (73 to 96)	0.50	0.32	Very low
1 [G]	64	Wound breakdown	0.39	0 (0 to 14)	95 (83 to 99)	0.00	0.41	Very low

[G] = Gardner et al. (2009)

CI = confidence interval

Summary of GRADE profile 4: Swab cultures

Study characteristics			Summary of findings	
No. of studies	No. of patients (wounds)	Outcomes	Association between swabs and deep tissue cultures	GRADE quality
Swab cultures in diabetic wounds not involving bone (reference standard: deep tissue biopsy)				
1 [S]	56 (60)	Swabs contained all organisms found in deep tissue biopsy	49/60 (82%)	Low
1 [S]	56 (60)	Swabs and deep tissue cultures identical	37/60 (62%)	Low
1 [S]	56 (60)	Swabs contained all organisms found in deep tissue biopsy plus additional organisms	12/60 (20%)	Low
1 [S]	56 (60)	Swabs lacked organism(s) found in deep tissue biopsy	11/60 (18%)	Low

[S] = Slater et al. (1997)

The diagnostic accuracy of different tests in diagnosing osteomyelitis

From the systematic searches, 26 studies were identified that met the inclusion/exclusion criteria. Most of these studies investigated the diagnostic accuracy of different imaging tests in diagnosing osteomyelitis. Only five studies investigated the diagnostic accuracy of blood tests and the use of clinical signs and symptoms. The quality of the evidence was of moderate/low quality, and was presented in the summary of GRADE profiles and evidence statements (which were cross-referred to the relevant summary of GRADE profiles) (also see results of individual studies in appendix E; full GRADE evidence profiles in appendix D; forest plots [where appropriate] in appendix F; summary of ROC [where appropriate] in appendix F; Van der Bruel plots [where appropriate] in appendix G).

Summary of GRADE profile 5: Imaging (single testing)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
See appendix C: Full GRADE evidence profile 6 – MRI								
10 [A, B, C, E, L, M, R, W, We, Y]	Range: 14 to 62	Range: 0.33 to 0.86	Range: 77 to 100	Range: 60 to 100	Range: 0.75 to 100	Range: 0 to 0.62	Range: 0.38 to 1.0	Low
See appendix C: Full GRADE evidence profile 7 – 99mTc-MDP-labelled scintigraphy								
11 [C, D, E, Hd, Hy, K, L, N, Pa, Po, Y]	Range: 22 to 94	Range: 0.29 to 0.88	Range: 50 to 100	Range: 0 to 67	Range: 0.36 to 0.95	Range: 0.0 to 1.0	Range: -0.06 to 0.58	Low
See appendix C: Full GRADE evidence profile 8 – 99mTc-HMPAO-labelled scintigraphy								
3 [D, Hd, Hy]	Range: 52 to 122	Range: 0.40 to 0.66	Range: 86 to 91	Range: 56 to 97	Range: 0.8 to 0.94	Range: 0.09 to 0.23	Range: 0.47 to 0.85	Moderate
See appendix C: Full GRADE evidence profile 9: In-WBC								
8 [C, Hd, K, La, L, N1, N2, Pa]	Range: 12 to 111	Range: 0.27 to 0.68	Range: 33 to 100	Range: 22 to 78	Range: 0.28 to 0.85	Range: 0.0 to 0.40	Range: 0.01 to 0.78	Low
See appendix C: Full GRADE evidence profile 10: anti-granulocyte Fab' fragment antibody scintigraphy								
1 [Ru] 4 hours	78	0.79	92 (82 to 97)	75 (48 to 93)	0.93	0.29	0.67	Moderate
1 [Ru] 24 hours	78	0.79	92 (82 to 97)	88 (62 to 98)	0.97	0.26	0.80	Moderate
See appendix C: Full GRADE evidence profile 11: plain radiographs								
8 [C, D, La, L, N, W, We, Y]	Range: 26 to 62	Range: 0.29 to 0.86	Range: 22 to 75	Range: 17 to 94	Range: 0.17 to 0.89	Range: 0.24 to 0.67	Range: -0.40 to 0.50	Low
See appendix C: Full GRADE evidence profile 12: 99mTc-labelled monoclonal antigranulocyte antibody								
1 [Pa]	25	0.40	90	67	0.64	0.09	0.57	Low
See appendix C: Full GRADE evidence profile 13: probe-to-bone								
2 [G, S]	Range: 76 to 104	Range: 0.20 to 0.66	Range: 0.38 to 0.66	Range: 0.85 to 0.92	Range: 0.38 to 0.66	Range: 0.08 to 0.15	Range: 0.30 to 0.51	Low

[A] = Al-Khawari (2007): reference standard = histological analysis

[B] = Beltran (1990): reference standard = aspiration/pathological examination/plain films

[C] = Croll (1996): reference standard = pathological specimen or bone culture

[D] = Devillers (1998): reference standard = radiographic/bacteriological/histological results/clinical follow-up

[E] = Ertugrul (2006): reference standard = histopathological analysis

[G] = Grayson (1995): reference standard = histological and microbiology tests in detecting osteomyelitis

[Hd] = Harwood (1999): reference standard = histological and/or microbiological cultures

[Hy] = Harvey (1997): reference standard = histology, bone cultures and radiographic results

[K] = Keenan (1989): reference standard = culture and/or histological examination

[La] = Larcos (1991): reference standard = bone culture/biopsy/clinical follow-up

[L] = Levine (1994): reference standard = pathological/histological/surgical examination/clinical follow-up

[M] = Morrison (1995): reference standard = histological analysis or clinical and radiographic demonstration despite conservative antibiotic therapy

[N] = Newman (1991): reference standard = bone biopsy and culture

[N1] = Newman (1991) (4 hours): reference standard = bone biopsy and culture

[N2] = Newman (1991) (24 hours): reference standard = bone biopsy and culture

[Pa] = Palestro (2003): reference standard = bone biopsy and culture/clinical follow-up

[Po] = Poirier (2002): reference standard = radiological examination or histopathological analysis

[R] = Rozzanigo (2009): reference standard = bacteriological and/or histological tests

[RU] = Rubello (2004): reference standard = microbiological findings/CT scan/MRI/clinical follow-up

[S] = Shone (2006): reference standard = clinical signs of osteomyelitis, supported by MRI and microbiological analysis of deep tissue samples.

[W] = Wang (1990): reference standard = histological examination

[We] = Weinstein (1993): reference standard = histological examination

[Y] = Yuh (1989): reference standard = pathological tests

99mTc = technetium-99m; MRI = magnetic resonance imaging.

Summary of GRADE profile 6: Imaging (combination tests): other imaging tests (combination)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
99mTc-MDP-labelled scintigraphy + In-WBC								
2 [K, Pa]	25 & 39	0.40 & 0.38	Range: 80 to 100	Range: 79 to 80	Range: 0.73 to 0.75	Range: 0.0 to 0.14	Range: 0.60 to 0.79	Low
99mTc-labelled monoclonal antigranulocyte antibody + 99mTc-MDP-labelled scintigraphy								
1 [Pa]	25	0.40	90 (55 to 100)	67 (38 to 88)	0.64	0.09	0.50	Low
99mTc-MDP-labelled scintigraphy + 99mTc-HMPAO-labelled scintigraphy								
1 [Po]	83	0.49	93 (80 to 96)	98 (87 to 100)	0.97	0.07	0.91	Low
99mTc-MDP-labelled scintigraphy + Gallium 67 citrate								
1 [We]	22	0.73	69 (41 to 89)	83 (36 to 100)	0.92	0.50	0.52	Low

[K] = Keenan (1989): reference standard = culture and/or histological examination

[Pa] = Palestro (2003): reference standard = bone biopsy and culture or clinical follow-up

[Po] = Poirer (2002): reference standard = radiological examination or histopathological analysis

[We] = Weinstein (1993): reference standard = histological examination

99mTc = technetium-99m.

Summary of GRADE profile 7: Blood tests (single test): Erythrocyte sedimentation rate and other tests (single study)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
ESR ≥ 60 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	89 to 92	68 to 90	Range: 0.76 to 0.94	Range: 0.12 to 0.18	Range: 0.60 to 0.79	Low
ESR ≥ 65 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	88 to 89	73 to 90	Range: 0.78 to 0.94	Range: 0.16 to 0.18	Range: 0.61 to 0.79	Low
ESR ≥ 70 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	83 to 89	77 to 100	Range: 0.80 to 1.00	Range: 0.17 to 0.19	Range: 0.60 to 0.89	Low
ESR > 70 mm/h								
2 [M, N]	28 & 43	0.51 & 0.64	28 to 91	95 to 100	Range: 0.95 to 1.00	Range: 0.09 to 0.57	Range: 0.28 to 0.86	Low
ESR ≥ 75 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	79 to 84	82 to 100	Range: 0.83 to 1.00	Range: 0.22 to 0.23	Range: 0.61 to 0.84	Low
ESR ≥ 80 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	71 to 79	91 to 90	Range: 0.89 to 1.00	Range: 0.26 to 0.29	Range: 0.62 to 0.79	Low
ESR > 100 mm/h								
1 [N]	39	0.67	23	100	1.00	0.61	0.23	Moderate
Haematocrit > 36%								
1 [M]	43	0.51	95 (77 to 100)	86 (64 to 97)	0.88	0.05	0.81	Low
Haemoglobin < 12 g/dL								
1 [M]	43	0.51	82 (60 to 95)	90 (70 to 99)	0.90	0.17	0.72	Low
Platelet count > $400x10^9$/L								
1 [M]	43	0.51	45 (24 to 68)	95 (76 to 100)	0.91	0.37	0.40	Low
Red cell distribution width > 14.5								
1 [M]	43	0.51	68 (45 to 86)	62 (38 to 82)	0.65	0.35	0.30	Low
White cell count > $400x10^9$/L								
1 [M]	43	0.51	50 (28 to 72)	81 (58 to 95)	0.73	0.39	0.31	Low

[E] = Ertugrul (2009): reference standard = histopathology/bone tissue culture/MRI conventional spin echo

[K] = Kaleta (2001): reference standard = histological examination

[M] = Malabu (2001): reference standard = bone scan/MRI/radiographs

[N] = Newman (1991): reference standard = bone biopsy and culture

CI = confidence interval; ESR = erythrocyte sedimentation rate.

Summary of GRADE profile 8: Other tests (single tests)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
Microbiological processing								
1 [E]	31	0.84	92 (75 to 99)	60 (15 to 95)	0.92	0.40	0.52	Low
Ulcer inflammation								
1 [N]	41	0.68	36 (19 to 56)	81 (54 to 96)	0.77	0.58	0.17	Moderate
Clinical judgement								
1 [N]	41	0.68	32 (16 to 52)	100 (75 to 100)	1.00	0.59	0.32	Moderate
Bone exposure								
1 [N]	41	0.68	32 (16 to 52)	100 (75 to 100)	1.00	0.59	0.32	Moderate

[E] = Ertugrul (2006): reference standard = histopathological analysis

[N] = Newman (1991): reference standard = bone biopsy and culture

CI = confidence interval

Summary of GRADE profile 9: Other tests (combination tests): wound sizes (and erythrocyte sedimentation rate)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
Wound size ≥ 2cm^2								
2 [E, N]	40 & 46	Range: 0.52 to 0.66	Range: 56 to 88	Range: 77 to 93	Range: 0.81 to 0.94	Range: 0.15 to 0.48	Range: 0.49 to 0.65	Low
Wound size ≥ 3 cm^2								
1 [E]	46	0.52	79	77	0.79	0.23	0.56	Low
Wound size ≥ 4 cm^2								
1 [E]	46	0.52	67	91	0.89	0.29	0.58	Low
Wound size ≥ 5 cm^2								
1 [E]	46	0.52	50	95	0.92	0.36	0.45	Low
ESR rate ≥ 65 mm/h + wound size ≥ 2 cm²								
1 [E]	46	0.52	83	77	0.80	0.19	0.60	Low
ESR rate ≥ 70 mm/h + wound size ≥ 2cm²								
1 [E]	46	0.52	79	82	0.83	0.22	0.61	Low

[E] = Ertugrul (2006): reference standard = histopathological analysis

[N] = Newman (1991): reference standard = bone biopsy and culture

ESR = erythrocyte sedimentation rate.

The clinical utility of assessment, investigative or diagnostic tools for examining peripheral arterial disease in people with diabetic foot problems

From the systematic searches, only three studies were identified that met the inclusion/exclusion criteria. These three studies were of low quality and therefore needed cautious interpretation. The evidence was presented in the summary of GRADE profiles evidence statements (which were cross-referred to relevant summary of GRADE profiles) (also see results from individual studies in appendix E; full GRADE evidence profiles in appendix D).

Summary of GRADE profile 10: peripheral arterial disease

No. of studies	No. of patients	Predictor(s)	Side of the leg	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	GRADE quality
Clinical examination of PAD (reference standard: AAI ≤ 0.5)						
1 [B]	605	Abnormal pulses and history of PAD	Right	53 (39 to 68)	91 (88 to 93)	Low
1 [B]	587	Abnormal pulses and history of PAD	Left	50 (35 to 65)	91 (89 to 93)	Low
1 [B]	605	Abnormal pulses or history of PAD	Right	93 (86 to 100)	58 (50 to 62)	Low
1 [B]	587	Abnormal pulses or history of PAD	Left	100 (93 to 100)	58 (54 to 62)	Low
1 [B]	605	Abnormal pulses and claudication <1 block	Right	33 (19 to 46)	95 (93 to 97)	Low
1 [B]	587	Abnormal pulses and claudication <1 block	Left	36 (22 to 51)	94 (92 to 96)	Low
1 [B]	605	Abnormal pulses or claudication <1 block	Right	83 (72 to 94)	71 (67 to 75)	Low
1 [B]	587	Abnormal pulses or claudication <1 block	Left	86 (76 to 97)	71 (67 to 75)	Low
No. of studies	No. of patients	Outcome	2 reviewers	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	GRADE Quality
Diagnostic accuracy of hybrid MRA for critical limb ischaemia (reference standard: DSA)						
1 [L]	31	Stenoses ≥ 50%	1	95 (86 to 98)	98 (95 to 99)	Low
1 [L]	31	Stenoses ≥ 50%	2	96 (88 to 99)	98 (95 to 99)	Low
1 [L]	31	Arterial occlusions	1	95 (88 to 97)	98 (96 to 99)	Low
1 [L]	31	Arterial occlusions	2	90 (83 to 94)	99 (97 to 100)	Low
No. of studies	No. of patients	Visualisation of arterial segments	Sensitivity and specificity	Other analysis		GRADE Quality
Comparison of contrast-enhanced MRA with DSA and change of treatment plans						
1 [K]	24	Anterior tibial; posterior tibial; peroneal; dorsal pedal; medial plantar; lateral plantar; pedal arch	N/A (no reference standard)	MRA was significantly better than DSA for dorsal pedal artery, lateral plantar arteries, and pedal arch, with $p < 0.05$ MRA revealed a patent vessel that was not seen on DSA (suitable for distal bypass grafting) in 9/24 (38%) patients, which led to a change of treatment plans for 7 patients.		Low

[B] = Boyko et al. (1997)

[L] = Lapeyre et al. (2005)

[K] = Kreitner et al. (2006)

AAI = ankle–arm index; CI = confidence interval; DSA = digital subtraction angiography; MRA = magnetic resonance angiography; PAD = peripheral arterial disease.

The clinical utility of assessment, investigative or diagnostic tools for examining Charcot arthropathy in people with diabetic foot problems

No studies were identified that met the inclusion/exclusion criteria.

3.2.3 Evidence statements

The clinical utility of different diabetic ulcer/wound scores (see Summary of GRADE profile 2)

3.2.3.1 Overall there was no strong evidence to suggest which diabetic/wound scores were better than others.

- *One observational study with 194 participants suggested that both the grades of the Wagner wound score and the grades and stages of the University of Texas diabetic wound score were positively associated with an increased number of amputations. However, only the stages of the University of Texas diabetic wound score had a predictive effect on healing time. (Low quality)*
- *One observational study with 1000 participants suggested that the scores of the Diabetic ulcer severity score (DUSS) were correlated to the chance of wound healing. (Low quality)*
- *One subjective qualitative evaluation of 7 wound scores suggested that the MacFarlane and Jeffcoate Nottingham wound score had the highest clinical utility, followed by the Lavery et al. wound score (1996); the Foster and Edmunds wound score (2000); and the Wagner wound score. (Very low quality)*

The clinical utility of assessment and diagnostic tools for diabetic foot infections (see Summary of GRADE profile 3 and 4)

Clinical signs (reference standard: high microbial loads > 1 million organisms per gram of tissue)

3.2.3.2 One observational study with 64 participants suggested that serous exudate and sanguineous exudate were significantly associated with diabetic foot infection. (Very low quality)

Swab cultures (reference standard: deep tissue biopsy)

3.2.3.3 One observational study with 56 participants suggested that swab cultures were associated with deep tissue biopsy in diagnosing diabetic foot infections. However, the study did not provide significant accuracy analysis for the association between swab cultures and deep tissue biopsy. (Low quality)

The diagnostic accuracy of different tests in diagnosing osteomyelitis
Imaging (single testing) (see Summary of GRADE profile 5)

3.2.3.4 Eleven observational studies with a range of participants (22 to 94) suggested that 99mTc-MDP-labelled scintigraphy had a sensitivities range from 50% to 100%, and a specificities range from 0% to 67% in diagnosing osteomyelitis in people with diabetic foot problems, with a Youden index range from -0.06 to 0.58. (Low quality)

3.2.3.5 Ten observational studies with a range of participants (14 to 62) suggested that MRI had a sensitivities range from 77% to 100%, and a specificities range from 60% to 100%, with a Youden index range from 0.38 to 1.00. (Low quality)

3.2.3.6 Eight observational studies with a range of participants (12 to 111) suggested that In-WBC scans had a sensitivities range from 33% to 100%, and a specificities range from 22% to 78%, with a Youden index range from 0.01 to 0.78. (Low quality)

3.2.3.7 Eight observational studies with a range of participants (26 to 62) suggested that plain radiographs had a sensitivities range from 22% to 75%, and a specificities range from 17% to 94%, with a Youden index range from -0.40 to 0.50. (Low quality)

3.2.3.8 Three observational studies with a range of participants (52 to 122) suggested that 99mTc-HMPAO-labelled scintigraphy had a sensitivities range from 86% to 91%, and a specificities range from

56% to 97%, with a Youden index range from 0.47 to 0.85. (Low quality)

3.2.3.9 *One observational study with 78 participants suggested that anti-granulocyte Fab' fragment antibody scintigraphy had sensitivity of 92% (both 4 hours and 24 hours), and specificities of 75% (4 hours) and 88% (24 hours), with a Youden index of 0.67 and 0.80. (Moderate quality)*

3.2.3.10 *One observational study with 25 participants suggested that 99mTc-labelled monoclonal antigranulocyte antibody (Moab) had sensitivity of 90%, and specificity of 67%, with a Youden index of 0.57. (Low quality)*

3.2.3.11 *Two observational studies with 76 and 104 participants suggested that probe-to-bone testing had sensitivities of 38% and 66%, and specificities of 85% and 92% respectively, with a Youden index range from 0.30 to 0.51. (Low quality)*

Imaging (combination testing) (see Summary of GRADE profile 6)

3.2.3.12 *Two observational studies with 25 and 39 participants suggested that In-WBC plus 99mTc-MDP-labelled scintigraphy had sensitivities of 80% and 100%, and specificities of 80% and 79% respectively, with a Youden index range from 0.60 to 0.79. (Low quality)*

3.2.3.13 *One observational study with 25 participants suggested that Moab plus 99mTc-MDP-labelled scintigraphy had sensitivity of 90% and specificity of 67%, with a Youden index of 0.50. (Low quality)*

3.2.3.14 *One observational study with 83 participants suggested that 99m-HMPAO plus 99mTc-MDP-labelled scintigraphy had sensitivity of 93% and specificity of 98%, with a Youden index of 0.91. (Low quality)*

3.2.3.15 One observational study with 22 participants suggested that 99mTc-MDP-labelled scintigraphy plus gallium-67 citrate scans had sensitivity of 69% and specificity of 83%, with a Youden index of 0.52. (Low quality)

Erythrocyte sedimentation rate and wound sizes (see Summary of GRADE profile 7 and 9)

3.2.3.16 Two observational studies with 29 and 46 participants suggested that ESR ≥ 60 mm/h had sensitivities of 89% and 92% and specificities of 68% and 90% respectively, with a Youden index range from 0.60 to 0.79. (Low quality)

3.2.3.17 Two observational studies with 29 and 46 participants suggested that ESR ≥ 65 mm/h had sensitivities of 88% and 89% and specificities of 73% and 90% respectively, with a Youden index range from 0.61 to 0.79. (Low quality)

3.2.3.18 Two observational studies with 29 and 46 participants suggested that ESR ≥ 70 mm/h had sensitivities of 83% and 89% and specificities of 77% and 100% respectively, with a Youden index range from 0.60 to 0.89. (Low quality)

3.2.3.19 Two observational studies with 28 and 43 participants suggested that ESR > 70 mm/h had sensitivities of 28% and 91% and specificities of 95% and 100% respectively, with a Youden index range from 0.28 to 0.86. (Low quality)

3.2.3.20 Two observational studies with 29 and 46 participants suggested that ESR ≥ 75 mm/h had sensitivities of 79% and 84% and specificities of 82% and 100% respectively, with a Youden index range from 0.61 to 0.84. (Low quality)

3.2.3.21 Two observational studies with 29 and 46 participants suggested that ESR ≥ 80 mm/h had sensitivities of 71% and 79% and specificities of 91% and 90% respectively, with a Youden index range from 0.62 to 0.79. (Low quality)

3.2.3.22 One observational study with 39 participants suggested that ESR > 100 mm/h had sensitivity of 23% and specificity of 100%, with a Youden index of 0.23. (Moderate quality)

3.2.3.23 Two observational studies with 40 and 46 participants suggested that wound size ≥ 2 cm^2 had sensitivities of 56% and 88% and specificities of 77% and 93% respectively, with a Youden index range from 0.49 to 0.65. (Low quality)

3.2.3.24 One observational study with 46 participants suggested that wound size ≥ 3 cm^2 had sensitivity of 79% and specificity of 77%, with a Youden index of 0.56. (Low quality)

3.2.3.25 One observational study with 46 participants suggested that wound size ≥ 4 cm^2 had sensitivity of 67% and specificity of 91%, with a Youden index of 0.58. (Low quality)

3.2.3.26 One observational study with 46 participants suggested that wound size ≥ 5 cm^2 had sensitivity of 50% and specificity of 95%, with a Youden index of 0.45. (Low quality)

Combination of erythrocyte sedimentation rate and wound sizes (see Summary of GRADE profile 9)

3.2.3.27 One observational study with 46 participants suggested that ESR rate ≥ 65 mm/h plus wound size ≥ 2 cm^2 had sensitivity of 83% and specificity of 77%, with a Youden index of 0.60. (Low quality)

3.2.3.28 One observational study with 46 participants suggested that ESR rate ≥ 70 mm/h plus wound size ≥ 2 cm^2 had sensitivity of 79% and specificity of 82%, with a Youden index of 0.61. (Low quality)

Other tests or examinations for diagnosing osteomyelitis (see Summary of GRADE profile 7)

3.2.3.29 There was limited moderate or low-quality evidence (single study with less than 50 participants) that suggested haematocrit >36%; haemoglobin <12 g/dL; platelet count >400x10^9/L; red cell

distribution width >14.5; white cell count >400x10 ^{9}/L; microbiological processing; clinical judgement; ulcer inflammation; and bone exposure had some accuracy in diagnosing osteomyelitis in people with diabetic foot problems.

The clinical utility of assessment, investigative or diagnostic tools for examining peripheral arterial disease (PAD) in people with diabetic foot problems (see Summary of GRADE profile 10)

Clinical examination with ankle–arm index (AAI) ≤ 0.5 as reference standard:

3.2.3.30 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses and history of PAD had sensitivities of 53% (right leg) and 50% (left leg), and specificity of 91% (both legs) in diagnosing PAD in people with diabetic foot problems. (Low quality)

3.2.3.31 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses or history of PAD had sensitivities of 93% (right leg) and 100% (left leg), and specificity of 58% (both legs). (Low quality)

3.2.3.32 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses and claudication <1 block had sensitivities of 33% (right leg) and 36% (left leg), and specificities of 95% (right leg) and 94% (left leg). (Low quality)

3.2.3.33 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses or claudication <1 block had sensitivities of 83% (right leg) and 86% (left leg), and specificity of 71% (both legs). (Low quality)

Hybrid magnetic resonance angiography (MRA) for critical limb ischaemia with digital subtraction angiography (DSA) as reference standard:

3.2.3.34 One observational study with 31 participants suggested that stenoses ≥ 50% had sensitivities of 95% (rater one) and 96% (rater

two), and specificity of 98% (both raters) in diagnosing critical limb ischaemia in people with diabetic foot problems. (Low quality)

3.2.3.35 *One observational study with 31 participants suggested that arterial occlusions had sensitivities of 95% (rater one) and 90% (rater two), and specificities of 98% (rater one) and 99% (rater two). (Low quality)*

Comparison of contrast-enhanced MRA with DSA and change of treatment plans:

3.2.3.36 *One observational study with 24 participants suggested that MRA was significantly better than DSA for investigating dorsal pedal artery, lateral plantar arteries and pedal arch, which led to a change of treatment plans for 7 patients.*

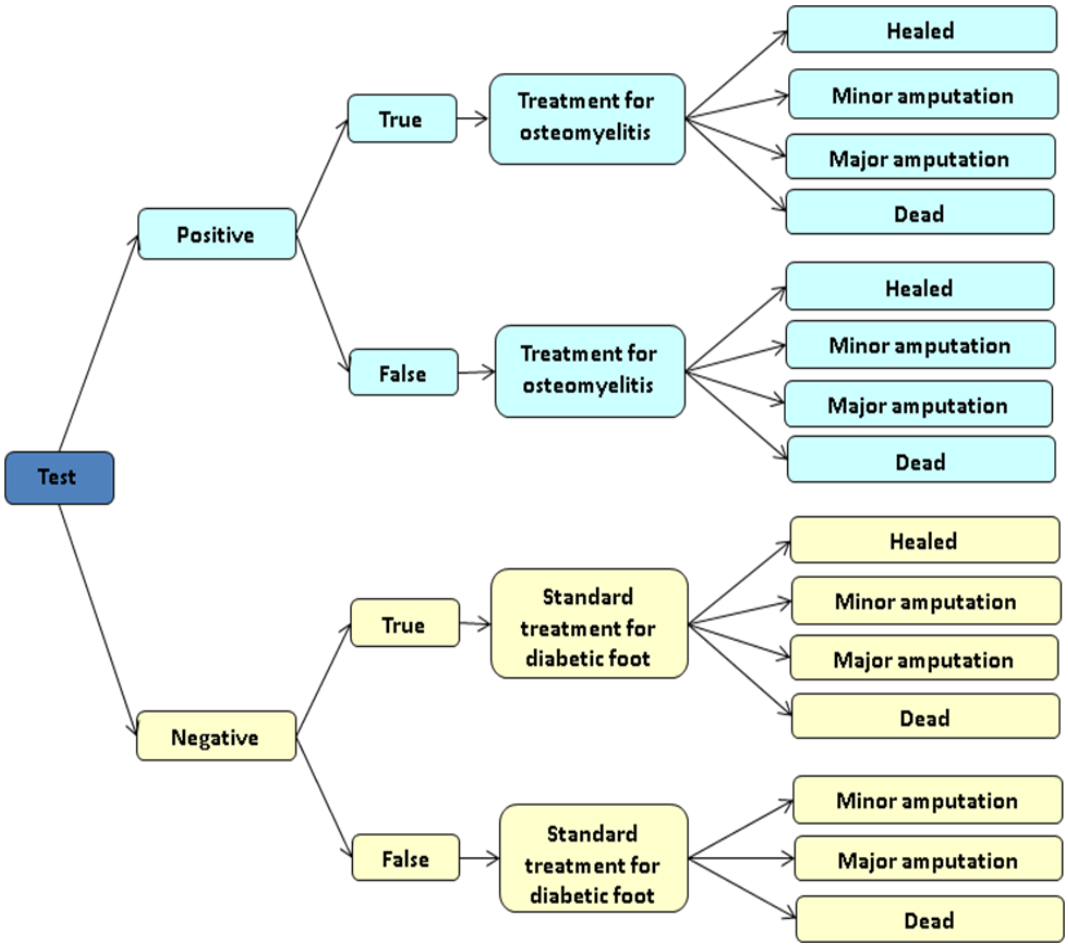
The clinical utility of assessment, investigative or diagnostic tools for examining Charcot arthropathy in people with diabetic foot problems

No studies were identified that met the inclusion/exclusion criteria.

3.2.4 Health economic modelling

A search of the literature did not identify any suitable published cost-effectiveness papers. Therefore, a de novo model was constructed. The model was a decision tree constructed in TreeAGE, with standard outcomes for a diagnostic technology (true positive, false positive, true negative and false negative). The structure is outlined in figure 1HE. The final outcomes of healed, amputation and dead are based on previous assessments of preventative treatments for diabetic foot problems and the outcomes in the clinical review.

Figure 1HE: Osteomyelitis model structure



In current practice, all patients receive an X-ray on admission, and if osteomyelitis is suspected an MRI is performed. Therefore, the true comparison is X-ray compared with X-ray plus MRI. However, the outcome of the X-ray does not lead to decisions on whether to conduct a MRI. To accurately represent the opportunity cost, no resource use was applied to performing an X-ray.

The sensitivity and specificity of MRI and X-ray were derived from the clinical review, and by choosing the mid-points from the ranges quoted. These studies were also the reference for the prevalence of osteomyelitis in this population.

The model assumed that all people who test positive for osteomyelitis get appropriate treatment and those who test negative get standard treatment.

Two simplifying assumptions were incorporated into the model: firstly, that people without osteomyelitis but incorrectly diagnosed (false positives) have the same outcomes as those without osteomyelitis correctly diagnosed (true negatives), and secondly, that people with osteomyelitis not receiving appropriate treatment (false negatives) have worse outcomes than those diagnosed correctly who receive appropriate treatment. For the base case, it was assumed that the outcomes in the false-negative arm were amputation or death. This represents a very extreme situation and was examined in the sensitivity analysis.

No long-term outcomes were considered in this analysis because there was no evidence on the long-term progression of people with osteomyelitis, or on the costs for management and readmissions. This is a potentially severe limitation of the analysis.

Outcomes are required for all these treatment arms. No suitable data were reported in the clinical studies identified by the review. Therefore, two approaches were adopted to inform the outcomes of treatment. Firstly, cost-effectiveness studies (hereafter referred to as the cost-effectiveness analysis) examining prevention of diabetic foot problems, which included the outcomes treatment of different severities for a year. The outcomes from these studies were healed, minor and major amputations, and death.

Secondly, the GDG were asked for any clinical papers that could be used to inform the model structure (hereafter referred to as the clinical study analysis). Three papers were identified to inform the arms of the model. The false-negative arm was assumed to be represented by a study that examined people not responding to treatment. These studies did not distinguish between minor and major amputations and therefore these states were merged into one state.

Utilities data were obtained from cost-effectiveness studies and several sets were used in sensitivity analyses. Costs were obtained from published studies and compared to NHS reference costs for validation. The cost of osteomyelitis treatment was assumed to be mainly made up of the cost of antibiotics. This is

because they are given for a longer duration compared with standard care (6 weeks versus 14 days) and are often given intravenously instead of orally.

The cost-effectiveness results for the two analyses are presented in table 1HE and 2HE.

Table 1HE: Deterministic and probabilistic cost-effectiveness results (per person) for the cost-effectiveness analysis

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
X-ray	0.4274	10083	-	-	-
MRI	0.4420	9923	0.0145	-160	Dominates
Probabilistic					
X-ray	0.4279	9886	-	-	-
MRI	0.4422	9728	0.0143	-158	Dominates

ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

Table 2HE: Deterministic and probabilistic cost-effectiveness results (per person) for the clinical study analysis

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
X-ray	0.4151	7901	-	-	-
MRI	0.4611	6868	0.0460	-1033	Dominates
Probabilistic					
X-ray	0.4135	7896	-	-	-
MRI	0.4590	6842	0.0455	-1027	Dominates

ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

These results indicate that using MRI is a cost-saving intervention. This is attributable to the cost of amputations (in excess of £10,000). If prompt treatment of osteomyelitis is associated with improved outcomes and reduced amputation rates, then resources could be saved and improvements made in QALYs.

The sensitivity analysis that examined the outcomes for a false negative indicated that the amputation rate would need to be 16% to 30% higher compared with the true-positive arm. In other words, inappropriate treatment results in an increase in amputation rates of 16% to 30%. In addition, there appears to be limited benefit in combining an X-ray with an MRI because MRI is more sensitive and more specific than an X-ray.

The probabilistic sensitivity analyses indicated that the conclusions of the base-case analysis are associated with high probability of being cost effective. No other sensitivity analysis materially affected the conclusion that MRI was a cost-saving diagnostic tool.

The results for £20,000 and £30,000 per QALY thresholds are presented in table 3HE for both analyses.

Table 3HE: Probability of magnetic resonance imaging being cost effective

Cost-effectiveness threshold (£ per QALY)	Probability of being cost effective	
	Cost-effectiveness analysis	Clinical study analysis
£20,000	0.91	1
£30,000	0.94	1

QALY = quality-adjusted life year.

These analyses indicate that MRIs are likely to be cost effective if delayed treatment for osteomyelitis is associated with worse outcomes and increased amputation rates. The GDG considered that, while no high-quality evidence was available to demonstrate this, it was a reasonable assumption given current clinical knowledge. Therefore, MRI appears to be a cost-effective use of resources. Please see appendix D for more details.

3.2.5 Evidence to recommendations

The clinical utility of different diabetic ulcer/wound scores

Quality of the evidence

The GDG agreed that there was limited evidence on the clinical utility of different diabetic ulcer/wound scores, and that there was no strong evidence to suggest which scores were better than others. Therefore, the GDG felt that it was not appropriate to recommend a particular score.

Other considerations

Although no particular score was recommended, the GDG felt that key characteristics of the foot (which were in most wound scores) should be documented after the initial assessment to monitor treatment progress. These key characteristics are size and depth of the ulcer; signs of infection (for

example, abscess and/or pus); ischaemia; neuropathy; gangrene; and deformity.

The clinical utility of assessment, investigative or diagnostic tools for diabetic foot infections

Quality of the evidence

The GDG agreed that there was limited evidence of low or very low quality.

Trade-off between clinical benefits and harms

Although there was a lack of evidence, the GDG considered that the accurate diagnosis of diabetic foot infections is important and has clinical benefits in term of choosing the appropriate antibiotic treatment, and that delayed appropriate treatment may incur further harm to patients. Therefore, the GDG came to the consensus that deep tissue biopsy (the gold standard commonly used in clinical practice) should be recommended to confirm suspected diabetic foot infections without osteomyelitis.

Other considerations

Although there was a lack of evidence, the GDG came to the consensus that swab cultures could be an alternative to deep tissue biopsy, if deep tissue samples were not possible to obtain due to the nature and/or severity of the wound.

The diagnostic accuracy of different tests in diagnosing osteomyelitis

Quality of the evidence

Most of the evidence was of low quality and there was only limited evidence on combination testing. Therefore, the GDG agreed that the discussion should focus on single imaging tests that have high volume of evidence, which were MRI (10 studies), 99mTc-MDP scintigraphy (11 studies), In-WBC (8 studies) and plain radiographs (8 studies).

Trade-off between clinical benefits and harms

The GDG further discussed the clinical benefits and harms of accurate diagnosis of osteomyelitis. They agreed that it is important to diagnose osteomyelitis to prevent delayed treatment, which potentially could lead to amputation. The GDG also agreed that MRI should be considered as a

diagnostic tool for suspected osteomyelitis after further discussion of the evidence and clinical utility based on the following:

- The sensitivity and specificity of MRI compared with 99mTc-MDP-labelled scintigraphy, In-WBC and plain radiographs (see Summary of GRADE profile 5)
- The summary of ROC curve and Youden index of MRI compared with 99mTc-MDP-labelled scintigraphy, In-WBC and plain radiographs (see appendix F)
- The Van der Bruel plots of MRI compared with 99mTc-MDP-labelled scintigraphy, In-WBC and plain radiographs (see appendix G).

Although the scans appear to be more accurate in the diagnosis of osteomyelitis, such scans are invasive and have an increased risk of potential adverse events. The GDG therefore considered that the accuracy of In-WBC is adequate for the diagnosis of osteomyelitis in patients in whom MRI is contraindicated.

Trade-off between net health benefits and resource use

As the GDG agreed that MRI should be considered as a diagnostic tool for suspected osteomyelitis, further health economic evaluation was conducted to assess its cost effectiveness. The economic analysis indicated that MRI would be a cost-saving intervention. More accurate diagnosis is associated with fewer amputations, therefore leading to improved health outcomes and cost savings. However, the GDG acknowledged that the model was based on poor data and was very simplistic in structure. They also noted that no long-term outcomes were included in the model, and considered that if such outcomes were included then the results would improve further.

Other considerations

Based on the GDG's knowledge, experience and expertise, a consensus was reached that if MRI is contraindicated, In-WBC may be performed as an alternative to MRI to investigate osteomyelitis.

Although X-ray and probe-to-bone are widely used in current practice, the GDG agreed that they should not be used to exclude osteomyelitis due to a

lack of strong evidence. The GDG also came to the agreement that 99mTc-MDP-labelled scintigraphy, 99mTc-HMPAO-labelled scintigraphy, antigranulocyte Fab' fragment antibody scintigraphy and 99mTc-labelled monoclonal antigranulocyte antibody scintigraphy should not be used to diagnose osteomyelitis, due to a lack of robust evidence.

The clinical utility of assessment, investigative or diagnostic tools for examining peripheral arterial disease in people with diabetic foot problems

Quality of the evidence

The GDG agreed that there was insufficient evidence (only three low-quality studies) to warrant specific recommendation on the diagnosis of PAD in people with diabetic foot problems.

Other considerations

Although there was insufficient evidence to warrant specific recommendations on the diagnosis of PAD, the GDG agreed that early identification of suspected limb ischaemia and referral to a specialist are important to ensure patients receive appropriate care in hospital. Based on the GDG's knowledge, expertise and experience, a consensus was reached to recommend the following:

- Obtain a history of any previous cardiovascular events and symptoms, including previous treatments and/or procedures.
- Inspect the limb for gangrene, tissue loss and absence or presence of a peripheral pulse, as well as the colour and temperature of the limb.
- Document the ankle–brachial pressure of the limb where clinically possible.
- Arrange prompt specialist assessment of patients with risk factors, symptoms and signs of limb ischaemia.

The clinical utility of assessment, investigative or diagnostic tools for examining Charcot arthropathy in people with diabetic foot problems

Quality of the evidence

No studies were identified that met the inclusion/exclusion criteria. In the absence of evidence, the GDG came to the consensus that X-ray may be used to investigate suspected Charcot arthropathy.

Further discussion on initial examination and key principles of care

The GDG came to the consensus that early examination of the patient's feet is important and should include:

- removing the patient's shoes, socks, bandages and dressings
- examining the feet and documenting any evidence of neuropathy, ischaemia, ulceration, inflammation or infection, deformity, or Charcot arthropathy, and also X-raying the affected foot (or feet).

The GDG also came to the consensus that assessing the signs and symptoms of systemic sepsis, deep-seated infection, Charcot arthropathy and acute limb ischaemia is important. The GDG further agreed that specialist initial assessments (cardiovascular risk; vascular and orthotic assessment; need for physiotherapy and pain management; infections; glycaemia control) should be carried out by the multidisciplinary foot care team.

3.2.6 Recommendations and research recommendations for the assessment, investigation and diagnosis of diabetic foot problems

Recommendations for the assessment, investigation and diagnosis of diabetic foot problems

Initial examination and assessment

Recommendation 1.2.11

Remove the patient's shoes, socks, bandages and dressings and examine their feet for evidence of:

- neuropathy
- ischaemia
- ulceration
- inflammation and/or infection
- deformity
- Charcot arthropathy.

Document any identified new and/or existing diabetic foot problems.

Recommendation 1.2.12

Consider a diagnosis of Charcot arthropathy if there is deformity, redness or warmth. Refer to an appropriate specialist to confirm the diagnosis.

Recommendation 1.2.13

Examine the patient for signs and symptoms of systemic sepsis (such as fever, tachycardia, hypotension, reduced consciousness or altered cognitive state).

Recommendation 1.2.14

X-ray the patient's affected foot (or feet) to determine the extent of the foot problem.

Recommendation 1.2.15

If the patient has a diabetic foot ulcer, assess and document:

- deformity
- gangrene

- ischaemia
- neuropathy
- signs of infection
- the size and depth of the ulcer.

Recommendation 1.2.16

Obtain urgent advice from an appropriate specialist if any of the following are present:

- Fever or any other signs or symptoms of systemic sepsis.
- Clinical concern that there is a deep-seated infection (for example palpable gas).
- Limb ischaemia.

Multidisciplinary foot care team

Recommendation 1.2.5

The multidisciplinary foot care team should:

- assess and treat the patient's diabetes, which should include interventions to minimise the patient's risk of cardiovascular events, and any interventions for pre-existing chronic kidney disease or anaemia (please refer to 'Chronic kidney disease' [NICE clinical guideline 73] and 'Anaemia management in people with chronic kidney disease' [NICE clinical guideline 114])
- assess, review and evaluate the patient's response to initial medical, surgical and diabetes management
- assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
- assess the patient's pain and determine the need for treatment and access to specialist pain services
- perform a vascular assessment to determine the need for further interventions
- review the treatment of any infection
- determine the need for interventions to prevent the deterioration and

development of Achilles tendon contractures and other foot deformities

- perform an orthotic assessment and treat to prevent recurrent disease of the foot
- have access to physiotherapy
- arrange discharge planning, which should include making arrangements for the patient to be assessed and their care managed in primary and/or community care, and followed up by specialist teams. Please refer to 'Type 2 diabetes: prevention and management of foot problems' (NICE clinical guideline 10).

Investigation of suspected diabetic foot infection

Recommendation 1.2.18

If a moderate to severe soft tissue infection is suspected and a wound is present, send a soft tissue sample from the base of the debrided wound for microbiological examination. If this cannot be obtained, a superficial swab may provide useful information on the choice of antibiotic therapy.

Recommendation 1.2.19

If osteomyelitis is suspected and initial X-ray does not confirm the presence of osteomyelitis, use magnetic resonance imaging (MRI). If MRI is contraindicated, white blood cell (WBC) scanning may be performed instead.

Recommendation 1.2.20

Do not exclude osteomyelitis on the basis of X-rays alone. X-rays should be used for alternative diagnoses, such as Charcot arthropathy.

Recommendation 1.2.21

Do not exclude osteomyelitis on the basis of probe-to-bone testing

Recommendation 1.2.22

Do not use the following bone scans to diagnose osteomyelitis: 99mTc-MDP-labelled scintigraphy, 99mTc-HMPAO-labelled scintigraphy, antigranulocyte Fab' fragment antibody scintigraphy or 99mTc-labelled monoclonal antigranulocyte antibody scintigraphy.

Assessment of suspected limb ischaemia

Recommendation 1.2.37

If limb ischaemia is suspected, obtain a history of any previous cardiovascular events and symptoms, including previous treatments and/or procedures.

Recommendation 1.2.38

Inspect the limb for the following:

- Colour and temperature.
- Presence of gangrene or tissue loss.
- Presence or absence of a peripheral pulse.

Recommendation 1.2.39

Measure and document the ankle–brachial pressure where clinically possible, ensuring careful interpretation of the results.

Recommendation 1.2.40

Arrange prompt specialist assessment of patients with risk factors, symptoms and signs of limb ischaemia to ensure an accurate diagnosis.

Research recommendations for the assessment, investigation and diagnosis of diabetic foot problems

See appendix A for a list of all research recommendations.

No research recommendations have been made for this section.

3.3 Debridement, wound dressings and off-loading

3.3.1 Review question

What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading in treating diabetic foot problems?

3.3.2 Evidence review

This particular review question was split into three sub-sections: i) surgical or non-surgical debridement; ii) wound dressings; and iii) off-loading. The systematic search retrieved 9817 studies. Of these, 14 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). One Cochrane review was identified for surgical or non-surgical debridement (which included five studies); six studies were identified for wound dressings; and seven studies were identified for off-loading. Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles.
- Full GRADE evidence profiles (see appendix D).
- Forest plots from meta-analysis (where appropriate) (see appendix H).
- Evidence statements.

Table 3: Characteristics of included studies

Author	Total no. of patients	Interventions	Follow-up period	Primary outcomes
Debridement				
Edwards et al. (2009)	46 198 140	Surgical debridement vs. non-surgical management Hydrogel vs. good wound care Hydrogel vs. larvae therapy	6 months 12–20 weeks Not reported	• Complete wound healing • Ulcer recurrence • > 50% wound reduction • Complications • Adverse events
Off-loading				
Van de Weg et al. (2008)	43	TCC + standard care vs. custom-made footwear + standard care Standard care = standard wound care + debridement	16 weeks	• Complete wound healing • Wound surface reduction
Katz et al. (2005)	41	TCC + standard care vs. RCW (iTCC) + standard care. Standard care = standard wound care + debridement	12 weeks	• Complete wound healing • Treatment-related AEs
Ganguly et al. (2008)	55	TCC + standard care vs. simple dressing (mupirocin ointment and sterile gauze) + standard care Standard care = debridement	Until complete epithelialisation and 6 months after healing.	• Complete wound healing
Armstrong et al. (2001)	63	TCC + standard care vs. RCW + standard care vs. half shoes + standard care Standard care = standard wound care + debridement	12 weeks	• Complete wound healing • Mean healing time
Mueller et al. (1989)	40	TCC + standard care vs. traditional dressing treatment (wet-to-dry saline dressing) + standard care Standard care = standard protocol	6 weeks	• Complete wound healing
Nube et al. (2006)	32	Felt deflective padding to the skin + standard care vs. felt deflective padding within the shoe + standard care (control) Standard care = standard wound care + debridement	4 weeks or until healing	• Wound size reduction at week 4
Piagessi et al. (2007)	40	TCC + standard care vs. instant casting (Optima Diab device) + standard care Standard care = standard wound care + debridement	12 weeks and up to complete re-epithelialisation	• Complete wound healing • Mean healing time • Treatment-related AEs

Dressings				
Piagessi et al. (2001)	20	Aquacel (carboxyl methyl-cellulose dressing) + debridement vs. saline-moistened gauze + debridement	8 weeks or until complete re-epithelisation	• Achieved granulation tissue • Mean healing time • Complication (infection)
Veves et al. (2002)	276	Promogan (collagen/oxidised regenerated cellulose dressing) +debridement vs. saline-moistened gauze + debridement	12 weeks	• Complete wound healing • Wound surface reduction • Wound-related AEs
Jude et al. (2007)	134	Hydrofiber (ionic silver dressing) + debridement vs. calcium alginate dressing + debridement	8 weeks	• Complete wound healing • Wound surface reduction • Withdrawal due to AEs • Mean healing time • Wound-related complications • Treatment-related AEs
Foster et al. (1994)	30	Polyurethane foam dressing + debridement and antibiotics vs. alginate dressing + debridement and antibiotics	8 weeks	• Complete wound healing
Shukrimi et al. (2008)	30	Honey dressing + debridement and antibiotics vs. standard dressing (normal saline cleansing and povidone-soaked gauze) + debridement and antibiotics	Wound ready for surgical closure or needed further debridement	• Mean time for wound to be ready for surgical closure
Jeffcoate et al. (2009)	317	Non-adherent gauze + standard care vs. Inadine (iodine impregnated dressing) + standard care vs. Aquacel (carboxyl methyl-cellulose dressing) + standard care Standard care = debridement and off-loading with standard wound care	24 weeks	• Complete wound healing • Mean healing time • Major and minor amputation • Withdrawal due to AEs • Complication (infection)

AEs = adverse events; RCW (iTCC) = removable cast walker (rendered irremovable by single roll of fibreglass casting); TCC = total contact casting.

Clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems

One Cochrane review (which included five studies) on the clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems was identified and included. The evidence was synthesised and presented in the following summary of GRADE profiles (for full GRADE evidence profiles, see appendix D).

Summary of GRADE profile 11: Surgical debridement vs. conventional non-surgical debridement for diabetic foot ulcers

No of studies	Design	Surgical debridement	Conventional non-surgical management	RR/NNTB (95% CI)	Absolute	GRADE quality
Number of ulcers completely healed (6-month follow-up)						
1 [E]	RCT	21/22 (95.5%)	19/24 (79.2%)	RR 1.21 (0.96 to 1.51) NNTB = N/A	166 more per 1000 (from 32 fewer to 404 more)	Low
Ulcer recurrence rates (6-month follow-up)						
1 [E]	RCT	3/22 (13.6%)	8/24 (33.3%)	RR 0.41 (0.12 to 1.35) NNTB = N/A	196 fewer per 1000 (from 293 fewer to 117 more)	Low
Number of adverse events (complications) (6-month follow-up)						
1 [E]	RCT	1/22 (4.5%)	3/24 (12.5%)	RR 0.36 (0.03 to 2.65) NNTB = N/A	80 fewer per 1000 (from 121 fewer to 206 more)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included study = Piaggessi el al. (1998)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 12: Hydrogel vs. gauze or good wound care (control) for diabetic foot ulcers

No of studies	Design	Hydrogel	Gauze or good wound care	RR/NNTB (95% CI)	Absolute	GRADE quality
Number of ulcers completely healed (follow-up ranged from 12–20 weeks)						
3 [E]	RCT	51/99 (51.5%)	28/99 (28.3%)	RR 1.84 (1.3 to 2.61) NNTB = 4 (3 to 10)	238 more per 1000 (from 85 more to 456 more)	Low
Number of adverse events (complications) (follow-up ranged from 12–20 weeks)						
3 [E]	RCT	22/99 (22.2%)	36/99 (36.4%)	RR 0.60 (0.38 to 0.95) NNTB = 7 (4 to 69)	146 fewer per 1000 (from 18 fewer to -226 fewer)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included studies = D'Hemecourt el al. (1998) (20 weeks); Jensen el al. (1998) (16 weeks); Vandeputte et al. (1997) (12 weeks).

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 13: Hydrogel vs. larvae therapy for diabetic foot ulcers

No of studies	Design	Larvae	Hydrogel	RR/NNTB (95% CI)	Absolute	GRADE quality
Wound area reduction > 50% (follow-up not reported)						
1 [E]	RCT	36/70 (51.4%)	19/70 (27.1%)	RR 1.89 (1.21 to 2.96) NNTB = 4 (3 to 12)	241 more per 1000 (from 57 more to 531 more)	Low
Number of ulcers completely healed (follow-up not reported)						
1 [E]	RCT	5/70 (7.1%)	2/70 (2.9%)	RR 2.50 (0.5 to 12.46) NNTB = N/A	44 more per 1000 (from 15 fewer to 332 more)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included study = Markevich el al. (2000)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Clinical effectiveness of off-loading in treating diabetic foot problems

Seven studies on the clinical effectiveness of off-loading in treating diabetic foot problems were identified and included. The evidence was synthesised and presented in the following summary of GRADE profiles (for full GRADE evidence profiles, see appendix D). Most studies included were head-to-head trials (comparing different types of off-loading technologies), with total contact casting (TCC) as a commonly used standard comparator.

Summary of GRADE profile 14: Total contact casting vs. custom-made temporary footwear

No of studies	Design	TCC	CTF	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (16 weeks)						
1 [V]	RCT	6/23 (26.1%)	6/20 (30%)	RR 0.87 (0.33 to 2.27) NNTB = N/A	4 fewer per 100 (from 20 fewer to 38 more)	Moderate
Wound surface reduction (cm^2) (16 weeks)						
1 [V]	RCT	23	20	Mean reduction (cm^2) (SD): TCC = -2.88 (2.5); CTF = -2.16 (3.4) Adjusted mean difference: 0.10 (95% CI: -0.92 to 0.72), p = 0.81		Moderate

[v] = Van de Weg et al. (2008)

CI = confidence interval; CTF = custom-made temporary footwear; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; TCC = total contact casting.

Summary of GRADE profile 15: Total contact casting vs. removable cast walker (rendered unremovable by single roll of fibreglass casting)

No of studies	Design	TCC	RCW (iTCC)	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [K]	RCT	15/20 (75%)	17/21 (81%)	RR 0.93 (0.67 to 1.29) NNTB = N/A	6 fewer per 100 (from 27 fewer to 23 more)	Low
Treatment-related AEs (12 weeks)						
1 [K]	RCT	13/20 (65%)	8/21 (38.1%)	RR 1.71 (0.91 to 3.21) NNTH = N/A	27 more per 100 (from 3 fewer to 84 more)	Low

[K] = Katz et al. (2005)

CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RCW (iTCC) = removable cast walker (rendered unremovable by single roll of fibreglass casting); RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 16: Total contact casting vs. dressing (mupirocin ointment and sterile gauze)

No of studies	Design	TCC	Dressing	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (6 months)						
1 [G]	RCT	36/39 (92.3%)	25/33 (75.8%)	RR 1.22 (0.98 to 1.51) NNTB = N/A	17 more per 100 (from 2 fewer to 39 more)	Low

[G] = Ganguly et al. (2008)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 17: Total contact casting vs. removable cast walker

No of studies	Design	TCC	RCW	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [A]	RCT	17/19 (89.5%)	13/20 (65%)	RR 1.38 (0.96 to 1.97) NNTB = N/A	25 more per 100 (from 3 fewer to 63 more)	Low
Mean healing time (days)						
1 [A]	RCT	19	20	Mean healing time (days) (SD): TCC = 33.5 (5.9); RCW = 50.4 (7.2), p = 0.07		Low

[A] = Armstrong et al. (2001)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RCW = removable cast walker; RR = relative risk; SD = standard deviation; TCC = total contact casting.

Summary of GRADE profile 18: Total contact casting vs. half-shoes

No of studies	Design	TCC	Half-shoes	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [A]	RCT	17/19 (89.5%)	14/24 (58.3%)	RR 1.53 (1.06 to 2.22) NNTB = N/A	31 more per 100 (from 3 more to 71 more)	Low
Mean healing time (days)						
1 [A]	RCT	19	24	Mean healing time (days) (SD): TCC = 33.5 (5.9); Half-shoes = 61.0 (6.5), p = 0.005		Low

[A] = Armstrong et al. (2001)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 19: Removable cast walker vs. half-shoes

No of studies	Design	RCW	Half-shoes	R/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [A]	RCT	13/20 (65%)	14/24 (58.3%)	RR 1.11 (0.70 to 1.78) NNTB = N/A	6 more per 100 (from 17 fewer to 45 more)	Low

[A] = Armstrong et al. (2001)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RCW = removable cast walker; RR = relative risk.

Summary of GRADE profile 20: Total contact casting vs. dressing (wet-to-dry dressing)

No of studies	Design	TCC	Dressing	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (6 weeks)						
1 [M]	RCT	19/21 (90.5%)	6/19 (31.6%)	RR 2.87 (1.46 to 5.63) NNTB = N/A	59 more per 100 (from 15 more to 100 more)	Low

[M] = Mueller et al. (1989)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 21: Total contact casting vs. instant casting (Optima Diab device)

No of studies	Design	TCC	Instant casting	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [P]	RCT	19/20 (95%)	17/20 (85%)	RR 1.12 (0.91 to 1.38) NNTB = N/A	10 more per 100 (from 8 fewer to 32 more)	Low
Mean healing time (weeks)						
1 [P]	RCT	20	20	Mean healing time (weeks) (standard deviation): TCC = 6.5 (4.4); instant casting = 6.7 (3.4), p = 0.874		Low
Treatment-related adverse events (12-week follow-up)						
1 [P]	RCT	4/20 (20%)	5/20 (25%)	RR 0.80 (0.25 to 2.55) NNTH = N/A	5 fewer per 100 (from 19 fewer to 39 more)	Low

[P] = Piaggesi et al. (2007)

CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 22: Felt deflective padding (to the skin) vs. felt deflective padding (within the shoe)

No of studies	Design	To the skin	Within the shoe	Outcomes	Absolute	GRADE quality
Wound surface reduction (%)						
1 [N]	RCT	15	17	Wound surface reduction (%): Skin = 73%; Shoe = 74%, z = 0.02, p = 0.9		Low

[N] = Nube et al. (2006)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Clinical effectiveness of different wound dressings in treating diabetic foot problems

Six studies on the clinical effectiveness of wound dressings in treating diabetic foot problems were identified and included. The evidence was synthesised and presented in the following summary of GRADE profiles (for full GRADE evidence profiles, see appendix D). Most studies included were head-to-head trials comparing different types of dressings.

Summary of GRADE profile 23: Aquacel vs. saline-moistened gauze

No of studies	Design	Aquacel	SMG	RR/NNTB (95% CI)	Absolute	GRADE quality
Achieved granulation tissue (8 weeks)						
1 [P]	RCT	4/10 (40%)	1/10 (10%)	RR 4.00 (0.54 to 29.81) NNTB = N/A	30 more per 100 (from 5 fewer to 100 more)	Low
Mean healing time (days)						
1 [P]	RCT	10	10	Mean healing time (days) (standard deviation): Aquacel = 127 (46); SMG = 234 (61), p < 0.001		Low
Complication (infection) (8 weeks)						
1 [P]	RCT	1/10 (10%)	3/10 (30%)	RR 0.33 (0.04 to 2.69) NNTH = N/A	20 fewer per 100 (from 29 fewer to 51 more)	Low

[P] = Piagessi et al. (2001)

Aquacel = sodium carboxyl-methyl-cellulose dressing; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; SMG = saline-moistened gauze.

Summary of GRADE profile 24: Promogran vs. saline-moistened gauze

No of studies	Design	Promogran	SMG	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [V]	RCT	51/104 (49.5%)	39/84 (46.4%)	RR 1.06 (0.78 to 1.43) NNTB = N/A	3 more per 100 (from 10 fewer to 20 more)	Low
Wound surface reduction (%) (12 weeks)						
1 [V]	RCT	104	84	Mean wound surface reduction (%): Promogran = 64.5%; SMG = 63.8%, p > 0.05		Low
Wound-related serious adverse events (12 weeks)						
1 [V]	RCT	25/104 (24%)	35/84 (41.7%)	RR 0.58 (0.38 to 0.88) NNTH = N/A	18 fewer per 100 (from 5 fewer to 26 fewer)	Low

[V] = Veves et al. (2002)

CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; Promogran = collagen/oxidised regenerated cellulose dressing; RCT = randomised controlled trial; RR = relative risk; SMG = saline-moistened gauze.

Summary of GRADE profile 25: Hydrofiber dressing vs. calcium alginate

No of studies	Design	AQAg	CA	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (8 weeks)						
1 [J]	RCT	21/67 (31.3%)	15/67 (22.4%)	RR 1.40 (0.79 to 2.47) NNTB = N/A	9 more per 100 (from 5 fewer to 33 more)	Low
Wound surface reduction (%) (8 weeks)						
1 [J]	RCT	67	67	Mean wound surface reduction (%) (SD): AQAg = 58.1 (53.1); CA = 60.5 (42.7), p = 0.948		Low
Mean healing time (days)						
1 [J]	RCT	67	67	Mean healing time (days) (SD): AQAg = 52.6 (1.8); CA = 57.7 (1.7), p = 0.340		Low
Withdrawal due to adverse events (unspecified) (8 weeks)						
1 [J]	RCT	8/67 (11.9%)	13/67 (19.4%)	RR 0.61 (0.27 to 1.39) NNTH = N/A	8 fewer per 100 (from 14 fewer to 8 more)	Low
Wound-related complications (8 weeks)						
1 [J]	RCT	23/67 (34.3%)	26/67 (38.8%)	RR 0.88 (0.57 to 1.38) NNTH = N/A	5 fewer per 100 (from 17 fewer to 15 more)	Low
Treatment-related adverse events (8 weeks)						
1 [J]	RCT	11/67 (16.4%)	9/67 (13.4%)	RR 1.22 (0.54 to 2.76) NNTH = N/A	3 more per 100 (from 6 fewer to 24 more)	Low

[J] = Jude et al. (2007)

AQAg = Hydrofiber dressing; CA = calcium alginate; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 26: Polyurethane foam vs. alginate

No of studies	Design	Polyurethane	Alginate	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (8 weeks)						
1 [F]	RCT	9/15 (60%)	8/15 (53.3%)	RR 1.13 (0.60 to 2.11) NNTB = N/A	7 more per 100 (from 21 fewer to 59 more)	Low

[F] = Foster et al. (1994)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 27: Honey dressing vs. povidone-soaked gauze

No of studies	Design	Honey	Povidone	RR/NNTB (95% CI)	Absolute	GRADE quality
Mean time for wound to be ready for surgical closure (days)						
1 [S]	RCT	15	15	Mean time for wound to be ready for surgical closure (days) (range): Honey = 14.4 (7–26); povidone = 15.4 (9–36), p > 0.05.		Low

[S] = Shukrime et al. (2008)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 28: Aquacel vs. non-adherent gauze (1)

No of studies	Design	Aquacel	N-A	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (24 weeks)						
1 [J]	RCT	46/103 (44.7%)	41/106 (38.7%)	RR 1.15 (0.84 to 1.59) NNTB = N/A	6 more per 100 (from 6 fewer to 23 more)	Moderate
Mean healing time (days)						
1 [J]	RCT	103	106	Mean healing time (days) (SD): Aquacel = 130.7 (52.4); N-A = 125.8 (55.9), p > 0.05		Moderate
Major and minor amputation						
1 [J]	RCT	4/103 (3.9%)	2/106 (1.9%)	RR 2.06 (0.39 to 10.99) NNTB = N/A	2 more per 100 (from 1 fewer to 19 more)	Moderate
Withdrawal due to adverse events (24 weeks)						
1 [J]	RCT	11/103 (10.7%)	15/106 (14.2%)	RR 0.75 (0.36 to 1.56) NNTH = N/A	4 fewer per 100 (from 9 fewer to 8 more)	Moderate
Complication (infection)						
1 [J]	RCT	9/103 (8.7%)	7/106 (6.6%)	RR 1.32 (0.51 to 3.42) NNTH = N/A	2 more per 100 (from 3 fewer to 16 more)	Moderate

[J] = Jeffcoate et al. (2009)

Aquacel = sodium carboxyl-methyl-cellulose dressing; CI = confidence interval; N-A = non-adherent, knitted, viscose filament gauze; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 29: Aquacel vs. Inadine (2)

No of studies	Design	Aquacel	Inadine	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (24 weeks)						
1 [J]	RCT	46/103 (44.7%)	48/108 (44.4%)	RR 1.00 (0.74 to 1.36) NNTB = N/A	0 fewer per 100 (from 12 fewer to 16 more)	Moderate
Mean healing time (days)						
1 [J]	RCT	103	108	Mean healing time (days) (standard deviation): Aquacel = 130.7 (52.4); Inadine = 127.8 (54.2), p > 0.05		Moderate
Major and minor amputation						
1 [J]	RCT	4/103 (3.9%)	1/108 (0.9%)	RR 4.19 (0.48 to 36.91) NNTB = N/A	3 more per 100 (from 0 fewer to 32 more)	Moderate
Withdrawal due to adverse events (24 weeks)						
1 [J]	RCT	11/103 (10.7%)	9/108 (8.3%)	RR 1.28 (0.55 to 2.96) NNTH = N/A	2 more per 100 (from 4 fewer to 16 more)	Moderate
Complication (infection)						
1 [J]	RCT	9/103 (8.7%)	12/108 (11.1%)	RR 0.79 (0.36 to 1.79) NNTH = N/A	2 fewer per 100 (from 7 fewer to 9 more)	Moderate

[J] = Jeffcoate et al. (2009)

Aquacel = sodium carboxyl-methyl-cellulose dressing; CI = confidence interval; inadine = iodine impregnated dressing; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 30: Non-adherent gauze vs. Inadine (3)

No of studies	Design	N-A	Inadine	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (24 weeks)						
1 [J]	RCT	41/106 (38.7%)	48/108 (44.4%)	RR 0.87 (0.63 to 1.20) NNTB = N/A	6 fewer per 100 (from 16 fewer to 9 more)	Moderate
Mean healing time (days)						
1 [J]	RCT	106	108	Mean healing time (days) (standard deviation): N-A = 125.8 (55.9); inadine = 127.8 (54.2), p > 0.05		Moderate
Major and minor amputation						
1 [J]	RCT	2/106 (1.9%)	1/108 (0.9%)	RR 2.04 (0.19 to 22.14) NNTB = N/A	1 more per 100 (from 1 fewer to 19 more)	Moderate
Withdrawal due to adverse events (24 weeks)						
1 [J]	RCT	15/106 (14.2%)	9/108 (8.3%)	RR 1.70 (0.78 to 3.71) NNTH = N/A	6 more per 100 (from 2 fewer to 22 more)	Moderate
Complication (infection)						
1 [J]	RCT	7/106 (6.6%)	12/108 (11.1%)	RR 0.59 (0.24 to 1.45) NNTH = N/A	5 fewer per 100 (from 8 fewer to 5 more)	Moderate

[J] = Jeffcoate et al. (2009)

CI = confidence interval; inadine = iodine impregnated dressing; N-A = non-adherent, knitted, viscose filament gauze; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

3.3.3 Evidence statements

Clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems

Surgical debridement vs. conventional non-surgical management (see Summary of GRADE profile 11)

3.3.3.1 One RCT with 46 participants showed that when surgical debridement was compared with conventional non-surgical management, there was no significant difference in the number of ulcers completely healed; ulcer recurrence rates; or the number of adverse events. (Low quality)

Hydrogel vs. gauze or good wound care (see Summary of GRADE profile 12)

3.3.3.2 Three RCTs with a total number of 198 participants showed that participants who received hydrogel were significantly more likely to have their ulcers completely healed, and significantly less likely to have adverse events compared with participants who received gauze or good wound care. (Low quality)

Hydrogel vs larvae therapy (see Summary of GRADE profile 13)

3.3.3.3 One RCT with 140 participants showed that participants who received larvae therapy were significantly more likely to have more than 50% wound reduction compared with participants who received hydrogel. However, in the 2 groups there was no significant difference in the number of ulcers completely healed. (Low quality)

Clinical effectiveness of off-loading in treating diabetic foot problems

Total contact casting vs. custom-made temporary footwear (see Summary of GRADE profile 14)

3.3.3.4 One RCT with 43 participants showed that there was no significant difference in complete wound healing or mean wound surface reduction between participants who received total contact casting (TCC) and custom-made temporary footwear. (Moderate quality)

Total contact casting vs. mupirocin ointment and sterile gauze (see Summary of GRADE profile 16)

3.3.3.5 One RCT with 72 participants showed that there was no significant difference in complete wound healing between participants who received TCC and simple dressing (mupirocin ointment and sterile gauze). (Low-quality)

Total contact casting vs. removable cast walker (rendered irremovable) (see Summary of GRADE profile 15)

3.3.3.6 One RCT with 41 participants showed no significant differences in complete wound healing and treatment-related adverse events between participants who received TCC or a removable cast walker (rendered irremovable by a single roll of fibreglass casting). (Low-quality)

Total contact casting vs. removable cast walker vs half-shoes (see Summary of GRADE profile 17, 18 and 19)

3.3.3.7 *One RCT with 63 participants showed that there was no significant difference in complete wound healing among participants who received TCC, removable cast walkers or half-shoes. (Low quality)*

3.3.3.8 *One RCT with 43 participants showed that the mean wound healing time of participants who received TCC was significantly shorter compared with participants who received half-shoes. (Low quality)*

Total contact casting vs. wet-to-dry dressing (see Summary of GRADE profile 20)

3.3.3.9 *One RCT with 40 participants showed that participants who received TCC were significantly more likely to have complete wound healing compared with participants who received traditional dressings (wet-to-dry dressings). (Low quality)*

Total contact casting vs. instant casting (Optima Diab device) (see Summary of GRADE profile 21)

3.3.3.10 *One RCT with 40 participants showed no significant differences in complete wound healing, mean wound healing time and treatment-related adverse events between participants who received TCC and instant casting (Optima Diab device). (Low quality)*

Felt deflective padding (to the skin) vs. felt deflective padding (within the shoe) (see Summary of GRADE profile 22)

3.3.3.11 *One RCT with 32 participants showed no significant difference in mean wound surface reduction between participants who received felt deflective padding (to the skin) and felt deflective padding (within the shoe). (Low quality)*

Clinical effectiveness of different wound dressings in treating diabetic foot problems

Aquacel vs. saline-moistened gauze (see Summary of GRADE profile 23)

3.3.3.12 One RCT with 20 participants showed no significant differences in the number of participants who achieved granulation tissue and number of complications (infections) between participants who received Aquacel and saline-moistened gauze. (Low quality)

3.3.3.13 The RCT with 20 participants showed that the mean wound healing time of participants who received Aquacel was significantly shorter compared with participants who received saline-moistened gauze. (Low quality)

Promogran vs. saline-moistened gauze (see Summary of GRADE profile 24)

3.3.3.14 One RCT with 188 participants showed no significant differences in complete wound healing and mean wound surface reduction between participants who received Promogran and saline-moistened gauze. (Low quality)

3.3.3.15 The RCT with 188 participants showed that participants who received Promogran had significantly fewer wound-related adverse events compared with participants who received saline-moistened gauze. (Low quality)

Hydrofiber dressing vs. calcium alginate dressing (see Summary of GRADE profile 25)

3.3.3.16 One RCT with 134 participants showed no significant differences in the following outcomes between participants who received Hydrofiber dressing and calcium alginate dressing. (Low quality):

- *Complete wound healing.*
- *Mean wound surface reduction.*

- *Mean healing time.*
- *Withdrawal due to adverse events.*
- *Wound-related complications.*
- *Treatment-related adverse events.*

Polyurethane foam dressing vs. alginate dressing (see Summary of GRADE profile 26)

3.3.3.17 One RCT with 30 participants showed no significant difference in complete wound healing between participants who received polyurethane foam dressing and alginate dressing. (Low quality)

Honey dressing vs. povidone-soaked gauze (see Summary of GRADE profile 27)

3.3.3.18 The same RCT with 30 participants showed no significant difference in the mean time for wounds to be ready for surgical closure between participants who received honey dressing and povidone-soaked gauze. (Low quality)

Aquacel vs. Inadine vs. non-adherent, knitted, viscose filament gauze (see Summary of GRADE profile 28, 29 and 30)

3.3.3.19 One RCT with 317 participants showed no significant differences in the following outcomes among participants who received Aquacel or Inadine dressing or non-adherent knitted viscose filament gauze. (Moderate quality):

- *Complete wound healing.*
- *Mean healing time.*
- *Major and minor amputation.*
- *Withdrawal due to adverse events.*
- *Complications (infection).*

3.3.4 Health economic modelling

No health economic modelling was conducted for this question.

3.3.5 Evidence to recommendations

Clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems

Quality of the evidence

The GDG agreed that because the evidence was limited and of low quality, it was not appropriate to recommend specific techniques for debridement.

Other considerations

Although there was insufficient evidence to recommend specific techniques, the GDG agreed that debridement is important to promote wound healing, particularly for wounds with extensive necrotic tissue. The GDG discussed factors that should be considered before carrying out debridement. Based on the GDG's experience, knowledge and expertise, consensus was reached that debridement should only be carried out by members of the multidisciplinary foot care team with specialist skills, and that the technique chosen should best match their specialist expertise, clinical experience, patient preference and the site of the ulcer.

Clinical effectiveness of off-loading in treating diabetic foot problems

Quality of the evidence

The GDG agreed that because the evidence was inconclusive (most head-to-head comparisons showed no significant difference between the two comparators) and was of low quality, it was not appropriate to recommend specific techniques for off-loading.

Other considerations

Although there was insufficient evidence to recommend specific techniques, the GDG agreed that off-loading is important to promote wound healing by relieving pressure on the wound. The GDG reached consensus that off-loading should be a standard part of wound management.

The GDG further discussed the NICE guideline on pressure ulcers (NICE clinical guideline 29), and agreed that patients should have access to appropriate pressure-relieving support surfaces and strategies in line with CG29 to minimise the risk of pressure ulcer development on the affected and unaffected limb during their hospital stay.

Clinical effectiveness of wound dressings in treating diabetic foot problems

Quality of the evidence

The GDG agreed that because the evidence was inconclusive (most head-to-head comparisons showed no significant difference between the two comparators) and was of moderate/low quality, it was not appropriate to recommend specific wound dressings.

Other considerations

The GDG agreed that the use of dressings should be a standard part of wound management to prevent infections of the wound. In the absence of strong evidence on particular wound dressings, the GDG came to the consensus that the multidisciplinary foot care team should use the wound dressings with the lowest acquisition cost, taking into account their clinical assessment of the wound, the experience and preferences of the patient, and the clinical circumstances.

3.3.6 Recommendations and research recommendations for debridement, wound dressings and off-loading

Recommendations for debridement, wound dressings and off-loading

Management of diabetic foot ulcers

Debridement, dressings and off-loading

Recommendation 1.2.31

Debridement should only be done by healthcare professionals from the multidisciplinary foot care team, using the technique that best matches their specialist expertise, clinical experience, patient preference, and the site of the ulcer.

Recommendation 1.2.32

When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

Recommendation 1.2.33

Offer off-loading for patients with diabetic foot ulcers. Healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use the technique with the lowest acquisition cost.

Recommendation 1.2.34

Use pressure-relieving support surfaces and strategies in line with ‘Pressure ulcers’ (NICE clinical guideline 29) to minimise the risk of pressure ulcers developing.

Research recommendations for debridement, wound dressings and off-loading

See appendix A for a list of all research recommendations.

What is the optimum wound-healing environment and what is the optimum dressing to treat diabetic foot ulcers Further research should be undertaken to determine whether total contact foot casting is clinically effective and cost effective compared with other forms of off-loading in patients with neuropathic ulcers

3.4 Antibiotics for diabetic foot infections

3.4.1 Review question

What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)?

3.4.2 Evidence review

The systematic search retrieved 9817 studies. Of these, 13 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). All 13 studies were head-to-head trials of different antibiotics, and there were no 2 studies with the same pair-wise comparisons. Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles.
- Full GRADE evidence profiles (see appendix D).
- Evidence statements.

Table 4: Characteristics of included studies

ANTIBIOTICS		
Study	Clinical variables	Outcome of interest
Lipsky et al. (1997)	IV ofloxacin changed when appropriate to 400 mg orally every 12 h. IV ampicillin/sulbactam every 6 h changed when appropriate to 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 h.	Cured or improved condition of ulcers Eradication of original pathogens or not Adverse events
Grayson et al. (1994)	Imipenem/cilastatin (I/C; 500 mg IV every 6 h). Ampicillin/sulbactam (A/S; 3 g IV every 6 h).	Cured or improved condition of ulcers Eradication of original pathogens or not Recurrence of infection after average 1-year follow-up Adverse events
Erstad et al. (1997)	Cefoxitin 2 g every 6 h. Ampicillin/sulbactam 3 g every 6 h.	Cured or improved condition of ulcers Eradication of original pathogens or not Duration of hospitalisation Adverse events
Harkless et al. (2005)	IV piperacillin/tazobactam (P/T) (4 g/0.5 g every 8 h). IV ampicillin/sulbactam (A/S 2 g/1 g every 6 h).	Cured or improved condition of ulcers Adverse events
Tan et al. (1993)	Piperacillin-tazobactam (P/T), 3 g and 375 mg respectively for 5 days and at least 48 h after resolution of signs and symptoms. Ticarcillin-clavulanate (T/C), 3 g and 100 mg respectively for 5 days and at least 48 h after resolution of signs and symptoms.	Cured or improved condition of ulcers Adverse events
Bouter et al. (1996)	Piperacillin 3000 mg QID in combination with clindamycin 600 mg (P/CL) 2 times daily Imipenem/cilastatin (I/C) 500 mg 4 times daily	Cured or improved condition of ulcers Eradication of original pathogens or not Adverse events
Lipsky et al. (2007)	IV therapy for at least 3 days with moxifloxacin (400 mg/day). Then switched to oral therapy with moxifloxacin 400 mg/day Piperacillin-tazobactam (P/T) (3.0 g/0.375 g every 6 h) for at least 3 days then switched to amoxicillin-clavulanate (A/C) suspension 800 mg every 12 h	Clinical cure rates at the TOC (test-of cure) visit (10–42 days post-therapy) Eradication of original pathogens or not Adverse events
Lipsky et al. (2008)	Pexiganan cream twice daily Or placebo cream twice daily Ofloxacin tablets 200 mg orally twice daily or placebo tablets orally twice daily	Cured or improved condition of ulcers Eradication of original pathogens or not Wound assessments

		Adverse events
Lipsky et al. (2004)	Linezolid (600 mg every l2 h either IV or orally) Ampicillin-sulbaclam (A/S, 1.5-3 g every 6 h IV), or amoxicillin-clavulanate (A/C, 500-875 mg every 8–12 h orally).	Cured or improved condition of ulcers Adverse events
Lipsky et al. (2005)	Daptomycin (4 mg/kg every 24 h IV over 30 min) Vancomycin 1 g every 12 h IV over 60 min or a semi-synthetic penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin, per the investigator's choice) given in equally divided doses totalling 4–12 g/day IV].	Clinical success rates Adverse events
Lipsky et al. (2005)	IV ertapenem (1 g bolus, followed by a saline placebo every 6 h for 3 additional doses). IV piperacillin/tazobactam (P/T 3-375 g every 6 h).	Favourable clinical response Eradication of original pathogens or not Adverse events
Hughes et al. (1987)	Ceftizoxime, up to 4 g IV every 8 h. Cefoxitin, up to 2 g IV every 4 h.	Clinical responses at 3, 6, 9, and 12 months Adverse events
HTA report Lipsky et al. (1990)	Clindamycin 300 mg orally, 4 times daily for 2 weeks. Cephalexin 500 mg orally, 4 times daily for 2 weeks	Complete healing at 2 weeks Improved lesions Adverse effects

IV = intravenously.

Summary of GRADE profile 31: Quinolones vs. broad-spectrum penicillins

Ofloxacin (IV to oral) vs. ampicillin/sulbactam (IV) amoxicillin/clavulanic acid (oral) (Lipsky et al. 1997)

No of studies	Design	Ofloxacin (IV to oral)	Ampicillin/ sulbactam (IV) to amoxicillin/ clavulanic acid (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 7 days)						
1	RCT	40/47 (85.1%)	34/41 (82.9%)	RR 1.03 (0.85 to 1.23) NNTB = N/A	2 more per 100 (from 12 fewer to 19 more)	Low
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 7 days)						
1	RCT	39/47 (83%)	36/41 (87.8%)	RR 0.95 (0.79 to 1.12) NNTB = N/A	4 fewer per 100 (from 18 fewer to 11 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 7 days)						
1	RCT	33/47 (70.2%)	38/43 (88.4%)	RR 0.79 (0.64 to 0.99) NNTB = 6 (3 to 79)	19 fewer per 100 (from 1 fewer to 32 fewer)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 7 days)						
1	RCT	18/19 (94.7%)	15/18 (83.3%)	RR 1.14 (0.90 to 1.43) NNTB = N/A	12 more per 100 (from 8 fewer to 36 more)	Low
No. of patients experienced treatment-related AEs (follow-up 7 days)						
1	RCT	17/47 (36.2%)	9/41 (22%)	RR 1.65 (0.83 to 3.29) NNTH = N/A	14 more per 100 (from 4 fewer to 50 more)	Low

Dosage: Ofloxacin 400 mg (IV and oral) every 12 hours. AmpiciIlin (1 to 2 g)/sulbactam (0.5 to 1 g) (IV) every 6 hours; then 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 hours.

[a] Cured = disappearance of all signs and symptoms associated with active infection.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 32: Broad-spectrum beta-lactam carbapenems vs. broad-spectrum penicillins

Imipenem/cilastatin (IV) vs. ampicillin/sulbactam (IV) (Grayson et al. 1994)

No of studies	Design	Imipenem /cilastatin (IV)	Ampicillin /sulbactam (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (unit: no. of infections) (follow-up 6 days[1])						
1	RCT	39/48 (81.3%)	41/48 (85.4%)	RR 0.95 (0.80 to 1.14) NNTB = N/A	4 fewer per 100 (from 17 fewer to 12 more)	Low
Microbiological outcome: infections achieved eradiction of pathogen(s) (follow-up 6 days[1])						
1	RCT	32/48 (66.7%)	36/48 (75%)	RR 0.89 (0.69 to 1.15) NNTB = N/A	8 fewer per 100 (from 23 fewer to 11 more)	Low
No. of patients experienced significant[b] AEs (follow-up 6 days[1])						
1	RCT	7/46 (15.2%)	9/47 (19.1%)	RR 0.79 (0.32 to 1.96) NNTH = N/A	4 fewer per 100 (from 13 fewer to 18 more)	Low

Dosage: Imipenem/cilastatin (500 mg) every 6 hours. Ampicillin/sulbactam (3 g) every 6 hours.

[a] Cured = resolution of soft tissue infection.

[b] Significant = a severe reaction necessitating withdrawal of the study treatment.

[1] 6 days or until therapy was completed.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 33: Cephalosporins vs broad-spectrum penicillins

Cefoxitin (IV) vs ampicillin/sulbactam (IV) (Erstad et al. 1997)

No of studies	Design	Cefoxitin (IV)	Ampicillin/ sulbactam (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 5 days[1])						
1	RCT	7/18 (38.9%)	1/18 (5.6%)	RR 7.00 (0.95 to 51.25) NNTB = N/A	33 more per 100 (from 0 fewer to 279 more)	Low
Clinical outcome: length of hospital stay (days)						
1	RCT	18	18	Mean length of hospital stay (days) (range): Cefoxitin = 12.1 (4 to 39) Ampicillin/sulbactam = 21.1 (6 to 58), p = 0.06		Low
No. of patients experienced treatment- related AEs (follow-up 5 days[1])						
1	RCT	6/18 (33.3%)	7/18 (38.9%)	RR 0.86 (0.36 to 2.05) NNTH = N/A	5 fewer per 100 (from 25 fewer to 41 more)	Low

Dosage: Cefoxitin 2 g every 6 hours; Ampicillin/sulbactam 3 g every 6 hours, for at least 5 days.

[a] Cured = disappearance of all signs and symptoms associated with active infection.

[1] 5 days but could be more to the discretion of the attending surgeon.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 34: Antipseudomonal penicillins vs. broad-spectrum penicillins

Piperacillin/tazobactam (IV) vs. ampicillin/sulbactam (IV) (Harkless et al. 2005)

No of studies	Design	Piperacillin/ tazobactam (IV)	Ampicillin/ sulbactam (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up 14–21 days)						
1	RCT	99/139 (71.2%)	100/150 (66.7%)	RR 1.07 (0.92 to 1.25) NNTB = N/A	5 more per 100 (from 5 fewer to 17 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 14–21 days)						
1	RCT	51/65 (78.5%)	46/64 (71.9%)	RR 1.09 (0.89 to 1.33) NNTB = N/A	6 more per 100 (from 8 fewer to 24 more)	Low
No. of patients experienced at least 1 treatment-related AE (follow-up 14–21 days)						
1	RCT	29/155 (18.7%)	21/159 (13.2%)	RR 1.42 (0.85 to 2.37) NNTH = N/A	6 more per 100 (from 2 fewer to 18 more)	Low
Withdrawals due to treatment-related AEs (follow-up 14–21 days)						
1	RCT	18/155 (11.6%)	13/159 (8.2%)	RR 1.42 (0.72 to 2.80) NNTH = N/A	3 more per 100 (from 2 fewer to 15 more)	Low

Dosage: Piperacillin/tazobactam (4 g/0.5 g every 8 h); Ampicillin/sulbactam (2 g/1 g every 6 h), for 4 to 14 days.

[a] Cured or improvement = resolution of signs and symptoms or sufficient clinical improvement that the majority of symptoms of infection had abated.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 35: Antipseudomonal penicillins vs. Antipseudomonal penicillins

Piperacillin/tazobactam (IV) vs. ticarcillin/clavulanate (IV) (Tan et al. 1993)

No of studies	Design	Piperacillin/ tazobactam (IV)	Ticarcillin/ calvulanate (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 10–14 days)						
1	RCT	7/18 (38.9%)	6/17 (35.3%)	RR 1.10 (0.46 to 2.62) NNTB = N/A	4 more per 100 (from 19 fewer to 57 more)	Low

Dosage: Piperacillin/tazobactam (3 g/375 mg) every 6 hours; Ticarcillin/clavulanate (3 g/100 mg) every 6 hours, for at least 5 days.

[a] Cured = resolution of signs and symptoms.

CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 36: Beta-lactam carbapenems vs. antipseudomonal penicillins + clindamycin

Imipenem/cilastatin (IV) vs. piperacillin/clindamycin (IV) (Bouter et al. 1996)

No of studies	Design	Imipenem/ cilastatin (IV)	Piperacillin/ clindamycin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 10 days)						
1	RCT	4/21 (19%)	6/24 (25%)	RR 0.76 (0.25 to 2.34) NNTB = N/A	6 fewer per 100 (from 19 fewer to 33 more)	Low
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 10 days)						
1	RCT	9/20 (45%)	16/23 (69.6%)	RR 0.65 (0.37 to 1.13) NNTB = N/A	24 fewer per 100 (from 44 fewer to 9 more)	Low
No. of patients experienced treatment-related AEs (follow-up 10 days)						
1	RCT	18/21 (85.7%)	12/24 (50%)	RR 1.71 (1.11 to 2.65) NNTH = 3 (2 to 12)	36 more per 100 (from 6 more to 83 more)	Low

Dosage: Piperacillin (3000 mg QID) + clindamycin (600 mg TID); Imipenem/cilastatin (500 mg QID), for at least 10 days.

[a] Cured = resolution of signs and symptoms.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 37: Quinolones vs. antipseudomonal penicillins + broad-spectrum penicillins

Moxifloxacin (IV to oral) vs. piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral) (Lipsky et al. 2007)

No of studies	Design	Moxifloxacin (IV to oral)	Piperacillin/ tazobactam (IV) to moxifloxin vs amoxillin/ clavulanate (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 10–42 days)						
1	RCT	28/63 (44.4%)	25/64 (39.1%)	RR 1.14 (0.75 to 1.72) NNTB = N/A	5 more per 100 (from 10 fewer to 28 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 10–42 days)						
1	RCT	24/37 (64.9%)	27/42 (64.3%)	RR 1.01 (0.73 to 1.40) NNTB = N/A	1 more per 100 (from 17 fewer to 26 more)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 10–42 days)						
1	RCT	2/6 (33.3%)	7/12 (58.3%)	RR 0.57 (0.17 to 1.95) NNTB = N/A	25 fewer per 100 (from 48 fewer to 55 more)	Low
No. of patients experienced treatment-related AEs (follow-up 10–42 days)						
1	RCT	20/63 (31.7%)	8/64 (12.5%)	RR 2.54 (1.21 to 5.34) NNTH = 5 (3 to 20)	19 more per 100 (from 3 more to 54 more)	Low
Withdrawals due to treatment-related AEs (follow-up 10–42 days)						
1	RCT	15/63 (23.8%)	15/64 (23.4%)	RR 1.02 (0.54 to 1.90) NNTH = N/A	0 more per 100 (from 11 fewer to 21 more)	Low

Dosage: Moxifloxacin (400 mg/day) (IV for at least 3 days), then 400 mg orally; Piperacillin/tazobactam (3.0 g/0.375 g every 6 hours) for at least 3 days, then amoxicillin/clavulanate (800 mg every 12 hours orally), for total duration of 7 to 14 days.

[a] Cured = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 38: Pexiganan cream (topical) vs. ofloxacin (oral) (quinolones) (Lipsky et al. 2008)

No of studies	Design	Pexiganan cream	Ofloxacin (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up 21 days)						
1	RCT	363/418 (86.8%)	377/417 (90.4%)	RR 0.96 (0.91 to 1.01) NNTB = N/A	4 fewer per 100 (from 8 fewer to 1 more)	High
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 21 days)						
1	RCT	154/327 (47.1%)	160/338 (47.3%)	RR 0.99 (0.85 to 1.17) NNTB = N/A	0 fewer per 100 (from 7 fewer to 8 more)	High
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 21 days)						
1	RCT	203/370 (54.9%)	233/379 (61.5%)	RR 0.89 (0.79 to 1.01) NNTB = N/A	7 fewer per 100 (from 13 fewer to 1 more)	High
Pathogen outcome: eradication of Gram- aerobes (unit: patient) (follow-up 21 days)						
1	RCT	75/111 (67.6%)	72/103 (69.9%)	RR 0.97 (0.81 to 1.16) NNTB = N/A	2 fewer per 100 (from 13 fewer to 11 more)	High

Dosage: Pexiganan cream (twice daily); ofloxacin tablets (200 mg orally twice daily), for at least 14 days.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 39: Oxazolidinone vs. broad-spectrum penicillins

Linezolid (IV or oral) vs. ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral) (Lipsky et al. 2004)

No of studies	Design	Linezolid (IV)	Ampicillin/ sulbactam (IV) or amoxicillin /clavulanate (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 15–21 days)						
1	RCT	165/203 (81.3%)	77/108 (71.3%)	RR 1.14 (0.99 to 1.31) NNTB = N/A	10 more per 100 (from 1 fewer to 22 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 15–21 days)						
1	RCT	143/185 (77.3%)	71/100 (71%)	RR 1.09 (0.94 to 1.26) NNTB = N/A	6 more per 100 (from 4 fewer to 18 more)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: patient) (follow-up 15–21 days)						
1	RCT	65/81 (80.2%)	23/34 (67.6%)	RR 1.19 (0.92 to 1.53) NNTB = N/A	13 more per 100 (from 5 fewer to 36 more)	Low
No. of patients experienced treat-related AEs (follow-up 15–21 days)						
1	RCT	64/241 (26.6%)	12/120 (10%)	RR 2.66 (1.49 to 4.73) NNTH = 6 (4 to 12)	17 more per 100 (from 5 more to 37 more)	Low
Withdrawals due to treatment-related AEs (follow-up 15–21 days)						
1	RCT	18/241 (7.5%)	4/120 (3.3%)	RR 2.24 (0.78 to 6.47) NNTH = N/A	4 more per 100 (from 1 fewer to 18 more)	Low

Dosage: Linezolid (600 mg every 12 h either IV or per oral); ampicillin/sulbaclam (1.5 to 3 g every 6 h IV), or amoxicillin/clavulanate (500-875 mg every 8–12 hours orally), for 7 to 28 days.

[a] Cured = resolution of all signs and symptoms.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 40: Lipopeptide antibiotics vs. glycopeptide antibiotics

Daptomycin (IV) vs. vancomycin (IV) (Lipsky et al. 2005)

No of studies	Design	Daptomycin (IV)	Vancomycin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 6–-20 days)						
1	RCT	10/14 (71.4%)	20/29 (69%)	RR 1.04 (0.69 to 1.56) NNTB = N/A	3 more per 100 (from 21 fewer to 39 more)	Low

Dosage: Daptomycin (4 mg/kg every 24 hours IV over 30 mins); vancomycin (1 g every 12 hours IV over 60 mins), for 7 to 14 days.

[a] Cured = resolution of all signs and symptoms.

CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 41: Lipopeptide antibiotics vs. narrow-spectrum penicillins

Daptomycin (IV) vs. nafcillin or oxacillin or cloxacillin or flucloxacillin (IV) (Lipsky et al. 2005)

No of studies	Design	Daptomycin (IV)	Nafcillin or cloxacillin or flucloxacillin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 6–20 days)						
1	RCT	16/25 (64%)	19/27 (70.4%)	RR 0.91 (0.62 to 1.33) NNTB = N/A	6 fewer per 100 (from 27 fewer to 23 more)	Low

Dosage: Daptomycin (4 mg/kg every 24 hours IV over 30 mins) for 7 to 14 days; or a narrow-spectrum penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin, depending on the investigator's choice, given in equally divided doses totalling 4 to 12 g/day IV).

[a] Cured = resolution of all signs and symptoms.

CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 42: Antipseudomonal penicillins vs. broad-spectrum beta-lactam carbapenems

Piperacillin/tazobactam (IV) vs. ertapenem (IV) (Lipsky et al. 2005)

No of studies	Design	Piperacillin/ tazobactam (IV)	Ertapenem (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 5 days)						
1	RCT	202/219 (92.2%)	213/226 (94.2%)	RR 0.98 (0.93 to 1.03) NNTB = N/A	2 fewer per 100 (from 7 fewer to 3 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 5 days)						
1	RCT	122/146 (83.6%)	135/151 (89.4%)	RR 0.93 (0.85 to 1.02) NNTB = N/A	6 fewer per 100 (from 13 fewer to 2 more)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 5 days)						
1	RCT	40/51 (78.4%)	62/67 (92.5%)	RR 0.85 (0.72 to 0.99) NNTB = 7 (4 to 62)	14 fewer per 100 (from 1 fewer to 26 fewer)	Low
No. of patients experienced treatment-related AEs (follow-up 5 days)						
1	RCT	57/291 (19.6%)	44/295 (14.9%)	RR 1.31 (0.92 to 1.88) NNTH = N/A	5 more per 100 (from 1 fewer to 13 more)	Low
Withdrawals due to treatment-related AEs (follow-up 5 days)						
1	RCT	6/291 (2.1%)	3/295 (1%)	RR 2.03 (0.51 to 8.03) NNTH = N/A	1 more per 100 (from 0 fewer to 7 more)	Low

Dosage: Ertapenem (1 g bolus, followed by a saline placebo every 6 hours for 3 additional doses, IV); piperacillin/tazobactam (3 to 375 g every 6 hours, IV), for 5 days.

[a] Cured = resolution of all signs and symptoms.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 43: Cephalosporins vs. cephalosporins

Ceftizoxime (IV) vs. cefoxitin (IV) (Hughes et al. 1987)

No of studies	Design	Ceftizoxime (IV)	Cefoxitin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up varied)						
1	RCT	23/28 (82.1%)	17/26 (65.4%)	RR 1.21 (0.88 to 1.66) NNTB = N/A	14 more per 100 (from 8 fewer to 43 more)	Low
No. of patients experienced treatment-related AEs (follow-up varied)						
1	RCT	16/33 (48.5%)	19/30 (63.3%)	RR 0.77 (0.49 to 1.19) NNTH = N/A	15 fewer per 100 (from 32 fewer to 12 more)	Low

Dosage: Ceftizoxime, up to 4 g IV every 8 hours. Cefoxitin, up to 2 g IV every 4 hours.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 44: Lincosamide antibiotics vs. cephalosporins

Clindamycin (oral) vs. cephalexin (oral) (Lipsky et al. 1990)

No of studies	Design	Clindamycin (oral)	Cephalexin (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up varied)						
1	RCT	10/25 (40%)	9/27 (33.3%)	RR 1.20 (0.59 to 2.46) NNTB = N/A	7 more per 100 (from 14 fewer to 49 more)	Low

Dosage: Clindamycin (300 mg orally), 4 times daily for 2 weeks. Cephalexin (500 mg orally), 4 times daily for 2 weeks.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

3.4.3 Evidence statements

Ofloxacin (IV to oral) vs. ampicillin/sulbactam (IV) to amoxicillin/clavulanic acid (oral) (see Summary of GRADE profile 31)

3.4.3.1 One RCT with 88 participants showed no significant difference in the number of clinical cures, eradication of pathogen(s) overall, eradication of Gram-negative aerobes and the number of treatment-related adverse events between participants who received ofloxacin (IV to oral) and participants who received ampicillin/sulbactam (IV) to amoxicillin/clavulanic acid (oral). (Low quality)

However,

3.4.3.2 The same RCT with 88 participants showed that the eradication of Gram-positive aerobes in patients who received ampicillin/sulbactam (IV) to amoxicillin/clavulanic acid (oral) was significantly higher compared with patients who received ofloxacin (IV to oral). (Low quality)

Imipenem/cilastatin (IV) vs. ampicillin/sulbactam (IV) (see Summary of GRADE profile 32)

3.4.3.3 One RCT with 96 participants showed no significant differences in the number of clinical cures, eradication of pathogen(s) overall and the number of treatment-related adverse events between participants who received imipenem/cilastatin (IV) and participants who received ampicillin/sulbactam (IV). (Low quality)

Cefoxitin (IV) vs. ampicillin/sulbactam (IV) (see Summary of GRADE profile 33)

3.4.3.4 One RCT with 36 participants showed no significant differences in the number of clinical cures, length of hospital stay and treatment-related adverse events between participants who received cefoxitin (IV) and participants who received ampicillin/sulbactam (IV). (Low quality)

Piperacillin/tazobactam (IV) vs. ampicillin/sulbactam (IV) (see Summary of GRADE profile 34)

3.4.3.5 One RCT with 314 participants showed no significant differences in the number of clinical cures or improvements, eradication of Gram-positive aerobes, treatment-related adverse events, and withdrawals due to treatment-related adverse events between participants who received piperacillin/tazobactam (IV) and participants who received ampicillin/sulbactam (IV). (Low quality)

Piperacillin/tazobactam (IV) vs. ticarcillin/clavulanate (IV) (see Summary of GRADE profile 35)

3.4.3.6 One RCT with 35 participants showed no significant differences in the number of clinical cures between participants who received piperacillin/tazobactam (IV) and participants who received ticarcillin/clavulanate (IV). (Low quality)

Imipenem/cilastatin (IV) vs. piperacillin/clindamycin (IV) (see Summary of GRADE profile 36)

3.4.3.7 One RCT with 45 participants showed no significant differences in the number of clinical cures and eradication of pathogen(s) overall between participants who received imipenem/cilastatin (IV) and participants who received piperacillin/clindamycin (IV). (Low quality)

However,

3.4.3.8 The same RCT with 45 participants showed that the number of treatment-related adverse events in patients who received imipenem/cilastatin (IV) was significantly higher compared with participants who received piperacillin/clindamycin (IV). (Low quality)

Moxifloxacin (IV to oral) vs. piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral) (see Summary of GRADE profile 37)

3.4.3.9 One RCT with 127 participants showed no significant differences in the number of clinical cures, eradication of pathogens (both Gram-positive and Gram-negative aerobes), and withdrawals due to treatment-related adverse events between participants who received moxifloxacin (IV to oral) and participants who received piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral). (Moderate quality)

However,

3.4.3.10 The same RCT with 127 participants showed that the number of participants who experienced treatment-related adverse events was significantly higher in those receiving moxifloxacin (IV to oral) compared with those receiving piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral). (Moderate quality)

Pexiganan cream (topical) vs. ofloxacin (oral) (see Summary of GRADE profile 38)

3.4.3.11 One RCT with 835 participants showed no significant differences in the number of clinical cures and eradication of pathogen(s) (including both Gram-positive and Gram-negative aerobes) between participants who received Pexiganan cream (topical) and participants who received ofloxacin (oral). (High quality)

Linezolid (IV or oral) vs. ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral) (see Summary of GRADE profile 39)

3.4.3.12 One RCT with 361 participants showed no significant differences in the number of clinical cures, eradication of both Gram-positive and Gram-negative aerobes, and withdrawals due to treatment-related adverse events between participants who received linezolid (IV or oral) and participants who received ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral). (Low quality)

However,

3.4.3.13 The same RCT with 361 participants showed that the number of participants who experienced treatment-related adverse events was significantly higher in those who received linezolid (IV or oral) compared with those who received ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral). (Low quality)

Daptomycin (IV) vs. vancomycin (IV) (see Summary of GRADE profile 40)

3.4.3.14 One RCT with 43 participants showed no significant difference in the number of clinical cures between participants who received Daptomycin (IV) and participants who received vancomycin (IV). (Low quality)

Daptomycin vs. nafcillin or cloxacillin or flucloxacillin (IV) (see Summary of GRADE profile 41)

3.4.3.15 One RCT with 52 participants showed no significant difference in the number of clinical cures between participants who received Daptomycin (IV) and participants who received nafcillin or cloxacillin or flucloxacillin (IV). (Low quality)

Piperacillin/tazobactam (IV) vs. ertapenem (IV) (see Summary of GRADE profile 42)

3.4.3.16 One RCT with 586 participants showed no significant difference in the number of clinical cures between participants who received piperacillin/tazobactam (IV) and participants who received ertapenem (IV). (Moderate quality)

3.4.3.17 The same RCT with 586 participants showed no significant differences in the eradication of Gram-positive aerobes, the number of participants experiencing adverse events, and withdrawals due to treatment-related adverse events between participants who received piperacillin/tazobactam (IV) and participants who received ertapenem (IV). (Low quality)

However,

3.4.3.18 The same RCT with 586 participants showed that the eradication of Gram-negative aerobes was significantly higher in participants receiving ertapenem (IV) compared with those receiving piperacillin/tazobactam (IV). (Low quality)

Ceftizoxime (IV) vs. cefoxitin (IV) (see Summary of GRADE profile 43)

3.4.3.19 One RCT with 63 participants showed no significant differences in the number of clinical cures and treatment-related adverse events between participants who received ceftizoxime (IV) and participants who received cefoxitin (IV). (Low quality)

Clindamycin (oral) vs. cephalexin (oral) (see Summary of GRADE profile 44)

3.4.3.20 One RCT with 52 participants showed no significant difference in complete healing between participants who received clindamycin (oral) and participants who received cephalexin (oral). (Low quality)

3.4.4 Health economic modelling

No health economic modelling was conducted for this question.

3.4.5 Evidence to recommendations

The clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)

Quality of the evidence

The GDG agreed that the evidence was inconclusive (almost all head-to-head comparisons of different antibiotics showed no significant differences and there were no two studies with the same pair-wise comparisons) and was of low quality. Due to insufficient evidence, the GDG felt that it was not possible to make recommendations on individual antibiotics.

Other considerations

Although there was insufficient evidence to recommend individual antibiotics, the GDG agreed that antibiotic treatment is crucial to treat diabetic foot infections. With reference to the GDG's experience, knowledge and skills, the GDG reached consensus on the following:

- Each hospital should have antibiotic guidelines for treating diabetic foot infections; and MRSA should be treated based on local and national guidance.
- Antibiotic therapy for suspected osteomyelitis should not be delayed pending MRI results.
- Empirical antibiotic therapy should be started based on severity, followed by a definitive antibiotic regimen that is informed by microbiology results.
- Antibiotics with the lowest acquisition cost appropriate for the clinical situation and severity should be used. Antibiotics with activity against Gram-positive organisms should be used for mild infections and antibiotics

with activity against both Gram-positive and Gram-negative organisms (including anaerobic bacteria) should be used for moderate and severe infections.

- The route of administration should be:
  - mild infections: oral
  - moderate infections: oral or intravenous (based on the clinical situation and choice of antibiotics)
  - severe infections: intravenous initially then reassessed, based on the clinical situation.
- Prolonged antibiotic therapy for mild soft tissue infections should not be offered.

3.4.6 Recommendations and research recommendations for antibiotics for diabetic foot infections

Recommendations for antibiotics for diabetic foot infections

Management of diabetic foot infection

Recommendation 1.2.23

Each hospital should have antibiotic guidelines for the management of diabetic foot infections.

Recommendation 1.2.24

Do not delay starting antibiotic therapy for suspected osteomyelitis pending the results of the MRI scan

Recommendation 1.2.25

Start empirical antibiotic therapy based on the severity of the infection, using the antibiotic appropriate for the clinical situation and the severity of the infection, and with the lowest acquisition cost.

Recommendation 1.2.26

For mild infections, offer oral antibiotics with activity against Gram-positive organisms.

Recommendation 1.2.27

For moderate and severe infections, offer antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria. The route of administration is as follows:

- Moderate infection: oral or intravenous antibiotics, based on the clinical situation and the choice of antibiotic (see recommendation 1.2.23).
- Severe infection: start with intravenous antibiotics then reassess, based on the clinical situation (see recommendation 1.2.23)

Recommendation 1.2.28

The definitive antibiotic regimen and the duration of treatment should be informed by both the results of the microbiological examination and the clinical response to empiric antibiotic therapy.

Recommendation 1.2.29

Do not use prolonged antibiotic therapy for mild soft tissue infections.

Recommendation 1.2.30

Treat infections with MRSA in line with local and national guidance.

Research recommendations for antibiotics for diabetic foot infections

See appendix A for a list of all research recommendations.

No research recommendations have been made for this topic

3.5 Adjunctive treatments for diabetic foot problems

3.5.1 Review question

What is the clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems, for example, dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy and electrical stimulation?

3.5.2 Evidence review

The systematic search retrieved 9817 studies. Of these, 37 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). From these 37 studies, 14 studies were on growth factors (G-CSF = 5; PDGF = 4; EGF = 4; TGF-β = 1); six studies were on hyperbaric oxygen therapy; seven studies were on dermal or skin substitutes; three studies were on negative pressure wound therapy; and seven studies were on other adjunctive treatments (electrical stimulation therapy, plasma gel, regenerative tissue matrix, dalteparin). Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles.
- Full GRADE evidence profiles (see appendix D).
- Forest plots from meta-analysis (see appendix H).
- Evidence statements.

Table 5: Characteristics of included studies

Author	Total no. of patients	Interventions	Dosage	Follow-up period	Primary outcomes
Growth factors					
Granulocyte colony-stimulating factor (G-CSF)					
de Lalla et al. (2001)	40	G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.	263 micrograms subcutaneously daily for 21 days.	9 weeks, then 6 months	Amputation; overall need for surgical interventions; improvement on infection status; treatment-related AEs
Gough et al. (1997)	40	G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 7 days.	7 days treatment, follow-up unclear.	Amputation; complete wound healing; overall need for surgical interventions; resolution of infection; improvement on infection status; treatment-related AEs
Kastenbauer et al. (2003)	40	G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 10 days.	10 days treatment, follow-up unclear.	Amputation; complete wound healing; overall need for surgical interventions; improvement on infection status; treatment-related AEs
Viswanathan et al. (2003)	20	G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 7 days.	7 days treatment, follow-up unclear.	Amputation; overall need for surgical interventions; length of hospital stay (days); improvement on infection status
Yonem et al. (2001)	30	G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 3 or more days.	Unclear.	Amputation; overall need for surgical interventions; length of hospital stay (days)
Platelet-derived growth factor (PDGF)					
D'Hemecourt et al. (2005)	112	PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	100 micrograms/g becaplermin gel, change daily.	20 weeks	Complete wound healing; withdrawal due to treatment-related AEs; at least 1 treatment-related AEs
Hardikar et al. (2005)	110	PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	0.01% gel with 100 micrograms of rhPDGF-BB/g.	10 weeks, then 20 weeks follow-up	Complete wound healing; mean healing time
Robson et al. (2005)	146	PDGF + standard care vs. standard care only (control). Standard care = debridement, adaptic dressing, off-	0.01% becaplermin gel, change daily, over 20 weeks.	20 weeks	Complete wound healing

		loading.			
Wieman et al. (1998)	383	PDGF + standard care vs. placebo + standard care (control). Standard care = debridement, dressing, off-loading.	0.01% Becaplermin gel 30 micrograms or 100 micrograms daily, over 20 weeks.	20 weeks than 3 months	Complete wound healing; withdrawal due to treatment-related AEs
Epidermal growth factor (EGF)					
Afshari et al. (2005)	50	EGF + standard care vs. placebo + standard care only (control). Standard care = debridement, dressing.	1 mg of EGF/1000 mg of 1% silver sulfadiazine, once a day for 28 days.	4 weeks	Length of hospital stay (days); complete wound healing
Fernandez-Montequinn et al. (2009)	149	EGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	25 or 75 micrograms rhEGF in 5ml water for injection, daily for 2 weeks.	2 weeks	At least 50% wound reduction; treatment-related AEs - burning sensation; treatment-related AEs - shivering
Tsang et al. (2003)	59	EGF + standard care vs. standard care only (control). Standard care = Actovegin cream, debridement, dressing.	0.02% or 0.04% [wt/wt] hEGF cream + 5% Actovegin cream, daily for 12 weeks.	12 weeks then 24 weeks	Amputation; complete wound healing
Viswanathan et al. (2006)	57	EGF vs. placebo (no mention of standard wound care).	150 micrograms rhEGF cream, twice daily, for 15 weeks.	15 weeks	Complete wound healing.
Transforming growth factor beta (TGF-β)					
Robson et al. (2000)	155	TGF-β + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	Topical collagen sponges contained TGF-β 0.05 micrograms/cm^2, 0.5 micrograms/cm^2, or 5.0 micrograms/cm^2, twice weekly, for 21 weeks.	21 weeks	Complete wound closure.
Hyperbaric oxygen therapy (HBOT)					
Abidia et al. (2003)	18	HBOT vs. specialised wound management alone.	At 2.4 ATA for 90 mins on 30 occasions over 6 weeks.	6 weeks	Major amputation; minor amputation; complete wound healing
Doctor et al. (1992)	30	HBOT + standard care vs. standard care only (control). Standard care = dressing and debridement.	At 3.0 ATA on 4 occasions over 6 weeks.	4 weeks	Major amputation; minor amputation
Duzgun et al.	100	HBOT + standard care vs. standard care only	At 2.0 to 3.0 ATA for 90	20 to 30 days	Major amputation; minor amputation;

(2008)		(control). Standard care = dressing and debridement.	mins, twice a day, followed by once a day (alternating) for a period of 20 to 30 days.		complete wound healing; required surgical interventions
Faglia et al. (1996)	70	HBOT vs. specialised wound management alone.	At 2.2 to 2.5 ATA for 90 mins on 39 occasions over 6 weeks.	6 weeks	Major amputation
Kessler et al. (2003)	27	HBOT + standard care vs. standard care only (control). Standard care = off-loading.	At 2.5 ATA for 90 mins, twice a day, 5 days per week for 2 weeks.	2 weeks, than 1 month follow-up	Complete wound healing; mean reduction of ulcer surface area
Londahl et al. (2010)	90	HBOT + standard care vs. sham HBOT + standard care Standard care = antibiotic treatment, revascularisation, debridement, off-loading, and metabolic control.	At 2.5 ATA for 90 mins, 5 days per weeks for 8 to 10 weeks, no more than 40 sessions.	1 year	Major amputation; complete wound healing
Dermal or skin substitutes (DSS)					
Caravaggi et al. (1996)	79	DSS + standard care vs. non-adherent paraffin gauze + standard care. Standard care = debridement and off-loading.	1 or 2 applications for 7 to 10 days.	11 weeks	Complete wound healing; withdrawal due to ulcer-related AEs; overall ulcer-related AEs
Gentzknow et al. (1996)	25	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	1 application weekly for a total of 8 applications.	12 weeks	Complete wound healing; at least 50% wound closure; overall ulcer-related AEs
Marston et al. (2003)	245	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	Up to 7 applications weekly.	12 weeks	Complete wound healing; required surgical interventions; overall ulcer-related AEs
Naughton et al. (1997)	281	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	8 applications weekly.	12 weeks	Complete wound healing
Pham et al. (1999)	33	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	Maximum 5 applications from week to week 4.	12 weeks	Complete wound healing
Veves et al. (2001)	208	DSS + standard care vs. moistened gauze + standard care.	Maximum 5 applications from week to week 4.	12 weeks	Complete wound healing; median time to complete closure; withdrawal due to

		Standard care = debridement and off-loading.			ulcer-related AEs; overall ulcer-related AEs
Puttirutvong et al. (2004)	80	Meshed skin graft + standard care vs. split thickness skin graft + standard care Standard care = daily dressing	Unclear	6 months	Mean healing time.
Negative pressure wound therapy (NPWT)					
Blume et al. (2008)	335	NPWT + standard care vs. moist wound therapy + standard care (control). Standard care = off-loading.	Change every 48 to 72 hours.	16 weeks	Amputation; complete wound closure; median time to 75% wound closure; overall ulcer-related AEs.
Etoz et al. (2004)	24	NPWT vs. saline moistened gauze (control)	Change every 48 hours.	12 to 20 days	Mean reduction wound surface area (cm^2).
Williams et al. (2005)	162	NPWT + standard care vs. moist wound therapy + standard care (control). Standard care = off-loading.	Change every 48 hours.	16 weeks	Amputation; complete wound closure; median time to achieve 75–100% granulation; overall treatment-related AEs.
Other adjunctive treatments					
Electrical stimulation therapy					
Moretti et al. (2009)	30	External shock wave therapy + standard care vs. standard care only (control). Standard care = debridement, off-loading, antibiotics if needed.	3 sessions (1 or 2 mins) per day, with 0.03 mJ/mm^2 using electromagnetic lithotripter.	20 weeks	Complete wound healing, mean healing time (days)
Peters et al. (2001)	40	Electrical stimulation vs. placebo stimulation with no current (control).	50V with 80 twin peaks per second, every night for 8 hours.	12 weeks	Complete wound healing.
Autologous platelet-rich plasma gel					
Driver et al. (2006)	72	Autologous platelet-rich plasma gel + standard care vs. saline gel + standard care only (control). Standard care = dressing, off-loading.	Unclear.	12 weeks	Complete wound healing, median time to complete wound closure.
Acellular dermal regenerative tissue matrix					
Reyzelman et al. (2009)	85	Acellular dermal matrix + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	Single application.	12 weeks	Complete wound healing, healing rate (adjusted hazard ratio).

RGD peptide matrix					
Steed et al. (1995)	65	RGD peptide matrix + standard care vs. saline gauze + standard care only (control). Standard care = debridement, dressing.	Twice per week	10 weeks	Complete wound healing
OASIS wound matrix vs. PDGF					
Niezgoda et al. (2005)	73	OASIS wound matrix + standard care vs. PDGF + standard care. Standard care = debridement, off-loading.	OASIS = clinician to decide on weekly basis to change or not. PDGF = applied weekly for 12 hours.	12 weeks	Complete wound healing, ulcer recurrence.
Dalteparin (injection) (for diabetic patients with peripheral arterial occlusive disease)					
Kalani et al. (2003).	85	Dalteparin (injection) + standard care vs. placebo saline + standard care. Standard care = dressing, debridement, off-loading, antibiotic if required.	0.2 ml (Fragmin, 25000 units/ml) for maximum of 6 months.	6 months	Amputation, complete wound healing, at least 50% wound reduction.

AE = adverse events; ATA = absolute atmospheres; RGD = arginine-glycine-aspartic acid; rhEGF = recombinant human epidermal growth factor.

Growth factors

Summary of GRADE profile 45: Adjunctive treatment: Growth factors: Granulocyte colony-stimulating factor (G-CSF)

No of studies	Design	G-CSF	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Amputation (follow-up 10 days to 6 months)						
5 [de, G, K, V, Y]	RCT	6/85 (7.1%)	15/83 (18.1%)	RR 0.41 (0.18 to 0.95) NNTB = 9 (5 to 96)	11 fewer per 100 (from 1 fewer to 15 fewer)	Low
Complete wound healing (follow-up: unclear)						
2 [G, K]	RCT	4/39 (10.3%)	0/40 (0%)	RR 9.45 (0.54 to 164.49) NNTB = N/A	0 more per 100 (from 0 fewer to 0 more)	Low
Overall need for surgical interventions (follow-up: varied)						
5 [de, G, K, V, Y]	RCT	11/85 (12.9%)	29/79 (36.7%)	RR 0.37 (0.2 to 0.68) NNTB = 4 (3 to 9)	23 fewer per 100 (from 12 fewer to 29 fewer)	Low
Length of hospital stay (days) (follow-up: varied)						
2 [V, Y]	RCT	25	25	Mean (days) (SD): Mean difference = -1.40 (95%CI: -2.27 to -0.53)		Low
Resolution of infection (follow-up: varied)						
1 [G]	RCT	11/20 (55%)	4/20 (20%)	RR 2.75 (1.05 to 7.2) NNTB = 3 (2 to 21)	35 more per 100 (from 1 more to 100 more)	Moderate
Improvement on infection status (follow-up: varied)						
4 [de, G, K, V]	RCT	49/70 (70%)	35/70 (50%)	RR 1.40 (1.06 to 1.85) NNTB = 5 (3 to 27)	20 more per 100 (from 3 more to 42 more)	Low
Treatment-related AEs (follow-up: varied)						
3 [de, G, K]	RCT	5/60 (8.3%)	0/57 (0%)	RR 5.59 (0.71 to 44.05) NNTH = N/A	0 more per 100 (from 0 fewer to 0 more)	Low

[de] = de Lalla et al. (2001). G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.

[G] = Gough et al. (1997). G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.

[K] = Kastenbauer et al. (2003). G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.

[V] = Viswanathan et al. (2003). G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.

[Y] = Yonem et al. (2001). G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.

AE = adverse event; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 46: Adjunctive treatment: Growth factors: Platelet-derived growth factor (PDGF)

No of studies	Design	PDGF	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (follow-up mean 20 weeks)						
4 [D, H, R, W]	RCT	202/419 (48.2%)	115/325 (35.4%)	RR 1.38 (1.16 to 1.64) NNTB = 8 (5 to 18)	13 more per 100 (from 6 more to 23 more)	Moderate
Withdrawal due to treatment-related adverse events (follow-up 20 weeks)						
2 [D, W]	RCT	29/290 (10%)	26/195 (13.3%)	RR 0.94 (0.54 to 1.63) NNTH = N/A	1 fewer per 100 (from 6 fewer to 8 more)	Low
At least 1 treatment-related adverse event (follow-up 20 weeks)						
1 [D]	RCT	22/34 (64.7%)	48/68 (70.6%)	RR 0.92 (0.68 to 1.23) NNTH = N/A	6 fewer per 100 (from 23 fewer to 16 more)	Low
Mean healing time (days)						
1 [H]	RCT	58	55	Mean (days): PDGF = 46; control = 61, p = < 0.001		Low

[D] = D'Hemecourt et al. (2005). PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.

[H] = Hardikar et al. (2005). PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.

[R] = Robson et al. (2005). PDGF + standard care vs. standard care only (control). Standard care = debridement, adaptic dressing, off-loading.

[W] = Wieman et al. (1998). PDGF + standard care vs. placebo + standard care (control). Standard care = debridement, dressing, off-loading.

NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 47: Adjunctive treatment: Growth factors: Epidermal growth factor (EGF)

No of studies	Design	EGF	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Amputation (follow-up mean 24 weeks)						
1 [T]	RCT	2/40 (5%)	2/19 (10.5%)	RR 0.47 (0.07 to 3.12) NNTB = N/A	6 fewer per 100 (from 10 fewer to 22 more)	Low
Length of hospital stay (days) (follow-up 4 weeks)						
1 [A]	RCT	30	20	Mean (days) (SD): EGF = 29.6 (20.95); control = 28.9 (15.1) Mean difference = 0.70 (95%CI: -9.3 to 10.7)		Low
Complete wound healing (follow-up 4 to 24 weeks)						
3 [A, T, V]	RCT	69/99 (69.7%)	33/67 (49.3%)	RR 1.41 (0.76 to 2.63) NNTB = N/A	20 more per 100 (from -12 fewer to 80 more)	Low
At least 50% wound reduction (follow-up 2 weeks)						
1 [F]	RCT	78/101 (77.2%)	19/48 (39.6%)	RR 1.95 (1.35 to 2.81) NNTB = 3 (2 to 5)	38 more per 100 (from 14 more to 72 more)	Low
Treatment-related AEs - burning sensation (follow-up 2 weeks)						
1 [F]	RCT	22/101 (21.8%)	14/48 (29.2%)	RR 0.75 (0.42 to 1.33) NNTB = N/A	7 fewer per 100 (from 17 fewer to 10 more)	Low
Treatment-related AEs - shivering (follow-up 2 weeks)						
1 [F]	RCT	25/101 (24.8%)	2/48 (4.2%)	RR 5.94 (1.47 to 24.06) NNTH = 5 (3 to 11)	21 more per 100 (from 2 more to 97 more)	Low

[A] = Afshari et al. (2005). EGF + standard care vs placebo + standard care only (control). Standard care = debridement, dressing.

[F] = Fernandez-Montequinn et al. (2009). EGF + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.

[T] = Tsang et al. (2003). EGF + standard care vs standard care only (control). Standard care = Actovegin cream, debridement, dressing.

[V] = Viswanathan et al. (2006). EGF vs placebo (no mention of standard wound care).

AE = adverse event; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 48: Adjunctive treatment: Growth factors: Transforming growth factor beta (TGF-β)

No of studies	Design	TGF-β	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (week 21) (follow-up 21 weeks)						
1 [R]	RCT	77/131 (58.8%)	17/24 (70.8%)	RR 0.83 (0.62 to 1.11) NNTB = N/A	12 fewer per 100 (from 27 fewer to 8 more)	Moderate

[R] = Robson et al. (2000). TGF-β + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Hyperbaric oxygen therapy

Summary of GRADE profile 49: Adjunctive treatment: Hyperbaric oxygen therapy (HBOT)

No of studies	Design	HBOT	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Major amputation (follow-up varied)						
5 [A, D, Du, F, L]	RCT	11/158 (6.9%)	37/150 (24.7%)	RR 0.30 (0.16 to 0.55) NNTB = 6 (4 to 10)	17 fewer per 100 (from 11 fewer to 21 fewer)	Low
Minor amputation (follow-up varied)						
3 [A, D, Du]	RCT	10/74 (13.5%)	26/74 (35.1%)	RR 0.92 (0.11 to 7.9) NNTB = N/A	3 fewer per 100 (from 31 fewer to 100 more)	Moderate
Complete wound healing (week 4–6) (follow-up 4 to 6 weeks)						
3 [A, Du, K, L]	RCT	67/121 (55.4%)	16/114 (14.0%)	RR 3.46 (0.91 to 13.12) NNTB = N/A	34 more per 100 (from 1 fewer to 100 more)	Moderate
Required surgical interventions (follow-up 1 months)						
1 [Du]	RCT	8/50 (16%)	50/50 (100%)	RR 0.17 (0.09 to 0.31) NNTB = 1 (1 to 2)	83 fewer per 100 (from 69 fewer to -91 fewer)	Moderate
Mean reduction of ulcer surface area (week 4)						
1 [K]	RCT	14	13	Mean (%) (SD): HBOT = 61.9 (23.3); control = 55.1 (21.5), p > 0.05		Low

[A] = Abidia et al. (2003). HBOT vs. specialised wound management alone.

[D] = Doctor et al. (1992). HBOT + standard care vs. standard care only (control). Standard care = dressing and debridement.

[Du] = Duzgun et al. (2008). HBOT + standard care vs. standard care only (control). Standard care = dressing and debridement.

[F] = Faglia et al. (1996). HBOT vs. specialised wound management alone.

[K] = Kessler et al. (2003). HBOT + standard care vs. standard care only (control). Standard care = off-loading.

[L] = Londahl et al. (2010). HBOT + standard care vs. sham HBOT + standard care. Standard care = antibiotics treatment, revascularisation, debridement, off-loading, and metabolic control.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Dermal or skin substitutes

Summary of GRADE profile 50: Adjunctive treatment: Dermal or skin substitutes (DSS)

No of studies	Design	Dermal or skin grafts	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (week 12) - ALL (follow-up 12 weeks)						
6 [C, G, M, N, P, V]	RCT	202/452 (44.7%)	128/419 (30.5%)	RR 1.46 (1.22 to 1.73) NNTB = 7 (5 to 13)	14 more per 100 (from 7 more to 22 more)	Moderate
SUBGROUP: Complete wound healing (week 12) - Dermagraft (follow-up 12 weeks)						
3 [G, M, N]	RCT	99/281 (35.2%)	67/270 (24.8%)	RR 1.44 (1.11 to 1.87) NNTB = 10 (6 to 36)	11 more per 100 (from 3 more to 22 more)	Low
SUBGROUP: Complete wound healing (week 12) - Graftskin (follow-up 12 weeks)						
1 [V]	RCT	63/112 (56.3%)	36/96 (37.5%)	RR 1.50 (1.11 to 2.04) NNTB = 5 (3 to 20)	19 more per 100 (from 4 more to 39 more)	Low
SUBGROUP: Complete wound healing (week 12) - Hyalograft (follow-up 12 weeks)						
1 [C]	RCT	28/43 (65.1%)	18/36 (50%)	RR 1.30 (0.88 to 1.93) NNTB = N/A	15 more per 100 (from -6 fewer to 46 more)	Low
SUBGROUP: Complete wound healing (week 12) - Human skin equivalent (follow-up 12 weeks)						
1 [P]	RCT	12/16 (75%)	7/17 (41.2%)	RR 1.82 (0.97 to 3.44) NNTB = N/A	34 more per 100 (from -1 fewer to 100 more)	Low
At least 50% wound closure (week 12) - Dermagraft (follow-up 12 weeks)						
1 [G]	RCT	9/12 (75%)	3/13 (23.1%)	RR 3.25 (1.14 to 9.24) NNTB = 2 (1 to 8)	52 more per 100 (from 3 more to 100 more)	Low
Required surgical interventions (unit: ulcers) - Dermagraft						
1 [M]	RCT	13/163 (8%)	22/151 (14.6%)	RR 0.55 (0.29 to 1.05) NNTB = N/A	7 fewer per 100 (from 10 fewer to 1 more)	Low
Median time to complete closure (days) - Graftskin						
1 [V]	RCT	112	96	Median (days) (K-M): Graftskin = 65; control 90, p = 0.0026		Low
Withdrawal due to ulcer-related AEs - Graftskin/Hyalograft						
2 [C, V]	RCT	9/155 (5.8%)	15/132 (11.4%)	RR 0.51 (0.23 to 1.13) NNTH = N/A	6 fewer per 100 (from 9 fewer to 1 more)	Low
Overall ulcer-related AEs – Dermagraft/Graftskin						
4 [C, G, M, V]	RCT	72/297 (24.2%)	108/260 (41.5%)	RR 0.58 (0.46 to 0.74) NNTH = 6 (4 to 11)	17 fewer per 100 (from 11 fewer to -22 fewer)	Low

[C] = Caravaggi et al. (1996). DSS + standard care vs. non-adherent paraffin gauze + standard care. Standard care = debridement and off-loading.
[G] = Gentzknow et al. (1996). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[M] = Marston et al. (2003). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[N] = Naughton et al. (1997). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[P] = Pham et al. (1999). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[V] = Veves et al. (2001). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.

AE = adverse event; CI = confidence interval; K-M = Kaplan-Meier; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 51: Adjunctive treatment: Dermal or skin substitutes (DSS)

No of studies	Design	Meshed skin graft	Split thickness skin graft	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (week 12) - ALL (follow-up 12 weeks)						
1 [P]	RCT	36	44	Meshed skin graft = 19.84 (7.37) Split thickness skin graft = 20.36 (7.21), p > 0.05		Low

[P] = Puttirutvong et al. (2004). Meshed skin graft + standard care vs. split thickness skin graft + standard care. Standard care = daily dressing

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial.

Negative pressure wound therapy

Summary of GRADE profile 52: Adjunctive treatment: Negative pressure wound therapy (NPWT)

No of studies	Design	NPWT	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Amputation						
2 [B, W]	RCT	9/246 (3.7%)	26/251 (10.4%)	RR 0.35 (0.17 to 0.74) NNTB = 15 (9 to 43)	7 fewer per 100 (from 3 fewer to -9 fewer)	Low
Complete wound closure (week 16) (follow-up 16 weeks)						
2 [B, W]	RCT	116/246 (47.2%)	81/251 (32.3%)	RR 1.47 (1.18 to 1.84) NNTB = 7 (4 to 16)	15 more per 100 (from 6 more to 27 more)	Low
Mean reduction wound surface area (cm^2)						
1 [E]	RCT	12	12	Mean reduction (cm^2) (SD): NPWT = 20.4 (11.7); control = 9.5 (4.11) Mean difference = 10.9 (95%CI: 3.88 to 17.92)		Low
Median time to 75% wound closure (days)						
1 [B]	RCT	169	166	Median time (K-M) (days): NPWT = 58 (95%CI: 53 to 78) Control = 84 (95%CI: 58 to 89), p = 0.014		Low
Median time to achieve 75%-100% granulation (days) (baseline 0%-25% granulation)						
1 [W]	RCT	77	85	Median time (K-M) (days): NPWT = 42 (95%CI: 14 to 56) Control = 82 (95%CI: 28 to 112), p = 0.01		Low
Overall ulcer-related AEs						
1 [B]	RCT	15/169 (8.9%)	11/166 (6.6%)	RR 1.34 (0.63 to 2.83) NNTH = N/A	2 more per 100 (from -2 fewer to 12 more)	Low
Overall treatment-related AEs						
1 [W]	RCT	9/77 (11.7%)	11/85 (12.9%)	RR 0.90 (0.40 to 2.06) NNTH = N/A	1 fewer per 100 (from 8 fewer to 14 more)	Low

[B] = Blume et al. (2008): NPWT + standard care vs. control (moist wound therapy) + standard care. Standard care = off-loading.

[E] = Etoz et al. (2004): NPWT vs. control (saline moistened gauze)

[W] = Williams et al. (2005): NPWT + standard care vs. control (moist wound therapy) + standard care. Standard care = off-loading.

AE = adverse event; CI = confidence interval; K-M = Kaplan-Meier; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Other adjunctive treatments

Summary of GRADE profile 53: Other adjunctive treatments: Electrical stimulation therapy (EST)

No of studies	Design	EST	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks) (follow-up 12 weeks): electrical stimulation						
1 [P]	RCT	13/20 (65%)	7/20 (35%)	RR 1.86 (0.94 to 3.70) NNTB = N/A	30 more per 100 (from -2 fewer to 94 more)	Low
Complete wound healing (20 weeks) (follow-up 20 weeks): ESWT						
1 [M]	RCT	8/15 (53.3%)	5/15 (33.3%)	RR 1.6 (0.68 to 3.77) NNTB = N/A	20 more per 100 (from -11 fewer to 92 more)	Low
Mean healing time (days): ESWT						
1 [M]	RCT	15	15	Mean (days) (SD): ESWT = 60.8 (4.7); control = 82.2 (4.7) p < 0.001		Low

[M] = Moretti et al. (2009). ESWT + standard care vs. standard care only (control). Standard care = debridement, off-loading, antibiotics if needed.

[P] = Peters et al. (2001). EST vs. placebo stimulation with no current (control).

AE = adverse event; CI = confidence interval; ESWT = electrical shock wave therapy; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 54: Other adjunctive treatments: Autologous platelet-rich plasma gel

No of studies	Design	Autologous platelet-rich plasma gel	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [D]	RCT	13/40 (32.5%)	9/32 (28.1%)	RR 1.16 (0.57 to 2.35) NNTB = N/A	4 more per 100 (from 12 fewer to 38 more)	Low
Median time to complete wound closure (days)						
1 [D]	RCT	40	32	Median time (days) Treatment = 45; control = 85, Log-rank p = 0.126.		Low

[D] = Driver et al. (2006). Autologous platelet-rich plasma gel + standard care vs saline gel + standard care only (control). Standard care = dressing, off-loading.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 55: Other adjunctive treatments: Acellular dermal regenerative tissue matrix

No of studies	Design	Acellular dermal matrix	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (follow-up 12 weeks)						
1 [R]	RCT	32/46 (69.6%)	18/39 (46.2%)	RR 1.50 (1.02 to 2.22) NNTB = 4 (2 to 44)	23 more per 100 (from 1 more to 56 more)	Low
Healing rate (adjusted HR)						
1 [R]	RCT	46	39	Healing rate: Adjusted HR = 2.0 (95%CI: 1.0 to 3.5)		Low

[R] = Reyzelman et al. (2009). Acellular dermal matrix + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.

CI = confidence interval; HR = hazard ratio; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 56: Other adjunctive treatments: OASIS wound matrix vs. platelet derived growth factor (PDGF)

No of studies	Design	OASIS	PDGF	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks) (follow-up 12 weeks)						
1 [N]	RCT	18/37 (48.6%)	10/36 (27.8%)	RR 1.75 (0.94 to 3.26) NNTB = N/A	21 more per 100 (from 2 fewer to 63 more)	Low
Ulcer recurrence (6 months) (follow-up 6 months)						
1 [N]	RCT	5/19 (26.3%)	6/18 (33.3%)	RR 0.79 (0.29 to 2.12) NNTB = N/A	7 fewer per 100 (from 24 fewer to 37 more)	Low

[N] = Niezgoda et al. (2005). Oasis wound matrix + standard care vs PDGF + standard care. Standard care = debridement, off-loading.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 57: Other adjunctive treatments: Arginine-glycine-aspartic acid (RGD) peptide matrix

No of studies	Design	RGD peptide matrix	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (10 weeks) (follow-up 10 weeks)						
1 [S]	RCT	14/40 (35.0%)	2/25 (8.0%)	RR 4.36 (1.08 to 17.65) NNTB = 4 (2 to 16)	27 more per 100 (from 1 fewer to 100 more)	Low

[S] = Steed el al. (1995). RGD peptide matrix + standard care vs saline gauze + standard care only (control). Standard care = debridement, dressing.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 58: Other adjunctive treatments: Dalteparin (for diabetic patients with peripheral arterial occlusive disease [PAOD])

No of studies	Design	Dalteparin (injection)	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (6 months) (follow-up 6 months)						
1 [K]	RCT	14/43 (32.6%)	9/42 (21.4%)	RR 1.52 (0.74 to 3.13) NNTB = N/A	11 more per 100 (from 6 fewer to 46 more)	Low
At least 50% wound reduction (follow-up 6 months)						
1 [K]	RCT	15/43 (34.9%)	10/42 (23.8%)	RR 1.33 (0.69 to 2.56) NNTB = N/A	8 more per 100 (from 7 fewer to 37 more)	Low
Amputation (follow-up 6 months)						
1 [K]	RCT	2/43 (4.7%)	8/42 (19%)	RR 0.24 (0.06 to 1.08) NNTB = N/A	14 fewer per 100 (from 18 fewer to 2 more)	Low

[K] = Kalani et al. (2003). Dalteparin (injection) + standard care vs. placebo saline + standard care. Standard care = dressing, debridement, off-loading, antibiotic if required.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

3.5.3 Evidence statements

Growth factor (G-CSF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 45)

Diabetic foot-related outcomes:

3.5.3.1 Five RCTs with a total number of 168 participants showed that participants who received G-CSF with standard wound care were significantly less likely to have an amputation or other surgical interventions when compared with participants who received standard wound care alone. (Low quality)

3.5.3.2 Two RCTs with a total number of 50 participants showed that participants who received G-CSF with standard wound care had a significantly shorter length of hospital stay, when compared with participants who received standard wound care alone. (Low quality)

3.5.3.3 One RCT with 40 participants showed that participants who received G-CSF with standard wound care were significantly more likely to have resolution of infection (moderate quality) when compared with participants who received standard wound care alone.

3.5.3.4 *Four RCTs with a total number of 140 participants showed that participants who received G-CSF with standard wound care were significantly more likely to have an improvement on infection status (low quality) when compared with participants who received standard wound care alone.*

However,

3.5.3.5 *Two RCTs with a total number of 79 participants showed no significant difference in complete wound healing between participants who received G-CSF with standard wound care and participants who received standard wound care alone. (Low quality)*

Adverse events:

3.5.3.6 *Three RCTs with a total number of 117 participants showed no significant difference in the number of treatment-related adverse events between participants who received G-CSF with standard wound care and participants who received standard wound care alone. (Low quality)*

Growth factors (PDGF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 46)

Diabetic foot-related outcomes:

3.5.3.7 *Four RCTs with a total number of 744 participants showed that participants who received PDGF with standard wound care were significantly more likely to have complete wound healing when compared with participants who received standard wound care alone. (Moderate quality)*

3.5.3.8 *One RCT with 113 participants showed that participants who received PDGF with standard wound care had a significantly shorter wound healing time compared with participants who received standard wound care alone. (Low quality)*

Adverse events:

3.5.3.9 Two RCTs with a total number of 485 participants showed no significant differences in the number of withdrawals due to treatment-related adverse events between participants who received PDGF with standard wound care and participants who received standard wound care alone. (Low quality)

3.5.3.10 One RCT with 102 participants showed no significant differences in the number of at least one treatment-related adverse event between participants who received PDGF with standard wound care and participants who received standard wound care alone. (Low quality).

Growth factors (EGF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 47)

Diabetic foot-related outcomes:

3.5.3.11 One RCT with 59 participants showed no significant differences in the number of amputations between participants who received EGF with standard wound care and participants who received standard wound care alone. (Low quality)

3.5.3.12 One RCT with 50 participants showed no significant differences in the length of hospital stay between participants who received EGF with standard wound care and participants who received standard wound care alone. (Low quality)

3.5.3.13 Three RCTs with a total number of 166 participants showed no significant difference in complete wound healing between participants who received EGF with standard wound care and participants who received standard wound care alone. (Low quality)

However,

3.5.3.14 One RCT with 149 participants showed that participants who received EGF with standard wound care were significantly more

likely to achieve at least 50% wound reduction when compared with participants who received standard wound care alone. (Low quality)

Adverse events:

3.5.3.15 *One RCT with 149 participants showed that participants who received EGF with standard wound care were significantly more likely to have shivering (treatment-related) when compared with participants who received standard wound care alone. However, there was no significant difference in those who experienced a burning sensation (treatment-related). (Low quality)*

Growth factors (TGF-β) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 48)

Diabetic foot-related outcomes:

3.5.3.16 *One RCT with 155 participants showed no significant difference in complete wound healing between participants who received TGF-β with standard wound care and participants who received standard wound care alone. (Moderate quality)*

Hyperbaric oxygen therapy (HBOT) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 49)

Diabetic foot-related outcomes:

3.5.3.17 *Five RCTs with a total number of 308 participants showed that participants who received HBOT with standard wound care were significantly less likely to have a major amputation (low quality) when compared with participants who received standard wound care alone.*

3.5.3.18 *One RCT with 100 participants showed that participants who received HBOT with standard wound care were significantly less likely to have other surgical interventions (moderate quality) when compared with participants who received standard wound care alone.*

However,

3.5.3.19 Three RCTs with a total number of 148 participants showed no significant differences in the number of minor amputations between participants who received HBOT with standard wound care and participants who received standard wound care alone. (Moderate quality).

3.5.3.20 Three RCTs with a total number of 235 participants showed no significant differences in complete wound healing between participants who received HBOT with standard wound care and participants who received standard wound care alone. (Moderate quality).

3.5.3.21 One RCT with 27 participants showed no significant difference in the reduction of ulcer surface area between participants who received HBOT with standard wound care and participants who received standard wound care alone. (Low quality)

Dermal or skin substitutes as an adjunctive treatment to standard wound care (see Summary of GRADE profile 50 and 51)

Diabetic foot-related outcomes:

3.5.3.22 Six RCTs with a total number of 871 participants showed that participants who received dermal or skin substitutes (overall) with standard wound care were significantly more likely to have complete wound healing when compared with participants who received standard wound care alone. (Moderate quality). However, when subgroup analysis was carried out on the types of dermal or skin substitutes, only Dermagraft and Graftskin achieved the above effect, not Hyalograft or human skin equivalent. (Low quality)

3.5.3.23 One RCT with 25 participants showed that participants who received Dermagraft with standard wound care were significantly more likely to achieve at least 50% wound closure when compared

with participants who received standard wound care alone. (Low quality)

However,

3.5.3.24 One RCT with 314 participants showed no significant difference in the number of surgical interventions between participants who received Dermagraft with standard wound care and participants who received standard wound care alone. (Low quality)

Adverse events:

3.5.3.25 Two RCTs with a total number of 287 participants showed no significant difference in the number of withdrawals due to ulcer-related adverse events between participants who received Graftskin/Hyalograft with standard wound care and participants who received standard wound care alone. (Low quality)

3.5.3.26 Four RCTs with a total number of 557 participants showed that participants who received Dermagraft/Graftskin with standard wound care were significantly less likely to have ulcer-related adverse events, when compared with participants who received standard wound care alone. (Low quality)

Negative pressure wound therapy (NPWT) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 52)

Diabetic foot-related outcomes:

3.5.3.27 Two RCTs with a total number of 497 participants showed that participants who received NPWT with standard wound care were significantly less likely to have an amputation, and significantly more likely to have complete wound closure, when compared with participants who received standard wound care alone . (Low quality)

3.5.3.28 One RCT with 24 participants showed that participants who received NPWT with standard wound care had a significantly

higher reduction in wound surface area, when compared with participants who received standard wound care alone. (Low quality)

3.5.3.29 *One RCT with 335 participants showed that participants who received NPWT with standard wound care had a significantly shorter time to achieve wound closure when compared with participants who received standard wound care alone. (Low quality)*

3.5.3.30 *One RCT with 162 participants showed that participants who received NPWT with standard wound care had a significantly shorter time to achieve granulation when compared with participants who received standard wound care alone. (Low quality)*

Adverse events:

3.5.3.31 *One RCT with 335 participants showed no significant differences in the number of ulcer-related adverse events between participants who received NPWT with standard wound care and participants who received standard wound care alone. (Low quality)*

3.5.3.32 *One RCT with 162 participants showed no significant differences in the number of treatment-related adverse events between participants who received NPWT with standard wound care and participants who received standard wound care alone. (Low quality)*

Electrical stimulation therapy as an adjunctive treatment to standard wound care (see Summary of GRADE profile 53)

Diabetic foot-related outcomes:

3.5.3.33 *One RCT with 40 participants (electrical stimulation) and one RCT with 30 participants (electrical shock wave therapy) showed there was no significant difference in complete wound healing between participants who received electrical stimulation therapy with standard wound care and participants who received standard wound care. (Low quality)*

3.5.3.34 The RCT with 30 participants showed that participants who received electrical shock wave therapy with standard wound care had significantly shorter healing time, when compared with participants who received standard wound care alone. (Low quality)

Autologous platelet-rich plasma gel as an adjunctive treatment to standard wound care (see Summary of GRADE profile 54)

Diabetic foot-related outcomes:

3.5.3.35 One RCT with 72 participants showed no significant differences in complete wound healing or median time to complete wound healing between participants who received autologous platelet-rich plasma gel with standard wound care and participants who received standard wound care alone. (Low quality)

Acellular dermal regenerative tissue matrix as an adjunctive treatment to standard wound care (see Summary of GRADE profile 55)

Diabetic foot-related outcomes:

3.5.3.36 One RCT with 85 participants showed that participants who received acellular dermal regenerative tissue matrix with standard wound care were significantly more likely to have complete wound healing and a faster healing rate, when compared with participants who received standard wound care alone. (Low quality)

OASIS wound matrix vs growth factor (PDGF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 56)

Diabetic foot-related outcomes:

3.5.3.37 One RCT with 73 participants showed no significant differences in complete wound healing or ulcer recurrence between participants who received OASIS wound matrix with standard wound care and participants who received PDGF with standard wound care alone. (Low quality)

RGD peptide matrix as an adjunctive treatment to standard wound care (see Summary of GRADE profile 57)

Diabetic foot-related outcomes:

3.5.3.38 *One RCT with 65 participants showed that complete wound healing in participants who received RGD peptide matrix with standard wound care was significantly higher than participants who received saline gauze with standard wound care alone. (Low quality)*

Dalteparin as an adjunctive treatment to standard wound care for diabetic patients with peripheral arterial occlusive disease (PAOD) (see Summary of GRADE profile 58)

Diabetic foot-related outcomes:

3.5.3.39 *One RCT with 85 participants showed there were no significant differences in complete wound healing, at least 50% reduction in wound size, and amputation, between participants who received dalteparin with standard wound care, and participants who received standard wound care alone. (Low quality)*

3.5.4 Health economic modelling

Negative pressure wound therapy and hyperbaric oxygen therapy.

The analysis of adjunctive therapies borrows several elements from the osteomyelitis analysis. The model structure is outlined below in figure 2HE.

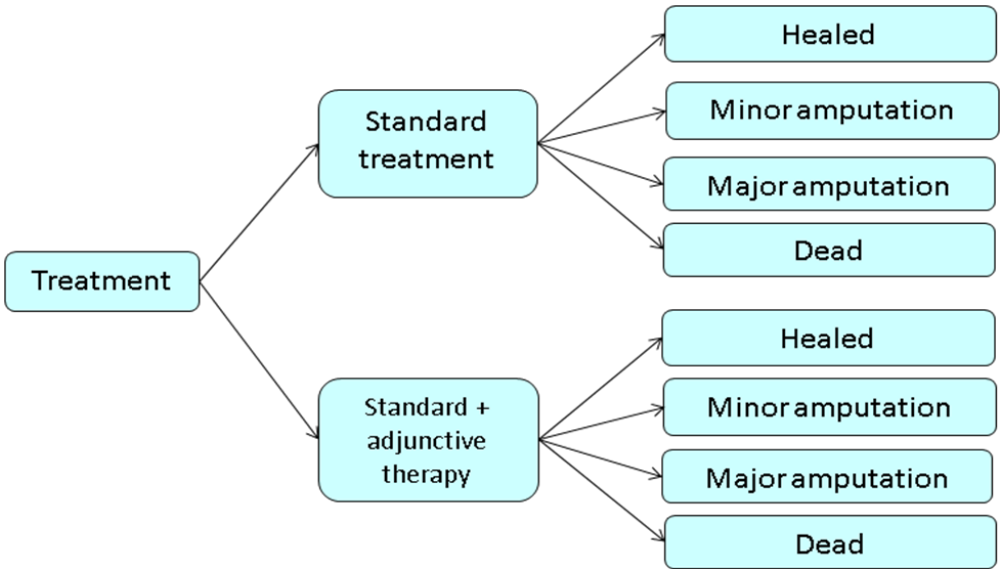


Figure 2HE: Adjunctive therapies model structure

The evidence review was once again the source of the clinical outcome data. These are reproduced in table 4HE.

Table 4HE. Clinical outcomes for adjunctive therapies

Outcome	Standard therapy	HBOT + standard therapy	NPWT + standard therapy
Healed (%)	15.6	63.2	80.34
Minor amputation (%)	35.1	13.5	3.66
Major amputation (%)	33.3	7.3	
Dead (%)	16	16	16

HBOT = hyperbaric oxygen therapy; NPWT = negative pressure wound therapy.

There was no evidence that the treatments had any effect on mortality, and there was no record of how many people actually died in the studies. Therefore, the mortality estimates were extrapolated from the cost-effectiveness study analysis (16%) and applied to the analysis. All these estimates were for 12 months.

The results for the treatments are presented below in table 5HE for negative pressure wound therapy and table 6HE for hyperbaric oxygen therapy.

Table 5HE: Cost-effectiveness results for negative pressure wound therapy (NPWT)

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
Standard	0.4740	4542	-	-	-
NPWT	0.4935	5512	0.0195	970	49691
Probabilistic					
Standard	0.4728	4550	-	-	-
NPWT	0.4923	5541	0.0195	991	50821

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Table 6HE: Cost-effectiveness results for hyperbaric oxygen therapy (HBOT)

	Cost (£)	QALY	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic					
Standard	9599.6	0.4094	-	-	-
HBOT	11250	0.4773	1650.4	0.0674	24,486
Probabilistic					
Standard	9621	0.4091	-	-	-
HBOT	11318	0.4764	1697	0.0673	25,215

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The results of the cost-effectiveness acceptability curves are presented in table 7HE.

Table 7HE: Probability of adjunctive treatments being cost effective.

Threshold	Hyperbaric oxygen therapy	Negative pressure wound therapy
£20,000	0.44	0.152
£30,000	0.54	0.264

These results indicate that NPWT is associated with ICERs above what is normally considered cost effective, and are unlikely to be cost effective. HBOT is associated with ICER between £20,000 per QALY and £30,000 per QALY and therefore, consideration must be given to issues of the uncertainty in the analysis. The probabilistic analysis indicates that HBOT has just over 50% probability of being cost effective at £30,000 per QALY threshold.

Sensitivity analysis indicated that it would be possible for the treatments to be considered cost effective if the difference in utility between healed and amputation was increased, the cost of amputations was higher and the costs of the interventions were reduced. The GDG noted the absence of long-term benefits in the analysis and considered that their inclusion would reduce the ICERs. However, the GDG considered that, given the uncertainty around the clinical estimates, the cost effectiveness of these therapies had not been demonstrated. Please see appendix I.

3.5.5 Evidence to recommendations

The clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems

Growth factors

Relative value placed on the outcomes considered

As adjunctive treatments were not considered as part of standard care and can be very costly, the GDG agreed that evidence on these adjunctive treatments needed to demonstrate positive effects on critical outcomes, such as preventing amputation or other surgical interventions, in order to warrant further discussion on recommendations.

Quality of the evidence

The GDG agreed that almost all the evidence was of low quality. From the evidence, only G-CSF demonstrated positive effects in 5 outcomes (including critical outcomes). There was no strong evidence on the clinical effectiveness of PDGF, EGF and TGF-β.

Other considerations

The GDG further discussed the applicability of G-CSF. The GDG agreed that G-CSF may not be applicable to the acute setting and care pathway of this particular guideline. G-CSF should only be applied to wounds that are stabilised and without moderate or severe infections, but by this point patients would have already been discharged back to primary or community settings. Given this lack of applicability to the acute hospital setting and the low-quality evidence, the GDG came to the consensus that G-CSF should not be offered as an adjunctive treatment for in-hospital patients, unless as part of a clinical trial. The same consensus was reached for PDGF, EGF and TGF-β.

Hyperbaric oxygen therapy (HBOT)

Relative value placed on the outcomes considered

(See the same section under Growth factors).

Quality of the evidence

The GDG agreed that the evidence was of low to moderate quality, and two out of the five outcomes demonstrated statistically significant positive effects. As HBOT has some low- to moderate-quality evidence on positive effects on

critical outcomes (reducing major amputation and other surgical interventions), a health economic evaluation should be carried out to further assess its cost effectiveness as an adjunctive treatment for diabetic foot problems.

Trade-off between net health benefits and resource use

The GDG noted that the cost-effectiveness results were between £20,000 and £30,000 per QALY gained and, therefore, required consideration of the uncertainty in the analysis. They noted the absence of long-term outcomes and the low quality of the clinical data that was used to populate the model, therefore giving highly uncertain results.

Dermal or skin substitutes

Relative value placed on the outcomes considered

(See the same section under Growth factors).

Quality of the evidence

The GDG agreed that the evidence was of low quality. When the GDG further examined the evidence, only low-quality evidence on Dermagraft and Graftskin demonstrated positive effects on complete wound healing; at least 50% wound closure; and median time to complete closure. However, no positive effect was demonstrated on the critical outcome (reduction in amputation).

Other considerations

The GDG further discussed the applicability of Dermagraft and Graftskin. The GDG agreed that Dermagraft or Graftskin should not be offered as an adjunctive treatment for in-hospital patients, unless as part of a clinical trial because of the following reasons:

- Low-quality evidence.
- Lack of evidence on critical outcomes (prevent amputation or other surgical interventions).
- High cost implications.
- Currently not widely used in the UK.

Negative pressure wound therapy (NPWT)

Relative value placed on the outcomes considered

(See the same section under Growth factors).

Quality of the evidence

The GDG agreed that the evidence was of low quality, and five out of the seven outcomes demonstrated positive effects. As NPWT has some evidence on positive effects on critical outcome (reducing amputation), a health economic evaluation should be carried out to further assess its cost effectiveness as an adjunctive treatment for diabetic foot problems.

Trade-off between net health benefits and resource use

The GDG noted the cost effectiveness results were higher than what is normally considered cost effective and considered to be highly uncertain given the absence of long-term outcomes and the low quality of the clinical data. However, the GDG considered that there was evidence of positive effects on a critical outcome, reducing amputation. There was also a recognition that this intervention is widely used and available in clinical practice, with clinical expertise supporting its success in the inpatient management of diabetic foot problems despite the limited clinical evidence available. The GDG therefore recommended the use of the intervention in the context of a clinical trial or as a rescue therapy to prevent amputation.

Other adjunctive treatments

Relative value placed on the outcomes considered

(See the same section under Growth factors).

Quality of the evidence

The GDG agreed that the evidence was very limited (very small number of studies) and was of low quality. Due to a lack of evidence, the GDG came to the consensus that electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and deltaparin should not be offered as adjunctive treatments for in-hospital patients, unless as part of a clinical trial.

3.5.6 Recommendations and research recommendations for adjunctive treatments for diabetic foot problems

Recommendations for adjunctive treatments for diabetic foot problems

Adjunctive treatments

Recommendation 1.2.35

Negative pressure wound therapy should not be routinely used to treat diabetic foot problems, but may be considered in the context of a clinical trial or as rescue therapy (when the only other option is amputation).

Recommendation 1.2.36

Do not offer the following treatments for the inpatient management of diabetic foot problems, unless as part of a clinical trial:

- Dermal or skin substitutes.
- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and deltaparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy.

Research recommendations for adjunctive treatments for diabetic foot problems

See appendix A for a list of all research recommendations.

Further research should be undertaken to determine the clinical and cost effectiveness of negative pressure wound therapy for diabetic foot problems.

Further research should be undertaken to determine the clinical and cost effectiveness of hyperbaric oxygen therapy for diabetic foot problems.

3.6 Timing for surgical management to prevent amputation

3.6.1 Review question

When is the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems?

3.6.2 Evidence review

The systematic search retrieved 9817 studies. No studies were identified that met the inclusion/exclusion (for the review protocol and inclusion/exclusion criteria, please see appendix B), therefore no studies were included.

3.6.3 Evidence statements

No studies were identified that met the inclusion/exclusion criteria; therefore no evidence statement was generated.

3.6.4 Health economic modelling

No health economic modelling was conducted for this question.

3.6.5 Evidence to recommendations

As no evidence was identified, the GDG felt that they could not make any recommendation on the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems. The GDG agreed that the current recommendation on obtaining urgent advice from an appropriate specialist experienced in managing diabetic foot problems (recommendation 1.2.16) was appropriate and sufficient in the absence of evidence.

3.6.6 Recommendations and research recommendations for timing for surgical management to prevent amputation

No recommendations have been made for this review question (see evidence to recommendations)

Research recommendations for timing for surgical management to prevent amputation

See appendix A for a list of all research recommendations.

Does early revascularisation improve outcomes in patients with diabetes and a foot ulcer? What are the best indicators of the need to revascularise the leg in patients with diabetes and a foot ulcer?

4 Notes on the scope of the guideline

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from www.nice.org.uk/guidance/CG119 – click on 'How this guidance was produced'.

5 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG119).

6 Other versions of this guideline

6.1 Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG119/QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2467).

6.2 'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG119/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2468).

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about diabetic foot problems.

7 Related NICE guidance

Published

- Anaemia management in people with chronic kidney disease. NICE clinical guideline 114 (2011). Available from www.nice.org.uk/guidance/CG114
- Venous thromboembolism: reducing the risk. NICE clinical guideline 92 (2010). Available from www.nice.org.uk/guidance/CG92
- Type 2 diabetes: newer agents. NICE clinical guideline 87 (2009). Available from www.nice.org.uk/guidance/CG87
- Surgical site infection. NICE clinical guideline 74 (2008). Available from www.nice.org.uk/guidance/CG74
- Chronic kidney disease. NICE clinical guideline 73 (2008). Available from www.nice.org.uk/guidance/CG73
- Lipid modification. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
- Type 2 diabetes (update). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/guidance/CG66
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from www.nice.org.uk/guidance/CG50
- Pressure ulcers. NICE clinical guideline 29 (2005). Available from www.nice.org.uk/guidance/CG29
- Type 1 diabetes. NICE clinical guideline 15 (2004). Available from www.nice.org.uk/guidance/CG15
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10
- Preoperative tests. NICE clinical guideline 3 (2003). Available from www.nice.org.uk/guidance/CG3

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Type 2 diabetes: preventing pre-diabetes in adults. NICE public health guidance. Publication expected June 2011.

- Type 2 diabetes: preventing the progression from pre-diabetes. NICE public health guidance. Publication expected May 2012.
- Lower limb peripheral arterial disease. NICE clinical guideline. Publication expected October 2012.

8 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

9 Contributors

The Guideline Development Group

Peter Barry - GDG Chair

Consultant in Paediatric Intensive Care, University Hospitals of Leicester NHS Trust and Honorary Senior Lecturer, Department of Child Health, University of Leicester

Amanda Adler

Consultant Physician, Addenbrooke's Hospital

Anthony Berendt

Consultant Physician, Nuffield Orthopaedic Centre

Mark Collier

Nurse Consultant - Tissue Viability, United Lincolnshire Hospitals NHS Trust

Sunil Dhar

Consultant Orthopaedic Surgeon, University Hospitals of Nottingham

Nirupam Goenka

Consultant Physician, Countess of Chester NHS Foundation Trust

Katherine Hill

Patient member

Gerry Rayman

Consultant Physician, Ipswich Hospital NHS Trust

Clifford Shearman

Professor of Vascular Surgery/Consultant Vascular Surgeon, University of Southampton, Southampton General Hospital

Louise Stuart

Consultant Podiatrist, NHS Manchester

Gloria Travers

Patient member

The Short Clinical Guidelines Technical Team

A Short Clinical Guidelines Technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments. The following NICE employees made up the technical team for this guideline.

Lynda Ayiku
Information Specialist

Michael Heath
Programme Manager

Kim Jeong
Technical Analyst (Health Economics)

Prashanth Kandaswamy
Technical Adviser (Health Economics)

Victoria Kelly
Project Manager

Yaminah Rajput (2009-2010)
Assistant Technical Analyst (Health Economics)

Beth Shaw
Technical Adviser

Faisal Siddiqui
Assistant Technical Analyst

Toni Tan
Technical Analyst (2009-2010)

The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

Mike Drummond - Chair
Director, Centre for Health Economics, University of York

Catherine Arkley
Lay member

Sarah Fishburn
Lay member

Ruth Stephenson
Consultant in Anaesthetics Clinical Ethics Lead, NHS Grampian

NICE Centre for Clinical Practice

Sharon Summers-Ma
Associate Director

Rachel Ryle
Guideline Commissioning Manager (from September 2010)

Claire Turner
Guidelines Commissioning Manager (until August 2010)

Emma Banks
Guideline Coordinator

Editors

Sarah Palombella

Senior Medical Editor

Alan Pedder

Medical Editor

Declarations of interests

For the declarations of interests of all the contributors to this guideline, see www.nice.org.uk/guidance/CG119

Diabetic foot problems: inpatient management of diabetic foot problems

NICE guideline

Guideline Appendices

Content

Appendix A Scope
Appendix B List of all research recommendations
Appendix C Guideline development methods (search strategies and review protocols)
Appendix D References of all included studies
Appendix E Full GRADE evidence profiles
Appendix F Results of individual studies (Review question 2)
Appendix G Summary of ROC and forest plots (Review question 2)
Appendix H Van der Bruel plots (Review question 2)
Appendix I Meta-analysis and forest plots (Review question 3 and 5)
Appendix J Full health economic models
Appendix K Evidence tables
Appendix L List of excluded studies
Appendix M Glossary and abbreviations
Appendix N Declaration of interests
Appendix O Authorship and citation

Appendix A Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

DRAFT SCOPE

1 Guideline title

Diabetic foot problems: inpatient management of diabetic foot problems

1.1 Short title

Diabetic foot problems.

2 The remit

The Department of Health has asked NICE: 'To produce a short clinical guideline on the inpatient management of diabetic foot problems'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Diabetes mellitus is one of the most common chronic diseases in the UK and its prevalence is increasing. By 2025 it is estimated that more than 4 million people will have diabetes. In 2009 in the UK, the number of people estimated to have either type 1 or type 2 diabetes was 2.6 million, a prevalence of 4%, with 1.9 million actually being registered as having diabetes. Type 2 diabetes is up to six times more common in people of South Asian descent, and up to three times more common in people of African and African-Caribbean origin. The life expectancy of people with diabetes is shortened by up to 15 years, and 75% die of macrovascular complications.

b) The annual incidence of diabetic foot ulceration in the UK varies from 1.0 to 3.6%, with a prevalence of 5%. At some point in their lives 15% of people with diabetes will have a diabetic foot ulcer, although recent studies suggest that the lifetime risk may be as high as 25%. The number of people with diabetic

foot ulcers is expected to increase as the number of people with diabetes increases.

c) Diabetes is the most common cause of non-traumatic limb amputation, with diabetic foot ulcers preceding more than 80% of amputations in people with diabetes. After a first amputation, people with diabetes are twice as likely to have a subsequent amputation as people without diabetes. Mortality rates after diabetic foot ulceration and amputation are high, with up to 70% of people dying within 5 years of having an amputation. Although people of South Asian descent and people of African and African-Caribbean origin are more at risk of diabetes, there is no evidence that the prevalence of diabetic foot ulceration and amputation is higher in these subgroups than in the general population of people with diabetes in the UK.

d) Diabetic foot problems are predominantly a result of either diabetic neuropathy (nerve damage or degeneration) or peripheral vascular disease (poor blood supply because of disease of the large and medium sized blood vessels in the legs) or a combination of the two. Diabetic foot problems have a significant financial impact on the NHS through primary care, outpatient costs, increased bed occupancy and prolonged stays in hospital.

3.2 Current practice

a) Despite the publication of strategies on commissioning specialist services for the management and prevention of diabetic foot problems in hospital ('Putting feet first', Diabetes UK 2009; 'Improving emergency and inpatient care for people with diabetes', Department of Health 2008), there is variation in practice in the inpatient management of diabetic foot problems. This variation results from a wide variety of factors. These include the varying levels of organisation of care for people with diabetes and diabetic foot problems between admission to an acute care setting and discharge. This variability depends on geography, individual trusts, individual specialties (such as whether the service is managed by vascular surgery, general surgery, orthopaedics, diabetologists, general physicians) and availability of podiatrists with expertise in diabetic foot disease.

b) Amputation rates vary up to fourfold in the UK because of a variety of factors, including varying professional opinions within the field. Also, the management of infection in the diabetic foot is not consistent because hospitals have different antimicrobial protocols for diabetic foot ulcers.

c) A previous NICE clinical guideline on prevention and management of foot problems in type 2 diabetes (NICE clinical guideline 10, 2004) concentrated on the detection, general management and treatment of diabetic foot ulcers and the care pathway ends at referral to a multidisciplinary foot care team. There is currently no evidence-based clinical guideline for use in England, Wales and Northern Ireland that provides detailed recommendations on the key components of inpatient care of people with diabetic foot problems from hospital admission onwards.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 years and older) with or at a particular high risk[1] of diabetic foot problems admitted to hospital.

b) No patient subgroups have been identified as needing specific consideration.

4.1.2 Groups that will not be covered

a) Children (younger than 18 years).

[1] 'High risk' as defined in NICE clinical guideline 10.

4.2 Healthcare setting

a) Inpatient secondary care and tertiary care.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

- Key components and organisation of patient hospital care for diabetic foot promblems from hospital admission to discharge planning.
- Assessment and investigation of diabetic foot problems[2], including vascular and orthopaedic investigations when appropriate, and referral to specialist care and treatment within hospital
- Clinical and cost-effectiveness of treatments for diabetic foot problems, including:
  - surgical or non-surgical debridement, wound dressings, off-loading (removal of weight bearing)
  - antibiotic regimens and antimicrobial therapy for infected diabetic foot problems (with or without osteomyelitis)
  - other adjunctive treatments, including dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy, electrical stimulation
  - optimal timing for other clinical interventions, including revascularisation and orthopaedic interventions, to prevent amputation.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

[2] Recommendations on foot examination and risk identification in this section will cross-refer to NICE clinical guideline 10.

4.3.2 Clinical issues that will not be covered

a) Diabetic foot examination and risk classification (this is covered in NICE clinical guideline 10).

b) Surgical procedures for amputation.

c) Treatment of physical morbidity (e.g. specialist footwear) and rehabilitation as a result of diabetic foot problems or after amputation.

d) Treatment of peripheral vascular disease (other than timings of revascularisation for people with diabetic foot problems).

e) Treatment of Charcot osteoarthropathy (other than timings of orthopaedic interventions for people with diabetic foot problems).

f) Treatment of diabetic neuropathy.

g) General management of diabetes, co-morbidities and complications of diabetes other than diabetic foot problems.

4.4 Main outcomes

a) Rates and extent of amputation (major or minor).

b) Length of hospital stay.

c) Rates of hospital readmission.

d) Mortality.

e) Health related quality of life (QoL) of people with diabetic foot problems. Ideally this will include data from validated generic instruments such as the EQ-5D that are able to provide a single index value of health status (on a scale of 0 to 1). Generic health survey questionnaire data, such as from the Short Form 36, may also be appropriate.

f) Complications.

g) Adverse effects of treatment.

h) Resource use and costs.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and costs will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see section 6, 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in April 2010.

5 Related NICE guidance

5.1 Published guidance

5.1.1 Other related NICE guidance

- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10
- Type 2 diabetes: newer agents. NICE clinical guideline 87 (2009). Available from www.nice.org.uk/guidance/CG87
- Surgical site infection. NICE clinical guideline 74 (2008). Available from www.nice.org.uk/guidance/CG74
- Lipid modification. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
- Type 2 diabetes (update). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/guidance/CG66

- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from www.nice.org.uk/guidance/CG50
- Venous thromboembolism (surgical). NICE clinical guideline 46 (2007). Available from www.nice.org.uk/guidance/CG46
- Type 1 diabetes. NICE clinical guideline 15 (2004). Available from www.nice.org.uk/guidance/CG15
- Preoperative tests. NICE clinical guideline 3 (2003). Available from www.nice.org.uk/guidance/CG3

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website).

- Lower limb peripheral arterial disease. NICE clinical guideline. Publication date expected October 2012. .
- Type 2 diabetes: preventing pre-diabetes in adults. NICE public health guidance. Publication expected June 2011.

Type 2 diabetes: preventing the progression from pre-diabetes. NICE public health guidance. Publication expected May 2012.

6 Further information

Information on the guideline development process is provided in:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS’
- ‘The guidelines manual’.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

Further research should be undertaken to determine the clinical and cost effectiveness of the following therapies; negative pressure wound therapy, total contact casting, hyperbaric oxygen therapy and surgical debridement for diabetic foot problems

The majority of major limb amputations occur in people with diabetes. In 85% of cases this is preceded by a non-healing ulcer or foot wound on the feet of people with diabetes are recognised as problematic to heal. Delayed healing results in inconvenience an increased morbidity, risk of amputation for patients, increased use of wound healing products and increased length of hospital stay. There is a need to improve the rate and success of wound healing in this patient group. Topical negative pressure therapy (TNP), Total Contact Casting (TCC), Hyperbaric Oxygen Therapy (HBOT) and Surgical Debridement is widely used and held to be an advantage by many health care professionals. However there is no convincing evidence to support its use. It can be expensive, requires trained personnel to administer the intervention and may require the patient to remain in hospital during treatment if it is not available in the community.

A randomised clinical trial enrolling only patients with diabetic foot problems receiving HBOT is required to assess the costs associated with this intervention.

What is the optimum wound-healing environment and what is the optimum dressing to treat diabetic foot ulcers?

Nearly all patients admitted to hospital with a Diabetic Foot Problem will either already have or shortly following admission have (as a result of a planned intervention) a wound which requires an appropriate wound dressing. Despite numerous articles having been written describing the benefits of a range of interactive wound management materials on a range of wounds, these have generally been on chronic wounds such as leg ulcers and pressure ulcers and have not been specifically tested on patients with diabetic foot wounds. It is therefore difficult to extrapolate any findings to this specific patient group due to the diversity of the concomitant conditions that may be present at the same time

as the wound. In addition, these reports have usually been derived from either a single or multiple case study design and have been non-comparative. To date there is little evidence to confirm what is the best environment for healing to take place within a wound on a patients diabetic foot, or to support which is / are the best wound management material(s) to support the natural healing process. Whilst there has been a little research undertaken comparing traditional wound dressings materials (gauze based) with more modern interactive materials (alginates / hydrocolloids) to date this has been inconclusive and generally of poor quality. A randomised clinical trial enrolling only patients with diabetic foot problems receiving an optimal dressing type is required to assess the costs associated with this intervention.

Does early revascularisation improve outcome in patients with diabetes and a foot ulcer?

Peripheral arterial disease (PAD) is very common in patients with diabetes and reduces the blood supply to the limb. It is easy to identify PAD by non-invasive imaging but this does not indicate whether revascularisation is indicated as the patients may have compensated for the PAD with collaterals (side channels) and have adequate circulation to heal the wound. Revascularisation procedures such as angioplasty and bypass surgery are invasive, carry risk and are costly. However, delay in revascularisation is associated with worse outcomes and increases risk of limb loss. There is no evidence for the best type of re-vascularisation procedure or of the optimum time to carry this out in patients with diabetes. There is no evidence or consensus which patients with diabetes and foot wounds need the circulation to their leg improving (revascularisation) to allow healing of their foot wound. Reduced blood supply impairs wound healing. Patients with diabetes and foot complications in the presence of reduced circulation have the worst prognosis of all such patients and are the most likely to suffer amputation. A randomised clinical trial enrolling only patients with diabetic foot problems receiving an early revascularisation is required to assess the costs associated with this intervention.

What are the best indicators of the need to revascularise the leg in patients with diabetes and a foot ulcer?

Peripheral arterial disease (PAD) is very common in patients with diabetes and reduces the blood supply to the limb. It is easy to identify PAD by non-invasive imaging but this does not indicate whether revascularisation is indicated as the patients may have compensated for the PAD with collaterals (side channels) and have adequate circulation to heal the wound.

Revascularisation procedures such as angioplasty and bypass surgery are invasive, carry risk and are costly. However, delay in revascularisation is associated with worse outcomes and increases risk of limb loss. There is no evidence or consensus on which patients with diabetes and foot wounds need the circulation to their leg improving (revascularisation) to allow healing of their foot wound. A prospective study enrolling only patients with diabetic foot problems looking at the best indicators of the need to revascularise is required to assess the costs associated with this intervention.

Appendix C Guideline development methods

This guideline was developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

Search strategies

MEDLINE search strategies for the 'Diabetic foot problems' guideline

Search strategies

Scoping searches

- Scoping searches were undertaken on the following websites and databases (listed in alphabetical order) in November 2009 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

• **Guidelines/websites**	• **Systematic reviews/economic evaluations**
• 3M Health Care Ltd • Abbott Vascular • American Association of Clinical Endocrinologists • American College of Foot and Ankle Surgeons • American College of Physicians - Diabetes portal (foot problems) • American Diabetes Association	• BMJ Clinical Evidence • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • Health Economic Evaluations Database (HEED) • Health Technology Assessment (HTA) Database • NHS Economic Evaluation

• American Podiatric Medical Association • American Professional Wound Care Association (APWCA) • Ark Therapeutics • Association For The Advancement of Wound Care (AAWC) • Association of British Clinical Diabetologists ABCD • Australian Diabetes Society • Australasian Podiatry Council • Australian Wound Management Association • Boston Scientific • British Medical Association (BMA) • British Society for Antimicrobial Chemotherapy • British Society for Paediatric Endocrinology and Diabetes (BSPED) • Canadian Association of Wound Care • Canadian Diabetes	Database (NHS EED) • NHS R&D Service Delivery and Organisation (NHS SDO) Programme • National Institute for Health Research (NIHR) Health Technology Assessment Programme • TRIP Database

Association • Canadian Medical Association Infobase • Centers for Disease Control and Prevention website (US) • Clinical Knowledge Summaries • ConvaTec • Cordis (Johnson & Johnson) • Department of Health • Diabetes 1.org • Diabetes Australia • Diabetes Federation of Ireland • Diabetes Lower Extremity Research Group – DIALEX • Diabetes Network • Diabetes New Zealand • Diabetes UK • The Diabetic Foot: a resource for health care professionals • Diabetic Foot Online • European Association for the Study of Diabetes • European Pressure Ulcer Advisory Panel	

• European Tissue Repair Society • European Wound Management Association • Foot.com • Foot in Diabetes (UK) • Guidelines International Network (GIN) • International Diabetes Federation • International Diabetes Institute • International Working Group on the Diabetic Foot • Joslin Diabetes Center • KCI Medical Ltd • Molnlycke Health Care • National Audit Office • National Center for Chronic Disease Prevention and Health Promotion: Diabetes Public Health Resource • National Diabetes Education Initiative • National Diabetes Information	

Clearinghouse (NDIC) • National Guideline Clearing House (US) • National Health and Medical Research Council (Australia) • National Institute for Health and Clinical Excellence (NICE) - published & in development • National Institute for Health and Clinical Excellence (NICE) - Topic Selection • National Institute for Innovation and Improvement • NHS Diabetes/National Diabetes Support Team • NHS Evidence – National Library of Guidelines • NHS Evidence - Specialist Collections • New Zealand Guidelines Group • Oxford International Wound Foundation • The Podiatry Institute USA • Royal College of General Practitioners	

• Royal College of Nursing • Royal College of Paediatrics and Child Health • Royal College of Physicians • Royal College of Surgeons • Scottish Diabetes Specialist Podiatrists (SDSP) • Scottish Intercollegiate Guidelines Network (SIGN) • The Society of Chiropodists and Podiatrists • Society for Endocrinology, Metabolism and Diabetes Of South Africa • South African Diabetic Foot Working Group • Tissue Viability Society • World Diabetes Foundation • World Health Organisation (WHO) – Diabetes • World Union of Wound Healing Societies • World Wide Wounds • Wound Care Information	

Network • Wound Care Institute • Wound Care Society • The Wound Healing Research Unit • Wound Management Association of Ireland • Wounds UK	

Main searches

Sources searched for the guideline

- Allied and Complementary Medicine Database – AMED (HDAS/Search 2)
- British Nursing Index – BNI (HDAS/Search 2)
- Health Business Elite (HDAS/Search 2)
- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley and CRD website)
- Health Technology Assessment Database – HTA (Wiley and CRD website)
- Cumulative Index to Nursing and Allied Health Literature - CINAHL (HDAS/Search 2)
- EMBASE (Ovid)
- Health Management Information Consortium - HMIC (HDAS/Search 2)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PsycINFO (Ovid)

Identification of evidence on diabetic foot problems

- The searches were conducted between the 24th-25th of February 2010. The aim of the searches was to identify evidence on diabetic foot problems.
- The MEDLINE search strategy is presented below. It was translated for use in all of the other databases.

Database: Ovid MEDLINE(R) <1950 to February Week 2 2010>

- 1 Diabetic Foot/
- 2 (diabet$ and (foot$ or feet$)).tw.
- 3 1 or 2

Economic evaluations and quality of life data

Sources searched to identify economic evaluations

- NHS Economic Evaluation Database – NHS EED (Wiley and CRD website
- Health Economic Evaluations Database – HEED (Wiley)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Identification of health economics and quality of life studies on diabetic foot problems

- The searches were undertaken between 25th February – 3rd March 2010. The MEDLINE search strategy that was used is presented in the section above (**Identification of evidence on diabetic foot problems**). Search filters to retrieve economic evaluations and quality of life papers were appended to the search strategies to identify relevant evidence. The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

- **Economic evaluations**

  1 Economics/
  2 exp "Costs and Cost Analysis"/
  3 Economics, Dental/
  4 exp Economics, Hospital/
  5 exp Economics, Medical/
  6 Economics, Nursing/
  7 Economics, Pharmaceutical/
  8 Budgets/

9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj2 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj2 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

- **Quality of life**
  1 "Quality of Life"/
  2 quality of life.tw.
  3 "Value of Life"/
  4 Quality-Adjusted Life Years/
  5 quality adjusted life.tw.
  6 (qaly$ or qald$ or qale$ or qtime$).tw.
  7 disability adjusted life.tw.
  8 daly$.tw.
  9 Health Status Indicators/
  10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
  11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Review protocols and clinical questions

Review Protocol

List of Key Clinical Issues and Review Questions

Key Clinical Issues	Review Questions
Key components and organisation of hospital care throughout the care pathway from hospital admission to discharge planning, including: • Assessment and investigation of diabetic foot problems , including vascular and orthopaedic investigations when appropriate, and timing for referral to specialist care and treatment within hospital • Clinical and cost-effectiveness of treatments for diabetic foot problems, including: – surgical or non-surgical debridement, wound dressings, off-loading (removal of weight bearing) – antibiotic regimens and antimicrobial therapy for infected diabetic foot problems (with or without osteomyelitis) – other adjunctive treatments, including dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy, electrical stimulation – timing for surgical management, including revascularisation and orthopaedic interventions, to prevent amputations.	***Review question 1:*** *What are the key components and organisations of hospital care to ensure optimal management of people with diabetic foot problems?* ***Review question 2:*** *What are the clinical utilities of different assessment,investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?* ***Review question 3:*** *What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading in treating diabetic foot problems?* ***Review question 4:*** *What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)?* ***Review question 5:*** *What is the clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems, for example, dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy and electrical stimulation?* ***Review question 6:*** *When is the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems?*

Review Protocol

	Details	Notes & Status
1. Review question 1	*What are the key components and organisations of hospital care to ensure optimal management of people with diabetic foot problems?*	
2. Objectives	To identify best practice and organisation of hospital care for diabetic foot problems.	
3. Language	*English only*	
4. Study design	*No restrictions.*	Any studies that addressed service delivery issues.
5. Status	*Published papers (full papers only)*	
6. Population & Healthcare setting	Inclusion: • Adults (18 and older) with or at a particular high risk of diabetic foot problems. Setting: • Secondary and tertiary care	
7. Intervention	• Key components of hospital care for diabetic foot problems • Service organisations and delivery of hospital care, from hospital admission to discharge planning, for diabetic foot problems.	
8. Comparisons	N/A	
9. Outcomes	• Rates and extent of amputation (major or minor) • Length of hospital stay • Rates of hospital readmission • Mortality • Health related quality of life (QoL) • Complications • Patient's satisfaction	
10. Other criteria for inclusion/ exclusion of studies	*Exclusion:* • *Studies on children (younger than 18)* • *Studies on key components and organizations of primary care.* • *Studies on key components and organizations of hospital care in different healthcare systems that were not applicable to the NHS.* • *Studies on care standards for general management of diabetes, comorbidities and complications of diabetes (other than diabetic foot problems).* • *Studies on key components and organizations of hospital care of other foot diseases (other than diabetic foot problems).*	
11. Search strategies	Please see previous section.	

12. Review strategies	• *Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.* • *Data on all included studies will be extracted into evidence tables.* • *Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.* • *All key outcomes from evidence will be presented in GRADE profiles, or modified evidence profiles, and further summarised in evidence statements.*	

	Details	Notes & Status
1. Review question 2	*What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?*	
2. Objectives	To identify best assessment and investigation strategies/routines for diabetic foot to ensure timely treatment.	
3. Language	*English only.*	
4. Study design	*Cross-sectional studies, case-control studies, RCTs, Cohort studies*	
5. Status	*Published papers (full papers only)*	
6. Population & Healthcare setting	Inclusion: • Adults (18 and older) with or at a particular high risk of diabetic foot problems. Setting: • Secondary and tertiary care	
7. Intervention	N/A	
8. Comparisons	Actual event rates, or appropriate reference standards (if available)	
9. Outcomes	• Diabetic foot problems: event rates of infection, serious ulceration, Charcot foot, peripheral vascular disease. Clinical utility or diagnostic test accuracy (if available) including: • test validity such as Face validity, Content validity, Construct validity, Concurrent validity, Criterion validity; • test reliability such as Internal reliability/consistency, Test-retest reliability, Inter-rater reliability. • sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio and area under the ROC analyses.	*Since the review question is more about clinical/test utility, not just 'diagnostic accuracy', studies that reported test validity (eg: face validity, content validity, construct validity, criterion validity) and test reliability (eg: internal reliability/consistency, test-retest reliability, inter-rater reliability) are also included.*
10. Other criteria for inclusion/ exclusion of studies	*Exclusion:* • *Initial diagnosis and classification of diabetic foot.* • *Assessment and investigation strategies/routines for children (younger than 18)* • *Assessment and investigation strategies/routines developed/derived outside adult diabetic foot population.* • *Assessment and investigation strategies/routines for other foot diseases/problems (other than*	

	diabetic foot problems) • *Assessment and investigation strategies/routines for primary care*	
11. Search strategies	Please see previous section.	
12. Review strategies	• *The NICE Methodology Checklist (QUADAS) will be used as a guide to appraise the quality of individual studies.* • *Data on all included studies will be extracted into evidence tables.* • *Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.* • *All key outcomes from evidence will be presented in GRADE profiles, or modified evidence profiles, Van der Bruel plots and further summarised in evidence statements.*	Due to significant heterogeneity, meta-analysis was not conducted.

	Details	**Notes & Status**
1. Review question 3	*What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading in treating diabetic foot problems?*	
2. Objectives	To identify the most effectiveness wound management for diabetic foot problems.	
3. Language	*English only*	
4. Study design	*RCT only.*	
5. Status	*Published papers (full papers only)*	
6. Population & Healthcare setting	Inclusion: • Adults (18 and older) with or at a particular high risk of diabetic foot problems. Setting: • Secondary and tertiary care	
7. Intervention	• surgical or non-surgical debridement • wound dressings • off-loading	
8. Comparisons	• Sham treatment (control); no treatment; standard care • Head-to-head comparisons of the above interventions	
9. Outcomes	• Rates and extent of amputation (major or minor) • Length of hospital stay • Rates of hospital readmission • Mortality • Health related quality of life (QoL) • Complications [or other diabetic foot related outcomes]	
10. Other criteria for inclusion/ exclusion of studies	*Exclusion:* • *Studies on children (younger than 18)* • *Non-randomised trials*	

	• *RCTs with < 10 study sample* • *Crossover studies with no washout period and no carry over effects analysis* • *Studies on other wound management (other than those listed in section 7)* • *Studies on wound management for other conditions/diseases (other than diabetic foot problems)* • *Studies on wound management specific for primary care.*	
11. Search strategies	Please see previous section.	
12. Review strategies	• *Data on all included studies will be extracted into evidence tables.* • *Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.* • *All key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.*	

	Details	**Notes & Status**
1. Review question 4	*What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)?*	
2. Objectives	To identify the most cost-effective treatment for infected diabetic foot problems.	
3. Language	*English only*	
4. Study design	*RCT only*	
5. Status	*Published papers (full papers only)*	
6. Population & Healthcare setting	Inclusion: • Adults (18 and older) with or at a particular high risk of diabetic foot problems. Setting: • Secondary and tertiary care	
7. Intervention	Antibiotic regimens for infected diabetic foot Antimicrobial therapies for infected diabetic foot	
8. Comparisons	• Placebo (control); no treatment; standard care • Head-to-head comparisons of the above interventions	
9. Outcomes	• Rates and extent of amputation (major or minor) • Length of hospital stay • Rates of hospital readmission • Mortality • Health related quality of life (QoL) • Complications [or other diabetic foot related outcomes]	
10. Other criteria for inclusion/ exclusion of	*Exclusion:* • *Studies on children (younger than 18)* • *Non-randomised trials*	

studies	• *RCTs with < 10 study sample* • *Crossover studies with no washout period and no carry over effects analysis* • *Studies on antibiotics and antimicrobial therapies for other infections (other than infected diabetic foot)*	
11. Search strategies	Please see previous section.	
12. Review strategies	• *Data on all included studies will be extracted into evidence tables.* • *Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.* • *All key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.*	

	Details	**Notes & Status**
1. Review question 5	*What is the clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems, for example, dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy and electrical stimulation?*	
2. Objectives	To identify the most cost-effective adjunctive treatment for diabetic foot problems.	
3. Language	*English only*	
4. Study design	*RCT only*	
5. Status	*Published papers (full papers only)*	
6. Population & Healthcare setting	Inclusion: • Adults (18 and older) with or at a particular high risk of diabetic foot problems. Setting: • Secondary and tertiary care	
7. Intervention	• Dermal or skin substitutes • Growth factors • Hyperbaric oxygen therapy • Bio-debridement • Topical negative pressure therapy • Electrical stimulation • *[and other adjunctive treatments identified]* • Above listed as combination therapy (with antibiotics, antimicrobial therapy or wound management)	
8. Comparisons	• Placebo or sham treatment (control); no treatment; standard care • As combination therapy (with antibiotics, antimicrobial therapy or wound management) compared to antibiotics, antimicrobial therapy or wound management alone. • Head-to-head comparisons of the above interventions	
9. Outcomes	• Rates and extent of amputation (major or minor) • Length of hospital stay	

	• Rates of hospital readmission • Mortality • Health related quality of life (QoL) • Complications [or other diabetic foot related outcomes]	
10. Other criteria for inclusion/ exclusion of studies	<u>*Exclusion:*</u> • *Studies on children (younger than 18)* • *Non-randomised trials* • *RCTs with < 10 study sample* • *Crossover studies with no washout period and no carry over effects analysis* • *Studies on adjunctive therapies for other conditions/diseases (other than diabetic foot problems)*	
11. Search strategies	Please see previous section.	
12. Review strategies	• *Data on all included studies will be extracted into evidence tables.* • *Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.* • *All key outcomes from evidence will be presented in GRADE profiles and further summarised in evidence statements.*	

	Details	**Notes & Status**
1. Review question 6	*When is the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems?*	
2. Objectives	To identify the optimal time for referral to surgical management to prevent amputation.	
3. Language	*English only*	
4. Study design	*RCTs and observational studies, excluding case series, case report and qualitative studies.*	
5. Status	*Published papers (full papers only)*	
6. Population & Healthcare setting	<u>Inclusion:</u> • Adults (18 and older) with or at a particular high risk of diabetic foot problems. <u>Setting:</u> • Secondary and tertiary care	
7. Intervention	• Early (optimal timing[1]) referrals to surgical management (including revascularization and orthopaedic interventions) for diabetic foot problems.	
8. Comparisons	• Late[1] referrals or no referral to surgical management for diabetic foot problems.	
9. Outcomes	• Rates and extent of amputation (major or minor) • Length of hospital stay • Rates of hospital readmission • Mortality	

	• Health related quality of life (QoL) • Complications [or other diabetic foot related outcomes]	
10. Other criteria for inclusion/ exclusion of studies	<u>*Exclusion:*</u> • *Studies on children (younger than 18)* • *Studies on the clinical effectiveness of different surgical procedures for diabetic foot problems.* • *Studies on optimal timing for surgical management for other foot diseases (other than diabetic foot problems).*	
11. Search strategies	Please see previous section.	
12. Review strategies	• *Appropriate NICE Methodology Checklists, depending on study designs, will be used as a guide to appraise the quality of individual studies.* • *Data on all included studies will be extracted into evidence tables.* • *Where statistically possible, a meta-analytic approach will be used to give an overall summary effect.* • *All key outcomes from evidence will be presented in GRADE profiles, or modified evidence profiles, and further summarised in evidence statements.*	

Appendix D References of all included studies

Review question 1 and 2

Total number of studies retrieved from searches = 9817	
Selection based on title and abstract = 318 (full papers ordered)	Excluded = 9499
Selection based on full papers = 40	Excluded = 278
Total number of studies included = 40	

Review question 3, 4 and 5

Total number of studies retrieved from searches = 9817	
Selection based on title and abstract = 320 (full papers ordered)	Excluded = 9497
Selection based on full papers = 64	Excluded = 256
Total number of studies included = 64	

Review question 6:

Total number of studies retrieved from searches = 9817	
Selection based on title and abstract = 111 (full papers ordered)	Excluded = 9706
Selection based on full papers = 0	Excluded = 111
Total number of studies included = 0	

Reference List

Afshari M, Larijani B, Fadayee M et al. (2005) Efficacy of topical epidermal growth factor in healing diabetic foot ulcers. Therapy 2: 759-65.

Al-Khawari HA, Al-Saeed OM, Jumaa TH et al. (2005) Evaluating diabetic foot infection with magnetic resonance imaging: Kuwait experience. Medical Principles & Practice 14: 165-72.

Armstrong DG, Nguyen HC, Lavery LA et al. (2001) Off-loading the diabetic foot wound: a randomized clinical trial. [Erratum appears in Diabetes Care 2001 Aug;24(8):1509]. Diabetes Care 24: 1019-22.

Beckert S, Witte M, Wicke C et al. (2006) A new wound-based severity score for diabetic foot ulcers: A prospective analysis of 1,000 patients. Diabetes Care 29: 988-92.

Beltran J, Campanini DS, Knight C et al. (1990) The diabetic foot: magnetic resonance imaging evaluation. Skeletal Radiology 19: 37-41.

Blume PA, Walters J, Payne W et al. (2008) Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care 31: 631-6.

Bouter KP, Visseren FLJ, Van Loenhout RMM et al. (1996) Treatment of diabetic foot infection: An open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy. International Journal of Antimicrobial Agents 7: 143-7.

Boyko EJ, Ahroni JH, Davignon D et al. (1997) Diagnostic utility of the history and physical examination for peripheral vascular disease among patients with diabetes mellitus. Journal of Clinical Epidemiology 50: 659-68.

Canavan RJ, Unwin NC, Kelly WF et al. (2008) Diabetes- and nondiabetes-related lower extremity amputation incidence before and after the introduction of better organized diabetes foot care: continuous longitudinal monitoring using a standard method. Diabetes Care 31: 459-63.

Caravaggi C, Faglia E, De GR et al. (2000) Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. Diabetes Care 23: 1746-51.

Caravaggi C, De GR, Faglia E (2001) A multicenter, randomized controlled clinical trial to evaluate the efficacy of hyaluronan based dermal and epidermal autologous grafts in the treatment of diabetic foot ulcers. Diabetic Foot Study Group of the EASD : A30.

Caravaggi C, De GR, Pritelli C et al. (2003) HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial. Diabetes Care 26: 2853-9.

Crane M, Werber B, Lavery LA (1999) Critical pathway approach to diabetic pedal infections in a multidisciplinary setting. Journal of Foot and Ankle Surgery 38: 82-3.

Croll SD, Nicholas GG, Osborne MA et al. (1996) Role of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. Journal of Vascular Surgery 24: 266-70.

Dargis V, Pantelejeva O, Jonushaite A et al. (1998) Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration: a prospective study. 7th Malvern Diabetic Foot Conference; 1998, 13-15 May; Malvern, UK : 23.

de LF, Pellizzer G, Strazzabosco M et al. (2001) Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection. Antimicrobial Agents & Chemotherapy 45: 1094-8.

Devillers A, Moisan A, Hennion F et al. (1998) Contribution of technetium-99m hexamethylpropylene amine oxime labelled leucocyte scintigraphy to the diagnosis of diabetic foot infection. European Journal of Nuclear Medicine 25: 132-8.

Doctor N, Pandya S, Supe A (1992) Hyperbaric oxygen therapy in diabetic foot. Journal of Postgraduate Medicine 38: 112-4.

Driver VR, Madsen J, Goodman RA (2005) Reducing amputation rates in patients with diabetes at a military medical center: the limb preservation service model. Diabetes Care 28: 248-53.

Driver VR, Hanft J, Fylling CP et al. (2006) A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy/wound management 52: 68-70, 72, 74.

Duzgun AP, Satir HZ, Ozozan O et al. (2008) Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. Journal of Foot & Ankle Surgery 47: 515-9.

Edwards J, Stapley S (2010) Debridement of diabetic foot ulcers. Cochrane Database of Systematic Reviews

Erstad BL, McIntyre J (1997) Prospective, randomized comparison of ampicillin/sulbactam and cefoxitin for diabetic foot infections. Vascular Surgery 31: 419-26.

Ertugrul BM, Savk O, Ozturk B et al. (2009) The diagnosis of diabetic foot osteomyelitis: examination findings and laboratory values. Medical Science Monitor 15: CR307-CR312.

Ertugrul MB, Baktiroglu S, Salman S et al. (2006) The diagnosis of osteomyelitis of the foot in diabetes: microbiological examination vs. magnetic resonance imaging and labelled leucocyte scanning. Diabetic Medicine 23: 649-53.

Etoz A, Ozgenel Y, Ozcan M (2004) The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial. Wounds: A Compendium of Clinical Research and Practice 16: 264-9.

Faglia E, Favales F, Aldeghi A et al. (1996) Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. Diabetes Care 19: 1338-43.

Fernandez-Montequin JI, Betancourt BY, Leyva-Gonzalez G et al. (2009) Intralesional administration of epidermal growth factor-based formulation (Heberprot-P) in chronic

diabetic foot ulcer: treatment up to complete wound closure. International Wound Journal 6: 67-72.

Foster AVM, Greenhill MT, Edmonds ME (1994) Comparing two dressings in the treatment of diabetic foot ulcers. Journal of Wound Care 3: 224-8.

Ganguly S, Chakraborty K, Mandal PK et al. (2008) A comparative study between total contact casting and conventional dressings in the non-surgical management of diabetic plantar foot ulcers. Journal of the Indian Medical Association 106: 237-9+244.

Gardener SE, Hillis SL, Frantz RA (2009) Clinical signs of infection in diabetic foot ulcers with high microbial load. Biological Research for Nursing 11: 119-28.

Gentzkow G, Iwasaki S, Haynie K et al. (1996) Decreased recurrence of healed diabetic foot ulcers treated with a cultured human dermis. 2nd Joint Meeting of the Wound Healing Society and the European Tissue Repair Society; 1996, 15-17 May; Boston MA : A128.

Gough A, Clapperton M, Rolando N et al. (1997) Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. Lancet 350: 855-9.

Grayson ML, Gibbons GW, Habershaw GM et al. (1994) Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients.[Erratum appears in Clin Infect Dis 1994 Oct;19(4):820]. Clinical Infectious Diseases 18: 683-93.

Grayson ML, Gibbons GW, Balogh K et al. (1995) Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA 273: 721-3.

Hardikar JV, Reddy YC, Bung DD et al. (2005) Efficacy of recombinant human platelet-derived growth factor (rhPDGF) based gel in diabetic foot ulcers: a randomized, multicenter, double-blind, placebo-controlled study in India. Wounds: A Compendium of Clinical Research and Practice 17: 141-52.

Harkless L, Boghossian J, Pollak R et al. (2005) An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. Surgical Infections 6: 27-40.

Harvey J, Cohen MM (1997) Technetium-99-labeled leukocytes in diagnosing diabetic osteomyelitis in the foot. Journal of Foot and Ankle Surgery 36: 209-14.

Harwood SJ, Valdivia S, Hung GL et al. (1999) Use of Sulesomab, a radiolabeled antibody fragment, to detect osteomyelitis in diabetic patients with foot ulcers by leukoscintigraphy. Clinical Infectious Diseases 28: 1200-5.

Hughes CE, Johnson CC, Bamberger DM et al. (1987) Treatment and long-term follow-up of foot infections in patients with diabetes or ischemia: a randomized, prospective, double-blind comparison of cefoxitin and ceftizoxime. Clinical Therapeutics 10: Suppl-49.

Jeffcoate WJ, Price PE, Phillips CJ et al. (2009) Randomised controlled trial of the use of the three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health Technology Assessment 13(54): 1-110.

Jude EB, Apelqvist J, Spraul M et al. (2007) Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. Diabetic Medicine 24: 280-8.

Kalani M, Apelqvist J, Blomback M et al. (2003) Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. Diabetes Care 26: 2575-80.

Kaleta JL, Fleischli JW, Reilly CH (2001) The diagnosis of osteomyelitis in diabetes using erythrocyte sedimentation rate: a pilot study. Journal of the American Podiatric Medical Association 91: 445-50.

Kastenbauer T, Hornlein B, Sokol G et al. (2003) Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers. Diabetologia 46: 27-30.

Katz IA, Harlan A, Miranda-Palma B et al. (2005) A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care 28: 555-9.

Keenan AM, Tindel NL, Alavi A (1989) Diagnosis of pedal osteomyelitis in diabetic patients using current scintigraphic techniques. Archives of Internal Medicine 149: 2262-6.

Kessler L, Bilbault P, Ortega F et al. (2003) Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care 26: 2378-82.

Kreitner KF, Kalden P, Neufang A et al. (2000) Diabetes and peripheral arterial occlusive disease: prospective comparison of contrast-enhanced three-dimensional MR angiography with conventional digital subtraction angiography. AJR American: 171-9.

Lapeyre M, Kobeiter H, Desgranges P et al. (2005) Assessment of critical limb ischemia in patients with diabetes: comparison of MR angiography and digital subtraction angiography. AJR American: 1641-50.

Larcos G, Brown ML, Sutton RT (1991) Diagnosis of osteomyelitis of the foot in diabetic patients: Value of ¹¹¹In-leukocyte scintigraphy. American Journal of Roentgenology 157: 527-31.

Larsson J, Apelqvist J, Agardh CD et al. (1995) Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabetic Medicine 12: 770-6.

Levine SE, Neagle CE, Esterhai JL et al. (1994) Magnetic resonance imaging for the diagnosis of osteomyelitis in the diabetic patient with a foot ulcer. Foot & Ankle International 15: 151-6.

Lipsky BA, Pecoraro RE, Larson SA et al. (1990) Outpatient management of uncomplicated lower-extremity infections in diabetic patients. Archives of Internal Medicine 150: 790-7.

Lipsky BA, Baker PD, Landon GC et al. (1997) Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. Clinical Infectious Diseases 24: 643-8.

Lipsky BA, Itani K, Norden C et al. (2004) Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. Clinical Infectious Diseases 38: 17-24.

Lipsky BA, Berendt AR, Embil J et al. (2004) Diagnosing and treating diabetic foot infections. Diabetes/Metabolism Research and Reviews 20: S56-S64.

Lipsky BA, Armstrong DG, Citron DM et al. (2005) Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet 366: 1695-703.

Lipsky BA, Stoutenburgh U (2005) Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. Journal of Antimicrobial Chemotherapy 55: 240-5.

Lipsky BA, Giordano P, Choudhri S et al. (2007) Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-clavulanate. Journal of Antimicrobial Chemotherapy 60: 370-6.

Lipsky BA, Holroyd KJ, Zasloff M (2008) Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. Clinical Infectious Diseases 47: 1537-45.

Malabu UH, Al-Rubeaan KA, Al-Derewish M (2007) Diabetic foot osteomyelitis: usefulness of erythrocyte sedimentation rate in its diagnosis. West African Journal of Medicine 26: 113-6.

Marston WA, Hanft J, Norwood P et al. (2003) The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care 26: 1701-5.

Moretti B, Notarnicola A, Maggio G et al. (2009) The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. BMC Musculoskeletal Disorders 10: 54.

Morrison WB, Schweitzer ME, Wapner KL et al. (1995) Osteomyelitis in feet of diabetics: clinical accuracy, surgical utility, and cost-effectiveness of MR imaging. Radiology 196: 557-64.

Mueller MJ, Diamond JE, Sinacore DR et al. (1989) Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care 12: 384-8.

Naughton G, Mansbridge J, Gentzkow G (1997) A metabolically active human dermal replacement for the treatment of diabetic foot ulcers. Artificial Organs 21: 1203-10.

Newman LG, Waller J, Palestro CJ et al. (1991) Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. JAMA 266: 1246-51.

Newman LG, Waller J, Palestro CJ et al. (1992) Leukocyte scanning with 111In is superior to magnetic resonance imaging in diagnosis of clinically unsuspected osteomyelitis in diabetic foot ulcers. Diabetes Care 15: 1527-30.

Niezgoda JA, Van Gils CC, Frykberg RG et al. (2005) Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. Advances in Skin & Wound Care 18: t-66.

Oyibo SO, Jude EB, Tarawneh I et al. (2001) A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. Diabetes Care 24: 84-8.

Palestro CJ, Caprioli R, Love C et al. (2003) Rapid diagnosis of pedal osteomyelitis in diabetics with a technetium-99m-labeled monoclonal antigranulocyte antibody. Journal of Foot & Ankle Surgery 42: 2-8.

Peters EJ, Lavery LA, Armstrong DG et al. (2001) Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. Archives of Physical Medicine & Rehabilitation 82: 721-5.

Pham HT, Rosenblum BI, Lyons TE et al. (1999) Evaluation of a human skin equivalent for the treatment of diabetic foot ulcers in a prospective, randomized, clinical trial. Wounds: A Compendium of Clinical Research and Practice 11: 79-86.

Piaggesi A, Baccetti F, Rizzo L et al. (2001) Sodium carboxyl-methyl-cellulose dressings in the management of deep ulcerations of diabetic foot. Diabetic Medicine 18: 320-4.

Poirier JY, Garin E, Derrien C et al. (2002) Diagnosis of osteomyelitis in the diabetic foot with a ^{99mTc}-HMPAO leucocyte scintigraphy combined with a ^{99mTc}-MDP bone scintigraphy. Diabetes and Metabolism 28: 485-90.

Puttirutvong P (2004) Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage. Journal of the Medical Association of Thailand 87: 66-72.

Remedios D, Valabhji J, Oelbaum R et al. (1998) 99mTc-nanocolloid scintigraphy for assessing osteomyelitis in diabetic neuropathic feet. [Review] [34 refs]. Clinical Radiology 53: 120-5.

Reyzelman A, Crews RT, Moore JC et al. (2009) Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. International Wound Journal 6: 196-208.

Robson MC, Hill DP, Woodske ME et al. (2000) Wound healing trajectories as predictors of effectiveness of therapeutic agents. Archives of Surgery 135: 773-7.

Robson MC, Steed DL, McPherson JM et al. (2002) Effects of transforming growth factor ÇY2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2: 133-46.

Robson MC, Payne WG, Garner WL et al. (2005) Integrating the results of phase IV (postmarketing) clinical trial with four previous trials reinforces the position that Regranex (becaplermin) Gel 0.01% is an effective adjunct to the treatment of diabetic foot ulcers. Journal of Applied Research 5: 35-45.

Rozzanigo U, Tagliani A, Vittorini E et al. (2009) Role of magnetic resonance imaging in the evaluation of diabetic foot with suspected osteomyelitis. Radiologia Medica 114: 121-32.

Rubello D, Casara D, Maran A et al. (2004) Role of anti-granulocyte Fab' fragment antibody scintigraphy (LeukoScan) in evaluating bone infection: acquisition protocol, interpretation criteria and clinical results. Nuclear Medicine Communications 25: 39-47.

Shaw J, Hughes CM, Lagan KM et al. (2007) An evaluation of three wound measurement techniques in diabetic foot wounds. Diabetes Care 30: 2641-2.

Shone A, Burnside J, Chipchase S et al. (2006) Probing the validity of the probe-to-bone test in the diagnosis of osteomyelitis of the foot in diabetes. Diabetes Care 29: 945-6.

Shukrimi A, Sulaiman AR, Halim AY et al. (2008) A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. Medical Journal of Malaysia 63: 44-6.

Slater RA, Lazarovitch T, Boldur I et al. (2004) Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. Diabetic Medicine 21: 705-9.

Steed DL, Ricotta JJ, Prendergast JJ et al. (1995) Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. RGD Study Group. Diabetes Care 18: 39-46.

Strauss MB, Aksenov IV (2005) Evaluation of diabetic wound classifications and a new wound score. [Review] [20 refs]. Clinical Orthopaedics & Related Research 439: 79-86.

Tan JS, Wishnow RM, Talan DA et al. (1993) Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin-tazobactam versus ticarcillin-clavulanate. The Piperacillin/Tazobactam Skin and Skin Structure Study Group. Antimicrobial Agents & Chemotherapy 37: 1580-6.

Tsang MW, Wong WK, Hung CS et al. (2003) Human epidermal growth factor enhances healing of diabetic foot ulcers. Diabetes Care 26: 1856-61.

Van De Weg FB, Van Der Windt DA, Vahl AC (2008) Wound healing: total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration. Prosthetics & Orthotics International 32: 3-11.

Veves A, Falanga V, Armstrong DG et al. (2001) Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes Care 24: 290-5.

Veves A, Sheehan P, Pham HT (2002) A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Archives of Surgery 137: 822-7.

Viswanathan V, Mahesh U, Jayaraman M et al. (2003) Beneficial role of granulocyte colony stimulating factor in foot infection in diabetic patients. Journal of the Association of Physicians of India 51: 90-1.

Viswanathan V, Pendsey S, Sekar N et al. (2006) A phase III study to evaluate the safety and efficacy of recombinant human epidermal growth factor (REGEN-D 150) in healing diabetic foot ulcers. Wounds: A Compendium of Clinical Research and Practice 18: 186-96.

Wang A, Weinstein D, Greenfield L et al. (1990) MRI and diabetic foot infections. Magnetic Resonance Imaging 8: 805-9.

Weinstein D, Wang A, Chambers R et al. (1993) Evaluation of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. Foot & Ankle 14: 18-22.

Wieman TJ (1998) Clinical efficacy of becaplermin (rhPDGF-BB) gel. American Journal of Surgery 176: 74S-9S.

Williams DT, Maegele M, Gregor S et al. (2006) Negative pressure therapy in diabetic foot wounds... Armstrong DG, Lavery LA et al. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet 2005;366:1704-10. Lancet 367: 725-8.

Yonem A, Cakir B, Guler S et al. (2001) Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. Diabetes, Obesity & Metabolism 3: 332-7.

Appendix E Full GRADE evidence profiles

Review question 1: What are the key components and organisations of hospital care to ensure optimal management of people with diabetic foot problems?

GRADE profile 1: Key components of care

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Summary of results	Quality
Outcome: Amputation										
1 [Cr]	Cohort	Serious[1]	no serious	no serious	Serious[2]	none	60	25	Percentage of major amputation: Intervention = 7%, control = 29%, p = 0.02	Very low
1 [D]	Cohort	no serious	no serious	no serious	Serious[2]	none	56	89	Percentage of amputation (major and minor): Intervention = 7%, control = 13.7%	Very low
1 [L]	Cohort	Serious[1]	no serious	no serious	Serious[3]	none	294	NK[4]	The incidence of major amputations decreased by 78% from 16.1 to 3.6/100 000 (p<0.001).	Very low
1 [Ca]	Cohort	Serious[5]	no serious	no serious	Serious[6]	none	223	NK[7]	Lower extremity amputation rates: From 564.3/100,000 persons in the 1st year to 176.0/100,000 persons in the 5th year.	Very low
1 [Dr]	Cohort	Serious[5]	no serious	no serious	Serious[6]	none	223	NK[7]	Lower extremity amputation rates: From 9.9/1000 persons in the 1st year to 1.8/1000 persons in the 5th year.	Very low
Hospital length of stay										
1 [Cr]	Cohort	Serious[1]	no serious	no serious	Serious[2]	none	60	25	Mean hospital length of stay (days): [year 1995]: Intervention = 5.4, control = 7.8, p < 0.05 [year 1996]: Intervention = 3.6, control = 8.7, p < 0.05	Very low
Hospital readmission										
1 [Cr]	Cohort	Serious[1]	no serious	no serious	Serious[2]	none	60	25	Percentage of hospital readmission: [year 1995]: Intervention = 7%, control = 18% [year 1996]: Intervention = 15%, control = 15%	Very low
Ulcer recurrence										

1 [D]	Cohort	no serious	no serious	no serious	Serious[2]	none	56	89	Percentage of ulcer recurrence: Intervention = 30.4%, control = 58.4%	Very low

[Ca] = Canavan et al. (2008): key components = Organized Diabetes Foot Care compared to standard care (composition of the organised care not described).
[Cr] = Crane et al. (1999): key components = Critical pathway approach to diabetic foot infections compared to standard care (the pathway was initiated in the emergency department utilizing committee-approved standing physician's orders and clinical progress records to facilitate transitions between departments).
[D] = Dargis et al. (1999): key components = Multidisciplinary approach compared to standard care (the multidisciplinary team staffed by a diabetologist, a rehabilitation physician, a podiatrist, orthopaedic, surgeons, and shoemakers).
[Dr] = Driver et al. (2005): key components = Multidisciplinary Foot Care (Limb Preservation Service Model) compared to standard care (services included prevention and education, wound care, infection management, surgical and hospital management, research and grant development, community and regional education, and the creation of orthotics, prosthetics, and shoes).
[L] = Larsson et al. (1995): key components = Multidisciplinary Foot Care Team Approach compared to standard care (the team consisting of a diabetologist and an orthopaedic surgeon assisted by a diabetes nurse, a podiatrist, and an orthotist and working in close cooperation with the Department of vascular surgery and the Department of infectious diseases. A programme for patient and staff education was also started).
NK = not known
[1] Pre- and post- design with historical control.
[2] Small sample.
[3] Unable to assess as sample of historical control group unknown.
[4] Actual number unknown, only reported participants treated prior to 1983.
[5] Simple uncontrolled trend analysis over 5 years period.
[6] Unable to assess.
[7] Actual number unknown, not reported.

Review question 2: What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?

SECTION 1: Diabetic ulcer/wound scores

GRADE evidence profile 2: Clinical utility of different wound scores

<table>
<tr><th colspan="3">Study characteristics</th><th colspan="5">Quality Assessment</th><th>Summary of findings</th><th></th></tr>
<tr><td>No. of studies</td><td>Design</td><td>Evaluation criteria[a]</td><td>Limitation</td><td>Inconsistency</td><td>Indirectness</td><td>Imprecision</td><td>Other consideration</td><td>Wound scores and Assessment scores</td><td>Quality</td></tr>
<tr><td colspan="10">Evaluation of diabetic foot wound scores</td></tr>
<tr><td>1
[S]</td><td>Qualitative</td><td>1. Number of criteria
2. Objectivity of findings to evaluate each criterion
3. Scoring permutations
4. Versatility
5. Guide to seriousness
6. Integration with wound information
7. Integration with patient information
8. Documentation of progress
9. Validity
10. Reliability</td><td>S
(b)</td><td>N</td><td>N</td><td>S
(c)</td><td>S
(d)</td><td>Assessment scores:
<table>
<tr><th>Test</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th><th>7</th><th>8</th><th>9</th><th>10</th><th>Total</th></tr>
<tr><td>WAG[1]</td><td>2</td><td>0</td><td>1</td><td>0</td><td>1</td><td>1</td><td>1</td><td>0</td><td>1</td><td>0</td><td>7</td></tr>
<tr><td>FOR[2]</td><td>2</td><td>0</td><td>2</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>4</td></tr>
<tr><td>KNI[3]</td><td>0</td><td>1</td><td>0</td><td>2</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>4</td></tr>
<tr><td>PEC[4]</td><td>1</td><td>0</td><td>1</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>3</td></tr>
<tr><td>LAV[5]</td><td>1</td><td>1</td><td>2</td><td>1</td><td>1</td><td>0</td><td>1</td><td>1</td><td>1</td><td>1</td><td>10</td></tr>
<tr><td>JEF[6]</td><td>2</td><td>2</td><td>0</td><td>1</td><td>2</td><td>0</td><td>1</td><td>1</td><td>1</td><td>1</td><td>11</td></tr>
<tr><td>FOS[7]</td><td>2</td><td>0</td><td>2</td><td>0</td><td>1</td><td>1</td><td>2</td><td>0</td><td>0</td><td>0</td><td>8</td></tr>
</table></td><td>Very low</td></tr>
<tr><td>No. of studies</td><td>Design</td><td>Type of wound scores</td><td>Limitation</td><td>Inconsistency</td><td>Indirectness</td><td>Imprecision</td><td>Other consideration</td><td>Wound scores and Assessment scores</td><td>Quality</td></tr>
<tr><td colspan="10">Comparison of Wagner wound score and University of Texas wound scores</td></tr>
<tr><td>1
[O]</td><td>Cross-sectional (194 patients)</td><td>• Wagner wound classification system (Grade 0 to 5)
• University of Texas diabetic wound classification system (Stage A to D, each stage has grade 1 to 3)</td><td>S
(e)</td><td>N</td><td>N</td><td>S
(f)</td><td>S</td><td><u>Positive trend with increased number of amputations</u>
Wagner grade: $X^2_{trend} = 21.0$, $p < 0.0001$
UT grade and stage: $X^2_{trend} = 23.7$, $p < 0.0001$ and $X^2_{trend} = 15.1$, $p = 0.0001$
<u>Cox regression analysis</u>
Only the UT stage had a predictive effect on healing time ($X^2 = 10.3$, df = 3, $p < 0.05$). The higher the stage at presentation, the less likely it was for that ulcer to heal within the study period (hazard ratio = 0.8, 95% CI: 0.67 to 0.98, $p < 0.05$).</td><td>Low</td></tr>
</table>

(1) = Wagner (1979), US
(2) = Forrest and Gamborg-Neilsen (1984), Sweden
(3) = Knighton et al. (1986), US
(4) = Pecoraro and Reiber (1990), US
(5) = Lavery et al. (1996), US
(6) = MacFarlane and Jeffcote (1999), UK
(7) = Foster and Edmunds (2000), UK
[S] = Strauss et al. (2005)
[O] = Oyibo et al. (2001)
(a) = Graded on a 3-point scale: 2 = good supporting data and/or the ability to measure the assessment was good; 1 = some supporting information and/or the ability to measure the assessment was fair; 0 = no supporting information and/or the ability to measure the assessment was poor or nonexistent.
(b) = Qualitative design with single rater, high risk of bias.
(c) = No range of the assessment scores as there was only one rater, cannot assess variability.
(d) = The assessment scores were derived by the rater and has not been validated. High risk of examiner's bias.
(e) = Both wound scores were not validated.
(f) = Unable to assess imprecision.

GRADE evidence profile 3: Clinical utility of Diabetic Ulcer Severity Score (DUSS)

<table>
<tr><th colspan="4">Study characteristics</th><th colspan="5">Quality Assessment</th><th colspan="2">Summary of findings</th></tr>
<tr><th>No. of studies</th><th>Design</th><th>No. of patients</th><th>Clinical parameters</th><th>Limitation</th><th>Inconsistency</th><th>Indirectness</th><th>Imprecision</th><th>Other consideration</th><th>Analysis</th><th>Quality</th></tr>
<tr><td colspan="11">Probability of healing</td></tr>
<tr><td>1
[B]</td><td>Cohort</td><td>1000</td><td>Palpable pedal pulses (1 = absence; 0 = presence)
Probing to bone (1 = yes; 0 = no)
Ulcer location (1 = foot; 0 = toe)
Multiple ulcerations (1 = multiple; 0 = single)</td><td>N</td><td>N</td><td>S
(a)</td><td>N</td><td>S
(b)</td><td>Multivariate analysis: demonstrated as independent variables, an increase of 1 point reduced the chance for healing by 35% (at the end of follow-up).</td><td>Low</td></tr>
<tr><td colspan="11">Wound duration and risk of surgical intervention (including amputation)</td></tr>
<tr><td>1
[B]</td><td>Cohort</td><td>1000</td><td>Palpable pedal pulses (1 = absence; 0 = presence)
Probing to bone (1 = yes; 0 = no)
Ulcer location (1 = foot; 0 = toe)
Multiple ulcerations (1 = multiple; 0 = single)</td><td>N</td><td>N</td><td>S
(a)</td><td>N</td><td>S
(b)</td><td><table><tr><th>Score</th><th>Wound duration (days) (median, range)</th><th>Surgery (%)</th></tr><tr><td>0</td><td>29 (2-597)</td><td>9</td></tr><tr><td>1</td><td>26.5 (1-2922)</td><td>17</td></tr><tr><td>2</td><td>31 (1-4018)</td><td>27</td></tr><tr><td>3</td><td>42 (1-18708)</td><td>37</td></tr><tr><td>4</td><td>61 (3-1516)</td><td>50</td></tr></table></td><td>Low</td></tr>
</table>

[B] = Beckert et al. (2006): follow-up of 365 days.
(a) = Direct outcomes unclear i.e. no information on how the wound scores affected treatment plans and hence probability of healing.
(b) = No validation in different data set or study population.

SECTION 2: The clinical utility of assessment and investigation strategies/routines in examining diabetic foot infections

GRADE evidence profile 4: Clinical signs of diabetic foot infections

Study characteristics				Quality Assessment					Summary of findings[a]					
No. of studies	Design	No. of patients	Clinical signs	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	Post-test probability (+ve)	Post-test probability (despite [-ve])	Quality
Clinical signs of diabetic foot infection (reference standard: high microbial loads > 1 million organisms per gram of tissue)														
1 [G]	Cross-sectional	64	Increasing pain[1]	N	N	N	S (a)	VS (b)	0.39	12 (26-32)	1 00 (90-100)	1.00	0.37	Very low
1 [G]	Cross-sectional	64	Erythema[2]	N	N	N	S (a)	VS (b)	0.39	32 (15-53)	77 (60-89)	0.47	0.53	Very low
1 [G]	Cross-sectional	64	Oedema[3]	N	N	N	S (a)	VS (b)	0.39	20 (6 -41)	77 (60-89)	0.36	0.40	Very low
1 [G]	Cross-sectional	64	Heat[4]	N	N	N	S (a)	VS (b)	0.39	12 (2-31)	84 (69-94)	0.33	0.40	Very low
1 [G]	Cross-sectional	64	Purulent exudate[5]	N	N	N	S (a)	VS (b)	0.39	28 (12-49)	64 (47-79)	0.33	0.42	Very low
1 [G]	Cross-sectional	64	Serous exudate[6]	N	N	N	S (a)	VS (b)	0.39	88 (69-97)	73 (64-81)	0.42	0.04	Very low
1 [G]	Cross-sectional	64	Sanguineous exudate[7]	N	N	N	S (a)	VS (b)	0.39	84 (64-95)	90 (76-97)	0.84	0.11	Very low
1 [G]	Cross-sectional	64	Delayed healing[8]	N	N	N	S (a)	VS (b)	0.39	48 (23-69)	54 (37-70)	0.40	0.39	Very low
1 [G]	Cross-sectional	64	Discoloured granulation[9]	N	N	N	S (a)	VS (b)	0.39	28 (12-49)	85 (69-94)	0.54	0.36	Very low
1 [G]	Cross-sectional	64	Friable granulation[10]	N	N	N	S (a)	VS (b)	0.39	0 (0-14)	77 (61-89)	0.00	0.46	Very low
1 [G]	Cross-sectional	64	Pocketing[11]	N	N	N	S (a)	VS (b)	0.39	40 (21-61)	59 (42-74)	0.38	0.40	Very low
1 [G]	Cross-sectional	64	Foul odour[12]	N	N	N	S (a)	VS (b)	0.39	20 (6-41)	87 (73-96)	0.50	0.32	Very low
1 [G]	Cross-sectional	64	Wound breakdown[13]	N	N	N	S (a)	VS (b)	0.39	0 (0-14)	95 (83-99)	0.00	0.41	Very low

(a) = Multiple and logistic regression showed multicollinearity and the author decided not to report the coefficients. Hence, the predictive value of individual signs reported above need to be interpreted with caution.
(b) = Selective reporting of the author (reporting bias) as the coefficients were not reported for assessment.
[G] = Gardner et al. (2009)
[1] = +LR = * (1.272 to infinity); -LR = 0.88 (0.708 to 1.008)

[2] = +LR = 1.38 (0.618 to 3.038); -LR = 0.884 (0.611 to 1.195)
[3] = +LR = 0.86 (0.330 to 2.162); -LR = 1.04 (0.766 to 1.355)
[4] = +LR = 0.78 (0.226 to 2.565); -LR = 1.04 (0.811 to 1.283)
[5] = +LR = 0.78 (0.360 to 1.590146); -LR = 1.12 (0.773 to 1.580)
[6] = +LR = 3.29 (2.327 to 4.610311); -LR = 0.16 (0.056 to 0.412)
[7] = +LR = 8.19 (3.473 to 20.938754; -LR = 0.17 (0.071 to 0.390)
[8] = +LR = 1.04 (0.595 to 1.73895; -LR = 0.96 (0.580 to 1.527)
[9] = +LR = 1.82 (0.708 to 4.6373; -LR = 0.85 (0.608 to 1.100)
[10] = +LR = * (0 to 0.597); -LR = 1.30 (1.057 to 1.595)
[11] = +LR = 0.97 (0.517 to 1.751); -LR = 1.01 (0.649 to 1.522)
[12]= +LR = 1.56 (0.523 to 4.576); -LR = 0.91 (0.687 to 1.143)
[13] = +LR = * (0 to 2.844); -LR = 1.05 (0.878 to 1.183)

GRADE evidence profile 5: Swab cultures

Study characteristics				Quality Assessment					Summary of findings	
No. of studies	Design	No. of patients (wound)	Outcomes	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Association between swabs and deep tissue cultures	Quality
Swab cultures in diabetic wounds not involving bone (reference standard: deep tissue biopsy)										
1 [S]	Cross-sectional	56 (60)	Swabs contained all organisms found in deep tissue biopsy	S (a)	N	N	N	S (b)	49/60 (82%)	Low
1 [S]	Cross-sectional	56 (60)	Swabs and deep tissue cultures identical	S (a)	N	N	N	S (b)	37/60 (62%)	Low
1 [S]	Cross-sectional	56 (60)	Swabs contained all organisms found in deep tissue biopsy plus additional organisms	S (a)	N	N	N	S (b)	12/60 (20%)	Low
1 [S]	Cross-sectional	56 (60)	Swabs lacked organism(s) found in deep tissue biopsy	S (a)	N	N	N	S (b)	11/60 (18%)	Low

[S] = Slater et al. (1997)
(a) = No blinding.
(b) = No direct analysis on the accuracy of swab culture, lack of data.

SECTION 3:Diagnostic accuracy of MRI imaging in diagnosing osteomyelitis in in-patients with diabetic foot problems

GRADE evidence profile 6 – MRI imaging

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
10 [A, B, C, E, L, M, R, W, We, Y]	Cross-sectional	Range: 14 to 62	S (a)	N	N	S (b)	N	Range: 0.33 to 0.86	Range: 77 to 100	Range: 60 to 100	Range: 0.75 to 100	Range: 0 to 0.62	Range: 0.38 to 1.0	Low

[A] = Al-Khawari (2007): reference standard = Histological analysis
[B] = Beltran (1990): reference standard = Aspiration/pathologic examination/plain films
[C] = Croll (1996): reference standard = Pathologic specimen or bone culture
[E] = Ertugrul (2006): reference standard = Histopathological analysis
[L] = Levine (1994): reference standard = Pathological/histological/surgical examination/clinical follow-up
[M] = Morrison (1995): reference standard = Histological analysis or clinical and radiographic demonstration despite conservative antibiotic therapy
[R] = Rozzanigo (2009): reference standard = Bacteriological and/or histological tests
[W] = Wang (1990): reference standard = Histological examination
[We] = Weinstein (1993): reference standard = Histological examination
[Y] = Yuh (1989): reference standard = Pathological tests
S = serious; N = no serious
(a) = 4 out of the 10 studies had no blinding; 4 out of the 10 studies with unclear selection criteria and baseline characteristics.
(b) = wide ranges of confidence intervals (see forest plot).

Diagnostic accuracy of 99mTc-MDP scintigraphy (bone scan) in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 7 – 99mTc-MDP scintigraphy

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
11 [C, D, E, Hd, Hy, K, L, N, Pa, Po, Y]	Cross-sectional	Range: 22 to 94	S (a)	N	N	S (b)	N	Range: 0.29 to 0.88	Range: 50 to 100	Range: 0 to 67	Range: 0.36 to 0.95	Range: 0.0 to 1.0	Range: -0.06 to 0.58	Low

[C] = Croll (1996): reference standard = Pathologic specimen or bone culture
[D] = Devillers (1998): reference standard = Radiographic/bacteriological/histological results/clinical follow-up
[E] = Ertugrul (2006): reference standard = Histopathological analysis
[Hd] = Harwood (1999): reference standard = Histological and/or microbiological cultures
[Hy] = Harvey (1997): reference standard = Histology, bone cultures and radiographic results
[K] = Keenan (1989): reference standard = Culture and/or histological examination
[L] = Larcos (1991): reference standard = Bone culture/biopsy/clinical follow-up
[N] = Newman (1991): reference standard = Bone biopsy and culture
[Pa] = Palestro (2003): reference standard = Bone biopsy and culture/clinical follow-up
[Po] = Poirier (2002): reference standard = Radiological examination or histopathological analysis
[Y] = Yuh (1989): reference standard = Pathological tests
S = serious; N = no serious
(a) = 5 out of the 11 studies had no blinding
(b) = wide ranges of confidence intervals (see forest plot).

Diagnostic accuracy of 99mTc-HMPAO scintigraphy (bone scan) in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 8 – 99mTc-HMPAO scintigraphy

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
3 [D, Hd, Hy]	Cross-sectional	Range: 52 to 122	S (a)	N	N	N	N	Range: 0.40 to 0.66	Range: 86 to 91	Range: 56 to 97	Range: 0.8 to 0.94	Range: 0.09 to 0.23	Range: 0.47 to 0.85	Moderate

[D] = Devillers (1998): reference standard = Radiographic/bacteriological/histological results/clinical follow-up
[Hd] = Harwood (1999): reference standard = Histological and/or microbiological cultures
[Hy] = Harvey (1997): reference standard = Histology, bone cultures and radiographic results
S = serious; N = no serious
(a) = 2 out of the 3 studies had no blinding

Diagnostic accuracy of In-WBC scan in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 9: In-WBC

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
8 [C, Hd, K, La, L, N1, N2, Pa]	Cross-sectional	Range: 12 to 111	S (a)	N	N	S (b)	N	Range: 0.27 to 0.68	Range: 33 to 100	Range: 22 to 78	Range: 0.28 to 0.85	Range: 0.0 to 0.40	Range: 0.01 to 0.78	Low

[C] = Croll (1996): reference standard = Pathologic specimen or bone culture
[Hd] = Harwood (1999): reference standard = Histological and/or microbiological cultures
[K] = Keenan (1989): reference standard = Culture and/or histological examination
[La] = Larcos (1991): reference standard = Bone culture/biopsy/clinical follow-up
[L] = Levine (1994): reference standard = Pathological/histological/surgical examination/clinical follow-up
[N1] = Newman (1991) (4 hours): reference standard = Bone biopsy and culture
[N2] = Newman (1991) (24 hours): reference standard = Bone biopsy and culture
[Pa] = Palestro (2003): reference standard = Bone biopsy and culture/clinical follow-up
S = serious; N = no serious
(a) = 4 out of the 8 studies had no blinding
(b) = wide ranges of confidence intervals (see forest plot).

Diagnostic accuracy of LeukoScan in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 10: LeukoScan (anti-granulocyte Fab' fragment antibody scintigraphy)

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
1 [Ru] 4hrs	Cross-sectional	78	S (a)	N	N	N	N	0.79	92 (82-97)	75 (48-93)	0.93	0.29	0.67	Moderate
1 [Ru] 24hrs	Cross-sectional	78	S (a)	N	N	N	N	0.79	92 (82-97)	88 (62-98)	0.97	0.26	0.80	Moderate

[Ru] = Rubello (2004): reference standard = Microbiological findings/CT scan/MRI/clinical follow-up
S = serious; N = no serious
(a) = selection criteria, characteristics of patients not reported.

Diagnostic accuracy of plain radiographs in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 11: plain radiographs

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
8 [C, D, La, L, N, W, We, Y]	Cross-sectional	Range: 26 to 62	S (a)	N	N	S (b)	N	Range: 0.29 to 0.86	Range: 22 to 75	Range: 17 to 94	Range: 0.17 to 0.89	Range: 0.24 to 0.67	Range: -0.40 to 0.50	Low

[C] = Croll (1996): reference standard = Pathologic specimen or bone culture
[D] = Devillers (1998): reference standard = Radiographic/bacteriological/histological results/clinical follow-up
[La] = Larcos (1991): reference standard = Bone culture/biopsy/clinical follow-up
[L] = Levine (1994): reference standard = Pathological/histological/surgical examination/clinical follow-up
[N] = Newman (1991): reference standard = Bone biopsy and culture
[W] = Wang (1990): reference standard = Histological examination
[We] = Weinstein (1993): reference standard = Histological examination
[Y] = Yuh (1989): reference standard = Pathological tests
S = serious; N = no serious
(a) = 4 out of the 8 studies had clear selection criteria (risk of selection bias).
(b) = wide ranges of confidence intervals (see forest plot).

Diagnostic accuracy of Moab in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 12: Moab

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
1 [Pa]	Cross-sectional	25	S (a)	N	N	S (b)	N	0.40	90	67	0.64	0.09	0.57	Low

[Pa] = Palestro (2003): reference standard = Bone biopsy and culture or clinical follow-up
S = serious; N = no serious
(a) = no blinding.
(b) = wide ranges of confidence intervals (see forest plot).

Diagnostic accuracy of probe-to-bone in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 13: Probe-to-bone

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
2 [G, S]	Cross-sectional	Range: 76 to 104	S (a)	N	N	S (b)	N	Range: 0.20 to 0.66	Range: 0.38 to 0.66	Range: 0.85 to 0.92	Range: 0.38 to 0.66	Range: 0.08 to 0.15	Range: 0.30 to 0.51	Low

[G] = Grayson (1995): reference standard = Histological and microbiology tests in detecting osteomyelitis

[S] = Shone (2006): reference standard = Clinical signs of osteomyelitis, supported by MRI and microbiologic analysis of deep tissue samples.

S = serious; N = no serious
(a) = no blinding.
(b) = wide ranges of confidence intervals (see forest plot).

Diagnostic accuracy of other imaging tests (combination) in diagnosing osteomyelitis in people with diabetic foot

GRADE evidence profile 14: other imaging tests (combination)

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
99mTc-MDP + In-WBC														
2 [K, Pa]	Cross-sectional	25 & 39	S (a)	N	N	S (b)	N	0.40 & 0.38	Range: 80 to 100	Range: 79 to 80	Range: 0.73 to 0.75	Range: 0.0 to 0.14	Range: 0.60 to 0.79	Low
Moab + 99mTc-MDP														
1 [Pa]	Cross-sectional	25	S (a)	N	N	S (b)	N	0.40	90 (55-100)	67 (38-88)	0.64	0.09	0.50	Low
99mTc-MDP + 99Tc-HMPAO														
1 [Po]	Cross-sectional	83	N	N	N	N	N	0.49	93 (80-96)	98 (87-100)	0.97	0.07	0.91	Low
99mTc-MDP + Gallium 67 citrate														
1 [We]	Cross-sectional	22	S (a)	N	N	S (b)	N	0.73	69 (41-89)	83 (36-100)	0.92	0.50	0.52	Low

[K] = Keenan (1989): reference standard = Culture and/or histological examination
[Pa] = Palestro (2003): reference standard = Bone biopsy and culture or clinical follow-up
[Po] = Poirer (2002): reference standard = Radiological examination or histopathological analysis
[We] = Weinstein (1993): reference standard = Histological examination
S = serious; N = no serious
(a) = no blinding.
(b) = wide ranges of confidence intervals (see forest plot).

GRADE evidence profile 15: ESR

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
ESR ≥ 60 mm/h														
2 [E, K]	Cross-sectional	29 & 46	S (a)	N	N	S (b)	N	0.52 & 0.66	89 to 92	68 to 90	Range: 0.76 to 0.94	Range: 0.12 to 0.18	Range: 0.60 to 0.79	Low
ESR ≥ 65 mm/h														
2 [E, K]	Cross-sectional	29 & 46	S (a)	N	N	S (b)	N	0.52 & 0.66	88 to 89	73 to 90	Range: 0.78 to 0.94	Range: 0.16 to 0.18	Range: 0.61 to 0.79	Low
ESR ≥ 70 mm/h														
2 [E, K]	Cross-sectional	29 & 46	S (a)	N	N	S (b)	N	0.52 & 0.66	83 to 89	77 to 100	Range: 0.80 to 1.00	Range: 0.17 to 0.19	Range: 0.60 to 0.89	Low
ESR > 70 mm/h														
2 [M, N]	Cross-sectional	28 & 43	S (c)	N	N	S (b)	N	0.51 & 0.64	28 to 91	95 to 100	Range: 0.95 to 1.00	Range: 0.09 to 0.57	Range: 0.28 to 0.86	Low
ESR ≥ 75 mm/h														
2 [E, K]	Cross-sectional	29 & 46	S (a)	N	N	S (b)	N	0.52 & 0.66	79 to 84	82 to 100	Range: 0.83 to 1.00	Range: 0.22 to 0.23	Range: 0.61 to 0.84	Low
ESR ≥ 80 mm/h														
2 [E, K]	Cross-sectional	29 & 46	S (a)	N	N	S (b)	N	0.52 & 0.66	71 to 79	91 to 90	Range: 0.89 to 1.00	Range: 0.26 to 0.29	Range: 0.62 to 0.79	Low
ESR > 100 mm/h														
1 [N]	Cross-sectional	39	N	N	N	S (b)	N	0.67	23	100	1.00	0.61	0.23	Moderate

[E] = Ertugrul (2009): reference standard = Histopathology/bone tissue culture/MRI conventional spin echo
[K] = Kaleta (2001): reference standard = Histological examination
[M] = Malabu (2001): reference standard = Bone scan/MRI/radiographs
[N] = Newman (1991): reference standard = Bone biopsy and culture
S = serious; N = no serious
(a) = 1 study no blinding, 1 study no clear selection criteria.
(b) = wide ranges of confidence intervals (see forest plot).
(c) = 1 study has no blinding.

GRADE evidence profile 16: wound sizes (and ERS)

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
Wound size ≥ 2 cm^2														
2 [E, N]	Cross-sectional	40 & 46	S (a)	N	N	S (b)	N	Range: 0.52 to 0.66	Range: 56 to 88	Range: 77 to 93	Range: 0.81 to 0.94	Range: 0.15 to 0.48	Range: 0.49 to 0.65	Low
Wound size ≥ 3 cm^2														
1 [E]	Cross-sectional	46	S (a)	N	N	S (b)	N	0.52	79	77	0.79	0.23	0.56	Low
Wound size ≥ 4 cm^2														
1 [E]	Cross-sectional	46	S (a)	N	N	S (b)	N	0.52	67	91	0.89	0.29	0.58	Low
Wound size ≥ 5 cm^2														
1 [E]	Cross-sectional	46	S (a)	N	N	S (b)	N	0.52	50	95	0.92	0.36	0.45	Low
ESR rate ≥ 65 mm/h + wound size ≥ 2 cm^2														
1 [E]	Cross-sectional	46	S (a)	N	N	S (b)	N	0.52	83	77	0.80	0.19	0.60	Low
ESR rate ≥70 mm/h + wound size ≥ 2 cm^2														
1 [E]	Cross-sectional	46	S (a)	N	N	S (b)	N	0.52	79	82	0.83	0.22	0.61	Low

[E] = Ertugrul (2009): reference standard = Histopathology/bone tissue culture/MRI conventional spin echo
[N] = Newman (1991): reference standard = Bone biopsy and culture
S = serious; N = no serious
(a) = no blinding
(b) = wide ranges of confidence intervals (see forest plot).

GRADE profile 17: other tests (single study)

Study characteristics			Quality Assessment					Summary of findings						
No. of studies	Design	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	Quality
Hematocrit > 36%														
1 [M]	Cross-sectional	43	S (a)	N	N	S (b)	N	0.51	95 (77-100)	86 (64-97)	0.88	0.05	0.81	Low
Hemoglobin < 12 g/dL														
1 [M]	Cross-sectional	43	S (a)	N	N	S (b)	N	0.51	82 (60-95)	90 (70-99)	0.90	0.17	0.72	Low
Platelet count > $400x10^9$/L														
1 [M]	Cross-sectional	43	S (a)	N	N	S (b)	N	0.51	45 (24-68)	95 (76-100)	0.91	0.37	0.40	Low
Red cell distribution width >14.5														
1 [M]	Cross-sectional	43	S (a)	N	N	S (b)	N	0.51	68 (45-86)	62 (38-82)	0.65	0.35	0.30	Low
White cell count > $400x10^9$/L														
1 [M]	Cross-sectional	43	S (a)	N	N	S (b)	N	0.51	50 (28-72)	81 (58-95)	0.73	0.39	0.31	Low
Microbiological processing														
1 [E]	Cross-sectional	31	S (a)	N	N	S (b)	N	0.84	92 (75-99)	60 (15-95)	0.92	0.40	0.52	Low
Clinical judgement														
1 [N]	Cross-sectional	41	N	N	N	S (b)	N	0.68	32 (16-52)	100 (75-100)	1.00	0.59	0.32	Moderate
Ulcer inflammation														
1 [N]	Cross-sectional	41	N	N	N	S (b)	N	0.68	36 (19-56)	81 (54-96)	0.77	0.58	0.17	Moderate
Bone exposure														
1 [N]	Cross-sectional	41	N	N	N	S (b)	N	0.68	32 (16-52)	100 (75-100)	1.00	0.59	0.32	Moderate

[M] = Malabu (2007): reference standard = Bone scan/MRI/radiographs
[E] = Ertugrul (2006): reference standard = Histopathological analysis
[N] = Newman (1991): reference standard = Bone biopsy and culture
S = serious; N = no serious
(a) = no blinding
(b) = wide ranges of confidence intervals

SECTION 4: The clinical utility of assessment and investigation strategies/routines in examining peripheral arterial disease

GRADE evidence profiles 18: PAD

Study characteristics					Quality Assessment					Summary of findings					
No. of studies	Design	No. of patients	Predictor(s)	Side of the leg	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	Likelihood ratio (+ve) [95%CI]	Likelihood ratio (-ve) [95%CI]	Quality
Clinical examination of PAD (reference standard: AAI ≤ 0.5)															
1 [B]	Cross-sectional	605	Abnormal pulses and history of PAD	Right	S (a)	N	N	N	S (b)	Unable to calculate	53 (39-68)	91 (88-93)	5.61 (3.85-8.17)	0.52 (0.38-0.71)	Low
1 [B]	Cross-sectional	587	Abnormal pulses and history of PAD	Left	S (a)	N	N	N	S (b)	Unable to calculate	50 (35-65)	91 (89-93)	5.55 (3.72-8.28)	0.55 (0.41-0.74)	Low
1 [B]	Cross-sectional	605	Abnormal pulses or history of PAD	Right	S (a)	N	N	N	S (b)	Unable to calculate	93 (86-100)	58 (50-62)	2.21 (1.95-2.51)	0.12 (0.04-0.35)	Low
1 [B]	Cross-sectional	587	Abnormal pulses or history of PAD	Left	S (a)	N	N	N	S (b)	Unable to calculate	100 (93-100)	58 (54-62)	2.39 (2.16-2.64)	0	Low
1 [B]	Cross-sectional	605	Abnormal pulses and claudication <1 block	Right	S (a)	N	N	N	S (b)	Unable to calculate	33 (19-46)	95 (93-97)	6.21 (3.58-10.76)	0.71 (0.58-0.87)	Low
1 [B]	Cross-sectional	587	Abnormal pulses and claudication <1 block	Left	S (a)	N	N	N	S (b)	Unable to calculate	36 (22-51)	94 (92-96)	6.08 (3.62-10.21)	0.68 (0.54-0.85)	Low
1 [B]	Cross-sectional	605	Abnormal pulses or claudication <1 block	Right	S (a)	N	N	N	S (b)	Unable to calculate	83 (72-94)	71 (67-75)	2.82 (2.34-3.40)	0.25 (0.13-0.46)	Low
1 [B]	Cross-sectional	587	Abnormal pulses or claudication <1 block	Left	S (a)	N	N	N	S (b)	Unable to calculate	86 (76-97)	71 (67-75)	2.94 (2.46-3.52)	0.19 (0.09-0.41)	Low
No. of studies	Design	No. of patients[c]	Outcome	Reviewer[d]	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity (%) [95%CI]	Specificity (%) [95%CI]	Likelihood ratio (+ve) [95%CI]	Likelihood ratio (-ve) [95%CI]	Quality
Diagnostic accuracy of hybrid MR angiography for critical limb ischemia (reference standard: digital subtraction angiography)															
1 [L]	Cross-sectional	31	Stenoses ≥ 50%	1	N	N	N	N	VS (b)	Unable to calculate	95 (86-98)	98 (95-99)	Unable to calculate	Unable to calculate	Low
1 [L]	Cross-sectional	31	Stenoses ≥ 50%	2	N	N	N	N	VS (b)	Unable to calculate	96 (88-99)	98 (95-99)	Unable to calculate	Unable to calculate	Low
1 [L]	Cross-sectional	31	Arterial occlusions	1	N	N	N	N	VS (b)	Unable to calculate	95 (88-97)	98 (96-99)	Unable to calculate	Unable to calculate	Low
1 [L]	Cross-sectional	31	Arterial occlusions	2	N	N	N	N	VS (b)	Unable to calculate	90 (83-94)	99 (97-100)	Unable to calculate	Unable to calculate	Low

No. of studies	Design	No. of patients	Visualization of arterial segments	Limitation	Inconsistency	Indirectness	Imprecision	Other consideration	Pre-test probability	Sensitivity and Specificity	Other analysis	Quality
Comparison of contrast-enhanced MR angiography with digital subtraction angiography (DSA) and change of treatment plans												
1 [K]	Cross-sectional	24	Anterior tibial; Posterior tibial; Peroneal; Dorsal pedal; Medial plantar; Lateral plantar; Pedal arch	S (e)	N	N	N	S (f)	Unable to calculate	N/A (no reference standard)	MR angiography was significantly better than DSA for dorsal pedal artery, lateral plantar arteries, and pedal arch, with $p < 0.05$ *MR angiography revealed a patent vessel that was not seen on DSA (suitable for distal bypass grafting) in 9/24 (38%) patients, which led to a change of treatment plans for 7 patients.*	Low

[B] = Boyko et al. (1997)
[L] = Lapeyre et al. (2005)
[K] = Kreitner et al. (2006)
(a) = No mention of blinding in the study.
(b) = No data on pre-test probability; reported results from 2 raters without further analysis.
(c) = Total of 310 segments were examined from the 31 patients
(d) = Outcomes were examined/rated by two separate reviewers
(e) = No defined reference standard, only simple comparisons.
(f) = No analysis on diagnostic accuracy.

Review question 3: What are the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading in treating diabetic foot problems?

Debridement

GRADE evidence profiles 19

Question: Surgical debridement vs conventional non-surgical management for diabetic foot ulcers

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical debridement	Conventional non-surgical debridement[a]	Relative risk/NNTB (95% CI)	Absolute	Quality
Number of ulcers completely healed (follow-up 6 months)											
1 [E]	RCT	serious[1]	no serious	no serious	serious[2]	none	21/22 (95.5%)	19/24 (79.2%)	RR 1.21 (0.96 to 1.51) NNTB = N/A	166 more per 1000 (from 32 fewer to 404 more)	Low
Ulcers recurrence rates (follow-up 6 months)											
1 [E]	RCT	serious[1]	no serious	no serious	serious[3]	none	3/22 (13.6%)	8/24 (33.3%)	RR 0.41 (0.12 to 1.35) NNTB = N/A	196 fewer per 1000 (from 293 fewer to 117 more)	Low
Number of adverse events (complications) (follow-up 6 months)											
1 [E]	RCT	serious[1]	no serious	no serious	serious[4]	none	1/22 (4.5%)	3/24 (12.5%)	RR 0.36 (0.03 to 2.65) NNTB = N/A	80 fewer per 1000 (from 121 fewer to 206 more)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included study = Piaggessi el al. (1998)
NNTB = number needed to treat to benefit.
[a] Conventional non-surgical management consisting of weight-bearing relief and regular dressings.
[1] Downgraded 1 level: unclear who conducted outcome assessment and hence unclear of assessor blinding (it was acceptable that blinding on participants and researchers were impossible to achieve); also loss to follow-up not reported.
[2] Downgraded 1 level: small study sample
[3] Downgraded 1 level: small study sample
[4] Downgraded 1 level: small study sample

GRADE evidence profiles 20

Question: Hydrogel vs gauze or good wound care (control) for diabetic foot ulcers

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrogel	Gauze or good wound care[a]	Relative risk/NNTB (95% CI)	Absolute	
Number of ulcers completely healed (follow-up: range: from 12 weeks to 20 weeks)											
3 [E]	RCT	serious[1]	no serious	no serious	serious[2]	none	51/99 (51.5%)	28/99 (28.3%)	RR 1.84 (1.3 to 2.61) NNTB = 4 (3 to 10)	238 more per 1000 (from 85 more to 456 more)	Low
Number of adverse events (complications) (follow-up: range: from 12 weeks to 20 weeks)											
3 [E]	RCT	serious[1]	no serious	no serious	serious[3]	none	22/99 (22.2%)	36/99 (36.4%)	RR 0.60 (0.38 to 0.95) NNTB = 7 (4 to 69)	146 fewer per 1000 (from 18 fewer to - 226 fewer)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included studies = D'Hemecourt el al. (1998) (20 weeks); Jensen el al. (1998) (16 weeks); Vandeputte et al. (1997) (12 weeks). NNTB = number needed to treat to benefit.

[a] Gauze = one study used wet-to-moist saline gauze; one study used dry gauze. Good wound care for all groups consisted of initial and ongoing sharp debridement of ulcers when necessary to remove nonviable tissue, daily saline dressing changes, off loading of pressure and systematic control of infection if present.

[1] Downgrade 1 level: unclear allocation concealment (all 3 studies); unclear blinding process (2 studies); 1 study did not conduct ITT analysis.

[2] Downgraded 1 level: small study sample

[3] Downgraded 1 level: small study sample

GRADE evidence profiles 21

Question: Hydrogel vs larvae therapy for diabetic foot ulcers

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Larvae	Hydrogel	Relative risk/NNTB (95% CI)	Absolute	
Wound area reduction > 50% (follow-up period not reported)											
1 [E]	RCT	serious[1]	no serious	no serious	serious[2]	none	36/70 (51.4%)	19/70 (27.1%)	RR 1.89 (1.21 to 2.96) NNTB = 4 (3 to 12)	241 more per 1000 (from 57 more to 531 more)	Low
Number of ulcers completely healed (follow-up period not reported)											
1 [E]	RCT	serious[1]	no serious	no serious	serious[3]	none	5/70 (7.1%)	2/70 (2.9%)	RR 2.50 (0.5 to 12.46) NNTB = N/A	44 more per 1000 (from 15 fewer to 332 more)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included study = Markevich el al. (2000)
NNTB = number needed to treat to benefit.
[1] Downgraded 1 level: lack of information in the study to assess limitations. Although the title stated double-blind, there was no mention of the process; also allocation concealment and loss to follow-up were not reported.
[2] Downgraded 1 level: small study sample
[3] Downgraded 1 level: small study sample

Off-loading

GRADE evidence profiles 22:

TCC vs CTF (custom-made temporary footwear)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCC	CTF	Relative (95% CI)	Absolute	
Complete wound healing (16 weeks)											
1 [V]	RCT	no serious	no serious	no serious	serious[1]	none	6/23 (26.1%)	6/20 (30%)	RR 0.87 (0.33 to 2.27)	4 fewer per 100 (from 20 fewer to 38 more)	MODERATE
Wound surface reduction (cm^2) (16 weeks)											
1 [V]	RCT	no serious	no serious	no serious	Serious[2]	none	23	20	Mean reduction (cm^2) (SD): TCC = -2.88 (2.5); CTF = -2.16 (3.4) Adjusted mean difference: 0.10 (95%CI: -0.92 to 0.72), p = 0.81		MODERATE

[1] Total no. of events < 300.
[2] Total no. of events < 400.
[v] = Van de Weg et al. (2008)
TCC = total contact casting

GRADE evidence profiles 23

TCC vs RCW (iTCC)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCC	RCW (iTCC)	Relative (95% CI)	Absolute	
Complete wound healing (12 weeks)											
1 [K]	RCT	serious[1]	no serious	no serious	serious[2]	none	15/20 (75%)	17/21 (81%)	RR 0.93 (0.67 to 1.29)	6 fewer per 100 (from 27 fewer to 23 more)	LOW
Treatment related AEs (12 weeks)											
1 [K]	RCT	serious[1]	no serious	no serious	serious[2]	none	13/20 (65%)	8/21 (38.1%)	RR 1.71 (0.91 to 3.21)	27 more per 100 (from 3 fewer to 84 more)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of event < 300.
[K] = Katz et al. (2005)
TCC = total contact casting
RCW (iTCC) = Removable cast walker (rendered irremovable by single roll of fibreglass casting).

GRADE evidence profiles 24

TCC vs dressing (mupirocin ointment and sterile gauze)

Quality assessment							Summary of findings				
							No of ulcers[3]		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCC	Dressing	Relative (95% CI)	Absolute	Quality
Complete wound healing (6 months)											
1 [G]	RCT	serious[1]	no serious	no serious	serious[2]	none	36/39 (92.3%)	25/33 (75.8%)	RR 1.22 (0.98 to 1.51)	17 more per 100 (from 2 fewer to 39 more)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[3] Number of patients: TCC = 29; dressing = 26.
[G] = Ganguly et al. (2008)
TCC = total contact casting

GRADE evidence profiles 25

TCC vs RCW (1)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCC	RCW	Relative (95% CI)	Absolute	Quality
Complete wound healing (12 weeks)											
1 [A]	RCT	serious[1]	no serious	no serious	serious[2]	none	17/19 (89.5%)	13/20 (65%)	RR 1.38 (0.96 to 1.97)	25 more per 100 (from 3 fewer to 63 more)	LOW
Mean healing time (days)											
1 [A]	RCT	serious[1]	no serious	no serious	Serious[3]	none	19	20	Mean healing time (days) (SD): TCC = 33.5 (5.9); RCW = 50.4 (7.2), p = 0.07		LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[3] Total no. of events < 400.
[A] = Armstrong et al. (2001)
TCC = total contact casting
RCW = Removable cast walker

GRADE evidence profiles 26

TCC vs Half-shoes (2)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCC	Half-shoes	Relative (95% CI)	Absolute	
Complete wound healing (12 weeks)											
1 [A]	RCT	serious[1]	no serious	no serious	serious[2]	none	17/19 (89.5%)	14/24 (58.3%)	RR 1.53 (1.06 to 2.22)	31 more per 100 (from 3 more to 71 more)	LOW
Mean healing time (days)											
1 [A]	RCT	serious[1]	no serious	no serious	Serious[3]	none	19	24	Mean healing time (days) (SD): TCC = 33.5 (5.9); Half-shoes = 61.0 (6.5), p = 0.005		LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[3] Total no. of events < 400.
[A] = Armstrong et al. (2001)
TCC = total contact casting
Half-shoes.

GRADE evidence profiles 27

RCW vs Half-shoes (3)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	RCW	Half-shoes	Relative (95% CI)	Absolute	
Complete wound healing (12 weeks)											
1 [A]	RCT	serious[1]	no serious	no serious	serious[2]	none	13/20 (65%)	14/24 (58.3%)	RR 1.11 (0.70 to 1.78)	6 more per 100 (from 17 fewer to 45 more)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[A] = Armstrong et al. (2001)
RCW = Removable cast walker
Half-shoes = Darco, Huntingdon, WV.

GRADE evidence profiles 28

TCC vs dressing (wet-to-dry dressing)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCC	Dressing	Relative (95% CI)	Absolute	
Complete wound healing (6 weeks)											
1 [M]	RCT	serious[1]	no serious	no serious	serious[2]	none	19/21 (90.5%)	6/19 (31.6%)	RR 2.87 (1.46 to 5.63)	59 more per 100 (from 15 more to 100 more)	LOW

[1] No mention of randomisation methods, no allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[M] = Mueller et al. (1989)
TCC = total contact casting

GRADE evidence profiles 29

TCC vs Instant casting (Optima Diab device)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TCC	Instant casting	Relative (95% CI)	Absolute	
Complete wound healing (12 weeks)											
1 [P]	RCT	serious[1]	no serious	no serious	serious[2]	none	19/20 (95%)	17/20 (85%)	RR 1.12 (0.91 to 1.38)	10 more per 100 (from 8 fewer to 32 more)	LOW
Mean healing time (weeks)											
1 [P]	RCT	serious[1]	no serious	no serious	Serious[3]	none	20	20	Mean healing time (weeks) (SD): TCC = 6.5 (4.4); Instant casting = 6.7 (3.4), p = 0.874		LOW
Treatment-related AEs (follow-up 12 weeks)											
1 [P]	RCT	serious[1]	no serious	no serious	serious[2]	none	4/20 (20%)	5/20 (25%)	RR 0.80 (0.25 to 2.55)	5 fewer per 100 (from 19 fewer to 39 more)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[3] Total no. of events < 400.
[P] = Piaggesi et al. (2007)
TCC = total contact casting

GRADE evidence profiles 30

Felt deflective padding (to the skin) vs felt deflective padding (within the shoe)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	To the skin	Within the shoe	Relative (95% CI)	Absolute	
Wound surface reduction (%)											
1 [N]	RCT	serious[1]	no serious	no serious	serious[2]	none	15	17	Wound surface reduction (%): Skin = 73%; Shoe = 74%, z = 0.02, p = 0.9		LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 400.
[N] = Nube et al. (2006)

Dressings

GRADE evidence profiles 31:

Aquacel vs Saline moistened gauze (SMG)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aquacel	SMG	Relative (95% CI)	Absolute	
Achieved granulation tissue (8 weeks)											
1 [P]	RCT	serious[1]	no serious	no serious	serious[2]	none	4/10 (40%)	1/10 (10%)	RR 4.00 (0.54 to 29.81)	30 more per 100 (from 5 fewer to 100 more)	LOW
Mean healing time (days)											
1 [P]	RCT	serious[1]	no serious	no serious	Serious[3]	none	10	10	Mean healing time (days) (SD): Aquacel = 127 (46); SMG = 234 (61), p < 0.001		LOW
Complication (infection) (8 weeks)											
1 [P]	RCT	serious[1]	no serious	no serious	serious[2]	none	1/10 (10%)	3/10 (30%)	RR 0.33 (0.04 to 2.69)	20 fewer per 100 (from 29 fewer to 51 more)	LOW

[1] No allocation concealment.
[2] Total no. of events < 300.
[3] Total no. of events < 400.
[P] = Piagessi et al. (2001)
Aquacel = sodium carboxyl-methyl-cellulose dressing

GRADE evidence profiles 32

Promogran vs Saline moistened gauze (SMG)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Promogran	SMG	Relative (95% CI)	Absolute	
Complete wound healing (12 weeks)											
1 [V]	RCT	serious[1]	no serious	no serious	serious[2]	none	51/104 (49.5%)	39/84 (46.4%)	RR 1.06 (0.78 to 1.43)	3 more per 100 (from 10 fewer to 20 more)	LOW
Wound surface reduction (%) (12 weeks)											
1 [V]	RCT	serious[1]	no serious	no serious	Serious[3]	none	104	84	Mean wound surface reduction (%): Promogran = 64.5%; SMG = 63.8%, P > 0.05		LOW
Wound-related serious AEs (12 weeks)											
1 [V]	RCT	serious[1]	no serious	no serious	serious[2]	none	25/104 (24%)	35/84 (41.7%)	RR 0.58 (0.38 to 0.88)	18 fewer per 100 (from 5 fewer to 26 fewer)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[3] Total no. of events < 400.
[V] = Veves et al. (2002)
Promogran = collagen/oxidized regenerated cellulose dressing.

GRADE evidence profiles 33

AQAg (hydrofiber dressing) vs CA (calcium alginate)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	AQAg	CA	Relative (95% CI)	Absolute	
Complete wound healing (8 weeks)											
1 [J]	RCT	serious[1]	no serious	no serious	serious[2]	none	21/67 (31.3%)	15/67 (22.4%)	RR 1.40 (0.79 to 2.47)	9 more per 100 (from 5 fewer to 33 more)	LOW
Wound surface reduction (%) (8 weeks)											
1 [J]	RCT	serious[1]	no serious	no serious	Serious[3]	none	67	67	Mean wound surface reduction (%) (SD): AQAg = 58.1 (53.1); CA = 60.5 (42.7), p = 0.948		LOW
Mean healing time (days)											
1 [J]	RCT	serious[1]	no serious	no serious	Serious[3]	none	67	67	Mean healing time (days) (SD): AQAg = 52.6 (1.8); CA = 57.7 (1.7), p = 0.340		LOW
Withdrawal due to AEs (unspecified) (8 weeks)											
1 [J]	RCT	serious[1]	no serious	no serious	serious[2]	none	8/67 (11.9%)	13/67 (19.4%)	RR 0.61 (0.27 to 1.39)	8 fewer per 100 (from 14 fewer to 8 more)	LOW
Wound-related complications (8 weeks)											
1 [J]	RCT	serious[1]	no serious	no serious	serious[2]	none	23/67 (34.3%)	26/67 (38.8%)	RR 0.88 (0.57 to 1.38)	5 fewer per 100 (from 17 fewer to 15 more)	LOW
Treatment-related AEs (8 weeks)											
1 [J]	RCT	serious[1]	no serious	no serious	serious[2]	none	11/67 (16.4%)	9/67 (13.4%)	RR 1.22 (0.54 to 2.76)	3 more per 100 (from 6 fewer to 24 more)	LOW

[1] Allocation concealment unclear, assessor not blinded.
[2] Total no. of events < 300.
[3] Total no. of events < 400.
[J] = Jude et al. (2007)

GRADE evidence profiles 34

Polyurethane foam vs Alginate

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Polyurethane	Alginate	Relative (95% CI)	Absolute	
Complete wound healing (8 weeks)											
1 [F]	RCT	serious[1]	no serious	no serious	serious[2]	none	9/15 (60%)	8/15 (53.3%)	RR 1.13 (0.60 to 2.11)	7 more per 100 (from 21 fewer to 59 more)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[F] = Foster et al. (1994)

GRADE evidence profiles 35

Honey dressing vs Povidone-soaked gauze

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Honey	Povidone	Relative (95% CI)	Absolute	
Mean time for wound to be ready for surgical closure (days)											
1 [S]	RCT	serious[1]	no serious	no serious	serious[2]	none	15	15	Mean time for wound to be ready for surgical closure (days) (range): Honey = 14.4 (7-26); povidone = 15.4 (9-36), p > 0.05.		LOW

[1] No allocation concealment.
[2] Total no. of events < 400.
[S] = Shukrime et al. (2008)

GRADE evidence profiles 36

Aquacel vs N-A (non-adherent, knitted, viscose filament gauze) (1)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aquacel	N-A	Relative (95% CI)	Absolute	
Complete wound healing (24 weeks)											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	46/103 (44.7%)	41/106 (38.7%)	RR 1.15 (0.84 to 1.59)	6 more per 100 (from 6 fewer to 23 more)	MODERATE
Mean healing time (days)											
1 [J]	RCT	no serious	no serious	no serious	Serious[2]	none	103	106	Mean healing time (days) (SD): Aquacel = 130.7 (52.4); N-A = 125.8 (55.9), p > 0.05		MODERATE
Major and minor amputation											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	4/103 (3.9%)	2/106 (1.9%)	RR 2.06 (0.39 to 10.99)	2 more per 100 (from 1 fewer to 19 more)	MODERATE
Withdrawal due to AEs (24 weeks)											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	11/103 (10.7%)	15/106 (14.2%)	RR 0.75 (0.36 to 1.56)	4 fewer per 100 (from 9 fewer to 8 more)	MODERATE
Complication (infection)											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	9/103 (8.7%)	7/106 (6.6%)	RR 1.32 (0.51 to 3.42)	2 more per 100 (from 3 fewer to 16 more)	MODERATE

[1] Total no. of events < 300.
[2] Total no. of events < 400.
[J] = Jeffcoate et al. (2009)
Aquacel = sodium carboxyl-methyl-cellulose dressing

GRADE evidence profiles 37
Aquacel vs Inadine (2)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aquacel	Inadine	Relative (95% CI)	Absolute	
Complete wound healing (24 weeks)											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	46/103 (44.7%)	48/108 (44.4%)	RR 1.00 (0.74 to 1.36)	0 fewer per 100 (from 12 fewer to 16 more)	MODERATE
Mean healing time (days)											
1 [J]	RCT	no serious	no serious	no serious	Serious[2]	none	103	108	Mean healing time (days) (SD): Aquacel = 130.7 (52.4); inadine = 127.8 (54.2), p > 0.05		MODERATE
Major and minor amputation											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	4/103 (3.9%)	1/108 (0.9%)	RR 4.19 (0.48 to 36.91)	3 more per 100 (from 0 fewer to 32 more)	MODERATE
Withdrawal due to AEs											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	11/103 (10.7%)	9/108 (8.3%)	RR 1.28 (0.55 to 2.96)	2 more per 100 (from 4 fewer to 16 more)	MODERATE
Complication (infection)											
1 [J]	RCT	no serious	no serious	no serious	serious[1]	none	9/103 (8.7%)	12/108 (11.1%)	RR 0.79 (0.36 to 1.79)	2 fewer per 100 (from 7 fewer to 9 more)	MODERATE

[1] Total no. of events < 300.
[2] Total no. of events < 400.
[J] = Jeffcoate et al. (2009)
Aquacel = sodium carboxyl-methyl-cellulose dressing
Inadine = iodine impregnated dressing

GRADE evidence profiles 38

N-A vs Inadine (3)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	N-A	Inadine	Relative (95% CI)	Absolute	
Complete wound healing (24 weeks)											
1	RCT	no serious	no serious	no serious	serious[1]	none	41/106 (38.7%)	48/108 (44.4%)	RR 0.87 (0.63 to 1.20)	6 fewer per 100 (from 16 fewer to 9 more)	MODERATE
Mean healing time (days)											
1	RCT	no serious	no serious	no serious	Serious[2]	none	106	108	Mean healing time (days) (SD): N-A = 125.8 (55.9); inadine = 127.8 (54.2), p > 0.05		MODERATE
Major and minor amputation											
1	RCT	no serious	no serious	no serious	serious[1]	none	2/106 (1.9%)	1/108 (0.9%)	RR 2.04 (0.19 to 22.14)	1 more per 100 (from 1 fewer to 19 more)	MODERATE
Withdrawal due to AEs											
1	RCT	no serious	no serious	no serious	serious[1]	none	15/106 (14.2%)	9/108 (8.3%)	RR 1.70 (0.78 to 3.71)	6 more per 100 (from 2 fewer to 22 more)	MODERATE
Complication (infection)											
1	RCT	no serious	no serious	no serious	serious[1]	none	7/106 (6.6%)	12/108 (11.1%)	RR 0.59 (0.24 to 1.45)	5 fewer per 100 (from 8 fewer to 5 more)	MODERATE

[1] Total no. of events < 300.
[2] Total no. of events < 400.
[J] = Jeffcoate et al. (2009)
N-A = non-adherent, knitted, viscose filament gauze
Inadine = iodine impregnated dressing

Review question 4: What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)?

GRADE evidence profiles 39:
Quinolones vs broad-spectrum penicillins
Ofloxacin (IV to oral) vs amplicilin/sulbactam (IV) amoxicillin/clavulanic (oral) (Lipsky et al. 1997)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ofloxacin (IV to oral)	Amplicilin/sulbactam (IV) to amoxicillin/ clavulanic (oral)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	40/47 (85.1%)	34/41 (82.9%)	RR 1.03 (0.85 to 1.23) NNTB = N/A	2 more per 100 (from 12 fewer to 19 more)	LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	39/47 (83%)	36/41 (87.8%)	RR 0.95 (0.79 to 1.12) NNTB = N/A	4 fewer per 100 (from 18 fewer to 11 more)	LOW
Pathogen outcome: Eradication of Gram+ aerobes (unit: pathogen) (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	33/47 (70.2%)	38/43 (88.4%)	RR 0.79 (0.64 to 0.99) NNTB = 6 (3 to 79)	19 fewer per 100 (from 1 fewer to 32 fewer)	LOW
Pathogen outcome: Eradication of Gram- aerobes (unit: pathogen) (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/19 (94.7%)	15/18 (83.3%)	RR 1.14 (0.90 to 1.43) NNTB = N/A	12 more per 100 (from 8 fewer to 36 more)	LOW
No. of patients experienced treatment-related adverse events (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	17/47 (36.2%)	9/41 (22%)	RR 1.65 (0.83 to 3.29) NNTH = N/A	14 more per 100 (from 4 fewer to 50 more)	LOW

Dosage: Ofloxacin 400 mg (IV and oral) every 12 hours. AmpiciIlin (1 to 2 g)/sulbactam (0.5 to 1g) (IV) every 6 hours; then 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 hours.
[a] Cured = disappearance of all signs and symptoms associated with active infection.
[1] Allocation concealment unclear.
[2] Total no. of events <300.

GRADE evidence profiles 40:

Broad-spectrum beta-lactam carbapenems vs broad-spectrum penicillins
Imipenem/cilastatin vs amplicilin/sulbactam (IV) (Grayson et al. 1994)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Imipenem /cilastatin (IV)	Amplicilin /sulbactam (IV)	Relative (95% CI)	Absolute	
Clinical outcome: cured[a] (unit: no. of infections) (follow-up 6 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	39/48 (81.3%)	41/48 (85.4%)	RR 0.95 (0.80 to 1.14) NNTB = N/A	4 fewer per 100 (from 17 fewer to 12 more)	LOW
Microbiological outcome: infections achieved eradiction of pathogen(s) (follow-up 6 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	32/48 (66.7%)	36/48 (75%)	RR 0.89 (0.69 to 1.15) NNTB = N/A	8 fewer per 100 (from 23 fewer to 11 more)	LOW
No. of patients experienced significant[b] AEs (follow-up 6 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	7/46 (15.2%)	9/47 (19.1%)	RR 0.79 (0.32 to 1.96) NNTH = N/A	4 fewer per 100 (from 13 fewer to 18 more)	LOW

Dosage: Imipenem/cilastatin (500 mg) every 6 hours. Ampicillin/sulbactam (3 g) every 6 hours.
[a] Cured = resolution of soft-tissue infection.
[b] Significant = a severe reaction necessitating withdrawal of the study treatment.
[1] 6 days or until therapy was completed.
[2] Allocation concealment unclear.
[3] Total no. of events <300.

GRADE evidence profiles 41:
Cephalosporins vs broad-spectrum penicillins
Cefoxitin vs amplicilin/sulbactam (IV) (Erstad et al. 1997)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cefoxitin (IV)	amplicilin/ sulbactam (IV)	Relative (95% CI)	Absolute	
Clinical outcome: cured[a] (follow-up 5 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	7/18 (38.9%)	1/18 (5.6%)	RR 7.00 (0.95 to 51.25) NNTB = N/A	33 more per 100 (from 0 fewer to 279 more)	LOW
Clinical outcome: length of hospital stay (days)											
1	RCT	serious[2]	no serious y	no serious	serious[4]	none	18	18	Mean length of hospital stay (days) (range): Cefoxitin = 12.1 (4 to 39) Ampicillin/sulbactam = 21.1 (6 to 58), p = 0.06		LOW
No. of patients experienced treatment- related AEs (follow-up 5 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	6/18 (33.3%)	7/18 (38.9%)	RR 0.86 (0.36 to 2.05) NNTH = N/A	5 fewer per 100 (from 25 fewer to 41 more)	LOW

Dosage: Cefoxitin 2 g every 6 hours; Ampicillin/sulbactam 3 g every 6 hours, for at least 5 days.
[a] Cured = disappearance of all signs and symptoms associated with active infection.
[1] 5 days but could be more to the discretion of the attending surgeon.
[2] Allocation concealment unclear.
[3] Total no. of event <300.
[4] Total no. of participants <400.

GRADE evidence profiles 42

Antipseudomonal penicilins vs broad-spectrum penicillins

Piperacillin/tazobactam vs amplicilin/sulbactam (IV) (Harkless et al. 2005)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin/ tazobactam (IV)	amplicilin/ sulbactam (IV)	Relative (95% CI)	Absolute	
Clinical outcome: cured or improvement[a] (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	99/139 (71.2%)	100/150 (66.7%)	RR 1.07 (0.92 to 1.25) NNTB = N/A	5 more per 100 (from 5 fewer to 17 more)	LOW
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	51/65 (78.5%)	46/64 (71.9%)	RR 1.09 (0.89 to 1.33) NNTB = N/A	6 more per 100 (from 8 fewer to 24 more)	LOW
No. of patients experienced at least 1 treatment-related AEs (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	29/155 (18.7%)	21/159 (13.2%)	RR 1.42 (0.85 to 2.37) NNTH = N/A	6 more per 100 (from 2 fewer to 18 more)	LOW
Withdrawals due to treatment-related AEs (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/155 (11.6%)	13/159 (8.2%)	RR 1.42 (0.72 to 2.80) NNTH = N/A	3 more per 100 (from 2 fewer to 15 more)	LOW

Dosage: Piperacillin/tazobactam (4 g/0.5 g q8h); Ampicillin/sulbactam (2 g/1 g q6h), for 4 to 14 days.

[a] Cured or improvement = resolution of signs and symptoms, or sufficient clinical improvement that the majority of symptoms of infection had abated.

[1] Open-labelled trial, no blinding.

[2] Total no. of events <300.

GRADE evidence profiles 43

Antipseudomonal penicilins vs Antipseudomonal penicilins

Piperacillin/tazobactam vs ticarcillin/calvulanate (IV) (Tan et al. 1993)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin/ tazobactam (IV)	ticarcillin/ calvulanate (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 10-14 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	7/18 (38.9%)	6/17 (35.3%)	RR 1.10 (0.46 to 2.62) NNTB = N/A	4 more per 100 (from 19 fewer to 57 more)	LOW

Dosage: Pipcracillin/tazobactam (3 g/375 mg) every 6 hours ; Ticarcillin/clavulanate (3 g/100 mg) every 6 hours, for at least 5 days.
[a] Cured = resolution of signs and symptoms.
[1] Allocation concealment unclear, extracted subgroup data.
[2] Total no. of events <300.

GRADE evidence profiles 44

Beta-lactam carbapenems vs antipseudomonal penicilins + clindamycin

Imipenem/cilastatin vs piperacilin/clindamycin (IV) (Bouter et al. 1996)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Imipenem/ cilastatin (IV)	piperacilin/ clindamycin (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 10 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	4/21 (19%)	6/24 (25%)	RR 0.76 (0.25 to 2.34) NNTB = N/A	6 fewer per 100 (from 19 fewer to 33 more)	LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 10 days)											
1	RCT	serious[1]	no serious	no serious indirectness	serious[2]	none	9/20 (45%)	16/23 (69.6%)	RR 0.65 (0.37 to 1.13) NNTB = N/A	24 fewer per 100 (from 44 fewer to 9 more)	LOW
No. of patients experienced treatment-related AEs (follow-up 10 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/21 (85.7%)	12/24 (50%)	RR 1.71 (1.11 to 2.65) NNTH = 3 (2 to 12)	36 more per 100 (from 6 more to 83 more)	LOW

Dosage: Piperacillin (3000 mg QID) + clindamycin (600 mg TID); Imipenem/cilastatin (500 mg QID), for at least 10 days.
[a] Cured = resolution of signs and symptoms.

[1] Allocation concealment unclear.
[2] Total no. of events <300.

GRADE evidence profiles 45

Quinolones vs antipseudomonal penicilins + broad-spectrum penecillins

Moxifloxacin (IV to oral) vs piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral) (Lipsky et al. 2007)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Moxifloxacin (IV to oral)	piperacillin/ tazobactam (IV) to moxifloxin vs amoxillin/ clavulanate (oral)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	28/63 (44.4%)	25/64 (39.1%)	RR 1.14 (0.75 to 1.72) NNTB = N/A	5 more per 100 (from 10 fewer to 28 more)	MODERATE
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	24/37 (64.9%)	27/42 (64.3%)	RR 1.01 (0.73 to 1.40) NNTB = N/A	1 more per 100 (from 17 fewer to 26 more)	MODERATE
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	2/6 (33.3%)	7/12 (58.3%)	RR 0.57 (0.17 to 1.95) NNTB = N/A	25 fewer per 100 (from 48 fewer to 55 more)	MODERATE
No. of patients experienced treatment-related AEs (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	20/63 (31.7%)	8/64 (12.5%)	RR 2.54 (1.21 to 5.34) NNTH = 5 (3 to 20)	19 more per 100 (from 3 more to 54 more)	MODERATE
Withdrawals due to treatment-related AEs (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	15/63 (23.8%)	15/64 (23.4%)	RR 1.02 (0.54 to 1.90) NNTH = N/A	0 more per 100 (from 11 fewer to 21 more)	MODERATE

Dosage: Moxifioxacin (400 mg/day) (IV for at least 3 days), then 400 mg orally; piperacillin/tazobactam (3.0 g/0.375 g every 6 hours) for at least 3 days, then amoxicillin/clavulanate (800 mg every 12 hours orally), for total duration of 7 to 14 days.
[a] Cured = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.
[1] Total no. of events <300.

GRADE evidence profiles 46

Pexiganan cream (topical) vs ofloxacin (oral) (quinolones) (Lipsky et al. 2008)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Pexiganan cream	ofloxacin (oral)	Relative (95% CI)	Absolute	
Clinical outcome: cured or improvement[a] (follow-up 21 days)											
1	RCT	no serious	no serious	no serious	no serious	none	363/418 (86.8%)	377/417 (90.4%)	RR 0.96 (0.91 to 1.01) NNTB = N/A	4 fewer per 100 (from 8 fewer to 1 more)	HIGH
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 21 days)											
1	RCT	no serious	no serious	no serious	no serious	none	154/327 (47.1%)	160/338 (47.3%)	RR 0.99 (0.85 to 1.17) NNTB = N/A	0 fewer per 100 (from 7 fewer to 8 more)	HIGH
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 21 days)											
1	RCT	no serious	no serious	no serious	no serious	none	203/370 (54.9%)	233/379 (61.5%)	RR 0.89 (0.79 to 1.01) NNTB = N/A	7 fewer per 100 (from 13 fewer to 1 more)	HIGH
Pathogen outcome: eradication of Gram- aerobes (unit: patient) (follow-up 21 days)											
1	RCT	no serious	no serious	no serious	no serious	none	75/111 (67.6%)	72/103 (69.9%)	RR 0.97 (0.81 to 1.16) NNTB = N/A	2 fewer per 100 (from 13 fewer to 11 more)	HIGH

Dosage: Pexiganan cream (twice daily); ofloxacin tablets (200 mg orally twice daily), for at least 14 days.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

GRADE evidence profiles 47

Oxazolidinone vs broad-spectrum penicillins

Linezolid (IV or oral) vs amplicillin/sulbactam (IV) or amoxicillin/clavulanate (oral) (Lipsky et al. 2004)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Linezolid (IV)	amplicillin/ sulbactam (IV) or amoxicillin /clavulanate (oral)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	165/203 (81.3%)	77/108 (71.3%)	RR 1.14 (0.99 to 1.31) NNTB = N/A	10 more per 100 (from 1 fewer to 22 more)	LOW
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	143/185 (77.3%)	71/100 (71%)	RR 1.09 (0.94 to 1.26) NNTB = N/A	6 more per 100 (from 4 fewer to 18 more)	LOW
Pathogen outcome: eradication of Gram- aerobes (unit: patient) (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	65/81 (80.2%)	23/34 (67.6%)	RR 1.19 (0.92 to 1.53) NNTB = N/A	13 more per 100 (from 5 fewer to 36 more)	LOW
No. of patients experienced treat-related AEs (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	64/241 (26.6%)	12/120 (10%)	RR 2.66 (1.49 to 4.73) NNTH = 6 (4 to 12)	17 more per 100 (from 5 more to 37 more)	LOW
Withdrawals due to treatment-related AEs (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/241 (7.5%)	4/120 (3.3%)	RR 2.24 (0.78 to 6.47) NNTH = N/A	4 more per 100 (from 1 fewer to 18 more)	LOW

Dosage: Linezolid (600 mg q12h either IV or per oral); ampicillin/sulbaclam (1.5 to 3 g q6h IV), or amoxicillin/clavulanate (500-875 mg every 8-12 hours orally), for 7 to 28 days.

[a] Cured = resolution of all signs and symptoms.

[1] Open-labelled study, no blinding.

[2] Total no. of events <300.

GRADE evidence profiles 48

Lipopeptide antibiotics vs glycopeptide antibiotics

Daptomycin (IV) vs vancomycin (IV) (Lipsky et al. 2005)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Daplomycin (IV)	Vancomycin (IV)	Relative (95% CI)	Absolute	
Clinical outcome: cured[a] (follow-up 6-20 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	10/14 (71.4%)	20/29 (69%)	RR 1.04 (0.69 to 1.56) NNTB = N/A	3 more per 100 (from 21 fewer to 39 more)	LOW

Dosage: Daptomycin (4 mg/kg every 24 hours IV over 30 mins); vancomycin (1 g every 12 hours IV over 60 mins), for 7 to 14 days.

[a] Cured = resolution of all signs and symptoms.

[1] Allocation concealment unclear.

[2] Total no. of events <300.

GRADE evidence profiles 49

Lipopeptide antibiotics vs narrow-spectrum penicillins

Daptomycin (IV) vs nafcillin or cloxacillin or flucloxacillin (IV) (Lipsky et al. 2005)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Daplomycin (IV)	nafcillin or cloxacillin or flucloxacillin (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 6-20 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	16/25 (64%)	19/27 (70.4%)	RR 0.91 (0.62 to 1.33) NNTB = N/A	6 fewer per 100 (from 27 fewer to 23 more)	LOW

Dosage: Daptomycin (4 mg/kg every 24 hours IV over 30 mins) for 7 to 14 days; or a narrow-spectrum penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin, depending on the investigator's choice, given in equally divided doses totalling 4 to12 g/day IV).

[a] Cured = resolution of all signs and symptoms.

[1] Allocation concealment not clear.

[2] Total no. of events <300.

GRADE evidence profiles 50

Antipseudomonal penicilins vs broad-spectrum beta-lactam carbapenems

Piperacillin/tazobactam (IV) vs ertapenem (IV) (Lipsky et al. 2005)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin/ tazobactam (IV)	ertapenem (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	no serious	none	202/219 (92.2%)	213/226 (94.2%)	RR 0.98 (0.93 to 1.03) NNTB = N/A	2 fewer per 100 (from 7 fewer to 3 more)	MODERATE
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	122/146 (83.6%)	135/151 (89.4%)	RR 0.93 (0.85 to 1.02) NNTB = N/A	6 fewer per 100 (from 13 fewer to 2 more)	LOW
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	40/51 (78.4%)	62/67 (92.5%)	RR 0.85 (0.72 to 0.99) NNTB = 7 (4 to 62)	14 fewer per 100 (from 1 fewer to 26 fewer)	LOW
No. of patients experienced treatment-related AEs (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	57/291 (19.6%)	44/295 (14.9%)	RR 1.31 (0.92 to 1.88) NNTH = N/A	5 more per 100 (from 1 fewer to 13 more)	LOW
Withdrawals due to treatment-related AEs (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	6/291 (2.1%)	3/295 (1%)	RR 2.03 (0.51 to 8.03) NNTH = N/A	1 more per 100 (from 0 fewer to 7 more)	ÅLOW

Dosage: Ertapenem (1g bolus, followed by a saline placebo every 6 hours for three additional doses, IV); piperacillin/tazobactam (3 to375 g every 6 hours, IV), for 5 days.

[a] Cured = resolution of all signs and symptoms.

[1] Open-labelled study, no blinding.

[2] Total no. of events <300.

GRADE evidence profiles 51
Cephalosporins vs cephalosporins
Cerftizoxime (IV) vs cefoxitin (IV) (Hughes et al. 1987)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cerftizoxime (IV)	cefoxitin (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured or improvement[a] (follow-up varied)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	23/28 (82.1%)	17/26 (65.4%)	RR 1.21 (0.88 to 1.66) NNTB = N/A	14 more per 100 (from 8 fewer to 43 more)	LOW
No. of patients experienced treatment-related AEs (follow-up varied)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	16/33 (48.5%)	19/30 (63.3%)	RR 0.77 (0.49 to 1.19) NNTH = N/A	15 fewer per 100 (from 32 fewer to 12 more)	LOW

Dosage: Ceftizoxime, up to 4 g IV every 8 hours. Cefoxitin, up to 2 g IV every 4 hours.
[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.
[1] Allocation concealment unclear, blinding unclear.
[2] Total no. of events <300.

GRADE evidence profiles 52

Lincosamide antibiotics vs cephalosporins

Clindamycin (oral) vs cephalexin (oral) (Lipsky et al. 1990)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	AB	control	Relative (95% CI)	Absolute	
Clinical outcome: complete healing (follow-up 2 weeks)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	10/25 (40%)	9/27 (33.3%)	RR 1.20 (0.59 to 2.46) NNTB = N/A	7 more per 100 (from 14 fewer to 49 more)	LOW

Dosage: Clindamycin (300 mg orally), four times daily for 2 weeks. Cephalexin (500 mg orally), four times daily for 2 weeks.

[1] Blinding and allocation concealment unclear.

[2] Total no. of events <300.

Review question 5: What is the clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems, for example, dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy and electrical stimulation?

GRADE evidence profiles 53
Adjunctive treatment: Growth factors (G-CSF)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	G-CSF	control	Relative (95% CI)	Absolute	
Amputation (follow-up 10 days to 6 months)											
5 [de, G, K, V, Y]	RCT	serious[1]	no serious	no serious	serious[2]	none	6/85 (7.1%)	15/83 (18.1%)	RR 0.41 (0.18 to 0.95) NNTB = 9 (5 to 96)	11 fewer per 100 (from 1 fewer to 15 fewer)	LOW
Complete wound healing (follow-up: unclear)											
2 [G, K]	RCT	serious[3]	no serious	no serious	serious[2]	none	4/39 (10.3%)	0/40 (0%)	RR 9.45 (0.54 to 164.49) NNTB = N/A	0 more per 100 (from 0 fewer to 0 more)	LOW
Overall need for surgical interventions (follow-up: varied)											
5 [de, G, K, V, Y]	RCT	serious[1]	no serious	no serious	serious[2]	none	11/85 (12.9%)	29/79 (36.7%)	RR 0.37 (0.2 to 0.68) NNTB = 4 (3 to 9)	23 fewer per 100 (from 12 fewer to 29 fewer)	LOW
Length of hospital stay (days) (follow-up: varied)											
2 [V, Y]	RCT	serious[3]	no serious	no serious	serious[4]	none	25	25	Mean (days) (SD): Mean difference = -1.40 (95%CI: -2.27 to -0.53)		LOW
Resolution of infection (follow-up: varied)											
1 [G]	RCT	no serious	no serious	no serious	serious[2]	none	11/20 (55%)	4/20 (20%)	RR 2.75 (1.05 to 7.2) NNTB = 3 (2 to 21)	35 more per 100 (from 1 more to 100 more)	MODERATE
Improvement on infection status (follow-up: varied)											
4 [de, G, K, V]	RCT	serious[5]	no serious	no serious	serious[2]	none	49/70 (70%)	35/70 (50%)	RR 1.40 (1.06 to 1.85) NNTB = 5 (3 to 27)	20 more per 100 (from 3 more to 42 more)	LOW
Treatment-related adverse events (follow-up: varied)											
3 [de, G, K]	RCT	serious[6]	no serious	no serious	serious[2]	none	5/60 (8.3%)	0/57 (0%)	RR 5.59 (0.71 to 44.05) NNTH = N/A	0 more per 100 (from 0 fewer to 0 more)	LOW

[de] = de Lalla et al. (2001). G-CSF + standard care vs standard care only (control). Standard care = standard wound care + antibiotics.

[G] = Gough et al. (1997). G-CSF + standard care vs placebo + standard care only (control). Standard care = standard wound care + antibiotics.
[K] = Kastenbauer et al. (2003). G-CSF + standard care vs placebo + standard care only (control). Standard care = standard wound care + antibiotics.
[V] = Viswanathan et al. (2003). G-CSF + standard care vs placebo + standard care only (control). Standard care = standard wound care + antibiotics.
[Y] = Yonem et al. (2001). G-CSF + standard care vs standard care only (control). Standard care = standard wound care + antibiotics.
[1] Allocation concealment unclear in 3 trials; 2 trials are open-labelled studies.
[2] Total no. of events <300.
[3] One trial lacks allocation concealment and blinding.
[4] Total no. of participants <400.
[5] Allocation concealment unclear in 2 trial; 1 open-labelled study.
[6] 2 trials lack allocation concealment and 1 open-labelled study.

GRADE evidence profiles 54
Adjunctive treatment: Growth factors (PDGF)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PDGF	control	Relative (95% CI)	Absolute	Quality
Complete wound healing (follow-up mean 20 weeks)											
4 [D, H, R, W]	RCT	serious[1]	no serious	no serious	no serious	none	202/419 (48.2%)	115/325 (35.4%)	RR 1.38 (1.16 to 1.64) NNTB = 8 (5 to 18)	13 more per 100 (from 6 more to 23 more)	MODERATE
Withdrawal due to treatment-related adverse events (follow-up 20 weeks)											
2 [D, W]	RCT	serious[2]	no serious	no serious	Serious[3]	none	29/290 (10%)	26/195 (13.3%)	RR 0.94 (0.54 to 1.63) NNTH = N/A	1 fewer per 100 (from 6 fewer to 8 more)	LOW
At least 1 treatment-related adverse events (follow-up 20 weeks)											
1 [D]	RCT	Serious[4]	no serious	no serious	Serious[3]	none	22/34 (64.7%)	48/68 (70.6%)	RR 0.92 (0.68 to 1.23) NNTH = N/A	6 fewer per 100 (from 23 fewer to 16 more)	LOW
Mean healing time (days)											
1 [H]	RCT	Serious[5]	no serious	no serious	Serious[6]	none	58	55	Mean (days): PDGF = 46; control = 61, p = < 0.001		LOW

[D] = D'Hemecourt et al. (2005). PDGF + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.
[H] = Hardikar et al. (2005). PDGF + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.
[R] = Robson et al. (2005). PDGF + standard care vs standard care only (control). Standard care = debridement, adaptic dressing, off-loading.
[W] = Wieman et al. (1998). PDGF + standard care vs placebo + standard care (control). Standard care = debridement, dressing, off-loading.
[1] All trials had no allocation concealment; 2 trials lacked blinding.
[2] Both trials had no allocation concealment; 1 trial lacked blinding.
[3] Total no. of events <300.
[4] No allocation concealment.
[5] No allocation concealment, lacked blinding.
[6] Total no. of participants <400.

GRADE evidence profiles 55
Adjunctive treatment: Growth factors (EGF)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	EGF	control	Relative (95% CI)	Absolute	
Amputation (follow-up mean 24 weeks)											
1 [T]	RCT	serious[1]	no serious	no serious	serious[2]	none	2/40 (5%)	2/19 (10.5%)	RR 0.47 (0.07 to 3.12) NNTB = N/A	6 fewer per 100 (from 10 fewer to 22 more)	LOW
Length of hospital stay (days) (follow-up 4 weeks)											
1 [A]	RCT	serious[3]	no serious	no serious	serious[4]	none	30	20	Mean (days) (SD): EGF = 29.6 (20.95); control = 28.9 (15.1) Mean difference = 0.70 (95%CI: -9.3 to 10.7)		LOW
Complete wound healing (follow-up 04 to 24 weeks)											
3 [A, T, V]	RCT	serious[5]	no serious	no serious	serious[2]	none	69/99 (69.7%)	33/67 (49.3%)	RR 1.41 (0.76 to 2.63) NNTB = N/A	20 more per 100 (from -12 fewer to 80 more)	LOW
At least 50% wound reduction (follow-up 2 weeks)											
1 [F]	RCT	serious[6]	no serious	no serious	serious[2]	none	78/101 (77.2%)	19/48 (39.6%)	RR 1.95 (1.35 to 2.81) NNTB = 3 (2 to 5)	38 more per 100 (from 14 more to 72 more)	LOW
Treatment-related adverse events - burning sensation (follow-up 2 weeks)											
1 [F]	RCT	serious[6]	no serious	no serious	serious[2]	none	22/101 (21.8%)	14/48 (29.2%)	RR 0.75 (0.42 to 1.33) NNTB = N/A	7 fewer per 100 (from 17 fewer to 10 more)	LOW
Treatment-related adverse events - shivering (follow-up 2 weeks)											
1 [F]	RCT	serious[6]	no serious	no serious	serious[2]	none	25/101 (24.8%)	2/48 (4.2%)	RR 5.94 (1.47 to 24.06) NNTH = 5 (3 to 11)	21 more per 100 (from 2 more to 97 more)	LOW

[A] = Afshari et al. (2005). EGF + standard care vs placebo + standard care only (control). Standard care = debridement, dressing.
[F] = Fernandez-Montequinn et al. (2009). EGF + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.
[T] = Tsang et al. (2003). EGF + standard care vs standard care only (control). Standard care = Actovegin cream, debridement, dressing.
[V] = Viswanathan et al. (2006). EGF vs placebo (no mention of standard wound care).
[1] Allocation concealment and blinding unclear.
[2] Total no. of events <300.
[3] Allocation concealment no clear; exclusion criteria not reported.
[4] Total no. of participants <400.
[5] 2 trials allocation concealment unclear; 1 trial lacked blinding; 1 trial exclusion criteria not reported.
[6] No allocation concealment.

GRADE evidence profiles 56
Adjunctive treatment: Growth factors (TGF-beta)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TGF beta	control	Relative (95% CI)	Absolute	
Complete wound healing (week 21) (follow-up 21 weeks)											
1 [R]	RCT	no serious	no serious	no serious	serious[1]	none	77/131 (58.8%)	17/24 (70.8%)	RR 0.83 (0.62 to 1.11) NNTB = N/A	12 fewer per 100 (from 27 fewer to 8 more)	MODERATE

[R] = Robson et al. (2000). TGF-beta + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.
[1] Total no. of events <300.

GRADE evidence profiles 57
Adjunctive treatment: Hyperbaric oxygen therapy (HBOT)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HBOT	control	Relative (95% CI)	Absolute	
Major amputation (follow-up varied)											
4 [A, D, Du, F, L]	RCT	serious[1]	no serious	no serious	serious[2]	none	11/158 (6.9%)	37/150 (24.7%)	RR 0.30 (0.16 to 0.55) NNTB = 6 (4 to 10)	17 fewer per 100 (from 11 fewer to 21 fewer)	LOW
Minor amputation (follow-up varied)											
3 [A, D, Du]	RCT	no serious	no serious	no serious	serious[2]	none	10/74 (13.5%)	26/74 (35.1%)	RR 0.92 (0.11 to 7.9) NNTB = N/A	3 fewer per 100 (from 31 fewer to 100 more)	MODERATE
Complete wound healing (week 4-6) (follow-up 4 to 6 weeks)											
3 [A, Du, K, L]	RCT	no serious	no serious	no serious	serious[2]	none	67/121 (55.4%)	16/114 (14.0%)	RR 3.46 (0.91 to 13.12) NNTB = N/A	34 more per 100 (from 1 fewer to 100 more)	MODERATE
Required surgical interventions (follow-up 1 months)											
1 [Du]	RCT	no serious	no serious	no serious	serious[2]	none	8/50 (16%)	50/50 (100%)	RR 0.17 (0.09 to 0.31) NNTB = 1 (1 to 2)	83 fewer per 100 (from 69 fewer to -91 fewer)	MODERATE
Mean reduction of ulcer surface area (week 4)											
1 [K]	RCT	serious[3]	no serious	no serious	serious[4]	none	14	13	Mean (%) (SD): HBOT = 61.9 (23.3); control = 55.1 (21.5) p > 0.05		LOW

[A] = Abidia et al. (2003). HBOT vs specialised wound management alone.
[D] = Doctor et al. (1992). HBOT + standard care vs standard care only (control). Standard care = dressing and debridement.
[Du] = Duzgun et al. (2008). HBOT + standard care vs standard care only (control). Standard care = dressing and debridement.
[F] = Faglia et al. (1996). HBOT vs specialised wound management alone.
[K] = Kessler et al. (2003). HBOT + standard care vs standard care only (control). Standard care = off-loading.
[L] = Londahl et al. (2010). HBOT + standard care vs sham HBOT + standard care. Standard care = antibiotics treatment, revascularisation, debridement, off-loading, and metabolic control.
[1] Allocation concealment unclear in 2 trials.
[2] Total no. of events <300.
[3] Allocation concealment unclear.
[4] Total no. of participants <400.

GRADE evidence profiles 58
Adjunctive treatment: Dermal or skin substitutes (DSS)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dermal or skin grafts	control	Relative (95% CI)	Absolute	
Complete wound healing (week 12) - *ALL* (follow-up 12 weeks)											
6 [C, G, M, N, P, V]	RCT	serious[1]	no serious	no serious	no serious	none	202/452 (44.7%)	128/419 (30.5%)	RR 1.46 (1.22 to 1.73) NNTB = 7 (5 to 13)	14 more per 100 (from 7 more to 22 more)	MODERATE
SUBGROUP: Complete wound healing (week 12) - *Dermagraft* (follow-up 12 weeks)											
3 [G, M, N]	RCT	serious[2]	no serious	no serious	serious[3]	none	99/281 (35.2%)	67/270 (24.8%)	RR 1.44 (1.11 to 1.87) NNTB = 10 (6 to 36)	11 more per 100 (from 3 more to 22 more)	LOW
SUBGROUP: Complete wound healing (week 12) - *Graftskin* (follow-up 12 weeks)											
1 [V]	RCT	serious[4]	no serious	no serious	serious[3]	none	63/112 (56.3%)	36/96 (37.5%)	RR 1.50 (1.11 to 2.04) NNTB = 5 (3 to 20)	19 more per 100 (from 4 more to 39 more)	LOW
SUBGROUP: Complete wound healing (week 12) - *Hyalograft* (follow-up 12 weeks)											
1 [C]	RCT	serious[5]	no serious	no serious	serious[3]	none	28/43 (65.1%)	18/36 (50%)	RR 1.30 (0.88 to 1.93) NNTB = N/A	15 more per 100 (from -6 fewer to 46 more)	LOW
SUBGROUP: Complete wound healing (week 12) - *Human skin equivalent* (follow-up 12 weeks)											
1 [P]	RCT l	serious[5]	no serious	no serious	serious[3]	none	12/16 (75%)	7/17 (41.2%)	RR 1.82 (0.97 to 3.44) NNTB = N/A	34 more per 100 (from -1 fewer to 100 more)	LOW
At least 50% wound closure (week 12) - Dermagraft (follow-up 12 weeks)											
1 [G]	RCT	serious[5]	no serious	no serious	serious[3]	none	9/12 (75%)	3/13 (23.1%)	RR 3.25 (1.14 to 9.24) NNTB = 2 (1 to 8)	52 more per 100 (from 3 more to 100 more)	LOW
Required surgical interventions (unit: ulcers) - Dermagraft											
1 [M]	RCT	serious[5]	no serious	no serious	serious[3]	none	13/163 (8%)	22/151 (14.6%)	RR 0.55 (0.29 to 1.05) NNTB = N/A	7 fewer per 100 (from 10 fewer to 1 more)	LOW
Median time to complete closure - Graftskin											
1 [V]	RCT	serious[4]	no serious	no serious	serious[6]	none	112	96	Median (days) (K-M): Graftskin = 65; control 90, p = 0.0026		LOW
Withdrawal due to ulcer-related AEs - Graftskin/Hyalograft											

2 [C, V]	RCT	serious[1]	no serious	no serious	serious[3]	none	9/155 (5.8%)	15/132 (11.4%)	RR 0.51 (0.23 to 1.13) NNTH = N/A	6 fewer per 100 (from 9 fewer to 1 more)	LOW
Overall ulcer-related AEs – Dermagraft/Graftskin											
4 [C, G, M, V]	RCT	serious[1]	no serious	no serious	serious[3]	none	72/297 (24.2%)	108/260 (41.5%)	RR 0.58 (0.46 to 0.74) NNTH = 6 (4 to 11)	17 fewer per 100 (from 11 fewer to -22 fewer)	LOW

[C] = Caravaggi et al. (1996). DSS + standard care vs. non-adherent paraffin gauze + standard care. Standard care = debridement and off-loading.
[G] = Gentzknow et al. (1996). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[M] = Marston et al. (2003). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[N] = Naughton et al. (1997). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[P] = Pham et al. (1999). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[V] = Veves et al. (2001). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
AE = adverse events.
[1] Allocation concealment unclear for all trials; 1 trial no blinding.
[2] Allocation concealment unclear for all trials.
[3] Total no. of events <300.
[4] Allocation concealment unclear; no blinding.
[5] Allocation concealment unclear.
[6] Total no. of participants <400.

GRADE evidence profiles 59
Adjunctive treatment: Dermal or skin substitutes (DSS)

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Meshed skin graft	Split thickness skin graft	Mean healing time (days) (SD)	Quality
Mean healing time (days) (follow-up 6 months)										
1 [P]	RCT	serious[1]	no serious	no serious	Serious[2]	none	36	44	Meshed skin graft = 19.84 (7.37) Split thickness skin graft = 20.36 (7.21) p > 0.05	LOW

Puttirutvong et al. (2004). Meshed skin graft + standard care vs split thickness skin graft + standard care. Standard care = daily dressing
[1] Allocation concealment unclear for all trials
[2] Total no. of participants <400.

GRADE evidence profiles 60
Adjunctive treatment: Negative pressure wound therapy (NPWT)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	control	Relative (95% CI)	Absolute	Quality
Amputation											
2 [B, W]	RCT	serious[1]	no serious	no serious	serious[2]	none	9/246 (3.7%)	26/251 (10.4%)	RR 0.35 (0.17 to 0.74) NNTB = 15 (9 to 43)	7 fewer per 100 (from 3 fewer to -9 fewer)	LOW
Complete wound closure (week 16) (follow-up 16 weeks)											
2 [B, W]	RCT	serious[1]	no serious	no serious	serious[2]	none	116/246 (47.2%)	81/251 (32.3%)	RR 1.47 (1.18 to 1.84) NNTB = 7 (4 to 16)	15 more per 100 (from 6 more to 27 more)	LOW
Mean reduction wound surface area (cm^2)											
1 [E]	RCT	serious[1]	no serious	no serious	serious[3]	none	12	12	Mean reduction (cm2) (SD): NPWT = 20.4 (11.7); control = 9.5 (4.11) Mean difference = 10.9 (95%CI: 3.88 to 17.92)		LOW
Median time to 75% wound closure											
1 [B]	RCT	serious[1]	no serious	no serious	serious[3]	none	169	166	Median time (K-M) (days): NPWT = 58 (95%CI: 53 to 78) Control = 84 (95%CI: 58 to 89), p = 0.014		LOW
Median time to achieve 75%-100% granulation (baseline 0%-25% granulation)											
1 [W]	RCT	serious[1]	no serious	no serious	serious[3]	none	77	85	Median time (K-M) (days): NPWT = 42 (95%CI: 14 to 56) Control = 82 (95%CI: 28 to 112), p = 0.01		LOW
Overall ulcer-related AEs											
1 [B]	RCT	serious[1]	no serious	no serious	serious[2]	none	15/169 (8.9%)	11/166 (6.6%)	RR 1.34 (0.63 to 2.83) NNTH = N/A	2 more per 100 (from -2 fewer to 12 more)	LOW
Overall treatment-related AEs											
1 [W]	RCT	serious[1]	no serious	no serious	serious[2]	none	9/77 (11.7%)	11/85 (12.9%)	RR 0.90 (0.40 to 2.06) NNTH = N/A	1 fewer per 100 (from 8 fewer to 14 more)	LOW

[B] = Blume et al. (2008): NPWT + standard care vs control (moist wound therapy) + standard care. Standard care = off-loading.
[E] = Etoz et al. (2004): NPWT vs control (saline moistened gauze)
[W] = Williams et al. (2005): NPWT + standard care vs control (moist wound therapy) + standard care. Standard care = off-loading.
AE = adverse events.
[1] Allocation concealment unclear.
[2] Total no. of events <300.
[3] Total no. of participants <400.

GRADE evidence profiles 61
Other adjunctive treatments: Electrical stimulation therapy

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	EST	control	Relative (95% CI)	Absolute	
Complete wound healing (12 weeks) (follow-up 12 weeks): Electrical stimulation (ES)											
1 [P]	RCT	serious[1]	no serious	no serious	serious[2]	none	13/20 (65%)	7/20 (35%)	RR 1.86 (0.94 to 3.70) NNTB = N/A	30 more per 100 (from -2 fewer to 94 more)	LOW
Complete wound healing (20 weeks) (follow-up 20 weeks): Shock wave therapy (ESWT)											
1 [M]	RCT	serious[3]	no serious	no serious	serious[2]	none	8/15 (53.3%)	5/15 (33.3%)	RR 1.6 (0.68 to 3.77) NNTB = N/A	20 more per 100 (from -11 fewer to 92 more)	LOW
Mean healing time (days): Shock wave therapy (ESWT)											
1 [M]	RCT	serious[3]	no serious	no serious	serious[4]	none	15	15	Mean (days) (SD): ESWT = 60.8 (4.7); control = 82.2 (4.7) p < 0.001		LOW

[M] = Moretti et al. (2009). ESWT + standard care vs standard care only (control). Standard care = debridement, off-loading, antibiotics if needed.
[P] = Peters et al. (2001). ES vs placebo stimulation with no current (control).
EST = electrical stimulation therapy.
[1] Allocation concealment unclear.
[2] Total no. of event <300.
[3] Allocation concealment unclear; no blinding.
[4] Total no. of participants <400.

GRADE evidence profiles 62
Other adjunctive treatments: Autologous platelet-rich plasma gel

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Autologous platelet-rich plasma gel	control	Relative (95% CI)	Absolute	Quality
Complete wound healing (12 weeks)											
1 [D]	RCT	serious[1]	no serious	no serious	serious[2]	none	13/40 (32.5%)	9/32 (28.1%)	RR 1.16 (0.57 to 2.35) NNTB = N/A	4 more per 100 (from 12 fewer to 38 more)	LOW
Median time to complete wound closure											
1 [D]	RCT	serious[1]	no serious	no serious	serious[3]	none	40	32	Median (days) (K-M): Treatment = 45; control = 85 Log-rank p = 0.126.		LOW

[D] = Driver et al. (2006). Autologous platelet-rich plasma gel + standard care vs saline gel + standard care only (control). Standard care = dressing, off-loading.
K-M = Kaplan-Meier.
[1] Allocation concealment unclear.
[2] Total no. of events <300.
[3] Total no. of participants <400.

GRADE evidence profiles 63
Other adjunctive treatments: Acellular dermal regenerative tissue matrix

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acellular dermal matrix	control	Relative (95% CI)	Absolute	Quality
Complete wound healing (follow-up 12 weeks)											
1 [R]	RCT	serious[1]	no serious	no serious	serious[2]	none	32/46 (69.6%)	18/39 (46.2%)	RR 1.50 (1.02 to 2.22) NNTB = 4 (2 to 44)	23 more per 100 (from 1 more to 56 more)	LOW
Healing rate (adjusted HR)											
1 [R]	RCT	serious[1]	no serious	no serious	serious[3]	none	46	39	Healing rate: Adjusted HR = 2.0 (95%CI: 1.0 to 3.5)		LOW

[R] = Reyzelman et al. (2009). Acellular dermal matrix + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.
[1] Allocation concealment and blinding unclear.
[2] Total no. of events <300.
[3] Total no. of participants <400.

GRADE evidence profiles 64
Other adjunctive treatments: OASIS wound matrix vs growth factor (PDGF)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	OASIS	PDGF	Relative (95% CI)	Absolute	
Complete wound healing (12 weeks) (follow-up 12 weeks)											
1 [N]	RCT	serious[1]	no serious	no serious	serious[2]	none	18/37 (48.6%)	10/36 (27.8%)	RR 1.75 (0.94 to 3.26) NNTB = N/A	21 more per 100 (from 2 fewer to 63 more)	LOW
Ulcer recurrence (6 months) (follow-up 6 months)											
1 [N]	RCT	serious[1]	no serious	no serious	serious[2]	none	5/19 (26.3%)	6/18 (33.3%)	RR 0.79 (0.29 to 2.12) NNTB = N/A	7 fewer per 100 (from 24 fewer to 37 more)	LOW

[N] = Niezgoda et al. (2005). Oasis wound matrix + standard care vs PDGF + standard care. Standard care = debridement, off-loading.
[1] Allocation concealment unclear.
[2] Total no. of event <300.

GRADE evidence profiles 65
Other adjunctive treatments: Arginine-glycine-aspartic acid (RGD) peptide matrix

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dalteparin (injection)	control	Relative (95% CI)	Absolute	
Complete wound healing (6 months) (follow-up 6 months)											
1 [S]	RCT	serious[1]	no serious	no serious	serious[2]	none	14/40 (35.0%)	2/25 (8.0%)	RR 4.36 (1.08 to 17.65) NNTB = 4 (2 to 16)	27 more per 100 (from 1 fewer to 100 more)	LOW

[S] = Steed el al. (1995). RGD peptide matrix + standard care vs saline gauze + standard care only (control). Standard care = debridement, dressing.
[1] Allocation concealment unclear.
[2] Total no. of event <300.

GRADE evidence profiles 66
Other adjunctive treatments: Dalteparin (for diabetic patients with PAOD)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dalteparin (injection)	control	Relative (95% CI)	Absolute	
Complete wound healing (6 months) (follow-up 6 months)											
1 [K]	RCT	serious[1]	no serious	no serious	serious[2]	none	14/43 (32.6%)	9/42 (21.4%)	RR 1.52 (0.74 to 3.13) NNTB = N/A	11 more per 100 (from 6 fewer to 46 more)	LOW
At least 50% wound reduction (follow-up 6 months)											
1 [K]	RCT	serious[1]	no serious	no serious	serious[2]	none	15/43 (34.9%)	10/42 (23.8%)	RR 1.33 (0.69 to 2.56) NNTB = N/A	8 more per 100 (from 7 fewer to 37 more)	LOW
Amputation (follow-up 6 months)											
1 [K]	RCT	serious[1]	no serious	no serious	serious[2]	none	2/43 (4.7%)	8/42 (19%)	RR 0.24 (0.06 to 1.08) NNTB = N/A	14 fewer per 100 (from 18 fewer to 2 more)	LOW

[K] = Kalani et al. (2003). Dalteparin (injection)+ standard care vs placebo saline + standard care. Standard care = dressing, debridement, off-loading, antibiotic if required.
[1] Allocation concealment unclear.
[2] Total no. of events <300.

Review question 6: When is the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems?

No study identified met the inclusion/exclusion criteria, therefore no study was included and no GRADE evidence profiles.

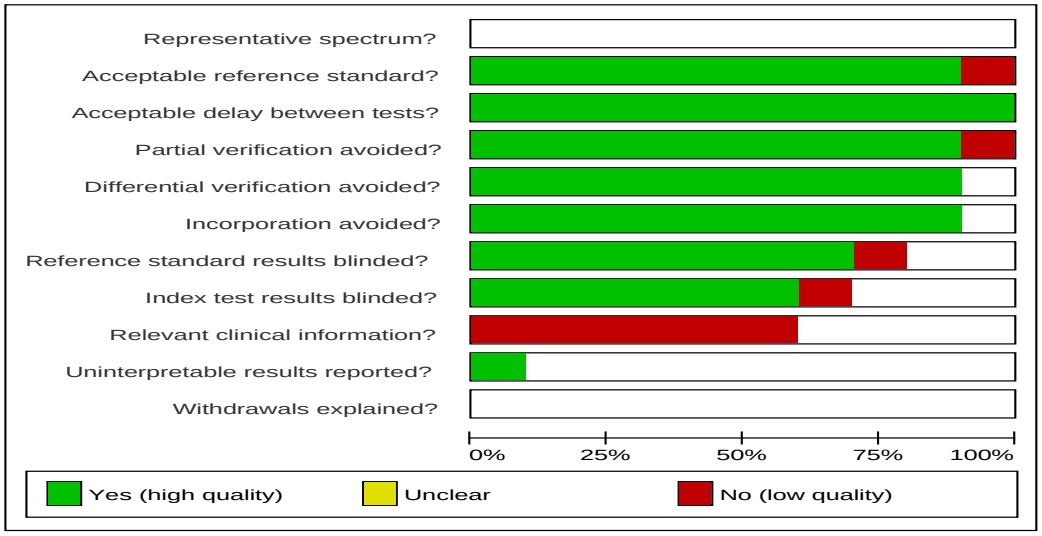
Appendix F Results of individual studies (Review question 2)

Review question 2: What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?

Table 1: Results of individual study – MRI imaging

Author	No. of patients	Reference test	Sen (%) (95%CI)	Spec (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Rozzanigo (2009)	16	Bacteriological and/or histological tests	100 (75-100)	67 (9-99)	0.93 (0.66-0.99)	0.00	0.67
Morrison (1995)	27	Histological analysis or clinical and radiographic demonstration despite conservative antibiotic therapy	82 (57-96)	80 (44-97)	0.88 (0.62-0.98)	0.27	0.62
Croll (1996)	27	Pathologic specimen or bone culture	89 (52-100)	100 (81-100)	1.00 (0.63-1.00)	0.05	0.89
Al-Khawari (2007)	19	Histological analysis	100 (72-100)	63 (24-91)	0.79 (0.49-0.95)	0.00	0.63
Ertugrul (2006)	28	Histopathological analysis	78 (56-93)	60 (15-95)	0.9 (0.68-0.99)	0.62	0.38
Yuh (1989)	29	Pathological tests	100 (86-100)	100 (40-100)	1.00 (0.86-1.00)	0.00	1.00
Wang (1990)	62	Histological examination	98 (88-100)	81 (54-96)	0.94 (0.83-0.98)	0.07	0.79
Beltran (1990)	14	Aspiration/pathologic examination/plain films	100 (54-100)	75 (35-97)	0.75 (0.35-0.97)	0.00	0.75
Levine (1994)	29	Pathological/histological/ surgical examination/ clinical follow-up	77 (46-95)	81 (54-96)	0.77 (0.46-0.95)	0.19	0.58
Weinstein (1993)	62	Histological examination	100 (92-100)	81 (54-96)	0.94 (0.83-0.99)	0.00	0.81

QUADAS methodological quality graph – MRI imaging (all 10 studies)



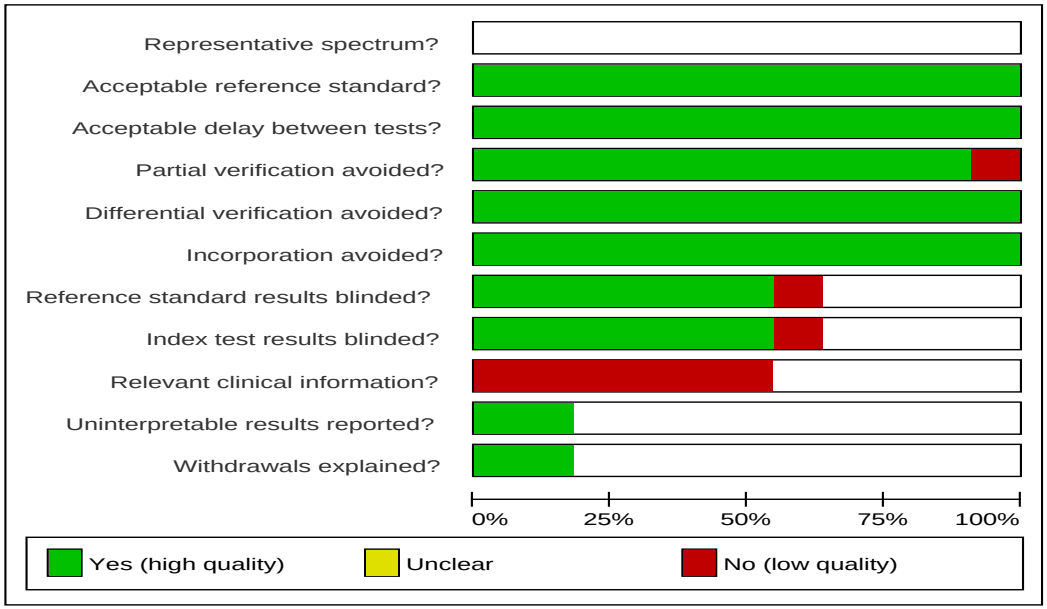
Note: those in 'white' in the graph should be 'yellow – unclear'. Many apologies for the software technical problem.

Table 2: Results of individual study – 99mTc-MDP scintigraphy

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spec (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Croll (1996)	22	Pathologic specimen or bone culture	50 (16-84)	50 (23-77)	0.36 (0.11-0.69)	0.36	0.00
Ertugrul (2006)	26	Histopathological analysis	91 (72-99)	67 (9-99)	0.95 (0.77-0.99)	0.50	0.58
Palestro (2003)	25	Bone biopsy and culture or clinical follow-up	90 (55-100)	27 (8-55)	0.45 (0.23-0.68)	0.20	0.17
Harwood (1999)	47	Histological and/or microbiological cultures	94 (80-99)	21 (5-51)	0.74 (0.58-0.86)	0.40	0.16
Keenan (1989)	94	Culture and/or histological examination	100 (91-100)	38 (25-51)	0.52 (0.40-0.64)	0.00	0.38
Poirier (2002)	83	Radiological examination or histopathological analysis	100 (91-100)	29 (16-45)	0.58 (0.45-0.69)	0.00	0.29
Yuh (1989)	21	Pathological tests	94 (73-100)	0 (0-71)	0.85 (0.62-0.97)	N/A	-0.06

Larcos (1991)	49	Bone culture/biopsy or clinical follow-up	93 (66-100)	57 (39-74)	0.46 (0.27-0.66)	0.05	0.50
Newman (1991)	39	Bone biopsy and culture	69 (48-86)	38 (14-68)	0.69 (0.48-0.87)	0.62	0.07
Harvey (1997)	31	Histology, bone cultures and radiographic results	91 (59-100)	40 (19-64)	0.45 (0.23-0.68)	0.11	0.31
Devillers (1998)	56	Radiographic/bacteriological/histological results or clinical follow up	100 (87-100)	30 (15-49)	0.55 (0.40-0.70)	0.00	0.30

QUADAS methodological quality graph – 99mTc-MDP scintigraphy (all 11 studies)



Note: those in 'white' in the graph should be 'yellow – unclear'. Many apologies for the software technical problem.

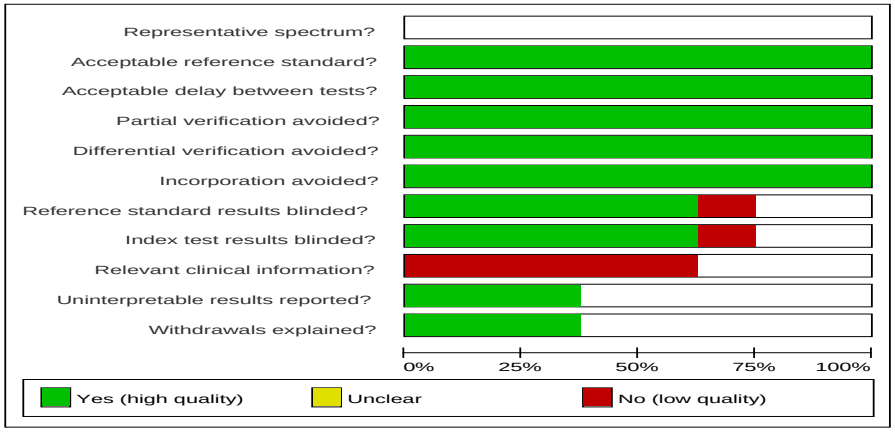
Table 3: Results of individual study – 99mTc-HMPAO scintigraphy

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spec (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Devillers (1998)	56	Radiographic/ bacteriological /histological results or clinical follow up	88 (70-98)	97 (83-100)	0.94 (0.79-0.99)	0.09	0.85
Harvey (1997)	52	Histology, bone cultures and radiographic results	86 (64-97)	90 (74-98)	0.86 (0.64-0.97)	0.10	0.76
Harwood (1999)	122	Histological and/or microbiological cultures	91 (83-96)	56 (40-72)	0.80 (0.71-0.88)	0.23	0.47

Table 4: Results of individual study – In-WBC scan

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spec (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Croll (1996)	19	Pathologic specimen or bone culture	33 (4-78)	69 (39-91)	0.33 (0.04-0.78)	0.31	-0.01
Palestro (2003)	25	Bone biopsy and culture or clinical follow-up	80 (44-97)	67 (38-88)	0.62 (0.32-0.86)	0.17	0.47
Harwood (1999)	111	Histological and/or microbiological cultures	79 (68-87)	67 (49-81)	0.83 (0.72-0.91)	0.4	0.46
Keenan (1989)	46	Culture and/or histological examination	100 (82-100)	78 (58-91)	0.76 (0.55-0.91)	0.00	0.78
Larcos (1991)	51	Bone culture/biopsy or clinical follow-up	79 (49-95)	22 (100-38)	0.28 (0.15-0.44)	0.27	0.01
Levine (1994)	12	Pathological/histological/ surgical examination/ clinical follow-up	80 (28-00)	29 (4-71)	0.44 (0.14-0.79)	0.33	0.09
Newman (1991) (4h)	35	Bone biopsy and culture	77 (55-92)	77 (46-95)	0.85 (0.62-0.97)	0.33	0.54
Newman (1991) (24h)	39	Bone biopsy and culture	88 (70-98)	69 (39-91)	0.85 (0.66-0.96)	0.25	0.57

QUADAS methodological quality graph – In-WBC scan (all 8 studies)



Note: those in 'white' in the graph should be 'yellow – unclear'. Many apologies for the software technical problem.

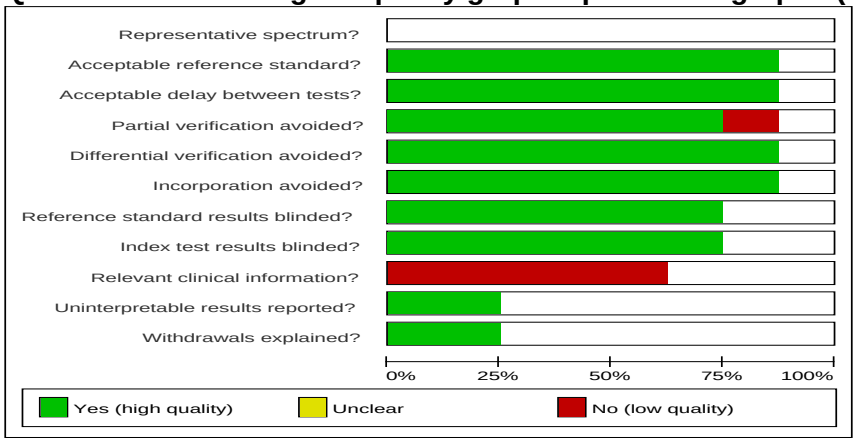
Table 5: Results of individual study - LeukoScan (anti-granulocyte Fab' fragment antibody scintigraphy)

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spec (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Rubello (2004) (4h)	78	Microbiological findings/CT scan /MRI/clinical follow-up	92 (82-97)	75 (48-93)	0.93 (0.84-0.98)	0.29	0.67
Rubello (2004) (24h)	78	Microbiological findings/CT scan /MRI/clinical follow-up	92 (82-97)	88 (62-98)	0.97 (0.88-0.99)	0.26	0.80

Table 6: Results of individual study - Plain radiographs

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Croll (1996)	27	Pathologic specimen or bone culture	22 (3-60)	94 (73-100)	0.67 (0.09-0.99)	0.29	0.06
Yuh (1989)	28	Pathological tests	75 (53-90)	75 (19-99)	0.95 (0.74-0.99)	0.67	0.50
Larcos (1991)	49	Bone culture/biopsy or clinical follow-up	43 (18-71)	17 (7-34)	0.17 (0.06-0.34)	0.57	-0.40
Levine (1994)	26	Pathological/histological/surgical examination /clinical follow-up	60 (26-88)	81 (54-96)	0.67 (0.30-0.93)	0.24	0.41
Wang (1990)	62	Histological examination	52 (37-67)	69 (41-89)	0.83 (0.64-0.94)	0.67	0.21
Newman (1991)	37	Bone biopsy and culture	28 (12-49)	92 (62-100)	0.88 (0.47-0.99)	0.62	0.20
Weinstein (1993)	62	Histological examination	52 (37-67)	81 (54-96)	0.89 (0.71-0.98)	0.63	0.33
Devillers (1998)	56	Radiographic/bacteriological/histological results or clinical follow up	54 (33-73)	83 (65-94)	0.74 (0.49-0.91)	0.33	0.37

QUADAS methodological quality graph – plain radiographs (all 8 studies)



Note: those in 'white' in the graph should be 'yellow – unclear'. Many apologies for the software technical problem.

Table 7: Results of individual study - Moab

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Palestro (2003)	25	Bone biopsy and culture or clinical follow-up	90 (55-100)	67 (38-88)	0.64 (0.35-0.87)	0.09	0.57

Table 8: Results of individual study: In-WBC scan + 99mTc-MDP scintigraphy

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Palestro (2003)	25	Bone biopsy and culture or clinical follow-up	80 (44-97)	80 (52-96)	0.73 (0.39-0.94)	0.14	0.60
Keenan (1989)	39	Culture and/or histological examination	100 (70-100)	79 (58-93)	0.75 (0.51-0.91)	0.00	0.79

Table 9: Results of individual study: Moab+99mTc-MDP bone scan

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Palestro (2003)	25	Bone biopsy and culture or clinical follow-up	90 (55-100)	67 (38-88)	0.64 (0.35-0.87)	0.09	0.57

Table 10: Results of individual study: 99m-HMPAO*+99mTc-MDP bone scan

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Poirier (2002)	83	Radiological examination or histopathological analysis	93 (80-98)	98 (87-100)	0.97 (0.86-0.99)	0.07	0.91

Table 11: Results of individual study: 99mTc-MDP+gallium-67 citrate scan

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Weinstein (1993)	22	Histological examination	69 (41-89)	83 (46-100)	0.92 (0.61-0.99)	0.5	0.52

Table 12: Results of individual study - ESR

Author	Cut-off (mm/h)	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Kaleta (2001)	≥60	29	Histological examination	92 (73-99)	68 (45-86)	0.94 (0.73-0.99)	0.18	0.60
Ertugrul (2009)	≥60	46	Histopathology/ bone tissue culture/MRI conventional spin echo	89 (67-99)	90 (55-100)	0.76 (0.56-0.90)	0.12	0.79
Kaleta (2001)	≥65	29	Histological examination	89 (67-99)	90 (55-100)	0.94 (0.73-0.99)	0.18	0.79
Ertugrul (2009)	≥65	46	Histopathology/bone tissue culture/MRI conventional spin echo	88 (68-97)	73 (50-89)	0.78 (0.58-0.91)	0.16	0.61
Kaleta (2001)	≥75	29	Histological examination	84 (60-97)	100 (69-100)	1.00 (0.79-1.00)	0.23	0.84
Ertugrul (2009)	≥75	46	Histopathology/bone tissue culture/MRI conventional spin echo	79 (58-93)	82 (60-95)	0.83 (0.61-0.95)	0.22	0.61
Kaleta (2001)	≥80	29	Histological examination	79 (54-94)	100 (69-100)	1.00 (0.78-1.00)	0.29	0.79
Ertugrul (2009)	≥80	46	Histopathology/bone tissue culture/MRI conventional spin echo	71 (49-81)	91 (71-99)	0.89 (0.67-0.99)	0.26	0.62
Kaleta (2001)	≥70	29	Histological examination	89 (67-99)	100 (69-100)	1.00 (0.80-1.00)	0.17	0.89
Ertugrul (2009)	≥70	46	Histopathology/bone tissue culture/MRI conventional spin echo	83 (63-95)	77 (55-92)	0.8 (0.59-0.93)	0.19	0.60
Newman (1991)	>70*	18	Bone biopsy and culture	28 (10-53)	100 (69-100)	1.00 (0.48-1.00)	0.57	0.28
Malabu (2007)	>70	22	Bone scan/MRI/radiographs	91 (71-99)	95 (76-100)	0.95 (0.76-0.99)	0.09	0.86
Newman (1991)	>100**	26	Bone biopsy and culture	23 (9-44)	100 (75-100)	1.00 (0.54-1.00)	0.61	0.23

*(noninflamed)

**(all ulcers)

Table 13: Results of individual study - Wound sizes

Author	Cut-off	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Ertugrul (2001)	≥2cm²	46	Histopathology/bone tissue culture/MRI conventional spin echo	88 (68-97)	77 (55-92)	0.81 (0.61-0.93)	0.15	0.65
Newman (1991)	>2cm²	40	Bone biopsy and culture	56 (35-75)	93 (66-100)	0.94 (0.70-0.99)	0.48	0.49
Ertugrul (2001)	≥3cm²	46	Histopathology/bone tissue culture/MRI conventional spin echo	79 (58-93)	77 (55-92)	0.79 (0.58-0.93)	0.23	0.56
Ertugrul (2001)	≥4cm²	46	Histopathology/bone tissue culture/MRI conventional spin echo	67 (45-84)	91 (71-99)	0.89 (0.65-0.99)	0.29	0.58
Ertugrul (2001)	≥5cm²	46	Histopathology/bone tissue culture/MRI conventional spin echo	50 (29-71)	95 (77-100)	0.92 (0.64-0.99)	0.36	0.45

Table 14: Results of individual study - ERS rate ≥65 + wound size ≥2cm²

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Ertugrul (2001)	46	Histopathology/bone tissue culture/MRI conventional spin echo	83 (63-95)	77 (55-92)	0.8 (0.59-0.93)	0.19	0.60

Table 15: Results of individual study - ERS rate ≥70 + wound size ≥2cm²

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Ertugrul (2001)	46	Histopathology/bone tissue culture/MRI conventional spin echo	79 (58-93)	82 (60-95)	0.83 (0.61-0.95)	0.22	0.61

Table 16: Results of individual study - Hematocrit >36%

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Malabu (2007)	43	Bone scan/MRI/radiographs	95 (77-100)	86 (64-97)	0.88 (0.68-0.97)	0.05	0.81

Table 17: Results of individual study - Hemoglobin <12g/dL

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Malabu (2007)	43	Bone scan/MRI/radiographs	82 (60-95)	90 (70-99)	0.9 (0.68-0.99)	0.17	0.72

Table 18: Results of individual study - Platelet count >400x10^9/L

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Malabu (2007)	43	Bone scan/MRI/radiographs	45 (24-68)	95 (76-100)	0.91 (0.59-0.99)	0.37	0.40

Table 19: Results of individual study - Red cell distribution width >14.5

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Malabu (2007)	43	Bone scan/MRI/radiographs	68 (45-86)	62 (38-82)	0.65 (0.43-0.84)	0.35	0.30

Table 20: Results of individual study - White cell count >400x10^9/L

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Malabu (2007)	43	Bone scan/MRI/radiographs	50 (28-72)	81 (58-95)	0.73 (0.45-0.92)	0.39	0.31

Table 21: Results of individual study - Microbiological processing

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Ertugrul (2006)	31	Histopathological analysis	92 (75-99)	60 (15-95)	0.92 (0.75-0.99)	0.4	0.52

Table 21: Results of individual study - Clinical judgement

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Newman (1991)	41	Bone biopsy and culture	32 (16-52)	100 (75-100)	1.00 (0.66-1.00)	0.59	0.32

Table 22: Results of individual study - Ulcer inflammation

Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Newman (1991)	41	Bone biopsy and culture	36 (19-56)	81 (54-96)	0.77 (0.46-0.95)	0.58	0.17

Table 23: Results of individual study Bone exposure

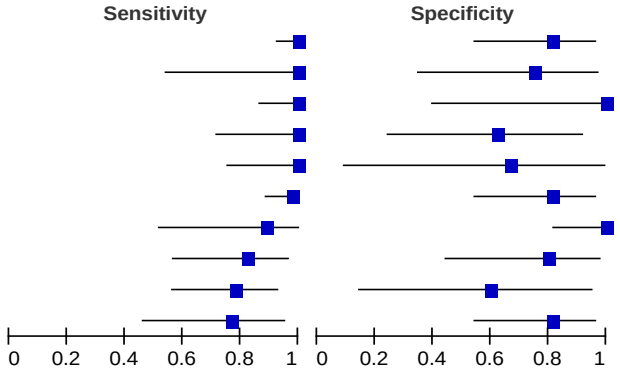
Author	No. of Patients	Reference test	Sen (%) (95%CI)	Spe (%) (95%CI)	Post-test prob (+ve) (95%CI)	Post-test prob (despite [-ve])	Youden Index
Newman (1991)	41	Bone biopsy and culture	32 (16-52)	100 (75-100)	1.00 (0.66-1.00)	0.59	0.32

Appendix G Summary of ROC and forest plots (Review question 2)

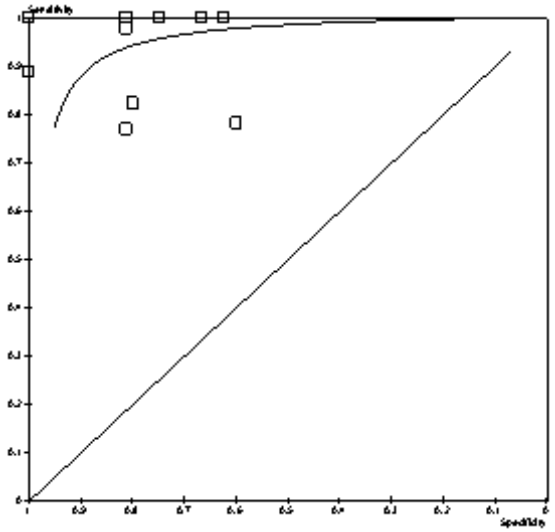
Review question 2: What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?

Forest plot 1: MRI imaging in diagnosing osteomyelitis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Weinstein 1993-MRI	46	3	0	13	1.00 [0.92, 1.00]	0.81 [0.54, 0.96]
Beltran 1990-MRI	6	2	0	6	1.00 [0.54, 1.00]	0.75 [0.35, 0.97]
Yuh 1989-MRI	25	0	0	4	1.00 [0.86, 1.00]	1.00 [0.40, 1.00]
Al-Khawari 2007-MRI	11	3	0	5	1.00 [0.72, 1.00]	0.63 [0.24, 0.91]
Rozzanigo 2009-MRI	13	1	0	2	1.00 [0.75, 1.00]	0.67 [0.09, 0.99]
Wang 1990-MRI	45	3	1	13	0.98 [0.88, 1.00]	0.81 [0.54, 0.96]
Croll 1996-MRI	8	0	1	18	0.89 [0.52, 1.00]	1.00 [0.81, 1.00]
Morrison 1995-MRI	14	2	3	8	0.82 [0.57, 0.96]	0.80 [0.44, 0.97]
Ertugrul 2006-MRI	18	2	5	3	0.78 [0.56, 0.93]	0.60 [0.15, 0.95]
Levine 1994-MRI	10	3	3	13	0.77 [0.46, 0.95]	0.81 [0.54, 0.96]

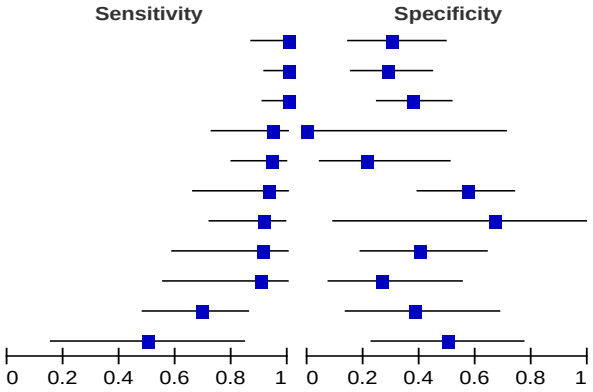


SROC 1: MRI imaging in diagnosing osteomyelitis

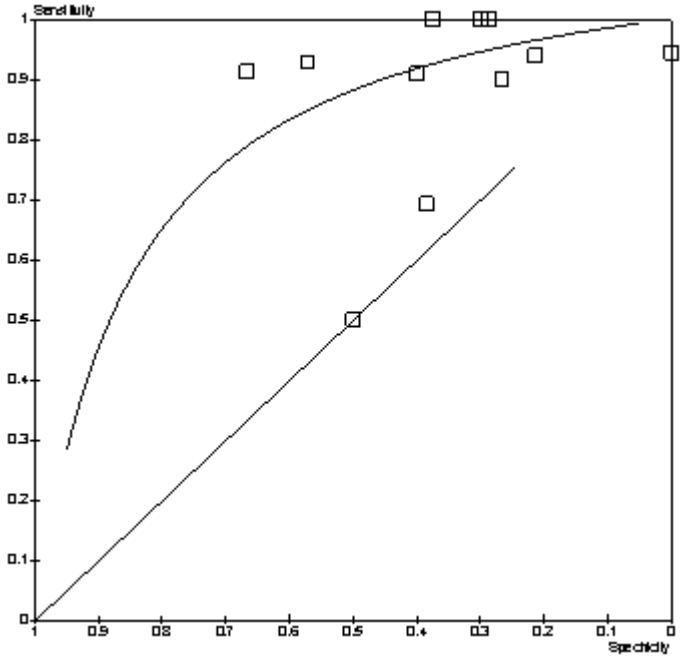


Forest plot 2: 99mTc-MDP scintigraphy (bone scan) in diagnosing osteomyelitis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Devillers 1998-99mTcMDP	26	21	0	9	1.00 [0.87, 1.00]	0.30 [0.15, 0.49]
Poirier 2002-99mTcMDP	41	30	0	12	1.00 [0.91, 1.00]	0.29 [0.16, 0.45]
Keenan 1989-99mTcMDP	38	35	0	21	1.00 [0.91, 1.00]	0.38 [0.25, 0.51]
Yuh 1989-99mTcMDP	17	3	1	0	0.94 [0.73, 1.00]	0.00 [0.00, 0.71]
Harwood 1999-99mTcMDP	31	11	2	3	0.94 [0.80, 0.99]	0.21 [0.05, 0.51]
Larcos 1991-99mTcMDP	13	15	1	20	0.93 [0.66, 1.00]	0.57 [0.39, 0.74]
Ertugrul 2006-99mTcMDP	21	1	2	2	0.91 [0.72, 0.99]	0.67 [0.09, 0.99]
Harvey 1997-99mTcMDP	10	12	1	8	0.91 [0.59, 1.00]	0.40 [0.19, 0.64]
Palestro 2003-99mTcMDP	9	11	1	4	0.90 [0.55, 1.00]	0.27 [0.08, 0.55]
Newman 1991-99mTcMDP	18	8	8	5	0.69 [0.48, 0.86]	0.38 [0.14, 0.68]
Croll 1996-99mTcMDP	4	7	4	7	0.50 [0.16, 0.84]	0.50 [0.23, 0.77]

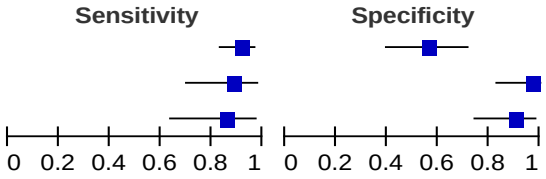


SROC 2: 99mTc-MDP scintigraphy (bone scan) in diagnosing osteomyelitis

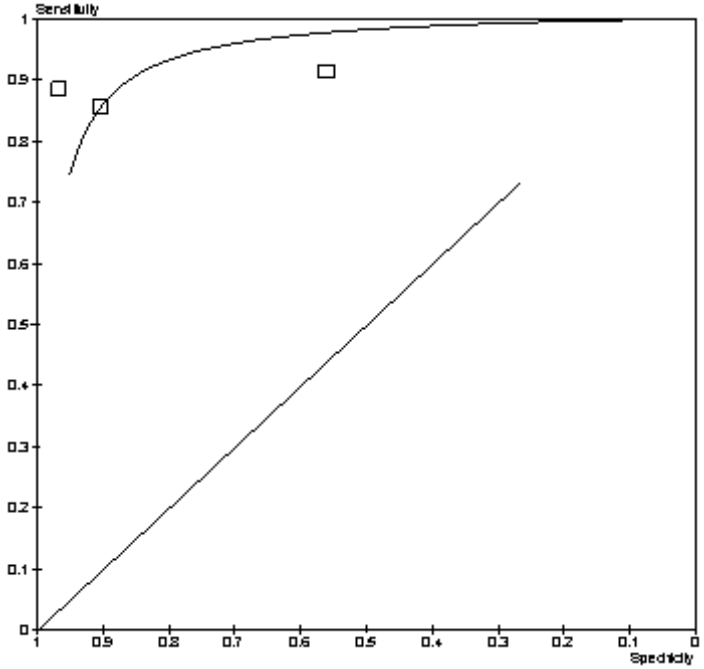


Forest plot 3: 99mTc-HMPAO scintigraphy (bone scan) in diagnosing osteomyelitis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Harwood 1999-99m-HMPAO	74	18	7	23	0.91 [0.83, 0.96]	0.56 [0.40, 0.72]
Devillers 1998-99mHMPAO	23	1	3	29	0.88 [0.70, 0.98]	0.97 [0.83, 1.00]
Harvey 1997-99mHMPAO	18	3	3	28	0.86 [0.64, 0.97]	0.90 [0.74, 0.98]

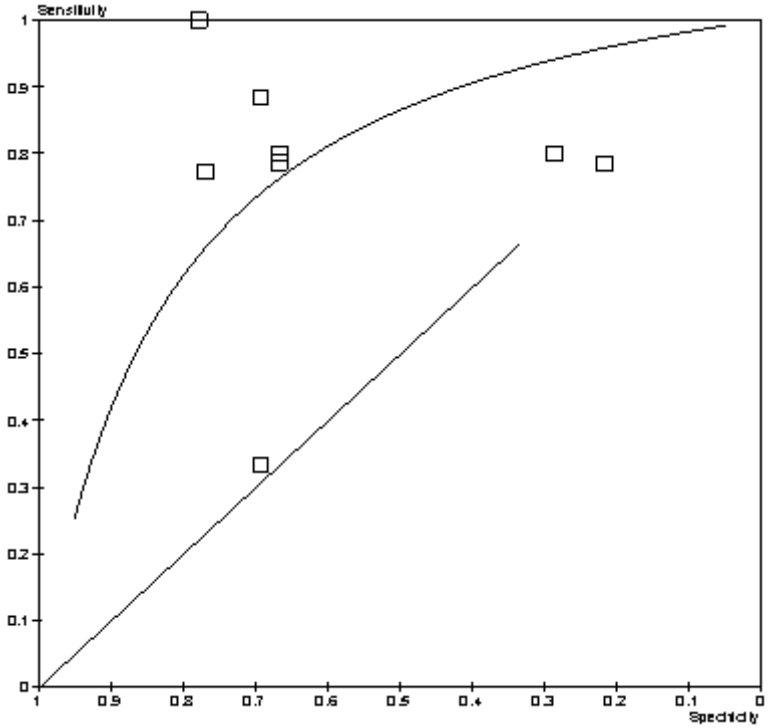


SROC 3: 99mTc-HMPAO scintigraphy (bone scan) in diagnosing osteomyelitis



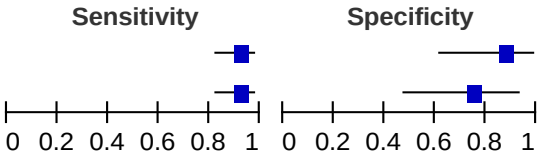
Forest plot 4: In-WBC scan in diagnosing osteomyelitis

SROC 4: In-WBC scan in diagnosing osteomyelitis

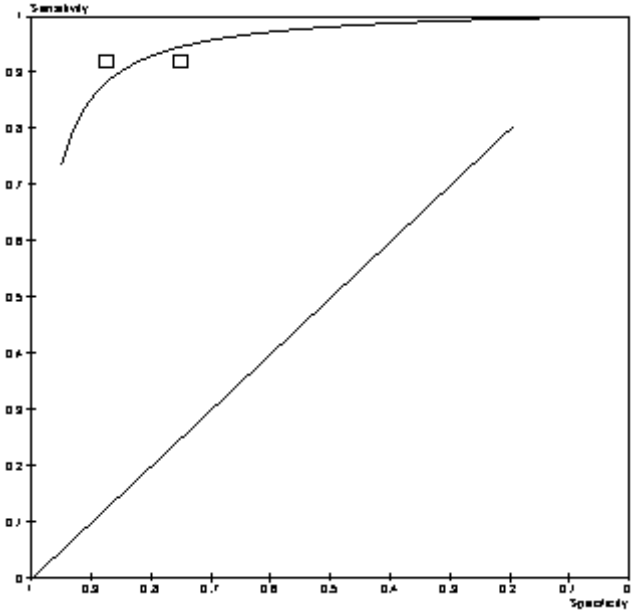


Forest plot 5: LeukoScan in diagnosing osteomyelitis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rubello 2004-LeukoSc(24h)	57	2	5	14	0.92 [0.82, 0.97]	0.88 [0.62, 0.98]
Rubello 2004-LeukoSc(4h)	57	4	5	12	0.92 [0.82, 0.97]	0.75 [0.48, 0.93]

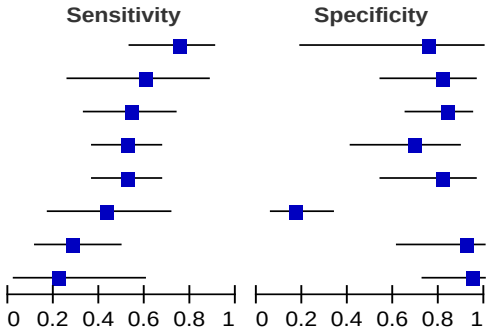


SROC 5: LeukoScan in diagnosing osteomyelitis

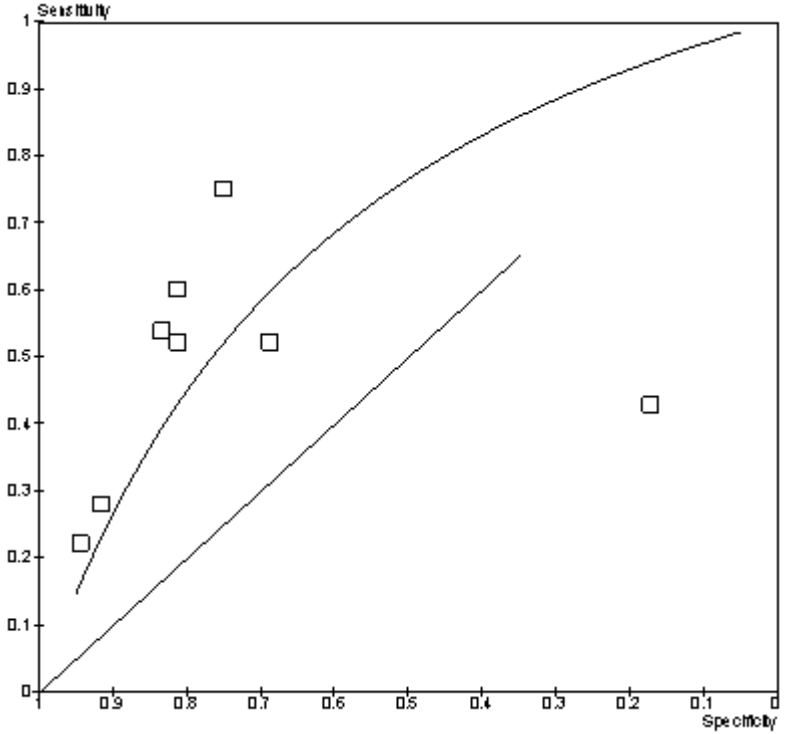


Forest plot 6: plain radiographs in diagnosing osteomyelitis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Yuh 1989-Radiographs	18	1	6	3	0.75 [0.53, 0.90]	0.75 [0.19, 0.99]
Levine 1994-Radiographs	6	3	4	13	0.60 [0.26, 0.88]	0.81 [0.54, 0.96]
Devillers 1998-Radiograph	14	5	12	25	0.54 [0.33, 0.73]	0.83 [0.65, 0.94]
Wang 1990-Xray	24	5	22	11	0.52 [0.37, 0.67]	0.69 [0.41, 0.89]
Weinstein 1993-Radiograph	24	3	22	13	0.52 [0.37, 0.67]	0.81 [0.54, 0.96]
Larcos 1991-Radiographs	6	29	8	6	0.43 [0.18, 0.71]	0.17 [0.07, 0.34]
Newman 1991-Roentgenogram	7	1	18	11	0.28 [0.12, 0.49]	0.92 [0.62, 1.00]
Croll 1996-Radiographs	2	1	7	17	0.22 [0.03, 0.60]	0.94 [0.73, 1.00]

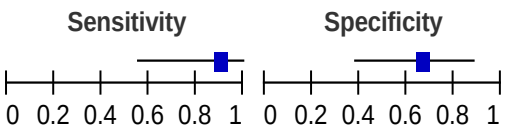


SROC 6: plain radiographs in diagnosing osteomyelitis



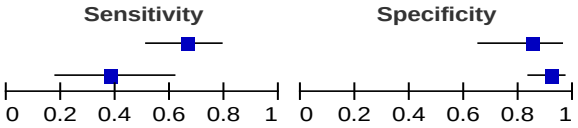
Forest plot 7: Moab in diagnosing osteomyelitis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Palestro 2003-Moab	9	5	1	10	0.90 [0.55, 1.00]	0.67 [0.38, 0.88]

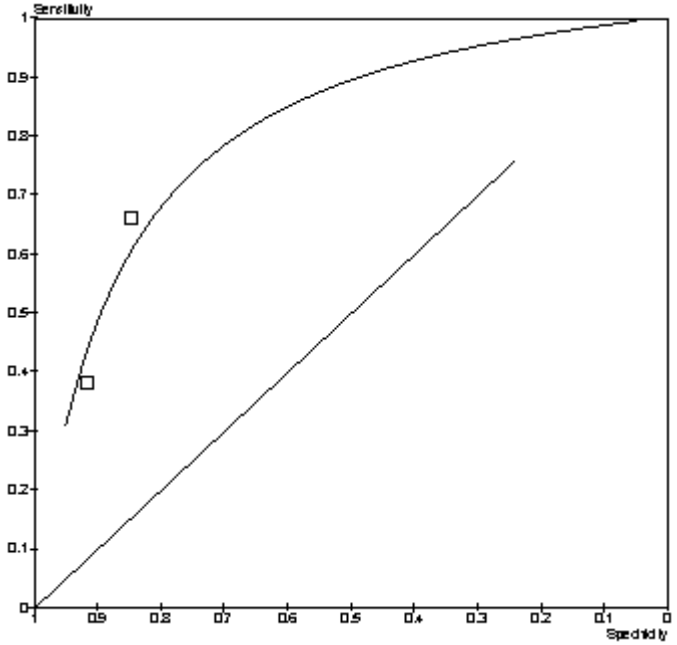


Forest plot 8: Probe-to-bone in diagnosing osteomyelitis

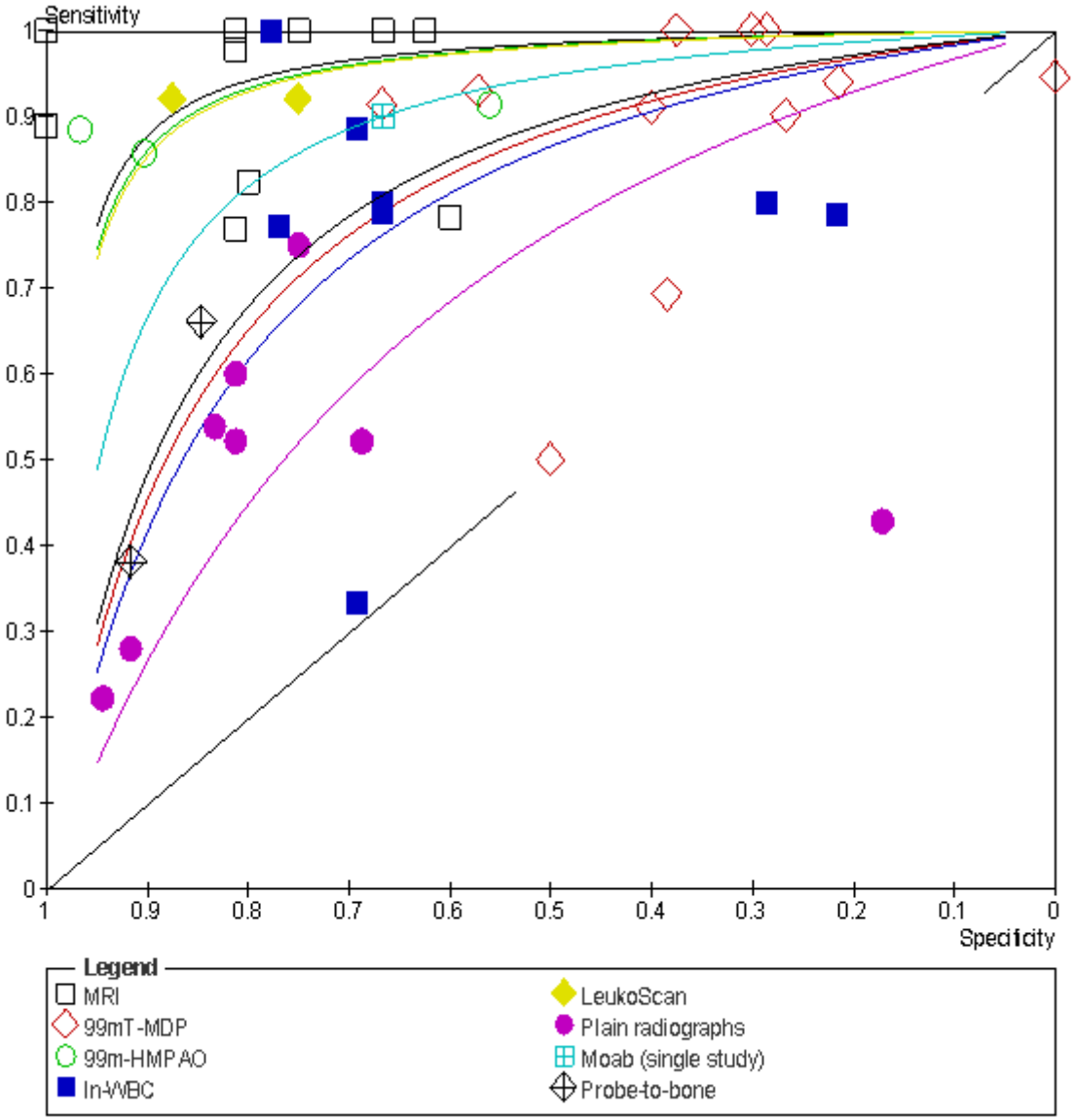
Study	TP	FP	FN	TN	Sensitivity	Specificity
Grayson 1995	33	4	17	22	0.66 [0.51, 0.79]	0.85 [0.65, 0.96]
Shone 2006	8	7	13	76	0.38 [0.18, 0.62]	0.92 [0.83, 0.97]



SROC 7: Probe-to-bone in diagnosing osteomyelitis



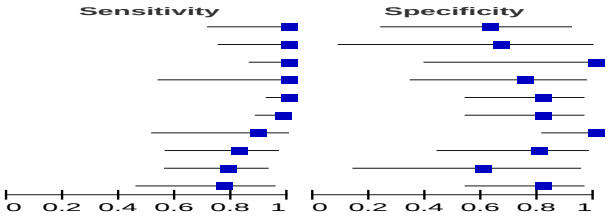
SROC 7: All single tests



Forest plots 8

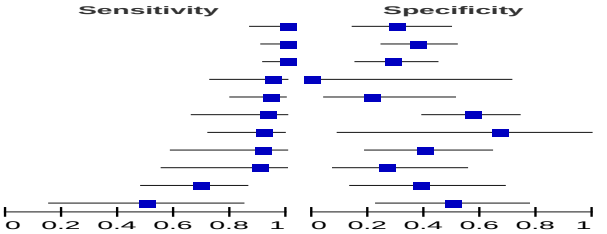
MRI

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Khawari 2007-MRI	11	3	0	5	1.00 [0.72, 1.00]	0.63 [0.24, 0.91]
Rozzanigo 2009-MRI	13	1	0	2	1.00 [0.75, 1.00]	0.67 [0.09, 0.99]
Yuh 1989-MRI	25	0	0	4	1.00 [0.86, 1.00]	1.00 [0.40, 1.00]
Beltran 1990-MRI	6	2	0	6	1.00 [0.54, 1.00]	0.75 [0.35, 0.97]
Weinstein 1993-MRI	46	3	0	13	1.00 [0.92, 1.00]	0.81 [0.54, 0.96]
Wang 1990-MRI	45	3	1	13	0.98 [0.88, 1.00]	0.81 [0.54, 0.96]
Croll 1996-MRI	8	0	1	18	0.89 [0.52, 1.00]	1.00 [0.81, 1.00]
Morrison 1995-MRI	14	2	3	8	0.82 [0.57, 0.96]	0.80 [0.44, 0.97]
Ertugrul 2006-MRI	18	2	5	3	0.78 [0.56, 0.93]	0.60 [0.15, 0.95]
Levine 1994-MRI	10	3	3	13	0.77 [0.46, 0.95]	0.81 [0.54, 0.96]



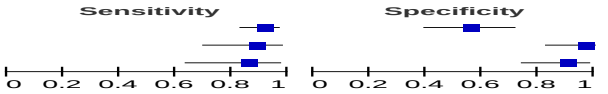
99mT-MDP

Study	TP	FP	FN	TN	Sensitivity	Specificity
Devillers 1998-99mTcMDP	26	21	0	9	1.00 [0.87, 1.00]	0.30 [0.15, 0.49]
Keenan 1989-99mTcMDP	38	35	0	21	1.00 [0.91, 1.00]	0.38 [0.25, 0.51]
Poirier 2002-99mTcMDP	41	30	0	12	1.00 [0.91, 1.00]	0.29 [0.16, 0.45]
Yuh 1989-99mTcMDP	17	3	1	0	0.94 [0.73, 1.00]	0.00 [0.00, 0.71]
Harwood 1999-99mTcMDP	31	11	2	3	0.94 [0.80, 0.99]	0.21 [0.05, 0.51]
Larcos 1991-99mTcMDP	13	15	1	20	0.93 [0.66, 1.00]	0.57 [0.39, 0.74]
Ertugrul 2006-99mTcMDP	21	1	2	2	0.91 [0.72, 0.99]	0.67 [0.09, 0.99]
Harvey 1997-99mTcMDP	10	12	1	8	0.91 [0.59, 1.00]	0.40 [0.19, 0.64]
Palestro 2003-99mTcMDP	9	11	1	4	0.90 [0.55, 1.00]	0.27 [0.08, 0.55]
Newman 1991-99mTcMDP	18	8	8	5	0.69 [0.48, 0.86]	0.38 [0.14, 0.68]
Croll 1996-99mTcMDP	4	7	4	7	0.50 [0.16, 0.84]	0.50 [0.23, 0.77]



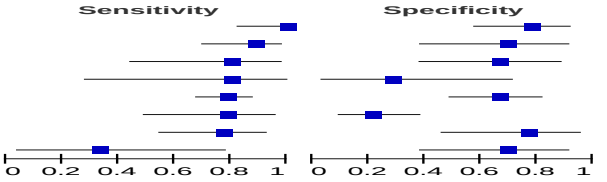
99m-HMPAO

Study	TP	FP	FN	TN	Sensitivity	Specificity
Harwood 1999-99m-HMPAO	74	18	7	23	0.91 [0.83, 0.96]	0.56 [0.40, 0.72]
Devillers 1998-99mHMPAO	23	1	3	29	0.88 [0.70, 0.98]	0.97 [0.83, 1.00]
Harvey 1997-99mHMPAO	18	3	3	28	0.86 [0.64, 0.97]	0.90 [0.74, 0.98]



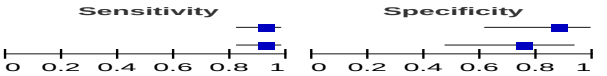
In-WBC

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keenan 1989-In-WBC	19	6	0	21	1.00 [0.82, 1.00]	0.78 [0.58, 0.91]
Newman 1991-In-WBC(24h)	23	4	3	9	0.88 [0.70, 0.98]	0.69 [0.39, 0.91]
Palestro 2003-In-WBC	8	5	2	10	0.80 [0.44, 0.97]	0.67 [0.38, 0.88]
Levine 1994-In-WBC	4	5	1	2	0.80 [0.28, 0.99]	0.29 [0.04, 0.71]
Harwood 1999-In-WBC	59	12	16	24	0.79 [0.68, 0.87]	0.67 [0.49, 0.81]
Larcos 1991-In-WBC	11	29	3	8	0.79 [0.49, 0.95]	0.22 [0.10, 0.38]
Newman 1991-In-WBC(4h)	17	3	5	10	0.77 [0.55, 0.92]	0.77 [0.46, 0.95]
Croll 1996-In-WBC	2	4	4	9	0.33 [0.04, 0.78]	0.69 [0.39, 0.91]



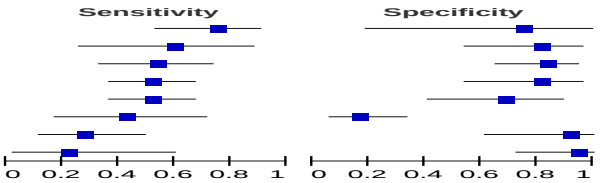
LeukoScan

Study	TP	FP	FN	TN	Sensitivity	Specificity
Rubello 2004-LeukoSc(24h)	57	2	5	14	0.92 [0.82, 0.97]	0.88 [0.62, 0.98]
Rubello 2004-LeukoSc(4h)	57	4	5	12	0.92 [0.82, 0.97]	0.75 [0.48, 0.93]



Plain radiographs

Study	TP	FP	FN	TN	Sensitivity	Specificity
Yuh 1989-Radiographs	18	1	6	3	0.75 [0.53, 0.90]	0.75 [0.19, 0.99]
Levine 1994-Radiographs	6	3	4	13	0.60 [0.26, 0.88]	0.81 [0.54, 0.96]
Devillers 1998-Radiograph	14	5	12	25	0.54 [0.33, 0.73]	0.83 [0.65, 0.94]
Weinstein 1993-Radiograph	24	3	22	13	0.52 [0.37, 0.67]	0.81 [0.54, 0.96]
Wang 1990-Xray	24	5	22	11	0.52 [0.37, 0.67]	0.69 [0.41, 0.89]
Larcos 1991-Radiographs	6	29	8	6	0.43 [0.18, 0.71]	0.17 [0.07, 0.34]
Newman 1991-Roentgenogram	7	1	18	11	0.28 [0.12, 0.49]	0.92 [0.62, 1.00]
Croll 1996-Radiographs	2	1	7	17	0.22 [0.03, 0.60]	0.94 [0.73, 1.00]

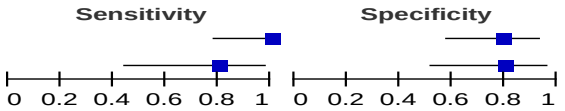


MDP+In-WBC

Forest plot 9: other imaging tests (combination) in diagnosing osteomyelitis

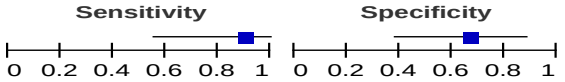
MDP+In-WBC

Study	TP	FP	FN	TN	Sensitivity	Specificity
Keenan 1989-MDP+In-WBC	15	5	0	19	1.00 [0.78, 1.00]	0.79 [0.58, 0.93]
Palestro 2003-MDP+In-MBC	8	3	2	12	0.80 [0.44, 0.97]	0.80 [0.52, 0.96]



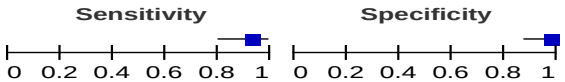
Moab+MDP (single study)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Palestro 2003-Moab+MDP	9	5	1	10	0.90 [0.55, 1.00]	0.67 [0.38, 0.88]



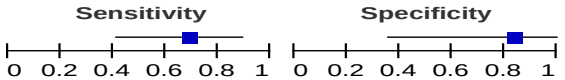
MDP+HMPAO (single study)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Poirer 2002-MDP+HMPAO	38	1	3	41	0.93 [0.80, 0.98]	0.98 [0.87, 1.00]

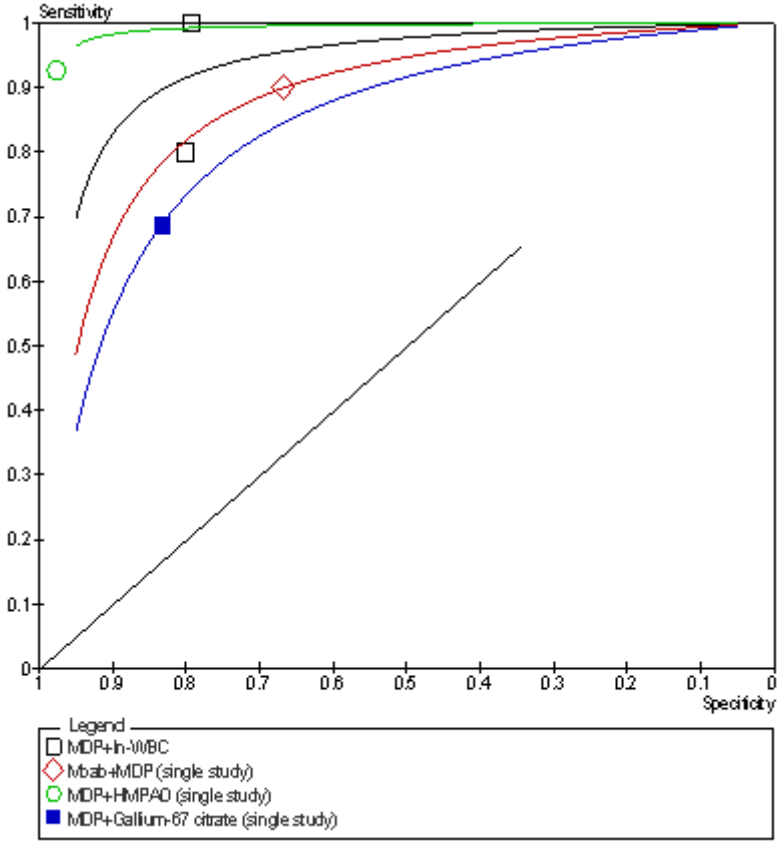


MDP+Gallium-67 citrate (single study)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Weinstein 1993-MDP+Galliu	11	1	5	5	0.69 [0.41, 0.89]	0.83 [0.36, 1.00]



SROC 9: other imaging tests (combination) in diagnosing osteomyelitis



Forest plot 10: ESR in diagnosing osteomyelitis

ERS≥60mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2009-ERS≥60	22	7	2	15	0.92 [0.73, 0.99]	0.68 [0.45, 0.86]
Kaleta 2001-ERS≥60	17	1	2	9	0.89 [0.67, 0.99]	0.90 [0.55, 1.00]

ERS≥65mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥65	17	1	2	9	0.89 [0.67, 0.99]	0.90 [0.55, 1.00]
Ertugrul 2009-ERS≥65	21	6	3	16	0.88 [0.68, 0.97]	0.73 [0.50, 0.89]

ERS≥75mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥75	16	0	3	10	0.84 [0.60, 0.97]	1.00 [0.69, 1.00]
Ertugrul 2009-ERS≥75	19	4	5	18	0.79 [0.58, 0.93]	0.82 [0.60, 0.95]

ERS≥80mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥80	15	0	4	10	0.79 [0.54, 0.94]	1.00 [0.69, 1.00]
Ertugrul 2009-ERS≥80	17	2	7	20	0.71 [0.49, 0.87]	0.91 [0.71, 0.99]

ERS≥70mm/h

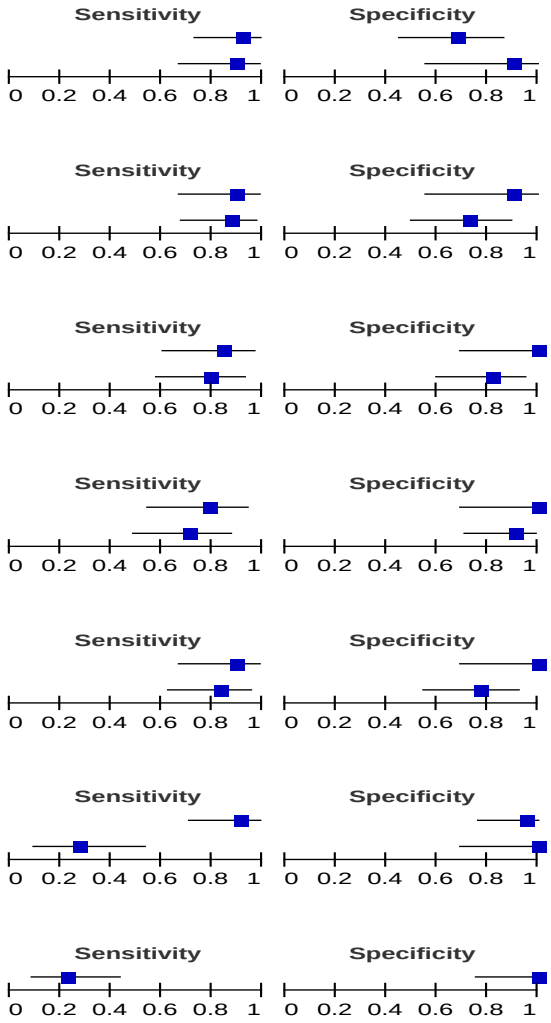
Study	TP	FP	FN	TN	Sensitivity	Specificity
Kaleta 2001-ERS≥70	17	0	2	10	0.89 [0.67, 0.99]	1.00 [0.69, 1.00]
Ertugrul 2009-ERS≥70	20	5	4	17	0.83 [0.63, 0.95]	0.77 [0.55, 0.92]

ERS>70mm/h

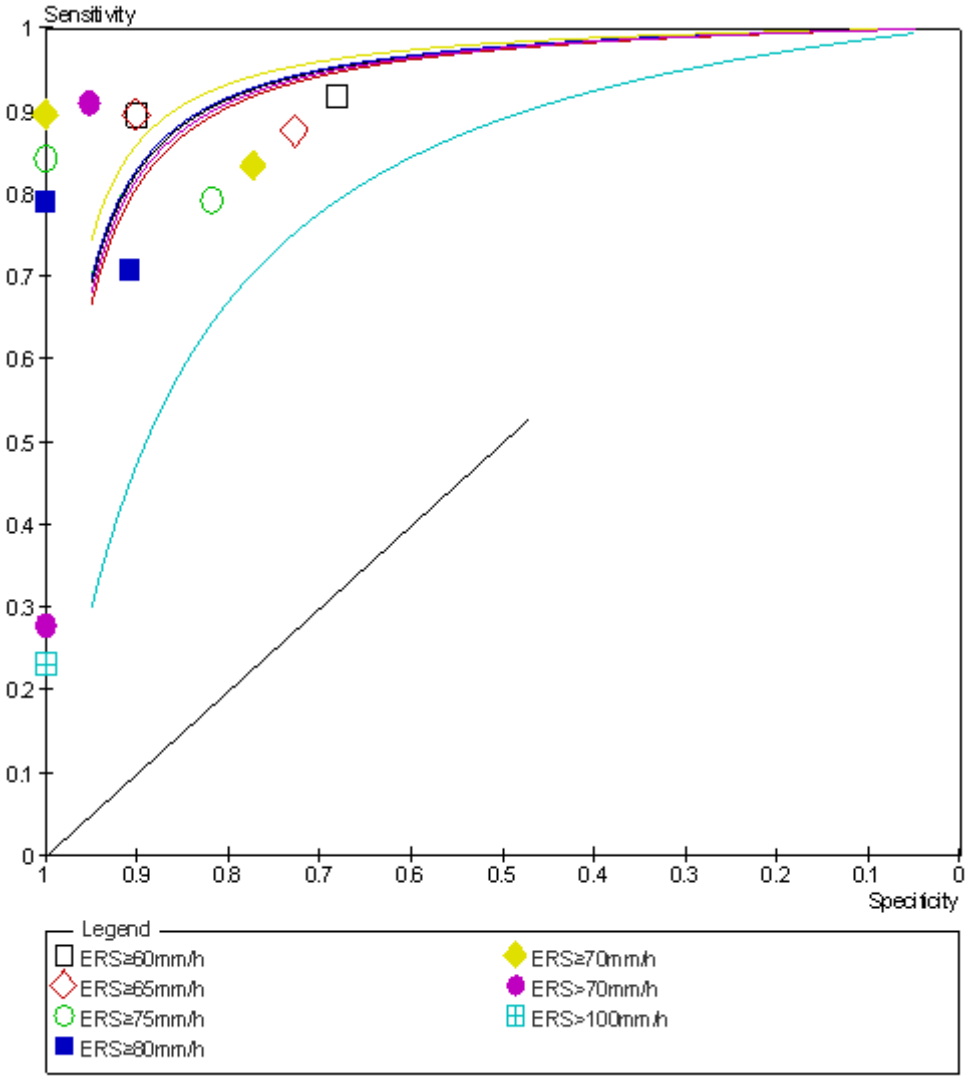
Study	TP	FP	FN	TN	Sensitivity	Specificity
Malabu 2007-ERS>70	20	1	2	20	0.91 [0.71, 0.99]	0.95 [0.76, 1.00]
Newman 1991-ERS>70	5	0	13	10	0.28 [0.10, 0.53]	1.00 [0.69, 1.00]

ERS>100mm/h

Study	TP	FP	FN	TN	Sensitivity	Specificity
Newman 1991-ERS>100	6	0	20	13	0.23 [0.09, 0.44]	1.00 [0.75, 1.00]



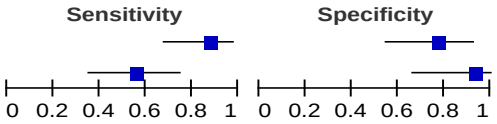
SROC 10: ERS in diagnosing osteomyelitis



Forest plot 11: wound sizes (and ESR) in diagnosing osteomyelitis

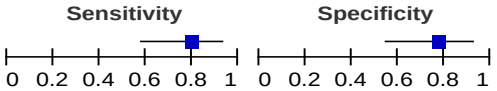
Wound≥2cm [2]

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2001-Wound≥2cm	21	5	3	17	0.88 [0.68, 0.97]	0.77 [0.55, 0.92]
Newman 1991-Wound≥2cm	15	1	12	13	0.56 [0.35, 0.75]	0.93 [0.66, 1.00]



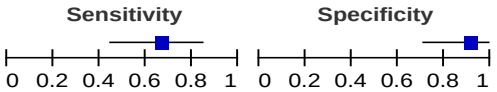
Wound≥3cm [2]

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2001-Wound≥3cm	19	5	5	17	0.79 [0.58, 0.93]	0.77 [0.55, 0.92]



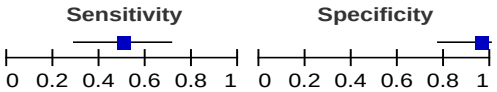
Wound≥4cm [2]

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2001-Wound≥4cm	16	2	8	20	0.67 [0.45, 0.84]	0.91 [0.71, 0.99]



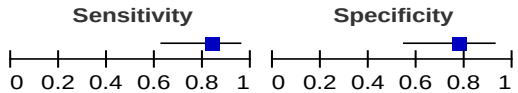
Wound≥5cm [2]

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2001-Wound≥5cm	12	1	12	21	0.50 [0.29, 0.71]	0.95 [0.77, 1.00]



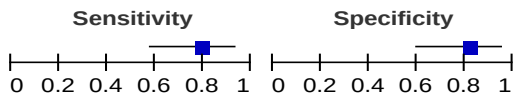
ERS≥65+Wound≥2cm [2]

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2001-ERS≥65+W2	20	5	4	17	0.83 [0.63, 0.95]	0.77 [0.55, 0.92]

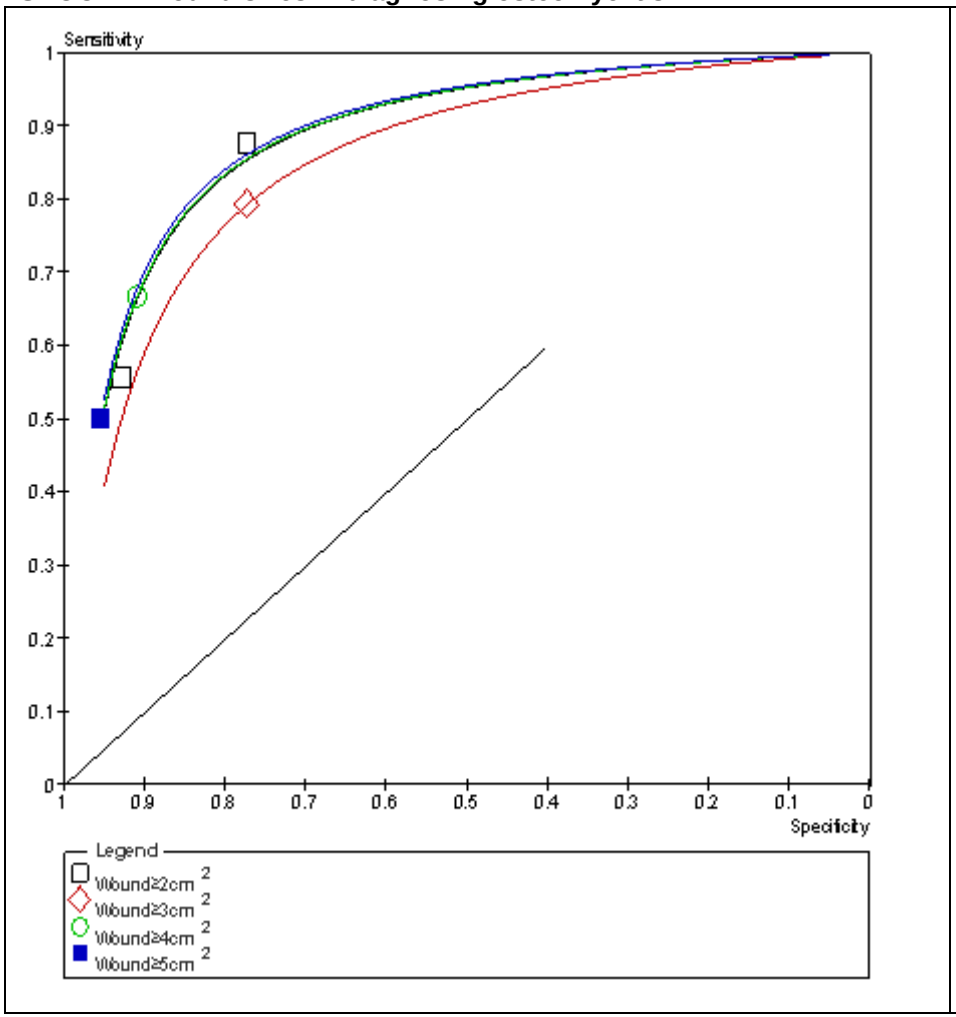


ERS≥70+Wound≥2cm [2]

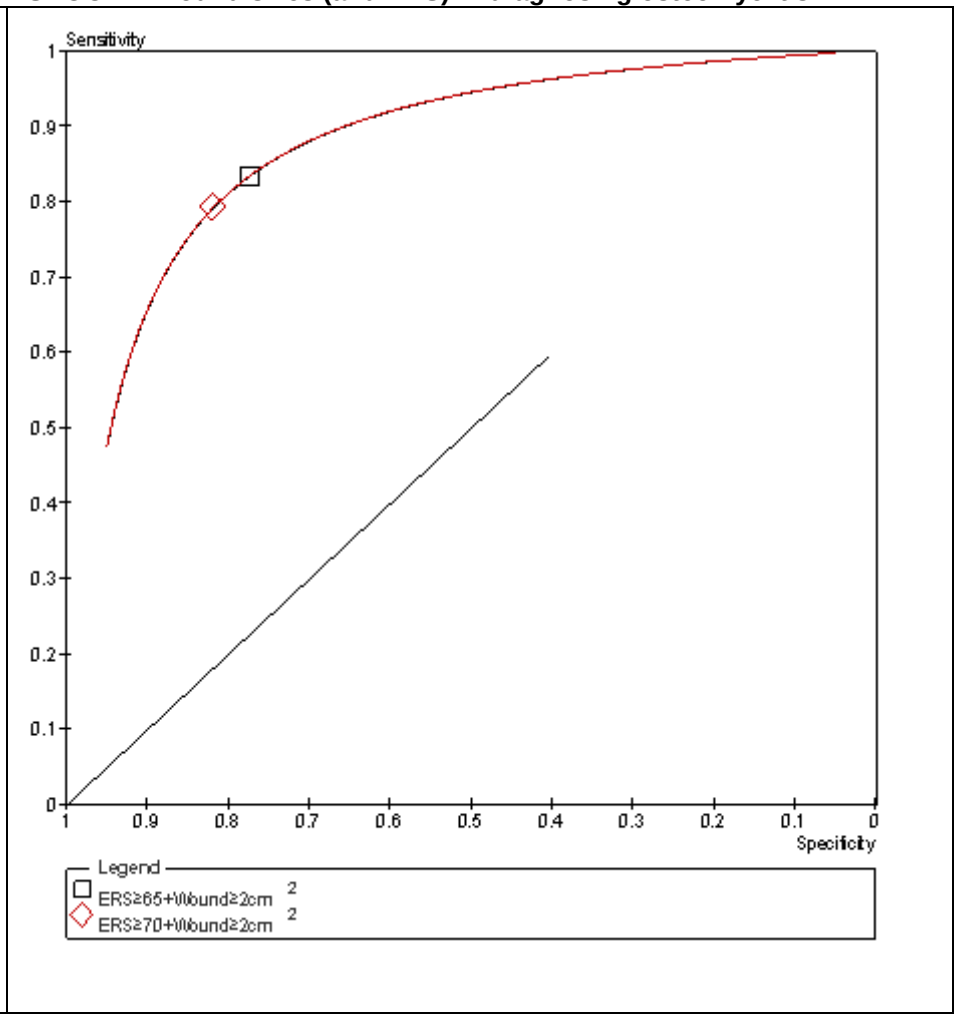
Study	TP	FP	FN	TN	Sensitivity	Specificity
Ertugrul 2001-ERS≥70+W2	19	4	5	18	0.79 [0.58, 0.93]	0.82 [0.60, 0.95]



SROC 11: wound sizes in diagnosing osteomyelitis



SROC 12: wound sizes (and ERS) in diagnosing osteomyelitis

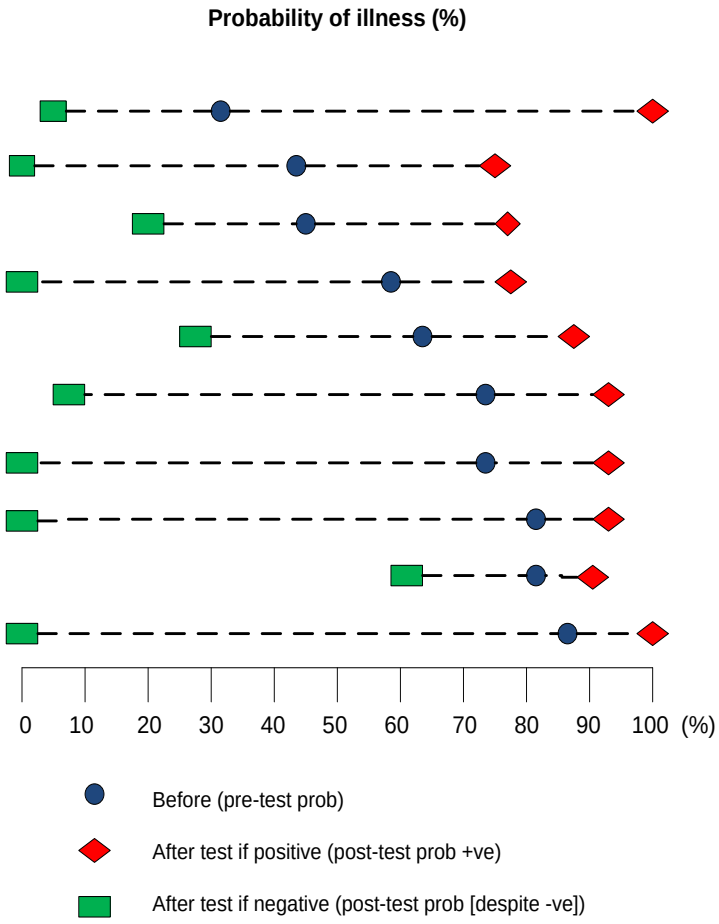


Appendix H Van der Bruel plots (Review question 2)

Review question 2: What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?

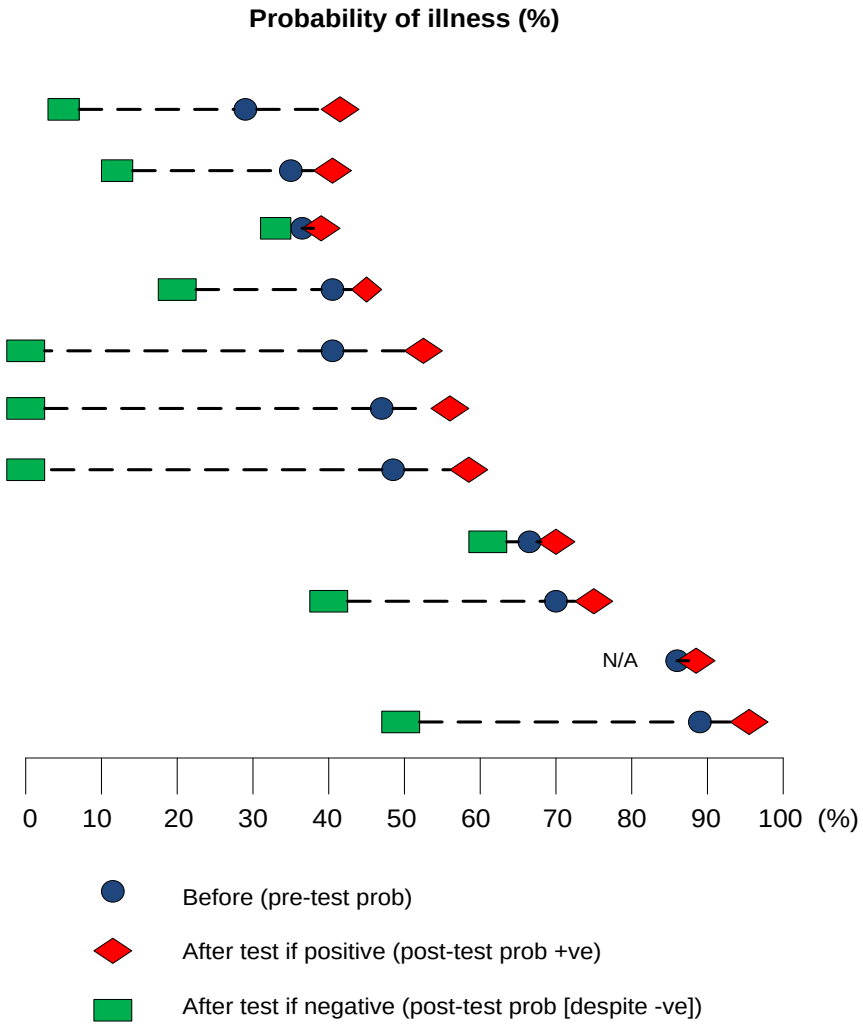
Plot 1: MRI in diagnosing osteomyelitis

Study	Pre-test probabilities	Likelihood ratios (95%CI)	
		Positive	Negative
Croll (1996)	0.33	N/A	0.11 (0.02-0.45)
Beltran (1990)	0.43	4.00 (1.36-13.07)	0.00 (0.00-0.57)
Levine (1994)	0.45	4.10 (1.61-12.02)	0.28 (0.09-0.67)
Al-Khawari (2007)	0.58	2.67 (1.31-7.03)	0.00 (0.00-0.45)
Morrison (1995)	0.63	4.12 (1.53-14.73)	0.22 (0.08-0.58)
Wang (1990)	0.74	5.22 (2.27-14.85)	0.03 (0.01-0.14)
Weinstein (1993)	0.74	5.33 (2.30-15.01)	0.00 (0.00-0.09)
Rozzanigo (2009)	0.81	3.00 (1.18-15.69)	0.00 (0.00-0.40)
Ertugrul (2006)	0.82	1.96 (0.94-6.74)	0.36 (0.14-1.16)
Yuh (1989)	0.86	N/A	0.00 (0.00-0.16)



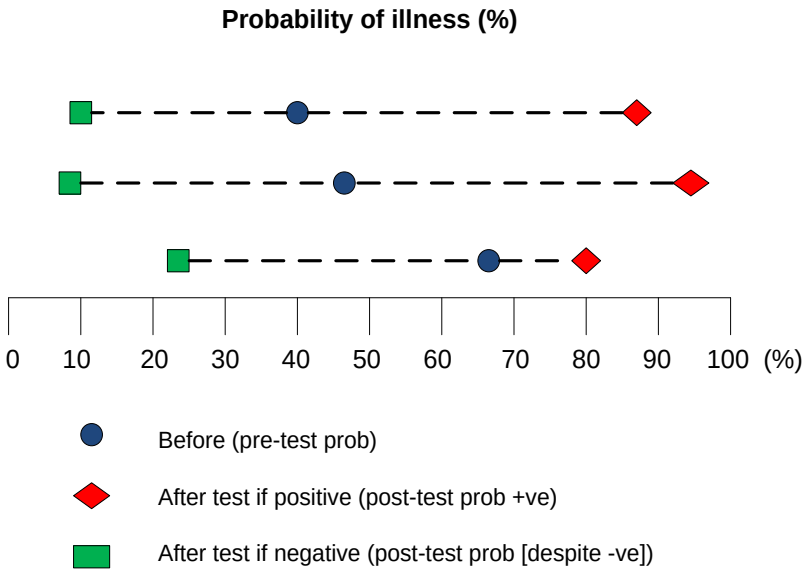
Plot 2: 99mTc-MDP scintigraphy in diagnosing osteomyelitis

Study	Pre-test probabilities	Likelihood ratios (95%CI)	
		Positive	Negative
Larcos (1991)	0.29	2.17 (1.42-3.37)	0.13 (0.02-0.57)
Harvey (1997)	0.35	1.51 (0.96-2.40)	0.23 (0.04-1.09)
Croll (1996)	0.36	1.00 (0.39-2.26)	1.00 (0.39-2.26)
Palestro (2003)	0.40	1.23 (0.77-1.92)	0.38 (0.06-2.05)
Keenan (1989)	0.40	1.6 (1.32-2.00)	0.00 (0.00-0.25)
Devillers (1998)	0.46	1.43 (1.12-1.89)	0.00 (0.00-0.44)
Poirier (2002)	0.49	1.4 (1.18-1.75)	0.00 (0.00-0.31)
Newman (1991)	0.67	1.13 (0.71-2.03)	0.8 (0.34-2.02)
Harwood (1999)	0.70	1.19 (0.96-1.80)	0.28 (0.06-1.32)
Yuh (1989)	0.86	0.94 (0.83-2.67)	*** (0.05-infinity)
Ertugrul (2006)	0.88	2.73 (1.24-14.89)	0.13 (0.03-0.64)



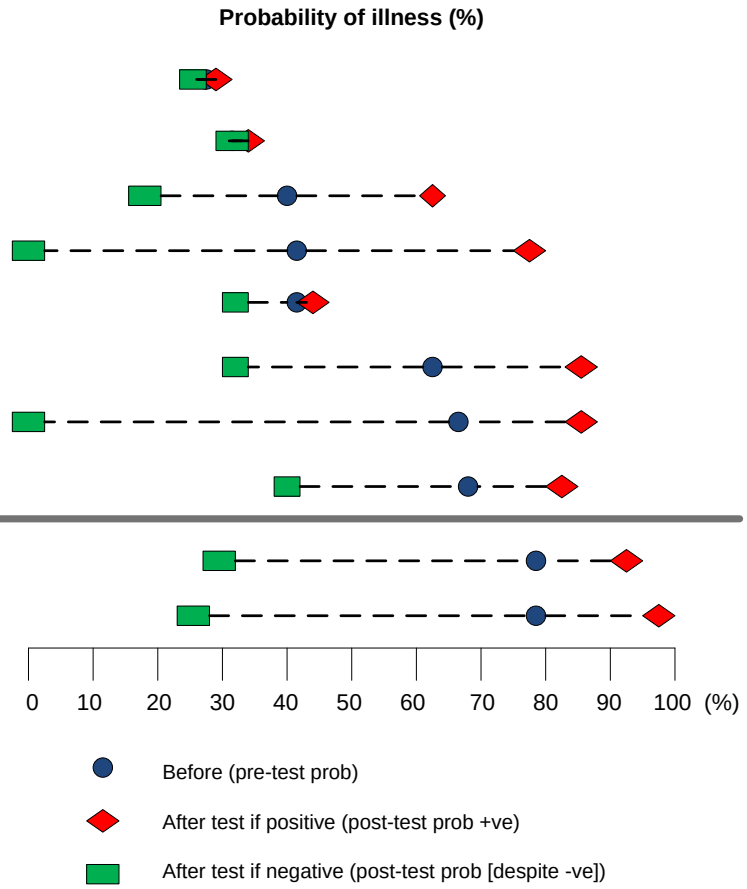
Plot 3: 99mTc-HMPAO scintigraphy

	Pre-test probabilities	Likelihood ratios (95%CI)	
		Positive	Negative
Harvey (1997)	0.40	8.85 (3.36-25.89)	0.16 (0.05-0.39)
Devillers (1998)	0.46	26.53 (5.27-150.2)	0.12 (0.04-0.30)
Harwood (1999)	0.66	2.08 (1.53-3.07)	0.15 (0.07-0.32)



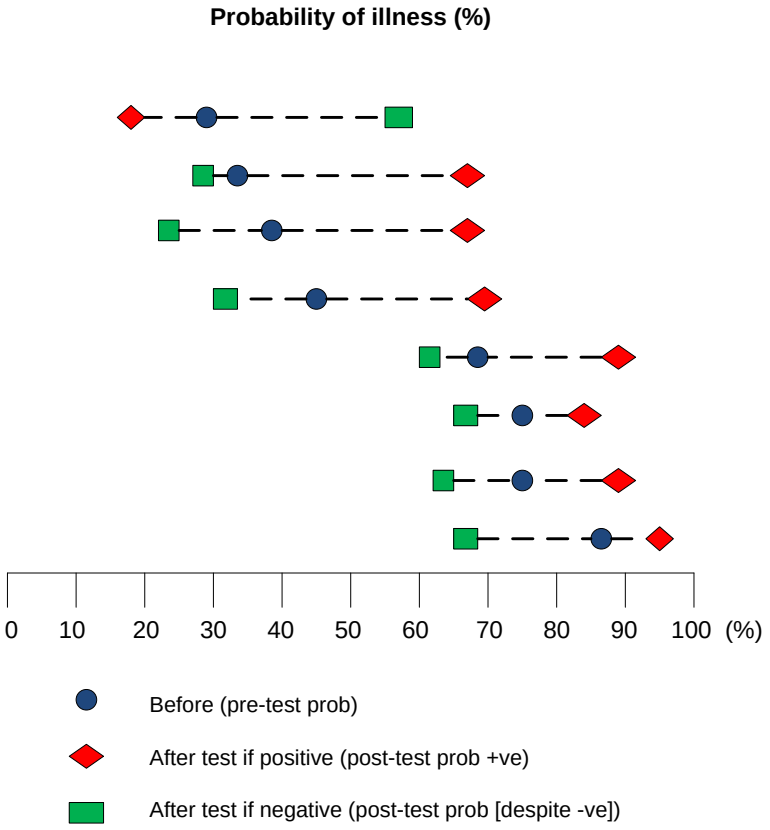
Plot 4: In-WBC scan & LeukoScan (anti-granulocyte Fab' fragment antibody scintigraphy)

	Pre-test probabilities	Likelihood ratios (95%CI)	
		Positive	Negative
Larcos (1991)	0.27	1.00 (0.65-1.34)	0.99 (0.31-2.84)
Croll (1996)	0.32	1.08 (0.27-3.72)	0.96 (0.41-1.79)
Palestro (2003)	0.40	2.40 (1.14-5.48)	0.30 (0.08-0.87)
Keenan (1989)	0.41	4.50 (2.37-9.21)	0.00 (0.00-0.22)
Levine (1994)	0.42	1.12 (0.49-2.37)	0.70 (0.10-4.16)
Newman (1991)[4]	0.63	3.35 (1.45-9.62)	0.29 (0.13-0.64)
Newman (1991)[24]	0.67	2.88 (1.49-7.03)	0.17 (0.06-0.47)
Harwood (1999)	0.68	2.36 (1.55-3.94)	0.32 (0.19-0.52)
Rubello (2004)[4]	0.79	3.67 (1.85-9.05)	0.11 (0.04-0.25)
Rubello (2004)[24]	0.79	7.35 (2.54-26.3)	0.09 (0.04-0.21)



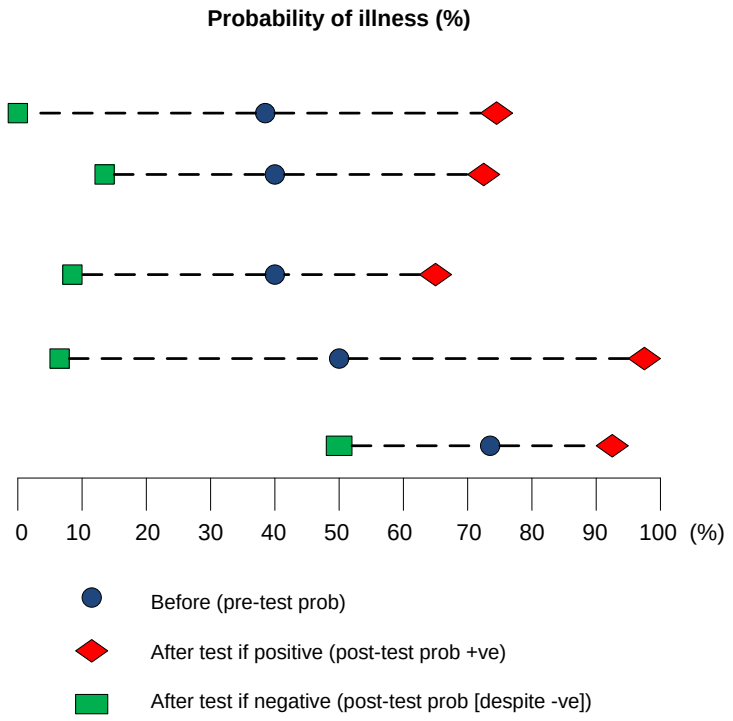
Plot 5: Plain radiographs

	Pre-test probabilities	Likelihood ratios (95%CI)	
		Positive	Negative
Larcos (1991)	0.29	0.52 (0.26-0.85)	3.33 (1.42-7.74)
Croll (1996)	0.33	4.00 (0.57-28.1)	0.82 (0.48-1.11)
Levine (1994)	0.38	3.20 (1.10-9.82)	0.49 (0.20-0.95)
Devillers (1998)	0.46	3.23 (1.43-7.78)	0.55 (0.34-0.83)
Newman (1991)	0.68	3.36 (0.67-20.2)	0.78 (0.56-1.16)
Wang (1990)	0.74	1.67 (0.86-3.83)	0.69 (0.45-1.16)
Weinstein (1993)	0.74	2.78 (1.14-8.15)	0.59 (0.40-0.91)
Yuh (1989)	0.86	3.00 (1.01-16.6)	0.33 (0.15-0.99)



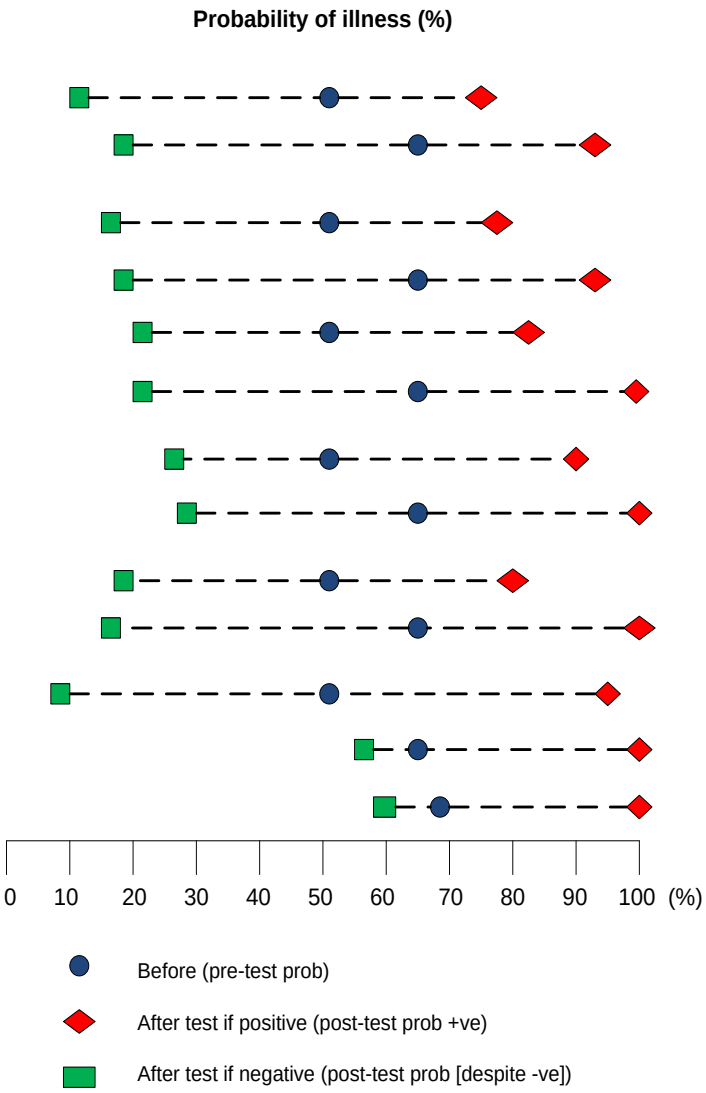
Plot 6: Combinations

	Pre-test probabilities	Likelihood ratios (95%CI)	
		Positive	Negative
99mTc-MDP + In-WBC scan			
Keenan (1989)	0.38	4.80 (2.36-10.5)	0.00 (0.00-0.26)
Palestro (2003)	0.40	4.00 (1.57-11.7)	0.25 (0.07-0.69)
99mTc-MDP + Moab			
Palestro (2003)	0.40	2.70 (1.37-6.04)	0.15 (0.03-0.66)
99mTc-MDP + 99m-HMPAO			
Poirier (2002)	0.49	38.9 (7.50-220.2)	0.08 (0.03-0.20)
99mTc-MDP + gallium-67 citrate scan			
Weinstein (1993)	0.73	4.13 (1.10-23.3)	0.38 (0.16-0.89)



Plot 7: ESR

	Pre-test probabilities	Likelihood ratios (95%CI)	
		Positive	Negative
ERS rate ≥60mm/h			
Ertugrul (2009)	0.52	2.88 (1.69-5.65)	0.12 (0.03-0.40)
Kaleta (2001)	0.66	8.95 (2.17-50.3)	0.12 (0.03-0.37)
ERS rate ≥65mm/h			
Ertugrul (2009)	0.52	3.21 (1.75-6.73)	0.12 (0.03-0.37)
Kaleta (2001)	0.66	8.95 (2.17-50.3)	0.12 (0.03-0.37)
ERS rate ≥75mm/h			
Ertugrul (2009)	0.52	4.35 (1.96-11.1)	0.25 (0.11-0.52)
Kaleta (2001)	0.66	N/A	0.16 (0.06-0.41)
ERS rate ≥80mm/h			
Ertugrul (2009)	0.52	7.79 (2.44-28.5)	0.32 (0.16-0.56)
Kaleta (2001)	0.66	N/A	0.21 (0.09-0.47)
ERS rate ≥70mm/h			
Ertugrul (2009)	0.52	3.67 (1.84-8.36)	0.22 (0.08-0.49)
Kaleta (2001)	0.66	N/A	0.11 (0.03-0.34)
ERS rate >70mm/h			
Malabu (2007)	0.51	19.09 (3.98-107.8)	0.09 (0.03-0.29)
Newman (1991)	0.64	N/A	0.72 (0.51-1.13)
ERS rate >100mm/h (all ulcers)			
Newman (1991)	0.67	N/A	0.77 (0.60-1.09)



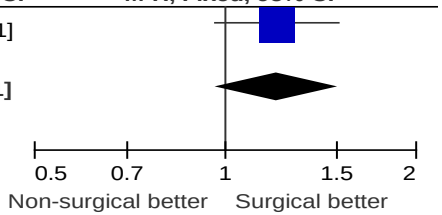
Appendix I Meta-analysis and forest plots (Review question 3 and 5)

Review question 3: What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading in treating diabetic foot problems?

Forest plots

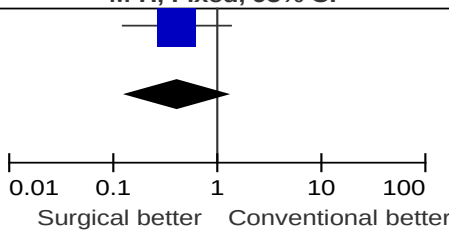
No. of ulcers completely healed

	Surgical Debridement		Non-Surgical Debridement			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Piaggessi 1998	21	22	19	24	100.0%	1.21 [0.96, 1.51]	
Total (95% CI)		**22**		**24**	**100.0%**	**1.21 [0.96, 1.51]**	
Total events	21		19				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							



Recurrence rates

	Surgical Debridement		Conservative T/t			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Piaggessi 1998	3	22	8	24	100.0%	0.41 [0.12, 1.35]	
Total (95% CI)		**22**		**24**	**100.0%**	**0.41 [0.12, 1.35]**	
Total events	3		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							

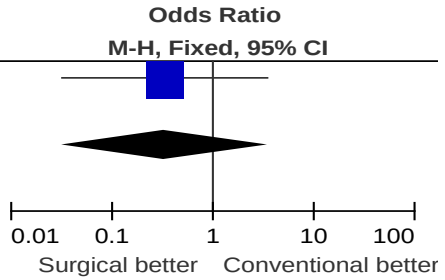


No. of adverse events (complications)

Study or Subgroup	Surgical Debridement Events	Total	Conservative T/t Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Piaggessi 1998	1	22	3	24	100.0%	0.33 [0.03, 3.47]
Total (95% CI)		**22**		**24**	**100.0%**	**0.33 [0.03, 3.47]**
Total events	1		3			

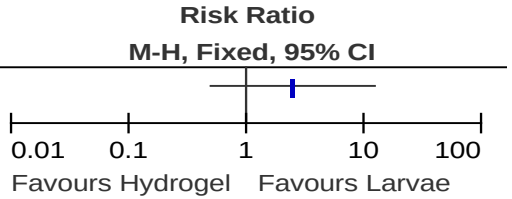
Heterogeneity: Not applicable

Test for overall effect: Z = 0.92 (P = 0.36)



No. of ulcers completely healed

Study or Subgroup	Larvae Events	Total	Hydrogel Events	Total	Risk Ratio M-H, Fixed, 95% CI
Markevich 2000	5	70	2	70	2.50 [0.50, 12.46]

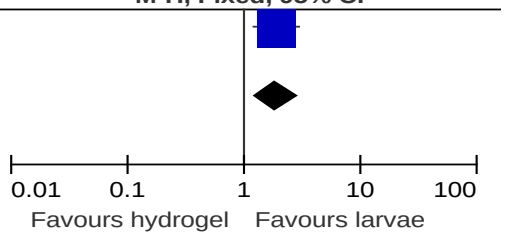


Reduction of wound area > 50%

Study or Subgroup	Larvae Events	Total	Hydrogel Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Markevich 2000	36	70	19	70	100.0%	1.89 [1.21, 2.96]
Total (95% CI)		**70**		**70**	**100.0%**	**1.89 [1.21, 2.96]**
Total events	36		19			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.81 (P = 0.005)

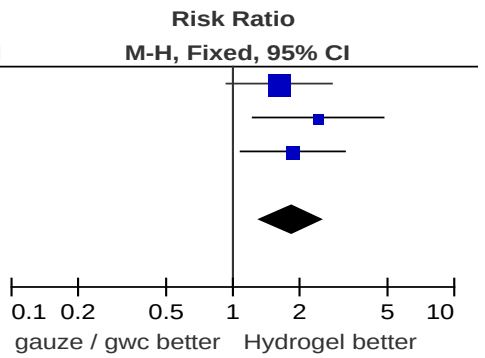


No. of ulcers completely healed

Study or Subgroup	Hydrogel Events	Total	gauze / gwc Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Hemecourt 1998	25	70	15	68	54.6%	1.62 [0.94, 2.80]
Jensen 1998	12	14	6	17	19.4%	2.43 [1.23, 4.79]
Vandeputte 1997	14	15	7	14	26.0%	1.87 [1.09, 3.21]
Total (95% CI)		**99**		**99**	**100.0%**	**1.84 [1.30, 2.61]**
Total events	51		28			

Heterogeneity: Chi² = 0.86, df = 2 (P = 0.65); I² = 0%

Test for overall effect: Z = 3.44 (P = 0.0006)

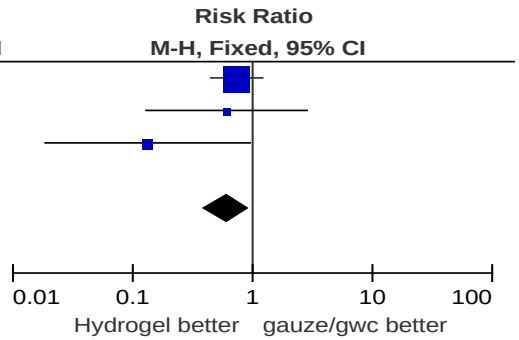


No. of adverse events (complications)

Study or Subgroup	Hydrogel Events	Total	gauze/gwc Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Hemecourt 1998	19	70	25	68	70.0%	0.74 [0.45, 1.21]
Jensen 1998	2	14	4	17	10.0%	0.61 [0.13, 2.84]
Vandeputte 1997	1	15	7	14	20.0%	0.13 [0.02, 0.95]
Total (95% CI)		**99**		**99**	**100.0%**	**0.60 [0.38, 0.95]**
Total events	22		36			

Heterogeneity: Chi² = 2.90, df = 2 (P = 0.23); I² = 31%

Test for overall effect: Z = 2.18 (P = 0.03)



Review question 5: What is the clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems, for example, dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy and electrical stimulation?

Adjunctive treatments: Forest plots

Section 1: Growth factors

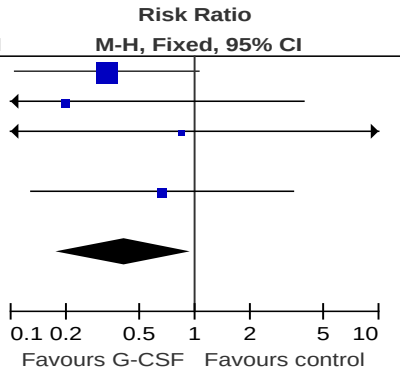
1) G-CSF

Amputation

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Lalla 2001	3	20	9	20	57.8%	0.33 [0.11, 1.05]
Gough 1997	0	20	2	20	16.0%	0.20 [0.01, 3.92]
Kastenbauer 2003	1	20	1	17	6.9%	0.85 [0.06, 12.59]
Viswanathan 2003	0	10	0	10		Not estimable
Yonem 2001	2	15	3	15	19.3%	0.67 [0.13, 3.44]
Total (95% CI)		**85**		**82**	**100.0%**	**0.41 [0.18, 0.95]**
Total events	6		15			

Heterogeneity: Chi² = 0.97, df = 3 (P = 0.81); I² = 0%

Test for overall effect: Z = 2.08 (P = 0.04)

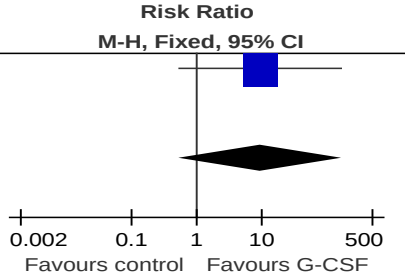


Complete wound healing

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gough 1997	4	19	0	20	100.0%	9.45 [0.54, 164.49]
Kastenbauer 2003	0	20	0	20		Not estimable
Total (95% CI)		**39**		**40**	**100.0%**	**9.45 [0.54, 164.49]**
Total events	4		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.54 (P = 0.12)

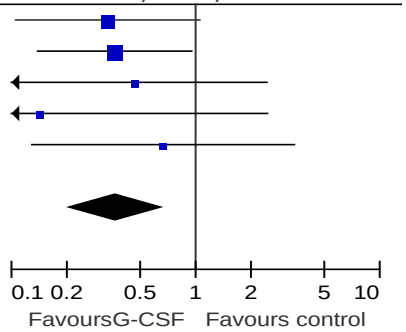


Overall need for surgical interventions

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Lalla 2001	3	20	9	20	30.0%	0.33 [0.11, 1.05]
Gough 1997	4	20	11	20	36.6%	0.36 [0.14, 0.95]
Kastenbauer 2003	2	20	3	14	11.8%	0.47 [0.09, 2.44]
Viswanathan 2003	0	10	3	10	11.7%	0.14 [0.01, 2.45]
Yonem 2001	2	15	3	15	10.0%	0.67 [0.13, 3.44]
Total (95% CI)		**85**		**79**	**100.0%**	**0.37 [0.20, 0.68]**
Total events	11		29			

Heterogeneity: Chi² = 1.03, df = 4 (P = 0.90); I² = 0%

Test for overall effect: Z = 3.21 (P = 0.001)

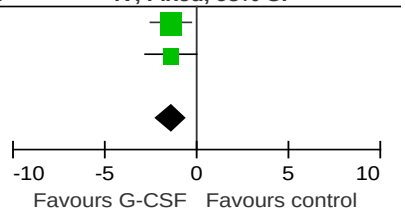


Length of hospital stay (days)

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Viswanathan 2003	7.4	0.8	10	8.8	1.6	10	61.3%	-1.40 [-2.51, -0.29]
Yonem 2001	26.9	2	15	28.3	1.9	15	38.7%	-1.40 [-2.80, -0.00]
Total (95% CI)			**25**			**25**	**100.0%**	**-1.40 [-2.27, -0.53]**

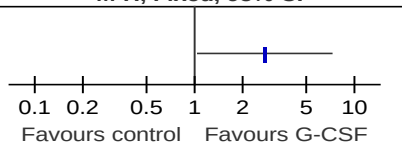
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 3.16 (P = 0.002)



Resolution of infection

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Lalla 2001	0	20	0	20		Not estimable
Gough 1997	11	20	4	20		2.75 [1.05, 7.20]

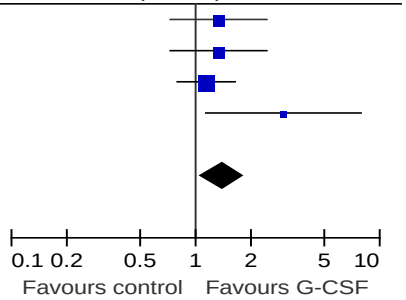


Improvement of infection status

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Lalla 2001	12	20	9	20	25.7%	1.33 [0.73, 2.44]
Gough 1997	12	20	9	20	25.7%	1.33 [0.73, 2.44]
Kastenbauer 2003	16	20	14	20	40.0%	1.14 [0.80, 1.64]
Viswanathan 2003	9	10	3	10	8.6%	3.00 [1.14, 7.91]
Total (95% CI)		**70**		**70**	**100.0%**	**1.40 [1.06, 1.85]**
Total events	49		35			

Heterogeneity: Chi² = 3.64, df = 3 (P = 0.30); I² = 18%

Test for overall effect: Z = 2.37 (P = 0.02)

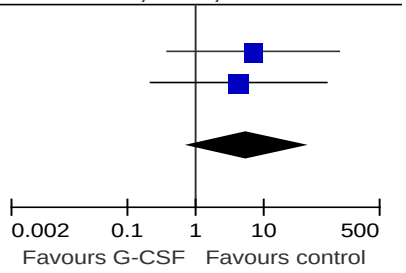


Treatment related AEs

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
de Lalla 2001	0	20	0	20		Not estimable
Gough 1997	3	20	0	20	48.1%	7.00 [0.38, 127.32]
Kastenbauer 2003	2	20	0	17	51.9%	4.29 [0.22, 83.57]
Total (95% CI)		**60**		**57**	**100.0%**	**5.59 [0.71, 44.05]**
Total events	5		0			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 1.63 (P = 0.10)



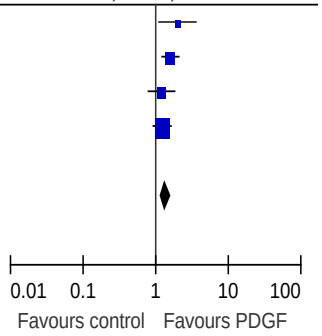
2) PDGF

Complete wound healing (week 20)

	PDGF+standard wound care		Standard wound care only			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
D'Hemecourt 2005	15	34	15	68	8.0%	2.00 [1.11, 3.59]	
Hardikar 2005	47	55	31	58	24.3%	1.60 [1.23, 2.08]	
Robson 2005	31	74	25	72	20.4%	1.21 [0.80, 1.83]	
Wieman 1998	109	256	44	127	47.3%	1.23 [0.93, 1.62]	
Total (95% CI)		**419**		**325**	**100.0%**	**1.38 [1.16, 1.64]**	
Total events	202		115				

Heterogeneity: Chi² = 3.83, df = 3 (P = 0.28); I² = 22%

Test for overall effect: Z = 3.63 (P = 0.0003)

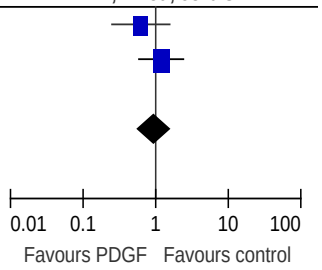


Withdrawal due to treatment-related AEs

	PDGF+standard wound care		Standard wound care only			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
D'Hemecourt 2005	5	34	16	68	44.4%	0.63 [0.25, 1.56]	
Wieman 1998	24	256	10	127	55.6%	1.19 [0.59, 2.41]	
Total (95% CI)		**290**		**195**	**100.0%**	**0.94 [0.54, 1.63]**	
Total events	29		26				

Heterogeneity: Chi² = 1.19, df = 1 (P = 0.27); I² = 16%

Test for overall effect: Z = 0.22 (P = 0.83)

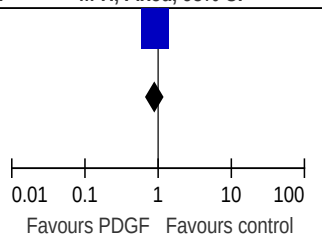


At least 1 treatment-related AEs

Study or Subgroup	PDGF+standard wound care Events	Total	Standard wound care only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Hemecourt 2005	22	34	48	68	100.0%	0.92 [0.68, 1.23]
Total (95% CI)		**34**		**68**	**100.0%**	**0.92 [0.68, 1.23]**
Total events	22		48			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.58 (P = 0.56)



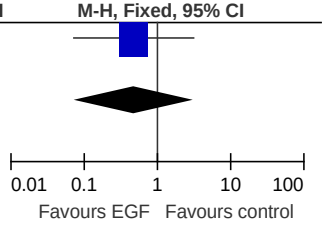
3) EGF

Amputation

Study or Subgroup	EGF+standard wound care Events	Total	Standard wound care only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tsang 2003	2	40	2	19	100.0%	0.47 [0.07, 3.12]
Total (95% CI)		**40**		**19**	**100.0%**	**0.47 [0.07, 3.12]**
Total events	2		2			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.78 (P = 0.44)

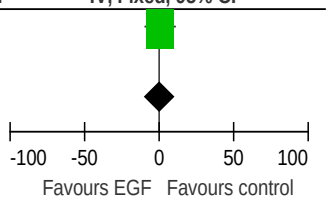


Length of hospital stay (days)

Study or Subgroup	EGF+standard wound care Mean	SD	Total	Standard wound care only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Afshari 2005	29.6	20.95	30	28.9	15.1	20	100.0%	0.70 [-9.30, 10.70]
Total (95% CI)			**30**			**20**	**100.0%**	**0.70 [-9.30, 10.70]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.14 (P = 0.89)

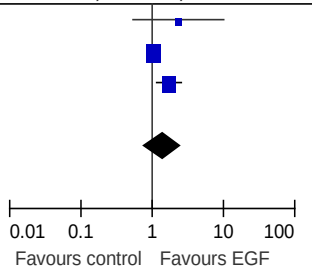


Complete wound healing (periods varied)

Study or Subgroup	EGF+standard wound care Events	Total	Standard wound care only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Afshari 2005	7	30	2	20	13.1%	2.33 [0.54, 10.11]
Tsang 2003	37	40	17	19	46.5%	1.03 [0.87, 1.23]
Viswanathan 2006	25	29	14	28	40.4%	1.72 [1.16, 2.57]
Total (95% CI)		**99**		**67**	**100.0%**	**1.41 [0.76, 2.63]**
Total events	69		33			

Heterogeneity: Tau² = 0.21; Chi² = 11.04, df = 2 (P = 0.004); I² = 82%

Test for overall effect: Z = 1.09 (P = 0.27)

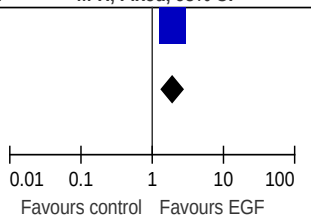


At least 50% wound reduction

Study or Subgroup	EGF+standard wound care Events	Total	Standard wound care only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez-Monntequin 2009	78	101	19	48	100.0%	1.95 [1.35, 2.81]
Total (95% CI)		**101**		**48**	**100.0%**	**1.95 [1.35, 2.81]**
Total events	78		19			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.59 (P = 0.0003)

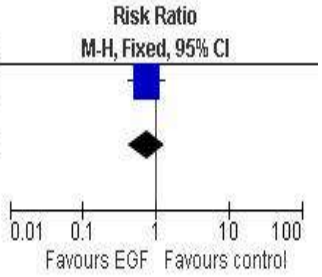


Treatment-related AEs – burning sensation

Study or Subgroup	EGF+standard wound care Events	Total	Standard wound care only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez-Monntequin 2009	22	101	14	48	100.0%	0.75 [0.42, 1.33]
Total (95% CI)		**101**		**48**	**100.0%**	**0.75 [0.42, 1.33]**
Total events	22		14			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.99 (P = 0.32)

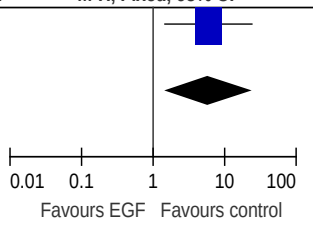


Treatment-related AEs – shivering

Study or Subgroup	EGF+standard wound care Events	Total	Standard wounf care only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fernandez-Monntequin 2009	25	101	2	48	100.0%	5.94 [1.47, 24.06]
Total (95% CI)		**101**		**48**	**100.0%**	**5.94 [1.47, 24.06]**
Total events	25		2			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.50 (P = 0.01)



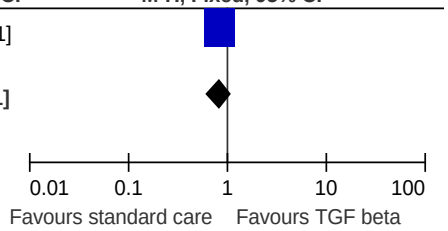
4): TGF-beta

Complete wound closure (T+SC vs. SC alone)

Study or Subgroup	TGF beta Events	Total	Standard wound care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Robson 2000	77	131	17	24	100.0%	0.83 [0.62, 1.11]
Total (95% CI)		**131**		**24**	**100.0%**	**0.83 [0.62, 1.11]**
Total events	77		17			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.24 (P = 0.21)



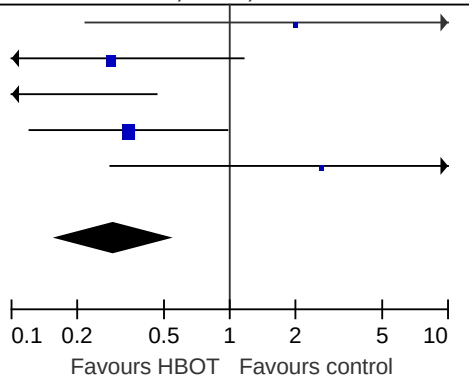
Section 2: Hyperbaric oxygen therapy

Major amputation

Study or Subgroup	HBOT Events	HBOT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abidia 2003	2	9	1	9	2.6%	2.00 [0.22, 18.33]
Doctor 1992	2	15	7	15	18.5%	0.29 [0.07, 1.16]
Duzgun 2008	0	50	17	50	46.2%	0.03 [0.00, 0.46]
Faglia 1996	4	36	11	34	29.9%	0.34 [0.12, 0.98]
Londahl 2010	3	48	1	42	2.8%	2.63 [0.28, 24.29]
Total (95% CI)		**158**		**150**	**100.0%**	**0.30 [0.16, 0.55]**
Total events	11		37			

Heterogeneity: Chi² = 9.35, df = 4 (P = 0.05); I² = 57%

Test for overall effect: Z = 3.80 (P = 0.0001)

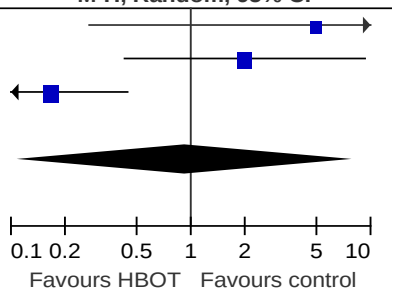


Minor amputation

Study or Subgroup	HBOT Events	HBOT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abidia 2003	2	9	0	9	24.3%	5.00 [0.27, 91.52]
Doctor 1992	4	15	2	15	35.7%	2.00 [0.43, 9.32]
Duzgun 2008	4	50	24	50	40.0%	0.17 [0.06, 0.45]
Total (95% CI)		**74**		**74**	**100.0%**	**0.92 [0.11, 7.90]**
Total events	10		26			

Heterogeneity: Tau² = 2.74; Chi² = 10.15, df = 2 (P = 0.006); I² = 80%

Test for overall effect: Z = 0.07 (P = 0.94)

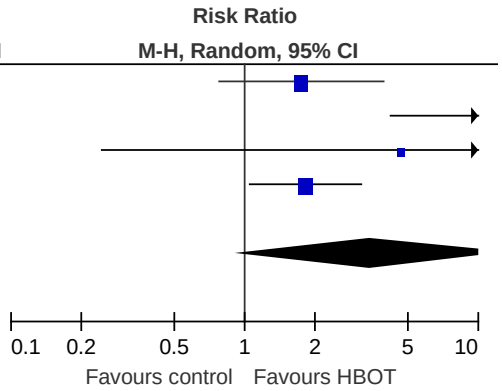


Complete wound healing (4-6weeks)

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abidia 2003	7	9	4	9	34.6%	1.75 [0.78, 3.93]
Duzgun 2008	33	50	0	50	14.7%	67.00 [4.22, 1064.23]
Kessler 2003	2	14	0	13	13.5%	4.67 [0.24, 88.96]
Londahl 2010	25	48	12	42	37.2%	1.82 [1.05, 3.16]
Total (95% CI)		**121**		**114**	**100.0%**	**3.46 [0.91, 13.12]**
Total events	67		16			

Heterogeneity: Tau² = 1.16; Chi² = 14.01, df = 3 (P = 0.003); I² = 79%

Test for overall effect: Z = 1.83 (P = 0.07)

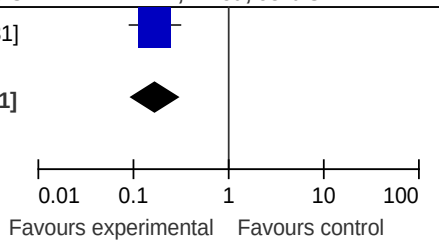


Required surgical interventions

Study or Subgroup	HBOT+standard care Events	Total	Standard care only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Duzgun 2008	8	50	50	50	100.0%	0.17 [0.09, 0.31]
Total (95% CI)		**50**		**50**	**100.0%**	**0.17 [0.09, 0.31]**
Total events	8		50			

Heterogeneity: Not applicable

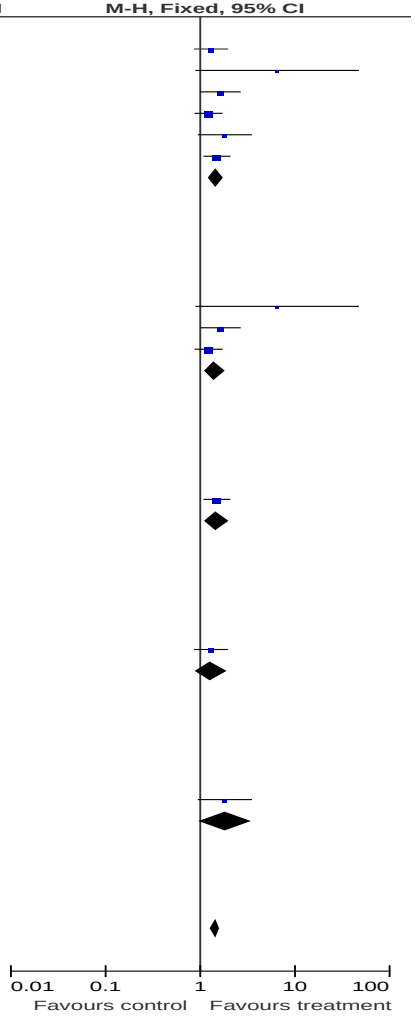
Test for overall effect: Z = 5.69 (P < 0.00001)



Section 3: Dermal or skin substitutes

Complete wound healing (week 12)

Study or Subgroup	Dermal/skin grafts+SWC Events	Total	SWC only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 All						
Caravaggi 1996 - Hyalogra	28	43	18	36	7.4%	1.30 [0.88, 1.93]
Gentzkow 1996 - Dermagraf	6	12	1	13	0.4%	6.50 [0.91, 46.43]
Marston 2003 - Dermagraft	39	130	21	115	8.4%	1.64 [1.03, 2.62]
Naughton 1997 - Dermagraf	54	139	45	142	16.7%	1.23 [0.89, 1.69]
Pham 1999 - HSE	12	16	7	17	2.6%	1.82 [0.97, 3.44]
Veves 2001 - Graftskin	63	112	36	96	14.6%	1.50 [1.11, 2.04]
Subtotal (95% CI)		**452**		**419**	**50.0%**	**1.46 [1.22, 1.73]**
Total events	202		128			
Heterogeneity: Chi² = 4.42, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 4.25 (P < 0.0001)						
1.2.2 Dermagraft						
Gentzkow 1996 - Dermagraf	6	12	1	13	0.4%	6.50 [0.91, 46.43]
Marston 2003 - Dermagraft	39	130	21	115	8.4%	1.64 [1.03, 2.62]
Naughton 1997 - Dermagraf	54	139	45	142	16.7%	1.23 [0.89, 1.69]
Subtotal (95% CI)		**281**		**270**	**25.5%**	**1.44 [1.11, 1.87]**
Total events	99		67			
Heterogeneity: Chi² = 3.53, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 2.73 (P = 0.006)						
1.2.3 Graftskin						
Veves 2001 - Graftskin	63	112	36	96	14.6%	1.50 [1.11, 2.04]
Subtotal (95% CI)		**112**		**96**	**14.6%**	**1.50 [1.11, 2.04]**
Total events	63		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.2.4 Hyalograft						
Caravaggi 1996 - Hyalogra	28	43	18	36	7.4%	1.30 [0.88, 1.93]
Subtotal (95% CI)		**43**		**36**	**7.4%**	**1.30 [0.88, 1.93]**
Total events	28		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
1.2.5 Human skin Equivalent						
Pham 1999 - HSE	12	16	7	17	2.6%	1.82 [0.97, 3.44]
Subtotal (95% CI)		**16**		**17**	**2.6%**	**1.82 [0.97, 3.44]**
Total events	12		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
Total (95% CI)		**904**		**838**	**100.0%**	**1.46 [1.29, 1.65]**
Total events	404		256			
Heterogeneity: Chi² = 8.84, df = 11 (P = 0.64); I² = 0%						
Test for overall effect: Z = 6.01 (P < 0.00001)						
Test for subgroup differences: Not applicable						

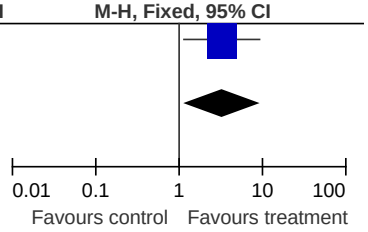


At least 50% wound closure (week 12)

Study or Subgroup	Dermal/skin graft+SWC Events	Total	SWC only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gentzkow 1996 - Dermagraf	9	12	3	13	100.0%	3.25 [1.14, 9.24]
Total (95% CI)		**12**		**13**	**100.0%**	**3.25 [1.14, 9.24]**
Total events	9		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.21 (P = 0.03)

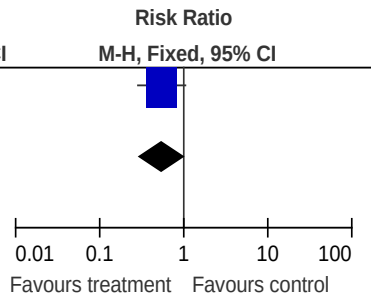


Surgical interventions (unit: ulcers)

Study or Subgroup	Dermal/skin graft+SWC Events	Total	SWC only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marston 2003 - Dermagraft	13	163	22	151	100.0%	0.55 [0.29, 1.05]
Total (95% CI)		**163**		**151**	**100.0%**	**0.55 [0.29, 1.05]**
Total events	13		22			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.82 (P = 0.07)

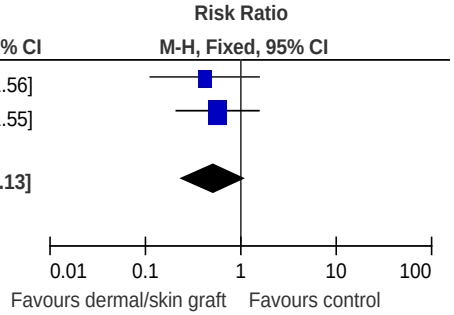


Withdrawal due to AEs – ulcer-related

Study or Subgroup	Dermal/skin graft+SWC Events	Total	SWC only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Caravaggi 1996 - Hyalogra	3	43	6	36	40.3%	0.42 [0.11, 1.56]
Veves 2001 - Graftskin	6	112	9	96	59.7%	0.57 [0.21, 1.55]
Total (95% CI)		**155**		**132**	**100.0%**	**0.51 [0.23, 1.13]**
Total events	9		15			

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%

Test for overall effect: Z = 1.67 (P = 0.10)

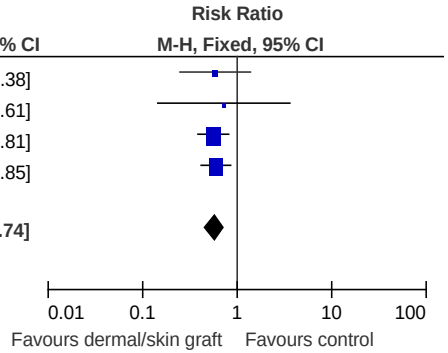


AEs – ulcer-related

Study or Subgroup	Dermal/skin grafts+SWC Events	Total	SWC only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Caravaggi 1996 - Hyalogra	7	43	10	36	9.4%	0.59 [0.25, 1.38]
Gentzkow 1996 - Dermagraf	2	12	3	13	2.5%	0.72 [0.14, 3.61]
Marston 2003 - Dermagraft	31	130	49	115	45.1%	0.56 [0.39, 0.81]
Veves 2001 - Graftskin	32	112	46	96	43.0%	0.60 [0.42, 0.85]
Total (95% CI)		**297**		**260**	**100.0%**	**0.58 [0.46, 0.74]**
Total events	72		108			

Heterogeneity: Chi² = 0.13, df = 3 (P = 0.99); I² = 0%

Test for overall effect: Z = 4.32 (P < 0.0001)



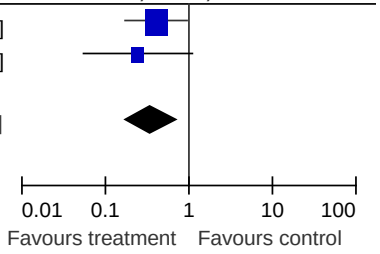
Section 4: Negative pressure wound therapy

Amputation (secondary)

Study or Subgroup	NPWT+SC Events	NPWT+SC Total	Moist wound therapy+SC Events	Moist wound therapy+SC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blume 2008	7	169	17	166	66.7%	0.40 [0.17, 0.95]
Williams 2005	2	77	9	85	33.3%	0.25 [0.05, 1.10]
Total (95% CI)		**246**		**251**	**100.0%**	**0.35 [0.17, 0.74]**
Total events	9		26			

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%

Test for overall effect: Z = 2.77 (P = 0.006)

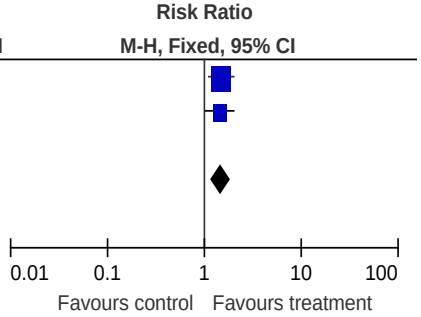


Complete wound closure (week 16)

Study or Subgroup	NWPT+ SC Events	NWPT+ SC Total	Moist wound therapy+SC Events	Moist wound therapy+SC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blume 2008	73	169	48	166	60.7%	1.49 [1.11, 2.01]
Williams 2005	43	77	33	85	39.3%	1.44 [1.03, 2.01]
Total (95% CI)		**246**		**251**	**100.0%**	**1.47 [1.18, 1.84]**
Total events	116		81			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%

Test for overall effect: Z = 3.42 (P = 0.0006)

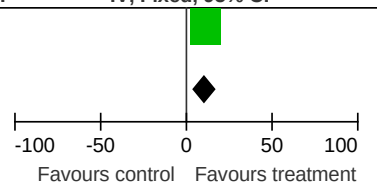


Mean reduction wound surface area (cm^2)

Study or Subgroup	NPWT Mean	NPWT SD	NPWT Total	Saline moistened gauze Mean	Saline moistened gauze SD	Saline moistened gauze Total	Weight	Mean Difference IV, Fixed, 95% CI
Etoz 2004	20.4	11.7	12	9.5	4.11	12	100.0%	10.90 [3.88, 17.92]
Total (95% CI)			**12**			**12**	**100.0%**	**10.90 [3.88, 17.92]**

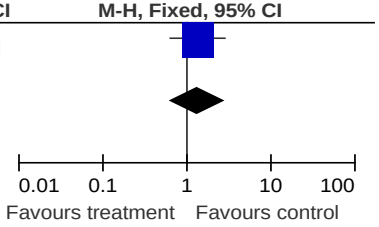
Heterogeneity: Not applicable

Test for overall effect: Z = 3.04 (P = 0.002)



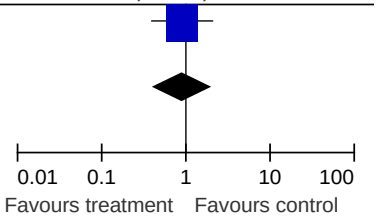
AEs – ulcer-related

	NPWT+SC		MOist wound therapy+SC			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Blume 2008	15	169	11	166	100.0%	1.34 [0.63, 2.83]	
Total (95% CI)		**169**		**166**	**100.0%**	**1.34 [0.63, 2.83]**	
Total events	15		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.77 (P = 0.44)							



AEs – treatment-related

	NPWT+SC		Moist wound therapy+SC			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Williams 2005	9	77	11	85	100.0%	0.90 [0.40, 2.06]	
Total (95% CI)		**77**		**85**	**100.0%**	**0.90 [0.40, 2.06]**	
Total events	9		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.24 (P = 0.81)							



Appendix J Full health economic models

Adjunctive therapies for the treatment of diabetic foot problems – cost effectiveness analysis

Introduction

NICE has been asked to produce a guideline on the management of diabetic foot problems. As part of this guideline two adjunctive therapies were considered: negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy (HBOT). What follows is the cost effectiveness analysis developed to support the guideline development group (GDG) in coming to recommendations. The quality of the data would usually preclude conducting an analysis given the poor quality of the clinical evidence. However, the GDG considered that cost effectiveness analysis would be required to help finalise recommendations. Where possible, this analysis has been conducted according to NICE methods outlined in the 'Guide to the methods of technology appraisals' (2008) and the 'Guidelines manual' (2009). Therefore, it attempts to follow the NICE reference case (the framework NICE requests all cost effectiveness analyses to follow) in the methodology utilised. It is advised that the full guideline should be read, as full definitions of terminology will be given there.

Given the paucity of available information, GDG opinion was used in the identification and selection of papers and data. In addition, the results presented should be considered exploratory given the significant issues in the quality of data and assumptions made.

Decision problem

The decision problem is described in Table 1 Decision problem.

Table 1 Decision problem

	Approach taken
Population	People with diabetic foot problems
Interventions	HBOT NPWT
Comparators	Standard care without HBOT and NPWT
Outcome(s)	Cost per QALY

Population

The population in this analysis represents those with diabetic foot problems who require adjunctive therapies. It can be assumed that these represent the more severe cases of diabetic foot problems since standard care would be sufficient for the majority of people.

Interventions

The two adjunctive therapies to be considered are HBOT and NPWT. These will be considered in combination with standard care. For this guideline these interventions will be examined as a class of interventions and individual types will not be examined.

Comparators

The comparator will be standard care alone

Literature search

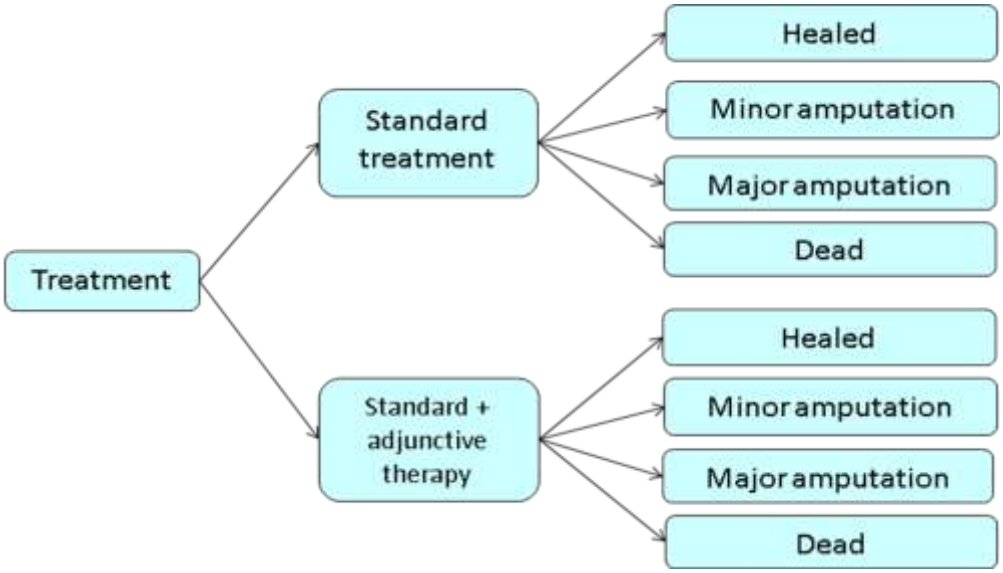
A literature search was carried out and a search was conducted for UK specific cost effectiveness papers. This approach was chosen since it is very difficult to extrapolate from papers from other countries. No UK-specific cost effectiveness papers were identified for either HBOT or NPWT. There are three identified papers on HBOT: Chuck et al 2008, Hailey et al 2007 and Guo et al 2003. The Guo et al 2003 paper provided the structural basis for all the models. However, it is difficult to identify the data sources that went into the model. In addition, it is not clear how long-term outcomes were incorporated into the model. No Markov model was included; instead it appeared that people stayed in the same state as they did at the end of year 1. So someone healed at the end of year 1 remained so for the whole analysis. This could result in overestimating the benefits of treatment since it does not include

any further hospitalisation or amputations. Therefore, a new analysis will be run with NHS-specific costs and clinical outcomes based on the clinical review.

Model structure

The model structure is summarised in Figure 1:

Figure 1 Model structure for adjunctive therapies



A decision tree was chosen because it covers the key outcomes for treatment, which is to improve immediate outcomes (i.e. amputations and so on). It is also the same structure used in Guo et al 2003 and Chuck et al 2008.

The outcomes chosen were based on work for diagnosing osteomyelitis (see appendix I). If data are not available on minor and major amputations, these two outcomes will be merged into one health state: amputations. The reason for not considering long-term outcomes via a Markov model was that there has been no long-term data on the effect of the treatments. This is covered in greater detail in the assumptions section.

Assumptions

Time horizon

The model did not include long-term outcomes. The reason for this was that there was a lack of data on the patient group. Attempts to attach Markov states to the decision tree resulted in difficulties including the appropriate costs and issues regarding the comparability of the patient groups. Alternative considerations included

including a long-term outcome variable based on the expected survival of someone with diabetic foot problems and relating them to the various outcomes and then using this figure to calculate a lifetime QALY value. This could then be combined with the expected costs of treatment to give an estimate of the lifetime cost per QALY. However, no estimates for a number of the key variables, including the lifetime costs for someone with a healed ulcer, was possible and therefore could not be included. The effect this has on the validity of the results will be discussed in the limitations section.

Treatments have no effect on mortality

The clinical effectiveness review did not find evidence for the adjunctive therapies having any effect on mortality. In part this was caused by the studies not recording mortality as an outcome. Therefore, mortality will be assumed to not be affected by treatment.

No quality of life impact of treatments

There was no evidence identified by the clinical review on the adverse events or quality of life effect of adjunctive therapies. Therefore, it will be assumed that they have no effect on quality of life.

Inputs

Clinical outcomes

The clinical outcomes for the adjunctive treatments will be based on the conclusions of the clinical review. For both treatments a meta-analysis was conducted and this will be the basis of the clinical outcomes. A summary is provided in Table 2 for both adjunctive treatments.

Table 2 Clinical outcomes for adjunctive treatments

Outcome (%)	HBOT analysis		NPWT analysis	
	Standard therapy	HBOT and standard care	Standard therapy	NPWT and standard care
Healed	15.6	63.2	73.6	80.34
Minor amputation	35.1	13.5	10.4	3.66
Major amputation	24.67	6.96		
Dead	16	16	16	16

There was no evidence that there is any effect on mortality. However, it is a recorded outcome of diabetic foot management. Though mortality will be excluded for the base case, sensitivity analyses will include mortality and various relative risks applied to represent potential reductions in death.

Utilities

The utilities were extrapolated from the diagnosis of osteomyelitis model. The base-case values are reproduced below in Table 3. Sensitivity analysis will be conducted using values from Ortegon et al 2004 and Sullivan et al 2002.

Table 3 Utility values included in model

Health state	Value
Primary healing	0.6
Healed after minor amputation	0.61
Healed after major amputation	0.31

Cost

The cost of amputations (major and minor) and standard treatment were extrapolated from osteomyelitis model (see appendix I). When amputations were merged into one state the cost was averaged. This may under/overestimate the cost impact given the relative proportion between minor and major amputations. The remaining variables that need defining are the cost of HBOT and NPWT.

Hyperbaric oxygen therapy

The NHS reference cost for HBOT states that a day case is £288 per session. Evidence from NORCOM (North Derbyshire, South Yorkshire and Bassetlaw Commissioning Consortium) suggests that the average cost for 30 sessions is approximately £8000. According to NHS Quality Improvement Scotland, the average number of sessions is approximately 30, with a maximum of 40. Estimates obtained during consultation from providers of HBOT gave a much lower estimate of £168 per session. Given that this figure comes directly from providers it will be used in the base-case analysis. Sensitivity analysis of 50% will be conducted around this figure.

Negative pressure wound therapy

There is no publicly listed price for NPWT and the GDG noted that there are a number of suppliers whose costs vary greatly.

NHS Yorkshire conducted an analysis when writing local specification for the provision of NPWT locally. This gave the cost per dressing for various systems and estimated the cost of weekly treatment to be £420. This was presented to the GDG and considered to be reflective of the true cost. This was then multiplied by the expected length of treatment of 4 weeks giving a total cost of £1680. The GDG considered this to be a reasonable estimate.

Summary of variables

Table 4 Variables included in probabilistic analysis

Variable	Mean	Lower limit	Upper limit	Distribution	A	B
Adjunctive therapy						
Hyperbaric oxygen therapy	5040	2520	7560	Uniform	N/A	N/A
Negative pressure wound therapy	1680	420	6720	Uniform	N/A	N/A
Utilities						
Healed	0.6	0.5	0.8	Beta	60	40
Minor amputation	0.61	0.4	0.8	Beta	61	39
Major amputation	0.31	0.2	0.6	Beta	31	69
Costs						
Standard treatment	3458	2000	15000	Gamma	1.65	2102
Minor amputation	5939	200	10000	Gamma	4.99	1485.25
Major amputation	14038	5000	25000	Gamma	3.99	3519.51

Analysis

Results

Deterministic and probabilistic results

The results are presented in Table 5 and Table 6.

Table 5 Base case results for NPWT

	QALY	Cost (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
Deterministic					
Standard	0.4740	4542	-	-	-
NPWT	0.4935	5512	0.0195	970	49691
Probabilistic					
Standard	0.4728	4550	-	-	-
NPWT	0.4923	5541	0.0195	991	50821

Table 6 Base case results for HBOT

	Cost (£)	QALY	Incremental Costs (£)	Incremental QALYs	ICER (£)
Deterministic					
Standard	9599.6	0.4094			
HBOT	11250	0.4773	1650.4	0.0674	24,486
Probabilistic					
Standard	9621	0.4091			
HBOT	11318	0.4764	1697	0.0673	25,215

Both these analyses indicate that NPWT and HBOT are associated with ICERs greater than what is considered cost effective.

Sensitivity analysis

One-to-one sensitivity analysis

The deterministic sensitivity analysis indicates that for HBOT, the cost is the key variable. For NPWT, the results indicate that if the cost of NPWT is very low and the cost of amputation is very high then NPWT could be cost effective.

Utility sensitivity analysis

Given the apparent inconsistency in the healed and minor amputation states, two additional utility estimates were used. The results are presented in

Table 7 and Table 8.

Table 7 Utility sensitivity analysis - HBOT

	QALY	Cost (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
Sullivan et al 2002					
Standard	0.6043	9600	-	-	-
HBOT	0.6599	11250	0.0556	1650	29689
Ortegon et al 2004					
Standard	0.5512	9600	-	-	-
HBOT	0.5652	11250	0.0140	1650	118003

Table 8 Utility sensitivity analysis - NPWT

	QALY	Cost (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
Sullivan et al 2002					
Standard	0.6818	4542	-	-	-
NPWT	0.6973	5512	0.0155	970	62654
Ortegon et al 2004					
Standard	0.5650	10146	-	-	-
NPWT	0.5690	14445	0.00404	4299	240175

Cost effectiveness planes

Figure 2 and Figure 3 are the cost effectiveness planes for HBOT and NPWT. These results indicate that the majority of the simulations are in the northeast quadrant, but it is possible that these interventions could be cost saving. However, the spread indicates that there is variation in the effectiveness and costs.

Figure 2 Cost effectiveness plane - HBOT

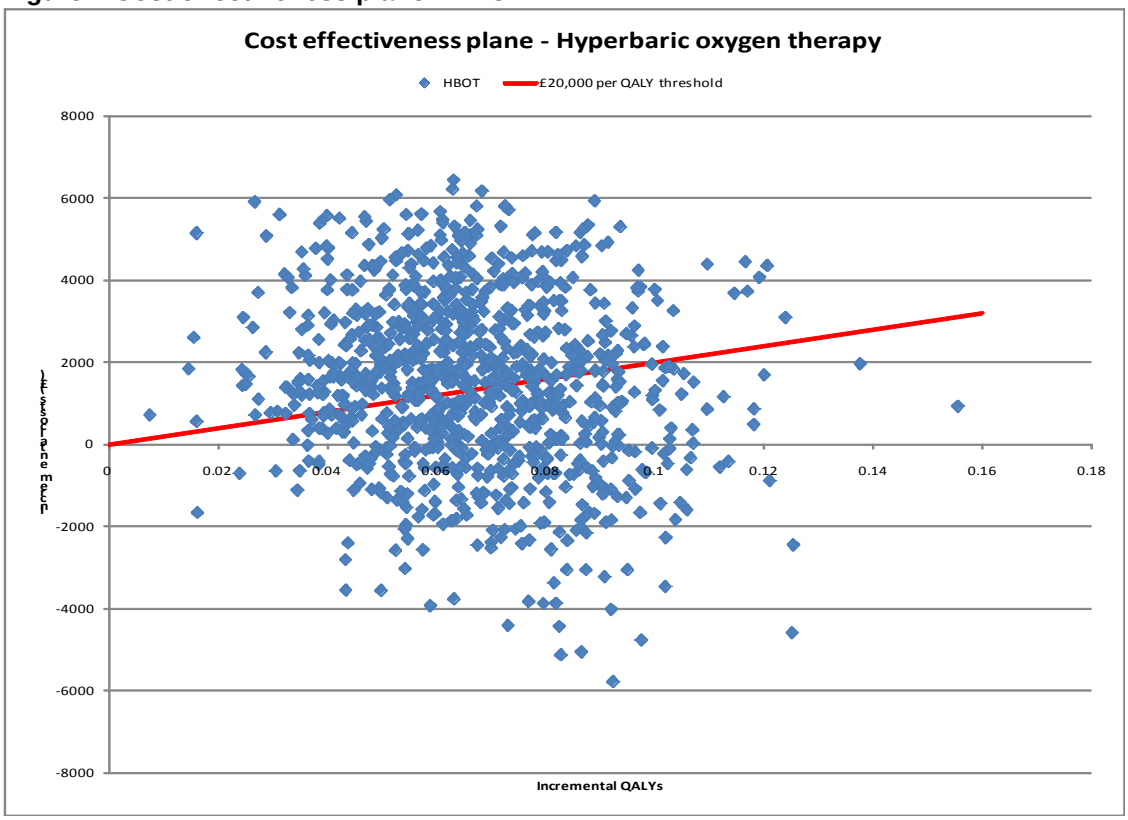
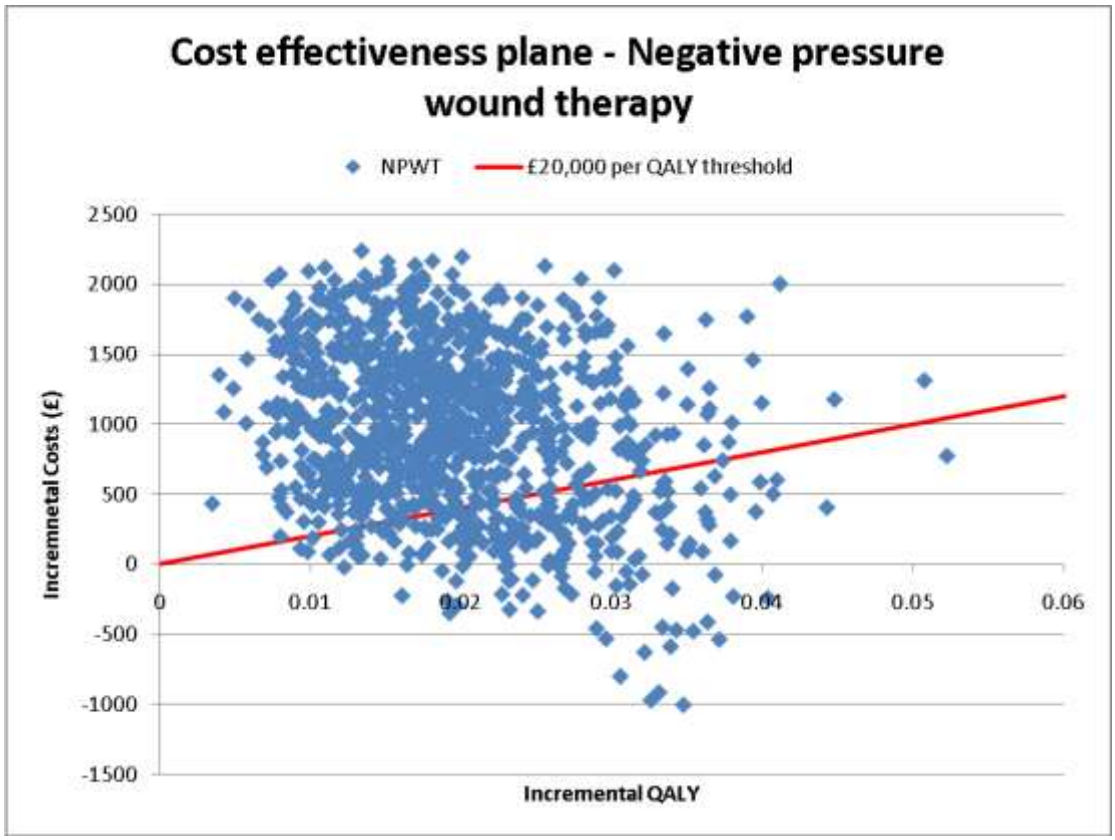


Figure 3 Cost effectiveness plane - NPWT



Cost effectiveness acceptability curves

The cost effectiveness curves for HBOT in Figure 4 and NPWT in Figure 5.

Figure 4 Cost effectiveness acceptability curve - HBOT

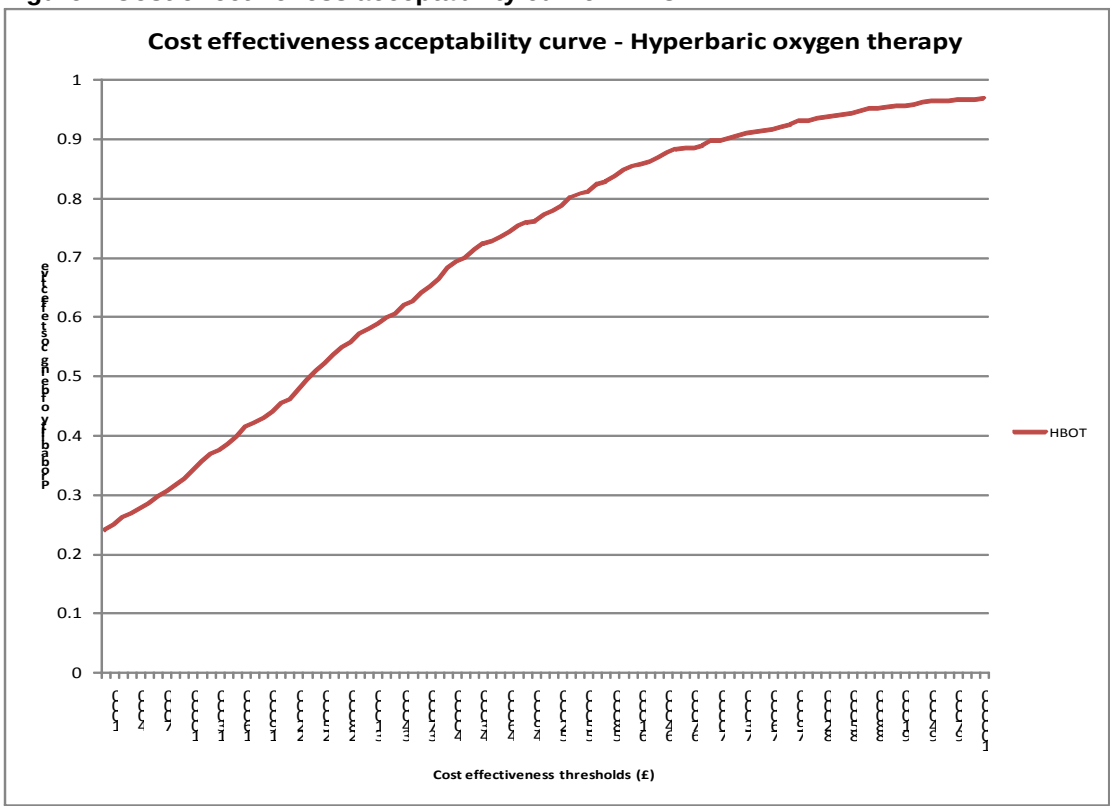


Figure 5 Cost effectiveness acceptability curve - NPWT

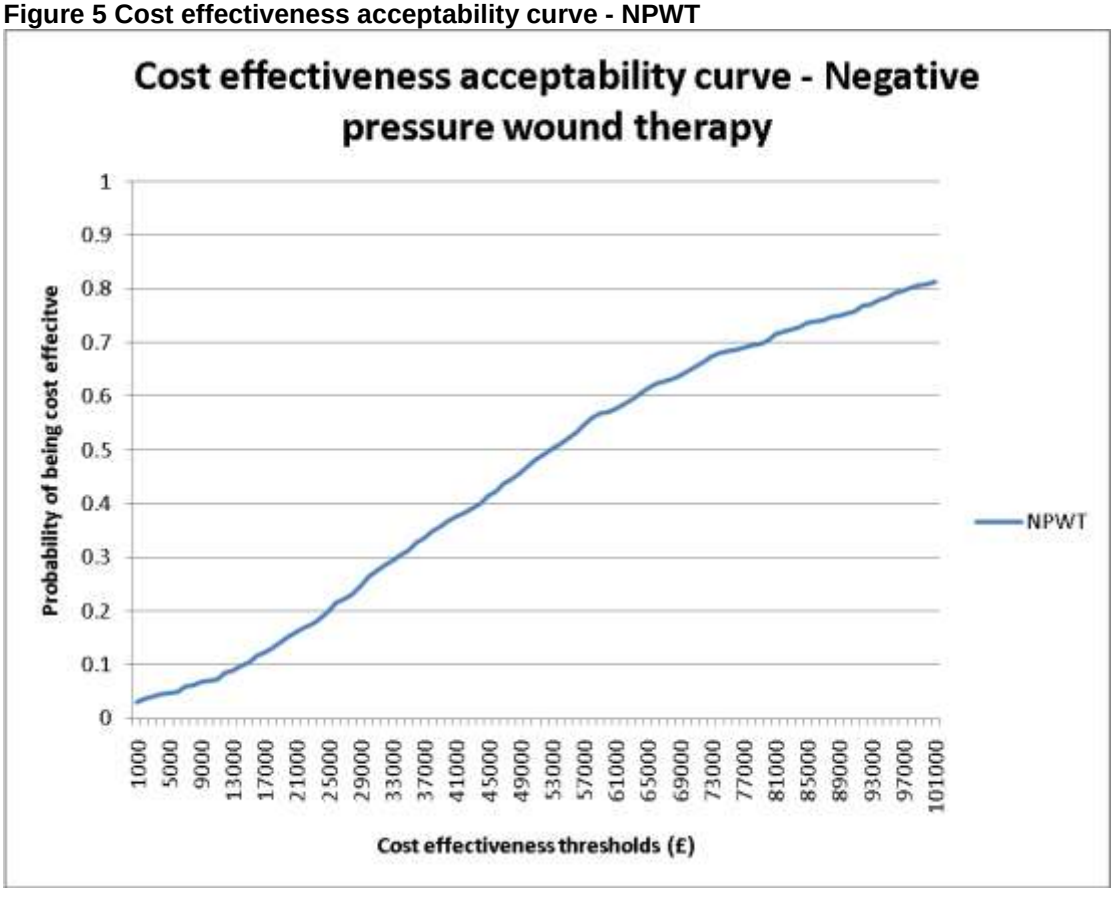


Table 9 Probability of being cost effective at different thresholds

Threshold	HBOT	NPWT
£20,000	0.44	0.152
£30,000	0.54	0.264

These results indicate that these treatments are associated with considerable uncertainty.

Limitations

Clinical data

The clinical data included in the analysis was generally of poor quality, and therefore the model is only as reliable as the data being inputted into it. This is especially true for the NPWT model where there was no data on its use in preventing primary amputations. Improved evidence of clinical effectiveness is required to help justify its use.

In addition, there was no clinical data identified on the effect these therapies have on mortality, and therefore potential benefits may not have been accounted for in the model.

No long-term outcomes

The model did not include long-term outcomes. The reason for this was that there was a lack of data on the patient group. Attempts to attach Markov states to the decision tree resulted in difficulties including the appropriate costs and issues regarding the comparability of the patient groups. Alternative considerations included including a long-term outcome variable based on the expected survival of someone with diabetic foot problems and relating them to the various outcomes, and then using this figure to calculate a lifetime QALY value. This could have then be combined with the expected costs of treatment to give an estimate of the lifetime cost per QALY. However, no estimates for a number of the key variables including the lifetime costs for someone with a healed ulcer was possible and therefore could not be included. This is a major limitation since people who have amputations generally have worse outcomes than those who don’t. As such, the benefits of the treatments may have been underestimated. Future work should look to properly address this by constructing a full decision tree and Markov model.

Costs

The costing was based on aggregate values from NHS reference costs. Other than the cost of the adjunctive therapies no other costs were included. Therefore, potential cost differences may have been excluded, for example any difference in hospital stay or additional medication given. The effect of this limitation on the cost effectiveness results is unknown.

Discussions and conclusions

The analysis constructed was highly exploratory and based on a simple model and has several limitations. Therefore, this economic analysis should not be considered to be a full cost effectiveness analysis, but exploratory to examine the potential impact of recommending adjunctive therapies. This analysis utilises methods and data that might not usually be done in a full high quality review.

Analyses by Chuck et al 2008 and Guo et al 2003 indicated that HBOT in particular could be potentially cost effective; however, both of these analyses used longer time horizons, which indicates that it is possible that the treatments could be cost effective if long-term outcomes are included. However, it is not clear in which patient group these treatments will be used in, therefore which set of long term outcomes to use.

The analysis conducted is highly uncertain; however, it does indicate that there is potential benefit of the treatments, especially for NPWT where the data is of very poor quality.

References

1. Chuck AW, Hailey D, Jacobs P et al. (2008) Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. International Journal of Technology Assessment in Health Care 24: 178-83.

2. Curtis L (2009) Unit Costs of Health and social care. Kent: Personal Social Services Research Unit

3. Department of Health, (2010) National Schedule of Reference Costs 2008-09 for NHS Trusts and PCTs Combined. available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591

4. Ghatnekar O, Persson U, Willis M et al. (2000) The cost-effectiveness in the UK of treating diabetic lower extremity ulcers with becaplermin gel. Journal of Medical Economics 3: 87-95.

5. Guo S, Counte MA, Gillespie KN et al. (2003) Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. International Journal of Technology Assessment in Health Care 19: 731-7.

6. Hailey D, Jacobs P, Perry DC et al. (2007) Adjunctive hyperbaric oxygen therapy for diabetic foot ulcer: An economic analysis. Technology report no.75 Ottawa: Canadian Agency for Drugs and Technologies in Health.

7. Ortegon MM, Redekop WK, Niessen LW (2004) Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. Diabetes Care 27: 901-7.

8. Ragnarson TG, Apelqvist J (2001) Prevention of diabetes-related foot ulcers and amputations: a cost-utility analysis based on Markov model simulations. Diabetologia 44: 2077-87.

9. Redekop WK, Stolk EA, Kok E et al. (2004) Diabetic foot ulcers and amputations: Estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes and Metabolism 30: 549-56.

10. NHS Quality improvement Scotland (2007) Hyperbaric oxygen therapy (HBOT) for the prevention and treatment of osteoradionecrosis following radiotherapy of head and neck cancer. Evidence note 15.

11. North Yorkshire and York PCT (2008) Service specification: Topical negative pressure available online http://www.northyorkshireandyork.nhs.uk/AdviceInformation/MakingDecisions/docs/ServiceSpecifications/VAC%20pump%20therap%20Sept08.pdf

12. Sullivan S, Lew D, Devine E et al. (2002) Health state preference assessment in diabetic peripheral neuropathy. Pharmaoeconomics 2002;20:1079–89.

13. Thomas N, Cox K (2006) Policy on hyperbaric oxygen therapy for patients with oral cancer. North Derbyshire, South Yorkshire and Bassetlaw Commissioning Consortium, available online http://www.sheffield.nhs.uk/boardmeetings/papers/spctagenda041207-30a.pdf [accessed 13/08/2010]

MRI for diagnosing osteomyelitis – cost effectiveness analysis

Introduction

NICE has been asked to produce a guideline on diabetic foot problems. During development of this guideline the use of MRI in the diagnosis of osteomyelitis in diabetic foot problems was noted as a priority for cost effectiveness analysis. What follows is the cost effectiveness analysis developed to support the guideline development group (GDG) in determining their recommendations. This analysis has been conducted according to NICE methods outlined in the 'Guide to the methods of technology appraisals' (2008) and the 'Guidelines manual' (2009). Therefore, it follows the NICE reference case (the framework NICE requests all cost effectiveness analysis to follow) in the methodology utilised. It is advised that the full guideline should be read, as full definitions of terminology will be given there.

Given the paucity of available information, GDG opinion was used in the identification and selection of papers and data. In addition, the results presented should be considered exploratory given the significant issues in the quality of data and assumptions made.

Decision problem

The decision problem for this guideline is described in Table 1 Decision problem0.

Table 100 Decision problem

	Approach taken
Population	People with suspected osteomyelitis and diabetic foot problems
Interventions	Magnetic resonance imaging (MRI)
Comparators	X-ray
Outcome(s)	Cost per QALY

Population

The population in this analysis will be those with diabetic foot problems and suspected osteomyelitis. This population represents a pre-selected population of people and therefore the prevalence of osteomyelitis is likely to be higher in this population than in the country. Data from the clinical review suggests a rate of 58.5%

on average from the MRI and X-ray diagnostic studies. This value will be used in the analysis but varied from 0.29 to 0.86 on the individual studies.

Interventions

Although MRI is the intervention, all patients receive an X-ray on admission. Therefore MRI alone and a combined X-ray and MRI should be the true intervention. However, the GDG indicated that all patients would receive an X-ray and then, if needed, an MRI. Therefore, the costs would cancel out across both arms.

Comparators

Only X-rays will be considered as a comparator as this represents standard care. In reality people may receive multiple X-rays. However, no evidence was identified for this use and therefore a one off X-ray will be considered with associated sensitivity and specificity.

Outcomes

The outcome that will be considered is the cost per QALY.

Literature reviews

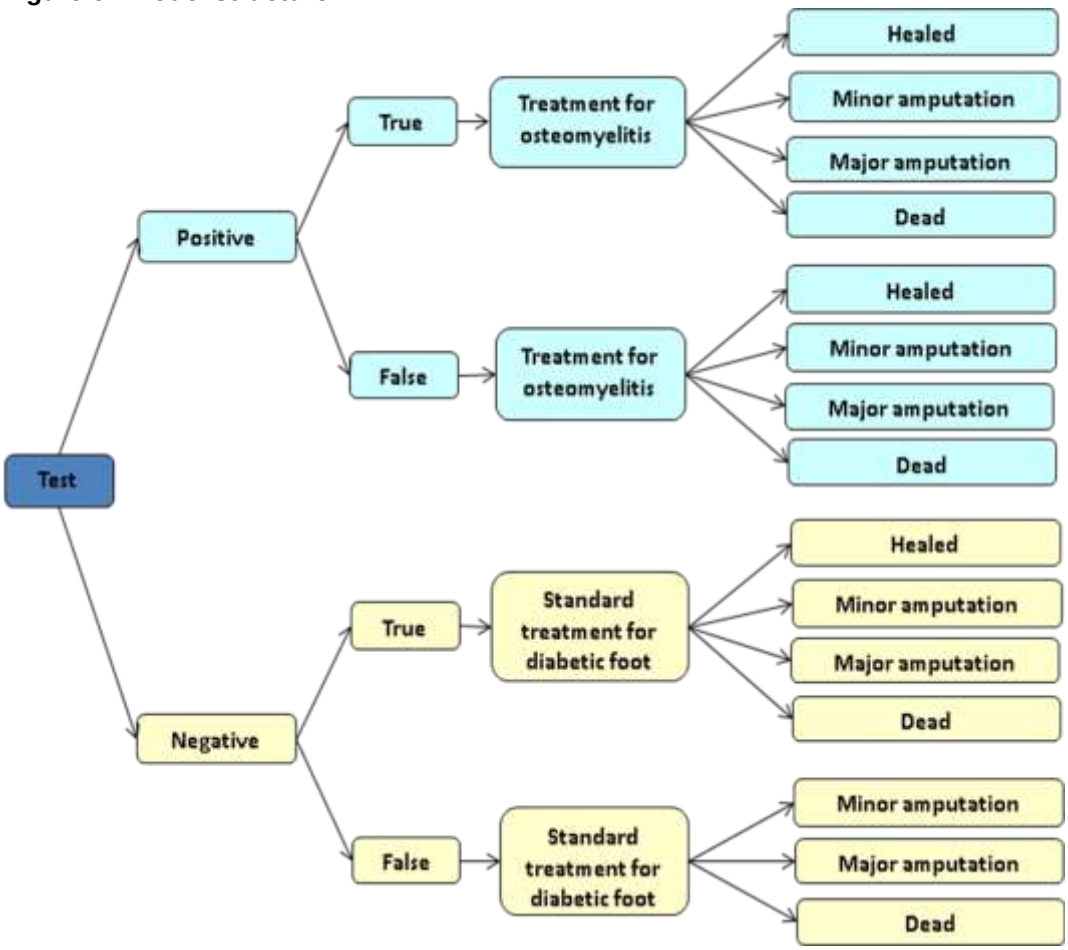
Cost effectiveness studies

No UK-specific cost utility studies for the diagnosis of osteomyelitis were identified by the literature search. One potential model that was identified was used by Eckman et al 1995. However, this analysis was from a US perspective. In addition, there was insufficient information within the paper to reconstruct the decision tree; therefore a de novo model will be required. Papers providing additional information included Tenneval et al 2001 and Ortegon et al 2004. The use of these papers will be discussed later.

Model structure

Figure outlines the model structure.

Figure 6 - Model structure



The structure reflects the traditional way of modelling a diagnostic. It is assumed that a positive test result will lead to treatment for osteomyelitis and that a negative result will lead to standard treatment. The potential outcomes are true-positive (the person tests positive and has the condition of interest), false-positive (the person tests positive but doesn't have the condition of interest), true-negative (the person tests negative and doesn't have the condition), and false-negative (the person tests negative and does have the condition of interest). These outcomes are defined by the sensitivity and specificity of the test, and also by the prevalence of the condition. The calculations are reproduced in Table 11.

Table 11 Calculation of outcomes

Outcome	Calculation
True positive	Prevalence x sensitivity
False positive	(1 – prevalence) x (1 – specificity)
True negative	(1 – prevalence) x specificity
False negative	Prevalence x (1-sensitivity)

The outcomes from the test result (healed, minor/major amputation and death) were chosen since they correlated with the outcomes from the clinical review and from previous papers on diabetes (Tennevall et al 2004). The proportions that correspond with each of these outcomes will be discussed in the clinical outcomes section.

A decision tree was chosen to model the outcomes from diagnosis since it best represents the short-term outcomes in hospital. A Markov model to reflect long-term outcomes would usually be included; however, no data were identified that examined outcomes beyond 12 months for the populations of interest. Therefore, only short-term outcomes will be considered in the base-case analysis. This will be discussed later in the assumptions section.

Assumptions

No difference between true negatives and false positives

True negatives will be assumed to be people with severe infections that could be mistaken for osteomyelitis, such as deep foot infections. There is unlikely to be any data on treating these patients for osteomyelitis; however, there may be adverse effects of treatment such as MRSA. Therefore, in the base case, no difference will be assumed. Although this is a significant assumption, negative effects will be incorporated into a sensitivity analysis.

False negatives

There is unlikely to be any data on the delayed treatment for osteomyelitis. It can be assumed that outcomes would be worse if treatment is delayed, and therefore amputations would be higher. Therefore, only amputations and death will be included as outcomes. This is a very extreme assumption and will therefore be relaxed in sensitivity analyses.

Time horizon

The model did not include long-term outcomes. The reason for this was that there was a lack of data on the patient group. Attempts to attach Markov states to the decision tree resulted in difficulties including the appropriate costs and issues regarding the comparability of the patient groups. Alternative considerations included including a long-term outcome variable based on the expected survival of someone with diabetic foot problems and relating them to the various outcomes, and then

using this figure to calculate a lifetime QALY value. This could then be combined with the expected costs of treatment to give an estimate of the lifetime cost per QALY. However, no estimates for a number of the key variables including the lifetime costs for someone with a healed ulcer was possible and therefore could not be included. The effect this has on the validity of the results will be discussed in the limitations section.

Inputs

Sensitivity and specificity of MRI and X-ray

The values for the sensitivity and specificity of MRI and X-rays were obtained from the clinical review. As no mean was quoted a mid point was used with the range used in sensitivity analysis. The values are presented in Table 1212:

Table 12 Sensitivity and specificity used in model

	X-ray	MRI
Sensitivity	0.485	0.885
Specificity	0.555	0.8

Outcomes

No appropriate data were identified in the clinical or cost effectiveness searches to populate the model. Therefore, two approaches will be used to obtain estimates for the potential outcomes of treatment. Option 1 is to use the data from the cost effectiveness papers identified. This would involve picking values that may not necessarily match our population, and assuming that the data was selected robustly. Option 2 is to use papers identified by the GDG as potential sources for outcome data. These two approaches will be expanded in the following sections.

Option 1: Cost effectiveness papers

The papers identified in searches were examined for data on osteomyelitis. Oretegon et al 2004 was the only paper to mention this condition explicitly. This gives outcomes for healed, minor amputation, major amputation and dead. As this was the only paper identified, these outcomes will be used for the true positives.

For the false-positives and true-negatives, data from severe deep infections will be used since they are the most likely to be mistaken for osteomyelitis. The data from Oretegon et al 2004 appears unsuitable since it assumes that no one with such

infections results in amputation, which lacks face validity. Therefore, data from Tennevall et al 2001 was used, which had transitions for people with deep foot infections. The outcomes from Tennevall et al 2001 will be used for all people without osteomyelitis.

The GDG considered that delayed treatment for osteomyelitis is associated with worse outcomes. It will therefore be assumed that the only outcomes from false negatives are amputations (minor and major). Therefore, the transitions from Oretegon et al 2004 were recalculated by removing the healed state and calculating which of the remaining three states people went (amputations minor/major and dead). This significantly increases the value of an accurate diagnosis. Therefore, outcomes associated with false negatives will be examined in sensitivity analysis. The final outcomes are presented in Table .

Table 13 Cost effectiveness study outcomes in model

Outcomes	True positive	False negative	False positive	True negative
Healed	0.257	0	0.40	0.4
Minor amputation	0.246	0.331	0.35	0.35
Major amputation	0.377	0.507	0.09	0.09
Dead	0.12	0.162	0.16	0.16

Option 2: Clinical study approach

Given time constraints, a full systematic review was not possible. Therefore the GDG was asked to identify papers that could be used to populate the model outlined in Figure . The GDG identified three studies that could be used to populate the model. The papers did not differentiate between major and minor amputations. Therefore, these outcomes will be merged into an amputation state and average costs and utilities will be applied.

- Jeffcoate et al 2006

This paper followed 449 patients with diabetic foot problems for 12 months. Patients were disaggregated based on their ulcer severity. The outcomes from this paper will be used for true negatives and false positives, as they represent a population of patients with severe diabetic foot problems but no identified osteomyelitis. The outcomes were based on the final outcomes at 12 months reported in the paper. These are reproduced in table 14 along with the outcome with which they were associated in the model.

Table 14 Calculation of clinical study outcomes

Outcome	% in trial	Outcome in model
Alive, without amputation and ulcer free	45	Healed – 74.8%
Alive, without amputation and persisting ulcer	24.7	
Alive, ulcer status unknown	5.1	
Alive after amputation and ulcer free	4.7	Amputation – 9.1%
Alive after amputation with unhealed amputation site	1.3	
Alive after amputation with another ulcer elsewhere	2.4	
Alive after amputation ulcer status unknown	0.7	
Dead, without amputation and ulcer free	4.2	Dead - 16.7%
Died, without amputation and with persisting ulcers	10.9	
Dies after amputation	1.6	

People with persisting ulcers were included in the healed state. It was decided not to include an unhealed state as this outcome was not reported across all the papers.

- Jeffcoate and Game 2008

This paper followed 147 patients with osteomyelitis for over a year. From this paper all patients' final outcomes were used to populate the true-positive arm. Table outlines the calculations.

Table 15 Outcomes from Jeffcoate and Game 2008

Outcome	Number in trial	% in trial
Healed	93	64.1%
Amputation required	41	28.3%
Died	11	7.6%

This paper was deemed appropriate to populate the true-positive arm as all the patients had osteomyelitis and received appropriate treatment.

- Valabhji et al 2009

This paper was used to inform the false negatives. This paper followed 53 osteomyelitis patients for median follow-up of 15 months. It included outcomes for patients where they did not respond treatment (n = 7). These shall be assumed to represent delayed treatment; in this case, all patients required amputation. Mortality was not reported based on amputation, but for the study as a whole (11%). Table new outlines the final outcomes from the clinical study papers.

Table 16 Final outcomes from the clinical study papers

Outcomes	True positive	False negative	False positive	True negative
Healed	0.641	0	0.748	0.748
Amputation	0.283	0.89	0.091	0.091
Dead	0.076	0.11	0.161	0.161

Summary

Table summarises the outcomes from the two approaches

Table 17 Summary of the outcomes from the two approaches

Outcome	Cost effectiveness studies				Clinical studies			
	True positive	False negative	False positive	True negative	True positive	False negative	False positive	True negative
Healed	0.257	0	0.40	0.4	0.641	0	0.748	0.748
Minor amputation	0.246	0.331	0.35	0.35				
Major amputation	0.377	0.507	0.09	0.09	0.283	0.89	0.091	0.091
Dead	0.12	0.162	0.16	0.16	0.076	0.11	0.161	0.161

The main difference between the two approaches is the proportion of amputations. This may represent the difference between the clinical situations and also

developments in treatment. Using both sets of clinical data should account for the two extremes.

Quality of life review

Literature

Instead of a full review of the literature for quality of life data, existing cost effectiveness papers were examined. This meant that any values should be appropriate for use in a cost effectiveness analysis. Fourteen studies were identified; of these, only Tennevall et al 2001 used the EQ-5D (the preferred instrument for calculating QALYs). This study used data from a postal survey of 440 patients with type 1 or type 2 diabetes. These values were subsequently used in later health economic analyses of diabetes and appear appropriate for the current analysis. A summary of the values are provided in Table :

Table 18 Utility values from Tennevall et al 2001

Health state	Value
Primary healing	0.6
Healed after minor amputation	0.61
Healed after major amputation	0.31

However, the value for minor amputations appears counterintuitive since it is greater than the value for primary healing. Alternatives from other cost effectiveness studies are provided in Table :

Table 11 Utility values from cost effectiveness studies

	Tennevall 2001	Sullivan et al 2002	Redekop et al 2004
Method of elicitation	EQ-5D	Standard gamble	Time trade off
Health state	Value		
Primary healing	0.6	0.84	0.68
Healed after minor amputation	0.61	0.74	0.68
Healed after major amputation	0.31	0.61	0.62

Sullivan et al 2002 is a study of 52 patients with type 1 or type 2 diabetes where values were elicited with standard gamble techniques. Oretgon et al 2004 used data from Redekop et al 2004, eliciting utility values using time trade off from 96 members

of the general public. Some analyses (Chuck et al 2008) have used the Tennevall et al 2001 values without alteration; others (Guo et al 2003) have assumed no difference between primary healing and minor amputation. For the base case, Tennevall et al 2001 will be used as the values were obtained via the EQ-5D method and matches NICE's reference case. However, Sullivan et al 2002 and Ortegon et al 2004 will be used in sensitivity analyses.

Costs

The key costs that need to be considered in the model are: MRI, X-ray, cost of treatment osteomyelitis, standard treatment and amputation (major and minor). These costs will be considered in more detail below.

MRI

The cost of MRI was obtained from the NHS reference costs by averaging RA01Z to RA07Z. This gave a cost of £211. This may be an underestimate given the number of MRIs that are carried out in the NHS each year. Therefore, an estimate suggested by the GDG of £600 will be examined in sensitivity analyses.

X-ray

There is no NHS reference cost for X-ray as it is usually included in the HRG code for procedures. However, costs of up to £150 will be used in sensitivity analyses.

Cost of treatment for osteomyelitis/standard care

The NHS reference cost for the inpatient treatment for someone with a diabetic foot problem is £3458 (KB03A). This is a standard cost and should represent an average patient with diabetic foot problems. However, osteomyelitis is associated with greater treatment costs, including longer courses of antibiotics. Advice from the GDG suggests that treatment varies considerably across the country. It appears from GDG consensus that on average treatment lasts for 6 weeks compared with 14 days for standard treatment, and that the most common combination is clindamycin and ciprofloxacin for osteomyelitis. We will assume that the standard care costs include the cost of antibiotics for standard care. The 6-week cost of clindamycin and ciprofloxacin varies significantly if oral or intravenous antibiotics are used. If all 6 weeks are assumed to be oral, the total cost is £407; however, if all the treatments are given as IV for the full 6 weeks, the total cost is £2226.67. In reality the true cost is likely to vary significantly, and therefore a midpoint of £1300 will be used.

However, given the uncertainty in this value, the difference between standard treatment and osteomyelitis treatment will be varied from £0 to £2500.

Amputation cost (minor/major)

A major component of the management of diabetic foot problems is the avoidance of amputations. Amputations are associated with worse outcomes, especially higher mortality and re-admittance rates.

The cost of amputations was obtained from Ghatnekar et al 2000 and uplifted to 2010 prices. For major amputations the cost was £14,058, and for minor the cost was £5939. These values are closely in line with the NHS reference cost of £12,132 for major amputation with major CC (complications) (QZ11A). For lower limb amputations it is greater than the NHS reference cost of £3284 for foot procedures for diabetes (QZ12Z). In addition, an international comparison across countries by Ragnarson and Tennevall 2004 indicated that the cost of amputation varied between £10,162 and £15,500 in the mid-1990s. Therefore, these values appear to have good face validity.

Analyses

Given the quality of the evidence available and the considerable uncertainties involved, significant sensitivity analyses will be required.

Deterministic sensitivity analysis

Outcomes from delayed osteomyelitis treatment

In both models it was necessary to make assumptions about the detrimental effect of delayed treatment of osteomyelitis. It was noted by the GDG that delayed treatment was associated with worse outcomes than prompt treatment; however, the size of the effect is unknown. Therefore, a sensitivity analysis will be conducted to examine the effect of the effect of delayed treatment. This will be done by using the outcomes from the true-positive arm and a factor added to the amputation rate such that, as the factor is increased, the rate of amputation will increase and the rate of healing falls. The factor for the cost effectiveness analyses will be the same for the minor and major analyses. This factor will also be varied in sensitivity analysis.

Adverse event from treatment

To account for potential adverse events from unnecessary treatment, an adverse event will be associated with –0.05 QALYs. It is possible that mortality could also be increased but there is no evidence of the potential effect. Thus the mortality rate will be increased by 2% to examine its effect.

Probabilistic sensitivity analysis

The outcomes from treatment were fitted to a Dirichelt distribution since separate beta distributions would have resulted in the probabilities summing to greater than 1.

All variables will be subject to sensitivity analysis. Table outlines all the variables with high low values and the distributions. For the beta distributions no standard errors or variances were reported; thus, A and B were calculated using the calculation of the mean (mean = A/(A+B)). For the gammas distributions, the standard deviations were calculated for costs derived from NHS reference costs by using the solver function in Microsoft Excel and for costs from Ghatnekar et al 2000 by assuming that 50% represented the standard deviation. The clinical outcomes were varied using Dirichlet distributions.

Table 20 Variables in probabilistic sensitivity analysis

Variable	Mean	Lower	Upper	Distribution	A	B
Prevalence	0.585	0.2925	0.8775	Beta	58.5	41.5
Sensitivity and specificity						
X-ray sensitivity	0.485	0.22	0.75	Beta	48.5	51.5
X-ray specificity	0.555	0.17	0.94	Beta	55.5	44.5
MRI sensitivity	0.885	0.77	1	Beta	88.5	11.5
MRI specificity	0.8	0.6	1	Beta	80	20
Utilities						
Healed	0.6	0.5	0.8	Beta	60	40
Minor amputation	0.61	0.4	0.8	Beta	61	39
Major amputation	0.31	0.2	0.6	Beta	31	69
Costs						
X-ray	0	0	150	Gamma	0.28	140.62
MRI	211	150	600	Gamma	36.28	5.83
Standard treatment	3458	2000	15000	Gamma	1.65	2102
Osteomyelitis treatment	1300	0	2500	Uniform		
Minor amputation	5939	200	10000	Gamma	4.99	1485.25
Major amputation	14038	5000	25000	Gamma	3.99	3519.51

Results

Base case

Deterministic and probabilistic

Table below summarises the main results from the analysis based on cost effectiveness papers and Table for the analysis based on clinical papers.

Table 21 Deterministic and probabilistic cost effectiveness results (per person) cost effectiveness papers

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
X-ray	0.4274	10083	-	-	-
MRI	0.4420	9923	0.0145	-160	Dominates
Probabilistic					
X-ray	0.4279	9886	-	-	-
MRI	0.4422	9728	0.0143	-158	Dominates

Table 22 Deterministic and probabilistic cost effectiveness results (per person) clinical papers

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
X-ray	0.4151	7901	-	-	-
MRI	0.4611	6868	0.0460	-1033	Dominates
Probabilistic					
X-ray	0.4135	7896	-	-	-
MRI	0.4590	6842	0.0455	-1027	Dominates

These results indicate that MRI is cost saving and more effective than X-ray alone. The main differences between the two analyses can be attributed to the difference in amputation rates. However, the conclusions are consistent.

Sensitivity analysis

Deterministic sensitivity analysis

One-to-one sensitivity analysis

In Table only values that cause the cost effectiveness results to change from MRI dominating X-ray are presented (using the maximum and minimum values outlined in Table 20).

Table 23 Deterministic sensitivity analysis results in cost effectiveness analysis

Variable	Input in model	ICER
Cost of major amputation	£25000	£7993
Cost of MRI	£600	£15169
Cost of osteomyelitis treatment	£2500	£389
X-ray sensitivity	0.75	£1558
X-ray specificity	0.94	£2752

All analyses based on the clinical studies indicate that MRI dominates X-ray. These results indicate that individual variables have little impact on the cost effectiveness decision.

Adverse event

The results of scenarios of including a QALY decrement and increasing mortality to account for adverse events are outlined below in Table and Table .

Table 24 Adverse event QALY effect of -0.05

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Cost effectiveness analyses					
X-ray	0.3615	10083	-	-	-
MRI	0.3689	9923	0.0074	-160	Dominates
Clinical study analyses					
X-ray	0.3917	7901	-	-	-
MRI	0.4611	6868	0.0694	-1033	Dominates

Table 25 The analysis based on increasing mortality by 2%

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Cost effectiveness analyses					
X-ray	0.4267	10083	-	-	-
MRI	0.4411	9923	0.0144	-160	Dominates
Clinical study analyses					
X-ray	0.4145	7901	-	-	-
MRI	0.4604	6868	0.0459	-1033	Dominates

Neither analysis changes the results, suggesting that adding MRSA or other additional events wouldn't affect the results. No additional costs were included; however, the inclusion would only improve the cost effectiveness analyses for MRI.

False negative outcomes

Sensitivity analysis was conducted on the proportion of amputations in the false negative outcomes. The proportions in Table and Table outlines the proportion of amputations that result in different cost effectiveness thresholds for each analysis.

Table 26 False negative outcomes - Cost effectiveness study

Threshold	Factor	Minor amputations	Major amputations
True positives	-	0.246	0.377
£30,000	1.164	0.286	0.439
£20,000	1.184	0.291	0.446
Dominates	1.244	0.306	0.469
Base case	1.346	0.331	0.507

Table 27 False negative outcomes - Clinical study outcomes

Threshold	Factor	Amputations
True positives	-	0.283
£30,000	1.28	0.362
£20,000	1.34	0.379
Dominates	1.52	0.43
Base case	3.14	0.89

These results indicate that delayed treatment needs to increase the risk of amputation by 16 – 30% for MRI to be considered cost effective for both analyses.

Utility values

A sensitivity analysis was conducted using the different utility values in Table and the results presented in Table and Table .

Table 28 Cost effectiveness analyses – utility values

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Sullivan et al 2002					
X-ray	0.6148	10083	-	-	-
MRI	0.6321	9923	0.0172	-160	Dominates
Ortegon et al 2004					
X-ray	0.561	10083	-	-	-
MRI	0.569	9923	0.009	-160	Dominates

Table 12 Clinical studies analyses – utility values

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Sullivan et al 2002					
X-ray	0.6491	7901	-	-	-
MRI	0.6885	6868	0.0394	-1033	Dominates
Ortegon et al 2004					
X-ray	0.5742	7901	-	-	-
MRI	0.5881	6868	0.0139	-1033	Dominates

These analyses indicate that, regardless of the utilities used, the decision remains the same.

Cost effectiveness planes

For the base case analyses, the cost effectiveness planes are presented below in Figure and Figure . Both plots indicate that the majority of the data is in the southeast quadrant (less expensive and more effective). In addition, the plots indicate that the majority of the variation in the model increases the cost saving.

Figure 7 Cost effectiveness plane - cost effectiveness analyses

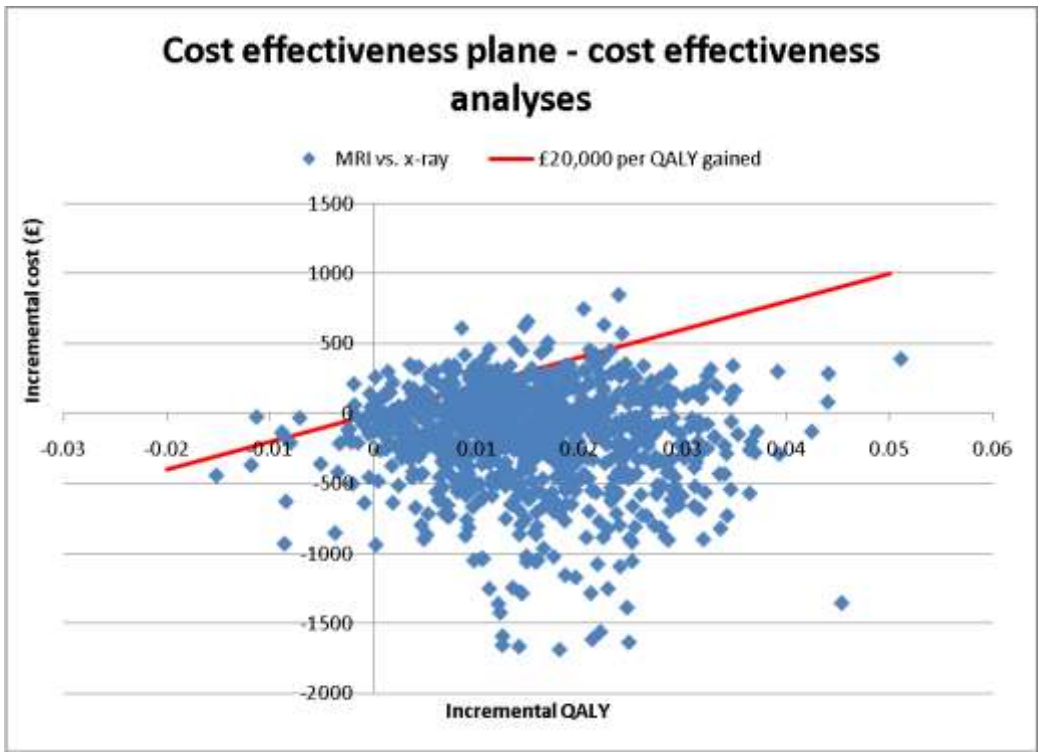
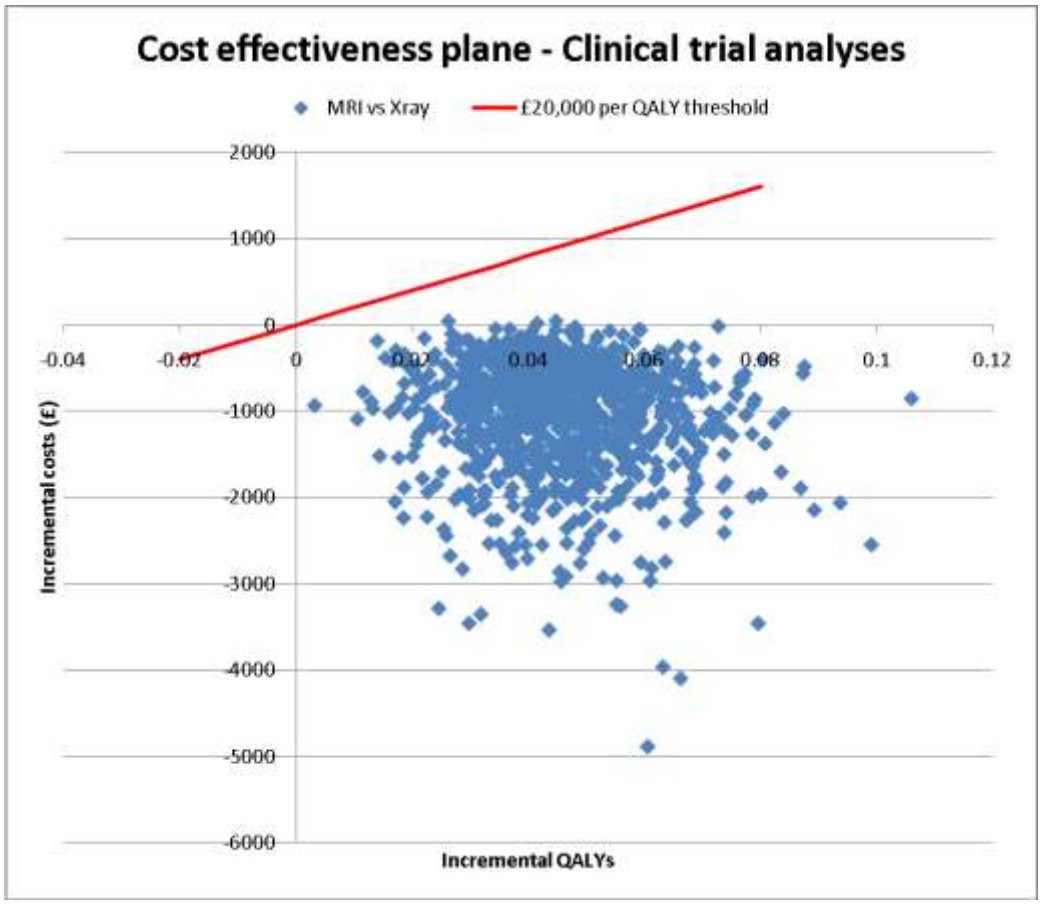


Figure 8 Cost effectiveness plane – clinical trial analyses



Cost effectiveness acceptability curves

The cost effectiveness acceptability curves for the analysis based on clinical and cost effectiveness studies base case analysis are presented in Figure and Figure .

Figure 9 Cost effectiveness acceptability curve – cost effectiveness analyses

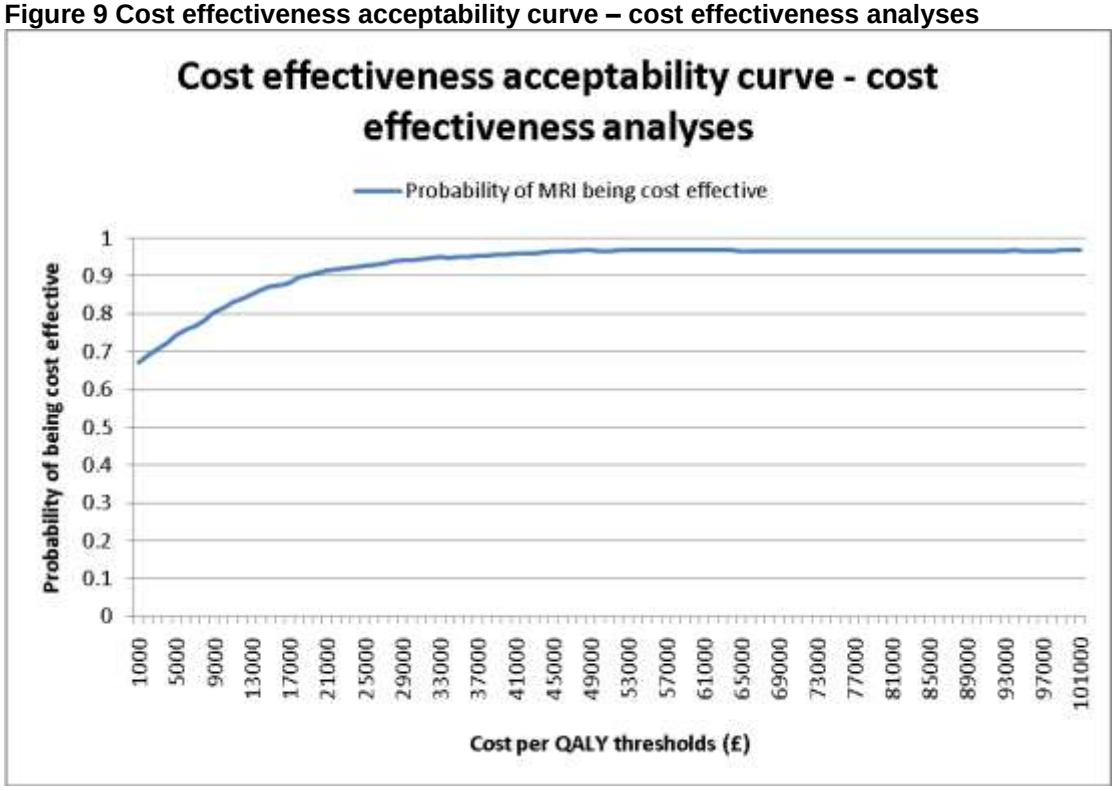
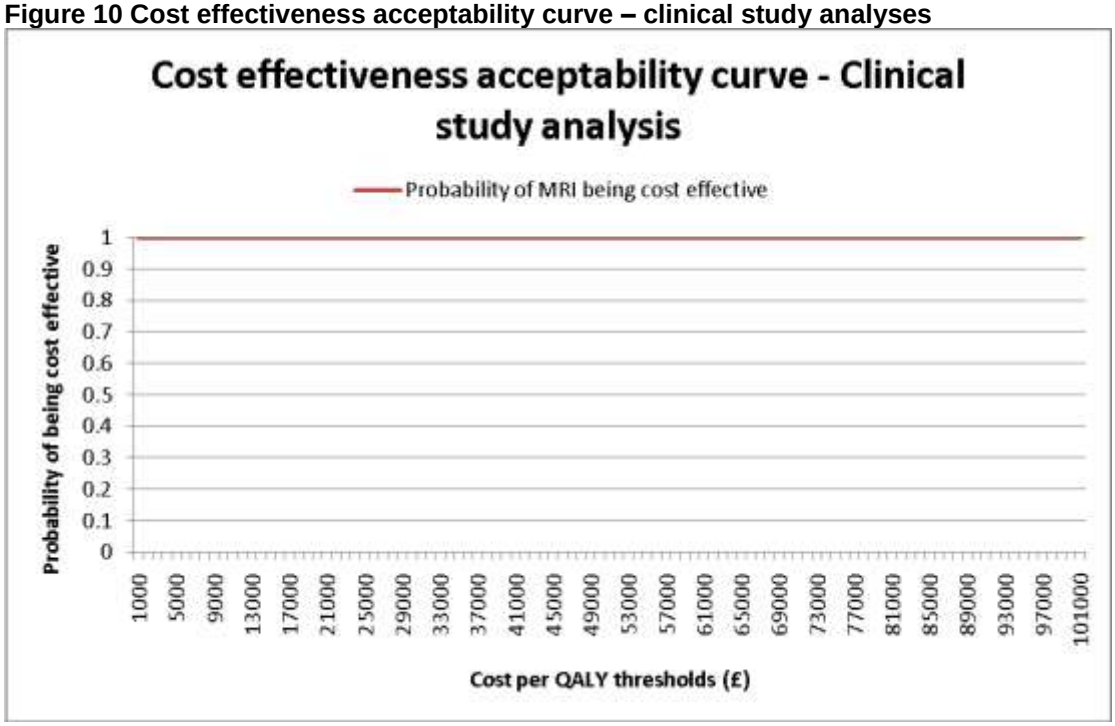


Figure 10 Cost effectiveness acceptability curve – clinical study analyses



The results for £20,000 and £30,000 per QALY thresholds are presented in Table for both analyses

Table 30 Probability of being cost effective at various cost effectiveness thresholds

	Probability of being cost effective	
Cost effectiveness threshold	Cost effectiveness analysis	Clinical study analysis
£20,000	0.91	1
£30,000	0.94	1

These results indicate that it is highly probable that the use of MRI in diagnosing osteomyelitis is more cost effective than X-rays using the base-case assumptions.

Probabilistic false negative outcomes

Another probabilistic sensitivity analysis was run with the false negative arm factor being varied as well as a uniform distribution from 1 to 12 for the clinical studies and 1 to 1.346 in the cost effectiveness study model. The probability of being cost effective at different cost effectiveness thresholds is presented in Table .

Table 31 Probability of MRI being cost effective: Varying false negative outcomes

Cost effectiveness threshold	Probability of being cost effective – CE model	Probability of being cost effective – clinical model
£20,000	0.41	0.83
£30,000	0.47	0.85

These indicate that variability around the outcomes for false negatives can adversely affect the cost effectiveness results. The clinical analysis maintains high probabilities of being cost effective. However the cost effectiveness analysis indicates

Limitations

The analysis has numerous and some severe limitations

No long-term outcomes

Due to a paucity of data on the relevant patient group no long-term outcomes were included in the analyses, and therefore may have underestimated the total costs and QALYs in the analysis. However, it is generally shown that people with amputations have worse outcomes than those without (Tennevall et al 2006). In addition, they generally cost more since they have higher recurrence rates. Thus the addition of long-term outcomes should improve the cost effectiveness estimates. However, the

total costs of treatment may be increased, so the effect on the results may be uncertain. However, future work should examine the inclusion of long-term outcomes to examine the effects on the final results.

False negative outcomes
This arm is probably the most important to the final results. If delayed treatment of osteomyelitis results in increased amputation rates then more accurate diagnosis is a cost effective intervention. However, if this does not hold, then MRI is not cost effective. No data explicitly explored this; the best data (available from Valabhji et al 2009) indicate that those who do not respond to treatment require amputations.

Poor quality of clinical data
The data used to populate the outcomes of treatment was of low quality and not systematically selected due to time constraints. The data came from different sources and therefore may be subject to bias and heterogeneity. Choosing appropriate endpoints and outcomes was made difficult due to the varying quality of papers and reporting. However, the GDG indicated that it was unlikely that any suitable data would be identified and that the data selected was appropriate to use. However, future work should carry out a more structured review for evidence.

Discussion and conclusion

In ‘Type 2 diabetes: the management of type 2 diabetes (update)’ (NICE clinical guideline 66), the School of Health and Related Research (ScHARR) stated that no economic analysis was possible due to an absence of sufficient evidence. It could be argued that not much has changed in the intervening years. However, the GDG considered that recommending MRI could have considerable economic impact on the NHS, especially during the current financial climate. Therefore, this economic analysis should not be considered to be a full cost effectiveness analysis, but exploratory to examine the potential impact of recommending MRI. This analysis utilises methods and data that might not usually be done in a full high quality review.

The results of this analysis indicated that MRI is a more effective and cost saving intervention. This appears to be a robust conclusion; however, with the caveats that have been iterated, this conclusion is highly uncertain but generally supports the use of MRI for diagnosing osetomyelitis.

References

1. Curtis L (2009) Unit Costs of Health and social care. Kent: Personal Social Services Research Unit

2. Department of Health, (2010) National Schedule of Reference Costs 2008-09 for NHS Trusts and PCTs Combined. available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591

3. Eckman MH, Greenfield S, Mackey WC et al. (1995) Foot infections in diabetic patients. Decision and cost-effectiveness analyses. JAMA 273: 712-20.

4. Game FL, Jeffcoate WJ (2008) Primarily non-surgical management of osteolyelitis of the foot in diabetes. Diabetologia 51: 962-967

5. Ghatnekar O, Persson U, Willis M et al. (2000) The cost-effectiveness in the UK of treating diabetic lower extremity ulcers with becaplermin gel. Journal of Medical Economics 3: 87-95.

6. Guo S, Counte MA, Gillespie KN et al. (2003) Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. International Journal of Technology Assessment in Health Care 19: 731-7.

7. Jeffcoate WJ, Ince P, Chipchase SY et al. (2006) Assessing the outcomes of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care 29(8): 17841787

8. Ortegon MM, Redekop WK, Niessen LW (2004) Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. Diabetes Care 27: 901-7.

9. Ragnarson TG, Apelqvist J (2001) Prevention of diabetes-related foot ulcers and amputations: a cost-utility analysis based on Markov model simulations. Diabetologia 44: 2077-87.

10. Redekop WK, Stolk EA, Kok E et al. (2004) Diabetic foot ulcers and amputations: Estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes and Metabolism 30: 549-56.

11. Sullivan S, Lew D, Devine E et al. (2002) Health state preference assessment in diabetic peripheral neuropathy. Pharmaoeconomics 2002;20:1079–89.

12. Tennvall GR, Apelqvist J (2004) Health-economic consequences of diabetic foot lesions. Clinical Infectious Diseases 39: S132-S139.

13. Valabhji J, Olver N, Samarasinghe D et al. (2009) Conservative management of diabetic forefoot ulceration complicated by underlying osteomyelitis: the benefits of magnetic resonance imaging. Diabetic Medicine 26: 1127-1134

Appendix K Evidence tables

Review question 1: What are the key components and organisations of hospital care to ensure optimal management of people with diabetic foot problems?

<table>
<tr><th colspan="6">Title: Critical Pathway Approach to Diabetic Pedal Infections in a Multidisciplinary Setting.</th></tr>
<tr><td>Study type</td><td>No. of people</td><td>Prevalence / incidence</td><td>Patient characteristics</td><td>Type of test</td><td>Reference standard</td><td>Results</td></tr>
<tr>
<td>ID:
2506

Author:
Crane et. al (1999)

Study type:
Cohort

Level of evidence:
(+)</td>
<td><u>Study group:</u>
CP (critical pathway)-60
NP(non pathway)-25
Conventional Group(1993)-30

<u>Control group:</u>
Non pathway people

<u>Study period:</u>
18 month (1995 to 1996)

<u>Setting:</u>
Roger Williams Medical Center</td>
<td>N/A</td>
<td><u>Inclusion /Exclusion(study group):</u>

All people admitted from January to June 1993, January to June 1995, and October 1995 to September 1996, with the applicable diagnostic codes [ICD-9(The data were searched using International Classification of Diseases, 9th revision diagnostic codes) codes 250.xx (Diabetes Mellitus) and its complications 707.1 (chronic ulcer, foot) and/or 785.4 (gangrene)] were included in this retrospective study. Those people in whom pedal disease was a secondary</td>
<td>To evaluate, utilizing clinical and financial outcomes, the critical pathway approach to diabetic foot infections in an inpatient setting.

In our program, the path is initiated in the emergency department utilizing committee-approved standing physician's orders and clinical progress records to facilitate transitions between departments.

The critical pathway, during the first 6 months of this investigation, was a voluntary podiatry-only logarithmic approach to emergency room people admitted with diabetic pedal infections. After the preliminary results were evaluated by the Critical Pathway Committee, the entire medical staff, regardless of specialty, were "highly encouraged" to admit</td>
<td>Conventional treatment</td>
<td>Table 1: Comparison of patient populations
<table>
<tr><th>Year</th><th>N</th><th>Male (%)</th><th>Avg Age</th><th>Avg LOS</th><th>Read missi ons</th><th>Major Amp utatio ns</th><th>Minor Amp utatio ns</th></tr>
<tr><td>1993</td><td>30</td><td>60%</td><td>72.6 (53-91)</td><td>14.4 (2-43)</td><td>20%</td><td>27%</td><td>30%</td></tr>
<tr><td>1995</td><td>38</td><td>60%</td><td>66.1 (32-95)</td><td>6.1 (1-16)</td><td>11%</td><td>18%</td><td>13%</td></tr>
<tr><td>1996</td><td>47</td><td>52%</td><td>65,1 (41 - 89)</td><td>5.1 (1-22)</td><td>15%</td><td>4%</td><td>38%</td></tr>
<tr><td>1995 CP</td><td>27</td><td>68%</td><td>63.0 (32-93)</td><td>5.4 (2-11)</td><td>7%</td><td>15%</td><td>11%</td></tr>
<tr><td>1995 NP</td><td>11</td><td>50%</td><td>73,8 (66-95)</td><td>7.8 (3-16)</td><td>18%</td><td>27%</td><td>18%</td></tr>
<tr><td>1996 CP</td><td>33</td><td>56%</td><td>64.2 (41 - 89)</td><td>3.6 (1-8)</td><td>15%</td><td>0%</td><td>45%</td></tr>
<tr><td>1996 NP</td><td>14</td><td>42%</td><td>67.4 (42-87)</td><td>8.7 (3-22)</td><td>15%</td><td>14%</td><td>21%</td></tr>
<tr><td>Total CP</td><td>60</td><td>61%</td><td>63.7 (32-</td><td>4.4 (2-</td><td>12%</td><td>7%</td><td>30%</td></tr>
</table>
</td>
</tr>
</table>

			diagnosis were excluded. <u>Characteristics of cases:</u> Refer to table 1. <u>Baseline Measurements:</u> Not applicable.	their people to the pathway from the emergency room. This, however, was not mandatory. The 1993 group was defined as the conventional methodology group and the 1995-1996 group was further stratified to either a critical pathway group or nonpathway group. Clinical outcomes were defined by amputation level, [i.e., toe, transmetatarsal (TMA), below knee (BKA), or above knee (AKA)] and readmission within 6 months for the same problem.		<table><tr><td></td><td></td><td></td><td>93}</td><td>11)</td><td></td><td></td><td></td></tr></table> CP-Critical pathway people; NP-non-pathway people; LOS-length of hospital stay. Data are presented as average (range) There was a significant decrease in the length of stay (LOS) and charges for people treated using the critical pathway in 1995 and 1996 compared to people treated in 1993 and to people treated in 1995 and 1996 in which the pathway was not used *(p* < .05). In addition, there was a significant decrease in the proportion of major amputations (BKA or AKA) in 1995 and 1996 as compared to baseline values (1993 = 23%, 1995-1996 = 7%, *p* = .02). Likewise, there was a significant decrease in the proportion of major amputations during 1995 and 1996 for people treated with the pathways model compared to people who were not treated with this approach (pathway = 7%, nonpathway — 29%, *p* < .001). There was not a significant difference in minor amputations (toe, ray, or transmetatarsal) or in people who did not require amputation in pathway versus nonpathway people in 1995-1996 versus 1993 (minor amputations: 1995-1996 = 38%, 1993 = 33%; no amputation: 1995-1996 = 54%, 1993 = 43%). There was also not a significant decrease in the proportion of people who required readmission in pathway versus nonpathway people (1993 = 20%, 1995-1996= 10%, *p=x* .17).
<u>Additional comments:</u>						

Reference:
Crane, M. and Werber, B. 1999, "Critical Pathway Approach to Diabetic Pedal Infections in a Multidisciplinary Setting." *Journal of Foot and Ankle Surgery,* vol. 38, no. 1, pp. 30-33.

Title: Benefits of a Multidisciplinary Approach in the Management of Recurrent Diabetic Foot Ulceration in Lithuania

<table>
<tr><th>Study type</th><th>No. of people</th><th>Prevalence / incidence</th><th>Patient characteristics</th><th>Type of test</th><th>Reference standard</th><th>Results</th></tr>
<tr>
<td>ID:
2624

Author:
Dargis et. al (1999)

Study type:
Cohort

Level of evidence:
(-)</td>
<td><u>Study group:</u>
Total-145 diabetic participants

<u>Control group:</u>
Patients presenting in the other cities formed the standard treatment group

<u>Study period:</u>
Not mentioned

<u>Setting:</u>
Not mentioned</td>
<td>N/A</td>
<td><u>Inclusion /Exclusion(study group):</u>

Diabetic patients with a history of previous ulceration (Wagner grades I and II) living in the Kaunas region were referred to the rehabilitation hospital.

<u>Characteristics of cases:</u>

<table>
<tr><th>Variable</th><th>Intervention group</th><th>Standard treatment group</th></tr>
<tr><td>Sex (F/M)</td><td>2 9 / 2 7</td><td>4 7 / 4 2</td></tr>
<tr><td>Age (years)</td><td>59.2 ± 13.4</td><td>58.5 ± 11.5</td></tr>
<tr><td>Diabetes duration (years)</td><td>14.0 ± 7.1</td><td>15.6 ± 7.8</td></tr>
<tr><td>NDS</td><td>8.1 ± 1.4</td><td>7.9 ± 1.7</td></tr>
<tr><td>VPT (V)</td><td>31.1 ± 12.1</td><td>33.9 ± 11.2</td></tr>
<tr><td>ABPI</td><td>1.14 ± 0.14</td><td>1.10 ± 0.17</td></tr>
<tr><td>Previous ulcers (n)</td><td>2.3 ± 0.9</td><td>2.1 ± 1.0</td></tr>
</table>

Data are means ± SD, %, or n.
NDS-Neuropathy disability score
VPT- Vibratory perception threshold
ABPI- Ankle brachial pressure index.

<u>Baseline Measurements:</u>
Not applicable.</td>
<td>To assess the ability of a multidisciplinary approach to diabetic foot care to reduce the incidence of recurrent ulceration and amputations compared with standard care.

The clinic is staffed by a multidisciplinary team consisting of a diabetologist, a rehabilitation physician, a podiatrist, orthopaedic surgeons, and shoemakers.

The intervention group received podiatry, education, and specialty footwear at the Kaunas centre for 2 years.

The standard treatment subjects were all screened at the baseline visit by visiting staff from Kaunas who also provided identical standard foot care education and advice at this first visit.</td>
<td>N/A</td>
<td>The intervention group had significantly fewer recurre n t ulcers during the 2-year period than the standard treatment group (30.4 vs. 58.4%, respectively;

Odds ratio [95% CI] 0.31 [0.14–0.67], x2 10.86, P , 0.001) and

Fewer amputations (7% [3 minor and 1 major] versus 13.7% [8 minor and 4 major], respectively).

The recurrent ulceration rate was thus almost halved.</td>
</tr>
<tr><td colspan="7"><u>Additional comments:</u>
Did not consider randomizing patients to intensive or standard treatment groups to be ethical because previous single-centre studies have demonstrated the effectiveness of intensive treatment and education programs</td></tr>
</table>

Reference:
Dargis, V, Pantelejeva, O, Jonushaite, A, Vileikyte, L, Boulton, AJ Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. *Diabetes Care* 1999; 22: 1428-31.

Title: Decreasing Incidence of Major Amputation in Diabetic Patients: a Consequence of a Multidisciplinary Foot Care Team Approach?						
Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 6065 Author: Larsson et. al (1995) Study type: Cohort Level of evidence: (-)	<u>Study group:</u> Total-294 diabetic participants <u>Control group:</u> Participants treated prior to 1983. <u>Study period:</u> Not mentioned <u>Setting:</u> Health care districts of Lund and Orup in southern Sweden	N/A	<u>Inclusion /Exclusion(study group):</u> Amputations in patients not residing in the Lund/ Orup health care district *(n* = 349), and amputations performed for reasons other than vascular disease and/or diabetes *(n* = 89), were excluded. <u>Characteristics of cases:</u> Male- 144 Female- 150 Median age- 77 (range- 32 to 94 years) <u>Baseline Measurements:</u> Not applicable.	To evaluate the changes in diabetes-related lower extremity amputations following the implementation of a multidisciplinary programme for prevention and treatment of diabetic foot ulcers. The instrument for implementing this programme is a team consisting of a diabetologist and an orthopaedic surgeon assisted by a diabetes nurse, a podiatrist, and an orthotist and working in close cooperation with the Department of vascular surgery and the Department of infectious diseases. A programme for patient and staff education was also started. The patients were followed by the same team both as in- and out-patients and throughout the process a high degree of continuity and accessibility was maintained.	N/A	The total annual incidence of primary amputations decreased by 49 %. The incidence of major amputations decreased by 78% from 16.1 to 3.6/100 000 inhabitants ($p<0.001$). The decrease was most marked in the oldest age group. The proportion of amputations at all levels performed in patients over 80 years of age decreased from 43% to 26% *($p<0.05$)* between the first and last 3-year period. In patients younger than 60 years, few amputations were performed and no change in incidence could be demonstrated in this age group. Calculated per 1000 diabetic subjects, with a 2.4% prevalence of diabetes, the total incidence of amputation decreased from 7.9 to 4.1 and the incidence of major amputations from 6.7 to 1.5.
<u>Additional comments:</u> Did not consider randomizing patients to intensive or standard treatment groups to be ethical because previous single-centre studies have demonstrated the effectiveness of intensive treatment and education programs						

Reference:

Larsson, J, Apelqvist, J, Agardh, CD, Stenstrom, A Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? *Diabetic Medicine* 1995; 12: 770-776.

Title: Diabetes- and Nondiabetes-Related Lower Extremity Amputation Incidence Before and After the Introduction of Better Organized Diabetes Foot Care.						
Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 2008 Author: Canavan et. al (2008) Study type: Cohort Level of evidence: (-)	<u>Study group:</u> Total-454 LEA (lower extremity amputation) 223-diabetic related <u>Control group:</u> Non-DRLEA <u>Study period:</u> July 1995 to June 2000 <u>Setting:</u> South Tees, UK	N/A	<u>Inclusion /Exclusion(study group):</u> Not mentioned <u>Characteristics of cases:</u> Not mentioned <u>Baseline Measurements:</u> Not applicable.	The aim was to present data on trends in DRLEAs (Diabetic Related Lower Extremity Amputation) and non-DRLEAs in the South Tees area over a continuous 5-year period. The Global Lower Extremity Amputation Study (GLEAS) group through collaboration developed a standard protocol for LEA data collection and can be used to arrive at population-based diabetes-related (DR) LEA and non-DRLEA rates for their own particular areas. Four independent data sources (operating theatre records, limb fitting centre records, hospital discharge data, and community diabetes register) were used to identify patients. LEAs were categorized as first and repeat, major and minor, diabetes related, and nondiabetes related. The denominator populations for non-DRLEAs were 1996 midyear estimates based on 1991 U.K. census data less the population with diabetes.	N/A	**<u>All LEAs (i.e., major, minor, first, and repeat)</u>** LEA rates went from 564.3 of 100,000 persons with diabetes in the first year to 176.0 of 100,000 persons with diabetes in the fifth year. For non-DRLEAs there was an increase from 12.3 to 22.8 of 100,000 persons without diabetes. The relative risk of a person with diabetes undergoing any LEA went from being 46 times that of a person without diabetes at the start of the study to being only 7.7 times that of a person without diabetes at the end of the 5 years.
<u>Additional comments:</u>						

Reference:
Canavan, RJ, Unwin, NC, Kelly, WF, Connolly, VM Diabetes- and nondiabetes-related lower extremity amputation incidence before and after the introduction of better organized diabetes foot care: continuous longitudinal monitoring using a standard method. *Diabetes Care* 2008; 31: 459-63.

Title: Reducing Amputation Rates in Patients With Diabetes at a Military Medical Center. The Limb Preservation Service model.						
Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 2932 Author: Driver et. al (2005) Study type: Cohort Level of evidence: (-)	Study group: Total-128 diabetic Control group: Not mentioned Study period: 1999 to 2003 Setting: Madigan Army Medical Centre (MAMC)	N/A	Inclusion /Exclusion(study group): Not mentioned Characteristics of cases: Not mentioned Baseline Measurements: Not applicable.	The aim was to evaluate the Limb Preservation Service (LPS), a multidisciplinary, state-of-the-art, foot care clinic for patients with diabetes. And the effect on LEAs. High-risk diabetic foot care has become a focused specialty providing standard and advanced care modalities in one setting. This includes prevention and education, wound care, infection management, surgical and hospital management, research and grant development, community and regional education, and the creation of orthotics, prosthetics, and shoes.	N/A	During this period, the number of diagnosed diabetic patients at MAMC increased 48% from 3,340 in 1999 to 4,940 in 2003. Concurrent with the increase in patients with diabetes at MAMC was a decrease in the number of inpatient LEAs from 33 in 1999 to just 9 in 2003. The incidence rate of LEAs in patients with diabetes at MAMC dropped from 9.9/ 1,000 to 1.8/1,000 over 5 years.
Additional comments:						

Reference:
Driver, VR, Madsen, J, Goodman, RA Reducing amputation rates in patients with diabetes at a military medical center: the limb preservation service model. *Diabetes Care* 2005; **28:** 248-53.

Review question 2: What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?

Title: Osteomyelitis of the Foot in Diabetic People: Evaluation with Plain Film, 99mTc-MDP Bone Scintigraphy, and MR Imaging.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 12070 Author: Yuh et. al (1989) Study type: Cross-sectional Level of evidence: (-)	Study group: Total-24 diabetic 30 MR studies Control group: 29 plain radiographs 20 technitium-99m methylene diphosphonate (^{99m}Tc-MDP) Study period: Not mentioned Setting: Not mentioned	MRI = 25/29 Bone = 18/21 Plain = 24/28	Inclusion /Exclusion(study group): Consecutively enrolled diabetic who had clinical suspicion of Osteomyelitis and/or non healing foot ulcers. . Characteristics of cases: Age range- 32-74 years (mean- 58.2 years) Baseline Measurements: Not applicable.	To determine the value of MR (magnetic resonance) for detecting osteomyelitis of the foot in diabetic All bone scans and plain films were obtained within 48 hr of the MR examinations.. 29 bone specimens from 14 were obtained by either biopsy (6) or amputation (8). 15 bones (10) had resolution of foot ulcers or cellulitis with only local wound care and/or a short course of oral antibiotics. These were considered clinically not to have Osteomyelitis (nonosteomyelitis) because there was no pathologic proof of bone infection.	Pathologic tests.	**Table 1: Results of examinations obtained with each technique in positive, negative, or nonosteomyelitis cases:** Category (No. of bones) / MR / Bone scan / Plain film +ve / -ve / +ve / -ve / +ve / -ve Positive Osteomyelitis (25): 25/25 / 0/25 / 17/18 / 1/18 / 18/24 / 6/24 Negative Osteomyelitis (4): 0/4 / 4/4 / 3/3 / 0/3 / 1/4 / 3/4 Nonosteomyelitis (15): 2/15 / 13/15 / 6/8 / 2/8 / 5/11 / 6/11 MR had the best performance, followed by plain films, and then bone scintiscans. Both MR and bone scans had a very low false-negative rate in the diagnosis of osteomyelitis. The false-positive rate was highest for bone scans, followed by plain films. When cases of nonosteomyelitis were included , there were increased false-positives in all three techniques, presumably caused by acute or recent trauma, soft-tissue infection, and/or vascular insufficiency./or plain radio

Additional comments:

Reference:
Yuh, W.T.C., Corson, J.D., Baraniewsky, H.M., Rezai, K., Shamma, A.R., Kathol, M.H., Sato, Y., El-Khoury, G.Y., Hawes, D.R., Platz, C.E., Cooper, R.R. and Corry, R.J. 1989, "Osteomyelitis of the Foot in Diabetic People: Evaluation with Plain Film, 99mTc-MDP Bone Scintigraphy, and MR Imaging." AJR, vol. 152, pp. 795-800.

Title: Osteomyelitis of the Foot in Diabetic People: Evaluation with Plain Film, 99mTc-MDP Bone Scintigraphy, and MR Imaging.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 12070 Author: Newman et. al (1992) Study type: Cross-sectional Level of evidence: (-)	Study group: Total-12 diabetic persons 16 diabetic foot ulcers Control group: MRI patients Study period: Sept. 1989 to Jun 1990 Setting: Mount Sinai Medical Centre.	7/16	Inclusion /Exclusion(study group): Exclusion criteria included myocardial infarction in the previous 6 months, severe peripheral vascular disease (ankle-brachial index <50%), ongoing antibiotic treatment for >7 previous days, or patient declining to participate. Characteristics of cases: Duration- 52 weeks (range = 1-364) Size- 0.5cm^2 (range = 0.25 to 0.35) Baseline Measurements: Not applicable.	To compare the accuracies of MRI and leukocyte scanning in diagnosing clinically unsuspected osteomyelitis in diabetic foot ulcers. Before bone biopsy and culture, all patients underwent leukocyte imaging and MRIs. The diagnosis of osteomyelitis was based on a positive bone culture and/or pathological criteria for osteomyelitis. Leukocyte imaging was classified as positive for osteomyelitis when focally increased activity was present on both dorsal and plantar images at 24h. MRI was considered positive for osteomyelitis if signal intensity decreased on T1WI and increased on T2WI in the bone in the area	Bone specimens for histology and culture	**Table 1: Results of WBC scans versus MRI in diagnosis of Osteomyelitis in diabetic foot ulcers.** | | | | | Predictive value | | | | Sensitivity | Specificity | Accuracy | Positive | Negative | | WBC scan (5) | 100 (7/7) | 67 (6/9) | 81 (13/16) | 70 (7/10) | 100 (6/6) | | MRI (%) | 29 (2/7)* | 78 (7/9) | 56 (9/16) | 50 (2/4) | 58 (7/12) | *p- 0.03 The leukocyte scan was 100% sensitive for diagnosing osteomyelitis in these diabetic foot ulcers, in contrast to a sensitivity of only 29% for MRI (p- 0.03) The specificities of the tests were similar: 67% for leukocyte scan, 78% for MRI. No significant relation was noted between a positive MRI or leukocyte scan and ulcer inflammation, ulcer size, or bone histology.

				of the foot ulcer. Pathological diagnosis required the presence of all 3 criteria including: osteonecrosis (the absence of osteocytes in their lacunae in the presence of nuclear staining for other cells in the section), marrow fibrosis, and inflammatory cells.		
Additional comments:						

Reference:
Newman, LG, Waller, J, Palestro, CJ, Hermann, G, Klein, MJ, Schwartz, M, Harrington, E, Harrington, M, Roman, SH, Stagnaro-Green, A Leukocyte scanning with 111In is superior to magnetic resonance imaging in diagnosis of clinically unsuspected osteomyelitis in diabetic foot ulcers. *Diabetes Care* 1992; **15:** 1527-30.

Title: A New Wound-Based Severity Score for Diabetic Foot Ulcers.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 1308 Author: Beckert et. al (2006) Study type: Cohort Level of evidence: (-)	Study group: Total-1000 diabetic Control group: NA Study period: Dec. 1997 to April 2004 Setting: Not mentioned	N/A	Inclusion /Exclusion(study group): All participants suffered from diabetes according to the criteria of the world health organisation. Characteristics of cases: Male: 675 (67.5); Female: 325 (32.5) Age (years) 69 (26–95) Number of visits 5 (2–60) Multiple ulcers 404 (40.4) Time of follow-up (days) 68 (3–365) Hospitalization 621 (62.1) **Wounds** Wound history (days) 31 (1–18,708) Wound area (cm2) 0.9 (0.1–123) Soft tissue infection at initial visit 354 (35.4) Probing to bone	To establish a new wound-based clinical scoring system (DUSS)for diabetic foot ulcers All ulcers were located below the ankle and assessed by a physician at the initial visit. Wounds were graded by measuring wound depth with a sterile blunt probe, and the deepest tissue involved was documented (dermis as grade 1, subcutaneous as grade 2, fascia as grade 3, muscle as grade 4, and bone as grade 5). **Diabetic ulcer severity score (DUSS)** Ulcers were classified by the abovementioned variables. Absent pedal pulses were scored as 1 while present pedal pulses were scored as 0. Bone involvement was defined as probing to bone (yes_1 or no_0).	Not mentioned	**Wound grading** Grade 1 29 (2.9) Grade 2 635 (63.5) Grade 3 20 (2.0) Grade 4 47 (4.7) Grade 5 269 (26.9) Initially, ulcers were graded with 29 (2.9%) ulcers classified as grade 1 635 (63.5%) as grade 2 20 (2.0%) as grade 3 47 (4.7%) as grade 4, and 269 (26.9%) as grade 5 There was a significantly lower probability of healing with respect to nonpalpable pulses (*P* =0.0009), probing to bone (*P* =0.0019), multiple ulcerations (*P* =0.00001), and foot versus toe ulcerations (*P*=0.00001). Multivariate analysis demonstrated these parameters as independent variables with significant impact on healing. **Table 1-Multivariate analysis of parameters reducing chances for healing** 95% CI significance / Odds ratio / lower / Upper Multiple ulcers 0.0001 0.648 0.540 0.778 Probing to bone 0.025 0.777 0.623 0.968 Location (foot ulcers) 0.0001 0.483 0.402 0.580 Non palpable 0.0001 0.723 0.603 0.868

			269 (26.9) Ulcer location Toe: 356 (35.6); foot: 644 (64.4) Palpable peripheral pulses 656 (65.6) **Surgery** Sharp debridement 1,000 (100) Bone resection 136 (13.6) Minor amputation 99 (9.9) Major amputation 26 (2.6) <u>Baseline Measurements:</u> Not mentioned	The site of ulceration was defined as toe (scored as 0) or foot (scored as 1) ulcer. People with multiple ulcerations were graded as 1 compared with those with single ulcers (scored as 0). Diabetic ulcer severity score (DUSS) was calculated by adding these separate gradings to a theoretical maximum of 4.		pulses However, local soft tissue infection, when diagnosed at the initial visit, did not influence probability of healing (*P* _ 0.5324). The new DUSS was calculated from the above-mentioned parameters, which have been shown as independent variables for healing. Dividing people into subgroups with the same DUSS, we found significantly different probabilities for healing. There was a 93% probability of healing for uncomplicated ulcers (score 0), decreasing to 57% for ulcers with a severity score of 4 (*P*= 0.0001). In addition, influence of the DUSS on healing was analyzed using a Cox regression model, confirming a high correlation between the new severity score and time to healing, resulting in a risk ratio of 0.648 (95% CI 0.589–0.714; *P*= 0.001). An increase in the DUSS by one score point reduced the chance for healing by 35%.
<u>Additional comments:</u>						

Reference:
Beckert, S., Konigsrainer, A., Coerper, S., Wicke, C. and Witte, M 2006, “A New Wound-Based Severity Score for Diabetic Foot Ulcers.” *Clinical effectiveness in Nursing*, vol. 29, no. 5, pp. 988-992.

Title: Diabetes and Peripheral Arterial Occlusive Disease: Prospective Comparison of Contrast-Enhanced Three-Dimensional MR Angiography with Conventional Digital Subtraction Angiography.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 5862 Author: Kreitner et. al (2006) Study type: Cross-sectional Level of evidence: (-)	Study group: Total-24 diabetic 24 underwent MR (magnetic resonance) angiography Control group: 24 underwent DSA (digital subtraction angiography) Study period: 6 months Setting: Not mentioned	Not mentioned	Inclusion /Exclusion(study group): According to the suggested standards of the Society of Cardiovascular and Interventional Radiology, all participants suffered from grade III chronic limb ischemia with either non healing ulceration or focal gangrene with diffuse pedal ischemia. Characteristics of cases: Male- 17 Female- 7 Age range- 53-84 years (mean- 69 years) Baseline Measurements	Evaluating arteries of the distal calf and foot Seven vascular segments were evaluated in each extremity: the distal anterior tibial, distal posterior tibial, distal peroneal, dorsal pedal artery, lateral plantar, medial plantar arteries, and the pedal arch. Segments were classified as patent or occluded. Patent segments were further classified as having 50% or less stenosis or greater than 50% stenosis. In cases with multiple sites of disease, only the site with the most severe disease was scored. After this review, each DSA study was paired	DSA (Digital subtraction angiography)	**Table**: **Visualization of Arterial Segments with Digital Subtraction Angiography (DSA) and Three-Dimensional Contrast-Enhanced MR Angiography (MRA)** Artery / No. of arterial segments seen / 95% CI / P value MRA and DSA / neither / MRA only / DSA only / total Anterior tibial: 14 / 9 / 1 / 0 / 24 / 0.75-1.08 / 0.317 Posterior tibial: 7 / 16 / 1 / 0 / 24 / 0.72-1.09 / 0.317 Peroneal: 12 / 10 / 2 / 0 / 24 / 0.62-1.10 / 0.157 Dorsal pedal: 13 / 6 / 5 / 0 / 24 / 0.26-0.87 / 0.025 Medial plantar: 7 / 14 / 3 / 0 / 24 / 0.48-1.00 / 0.083 Lateral plantar: 12 / 7 / 5 / 0 / 24 / 0.29-0.88 / 0.025 Pedal arch: 9 / 2 / 13 / 0 / 24 / -0.04-0.25 / 0.001 Overall: 74 / 64 / 30 / 0 / 168 / 0.55-0.76 / 0.001 Selective DSA technique: 34 / 32 / 4 / 0 / 70 / 0.78-0.99 / 0.046 Nonselective DSA technique: 40 / 32 / 26 / 0 / 98 / 0.36-0.64 / 0.001 Of a possible 168 segments, 74 were seen to be patent on DSA images, and 104 were seen to be patent on MR angiograms. Thirty vessel segments were seen exclusively on MR angiograms, and in none of the cases were any patent vessel segments revealed by DSA that were not shown by MR angiography. Statistical analysis of these results confirmed that MR angiograms were superior to DSA images for the visualization of patent vessel segments

			Not mentioned	with the appropriate MR angiographic study, and an assessment was performed of the overall image quality of the angiographic images. Each reviewer independently assigned a relative rank to each pair of examinations. The possible relative rankings ranged from 2 to –2 2- MR angiography was substantially better than DSA 1-MR angiography was moderately better than DSA 0-MR angiography and DSA were of equivalent quality -1-DSA was moderately better than MR angiography -2-DSA was substantially better than MR angiography).		($p < 0.001$). The superiority of MR angiography was statistically significant predominantly for inframalleolar vessels (dorsal pedal artery, lateral plantar arteries, and pedal arch), and it was independent from the DSA technique used. However, when comparing a selective DSA technique with MR angiography, the resulting p value ($p = 0.046$) was higher than that from the comparison of a nonselective technique with MR angiography ($p < 0.001$). **Table 2: Scoring by Two Observers of Patent Vessel Segments As Shown by MR Angiography and Digital Subtraction Angiography (DSA)** DSA / MR angiography: ≤50% stenosis / ≥50% st nosis / Total ≤50% stenos s: 33 / 3 / 3 ≥50% s enosis: 11 / 7 / 3 otal: 44 / 30 / 74 Of 74 vessel segments, 60 (81%) had an identical scoring. In 11 cases, the degree of stenosis was rated as more severe on DSA images, and in three cases, stenosis was scored as more severe on MR angiograms. In a patient-by-patient analysis, MR angiography revealed a patent vessel that was not seen on DSA and that would be suitable for distal bypass grafting in nine (38%) of 24 people. These findings led to a change of treatment plans for seven people **Table 3: Frequency of Changed Treatment Plans and Applied Digital Subtraction Angiography (DSA) Technique** Treatment / DSA technique: Selective / Nonselective / Total Change: 2 / 5 / 7 No change: 8 / 9 / 17 Total: 10 / 14 / 24 p value-0.653 Changes of treatment plans were made in two (20%) of 10 people with a selective DSA technique, and in five (36%) of 14 people with a nonselective DSA technique. This difference was not statistically significant ($p = 0.653$, Fisher's exact test).
Additional comments:						

Reference:

Kreitner, K.F., Kalden, P., Neufang, A., Duber, C., Krummenauer, F., Kustner, E., Laub, G., and Thelen, M. 2000, "Diabetes and Peripheral Arterial Occlusive Disease: Prospective Comparison of Contrast-Enhanced Three-Dimensional MR Angiography with Conventional Digital Subtraction Angiography." *AJR*, vol. 174, pp. 171-179.

Title: Assessment of Critical Limb Ischemia in People with Diabetes: Comparison of MR Angiography and Digital Subtraction Angiography.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 6037 Author: Lapeyre et. al (2005) Study type: Cross-sectional Level of evidence: (+)	Study group: Total-31 diabetic Control group: NA Study period: Feb. 2002 to Mar 2003 Setting: Department of vascular surgery.	Not reported	Inclusion /Exclusion(study group): All participants had diabetes mellitus. The inclusion criteria for this study were nonhealing ulceration or focal gangrene consistent with peripheral artery disease on physical examination by a vascular surgeon Additional exclusion criteria were prior below-knee amputation on the same side (*n* = 6), contraindication to MR (magnetic resonance) angiography (pacemaker, *n* = 5; claustrophobia, *n* = 2; ferromagnetic material, *n* = 3), previous arterial stenting that could render MR angiography inconclusive (*n* = 5), the nonavailability of MRI within 10 days after the initial clinical examination (*n* = 16), allergy	Assessment of critical limb ischemia MR angiography was performed first so that endovascular treatment could be performed during DSA (Digital subtraction angiography). DSA was always performed within 72 hr after MR angiography. Ten vascular segments were evaluated, comprising the upper two thirds of the superficial femoral artery, the lower third of the superficial femoral artery and the above-knee popliteal artery, the below-knee popliteal artery, the upper third of the anterior tibial artery, the lower two thirds of the anterior tibial artery, the tibioperoneal trunk, the tibial posterior artery, the peroneal artery,	DSA (Digital subtraction angiography) .	**Table 1: Sensitivity and Specificity of Hybrid MR Angiography for Stenoses Greater Than 50% (Group B) and Occlusion (Group C) for Both Reviewers** Group: Reviewer 1 — Sensitivity (%) / Specificity (%); Reviewer 2 — Sensitivity (%) / Specificity (%) Group B: 95 (86-98) / 98 (95-99) / 96 (88-99) / 98 (95-99) Group C: 95 (88-97) / 98 (96-99) / 90 (83-94) / 99 (97-100) Compared with DSA, the sensitivity of hybrid MR angiography for depicting arterial stenosis greater than 50% (group B) ranged from 95% to 96%, and specificity was close to 98%. For arterial occlusion (group C), the sensitivity of hybrid MR angiography ranged from 90% to 95%, and specificity ranged from 98% to 99%. **Table 2: Values of Cohen's Kappa Coefficient for Intertechnique Agreement for Each Observer and for Different Locations** κ Location: Reviewer 1 / Reviewer 2 Overall: 0. 3 (0.89-0.96) / 0.91 (0 87-0. 5) Suprapo iteal and poplit al vessels: 0.9 (0 90-1.00) / 0.98 (0.94-1.00) Infrapopliteal vessels: 0.91 (0.86-0.96) / 0.88 (0.83-0.94) For both reviewers and for all locations, kappa values for intertechnique agreement were greater than 0.88, corresponding to near perfect agreement . Interobserver agreement was high for all locations and for both MR angiography and DSA. Kappa values for interobserver agreement on DSA were 0.97 for infrapopliteal segments, 1 for suprapopliteal vessels, and 0.98 overall. For MR angiography, kappa values for interobserver agreement were, respectively, 0.98, 0.98, and 0.98.

			to iodinated contrast agents (*n* = 1), and refusal of DSA (*n* = 1). <u>Characteristics of cases:</u> Male- 22 Female- 9 Age range- 35-83 years (mean- 65 years, median- 65 years) 16 -trophic changes were non healing ulcers 15 - focal gangrene 3 undergoing dialysis <u>Baseline Measurements:</u> Not mentioned.	the dorsal arteries of the foot, and the plantar arteries of the foot (the lateral and medial plantar arteries were interpreted together). Segments were graded normal or stenosed less than 50% (group A), stenosed more than 50% (group B), or occluded (group C).		No differences in interpretation were found between MR angiography and DSA in 74% (23/31) of people for reviewer 2, and in 71% (22/31) of people for reviewer 1. Regarding the popliteal and suprapopliteal vessels, a perfect correlation between MR angiography and DSA was observed for 97% (30/31) of people by the two reviewers.
<u>Additional comments:</u>						

Reference:
Lapeyre, M., Kobeiter, H., Desgranges, P., Rahmouni, A., Becquemin, J.P., and Luciani, A.2005, "Assessment of Critical Limb Ischemia in People with Diabetes: Comparison of MR Angiography and Digital Subtraction Angiography." *AJR*, vol. 185, pp. 1641-1650.

Title: Diagnosis of Osteomyelitis of the Foot in Diabetic People: Value of 1111n-Leukocyte Scintigraphy.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 6043 Author: Larcos et. al (1991) Study type: Cross-sectional Level of evidence: (+)	Study group: Total-76 diabetic 51 selected (under went 111ln-WBC scans) 25 excluded because treatment was subsequently undertaken at other institutions, with no correspondence regarding outcome (*n* = 20), or these had multisystem disorders with inadequate documentation for the foot (*n* = 5). Control group: 49 ı"Tc-MDP (methylene diphosphonate) scans, and 49 plain radiographs Study period: April 1985 to Mar 1990 Setting: Not mentioned	111ln-WBC 14/51 ^{99m}Tc-MDP Scans 14/49 Plain Radiographs 14/49	Inclusion /Exclusion(study group): Not mentioned Characteristics of cases: Male- 31 Female- 20 Age range- 30-88 years (mean- 62 years) Mean duration of diabetes- 14 years 35 had ulcers adjacent to suspected areas of osteomyelitis 16 people-trophic changes were non healing ulcers 15 people- focal gangrene 3 people undergoing dialysis Baseline Measurements: Not mentioned.	The purpose of this study was to determine the usefulness of 1111n-WBC scintigraphy in a large heterogeneous group of diabetic people referred for investigation of possible pedal osteomyelitis. The presence or absence of osteomyelitis was established by surgery in 28 people and by a clinical follow-up of at least 2 months (range, 2-50 months; mean, 26 months) in the rest. The 111ln-WBC scan was considered abnormal if focal accumulation of radionuclide activity in bone exceeded background radioactivity. The three-phase bone scan was considered indicative of osteomyelitis if there was focal arterial hyperaemia associated with increased uptake of radionuclide by	Surgery (bone culture or biopsy) and Clinical Follow up	**Table 1: Sensitivity and Specificity of 111ln-WBC and ^{99m}Tc-MDP Scans and Radiographs in the Diagnosis of Pedal Osteomyelitis in Diabetic People** No. of people (%) Group/study / Sensitivity / Specificity All people **111ln-WBC** 11/14 (79) 29/37 (78) **^{99m}Tc-MDP Scans** 13/14 (93) 15/35 (43) **Radiographs** 6/14 (43) 29/35 (83) Neuroarthropathy **111ln-WBC** 1/1 (100) 7/10 (70) **^{99m}Tc-MDP Scans** 1/1 (100) 2/10 (20) **Radiographs** 0/1 (0) 8/10 (80) Antibiotics **111ln-WBC** 4/5 (80) 11/15 (73) Soft-tissue ulcers **111ln-WBC** 11/13 (85) 17/22 (77) Osteomyelitis of the foot was diagnosed in 14 people. Eleven of these 14 cases were identified correctly by using 1111n-WBC scanning. Of the 37 people without osteomyelitis, there were 29 true-negative and eight false-positive ıln-WBC studies The ^{99m}Tc-MDP scan was most sensitive but least specific for osteomyelitis, whereas radiographs were specific but insensitive. 11 people had neuropathic joint disease on radiographs.

				bone on delayed views. Osteomyelitis was diagnosed on the basis of radiographs when (1) bone destruction was present alone or in combination with soft-tissue swelling or osteopenia or peniosteal reaction, or (2) localized osteopenia or periosteal reaction occurred in the absence of fracture or neuropathic joint disease. The presence of significant neuroarthropathy also was recorded, as this may influence the sensitivity and specificity of 1111n-WBC scans.		The 111ln-WBC scan was both sensitive and relatively specific for osteomyelitis in this group. However, the ^{99m}Tc-MDP scans and radiographs lacked specificity and sensitivity, respectively. 111ln-WBC scintigraphy was also sensitive and specific in people with soft-tissue ulcers and in those people receiving antibiotics during investigation
Additional comments:						

Reference:
Larcos, G., Brown, M.L., and Sutton, R.T. 1991, “Diagnosis of Osteomyelitis of the Foot in Diabetic People: Value of 1111n-Leukocyte Scintigraphy.” *AJR*, vol. 157, pp. 527-531.

<table>
<tr><th colspan="6">Title: An evaluation of three wound measurement techniques in diabetic foot wounds.</th></tr>
<tr><th>Study type</th><th>No. of people</th><th>Prevalence / incidence</th><th>Patient characteristics</th><th>Type of test</th><th>Reference standard</th><th>Results</th></tr>
<tr>
<td>ID: 9842

Author: Shaw et. al (1991)

Study type: Cohort

Level of evidence: (-)</td>
<td><u>Study group:</u>
16 with neuropathic and neuroischemic diabetic foot wounds

<u>Control group:</u>
Not applicable.

<u>Study period:</u>
Not mentioned.

<u>Setting:</u>
Diabetic foot clinic in the Royal Hospitals Trust, Belfast.</td>
<td>N/A</td>
<td><u>Inclusion /Exclusion(study group):</u>

Not mentioned

<u>Characteristics of cases:</u>

Not mentioned

<u>Baseline Measurements:</u>

Not mentioned</td>
<td>To evaluate and compare three wound measurement techniques:

The Visitrak system (Smith and Nephew Healthcare, Hull, U.K.)

A digital photography and image processing system (Analyze, version 6.0; AnalyzeDirect, Lenexa, KS) and

An elliptical measurement method using the standard formula (_ab) for the calculation of the area of an ellipse.

Validity and repeatability within each method were investigated and determined by</td>
<td>Wound measurement in diabetic foot wounds.</td>
<td>Table 1—Summary of results reported on the validity and repeatability of three wound measurement methods in diabetic foot wounds
<table>
<tr><th>Method</th><th>Image of a known size (mm^2)</th><th>Mean area measured by each method (mm^2)</th><th>Percent difference</th><th>P</th><th>Calculable CVs for wound area measured by each method</th></tr>
<tr><td>Visitrak</td><td>25</td><td>19.5</td><td>-22</td><td><0.001</td><td>Mean CV 7%</td></tr>
<tr><td></td><td>100</td><td>98.5</td><td>-1.5</td><td>0.27</td><td></td></tr>
<tr><td></td><td>1,600</td><td>1,580.5</td><td>-1.2</td><td>0.06</td><td></td></tr>
<tr><td>Image processing</td><td>20</td><td>20.02</td><td>0.1</td><td>0.64</td><td>Mean CV 4.7%</td></tr>
<tr><td></td><td>20</td><td>20.01</td><td>0.0</td><td>0.73</td><td></td></tr>
<tr><td></td><td>37</td><td>34.3</td><td>-7.3</td><td><0.001</td><td></td></tr>
<tr><td>Elliptical</td><td>883</td><td>883.0</td><td>0.0</td><td>1.0</td><td>Mean CV 8.5%</td></tr>
<tr><td></td><td>5,361</td><td>5,338.2</td><td>-0.4</td><td>0.26</td><td></td></tr>
</table>
Validity varied across the three methods but was deemed to be acceptable overall.</td>
</tr>
</table>

				measuring images of a known size 20 times each. Repeatability and comparability were considered between each method of measurement on the wounds. Each wound was traced and measured a total of nine times; wound surface area was calculated in squared millimetres and means and SDs calculated.		The Visitrak method inaccurately measured images <25 mm^2 (*P*= 0.001), and the elliptical method tended to underestimate size in small wounds (*P* =0.001). The mean Coefficient of variation(CV) (*n*_46) for all wounds was calculated as 7.0 (Visitrak), 4.7 (image processing), and 8.5 (elliptical), indicating that repeatability was acceptable overall. Freidman's test indicated that no one measurement method was consistently more repeatable than another (*P*= 0.15). Analysis of comparability indicated that there were some differences between the three methods. Graphical analysis reported three outlying values (both high and low) using the image processing method; thus, wound measurement could be inaccurate either way compared with the other two methods. Differences were shown between the Visitrak and elliptical methods when analyzed alone (*t* test = 2.72, *P* = 0.017).
Additional comments:						

Reference:
Shaw, J, Hughes, CM, Lagan, KM, Bell, PM, Stevenson, MR An evaluation of three wound measurement techniques in diabetic foot wounds. *Diabetes Care* 2007; **30:** 2641-42.

Title: Unsuspected Osteomyelitis in Diabetic Foot Ulcers: Diagnosis and Monitoring by Leukocyte Scanning With Indium In 111 Oxyquinoline

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 7804 Author: Newman et. al (1991) Study type: Cross-sectional Level of evidence: (++)	Study group: Total-54 consecutive diabetic Selected 35 with 41 foot ulcers Control group: Not mentioned Study period: Dec. 1988 to April 1990. Setting: Both inpeople and outpeople at Mount Sinai Medical Centre, New York.	Bone biopsy and culture 28/41	Inclusion /Exclusion(study group): Exclusion criteria included ongoing antibiotic treatment for more than the 7 previous days (n = 4), myocardial infarction in the past 6 months (n = 0), bone biopsy that did not contain bone (n = 3), or peripheral vascular disease judged to be too severe to ensure optimal healing after bone biopsy (nonpalpable pulses and ankle-brachial index <50%, = 6). Also excluded were three people who declined participation and three people whose leukocyte scans were normal and who were assessed prior to the Mount Sinai School of Medicine Institutional Review Board's approval for biopsy procedures to be performed on people whose leukocyte	To compare results of roentgenograms, leukocyte scans with indium In 111 oxyquinoline, and bone scans with the diagnostic criterion standards of bone histologic and culture findings. Images were graded from 0 to 4 in intensity, based on the consensus of two physicians. Grade 0 images were equal to background activity. Image intensity was classified as: grade 1 (faintly increased), grade 2 (mildly increased), grade 3 (moderately increased), and grade 4 (markedly increased) activity. Studies were classified as positive for osteomyelitis when focally increased activity of grade 1 or	Bone Biopsy and culture.	**Table 1: Results of Clinical and Laboratory Characteristics Used to Diagnose Osteomyelitis** | | Sensitivity, No. (%) | Specificity, No. (%) | Accuracy*, No. (%) | | --- | --- | --- | --- | | Clinical judgement | 9/28 (32 | 13/13 (100) | 22/41 (54) | | Ulcer area >2cm^2 | 15/27 (56) | 12/13 (92) | 27/40 (68) | | Ulcer inflammation | 10/28 (36) | 10/13 (77) | 20/41 (49) | | Bone exposure | 9/28 (32) | 13/13 (100) | 22/41 (54) | | Erythrocyte sedimentation rate >70 mm/h, noninflamed ulcers | 5/18 (28) | 10/10 (100) | 15/28 (54) | | >100 mm/h, all ulcers | 6/26 (23) | 13/13 (100) | 19/39 (49) | *Accuracy is defined as the number of correct predictions divided by total predictions. **PHYSICAL EXAMINATION** The prevalence of osteomyelitis increased with increasing ulcer size (P = .003), and 15 (94%) of 16 ulcers more than 2 cm^2 in area had underlying osteomyelitis. An ulcer area greater than 2 cm^2 had a sensitivity of 56% and a specificity of 92% in the diagnosis of osteomyelitis. Thirteen (32%) of all 41 ulcers had apparent inflammation on inspection. Ten (77%) of 13 inflamed ulcers had underlying osteomyelitis, while osteomyelitis was present in 18 (64%) of 28 noninflamed ulcers (P=.42). The sensitivity of the presence of inflammation in diagnosing osteomyelitis in diabetic foot ulcers

			scans were normal. <u>Characteristics of cases:</u> Mean age- 55 years (± 11 years-SD) Mean duration of diabetes- 21.5 years (range- 5 to 30 years) in those with osteomyelitis 12 years (range- 5 to 20 years) in those without osteomyelitis. 61% had prior amputations Median ulcer duration- 4 months (range- 3 days to 7 years). There were no significant differences between people with and without osteomyelitis with regard to age, type of diabetes, previous amputations, ulcer duration, or presence of neuropathy, retinopathy, coronary artery disease, or hypertension. 28 (68%) of 41 diabetic foot ulcers had osteomyelitis, as determined by bone biopsy and culture.	greater intensity was present on both the dorsal and plantar images. Views at 4 and 24 hours were compared. Studies were considered positive for osteomyelitis when focal arterial hyperperfusion, focal hyperemia, and focally increased activity on bone images were present. Follow-up studies were determined as resolving osteomyelitis when the grade of intensity decreased by 1 or more and as having completely resolved when the grade of intensity <u>DIAGNOSIS OF OSTEOMYELITIS</u> The diagnosis of osteomyelitis was based on a positive bone culture and/or pathologic criteria for osteomyelitis. Pathologic criteria included osteonecrosis (the absence of osteocytes in their lacunae in the presence of nuclear staining for other cells		was 36%, and the specificity was 77%. Fifteen (37%) of the 41 ulcers were shallow, 17 (41%) were moderately deep, and nine (22%) exposed bone (visible in six, probed in three). Osteomyelitis was present beneath nine (100%) of the ulcers in which bone was exposed, 14 (82%) of 17 moderately deep ulcers, and five (33%) of 15 shallow ulcers (P= .001). The sensitivity of bone exposure in diagnosing osteomyelitis was 32% and the specificity was 100%. **<u>LABORATORY EXAMINATION</u>** Osteomyelitis was found in a greater proportion of foot ulcers as the erythrocyte sedimentation rate increased (P = .003) and was found in 100% of people with erythrocyte sedimentation rates greater than 70 mm/h but no evidence of inflammation on physical examination. Although the erythrocyte sedimentation rate was 100% specific in the diagnosis of osteomyelitis, it was only 28% sensitive. The prevalence of osteomyelitis also increased with rising alkaline phosphatase levels, although this trend did not reach statis¬ tical significance (P=.06). However, 100% of people with an alkaline phosphatase level greater than 135 U/L had osteomyelitis. There were no significant differences between people with and without osteomyelitis in terms of levels for hemoglobin Alc, glucose, serum cholesterol, triglycérides, serum urea nitrogen, creatinine, proteinuria, or white blood cells. Overall, people exhibited poor glycémie control with an average glycosylated hemoglobin level of 12.1%. Renal insufficiency was present in 15%, hyperlipidemia in 47%, and proteinuria in 54% of cases. **Table 2: Results of Noninvasive Imaging Techniques Used to Diagnose Osteomyelitis** | Test | Sensitivity, No. (%) | Specificity, No. (%) | Accuracy*, No. (%) | | Roentgenogram | 7/25 (28) | 11/12 (92) | 18/37 (49) |

			Baseline Measurements: Not mentioned	in the section), marrow fibrosis, and inflammatory cells.		

Bone scan	18/26 (69)	5/13 (39)	23/39 (59)
Leukocyte scan at 4 h	17/22 (77)	10/13 (77)	27/35 (77)
Leukocyte scan at 24 h	23/26 (89)	9/13 (69)	32/39 (82)

*Accuracy is defined as the number of correct predictions divided by total predictions.

The 24-hour leukocyte scan was more sensitive and accurate in diagnosing osteomyelitis in diabetic foot ulcers than roentgenogram, bone scan, or 4-hour leukocyte scan.

HISTOLOGIC FINDINGS

In 15 (54%) of the 28 ulcers with underlying osteomyelitis, histologic examination revealed all three criteria for osteomyelitis.

All but two of these cases had positive bone cultures.

Additional comments:

Reference:

Newman, LG, Waller, J, Palestro, CJ, Schwartz, M, Klein, MJ, Hermann, G, Harrington, E, Harrington, M, Roman, SH, Stagnaro-Green, A Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. *JAMA* 1991; **266:** 1246-51.

Title: Technetium-99-Labeled Leukocytes in Diagnosing Diabetic Osteomyelitis in the Foot

Study type	No. of people	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 4495 Author: Harvey et. al (1997) Study type: Cross-sectional Level of evidence: (-)	Study group: Total-52 diabetic Control group: Not mentioned Study period: 2 years. Setting: Veterans Affairs Medical Center-Miami (VAMC)	Tc-99 HMPAO 21/52 Tc-99 MDP 11/31	Inclusion /Exclusion(study group): who presented clinically with chronic, nonhealing foot ulcerations (Wagner Grades 2 and 3) and a clinical appearance of overlying soft tissue inflammation and cellulitis. Characteristics of cases: Not mentioned Baseline Measurements: Not mentioned	Scintigraphic Tc(Technetium) -99 HMPAO (hexa-methylpropylamine oxine) and MDP (methylene diphosphate)-labeled leukocyte studies were compared with histologic analysis, bone culture, and radiographic results in 52 diabetic people with clinical indications of suspected osteomyelitis in the foot.	Histology, bone cultures and radiographic results	**Table 1**: **Tc-99 HMPAO-labeled leukocyte scan results versus Tc-99 MDP delayed triphasic scintigraphy** N: 52 (Tc-99 HMPAO); 31 (Tc-99 MDP) TP: 18; 10 TN: 28; 8 FN: 3; 1 FP: 3; 12 SENSITIVITY: 86%; 91% SPECIFICITY: 90%; 40% ACCURACY: 88%; 58% 18 people produced true-positive results with 3 people indicating false negatives resulting in a sensitivity of 86%. 28 true negative and 3 false positive results produced a specificity of 90%. Total accuracy for Tc-99 HMPAO studies equalled 88%. Tc-99 MDP triphasic studies produced a sensitivity of 91% compared with 86% for the leukocyte labelled scans. Tc-99 MDP-triphasic scans showed a significant decrease in both specificity and accuracy when compared with the Tc-99 HMPAO scans. Most notable was the difference in specificity, 40% for the Tc-99 MDP triphasic scan compared with 90% for the Tc-99 HMPAO-labelled leukocyte scan. The difference in false positive results when comparing the two types of scintigraphy was particularly significant. Three false positive scans were noted with the leukocyte-labelled scan compared with 12 using the Tc-99 MDP triphasic scan.

Additional comments:

Reference:
Harvey, J, Cohen, MM Technetium-99-labelled leukocytes in diagnosing diabetic osteomyelitis in the foot. *Journal of Foot and Ankle Surgery* 1997; **36:** 209-14.

Title: Contribution of technetium-99m hexamethylpropylene amine oxime labelled leucocyte scintigraphy to the diagnosis of diabetic foot infection

Study type	No. of people	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 4495 Author: Devillers et. al (1998) Study type: Cross-sectional Level of evidence: (+)	Study group: Total-42 diabetic diabetic foot ulcers. Control group: Not mentioned Study period: Oct. 1992 to Nov. 1996 Setting: Endocrinology unit.	26/56	Inclusion /Exclusion(study group): Diabetic with single or multiple infectious foot lesions (perforating ulcerations or cellulitis) were considered for the study. Inclusion criteria were: no antibiotic treatment or discontinuation of antibiotics at least 1 week previously, and no history of vascular surgery or bone and joint curettage concerning the foot during the 6 months preceding scintigraphy. Characteristics of cases: Male- 30 Female- 12 Mean age- 63 years (range- 44-83 years) Type 1 DM- 22 Type 2 DM- 20 Concomitant conditions including arteriopathy (duplex Doppler), diabetic peripheral neuropathy, history of perforating plantar ulcers, fever and inflammatory syndrome	Standard radiography centered on the foot,, three-phase ^{99m}Tc-methylene diphospbonate (MDP) bone scintigraphy and HMPAO-LS (technetium-99m hexameth-ylpropylene amine oxime labelled leucocyte scintigraphy) were performed in all people. All examinations were conducted within a 3-day interval. A delay of 48 h separated the two scintigraphic studies. Radiographs Bone and joint infection was diag-nosed in cases showing evidence of lysis of the cortical bone or periarticular erosion facing a zone of isolated ulceration or associated with bone condensation and intraosseous abscess formation. HMPAO-LS was considered to be positive for osteomyelitis when there was an abnormal accumulation of leukocytes in a zone concordant with the area of uptake on bone scintigraphy. HMPAO-LS was considered to be negative for osteomyelitis when there was abnormal leucocyte accumulation in a zone not concor-dant with the area of uptake on bone scintigraphy (soft tissue in-fection or when no leucocyte accumulation was observed (no	Radiographic and/or bacteriological or histological results or clinical follow up	Among the 56 lesions investigated, there were 26 cases of proven osteomyelitis **Table 1: Imaging and bone biopsy results** No. TP TN FN FP Culture or histology 25 15 6 4 0 Initial radiography 56 14 25 12 5 Bone scintigraphy 56 26 9 0 21 HMPAO-LS 56 23 29 3 1 TP, True-positive; TN, true-negative; FN, false-negative; FP, false-positive Using the defined HMPAO-LS criteria, results of scintigraphy were as follows: 23 true-positives, one false-positive, 29 true-negatives, three false-negatives. Radiographs correctly identified 14 of the 26 sites of osteomyelitis and correctly eliminated the diagnosis of osteomyelitis in 25 out of 30 sites. **Table 2: Sensitivity, specificity and accuracy of various techniques for detecting osteomyelitis.** No. of site Sens. Spec. PPV NPV Accu. Culture or histology 25 78.9% 100% 100 % 60% 84% Initial radiography 56 53.8% 83.3% 73.6 % 67.5 % 69.6 % Bone scintigraphy 56 100% 30% 55.3 % 100 % 62.5 % HMPAO- 56 88.4% 96.6% 95.8 90% 92.9

			were recorded for each patient. Baseline Measurements: Not mentioned	infection). The final diagnosis of osteomyelitis was made on the basis of radiographic and/or bacteriological or histological results after bone biopsy or when clinical follow-up and radiographs repeated over 4 months showed evidence of osteomyelitis. Positive bacteriology (presence of one or more bacteria at direct examination or at culture) Positive histology (presence of bone necrosis, inflammatory infiltration and intrairabecular fibrosis) resulted in a diagnosis of osteomyelitis. Positive scintigraphy was considered to be true-positive if the final diagnosis was osteomyelitis and to be false-positive if the di-agnosis of osteomyelitis was not confirmed. Negative scintigraphy was considered to be true-negative if no other evidence in favour of underlying osteitis was obtained and to be false negative if osteomyelitis was confirmed on the basis of (a) clinical or radiographic findings during the follow-up or (b) bacteriological or histological criteria.		LS | | | | % | | % Sens-Sensitivity; Spec-specificity; PPV-positive predictive value; NPV- negative predictive value; Accu-accuracy Fourteen follow-up HMPAO-LS studies were performed approximately 4 months after the initial diagnosis of osteomyelitis (1 month after antibiotic withdrawal). In all cases, scintigraphy was negative for the initial infected site.
Additional comments:						

Reference:
Devillers, A, Moisan, A, Hennion, F, Garin, E, Poirier, JY, Bourguet, P Contribution of technetium-99m hexamethylpropylene amine oxime labelled leucocyte scintigraphy to the diagnosis of diabetic foot infection. *European Journal of Nuclear Medicine* 1998; 25: 132-38.

<table>
<tr><th colspan="7">Title: Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone</th></tr>
<tr><td>Study type</td><td>No. of people</td><td>Prevalence/ incidence</td><td>Patient characteristics</td><td>Type of test</td><td>Reference standard</td><td>Results</td></tr>
<tr>
<td>ID: 10106

Author: Slater et. al (1997)

Study type: Cohort

Level of evidence: (+)</td>
<td><u>Study group:</u>
Total-56

60 infected diabetic wounds

<u>Control group:</u>
Not mentioned

<u>Study period:</u>
January and September 2000

<u>Setting:</u>
Diabetic Foot Clinic of Assaf Harofeh Medical Center</td>
<td>Not mentioned</td>
<td><u>Inclusion /Exclusion(study group):</u>

Wounds included ulcers, sinus tracts, abscesses, and osteomyelitis. Wounds with gangrene, those with a dry, unbroken eschar and those in which surgical debridement was contraindicated (e.g. simple cellulitis, severe ischaemia, etc.) were excluded.

<u>Characteristics of cases:</u>

People: 56
Sex(M/F): 36/20
Age (years): 62.4 ± 11.7 (Range- 35-85)
Disease duration: 12.8 ± 9 years (range- 1-42)
Duration of the wound:
30 days or less: 30
Over 30 days: 30
27- received antibiotic treatment at time of specimen collection

<u>Baseline Measurements:</u>

Wound grade:
Grade 1: 8
Grade 2: 32
Grade 3: 20
Total number of wounds*: 60
Wound type
Ulcer- 30</td>
<td>Aim was to reappraise the reliability of swabs according to the depth and severity of the wound.

All wounds were graded according to the University of Texas Wound Classification System.
Grade 1 wounds were superficial;
Grade 2, extended into the subcutaneous tissue to the depth of tendon or capsule;
Grade 3, penetrated to bone or joint.

Two cultures were taken from every wound. The first swab was held in contact with the wound for at least 5 s before any debridement was done. At the end of debridement, a deep tissue sample (second) was taken at the junction of non-viable and viable tissue by using a new set of sterile instruments.</td>
<td>Deep tissue biopsy</td>
<td>There was little variation in the numbers and type of bacteria isolated by the two techniques of specimen collection.

Table 1: Correlation between swab and deep tissue cultures

<table>
<tr><td></td><td>No. of wounds (%}</td></tr>
<tr><td>Swabs contained all organisms found in deep tissue</td><td>49 (82)</td></tr>
<tr><td>Grade 1 & 2</td><td>36 (90}</td></tr>
<tr><td>Grade 3</td><td>13 (65)</td></tr>
<tr><td>Swabs and deep tissue cultures identical</td><td>37(62)</td></tr>
<tr><td>Swabs contained all organisms found in deep tissue plus additional organism(s)</td><td>12 (20)</td></tr>
<tr><td>Swabs lacked organism(s) found in deep tissue"</td><td>11(18)</td></tr>
</table>

Swabs were highly specific and sensitive in identifying specific bacterial strains recovered in deep tissue specimens: mean sensitivity 93% and mean specificity 96% P'< 0.001.

In 37 (62%) of the wounds, the swab and deep tissue specimens were identical.

In 12 (20%) wounds, the swab specimen identified all micro-organisms isolated from the deep tissue specimen, but also contained additional micro-organisms.

Thus, in 49/60 wounds (82%) swabs revealed all micro-organisms found in the deep tissue specimen.

Swabs were significantly more accurate in Grade 1-2 wounds</td>
</tr>
</table>

			Sinus tract—no osteomyelitis or abscess- 10 Deep abscess—no osteomyelitis- 5 Osteomyelitis- 15 36 wounds-0.5 to 1.5 cm in diameter 24- 1.6 to 6.5 cm in diameter. * Four people had two separate infected ulcers located in the same foot			than in Grade 3 wounds. For Grade 1-2 wounds, swabs identified all pathogens in the corresponding deep tissue specimen in 36/40 wounds (90%), whereas in Grade 3 wounds swabs identified all micro-organisms in just 13/20 (65%). People were divided according to the duration of their wounds: acute (< 30 days) or chronic (> 30 days). Swabs identified all pathogens present in the deep tissue specimens in 14/16 (88%) of acute Grade 1-2 wounds and in 22/24 (92%) of chronic wounds. The low number of Grade 3 wounds, 14 acute and six chronic, did not allow for a significant subgroup analysis. From the 150 isolates found by deep tissue biopsy, 137 (91%) also appeared in the swab culture. No significant correlation was found between culture results and the various clinical and demographic parameters of these people including age, gender, disease duration, HbA_{Ic}, wound location, and wound characteristics such as size and the presence of ischaemia or neuropathy.
Additional comments:						

Reference:
Slater, RA, Lazarovitch, T, Boldur, I, Ramot, Y, Buchs, A, Weiss, M, Hindi, A, Rapoport, MJ Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. *Diabetic Medicine* 2004; **21:** 705-9.

Title: Role of anti-granulocyte Fab fragment antibody scintigraphy (Leukoscan) in evaluating bone infection: acquisition protocol, interpretation criteria and clinical results.

Study type	No. of people	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 9317 Author: Rubello et. al (2004) Study type: Cross-sectional Level of evidence: (-)	<u>Study group:</u> Total-78 diabetic foot <u>Control group:</u> Not mentioned <u>Study period:</u> Sept. 1999 to Jun. 2002 <u>Setting:</u> Not mentioned.	62/78	<u>Inclusion /Exclusion(study group):</u> Not mentioned <u>Characteristics of cases:</u> Not mentioned <u>Baseline Measurements:</u> Not mentioned	The leukoscan was performed by acquiring both early 4h and delayed 18-24h planar images. The radiotracer uptake intensity on the infected site was graded using a 4-point visual scale: 0-absent 1-mild 2- moderate 3-intense uptake A final diagnosis was reached on the basis of microbiological findings or other laboratory and imaging techniques (such as computed tomography scan and magnetic resonance imaging) and a prolonged (>1 year) follow up or clinical survey. Results were calculated following 2 protocols: 1.Taking into consideration the findings of the early 4h Leukoscan imaging alone- Protocol A 2.considering both the early 4h and delayed 18-24h Leukoscan imaging- Protocol B In protocol B, a decreasing uptake intensity pattern was judged as a negative result	Microbiological findings or other laboratory and imaging techniques (such as computed tomography scan and magnetic resonance imaging) and a prolonged (>1 year) follow up.	**Table 1: True positive, false negative, true negative and false positive teukoScan results obtained evaluating early 4 h imaging alone {protocol A) and (in brackets) both early and delayed 24 h imaging (protocol B).** TP: Diabetic foot (n=78): 57 FN: 5 TN: 12(14) FP: 4(2) **Table 2: Sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy of LeukoScan considering the results of early 4 h imaging alone (protocol A) and (in brackets) both of early and delayed 24 h imaging {protocol B).** Diabetic foot (n=78): Sen (%) 91.9; Spe (%) 75.0 (87.5); NPV (%) 70.5 (73.6); PPV (%) 93.4 (96.6); Acc (%) 88.4 (91.0)

				while an increasing pattern as a positive result.		
Additional comments:						

Reference:
Rubello, D, Casara, D, Maran, A, Avogaro, A, Tiengo, A, Muzzio, PC Role of anti-granulocyte Fab' fragment antibody scintigraphy (LeukoScan) in evaluating bone infection: acquisition protocol, interpretation criteria and clinical results. *Nuclear Medicine Communications* 2004; **25:** 39-47.

Title: MRI AND DIABETIC FOOT INFECTIONS

Study type	No. of people	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 11433 Author: Wang et al. (1990) Study type: Cross-sectional Level of evidence: (-)	Study group: Total: 50 62 bone specimens Control group: Not mentioned Study period: Not mentioned Setting: Ranchos Los Amigos Medical Centre, Downey, California	46/62	Inclusion /Exclusion(study group): Not mentioned Characteristics of cases: Male-35 Female-15 Age range- 23 to 81 years (mean- 49 years) 31 -Insulin Dependent 19 -oral agents and diet Onset of symptoms: <6 weeks- 20 >6 weeks- 30 Baseline Measurements: Not mentioned.	The aim was to study the role of magnetic resonance imaging (MRI) and plain radiographs in evaluating osteomyelitis in the diabetic foot. For MRI, criteria for osteomyelitis included hypo- to isointensity in T1WI sequence and hyperintensity and homogeneous signals with either partial or entire involvement of the bone in STIR. Pathologic criteria for osteomyelitis included proliferation of inflammatory cells (such as lymphocytes, plasma cells, macrophages), fibrosis, bone necrosis, and new bone formation.	Histological Examination.	**X-ray** Total positive for osteomyelitis-19 people Total negative for osteomyelitis- 31 people **MRI** Total positive for osteomyelitis-37 people Total negative for osteomyelitis- 13 people X ray and MRI were reported as positive for osteomyelitis in 19 people. **Table 1: Comparison of MRI and X ray with pathology results (Bone specimens used).**

	MRI		Xray		
Pathology	+	-	+	-	Total
+	45 97.83 %	1 2.17%	24 52.17 %	22 47.83 %	46
-	3 18.75 %	13 81.25 %	5 31.25 %	11 68.75 %	16

The sensitivity of magnetic resonance imaging was 98% (45/46) and plain film was 52% (24/46).
The specificity of magnetic resonance imaging was 81% (13/16) and plain film was 69% (11/16).
The accuracy of magnetic resonance was 94% (58/62) while plain film was 56 percent (35/62)

Additional comments:

Reference:
Wang, A, Weinstein, D, Greenfield, L, Chiu, L, Chambers, R, Stewart, C, Hung, G, Diaz, F, Ellis, T MRI and diabetic foot infections. *Magnetic Resonance Imaging* 1990; **8:** 805-9.

Title: Diagnostic Utility of the History and Physical Examination for Peripheral Vascular Disease among People with Diabetes Mellitus

Study type	No. of people	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 1740 Author: Boyko et al. (1997) Study type: Cohort Level of evidence: (+)	<u>Study group:</u> Total: 631 AAI available for 605 right lower limbs AAI available for 587 left lower limbs <u>Control group:</u> Not mentioned <u>Study period:</u> Oct. 1990 to Oct. 1994 <u>Setting:</u> General internal medicine clinic at Veterans Affairs Medical centre, Seattle	Not mentioned	<u>Inclusion /Exclusion(study group):</u> Not mentioned <u>Characteristics of cases:</u> White males- 78.8% NIDDM-98.6% Mean Age- 63.4 years (±SD 9.8, range- 28 to 90) Mean duration of diabetes-11.3 years <u>Baseline Measurements:</u> Not mentioned.	The aim of the study was to describe the role of medical history information, physical examination findings, and clinical tests in diagnosing severe PVD associated with diabetes. Sample questions regarding medical history, symptoms, and risk factors for PVD were asked. Examiners graded palpable dorsalis pedis (DP) and posterior tibialis (PT) pulses as absent, diminished, or normal. Barely palpable pulses were coded as diminished, absent pulses as absent, and all others as normal. The examiners recorded the presence or absence of atrophic skin and distal lower limb hair growth. Dorsal foot skin temperature was felt with the dorsum of the	AAI ≤0.5	**NOTE:** Similar findings were obtained for each lower limb, so right sided data will be discussed and presented. The bootstrap was used to validate the logistic regression model [13]. A total of 2000 samples with replacement were generated for each model to be validated, with an n for each sample equal to the corresponding n for the logistic model The mean and standard deviations of the bootstrap coefficients were calculated, and compared with the corresponding mean and standard errors from the logistic models **Table 1: Sensitivity, specificity, and likelihood ratios of history and physical examination for the diagnosis of severe right lower limb PVD {AAI ≤0.5, overall prevalence = 7.6%) among 605 veterans.**

Self reported medical history questions	Sensitivity (n=46) (5)	Specificity (n= 559) (%)	Likelihood ration + (95% CI)	Likelihood ration - (95% C)
Age >65 years	82.6	53.5	1 8(1.5-2.1)	0.3 (0.2-0.6)
Diabetes duration >10 years	56.5	60.7	1.4(1.1-1.9)	0.7 (0.5-1.0)
Diabetes duration >20 years	21.7	84.3	1.4 (0.8-2.5)	0.9 (0.8-1.1)
Current smoker	0	98.4	0	1.0 (1.01-1.03)
History of lower limb ulcer	39.1	66.1	1.2 (0.8-1.7)	0.9 {0.7-1.2)
History of lower limb amputation	10.9	94.2	1.9 (0.8-4.6)	0.9 (0.85-1.05)
History of	52.6	52.8	1.1 (0.8-1.5)	0.9 (0.7-1.2)

examiner's hand, compared with the calf temperature, and recorded as cooler, normal, or increased.

We graded overall foot colour as normal, pale, red, or blue/purple.

Venous filling time was determined with the patient in the supine position. The time in seconds until the veins bulged above the skin level was recorded for each leg. Results were graded according to a published criterion as normal (<20 sec), or abnormal (>20 sec).

Capillary refill time was determined by applying firm digital pressure to the plantar skin of the distal great toe for five sec. Transient local pallor was considered *normal,* while greater than five seconds for return to usual skin colour was regarded as delayed refill.

We calculated the ankle-arm index (AAI). An AAI of 0.8 or less is generally considered suggestive of obstruction in the arteries proximal to the

cold feet				
History of blue/purple feet	16.7	88.8	1.5 (0.8-3.0)	0.9 (0.8-1.1)
History of claudication <1 block	50.0	87.4	4.0 (2.8-5.7)	0.6 (0.4-0.8)
History of peripheral vascular disease"	80.0	70.1	2.7 (2.2-3.2)	0.3 (0.2-0.5)
History of lower limb bypass	21.7	95.0	4.3 (2.3-8.4)	0.8 (0.7-1.0)
Absent lower limb hair	47.8	71.0	1.6 (1.2-2.3)	0.7 (0.6-1.0)
Atrophic skin	50.0	69.7	1.6(1.2-2.3)	0.7 (0.5-1.0)
Cool skin	65.2	47.0	1.2(1.0-1.5)	0.7 (0.5-1.1)
Blue/purple skin	23.9	85.3	1.6 (0.9-2.8)	0.9 (0.8-1.1)
Peripheral pulse absent or diminished	65.2	78.3	3.0 (2.3-3.9)	0.4 (0.3-0.7)
Capillary refill time ≥5 seconds	28.3	85.3	1.9 (1.2-3.2)	0.8 (0.7-1.0)
Venous filling time >20 seconds	22.0	93.9	3.6(1.9-6.8)	0.8 (0.7-1.0)
Infrared skin temperature, dorsal foot ≤ median	61.1	51.3	1.3(1.0-1.6)	0.8 (0.5-1.1)
Infrared skin temperature, great toe ≤ median	52.	50.5	1.1 (0.8-1.4)	0.9 (0.7-1.3)

AAI **—** ankle-arm index, CI = confidence interval, PVD = peripheral vascular disease.

				cuff, while a value ≤0.5 is considered severe. They chose the lower cut-off as their disease definition since it is generally agreed that people who achieve this level of ischemia should be followed closely by a vascular specialist.		**MEDICAL HISTORY QUESTIONS:** History of < 1 block claudication symptoms, previous physician diagnosis of PVD as reported by the patient, or previous vascular bypass operation were all associated with positive coefficient likelihood ratios ranging from 2.7 to 4.3, and post-test disease probabilities from 18% to 26% when a positive response was given by the patient. Patient age also was useful particularly if 65 years or younger, which was associated with a likelihood ratio of 0.3, and a post-test disease probability of 2%. Diabetes duration (defined as > 10 years versus <10 years, and >20 years versus <20 years), history of previous lower limb ulcer or amputation, and history of cold blue/purple feet were not very informative with regard to presence of low AAI. **PHYSICAL EXAMINATION OF THE LOWER LIMB:** Diminished peripheral foot pulses and delayed venous filling time were associated with the highest positive likelihood ratios. Positive findings for either of these tests were associated with post-test disease probabilities ranging from 20% to 23%. Positive findings for other clinical examination items were not associated with post test disease probabilities that differed substantially from the Clinical lower limb findings such as decreased hair; atrophic, cool, or blue/purple skin; pro longed capillary refill time; or measured skin temperature below the median value were not very informative clinically due to likelihood ratios close to 1.0. Although skin temperature has long been considered an indicator of vascular perfusion, infrared foot and toe skin temperatures below the median were not sensitive or specific for PVD. **Table 2: Results from the bootstrap validation of the logistic regression models predicting AAI ≤0.5**

	Right leg		Left leg	
Independent variables	Logistic model coefficient ± SE	Bootstrap mean coefficient ± SD	Logistic model coefficient ± SE	Bootstrap mean coefficient ± SD

						MODEL 1				
						Age	0.09 (0.03)	0.09 (0,04)	0.06 (0.03)	0.06 (0.03)
						History of PVD	1.90 (0.42)	2.04 (0.45)	1-66 (0.41)	1.72 (0.44)
						Venous filling time	0.06 (0.03)	0.07 (0.03)	0.08 (0.03)	0.08 (0.03)
						Diminished pulses	1.49 (0.38)	1.58 (0.41)	2.19 (0.42)	2.26 (0.48)
						MODEL 2				
						Age	0.07 (0,03)	0.08 (0.03)	0.05 (0.03)	0.08 (0.03)
						History of claudication	1.67 (0.38)	1.24 (0.41)	0.96 (0.40)	0.89 (0.39)
						Venous filling time	0.05 (0.03)	0.06 (0.03)	0.08 (0.03)	0.06 (0.03)
						Diminished pulses	1.65 (0.38)	1.73 (0.40)	2.21 (0.42)	2.35 (0.47)

AAI = ankle-arm index, PVD - peripheral vascular disease, SE = standard error, SD = standard deviation.

Table 3: The diagnostic utility of pedal pulse palpation and history of claudication or physician diagnosed PVD in detecting an AAI ≤0.5

	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio + (95% CI)	Likelihood ratio — (95% CI)
Right leg: abnormal pulses and history of PVD	0.53 (O.39-0.68)	0.91 (0.88-0.93)	5.61 (3.85-8.17)	0.52 (0.38-0.71)
Left leg: abnormal pulses and history of PVD	0.50 (0.35-0.65)	0.91 (0.89-0.93)	5.55 (3.72-8.28)	0.55 (0.41-0.74)
Right. leg; abnormal pulses or history of	0.93 (0.86-1.00)	0.58 (0.5-0.62)	2.21 (1.95-2.51)	0.12 (0.04-0.35)

PVD						
Left leg: abnormal pulses or history of PVD	1.00 (0.93-1.00)	0.58 (0.54-0.62)	2.39 (2.16-2.64)	0		
Right leg: abnormal pulses and claudication <1 block	0.33 (0.19-0.46)	0.95 (0.93-0.97)	6.21 (3.58-10.76)	0.71 (0.58-0.87)		
Left leg; abnormal pulses and claudication <1 block	0.36 (0.22-0.51)	0.94 (0.92-0.96)	6.08 (3.62-10.21)	0.68 (0.54-0.85)		
Right leg: abnormal pulses or claudication <1 block	0.83 (0.72-0.94)	0.71 (0.67-0.75)	2.82 (2.34-3.40)	0.25 (0.13-0.46)		
Left leg: abnormal pulses or claudication <1 block	0.86 (0.76-0.97)	0.71 (0.67-0.75)	2.94 (2.46-3.52)	0.19 (0.09-0.41)		

AAI- ankle-arm index, CI- confidence interval, PVD- peripheral vascular disease

Additional comments:

Reference:
Boyko, EJ, Ahroni, JH, Davignon, D, Stensel, V, Prigeon, RL, Smith, DG Diagnostic utility of the history and physical examination for peripheral vascular disease among people with diabetes mellitus. *Journal of Clinical Epidemiology* 1997; **50:** 659-68.

<table>
<tr><th colspan="7">Title: The Diagnosis of Osteomyelitis in Diabetes Using Erythrocyte Sedimentation Rate. A Pilot Study</th></tr>
<tr><td>Study type</td><td>No. of people</td><td>Prevalence/ incidence</td><td>Patient characteristics</td><td>Type of test</td><td>Reference standard</td><td>Results</td></tr>
<tr>
<td>ID: 5373

Author: Kaleta et al. (2001)

Study type: Cross-sectional

Level of evidence: (-)</td>
<td><u>Study group:</u>
Total: 29 diabetic

<u>Control group:</u>
Not mentioned

<u>Study period:</u>
Dec. 1998 to Dec. 1999

<u>Setting:</u>
Illinois Masonia Medical centre, Chicago</td>
<td>19/29</td>
<td><u>Inclusion /Exclusion(study group):</u>

Not mentioned

<u>Characteristics of cases:</u>

Number of with osteomyelitis-19
Male- 11
Female- 9
Age ± SD- 58.8 ± 11.0

<u>Baseline Measurements:</u>

Not mentioned.</td>
<td>It's an attempt to correlate an erythrocyte sedimentation rate value in which the presence of osteomyelitis can reasonably be predicted

The presence of osteomyelitis in people treated conservatively with 6 to 8 weeks of intravenous antibiotics was confirmed with positive results of at least two imaging modalities (bone scan, MRI, radiographs) or the ability to probe an open wound to bone.

Pathologic criteria included focal necrosis, intramedullary fibrosis, and extensive reactive and reparative changes.</td>
<td>Histological Examination. (pathologic reports)</td>
<td>Table 1: Statistical Significance Among Variables Tested In Cellulitis and Osteomyelitis Groups.

<table>
<tr><td></td><td>Osteomyelitis</td><td>Cellulitis</td><td></td></tr>
<tr><td>Variable</td><td>Mean ± SD</td><td>Mean ± SD</td><td>P value</td></tr>
<tr><td>Age</td><td>58.8 ±11.03</td><td>68.0 ±16.51</td><td>0.126</td></tr>
<tr><td>Hb</td><td>10.8 ±1.95</td><td>11.8 ±1.48</td><td>0.151</td></tr>
<tr><td>Hct</td><td>32.9 ± 5.51</td><td>36.1 ±4.06</td><td>0.126</td></tr>
<tr><td>Creatinine</td><td>1.3 ±0.60</td><td>1.4 ±0.59</td><td>0.668</td></tr>
<tr><td>ESR</td><td>104.3 ±31.12</td><td>43.4 ±15.20</td><td>0.000*</td></tr>
<tr><td>Gender</td><td></td><td></td><td>0.470</td></tr>
</table>
*- Correlation is significant at P=0.05.
ESR- erythrocyte sedimentation rate; Hb- haemoglobin; Hct- hematocrit

There was a significant difference in the mean erythrocyte sedimentation rate between the cellulitis and osteomyelitis groups (P < .001).

The osteomyelitis group demonstrated a mean erythrocyte sedimentation rate of 104 mm/h while the cellulitis group had a mean erythrocyte sedimentation rate of only 44 mm/h.

Of the variables tested in the two groups, the erythrocyte sedimentation rate was the only clinical measure that differed significantly between the groups. This result was further validated by the nonparametric test, the Mann-Whitney test, which also concluded that the only variable that differed between the two groups was the sedimentation rate.

When Spearman's rho correlation was used to determine any relationships among the variables tested, the erythrocyte sedimentation rate demonstrated a negative association with haematocrit (P = .022) and haemoglobin (P = .047).</td>
</tr>
</table>

A stepwise logistic regression analysis of diseased outcome demonstrated that the erythrocyte sedimentation rate was the most significant predictor of osteomyelitis (P - .007, B = .075) with respect to the other clinical measures.

Table 2: Sensitivity and Specificity of Erythrocyte Sedimentation Rate In Indicating Osteomyelitis

Cutoff Value (mm/h)	Sensitivity (%)	Specificity (%)	Positive Predictive value (%)	Negative Predictive value (%)
≥60	89.5	90	94.4	81.8
≥65	89.5	90	94.4	81.8
≥70	89.5	100	100.0	83.3
≥75	84.2	100	100.0	79.6
≥80	78.9	100	100.0	71.4

An erythrocyte sedimentation rate value equal to or greater than 70 mm/h was the optimal cut off, with the highest sensitivity (89.5%) and highest specificity (100%) for the presence of osteomyelitis. It also had the highest predictive value of 100% and negative predictive value of 83%.

Additional comments:

Reference:

Kaleta, JL, Fleischli, JW, Reilly, CH The diagnosis of osteomyelitis in diabetes using erythrocyte sedimentation rate: a pilot study. *Journal of the American Podiatric Medical Association* 2001; 91: 445-50.

<table>
<tr><th colspan="7">Title: The diabetic foot: magnetic resonance imaging evaluation</th></tr>
<tr><td>Study type</td><td>No. of people</td><td>Prevalence/ incidence</td><td>Patient characteristics</td><td>Type of test</td><td>Reference standard</td><td>Results</td></tr>
<tr>
<td>ID: 1354

Author: Beltran et al. (1990)

Study type: Cohort

Level of evidence: (-)</td>
<td><u>Study group:</u>
Total: 14 diabetic people

<u>Control group:</u>
Not mentioned

<u>Study period:</u>
Not mentioned

<u>Setting:</u>
Not mentioned</td>
<td>6/14</td>
<td><u>Inclusion /Exclusion(study group):</u>

Not mentioned

<u>Characteristics of cases:</u>

Mean age- 36 years (range- 21 to 48)

<u>Baseline Measurements:</u>

Not mentioned.</td>
<td>This study was undertaken as an attempt to assess the potential role of MRI in evaluating people with diabetic foot.

The MRI findings were classified as osteomyelitis, abscess, cellulitis, septic arthritis, tenosynovitis, and neuropathic joint.

MRI diagnostic criteria for each of these entities were as follows:
Osteomyelitis was diagnosed when high signal intensity (SI) was identified within the marrow space on long TR/TE sequences or relatively T2-weighted images (T2WI), with or without associated cortical bone destruction.

Abscess was diagnosed when well-defined high SI collections were seen in the soft tissues on T2WI.

Cellulitis was identified as ill-defined high SI areas from within the soft tissues on T2WI.

Tenosynovitis was diagnosed when high SI fluid was identified within tendon sheaths on T2WI.

Septic arthritis was diagnosed when high SI fluid was observed within the joint space on T2WI in association with other signs of infection in the adjacent soft tissues.
If no other signs of infection were present, we were unable to distinguish between septic arthritis and noninfected effusion.

Neuropathic joint was diagnosed when we</td>
<td>Aspiration, pathologic examination, and plain films,</td>
<td>Most of the people had infection localized to more than one site.

Table 1: Results

<table>
<tr><th>Diagnoses</th><th>Sites of infection</th><th>confirmed</th></tr>
<tr><td>Osteomyelitis</td><td>8</td><td>6*</td></tr>
<tr><td>Abscess</td><td>7</td><td>5</td></tr>
<tr><td>Neuropathic joint</td><td>5</td><td>5</td></tr>
<tr><td>Septic arthritis</td><td>4</td><td>0</td></tr>
<tr><td>Tenosynovitis</td><td>4</td><td>1</td></tr>
</table>

*4 pathologically; 2 empirically

Based on the MRI findings, the following diagnoses were made:

Osteomyelitis- 8
Abscess- 7
Neuropathic joint- 5
Septic arthritis- 4 and
Tenosynovitis- 4.</td>
</tr>
</table>

				observed irregular destruction of the subchondral cortices of a joint accompanied by low signal intensity of the underlying trabecular bone on short TR/TE or relatively T1WI with similar low SI on T2WI as well. Films were classified as positive, negative, or indeterminate for osteomyelitis or neuroarth-ropathy.		
Additional comments:						

Reference:
Beltran, J, Campanini, DS, Knight, C, McCalla, M The diabetic foot: magnetic resonance imaging evaluation. *Skeletal Radiology* 1990; **19:** 37-41.

Title: Magnetic Resonance Imaging For The Diagnosis Of Osteomyelitis In The Diabetic Patient With A Foot Ulcer.

Study type	No. of people	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 5373 Author: Levine et al. (1994) Study type: Cross-sectional Level of evidence: (-)	Study group: Total: 27 diabetic 29- MRI studies. Control group: Not mentioned Study period: Not mentioned Setting: Not mentioned.	13/29	Inclusion /Exclusion(study group): Not mentioned Characteristics of cases: Male- 12 Female- 15 Mean age- 51.6 years (range- 33 to 72) Baseline Measurements: Not mentioned.	The aim of the study is to compare the results of MRI, plain film radiography, indium-111-labelled leukocyte scintigraphy, and technetium-99m bone scan in the diagnosis of osteomyelitis in the diabetic foot. Since osteomyelitis can develop rapidly, only tests performed within 14 days of MRI were included in this study. Studies were read as consistent with active medullary osteomyelitis when an area of abnormal marrow with decreased signal intensity on T1-weighted images corresponded with an area of high signal intensity on T2-weighted images. Negative magnetic resonance studies demonstrated characteristic normal bone marrow signal on T1- and T2-weighted images.	Pathological (n=13) and histological (n= 5) determination, surgical observation (n= 7) and clinical resolution (n= 4).	**Table 1: Utility of Diagnostics Studies in the Diagnosis of Osteomyelitis in the Diabetic Patient with a Foot Ulcer** See table below. MRI was found to have a sensitivity of 77%, a specificity of 100%, and an accuracy of 90%. The sensitivity of plain film roentgenography was found to be 60%, the specificity, 81%, and the accuracy, 73%.

	Sensitivity	Specificity	Accuracy
Plain film roentgenography	60% (6/10)	81% (13/16)	73% (19/26)
Technetium bone scan	100% (3/3)	25% (2/6)	45% (5/11)
indium-labelled white blood cell scintigraphy	80% (4/5)	29% (2/7)	50% (6/12)
Magnetic resonance imaging	77% (10/13)	100% (13/16)	90% (23/29)

Additional comments:

Reference:
Levine, SE, Neagle, CE, Esterhai, JL, Wright, DG, Dalinka, MK Magnetic resonance imaging for the diagnosis of osteomyelitis in the diabetic patient with a foot ulcer. *Foot & Ankle International* 1994; 15: 151-56.

Title: **Evaluation of Magnetic Resonance Imaging in the Diagnosis of Osteomyelitis in Diabetic Foot Infections.**

Study type	No. of people	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 5373 Author: Weinstein et al. (1993) Study type: Cross-sectional Level of evidence: (-)	<u>Study group:</u> Total: 47 diabetic 62 bone specimens. <u>Control group:</u> Not mentioned <u>Study period:</u> Not mentioned <u>Setting:</u> Rancho Los Amigos Medical Center, Downey, California**.**	46/62	<u>Inclusion /Exclusion (study group):</u> Admission was based on clinical suspicion of osteomyelitis, nonhealing foot ulcer, or soft tissue infection of the foot. <u>Characteristics of cases:</u> Male- 32 Female- 15 Mean age- 49 years (range- 23 to 81) <u>Baseline Measurements:</u> Not mentioned.	The purpose of this investigation was to evaluate the role of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infection and to correlate pathological findings and clinical outcome. Magnetic resonance examinations were deemed positive when the T1 weighted marrow image showed areas of decreased signal intensity with corresponding high density areas on both short tau inversion recovery and T2 weighted images. Normal uninvolved bones were used as a reference standard. Criteria for the presence of osteomyelitis on plain radiographs included permeative radiolucencies, destructive changes, cortical defects, and periosteal reaction. Criteria for positive scans included increased blood flow, blood pool, and increased activity on ^{89}Tc bone scan with increased ^{67}Ga activity incongruent and disproportionate. A histological diagnosis of osteomyelitis was determined by the pathologist using criteria from Ackerman's textbook of surgical pathology, which include the combination of inflammatory ceils, fibrosis, bone necrosis, and new bone formation.	Histological examination.	62 bones were examined with magnetic resonance imaging (MRI) and plain film and 22 bones with a Tc/Ga scan. **Table 1: Pathological Correlation for Each Diagnostic Modality** Histology / MRI / Plain Film / Tc/Ga scan +ve / -ve / +ve / -ve / +ve / -ve Osteomyelitis: 46 / 0 / 24 / 22 / 11 / 5 No Osteomyelitis: 3 / 13 / 3 / 13 / 1 / 5 **Table 2: Results for each diagnostic modality**. Sen / Spe / Accu MRI: **100*** / **81** / **95*** Plain Film: **69** / **83** / **73** Tc/Ga scan: **52** / **81** / **60** ***-** statistically significant, P < .01 Magnetic resonance sensitivity was 100%, specificity was 81%, and accuracy was 95%. Plain radiograph sensitivity was 52%, specificity was 82%, and accuracy was 60%. Technetium and gallium sensitivity was 69%, specificity was 83%, and accuracy was 72%.
<u>Additional comments:</u>						

Reference:

Weinstein, D, Wang, A, Chambers, R, Stewart, CA, Motz, HA Evaluation of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. *Foot & Ankle* 1993; **14:** 18-22.

Title: Role of magnetic resonance imaging in the evaluation of diabetic foot with suspected osteomyelitis

Study type	No. of patients	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 9314 Author: Rozzanigo et al. (2009) Study type: Cross-sectional Level of evidence: (+)	Study group: Diabetic patients with foot ulcer = 16 Control group: N/A Study period: January 2006 and September 2007 Setting: Hospital, Italy.	13/16	Inclusion /Exclusion (study group): Diabetic patients with unilateral infected ulcer affecting the forefoot (10), the midfoot (2) and the hindfoot (4). Characteristics of patients: 11 men and 5 women Mean age (range) = 58 years (42–78) Baseline (at the entry of the study): The infected ulcer had been medicated, drained and treated with systemic antibiotics for at least 2 weeks, with little response. Follow-up Not clear	**MRI** Diagnosis based on: A primary sign of osteomyelitis on MRI is evidence of low-signal-intensity areas in the bone marrow on T1-weighted SE images, with higher signal intensity on STIR images and enhancement after contrast administration. Secondary signs are identified close to the altered bone marrow signal and include oedema caused by septic inflammation (cellulitis or phlegmon), soft-tissue abscess, skin ulcer and fistula, with possible interruption of the cortical bone. MRI conducted with a 1.5-Tesla superconductive unit and an extremity coil. 3 radiologists reviewed the MRIimages and the most experienced radiologist was considered the reference standard in the event of disagreement. Subgroup: 12 patients with suspected peripheral arteriopathy also underwent MR angiography (conducted with the bolus chase and moving table technique) and the images of each of the three vascular regions were judged as either adequate or inadequate for peripheral revascularization.	Clinical and laboratory data by means of bacteriological and/or histological tests.	Diagnostic accuracy for osteomyelitis: TP = 13 | FP = 1 FN = 0 | TN = 2 Sensitivity =1.00 Specificity = 0.67 PPV = 0.93 NPV = 1.00 Subgroup: After the MR angiography, 9/12 patients underwent vascular surgery: Surgical femoropopliteal bypass = 3 Endovascular angioplasty = 6 (with immediate technical success in 5/6 cases)
Comments:						

Reference:
Rozzanigo, U, Tagliani, A, Vittorini, E, Pacchioni, R, Brivio, LR, Caudana, R Role of magnetic resonance imaging in the evaluation of diabetic foot with suspected osteomyelitis. *Radiologia Medica* 2009; 114: 121-32.

Title: Osteomyelitis in feet of diabetics: clinical accuracy, surgical utility and cost-effectiveness of MRI

Study type	No. of patients	Prevalence/ incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 7474 Author: Morrison et al. (1995) Study type: Cross-sectional Level of evidence: (-)	Total = 59 patients with clinically suspected osteomyelitis (62 feet) <u>Study group:</u> diabetic patients = 27 feet <u>Control group:</u> nondiabetic patients = 35 feet <u>Study period:</u> Not reported. <u>Setting:</u> US hospital.	Study group: 17/27 No data on control group.	<u>Inclusion /Exclusion:</u> Patients with clinically suspected osteomyelitis <u>Characteristics of patients:</u> 39 male and 20 female Mean age (range) = 51 years (2-85). *Study group:* Neuropthic osteoarthropathy = 9 feet PVD = 5 feet <u>Baseline (at the entry of the study):</u> Not reported. <u>Follow-up</u> Mean (range) = 6 months (1-18) after treatment. The subgroup of 13 patients who underwent foot-sparing resection procedures were followed up for an average of 9 months.	**MRI** Diagnosis based on: Decreased signal intensity of marrow on T1-weighted images and increased signal intensity on T2-weighted images, with marrow enhancement after injection of gadopentetate dimeglumine. Also evaluated cortical interruption, rim-enhancing abscess within the marrow cavity, sequestrum formation, extension of a sinus tract from the bone to the skin surface. Performed with a i.5-T unit (Signa; GE Medical Systems, Milwaukee, Wis) and an extremity coil (GE Medical Systems). MR images were evaluated prospectively by 2 interpreters who had access to information on age, sex, and the clinical question of osteomyelitis in a particular region of the foot or ankle.	Histologic analysis of biopsy specimens OR clinical and radiographic demonstration of progression despite conservative antibiotic therapy.	Diagnostic accuracy for osteomyelitis: TP = 14 | FP = 2 FN = 3 | TN = 8 Sensitivity = 82% Specificity = 94% PPV = 0.88 NPV = 0.73 Differences in these values between study and control group were not statistically significant (sensitivity = $p > 0.30$; specificity = $p > 0.20$).

Comments:

Reference:

Morrison, WB, Schweitzer, ME, Wapner, KL, Hecht, PJ, Gannon, FH, Behm, WR Osteomyelitis in feet of diabetics: clinical accuracy, surgical utility, and cost-effectiveness of MR imaging. *Radiology* 1995; 196: 557-64

Title: Role of MRI in the diagnosis of osteomyelitis in diabetic foot infections						
Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 2523 Author: Croll et al. (1996) Study type: Cross-sectional Level of evidence: (-)	Study group: Patients with diabetic foot infection = 27 MRI = 27 Technetium bone scanning = 22 Indium leukocyte scanning = 19 Plain radiographs = 27 Control group: N/A Study period: November 1991 and December 1992 Setting: Lehigh Valley Hospital, Canada.	9/27	Inclusion /Exclusion (study group): Patients with diabetic foot infections admitted to the Lehigh Valley Hospital. Patients with obvious gangrene or a fetid foot who required immediate surgery were excluded from the study. Patients with cellulitis only were also excluded in the study. Characteristics of patients: 19 men and 8 women Mean age (range) = 66 years (34 to 82 years) Mean duration of diabetes = 20 years. Baseline (at the entry of the study): 7 patients had undergone previous vascular bypass procedures. Presenting signs included cellulitis (70%), seropurulent drainage (67%), leukocyte count greater than 10,000/mm 3 (33%), absent dorsalis pedis and posterior tibial pulses (44%), and neuropathy (67%). Patients with cellulitis only were not included in the study. Follow-up The subsequent treatment of patients was based on clinical judgment of the attending physician, who was not blinded to the results. Successful medical management was defined as a 5 to 10 days course of antibiotics and local care that resulted in a healed or improved ulcer at the time	**MRI** Performed with a 1.5 tesla Signa system (General Electric Mcdical Systems, Milwaukee, Wis.). Scans were obtained with a dedicated extremity coil. All patients underwent scanning in the axial oblique and coronal oblique planes. **Technetium bone scanning** Performed with a gamma camera and three-phase technique. Technetium-99 m-MDP was used in a dose of 20 uCi. **Indium leukocyte scanning (In-WBC)** After separation, washing, and resuspension of the lcukocytes were performed from 50ml blood sample, labeling was performed with 500 to 600 uCi of Indium-111 Oxine, and the cells were reinjected. Plantar and lateral or medial images of the infected foot were obtained the next day (18 to 24 hours after reinjection) and images were acquired for 10 minutes in each projection. **Plain radiographs** Not reported. Diagnosis based on: histologic findings of subpcriosteal new bone formation, lytic areas of bone loss, the presence of fibrosis, and infiltration ofpolymorphonuclear leukocytes and lymphocytes. Interpretation of the studies was done by staff radiologists and nuclear medicine specialists and was reviewed by the clinicians. The physicians were not	Confirmed or refuted by pathologic specimen, or bone culture.	Diagnostic accuracy for osteomyelitis: **MRI = 27** TP = 8 | FP = 0 FN = 1 | TN = 18 Sensitivity = 89% Specificity = 100% PPV = 1.00 NPV = 0.95 **99mTc-MDP bone scanning = 22** TP = 4 | FP = 7 FN = 4 | TN = 7 Sensitivity = 50% Specificity = 50% PPV = 0.36 NPV = 0.63 **Indium leukocyte scanning = 19** TP = 2 | FP = 4 FN = 4 | TN = 9 Sensitivity = 33% Specificity = 69% PPV = 0.33 NPV = 0.69 **Plain radiographs = 27** TP = 2 | FP = 1 FN = 7 | TN = 17 Sensitivity = 22% Specificity = 94% PPV = 0.67 NPV = 0.71

			of follow-up (2 to ó months).	specifically blinded to the results of the other diagnostic studies, but none was aware of the pathologic end point of the presence or absence of osteomyelitis before submitting their reports.		
Comments:						

Reference:
Croll, SD, Nicholas, GG, Osborne, MA, Wasser, TE, Jones, S Role of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. *Journal of Vascular Surgery* 1996; 24: 266-70.

<table>
<tr><th colspan="6">Title: Evaluating diabetic foot infection with MRI: Kuwait experience</th></tr>
<tr><td>Study type</td><td>No. of patients</td><td>Prevalence/ incidence</td><td>Patient characteristics</td><td>Type of test</td><td>Reference standard</td><td>Outcome measures</td></tr>
<tr><td>ID: 656

Author: Al-Khawari et al. (2007)

Study type: Cross-sectional

Level of evidence: (+)</td><td><u>Study group:</u>
Diabetic patient with suspected ankle and/or foot infection = 29 [MRI+histology = 19]

<u>Control group:</u>
N/A

<u>Study period:</u>
August 2000 to July 2002

<u>Setting:</u>
Al-Amiri Hospital, Kuwait.</td><td>11/19</td><td><u>Inclusion /Exclusion (study group):</u>
Diabetic patients referred from the Diabetic Foot Clinic in Al-Amiri Hospital, clinically suspected of having ankle and/ or foot infection were evaluated.

<u>Characteristics of patients:</u>
17 male and 12 female
Mean age (range) = 61 (41–81)

<u>Baseline (at the entry of the study):</u>
N/A

<u>Follow-up</u>
Not reported.</td><td>MRI
Osteomyelitis was diagnosed when focally increased bone marrow signal on FST_2WI and focally decreased marrow signal on T_1WI with or without cortical destruction, and focal marrow enhancement on postcontrast T_1WI was observed. Normal marrow signal on T_1WI with high signal on FST_2WI and marrow enhancement post contrast were also considered as osteomyelitis.

Performed using a 1.0-tesla superconducting magnet (General Electric, Signa Horizon). Surface coil (head coil) was used in all cases.

Two consultant radiologists qualified in MRI evaluated the MR images; the final MR diagnosis was made by consensus.</td><td>Culture growth or characteristic histological findings including aggregates of inflammatory cells (neutrophils, lymphocytes, histocytes and plasma cells), erosion of trabecular bone, and bone marrow changes that ranged from loss of normal marrow fat with acute osteomyelitis to fibrosis and reactive bone formation with chronic disease.</td><td>Diagnostic accuracy for osteomyelitis:

MRI = 19
<table><tr><td>TP = 11</td><td>FP = 3</td></tr><tr><td>FN = 0</td><td>TN = 5</td></tr></table>Sensitivity = 100%
Specificity = 62.5%
PPV = 0.79
NPV = 1.00

MRI helped surgical planning for limb salvage procedures in 6 of the patients with osteomyelitis and in 1 case which was clinically suspected to have osteomyelitis and proved to have cellulitis on MRI and histopathology</td></tr>
<tr><td colspan="6">Comments:</td></tr>
</table>

Reference:

Al-Khawari, HA, Al-Saeed, OM, Jumaa, TH, Chishti, F Evaluating diabetic foot infection with magnetic resonance imaging: Kuwait experience. *Medical Principles & Practice* 2005; 14: 165-72.

Title: The diagnosis of diabetic foot osteomyelitis: examination findings and laboratory values (clinical evaluation)

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Predictors	Reference standard	Outcome measures
ID: 3176 Author: Ertugrul et al. (2009) Study type: Cohort Level of evidence: (-)	<u>Study group:</u> Diabetic inpatients with diabetic foot lesions = 46 <u>Control group:</u> <u>Study period:</u> September 2004 and June 2007 <u>Setting:</u> The Diabetic Foot Council of the School of Medicine, Adnan Menderes University, Turkey.	24/46	<u>Inclusion /Exclusion (study group):</u> 46 consecutive diabetic inpatients with diabetic foot lesions (with or without foot ulcer). <u>Characteristics of patients:</u> 30 male and 16 female Age (mean±SD) = 64±9.2 yrs. (range: 46–82 yrs.) Duration of diabetes = 14±8.38 yrs (1–30 yrs) ESR level = 65.87±28.08 mm/h <u>Baseline (at the entry of the study):</u> Classification of Wagner: 1 patient (2%) = grade 0 7 patients (15%) = grade 1 12 patients (26%) = grade 2 14 patients (30%) = grade 3 9 patients (20%) = grade 4 3 patients (7%) = grade 5 27 patients (58.7%) had a history of a previous diabetic foot ulcer. 11 patients (24%) had lower extremity amputations at different levels <u>Follow-up</u> Not reported.	• Erythrocyte sedimentation rate (ERS) levels (60, 65, 70, 75, 80 mm/h) • Wound sizes (2, 3, 4, 5cm^2)	One of the following criteria as the diagnosis of osteomyelitis: 1. Histopathology based on the presence of osteonecrosis and infiltration with leukocytes or chronic inflammatory cells such as lymphocytes or plasma cells. 2. Microbiologic based on the presence of bacteria in bone-tissue culture. 3. MRI with conventional spin echo.	Osteomyelitis diagnosed by reference standards: positive = 24; negative = 22 ERS (mm/h) / Sen / Spe / PPV / NPV ≥60 / 92 / 68 / 76 / 88 ≥65 / 88 / 73 / 78 / 84 ≥70 / 83 / 77 / 80 / 81 ≥75 / 79 / 82 / 83 / 78 ≥80 / 71 / 91 / 90 / 74 Wound size(cm^2) ≥2 / 88 / 77 / 81 / 85 ≥3 / 79 / 77 / 79 / 77 ≥4 / 67 / 91 / 89 / 71 ≥5 / 50 / 95 / 92 / 64 ERS≥65 + wound size≥2 / 83 / 77 / 80 / 81 ERS≥70 + wound size≥2 / 79 / 82 / 83 / 78
Comments:						

Reference:

Ertugrul, BM, Savk, O, Ozturk, B, Cobanoglu, M, Oncu, S, Sakarya, S The diagnosis of diabetic foot osteomyelitis: examination findings and laboratory values. *Medical Science Monitor* 2009; 15: CR307-CR312.

Title: The diagnosis of osteomyelitis of the foot in diabetes: microbiological examination vs. MRI and labelled leucocyte scanning

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 3177 Author: Ertugrul et al. (2006) Study type: Cross-sectional Level of evidence: (-)	Study group: Diabetic patients with foot lesions = 31 Control group: N/A Study period: Not reported. Setting: Hospital in Turkey	26/31	Inclusion /Exclusion (study group): Diabetic patients with foot lesions were enrolled in the study. Patients had clinically suspected foot lesions with > grade 3 according to the classification of Wagner. Characteristics of patients: 23 male and 8 female Age (mean ± sd) = 62±8.8 years (range 40-77 years) Duration of diabetes = 16.8±8.9 years (range 1-35 years); Duration of foot infection = 3.6±3.1 months (range 0.5-12 months) Baseline (at the entry of the study): ESR = 87±25mm/h (range 37-120mm/h) CRP = 7.17±5.66 mg/dl (range 1-25.3 mg/di) Serum creatinine = 121 ± 91.9 umol/l (range 62-115 umol/i) WBC count = 11022±5131/mm3 (range 5020-31 880/mnr') Classification of Wagner: 11 patients (36%) = Grade 3 15 patients (48%) = Grade 4 5 patients (16%) = Grade 5 Follow-up One of the patients died due to septic shock during the follow-up period.	**Microbiological processing** Bone specimens for anaerobic cultures were cultured in Schaedler agar and then placed in an anaerobic chamber. Bone specimens for aerobic culture were processed in the laboratory using 5% sheep blood agar, MacConkey's agar and Sabouraud agar. Microbiological diagnosis of osteomyelitis was based on the presence of bacteria in bone-tissue culture **MRI** Performed on a Siemens Vision 1.5T (Siemens, Erlangen, Germany) using a knee coil. High signal intensity on TIRM, low signal intensity on T1 sequence and contrast enhancement as the definition of osteomyelitis. **Labelled leucocyte scan (99mTc-MDP)** Images were obtained using a Siemens Orbtter gamma camera connected to a Pegasys computer (ADAC, Miipitas, CA, USA) equipped with a collimator. Four-phase bone scintigraphy was performed using 740MBq (20 mCi) Tc^{99}m methylene diphonatc (MDP). An additional plantar image for 50,000 counts was obtained 24h after injection (4P-MDP). Combined 4P-MDP and Tc^{99}m WBC scans were considered positive for osteomyelitis when there was an abnormal accumulation of leucocytes in a zone concordant with the area of up-take on bone scintigraphy.	Histopathological diagnosis of osteomyelitis was based on the presence of osteonecrosis and infiltration with leucocytes or chronic inflammatory cells such as lymphocytes or plasma cells.	Diagnostic accuracy for osteomyelitis: **Microbiological processing = 31** TP = 24 | FP = 2 FN = 2 | TN = 3 Sensitivity = 92% Specificity = 60% PPV = 92% NPV = 60% **MRI = 28** TP = 18 | FP = 2 FN = 5 | TN = 3 Sensitivity = 78% Specificity = 60% PPV = 90% NPV = 37.5% **Labelled leucocyte scan = 26** TP = 21 | FP = 1 FN = 2 | TN = 2 Sensitivity = 91% Specificity = 67% PPV = 95% NPV = 50%
Comments:						

Reference: Ertugrul, MB, Baktiroglu, S, Salman, S, Unal, S, Aksoy, M, Berberoglu, K, Calangu, S The diagnosis of osteomyelitis of the foot in diabetes: microbiological examination vs. magnetic resonance imaging and labelled leucocyte scanning. *Diabetic Medicine* 2006; 23: 649-53.

Title: Rapid diagnosis of pedal osteomyelitis in diabetics with a Technetium-99m-Labelled Monoclonal Antigranulocyte Antibody

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 8153 Author: Palestro et al. (2003) Study type: Cross-sectional Level of evidence: (-)	<u>Study group:</u> Diabetic patients = 25 <u>Control group:</u> N/A <u>Study period:</u> Not reported <u>Setting:</u> Hospital, US.	10/25	<u>Inclusion /Exclusion (study group):</u> Diabetic patients older than 18 years of age with a peripheral leukocyte count of at least 2,500/mm3, who were suspected of having osteomyelitis underlying a pedal ulcer based on the presence of one or more of the following: localized pain, fever greater than 100°F for at least 3 days, elevated peripheral leukocyte count, elevated erythrocyte sedimentation rate, radiographic findings suggestive of osteomyelitis, or positive blood or wound cultures. Patients with granulating surgical incisions or who had received 7 or more days of antibiotic therapy at the time of enrollment were excluded <u>Characteristics of patients:</u> 17 men and 8 women 22 patients, the ulcer was in the forefoot, and in 3 it was in the mid-foot. <u>Baseline (at the entry of the study):</u> <u>Follow-up</u> Not reported	Patients were required to undergo WBC and 3-phase bone imaging within 1 week of the Moab. **Moab** The Moab was supplied as a lyophilized, sterile formulation, containing 250 micro g of antibody. At the time of use, 0.2-0.35 mL of 99mTc0_4 , containing 740-1,480 MBq of 99mTc, was added to the kit, and the mixture was then incubated at 37°C for 30 minutes. After incubation, a sufficient volume of 500 mg/mL ascorbic acid injection was added to the vial to bring the final preparation volume to 1mL. Patients were injected with 370-740 MBq (75-125 micro g) 99mTc-labelled antibody. Imaging was performed on a large field-of-view gamma camera equipped with a low-energy, high-resolution, parallel hole collimator. Images were interpreted as positive for osteomyelitis when focal activity, felt to be bony, was increased relative to adjacent activity. **In-WBC** For WBC, 40 mL of whole blood was withdrawn for labeling with ^{111}In-oxine, according to the method of Thakur et al. Approximately 18.5 MBq of ^{111}In-iabeled autologous leukocytes were injected and imaging was performed 18-30 hours later. Images were classified as positive for osteomyelitis when focally increased activity, equally well seen on the dorsal and plantar views, was present. **3-phase bone scintigraphy (99mTc-MDP)** Performed with 740 MBq of 99mTc-methylene diphosphonate. Imaging was performed on a large field-of-view gamma camera, equipped with a low-energy, high-resolution, parallel hole collimator. Focal hyperperfusion, focal hyperemia, and focally increased bony uptake on delayed images was interpreted as positive for osteomyelitis.	Bone biopsy examination and culture (20 patients). AND Made by an experienced clinician based on all available data (other than the results of the investigational agent) (5 patients).	Diagnostic accuracy for pedal osteomyelitis: **Moab = 25** TP = 9 | FP = 5 FN = 1 | TN = 10 Sensitivity = 90% Specificity = 67% **In-WBC = 25** TP = 8 | FP = 5 FN = 2 | TN = 10 Sensitivity = 80% Specificity = 67% **3-phase bone scintigraphy = 25** TP = 9 | FP = 11 FN = 1 | TN = 4 Sensitivity = 90% Specificity = 27% **Moab/3-phase bone = 25** TP = 9 | FP = 5 FN = 1 | TN = 10 Sensitivity = 90% Specificity = 67% **WBC/3-phase bone = 25** TP = 8 | FP = 3 FN = 2 | TN = 12 Sensitivity = 80% Specificity = 75%
Comments:						

Reference: Palestro, CJ, Caprioli, R, Love, C, Richardson, HL, Kipper, SL, Weiland, FL, Tomas, MB Rapid diagnosis of pedal osteomyelitis in diabetics with a technetium-99m-labelled monoclonal antigranulocyte antibody. *Journal of Foot & Ankle Surgery* 2003; 42: 2-8.

Title: 99mTc-Nanocolloid scintigraphy for assessing osteomyelitis in diabetic neuropathic feet

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 9006 Author: Remedios et al. (1998) Study type: Cross-sectional Level of evidence: (-)	Study group: Diabetic patients = 9 Control group: N/A Study period: Not reported Setting: Hospital, Middlesex, UK.	4/9	Inclusion /Exclusion (study group): Diabetic patients with peripheral neuropathy, chronic foot ulcers and clinical signs compatible with osteomyelitis were prospectively recruited. All had had plain radiography of the symptomatic foot and had already been imaged with 99mTc-mcthylene diphosphate (99mTc-MDP) bone scintigraphy. Characteristics of patients: 4 men and 5 women Mean age = 57 years Pedal ulcers were all on the plantar aspect, mostly related to the metatarsal heads and os-calcis Baseline (at the entry of the study): Follow-up 6 months.	All patients underwent examination with 99mTc-nanocolloid (99mTc-NC) marrow scintigraphy and MRI of the affected foot. **99mTc-nanocolloid (99mTc-NC)** Three phase marrow scintigraphy was performed using 400 MBq of intravenous WmTc-NC. Images were taken with a large field-of-view gamma camera equipped with a low energy, high resolution collimator using a 20% window centred at 140keV. Studies were considered to be positive for osteomyelitis if static images showed significantly more focal activity than corresponding blood pool images. Images were interpreted by two radiologists with a consensus opinion. **MRI** Performed using a 0.5 T superconductive magnet employing a head coil. Studies were considered to be positive for osteomyelitis if there was evidence of reduced marrow signal on T1 images and increased marrow signal on STIR or T2 images, particularly associated with adjacent deep ulceration. Images were interpreted by two radiologists with a consensus opinion.	Biopsy cores and surgical excision specimens were examined histologically and microbiologically. A positive diagnosis for osteomyelitis was taken as either microbiological and/or histological evidence of bone infection.	Diagnostic accuracy for osteomyelitis: **99mTc-nanocolloid (99mTc-NC) = 9** TP = 4 | FP = 2 FN = 0 | TN = 3 Sensitivity = 100% Specificity = 60% **MRI = 9** TP = 4 | FP = 1 FN = 0 | TN = 4 Sensitivity = 100% Specificity = 80%
Comments:						

Reference:
Remedios, D, Valabhji, J, Oelbaum, R, Sharp, P, Mitchell, R ^{99m}Tc-nanocolloid scintigraphy for assessing osteomyelitis in diabetic neuropathic feet. *Clinical Radiology* 1998; 53: 120-125.

Title: Diabetic foot osteomyelitis: usefulness of ESR in its diagnosis						
Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 6776 Author: Malabu et al. (2007) Study type: Cross-sectional Level of evidence: (-)	<u>Study group:</u> Diabetic patients = 43 <u>Control group:</u> N/A <u>Study period:</u> Jan to Dec 2005 <u>Setting:</u> King Abdulaziz University Hospital Diabetes Center Riyadh, Saudi Arabia	22/43	<u>Inclusion /Exclusion (study group):</u> Ambulant Saudi adults aged ≥40 years with type 2 diabetes attending KAUH Diabetes Center for foot ulcer and who fulfilled the inclusion criteria given below were recruited for the study. Patients were excluded if they had any of the following: (i) severe illness requiring hospital admission, (ii) associated illnesses such as nephrotic syndrome, chronic renal failure, hypothyroidism and hepatobiliary diseases or (iv) any illness known to cause anemia or raised ESR apart from diabetic foot ulcer. <u>Characteristics of patients:</u> *With osteomyelitis (n = 22):* 11 male and 11 female Mean age (SD) = 56.3 (12.2) Mean duration of diabetes (years, SD) = 19.9 (6.5) *With cellulitis (n = 21):* 12 male 9 female Mean age (SD) = 56.3 (12.6) Mean duration of diabetes (years, SD) = 15.3 (8.0) <u>Baseline (at the entry of the study):</u> *With osteomyelitis (n = 22):* Neuropathy = 14/22; Retinopathy = 7/22 Previous amputation = 8/22 *With cellulitis (n = 21):* Neuropathy = 12/21; Retinopathy = 10/21 Previous amputation = 9/21 Using Wagner classification revealed osteomyelitic patients having more severe disease with Grade3 in 20 patients and 2 patients Grade 4 as compared to 16 and 5 cellulitic patients having Grades 2 and 1 respectively <u>Follow-up</u> Not reported.	Haematological indices including: • ESR • Hematocrit • Hemoglobin • Platelet count • Red cell distribution width (RDW) • White cell count **Descriptions of indices not reported.*	Presence of osteomyelitis was confirmed by at least 2 imaging modalities (bone scan, MRI, radiographs) or the ability to probe an open wound to bone. The diagnosis of cellulitis was confirmed by correlating clinical signs of infection with positive wound cultures.	Diagnostic accuracy for osteomyelitis: **ESR >70** Sen = 90%; Spe = 94% PPV = 95%; NPV = 89% **Hematocrit >36%** Sen = 95%; Spe = 84% PPV = 86%; NPV = 94% **Hemoglobin < 12 g/dl** Sen = 81%; Spe = 90% PPV = 89%; NPV = 82% **Platelet count > 400 x 10^9/L** Sen = 45%; Spe = 95% PPV = 90%; NPV = 62% **RDW >14.5** Sen = 67%; Spe = 63% PPV = 63%; NPV = 67% **White cell count >400x10^9/L** Sen = 52%; Spe = 80% PPV = 73%; NPV = 62%
Comments:						

Reference: Malabu, UH, Al-Rubeaan, KA, Al-Derewish, M Diabetic foot osteomyelitis: usefulness of erythrocyte sedimentation rate in its diagnosis. *West African Journal of Medicine* 2007; 26: 113-16.

Title: Use of Sulesomab, a radio-labelled antibody fragment, to detect osteomyelitis in diabetic patients with foot ulcers by leukoscintigraphy

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 4507 Author: Harwood et al. (1999) Study type: Cross-sectional Level of evidence: (-)	<u>Study group:</u> Diabetic patients = 150 <u>Control group:</u> N/A <u>Study period:</u> N ot reported <u>Setting:</u> Hospital, US.	81/122	<u>Inclusion /Exclusion (study group):</u> Diabetic patients, presence of a foot ulcer with characteristics suggestive of osteomyelitis, non-pregnant, able to return for follow-up visits, no known allergies to mouse proteins, no history of renal insufficiency, and not currently taking any investigational therapy were included. <u>Characteristics of patients:</u> 123 men and 27 women Mean age = 58 years. (all ≥21 years) <u>Baseline (at the entry of the study):</u> Not reported <u>Follow-up</u> Not reported	**Sulesomab** (the Fab' fragment of the murine monoclonal antibody IMMU-MN3, which is reactive with NCA-90). Each patient was injected with 0.25 mg of Sulesomab, which was labelled with 15-25 mCi (555-925 MBq) of 99mTc. Planar images (10 minutes per view) were acquired 1-2 and 5-8 hours after injection. **In-WBC and 99mTc-bone scan** **Descriptions not reported.*	Definitive proof of osteomyelitis was based on histology and/or microbiological cultures obtained from bone biopsy specimens. Osteomyelitis was considered present if either or both results obtained were positive; otherwise, osteomyelitis was considered absent.	Diagnostic accuracy for osteomyelitis: 122/150 patients had technically readable Sulesomab images and were considered evaluable for efficacy analyses. **Sulesomab = 122** TP = 74 | FP = 18 FN = 7 | TN = 23 Sensitivity = 91% (95%CI: 83%-97%) Specificity = 56% (95%CI: 40%-72%) PPV = 80% (95%CI: 71%-88%) NPV = 77% (95%CI: 58%-90%) **In-WBC = 111** TP = 59 | FP = 12 FN = 16 | TN = 24 Sensitivity = 79% (95%CI: 68%-87%) Specificity = 67% (95%CI: 49%-81%) PPV = 83% (95%CI: 72%-91%) NPV = 60% (95%CI: 43%-75%) **99mTc-bone scan = 47** TP = 31 | FP = 11 FN = 2 | TN = 3 Sensitivity = 94% (95%CI: 80%-99%) Specificity = 21% (95%CI: 5%-51%) PPV = 74% (95%CI: 58%-86%) NPV = 60% (95%CI: 15%-95%)
Comments:						

Reference:

Harwood, SJ, Valdivia, S, Hung, GL, Quenzer, RW Use of Sulesomab, a radiolabelled antibody fragment, to detect osteomyelitis in diabetic patients with foot ulcers by leukoscintigraphy. *Clinical Infectious Diseases* 1999; 28: 1200-1205.

Title: Diagnosis of pedal osteomyelitis in diabetic patients using current scintigraphic techniques

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 5525 Author: Keenan et al. (1989) Study type: Cross-sectional Level of evidence: (+)	Study group: Diabetic patients = 77 (with total of 94 studies) Control group: N/A Study period: Not reported Setting: Hospital, US.	38/94	Inclusion /Exclusion (study group): Patients with long-standing diabetes mellitus who were referred to the nuclear medicine division for evaluation of possible infection involving one or more foot bones were considered eligible for inclusion in this study. Characteristics of patients: 39 men and 38 women) Age range = 23 to 81 years Mean age = 67 years 19 patients had multiple episodes of suspected OM; therefore, many patients were studied on more than one occasion Baseline (at the entry of the study): Patients with both chronic (>6 weeks) and acute (<6 weeks) symptoms were included in this study, and neuropathic joint disease was present in more than one third of the cases. Follow-up Not reported	**3-phase bone scintigraphy (99mTc-MDP)** Performed by intravenous injection of 20 to 25 mCi of technetium 99m methylenediphosphonate or hydroxymethylene-diphosphonate, followed by acquisition of serial 3-second flow images of the feet, either in the anterior or plantar projection, depending on the site of greatest concern. **In-WBC** Performed as outlined by McCarthy et al. 50 ml of venous blood was collected aseptically, and 250 to 300 micro-Ci of the final labelled leukocyte preparation was reinfused intravenously. The patients were imaged approximately 24 hours later in multiple projections; each image was acquired for at least 10 minutes. All studies were reviewed by two nuclear medicine physicians without any clinical or pathologic information. On occasions when scan readings differed, the final result was achieved by consensus.	The final diagnosis was established by culture and/or histologic examination following needle biopsy or open surgery.	Diagnostic accuracy for osteomyelitis: **99mTc-MDP = 94** TP = 38 / FP = 35 FN = 0 / TN = 21 Sensitivity = 100% Specificity = 38% **In-WBC = 46** TP = 19 / FP = 6 FN = 0 / TN = 21 Sensitivity = 100% Specificity = 78% **99mTc-MDP/In-WBC = 39** TP = 15 / FP = 5 FN = 0 / TN = 19 Sensitivity = 100% Specificity = 79%
Comments:						

Reference:

Keenan, AM, Tindel, NL, Alavi, A Diagnosis of pedal osteomyelitis in diabetic patients using current scintigraphic techniques. *Archives of Internal Medicine* 1989; 149: 2262-66.

Title: Diagnosis of osteomyelitis in the diabetic foot with a 99mTc-HMPAO Leucocyte scintigraphy combined with a 99mTc-MDP bone scintigraphy

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Outcome measures
ID: 8637 Author: Poirier et al. (2002) Study type: Cross-sectional Level of evidence: (+)	Study group: Diabetic patients = 75 (101 feet) [83 feet final inclusion] Control group: N/A Study period: November 1993 to March 2001 Setting: Hospital, France.	41/83	Inclusion /Exclusion (study group): Diabetic patients with suspected osteomyelitis from a foot ulcer. Inclusion criteria were: suspected bone or joint infection from a single or multiple foot ulcers and no history of vascular or foot surgery during the previous three months. Patients with acute limb-threatening infection or systemic infection were not included. Characteristics of patients: 46 males, 29 females Median age = 61.3 years (range: 40-86) Median duration of diabetes = 12 years (range 5-35) HbA_{Ic} = 8.7% (range 6.9-12) Baseline (at the entry of the study): Peripheral vascular or coronary diseases (n = 45) Peripheral neuropathy (n = 53) Previous foot ulcers (n = 48) Neuroarthropathy with Charcot joint (n = 5). Wagner scores: Grade 1 = 70; grade 2 = 10; grade 3 = 3; grade 4 and 5 = 0 Follow-up 18 feet were excluded: antibiotic treatment for bone infection (n = 8) or serious progressive cellulitis (n = 6), amputation of the ulcerated site during follow-up (n = 1), death (n = 1), absence of radiological follow-up (n = 2).	**Three-phase bone scintigraphy** Performed 24 hours after plain films, using 600 MBq 99mTc-MDP **Leucocytes labelling with 99mTc-HMPAO** Blood samples (42 ml) were collected on citric acid dextrose A. The granulocytes were labelled with 300 MBq of freshly prepared 99mTc-HMPAO (Ceretec, Amersham®); incubation lasted for 15 minutes at room temperature. Scintigraphic images were acquired 4 to 5 hours after injection with a gamma camera used for bone scintigraphy. 99mTc-HMPAO-Leu and 99mTc-MDP scans were performed within a 2-day interval. Each imaging study was independently evaluated by one experienced radiologist and one nuclear medicine physician who knew the site of interest but did not have any additional information The HMPAO-Leu/MDP scan was considered to be positive for osteomyelitis when there was an accumulation of leucocytes concordant in all the incidences with an abnormal uptake on bone scintigraphy	Osteomyelitis was diagnosed by radiological examination at inclusion or during follow-up: a needle bone biopsy for bacteriological and histological studies was performed only if accurate cultures could be obtained through uninvolved tissue and when the radiograph at inclusion was negative or doubtful contrasting with a positive bone scintigraphy. Histopathologic criteria for osteomyelitis include necrotic bone with inflammatory excudate adjacent to an extensive resorption.	Diagnostic accuracy for osteomyelitis: **99mTc-MDP bone = 83** TP = 41 | FP = 30 FN = 0 | TN = 12 Sensitivity = 100% Specificity = 28% **99mTc-HMPAO/MDP bone = 83** TP = 38 | FP = 1 FN = 3 | TN = 41 Sensitivity = 92.6% Specificity = 97.6%
Comments:						

Reference: Poirier, JY, Garin, E, Derrien, C, Devillers, A, Moisan, A, Bourguet, P, Maugendre, D Diagnosis of osteomyelitis in the diabetic foot with a ^{99mTc}-HMPAO leucocyte scintigraphy combined with a ^{99mTc}-MDP bone scintigraphy. *Diabetes and Metabolism* 2002; 28: 485-90.

Title: Clinical signs of infection in diabetic foot ulcers with high microbial loads

Study type	No. of patients	Prevalence / incidence	Patient characteristics	Predictor variables	Predicted outcomes	Outcome measures
ID: 3783 Author: Gardner et al. (2009) Study type: Cross-sectional Level of evidence: (-)	Study group: Patients with diabetic foot ulcers = 64 Control group: Study period: Setting: Department of Veterans Affairs Medical Center and an academic-affiliated tertiary hospital, US.	High microbial load = 25 Low microbial load = 39	Inclusion /Exclusion (study group): A convenience sample was recruited who (a) were > 18 years of age and (b) had one or more full-thickness, nonarterial DFUs. Participants with the following criteria were excluded: (a) WBC count < 1500 cells/mm3, (b) platelet count < 125,000/mm3, (c) coagulopathies, or (d) receiving anticoagulation therapy. Characteristics of patients: 49 men, 15 women Mean age (SD) = 55 (11.4) Wound size (cm^2, mean, SD) = 5.9 (8.29, 2.43) Wound depth (cm, mean, SD) = 0.6 (0.51, 0.40) Wound duration (weeks, mean SD) =33.9 (45.15, 14.00) Baseline (at the entry of the study): Treated with systemic antibiotics = 24 (37%) Follow-up Not reported	DFUs were clinically assessed for signs of infection without the knowledge of microbial load. Classical signs: Increasing pain Erythema Edema Heat Purulent exudate Signs specific to secondary wounds: Serous exudate Sanguinous exudate Delayed healing Discolored granulation Friable granulation Pocketing Foul odor Wound breakdown The Infectious Disease Society of America (IDSA) guidelines for diabetic foot infections: Purulent exudates or 2 or more signs of inflammation (i.e., pain, erythema, heat, or edema).	**High microbial load:** Ulcers with high microbial load were defined as > 1,000,000 organisms per gram of tissue.	Diagnostic accuracy for high microbial load:

	Sen (%)	Spe (%)	AUC (%)
Classical signs			
Increasing pain	12	100	56
Erythema	32	77	55
Edema	20	77	48
Heat	12	85	48
Purulent exudate	26	65	47
Signs specific to secondary wounds			
Serous exudate	88	21	54
Sanguinous exudate	83	9	46
Delayed healing	48	54	51
Discolored granulation	28	85	56
Friable granulation	0	77	38
Pocketing	4	92	48
Foul odor	20	87	54
Wound breakdown	0	97	49
IDSA combination	52	46	49

Comments:

Reference:

Gardener, SE, Hillis, SL, Frantz, RA Clinical signs of infection in diabetic foot ulcers with high microbial load. *Biological Research for Nursing* 2009; 11: 119-28.

Title: Evaluation of diabetic wound classifications and a new wound score (clinical utility)

Study type	No. of patients	Patient characteristics	Type of tests	Assessment criteria	Assessment scores
ID: 10474 Author: Strauss et al. (2005) Study type: Evaluation Level of evidence: (-)	Study group: N/A Control group: N/A Study period: N/A Setting: N/A	Inclusion /Exclusion (study group): N/A Characteristics of patients: N/A Baseline (at the entry of the study): N/A Follow-up N/A	• Wagner (1979), US • Forrest and Gamborg-Neilsen (1984), Sweden • Knighton et al. (1986), US • Pecoraro and Reiber (1990), US • Lavery et al. (1996), US • MacFarlane and Jeffcote (1999), UK • Foster and Edmunds (2000), UK	11. Number of criteria for evaluation 12. Objectivity of findings to evaluate each criterion 13. Scoring permutations 14. Versatility 15. Guide to seriousness 16. Integration with wound information 17. Integration with patient information 18. Documentation of progress 19. Validity 20. Reliability All wound score systems were evaluated using 10 assessments. Each assessment was graded on a three-point scale: 2 points indicated that there was good supporting data and/or the ability to measure the assessment was good; 1 point indicated that there was some supporting information and/or the ability to measure the assessment was fair; 0 points indicated that there was no supporting information and/or the ability to measure the assessment was poor or nonexistent.	

Test	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Tot.**
WAG	2	0	1	0	1	1	1	0	1	0	7
FOR	2	0	2	0	0	0	0	0	0	0	4
KNI	0	1	0	2	1	0	0	0	0	0	4
PEC	1	0	1	0	1	0	0	0	0	0	3
LAV	1	1	2	1	1	0	1	1	1	1	10
JEF	2	2	0	1	2	0	1	1	1	1	11
FOS	2	0	2	0	1	1	2	0	0	0	8

The new wound score:

Criteria	2* (best)	1* (fair-to-good)	0* (worst)
Appearance (Wound base)	Red	White, Yellow (or thin nonfluctuant eschar)	Black (necrotic, wet gangrene, or fluctuant eschar)
Size (Include undermining, recesses and tunneling)	Less than the surface area of the patient's thumb print	Thumbprint sized to fist sized	Larger than fist sized
Depth (Include maximum depth of probing)	Skin or subcutaneous tissue	Muscle and/or tendon	Bone and/or joint
Bio-burden	Colonized	Cellulitic and/or macerated margins	Septic (unstable blood sugars, leucocytosis, positive blood cultures etc)
Perfusion	Palpable pulses	Doppler pulses (triphasic or diphasic)	Monophasic or no pulses

*Note: use half points if things are mixed or between two scores
NOTE: the new wound score has 17 points from the same assessment.

Comments: High risk of bias.

Reference:

Strauss, MB, Aksenov, IV Evaluation of diabetic wound classifications and a new wound score. [Review] [20 refs]. *Clinical Orthopaedics & Related Research* 2005; 439: 79-86.

Title: Probing to bone in infected pedal ulcers - A clinical sign of underlying osteomyelitis in diabetic patients.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 4156 Author: Grayson et. al (1995) Study type: Cohort Level of evidence: (-)	Study group: Total-75 diabetic persons 76 infected foot ulcers Control group: Not mentioned Study period: 2 year from Dec. 1988 Setting: Hospital	50/76	Inclusion /Exclusion(study group): Patients who had infected pedal ulcers. Patients without pedal ulceration, with nonhealed recent surgical wounds, or with pedal infection that had been debrided in a manner likely to expose the adjacent bone were excluded. Characteristics of cases: Average age- 60± 12 years Male- 52 Female-23 Duration of diabetes- 19 ± 10 years Baseline Measurements: Not applicable.	To detect the relationship between the detection of bone by probing and the presence of osteomyelitis. In patients with open ulcers, probing was performed prior to debridement and when ulcers were covered by an eschar, probing was undertaken after debridement that was limited to removal of overlying eschar. Bone was considered palpable (positive probe test) when, on gentle probing, the evaluator detected a rock-hard, often gritty structure at the ulcer base without the apparent presence of any intervening soft tissue. The inability to detect bone (a negative probe test) was defined by the absence of such a finding.	Histology	Table 1 Investigation / Sensitivity % / Specificity % / PPV % / NPV % Probe to bone / 66 / 85 / 89 / 56 Probe to bone TP = 33 / FP = 4 FN = 17 / TN = 221

Additional comments:

Reference: Grayson ML, Gibbons GW, Balogh K et al. (1995) Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA 273: 721-3.

Title: Probing to bone in infected pedal ulcers - A clinical sign of underlying osteomyelitis in diabetic patients.

Study type	No. of people	Prevalence / incidence	Patient characteristics	Type of test	Reference standard	Results
ID: 9927 Author: Shone et. al (2006) Study type: Cross-sectional Level of evidence: (-)	Study group: Total-81 diabetic persons 104 foot ulcers Control group: Not mentioned Study period: Not mentioned Setting: Outpatient clinic	21/104	Inclusion /Exclusion(study group): Not mentioned Characteristics of cases: Nor mentioned Baseline Measurements: Not applicable.	To determine the validity of the probe-to-bone test in the diagnosis of osteomyelitis. Ulcers were probed by one of two specialist podiatrists following debridement.	Clinical signs of infection, radiologic evidence of bone destruction, supported by MRI and microbiologic analysis of deep tissue samples.	Table 1 Investigation / Sensitivity % / Specificity % / PPV % / NPV % Probe to bone / 38 / 91 / 53 / 85 Probe to bone TP = 8 / FP = 7 FN = 13 / TN = 76

Additional comments:

Reference: Shone A, Burnside J, Chipchase S et al. (2006) Probing the validity of the probe-to-bone test in the diagnosis of osteomyelitis of the foot in diabetes. Diabetes Care 29: 945-6**.**

Review question 3: What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading in treating diabetic foot problems?

Debridement

Title: Debridement of diabetic foot ulcers (Cochrane review)					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: Study type: Systematic review Authors: Edwards et al. (2009)	People with Type 1 or 2 diabetes, with an active foot ulcer of neuropathic, neuroischaemic or ischaemic aetiology.	Randomised controlled trials (RCTs), either published or unpublished, which measure the effects on ulcer healing of one or more methods of debridement in the treatment of diabetic foot ulcers. Review content assessed as up-to-date: 18 October 2009. The methodological strength of each study was appraised using a standard risk of bias checklist for the following criteria: • sequence generation; • allocation concealment; • blinding; • incomplete outcome data; • selective reporting of outcomes; • other bias. 5 RCTs were included. The reporting of inclusion and exclusion criteria was extremely variable amongst the 5 trials with only D'Hemecourt (1998) reporting precise inclusion and exclusion criteria. Although Jensen (1998) had clear inclusion criteria, no exclusion criteria were listed. In such cases where criteria were not listed, it was presumed that all people with diabetic foot ulcers were eligible for inclusion in the trial. Markevich (2000) makes no reference to inclusion or exclusion criteria. Three trials (Markevich 2000; Piaggessi 1998; Vandeputte	Comparison of any method of debridement (i.e. the removal of necrotic tissue from the wound, by either mechanical or non-mechanical debridement) with no debridement or an alternative method of debridement. Hydrogel vs. gauze or good wound care (3 studies) Hydrogel vs. larvae therapy (1 study) Surgical debridement vs. conventional non-surgical management (1 study) *Note: Good wound care for all groups consisted of initial and ongoing sharp debridement of ulcers when necessary to remove nonviable tissue, daily saline dressing changes, off loading of pressure and systematic control of infection if present* *Note: Gauze – one study used wet-to-moist saline gauze; one study used dry gauze.*	Range from 16 weeks to 6 months. *5 studies:* D'Hemecourt (1998): 20 weeks Jensen (1998): 16 weeks Markevich (2000): not reported Piaggessi (1998): 6 months Vandeputte (1997): 3 months	Meta-analyses were carried out where there are two studies or more. **Hydrogel vs. gauze or good wound care (3 studies); study period: 16 weeks – 3 months; total 198 participants:** *No. of ulcers completely healed:* RR = 1.84 (95%CI: 1.30 to 2.61) *No. of complications (adverse events) reported:* RR = 0.60 (95%CI: 0.38 to 0.95) **Hydrogel vs. larvae therapy (1 study); study period not reported; total 140 participants:** *Reduction of wound area > 50%:* RR = 1.89 (95%CI: 1.21 to 2.96) **Surgical debridement vs. conventional non-surgical management (1 study); at 6 months; total 46 participants:** *No. of ulcers completely healed:* RR = 1.21 (95%CI: 0.96 to 1.51) *Recurrence rates of ulcers:* RR = 0.41 (95%CI: 0.12 to 1.35) *No. of complications (adverse*

		1997) entered people with diabetic foot ulcers into their trials regardless of ulcer size, depth, duration or blood supply. Vandeputte (1997) had a single exclusion criterion of patients receiving systemic antibiotics.	*Note: Conventional non-surgical management consisting of weight-bearing relief and regular dressings.*		*events) reported:* RR = 0.33 (95%CI: 0.03 to 3.47)
Additional comments: Good quality systematic review. Only 2 studies mentioned setting (outpatient department, diabetic foot clinic), the remaining 3 studies did not reported setting. Sequence generation and allocation concealment were not reported for all 5 trials. Only 1 study reported blinding. Only 2 studies reported loss to follow-up and only 1 study conducted ITT. In the absence of adequate methodological reporting, all 5 trials were deemed to be at high risk of bias.					

Off-loading

Title: Wound Healing: Total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration.

Level of Evidence	Patient Population/ Characteristics	Selection/ Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 11112 Level of evidence: () Study type: RCT Authors: Van de Weg et al. (2008)	Total no. of patients: Baseline = 226 158-do not meet inclusion criteria 68-eligible, of which- 14- no interest 5- no transport 6- co-morbidity 43-randomised Allocated TCC-23 Received TCC-20 Allocated and received CTF-20 Before the intervention, ulcers were debrided of necrotic tissue; hypertrophic edges were removed. They received same educational guidelines on foot care. Baseline characteristics: TCC (n=23) / Shoe (n= 20) Age (years): 64.8 (10.8) / 58.1	Inclusion: Confirmed diabetes, sensory neuropathy, and a plantar ulcer Grade 1 or 2 using the Wagner scale. Exclusion: People unable to walk indoors, with dementia or life-threatening co-morbidity, ankle/brachial index <0.4	Total-contact casts (TCC) A well moulded and minimally padded non-removable below-knee cast that maintains contact with entire plantar aspect of the foot was used.	*Custom-made temporary footwear (CTF)* It was custom-made and supplied with a rigid leather socket stiffened with Rhenoflex, a composite of rubber and plastic with thermoplastic properties.	At 2,4,8 and 16 weeks	**Table 1: Decrease in wound surface (cm^2) after baseline (mean, SD) in patients with diabetic foot ulcers using a cast or footwear.** TCC / Shoe / Mean difference (95% CI) / Adjusted mean difference (95% CI)* At 2 weeks, n= 41: -0.98 (1.7) / -0.50 (1.5) / 0.48 (-0.55 to 1.51) p= 0.35 / 0.14 (-0.68 to 0.96) p= 0.73 At 4 weeks, n= 40: -1.76 (1.8) / -0.92 (1.4) / 0.84 (-0.19 to 1.87) p= 0.11 / 0.51 (-0.25 to 1.26) p= 0.19 At 8 weeks, n= 38: -1.64 (2.3) / -0.94 (2.7) / 0.70 (-0.98 to 2.38) p= 0.41 / 0.41 (-1.21 to 2.02) p= 0.61 At 16: -2.88 / -2.16 / 0.72 (- / 0.10 (-

	Mean, (SD), n=43		(11.1)	and/or osteomyelitis.			
	Gender, n=42 n (% female)*	7 (32%)	2 (10%)				
	Duration of diabetes (years) Median (IQR)*	12 (6.20)	12 (7.17)				
	Duration of ulcer (weeks) Median (IQR)	4 (3-8)	5 (4-8)				
	Wound surface (cm^2) at baseline Median (IQR)	3.6 (1.7-6.1)	1.9 (1.0-4.2)				
	Wound surface (cm^2) at baseline Mean (SD)	4.2 (3.1)	3.0 (3.1)				
	Ulcer Grade 1 (n)	2	2				
	Forefoot location (n)	20	18				

*1 missing value
SD-standard deviation, IQR- interquartile range
Setting:
Rehabilitation departments of 2 hospitals

weeks, n= 40	(2.5)	(3.4)	1.19 to 2.62) p= 0.45	0.92 to 0.72) p= 0.81

*-adjusted for differences in wound surface at baseline.

Reduction of wound surface area (WSA)

It was not significantly different between groups at any point during the follow up.

After adjustment for differences in baseline values, the difference between groups in reduction of wound surface was 0.10 cm^2 (95% CI -0.92 to 0.72)

Wound healing (days)

6 people wearing shoes (mean baseline WSA 4.5) and 6 people using a cast (mean baseline WSA 4.7) had a completely healed ulcer.

The mean time to healing was shorter for patients using a cast: 59 (SD-39) days for TCC vs. 90 (SD-12) days for CTF, but the difference in this small subgroup was not statistically significant (p= 0.11).

	Completely healed ulcer	Not completely healed	Total
TCC	6	17	23
CTF	6	14	20
Total	12	31	43

Relative Risk- 6/23 ÷ 6/20 = 0.866

Additional comments:
Allocation was concealed using opaque, sealed envelopes. Analysis of effectiveness was done according to the intention-to-treat principle. All analysis was adjusted for potential confounding. Accounted for people lost to follow up (n= 2) and discontinued (n= 3). Power calculation done.

Reference: Van De Weg, FB, Van Der Windt, DA, Vahl, AC Wound healing: total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration. *Prosthetics & Orthotics International* 2008; **32:** 3-11.

Title: A randomised trial of two irremovable Off-Loading devices in the management of plantar neuropathic diabetic foot ulcers.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 5478 Level of evidence: () Study type: RCT Authors: Katz et al. (2005)	<u>Total no. of patients:</u> Baseline = 41 TCC-20 4 lost to follow up iTCC-21 2 lost to follow up 1 found to have osteomyelitis Before the intervention, wounds were evaluated, debrided, and dressed <u>Baseline characteristics:</u> There were no statistically significant demographic differences between the two groups at study entry with respect to age, sex, race, type of diabetes, duration of diabetes, co morbid conditions, severity of neuropathy, or ulcer characteristics. <u>Setting:</u> Referral clinic	<u>Inclusion:</u> If they had chronic, non-ischemic, non-infected University of Texas stage Ia or IIA ulcers. They had moderate to severe neuropathy, with a loss of protective sensation. <u>Exclusion:</u> If they had clinical evidence of active infection at the ulcer site; active Charcot neuroarthropathy; significant peripheral arterial disease; inability to walk; or if they did not meet the entry criteria.	Removable cast walker (RCW) rendered irremovable (iTCC) They were wrapped circumferentially with a single roll of fibreglass casting material thus rendering them 'irremovable.'	*Total contact cast (TCC)*.	Weekly until 12 weeks.	**Proportions of people with ulcers healed in ≤12 weeks:** TCC= 74 ± 45% iTCC= 80 ± 41%, p= 0.65 If patients lost to follow up are excluded in this analysis, these proportions change to 93±26%- TCC and 94±24%-iTCC (p= 0.97) Of the ulcers that healed in the 12-week period, the median (mean) healing times were: 5 weeks-TCC 4 weeks- iTCC Complications (defined as any potential side effect from the treatment, no matter how minor) showed a relative risk reduction of 41% and absolute risk reduction of 27% (95% CI -4.3 to 58, p= 0.09) between the TCC and iTCC groups. **Table 1: Complication**

Complication	Total	TCC	iTCC	p
N	41	20	21	
Complications	21 (65)	13 (65)	8 (38)	0.09
Maceration	13 (32)	7 (35)	6 (29)	0.49
Broken cast	4 (10)	3 (15)	1 (5)	0.29
Second ulcer	3(7)	2 (10)	1 (5)	0.53
Abrasions	2 (5)	2 (10)	0 (0)	0.15
Toe amputations	2(5)	1 (5)	1 (5)	0.97
Oedema	1 (2)	1 (5)	0 (0)	0.33
Kissing ulcer	1(2)	1 (5)	0 (0)	0.33

Fall	1 (2)	0 (0)	1 (5)	0.33

Data are n(%)
65% of people that used TCC developed a complication
38% of people that used iTCC developed a complication.

Additional comments:
Randomisation was performed. Allocation concealment not mentioned. All parameters were analysed as intention to treat. Confounding not mentioned. Power calculation done.

Reference: Katz, IA, Harlan, A, Miranda-Palma, B, Prieto-Sanchez, L, Armstrong, DG, Bowker, JH, Mizel, MS, Boulton, AJ A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care* 2005; **28:** 555-59.

Title: **A comparative study between total contact casting and conventional dressings in the non-surgical management of diabetic plantar foot ulcers.**.

Level of Evidence	Patient Population/ Characteristics	Selection/ Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 3765 Level of evidence: () Study type: RCT Authors: Ganguly et al. (2008)	Total no. of patients: Baseline = 58 Category A-29 with 39 ulcers Category B-29 3 lost to follow up 26 left with 33 foot ulcers Baseline characteristics: There was no significant difference in distribution of subject characteristics between the two groups (P= 0.05). Setting: Not mentioned	Inclusion: Patients with diabetic foot ulcers. Exclusion: Not mentioned	Category A-total contact casting (n-29 patients with 39 ulcers) also had sharp debridement done.	Category B-simple dressing (used mupirocin ointment and sterile gauze)only (n-26 patients with 33 ulcers)	Until complete epithelisation and 6 months after healing.	Table 1: Showing classification of ulcers based on outcome Category / Total no. / Healed A / 39 / 36 B / 33 / 25 Table 2: Showing summary of the results Category / A / B Dropouts / 0 / 3 Patients completing the study / 29 / 26 Total no. of ulcers / 39 / 33 No. of ulcers healed / 36 / 25 No. of patients whose condition deteriorated / 1 / 5 **Relative risk- 36/39 ÷ 25/33 = 1.22** **Relative risk (surgical interventions)- 1/30 ÷ 5/26 = 0.17**

Additional comments:
People were randomized. Blinding not performed. No intention to treat analysis mentioned. Power calculation not mentioned. Concealment and confounding not mentioned.

Reference: Ganguly, S, Chakraborty, K, Mandal, PK, Ballav, A, Choudhury, S, Bagchi, S, Mukherjee, S A comparative study between total contact casting and conventional dressings in the non-surgical management of diabetic plantar foot ulcers. *Journal of the Indian Medical Association* 2008; **106:** 237-39+244.

Title: Off-loading the diabetic foot wound. A randomised clinical trial.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 951 Level of evidence: () Study type: RCT Authors: Armstrong et al. (2001)	<u>Total no. of patients:</u> Baseline = 75 12 failed to complete the study Total- 63 TCC-19 RCW-20 Half-shoe-24 All people were followed on a weekly basis for device inspection, wound care, and wound debridement. All wounds were surgically debrided as required on each visit. <u>Baseline characteristics:</u> No significant differences were observed in any of the characteristics evaluated, in-cluding age, sex, duration of diabetes, size or location of wounds, or duration of plantar wounds <u>Setting:</u> Not mentioned	<u>Inclusion:</u> All people had clinically significant loss of protective sensation (>25 V), at least one palpable foot pulse or a transcutaneous oximetry ($TcPo_2$) measurement higher than 40 mmHg, and a neuropathic plantar diabetic foot ulcer corresponding to grade 1A using the University of Texas Diabetic Foot Wound Classification System. <u>Exclusion:</u> If they had active infection, were unable to walk without wheelchair assistance, had wounds in locations on the heel, rear foot, or area other than the plantar aspect of the foot, or had severe peripheral vascular disease.	*Total contact cast (TCC)*. Were applied using a modification of the technique described by Kominsky.	Removable cast walker (RCW- the Aircast diabetic walker - Aircast, Summit, NJ) and Half-shoes (.Darco, Huntington, WV) Both were applied using the directions dispensed with the original packaging.	Weekly until 12 weeks.	The proportion of healing in people treated with TCC, RCW, and half-shoes was 89.5, 65.0, and 58.3% respectively. At 12 weeks, the proportion of healing was significantly higher in the TCC group than in people treated with the 2 other modalities (89.5 vs. 61.4%, P = 0.026, odds ratio 5.4, 95% CI 1.1-26.1). There was also a significant difference in cumulative wound survival at 12 weeks between patients treated with a TCC and both the RCW (P = 0.033) and the half-shoe (P = 0.012). Among patients healing within the 12-week period, the meantime to healing was significantly shorter in patients treated with the TCC compared with those treated with the half-shoe (33.5 ± 5.9 vs. 61.0 ± 6.5 days, respectively; P = 0.005). But not the RCW (50.4 ± 7.2 days, P = 0.07), with the numbers available for study. No falls or device-related ulcerations were reported during the course of study. Patients treated with the TCC were significantly less active (600.1 ± 320.0 daily steps) than those treated with the half-shoe (1,461.8 ± 1,452.3 daily steps, P — 0.04).

There was not a significant difference in activity between patients treated with the TCC and with the RCW (767.6 ± 563.3 daily steps, P=0.67) or between those treated wiih the RCW and with the half-shoe (P = 0.15).

TCC vs. RCW

	Complete wound healing	Not completely healed	Total
TCC	17	2	19
RCW	13	7	20
Total	30	9	39

RR= 0.894/0.65 = 1.37

TCC vs. Half-shoes

	Complete wound healing	Not completel y healed	Total
TCC	17	2	19
Half-shoes	14	10	24
Total	31	12	43

RR= 0.894/0.583= 1.53

RCW vs. Half shoes

	Complete wound healing	Not completely healed	Total
RCW	13	7	20
Half-shoes	14	10	24
Total	27	17	44

RR= 0.65/0.583= 1.11

Additional comments:
People were randomized through a computerized randomization schedule. Accounted for people lost to follow up or withdrawn. Concealment not mentioned. Confounding not mentioned. Power calculation done.

Reference: Armstrong, DG, Nguyen, HC, Lavery, LA, van Schie, CH, Boulton, AJ, Harkless, LB Off-loading the diabetic foot wound: a randomized clinical trial.[Erratum appears in Diabetes Care 2001 Aug;24(8):1509]. *Diabetes Care* 2001; **24:** 1019-22.

Title: Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 951 Level of evidence: () Study type: RCT Authors: Mueller et al. (1989)	<u>Total no. of patients:</u> Baseline = 40 TCC-21 TDT-19 Standard protocol for patients referred to the diabetic foot center was followed for all people. <u>Baseline characteristics:</u> There was no significant difference in distribution of subject characteristics between the two groups (P= 0.05). <u>Setting:</u> The diabetic foot center and physical therapy department at Washington University School of Medicine.	<u>Inclusion:</u> All people had been diagnosed with diabetes mellitus and currently had a plantar ulcer. <u>Exclusion:</u> Evidence of gross infection (no significant edema or drainage), osteomyelitis), or gangrene (visibly discolored or necrotic tissue). .	*Total contact cast (TCC)*. A total contact plaster shell was moulded around the lower leg.	Traditional dressing treatment (TDT). Procedures, except for casting, were identical for the TDT group. The wound was covered with a wet-to-dry dressing (sterile saline), and patients were instructed to change the dressing two to three times daily.	Weekly until 6 weeks.	In the TCC group, 19 of 21 (90%) ulcers healed in a mean time of 42 ± 29 days (range 8-91 days). In the TDT group, 6 of 19 (32%) ulcers healed in a mean time of 65 ± 29 days (range 12-92 days). None of the TCC group required hospitalization during this study. Five of 19 (26%) patients in the TDT group showed serious foot infection that required admission to a hospital. Two of these patients required a forefoot amputation. The $\chi 2$-value was statistically significant (P < .05), both for the number of ulcers healed ($\chi 2$= 12.36) and incidence of infection ($\chi 2$= 4.1). **TCC vs. TDT** Complete ulcer healing / Not completely healed / Total TCC: 19 / 2 / 21 TDT: 6 / 13 / 19 Total: 25 / 15 / 40 **RR= 0.904/0.315= 2.86**

<u>Additional comments:</u>
People were randomized. No power calculation mentioned. No intention to treat analysis done. Concealment and confounding not mentioned.

Reference: Mueller, MJ, Diamond, JE, Sinacore, DR, Delitto, A, Blair, VP, III, Drury, DA, Rose, SJ Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. *Diabetes Care* 1989; **12:** 384-88.

Title: The use of felt deflective padding in the management of plantar hallux and forefoot ulcers in patients with diabetes

Level of Evidence	Patient Population/ Characteristics	Selection/ Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 7910 Study type: RCT Authors: Nube et al. (2006)	Total no. of patients = 38 6 patients discontinued. Final analysis: Felt to the skin = 15; Felt within the shoe =17 All wounds were neuropathic in origin with the presence of peripheral neuropathy defined by a vibration perception threshold of over 30 V when tested with a biothesiomeler. <u>Skin group:</u> Median age (IQR) = 59 (50-70) Males = 14; females = 1 Type 2 diabetes = 14 Median duration of diabetes (years) (IQR) = 14 (10-19) Median HbAIc (%) (IQR) = 10.4 (6.8-11.4) Median duration of ulcer (months) = 11.5 Median size of ulcer (cm^2) = 0.5 <u>Shoe group:</u> Median age (IQR) = 56 (55-66) Males = 12; females = 5 Type 2 diabetes = 16 Median duration of diabetes (years) (IQR) = 12 (6-19) Median HbAIc (%) (IQR) = 8.5 (7.3-9.9) Median duration of ulcer (months) = 4.5 Median size of ulcer (cm^2) = 0.5	Patients presenting with grade 1 ulcers according to the Texas Wound Grading system were recruited consecutively from our foot clinic. <u>Inclusion:</u> 'Type 1 or Type 2 diabetes, plantar neuropathic foot ulcer of the hallux or metatarsal area, grade 1A or IB. <u>Exclusion:</u> Impalpable pulses or AB1 <0.6; highly exudative ulcer; deep sinus.	Felt deflective padding to the skin vs. felt deflective padding within the shoe At the weekly appointment, wound debridement was performed and *infections* were monitored and treated.	4 weeks or until healing	<u>Wound size reduction at week 4 (percentage change):</u> Skin = 73%; Shoe = 74% [z = 0.02, p = 0.9] Overall, 24 patients included in the analysis healed by week 14 (not reported which group these 24 patients were from).
<u>Additional comments:</u> All ulcers were randomly assigned by drawing lots to receive fell deflective padding adhered directly to the skin of the foot or adhered to the insole of the shoe. The randomisation was also stratified according to whether the ulcer was on the hallux or forefoot and whether it was greater or less than 1 cm2 in area. Setting not clear. No blinding, no allocation concealment, no ITT.					

Reference: NubÇ¸, VL, Molyneaux, L, Bolton, T, Clingan, T, Palmer, E, Yue, DK The use of felt deflective padding in the management of plantar hallux and forefoot ulcers in patients with diabetes. *Foot* 2006; **16:** 38-44.

Title: An off-the-shelf instant contact casting device for the management of diabetic foot ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/ Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 8506 Study type: RCT Authors: Piaggesi et al. (2007)	Total no. of patients = 40 Group A = 20 Group B = 20 Group A: Mean age (SD) = 61.1 (6.4) Mean duration of diabetes (years) (SD) = 13.4 (7.5) Mean A1C (%) (SD) = 7.6 (0.9) Mean area of lesions (cm^2) (SD) = 3.9 (1.8) Group B: Mean age (SD) = 59.8 (8.2) Mean duration of diabetes (years) (SD) = 14.7 (11.1) Mean A1C (%) (SD) = 7.9 (1.1) Mean area of lesions (cm^2) (SD) = 3.7 (1.6) Setting: Diabetic foot clinic of the University of Pisa between April and October 2005	Inclusion criteria: Type 1 or type 2 diabetes for a period of at least 5 years, have peripheral neuropathy as highlighted by insensitivity to a 10-g monofilament and by a vibration perception threshold measured at malleolus of at least 25 volts, a forefoot plantar ulcer for a period of at least 3 weeks with an area wider than 1 cm^2 graded 1A or 2A according to Texas University classification. Exclusion criteria: Peripheral vascular disease with an antebrachial pressure index <0.9; the presence of clinical signs of infection, including edema, erithema, increased local skin temperature, secretion, fever, and leukocytosis, confirmed by culture exams; previous ulcer in the same site in the last 6 months; probing to bone and/or radiographic signs of osteomyelilis; Charcot foot; bilateral ulceration; serum creatinine >2 mg/dl; any systemic pathology or therapy possibly interfering with the healing process; severe visual or motor impairment that could expose the patient to risk of accidents while participating in the study; and/or a life expectancy shorter than 1 year.	Optima Diab device (instant casting) (group A) vs. Standard Non-removable fiber-glass cast (TCC) (group B) Besides the off-loading treatment, patients received specific instructions on how to manage the off-loading devices and the standard therapy of neuropathic ulceration performed in our clinic according to the international consensus on the diabetic foot. Ulcers were surgically debrided, eliminating all the nonviable tissue, as well as any sinus or undermined zone, and exposing the entire area of the lesion.	Followed-up weekly for 12 weeks or up to complete reepithelialization of the lesions.	*Complete healing at 12 weeks:* Group A = 17/20 (85%) Group B = 19/20 (95%) RR = 0.89 (95%CI: 0.73 to 1.10) *Mean duration of healing time:* Group A = 6.7 ± 3.4 weeks (range 2-17); [P = 0.8745] Group B = 6.5 ± 4.4 weeks (range 2-14) *Treatment complications:* Group A = 5/20 Group B = 4/20 RR = 1.25 (95%CI: 0.39 to 3.99) *Patients' levels of satisfaction with the treatment (with VAS):* Group A = 8.45 ± 1.79 Group B = 6.85 ± 2.39 (P < 0.05)
Additional comments: Computer-generated randomization list, with ITT. No blinding, no allocation concealment.					

Reference: Piaggesi, A, Macchiarini, S, Rizzo, L, Palumbo, F, Tedeschi, A, Nobili, LA, Leporati, E, Scire, V, Teobaldi, I, Del, PS An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast. *Diabetes Care* 2007; **30:** 586-90.

Dressings

Title: Sodium carboxyl-methyl-cellulose dressings in the management of deep ulcerations of diabetic foot.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 8497 Level of evidence: () Study type: RCT Authors: Piagessi et al. (2001)	Total no. of patients: Baseline = 24 2-refused to give consent 1-considered unreliable 1-had neuroarthropathy 20-enrolled People underwent a brief medical history and thorough local examination. The people with purely neuropathic lesions also underwent an aggressive surgical debridement with elimination of all non-viable tissue, before being included in the study. Baseline characteristics: There was no significant difference in distribution of subject characteristics between the two groups (P= 0.05). Setting: Foot clinic	Inclusion: Age 18-75 years, type 1 or type 2 diabetes for over **5** years, foot ulcerations for more than 3 weeks, > **1** cm wide and! cm deep, good peripheral blood supply, with palpable peripheral pulses or an ankle-brachial pressure index (ABPI) > 0.9 Exclusion: Active infection, recent episodes of ketoacidosis, malignancies, any chronic pathology or systemic therapy which could obstruct the healing process were other exclusion criteria. Candidates for a major amputation were also excluded.	Group B (n=10)- Dressed with Carboxyl-methyl-cellulose dressing (Aquacel™; ConvaTec, UK)	Group A (n= 10)- Dressed with saline-moistened gauze	Weekly until 8 weeks, then until complete re-epithelisation.	**8 Weeks** **Table 1: Outcomes at week 8 of therapy (median[inter quartile range])** Variable | Group A | Group B | **R V (%)** | **5(15)** | **50 (26)** | **< 0.01** **GT (%)** | **32.5 (10)** | 60 **(40)** | **< 0.01** **RLV-Reduction of lesional volume; GT-granulation tissue** At the 8-week control visit all the variables chosen to monitor the development of the lesion healing process scored better in Group B patients than in Group A. **Aquacel vs. Saline moistened gauze (RLV)** | | RLV achieved | No RLV achieved | Total | | Aquacel | 3 | 7 | 10 | | Saline moistened gauze | 2 | 8 | 10 | | Total | 5 | 15 | 20 | RR= 0.3/0.2 = 1.5 **Aquacel vs. Saline moistened gauze (GT)** | | GT achieved | No GT achieved | Total | | Aquacel | 4 | 6 | 10 | | Saline moistened | 1 | 9 | 10 |

gauze			
Total	5	15	20

RR= 0.4/0.1 = 4

ILTC (intralesional temperature) was significantly higher in Group B than in Group A patients (34.76 ± 2.06 vs. 30.65 ± 1.36"C; P<0.01) and

ΔTC (difference in intralesional and perilesional temperature) was positive in Group B and negative in Group A patients (2.02 ± 1.67 vs.-2.71 ± 1.24; P < 0.01).

Adverse Events

Adverse events observed during treatment, apart from infections, which were considered as complications, included maceration of perilesional skin which was observed in 2 Group A and 1 Group B patients.

All the cases of infective complications (3/10 in Group A and 1/10 in Group B; P - 0.582) were confined to the area of the lesion.

Aquacel vs. Saline moistened gauze

	Adverse events	No adverse events	Total
Aquacel	1	9	10
Saline moistened gauze	3	10	10
Total	4	19	20

RR= 0.1/0.3 = 0.33

Healing Time:

						All patients in both groups healed during the observational period apart from one in Group A who underwent trans-metatarsal amputation due to infection. Healing time of patients in Group B was shorter than that observed in Group A (127 ± 46 vs. 234 ± 61 days; p < 0.001)
Additional comments: People were randomized. No intention to treat analysis mentioned. Power calculation not mentioned. Concealment and confounding not mentioned.						

Reference: Piaggesi, A, Baccetti, F, Rizzo, L, Romanelli, M, Navalesi, R, Benzi, L Sodium carboxyl-methyl-cellulose dressings in the management of deep ulcerations of diabetic foot. *Diabetic Medicine* 2001; **18:** 320-324.

Title: A RCT of promogran (collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic food ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/ Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 11260 Study type: RCT Authors: Veves et al. (2002)	Total no. of patients = 276 Promogan group = 138 Moistened gauze (control) = 138 <u>Promogan group:</u> Age, mean (range) = 58 (23-85) Male/female = 95/43 HbA_{tc} (range) (%) = 8.6 (5.3-14.0) Mean wound area (range) (cm^2) = 2.5 (0.2-27.4) Median wound duration (range) (mth) = 3 (1-84) <u>Control group:</u> Age, mean (range) = 59 (37-83) Male/female = 108/30 HbA_{tc} (range) (%) = 8.5 (4.9-13.1) Mean wound area (range) (cm^2) = 3.1 (0.1-42.4) Median wound duration (range) (mth) = 3 (1-144) <u>Setting:</u> US university teaching hospitals and primary care centres (11 centres in total)	Inclusion criteria: 18 years or older with a diabetic foot ulcer of at least 30 days duration; Wagner grade 1 to 2; an area of at least 1 cm^2; had adequate circulation with an oscillometer reading of the limb that had the target wound of at least 1 U; a wound that was debrided of necrotic/nonviable tissue at enrolment. Exclusion criteria: Clinical signs of infection; a target wound that had exposed bone; a concurrent illness or a condition that may have interfered with wound healing (eg, carcinoma, vasculitis, connective tissue disease, or an immune system disorder); known current abuse of alcohol or other drugs or treatment with dialysis, corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy at a dose that might have interfered with wound healing within the last 30 days before study enrolment; known hypersensitivity to any of the dressing components; unwillingness or inability or an ambulatory patient to be fitted with appropriate shoe gear or an off-loading device; and multiple diabetic ulcers on the same foot.	Promogan vs. moistened gauze (control) *[both with tape as the secondary dressing]* Surgical debridement of healthy tissue was per-formed in the studied ulcer during the initial and all follow-up visits when necessary. The debridement technique was standardized during an initial meeting of the investigators, at which all investigators were instructed to debride the wound until healthy granulating tissue or healthy bleeding tissue was reached. Frequency of changing the dressings differed between the 2 groups.	12 weeks or sooner if the patient discontinued the study or the wound healed. Follow-up evaluations were completed on a weekly basis.	Only 188 patients completed the study (104 in the Promogran group and 84 in the control group). <u>Wound completely healed (at 12 weeks or shorter):</u> Promogan group = 51/104 Moistened gauze (control) = 39/84 RR = 1.06 (95%CI: 0.78 to 1.43) <u>Mean percentage of wound size reduction (12 weeks):</u> Promogran group = 64.5% Control group = 63.8% <u>Mean time to healing (SD):</u> Promogran = 7.0±0.4 weeks Control = 5.8±0.4 weeks. <u>Nonserious adverse events:</u> Promogran = 37/104 (26.8%) Control = 34/84 (24.6%) RR = 0.88 (95%CI: 0.61 to 1.26) <u>Serious adverse events:</u> Promogran = 25/104 (18.1%) Control = 35/84 (25.4%) RR = 0.58 (95%CI: 0.38 to 0.88) *None of these events were described as related to the study dressings.*

<u>Additional comments:</u>
A stratified randomization was used in assigning treatments to patients on the basis of their wound area. Eligible patients were stratified in 2 groups, ie, patients with a wound area of less than or of at least 10 cm^2.
The same technique of off-loading was performed in each centre for both the controls and the Promogran-treated patients. However, the choice of the off-loading technique was left to

the individual investigator. No ITT.

Reference: Veves, A, Sheehan, P, Pham, HT A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Archives of Surgery* 2002; **137:** 822-27.

Title: Prospective randomised controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/ Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 5340 Study type: open-label-RCT Authors: Jude et al. (2007)	Stratification: 21 systemic antibiotics 113 no systemic antibiotics. AQAg = 67; CA = 67 AQAg group: Male/female = 46/21 Mean age (SD) = 58.9 (12.6) On antibiotics = 13 Ulcer duration (years) (SD) = 1.2 (2.1) Ulcer depth (cm) = 0.40 (0.45) Ulcer baseline area (cm^2) = 3.1 (4.1) AQAg group: Male/female = 53/14 Mean age (SD) = 61.1 (11.4) On antibiotics = 8 Ulcer duration (years) (SD) = 1.4 (2.6) Ulcer depth (cm) = 0.40 (0.39) Ulcer baseline area (cm^2) = 4.2 (7.8) Study period: Between December 2002 and February 2004 Setting: 18 European centres: 8 in the UK, 5 in France, 4 in Germany and 1 in Sweden.	Inclusion criteria: Adults with Type 1 or 2 DM, with HbA1c < 12.0%, serum creatinine < 200 umol/l and with Wagner Grade 1 or 2 DFUs of non-ischaemic aetiology (neuropathic or neuro-ischaemic ulcers, none solely ischacmic) were included in the study. Adults with diabetic foot infections were not excluded. Exclusion criteria: Patients were excluded from participation if allergic to a component of the dressings studied; known or suspected malignancy local to the study ulcer; had been on systemic antibiotics > 7 days prior to enrolment; had inadequate arterial perfusion, as defined by the ankle-to-brachial index < 0.8; great toe systolic blood pressure < 40 mmHg or forefoot TcP02 < 30 mmHg (subject supine) or <40 mmHg (subject sitting). When TcP02 was measured the electrode temperature was set at 44^oC. All wounds were > 1 cm^2 in area, stratified according to current use or non-use of systemic antibiotics for that ulcer on enrolment in the study.	Hydrofiber (ionic silver dressing) [AQAg] vs. calcium alginate dressing [CA] Standardized surgical debridement was performed at all centres at baseline prior to stratification and at subsequent dressing changes to remove callus and ensure that there was no more than 5% slough or eschar on the ulcer. Each primary dressing was covered with a sterile, non-adherent foam dressing. Accommodative footwear for non-plantar ulcers and off-loading for plantar ulcers were provided as required for individual subjects; the products used	8 weeks (evaluation every 7 days).	Wound completely healed at 8 weeks: AQAg = 21/67; CA = 15/67 RR = 1.40 (95%CI: 0.79 to 2.47) Discontinued due to adverse events: AQAg = 8/67; CA = 13/67 RR = 0.61 (95%CI: 0.27 to 1.39) Adverse events (complications): AQAg = 23/67; CA = 26/67 RR = (95%CI: Study-related adverse events: AQAg = 11/67; CA = 9/67 RR = 1.22 (95%CI: 0.54 to 2.76) Mean time in days to 100% healing: AQAg = 52.6 (1.8); CA = 57.7 (1.7), p = 0.340 8-week % reduction in ulcer area: AQAg = 58.1 (53.1); CA = 60.5 (42.7), p = 0.948 Ulcer depth reduction during 8-week: AQAg = 0.25 ±0.49 cm CA = 0.13 ±0.37 cm, p = 0.04

			were not specified		

Additional comments:
Patients stratified by antibiotic use on enrolment were randomly assigned to similar protocols including off-loading and secondary foam dressings for 8 weeks or until healing. Eligible individuals were randomly assigned to receive either AQAg or CA dressings according to instructions in a sealed envelope and stratified according to whether or not systemic antibiotics were being administered for treatment of the study ulcer.
ITT was conducted.

Reference: Jude, EB, Apelqvist, J, Spraul, M, Martini, J, Silver Dressing Study Group Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. *Diabetic Medicine* 2007; **24:** 280-288.

Title: Comparing two dressings in the treatment of diabetic foot ulcers.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 3544 Level of evidence: () Study type: RCT Authors: Foster et al. (1994)	Total no. of patients: Baseline = 58 Category A-29 with 39 ulcers Category B-29 3 lost to follow up 26 left with 33 foot ulcers Patients were prescribed appropriate antibiotics and debridement offered. Baseline characteristics: There was no significant difference in distribution of subject characteristics between the two groups Setting: Not mentioned	Inclusion: Aged at least 18 years, had a clean diabetic foot ulcer and were willing and able to comply with the study protocol. Exclusion: If the ulcer was sloughy, necrotic, or infected.	Polyurethane foam dressing (n-15)	Alginate dressing (n-15)	Weekly until ulcer was fully healed or 8 weeks.	**Healing** Polyurethane group-9/15 Alginate group- 8/15 **Relative risk- 9/15 ÷ 8/15 = 1.12** **Time to healing** No statistically significant difference between treatments was found with respect to time to healing. **Number of patients withdrawn from study** Polyurethane group-0/15 Alginate group- 4/15

Additional comments:
People were randomized. Blinding not performed. No intention to treat analysis mentioned. Power calculation not mentioned. Concealment and confounding not mentioned.

Reference: Foster, AVM, Greenhill, MT, Edmonds, ME Comparing two dressings in the treatment of diabetic foot ulcers. *Journal of Wound Care* 1994; **3:** 224-28.

Title: Comparing two dressings in the treatment of diabetic foot ulcers.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 9940 Level of evidence: () Study type: RCT Authors: Shukrimi et al. (2008)	Total no. of patients: Baseline = 30 All patients received appropriate antibiotics and the ulcers were debrided surgically. Baseline characteristics: There was no significant difference in distribution of subject characteristics between the two groups Setting: Hospital University Sains Malaysia	Inclusion: All non insulin dependent diabetes mellitus patients with Wagner grade II ulcers. Aged 35-65, transcutaneous oxygen tension of more than 30mmHg and serum albumin level of more than 35g/dl. Exclusion: Multiple medical co-morbidity, steroid therapy, neutrophil count <2000/mm^3	Honey dressing	Standard dressing which included cleansing with normal saline and covering with povidone-soaked gauze.	Daily until wound was either ready for surgical closure or needed further debridement.	**Time for wound to be ready for surgical closure (mean)** Honey dressing- 14.4 days (7 to 26) Standard dressing- 15.4 days (9-36) The difference in the duration was not statistically significant. **Adverse events** All patients in the honey group experienced less pain during dressing.
Additional comments: People were randomized. Blinding performed. No intention to treat analysis mentioned. Power calculation not mentioned. Concealment and confounding not mentioned.						

Reference: Shukrimi, A, Sulaiman, AR, Halim, AY, Azril, A. A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. *Medical Journal of Malaysia* 2008; **63:** 44-46.

Title: Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome and Results
ID: 5177 Level of evidence: () Study type: RCT	Total no. of patients: Baseline = 317 patients 88 withdrawals 229 evaluable patients N-A-106 Inadine-108 Aquacel-103	Inclusion: • Type 1 or 2 diabetes. • 18 years of age or more. • A foot ulcer which had been present for at least 6 weeks and had a cross-sectional area of between 25 and 2500 mm^2. • Able and willing to give informed	N-A (non adherent, knitted, viscose filament gauze product) vs. Inadine (iodine impregnated dressing) vs. Aquacel (newer hydrocolloid product) All patients received standard care which	2 weekly for 24 weeks	**Incidence of Healing** **Table 1: incidence of healing at 12 weeks analysed on the basis of ITT** Ongoing/with drawn (%) / Healed (%) / Total Inadine: 76 (70.4) / 32 (29.6) / 108 N-A: 79 (74.5) / 27 (25.5) / 106 Aquacel: 74 (71.8) / 29 (28.2) / 103

Authors: Jeffcoate et al. (2009)	Baseline characteristics: The distribution of baseline demographics between the groups was very similar by intervention. There was no statistical difference between the groups in terms of distribution by ulcer size at baseline, Setting: Multidisciplinary clinics across the UK.	consent. • Reasonably accessible by car to the hospital base. • Under routine review by the multidisciplinary clinic. Exclusion: • Those with a known allergy to any of the trial preparations (including iodine). • Any ulcer on either foot extending to tendon, periosteum or bone. • Infection of bone. • Soft tissue infection requiring treatment with systemic antibiotics. • An ulcer on a limb being considered for revascularisation. • Those chosen for management with a non-removable cast without a dressing window. • Gangrene on the affected foot. • Eschar which was not removable by clinical debridement. Those with evidence of a sinus or deep track. • Those in whom the hallux had been amputated on the affected side (preventing the measurement of toe pressure). • Those with an ankle:brachial pressure index (ABPI) of less than 0.7 or toe systolic pressure less than 30 mmHg. • Ulceration judged to be caused primarily by disease other than diabetes. • Patients with any other serious disease likely to compromise the outcome of the trial. • Patients with critical renal	included appropriate debridement and off-loading as and when necessary		

Total	229	88	317

The incidences of healing by 12 weeks for the three dressings were Inadine 29.6%, Aquacel 28.2% and N-A 25.5%. The differences between groups were not statistically significant.
Relative risk (Inadine vs. N-A)- 1.16 (0.75-1.80)
Relative risk (Inadine vs. Aquacel)- 1.05 (0.69-1.61)
Relative risk (Aquacel vs. N-A)- 1.11 (0.71-1.73)

Table 2: Incidence of healing: Week 12 (Per protocol basis)

	Ongoing/with drawn (%)	Healed (%)	Total
Inadine	64 (66.7)	32 (33.3)	96
N-A	53 (66.3)	27 (33.7)	80
Aquacel	52 (64.2)	29 (35.8)	81
Total	169	88	257

Per protocol basis- including only those participants who remained in the study until week 12 (and withdrawals being excluded).

The data suggest an overall healing rate of approximately 34% with no statistical difference between the groups.
Relative risk (Inadine vs. N-A)- 0.99 (0.65-1.50)
Relative risk (Inadine vs. Aquacel)- 0.93 (0.62-1.61)
Relative risk (Aquacel vs. N-A)- 1.06 (0.69-1.62)

Table 3: Incidence of healing: Week 24 (ITT)

	Ongoing/with drawn (%)	Healed (%)	Total
Inadine	60 (55.6)	48 (44.4)	108
N-A	65 (61.3)	41 (38.7)	106
Aquacel	57 (55.3)	46 (44.7)	103
Total	182	135	317

The overall healing rates for the three dressings were: Inadine 44%, Aquacel 45% and N-A 39%. These differences were not statistically significant.
Relative risk (Inadine vs. N-A)- 1.15 (0.84-1.58)
Relative risk (Inadine vs. Aquacel)- 1.00 (0.74-1.34)
Relative risk (Aquacel vs. N-A)- 1.15 (0.84-1.59)

disease (creatinine greater than 300 mmol/l), and those receiving immunosuppressants, systemic corticosteroid therapy (other than by inhalation) or any other preparation which could, in the opinion of the supervising clinician, have interfered with wound healing.
• Those living at such a distance (generally further than 10 miles) from the clinic as would have made frequent assessment visits inappropriately expensive and/or impractical.
• Those who withheld consent.

Table 4: withdrawal from study by dressing group at week 24

	Frequency	Percentage
Inadine	21	19.4
N-A	30	29.1
Aquacel	37	34.9
Total	88	100

However, there was a trend in the data whereby N-A had the poorest healing and the highest withdrawal rate, and the withdrawal rates were statistically significant at week 24: Inadine 19%, Aquacel 29%, N-A 35% (p = 0.038
Relative risk (Inadine vs. N-A)- 0.69 (0.42-1.12)
Relative risk (Inadine vs. Aquacel)- 0.54 (0.34-0.86)
Relative risk (Aquacel vs. N-A)- 1.27 (0.85-1.89)

Table 5: Incidence of healing: Week 24 (Per protocol basis)

	Ongoing/with drawn (%)	Healed (%)	Total
Inadine	39 (44.8)	48 (55.2)	87
N-A	28 (40.6)	41 (59.4)	69
Aquacel	27 (37)	46 (63)	73
Total	94	135	229

Per protocol analysis at week 24 suggested an overall healing rate approaching 60% with no statistical difference between the groups.
Relative risk (Inadine vs. N-A)- 0.93 (0.71-1.22)
Relative risk (Inadine vs. Aquacel)- 0.88 (0.68-1.13)
Relative risk (Aquacel vs. N-A)- 1.06 (0.82-1.38)

Time to healing

Table 6: Time to Healing in days by week 12 (ITT)

	Mean	SD	95% CI
Inadine (n-108)	74.1	20.6	70.2-78.1
N-A (n-103)	72.4	20.6	68.4-76.5
Aquacel	75.1	18.1	71.6-78.6

(n-106)					

There were no significant differences (p-0.61) between groups in time to healing using ITT

Table 7: Time to Healing in days by week 12 (Per protocol basis)

	Mean	SD	95% CI
Inadine (n-96)	72.9	21.6	68.5-77.3
N-A (n-81)	69.3	22.3	64.4-74.3
Aquacel (n-80)	72.3	20.1	67.8-76.8

There remained no statistically significant differences (p-0.5) between the groups when the analysis was repeated on a per protocol basis

Table 8: Time to Healing in days by week 24 (ITT)

	Mean	SD	95% CI
Inadine (n-108)	127.8	54.2	117.5-138.2
N-A (n-103)	125.8	55.9	114.9-136.7
Aquacel (n-106)	130.7	52.4	120.6-140.8

There are no significant differences in time to healing using ITT. The calculated mean time to healing for all 317 participants using these criteria was 129 days.

Table 9: Time to Healing in days by week 24 (Per protocol basis)

	Mean	SD	95% CI
Inadine (n-87)	118.1	56.3	106.1-130.1
N-A (n-73)	108.5	58.2	94.9-122.1
Aquacel (n-69)	110.7	55.6	97.4-124.1

When the analysis was repeated on a per protocol basis, the descriptive statistics changed but there were still no statistically significant differences between the groups.

Recurrence of Ulcers

Table 10: Recurrence of ulceration at the same site within 3-month follow-up for those whose index ulcer healed during the intervention phase

	Inadine	Aquacel	N-A	Total
Ulcer remained healed	32	35	37	104
Ulcer recurred at same site	7	3	3	13
Total	39	38	40	117

Of the 135 patients who healed during the intervention phase, only 117 provided information on the clinical status of the ulcer during the 3-month follow-up review.

Twelve of those patients for whom data are available (10%) had a recurrence during the 3-month review, but the difference between groups was not statistically significant.

Relative risk (Inadine vs. N-A)- 2.39 (0.67-8.60)
Relative risk (Inadine vs. Aquacel)- 2.27 (0.63-8.15)
Relative risk (Aquacel vs. N-A)- 1.05 (0.23-4.90)

Episodes of secondary infection

Table 11: Number of cases of infection reported as serious adverse event (SAE)

	Inadine	Aquacel	N-A
Number of episodes of infection as SAEs	10	7	7

Number of episodes of infection listed as SAE but unrelated to the index ulcer.	2	2	0
Total	12	9	7

Twenty-eight such episodes were registered as SAEs but there was no significant difference in incidence of SAEs between dressing
Groups.

Major and Minor amputation

Table 12: list of amputations according to dressing allocation

	Inadine	Aquacel	N-A
Minor amputation	1	3	1
Major amputation	0	1	1
Total	1	4	2

RR for both major and minor amputation:

Relative risk (Inadine vs. N-A)- 0.49 (0.05-5.33)
Relative risk (Inadine vs. Aquacel)- 0.24 (0.03-2.10)
Relative risk (Aquacel vs. N-A)- 2.06 (0.39-11)

Adverse events and Withdrawals

Serious adverse events

Table 13: Total No. of SAEs by dressing allocation.

Dressing	No. of SAEs
Inadine	37
N-A	35
Aquacel	28
Total	100

Only 11 of the 100 SAEs recorded were considered to be 'slightly or possibly' related to the dressing; these events were spread evenly across the intervention groups.
Relative risk (Inadine vs. N-A)- 1.04 (0.71-1.51)
Relative risk (Inadine vs. Aquacel)- 1.26 (0.84-1.90)
Relative risk (Aquacel vs. N-A)- 0.82 (0.54-1.25)

Withdrawals

Table 14: Withdrawal from study by dressing group at week 24

	Frequency	Percentage
Inadine	21	19.4
N-A	30	29.1
Aquacel	37	34.9
Total	88	100

There were a total of 88 withdrawals (21 for those using Inadine, 30 for Aquacel and 37 for N-A).The difference between groups was significant (p-0.038)
Relative risk (Inadine vs. N-A)- 0.69 (0.42-1.12)
Relative risk (Inadine vs. Aquacel)- 0.54 (0.34-0.86)
Relative risk (Aquacel vs. N-A)- 1.27 (0.85-1.89)

Additional comments:
People were randomized. Observer Blinding performed. Intention to treat analysis performed. Power calculation. Concealment and confounding not mentioned.

Reference: Jeffcoate, WJ, Price, PE, Phillips, CJ, Game, FL, Mudge, E, Davies, S, Amery, CM, Edmonds, ME, Gibby, OM, Johnson, AB, Jones, GR, Masson, E, Patmore, JE, Price, D, Rayman, G, Harding, KG Randomised controlled trial of the use of the three dressing preparations in the management of chronic ulceration of the foot in diabetes. *Health Technology Assessment* 2009; **13(54):** 1-110.

Review question 4: What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)?

<table>
<tr><th colspan="7">Title: Antibiotic Therapy for Diabetic Foot Infections: Comparison of Two Parenteral-to-Oral Regimens.</th></tr>
<tr><th>Level of Evidence</th><th>Patient Population/ Characteristics</th><th>Selection/Inclusion criteria</th><th>Intervention</th><th>Comparison</th><th>Follow-up</th><th>Outcome and Results</th></tr>
<tr>
<td>ID: 6489

Level of evidence: ()

Study type: RCT

Authors: Lipsky et al. (1997)</td>
<td><u>Total no. of patients:</u>
Baseline = 108
Ofloxacin regimen-55
8 excluded
Final number-47
Aminopenicillin regimen-53
12 excluded
Final number- 41

Any patient for whom culture of the admission specimen was sterile or yielded pathogens that were resistant to the study drugs or who developed osteomyelitis (as diagnosed by the investigator) during treatment with the study drugs was withdrawn from the study.

The total duration of therapy was to be 14 to 28 days, as clinically indicated.

<u>Baseline characteristics:</u>

There were no statistically significant differences in the demographic characteristics of the patients randomized to receive the two therapeutic arms.

The severity of infections was, on average, nearly identical in the two treatment groups.</td>
<td><u>Inclusion:</u>
Patients who had diabetes mellitus and a foot infection that required antibiotic therapy, as evidenced by purulent drainage, erythema, and swelling, and who were 18 years of age or older.

<u>Exclusion:</u>

Patients who had evidence of osteomyelitis, usually suspected because of clinical, laboratory, and plain radiograph findings, or who had an infection known to be caused by a microorganism resistant to any of the study drugs, were allergic to any of the study drugs or related compounds, were grossly underweight, had a seizure or major psychiatric disorder, were pregnant or nursing, were undergoing renal dialysis, or were likely to die during the study. Patients who had received potentially effective antimicrobial therapy within 48 hours before presentation. Those patients who required a second systemic antimicrobial for any reason</td>
<td>Ofloxacin—400 mg of ofloxacin intravenously that was changed when appropriate to 400 mg of ofloxacin orally every 12 hours.

Metronidazole was added if patient not improving(for improved coverage of anaerobic bacteria) to the ofloxacin regi-men.</td>
<td>Aminopenicillin — 1-2 g of ampicillin/0.5-1 g of sulbactam intravenously every 6 hours that was changed when appropriate to 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 hours.

Gentamicin, trimethoprimsulfamethoxazole, or another agent (for broader coverage of gram-negative bacilli) to the aminopenicillin regimen.</td>
<td>Third to seventh day or until therapy was completed</td>
<td>Therapy resulted in a cure or in improved conditions for 85% of the evaluable ofloxacin recipients and for 83% of the evaluable aminopenicillin recipients.

<table>
<tr><th></th><th>Cured or improved condition</th><th>Failed</th><th>Total</th></tr>
<tr><td>Ofloxacin</td><td>40</td><td>7</td><td>47</td></tr>
<tr><td>Aminopenicillin</td><td>34</td><td>7</td><td>41</td></tr>
<tr><td>Total</td><td>74</td><td>14</td><td>88</td></tr>
</table>
Cured- disappearance of all signs and symptoms associated with active infection
Improved- incomplete abatement of the signs or symptoms
Failed- no improvement during therapy

Relative Risk- 40/47 ÷ 34/41 = 1.02

The mean number of pathogens isolated from cultures of wound specimens taken at the time of enrolment of the evaluable patients was 1.6 (range, 0-7).

Cultures of specimens obtained while the patients were receiving therapy yielded an average of 0.2 isolate.

While those of specimens taken after completion of therapy yielded a mean of 0.1 isolate.

Microbiological outcomes:</td>
</tr>
</table>

	Setting: 12 centres across United States	other than as defined below or who were receiving a topical antimicrobial at .the site of infection				

	Cured or partially cured	Failed	To tal
Ofloxacin	39	8	47
Aminope nicillin	36	5	41
Total	75	13	88

Cured- eradication of the original pathogen(s)
Partially cured- eradication of some but not all of the original pathogens
Failed- persistence of the original pathogen(s).

Relative Risk- 39/47 ÷ 36/41 = 0.94

Eradication of Gram Positive)67%) and Negative (27%) organisms

Ofloxacin	Aminpenicillin	
33/47	38/43	Positive
18/19	15/18	Negative

Adverse events

Potential side effects were experienced by 36% of the ofloxacin recipients and 22% of the aminopenicillin recipients (not a statistically significant difference).

	Adverse event	No adverse event	Tota l
Ofloxacin	17	30	47
Aminope nicillin	9	32	41
Total	26	62	88

Relative Risk- 17/47 ÷ 9/41 = 1.65

Additional comments:
Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.

Reference: Lipsky, BA, Baker, PD, Landon, GC, Fernau, R Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. *Clinical Infectious Diseases* 1997; **24:** 643-48.

Title: Use of Ampicillin/Sulbactam Versus Imipencm/Cilastatin in the Treatment of Limb-Threatening Foot Infections in Diabetic Patient.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 4151 Level of evidence: () Study type: RCT Authors: Grayson et al. (1994)	<u>Total no. of patients:</u> Baseline = 92 No. of events-97 1 excluded (exacerbation of gout) Final no. of events: 96 I/C- 48 infections in 46 patients A/S- 48 infections in 47 patients. Patients' therapy was routine and consisted of bed rest, surgical drainage and debridement of infected ulcers and necrotic tissue, vigorous control of diabetes mellitus, and use of sterile wound dressings (gauze soaked with normal saline or one-quarter-strength povidone-iodine). When appropriate, arterial circulation of the lower limb was evaluated by non-invasive and arteriographic techniques. Surgery to improve the arterial circulation or amputation of unsalvageable tissues was performed at the discretion of the attending surgeon. <u>Baseline characteristics:</u> **I/C** Mean age: 61 years Duration of diabetes: 19 years	<u>Inclusion:</u> Requirement for hospitalization, age of ≥18 years, and presence of diabetes mellitus and limb-threatening infection involving the lower extremity (limb-threatening infection was defined by at least the presence of cellulitis, with or without ulceration or purulent discharge). Also included were patients who had recently received antibiotic therapy but had failed to demonstrate clinical improvement and whose cultures revealed one or more pathogens were eligible <u>Exclusion:</u> Known hypersensitivity to β-lactam antibiotics; requirement for other concomitant antibiotic treatment; serum creatinine level of ≥3.5 mg/dL; preg-nancy; illness so severe that the patient was likely to die within 48 hours; severe underlying disease that might interfere with evaluation of the therapeutic response; immune depression by virtue of	Imipenem/ cilastatin (I/C; 500 mg-IV every 6 hours) Doses were adjusted in patients with impaired renal function. 45 infections completed 20-dose regimen 2 infections-inadvertently received only 19 doses of study drug-both were clinically cured 1 infection-marked nausea and given	Ampicillin/sulbactam (A/S; 3 g-IV every 6 hours) Doses were adjusted in patients with impaired renal function. 45 infections completed 20-dose regimen 2 infections-added another antibiotic 1 infection-discharged after 4 days of therapy	Daily for first 6 days and then regularly until therapy was completed.	**Table 1: Clinical and microbiological outcomes of antibiotic therapy, as assessed on day 5 of empirical therapy and at the conclusion of parenteral therapy.** No. of episodes per group in which indicated outcome was noted I/C (48 episodes) — A/S (48 episodes) **Clinical** Cure: 28 / 39 / 29 / 41 Improvement: 17 / 0 / 18 / 0 Failure: 3 / 3 / 1 / 6 Indeterminate: 0 / 1 / 0 / 1 **Microbiological** Eradication: 17 / 32 / 20 / 36 Partial eradication: 18 / 3 / 15 / 5 Persistence: 7 / 2 / 6 / 3 Superinfection: 0 / 2 / 0 / 3 Indeterminate: 6 / 4 / 7 / 1 Upon completion of definitive parenteral therapy, cure was achieved in 81% of episodes treated with A/S and

	A/S Mean Age: 59 years Duration of diabetes: 20 years The vast majority of patients had relatively acute infection or exacerbated chronic infection with prominent local signs of aggressive infection. Patients in the treatment groups were similar in regard to severity of diabetes and presence of peripheral vascular disease, sensory neuropathy, and renal impairment. The sites and severity of infection, including the frequency of osteomyelitis, were similar for both treatment groups. <u>Setting:</u> Not mentioned	underlying disease, prior organ transplantation, or immunosuppressive drug therapy; and current involvement in a clinical study of an investigational drug.	13 doses only.			85% of those treated with 1/C (difference in cure rates, 4%; *95%* confidence interval, -11 % to 19%). | | Cure | No cure | Total | | I/C | 41 | 7 | 48 | | A/S | 39 | 9 | 48 | | Total | 80 | 16 | 96 | **Relative Risk- 41/47 ÷ 39/41 = 1.07** **Microbiological outcomes:** | | Eradication | No eradication | Total | | I/C | 36 | 12 | 48 | | A/S | 32 | 16 | 48 | | Total | 68 | 28 | 96 | **Relative Risk- 36/47 ÷ 32/41 = 0.98** **Eradication of Gram Positive and Negative organisms** | Imipenem/cilastatin | Ampicillin/sulbactam | | | 14/47 | 21/45 | Gram positive alone | | 0/47 | 0/45 | Gram negative alone | **Osteomyelitis:** Underlying osteomyelitis was associated with 11 of the 14 failures (six infections treated with A/S and five with I/C). However, among all patients, osteomyelitis was not associated with failure to eliminate soft-tissue infection; at the end of therapy, treatment failure was noted in 11 (19%) of the 59 infections in patients with osteomyelitis and three (8%) of the 37 infections in patients without

osteomyelitis (p= 0.26).

Recurrence of infection after average 1 year follow up:

Recurrence of infection at the original site was noted in 9 of 39 assessable patients treated with A/S and 8 of 41 assessable patients who received I/C.

Adverse events:

	No. (%) of patients with adverse reactions	
Adverse reactions	I/C (48 episodes)	A/S (48 episodes)
Significant	7 (15)	9 (19)
Moderate/possible	8 (17)	6 (13)
Mild/unlikely	1 (2)	2 (4)
Total	16	16

Significant- a severe reaction necessitating withdrawal of the study agent or specific treatment
Moderate- a reaction that did not necessitate withdrawal of the study agent or specific treatment
Mild- an event uncertainly associated with the study drug
The total incidence of adverse reactions was similar in both treatment groups

Additional comments:
Because pathogen identification and antimicrobial susceptibility testing is frequently not complete for 5 days in cases of polymicrobial infection, the initial 5 days or 120 hours of study therapy were considered to be the period of empirical therapy. A clinical and microbiological assessment was made at the end of empirical therapy. A final assessment of treatment outcome was made at the end of iv antimicrobial therapy.
Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.

Reference: Grayson, ML, Gibbons, GW, Habershaw, GM, Freeman, DV, Pomposelli, FB, Rosenblum, BI, Levin, E, Karchmer, AW Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients.[Erratum appears in Clin Infect Dis 1994 Oct;19(4):820]. *Clinical Infectious Diseases* 1994; **18:** 683-93.

<table>
<tr><th colspan="7">Title: Prospective, Randomized Comparison of Ampicillin/Sulbactam and Cefoxitin for Diabetic Foot Infections.</th></tr>
<tr><th>Level of Evidence</th><th>Patient Population/ Characteristics</th><th>Selection/Inclusion criteria</th><th>Intervention</th><th>Comparison</th><th>Follow-up</th><th>Outcome and Results</th></tr>
<tr>
<td>ID: 3174

Level of evidence: ()

Study type: RCT

Authors: Erstad et al. (1997)</td>
<td><u>Total no. of patients:</u>
Baseline = 36
Cefoxitin- 18
Ampicillin/sulbactam- 18

No other antimicrobials were administered during hospitalization, unless a patient failed to respond to the study antimicrobial therapy within forty-eight hours, in which case the patient was withdrawn from the investigation.

<u>Baseline characteristics:</u>

There were no significant differences in the baseline characteristics of the patients in the two groups on study entry

<u>Setting:</u>
University medical centre- Southern Arizona</td>
<td><u>Inclusion:</u>
At least Grade 1 foot infection and had not received successful antimicrobial therapy within the previous four-day period, as noted by clinical improvement.

<u>Exclusion:</u>

Known hypersensitivity to penicillins or cephalosporins, a calculated creatinine clearance less than 15 mL/minute, a recent history of drug or alcohol abuse, or a concomi-tant infection at a site other than the foot that required additional antimicrobials. Patients were also excluded if they were terminally ill, neu-tropenic (neutrophil count <1500/m^3), pregnant, or breastfeeding.</td>
<td>Cefoxitin-2 g every six hours

Therapy was given for at least 5 days but maximum duration was left to discretion of attending surgeon.</td>
<td>Ampicillin/sulbac tam — 3 g every six hours

Therapy was given for at least 5 days but maximum duration was left to discretion of attending surgeon.</td>
<td>Daily until therapy was stopped</td>
<td>Table: Clinical outcomes

<table>
<tr><th></th><th>Cefoxitin</th><th>Ampicillin/sulbactam</th></tr>
<tr><td>Cured</td><td>7</td><td>1</td></tr>
<tr><td>Improvement</td><td>9</td><td>14</td></tr>
<tr><td>Treatment failures</td><td>2</td><td>3</td></tr>
<tr><td>Total</td><td>18</td><td>18</td></tr>
</table>
Cured- complete alleviation of signs and symptoms of infection
Improvement- partial alleviation of signs and symptoms of infection
Failure- no improvement

Relative Risk- 7/18 ÷ 1/18 = 7.05

There was a significant difference (P-0.03) between treatment groups with more patients in the cefoxitin group classified as cured.

However, there was no significant difference in treatment outcome between the ampicillin/sulbactam (15/17) and cefoxitin (16/17) groups when both cure and improvement were considered.

Relative Risk- 15/18 ÷ 16/18 = 0.94

Similarly, there was no significant difference between groups in the proportion of patients who had changes in clinical signs and symptoms from baseline (just prior to study medication administration) to the end of therapy.

Duration of Hospitalisation</td>
</tr>
</table>

						The mean (range) duration of hospitalization was 21.1 (6.0-58.0) days in the ampicillin/sulbactam group and 12.1 (4.0-39.0) days in the cefoxitin group. **Bacteriologic evaluation:** 6 patients in the ampicillin/sulbactam group and 11 patients in the cefoxitin group were evaluable for bacteriologic outcome (ie, these patients had culturable material from the infected site prior to initiating the study antimicrobial). Eradication of the causative organisms occurred in all patients in the ampicillin/sulbactam group 6/6 (100%) compared with 8/11 (73%) patients in the cefoxitin group. **Adverse events:** Most adverse events were of minor clinical importance, gastrointestinal disturbances being particularly common in both the ampicillin/sul-bactam and the cefoxitin groups (39% and 33% of patients, respectively). **Relative Risk- 6/18 ÷ 7/18 = 0.86**
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was not mentioned. All parameters were analysed as intention to treat. Ten patients in the ampicillin/sulbactam group and 7 patients in the cefoxitin group had failed outpatient antimicrobial therapy prior to hospital admission. Most of the patients in the former group had received ciprofloxacin (at least 6 patients), and patients in the latter group had received a variety of antimicrobial agents. Three patients did not complete the five-day course of antimicrobial therapy, although all were included in the intention-to-treat analysis.						

Reference: Erstad, BL, McIntyre, J Prospective, randomized comparison of ampicillin/sulbactam and cefoxitin for diabetic foot infections. *Vascular Surgery* 1997; **31:** 419-26.

<table>
<tr><td colspan="7">Title: An Open-Label, Randomized Study Comparing Efficacy and Safety of Intravenous Piperacillin/Tazobactam and Ampicillin/Sulbactam for Infected Diabetic Foot Ulcers.</td></tr>
<tr><td>Level of Evidence</td><td>Patient Population/ Characteristics</td><td>Selection/Inclusion criteria</td><td>Intervention</td><td>Comparison</td><td>Follow-up</td><td>Outcome and Results</td></tr>
<tr>
<td>ID: 4446

Level of evidence: ()

Study type: RCT

Authors: Harkless et al. (2005)</td>
<td><u>Total no. of patients:</u>
Baseline = 314
P/T- 155
Modified all-treated (MAT)- 139
A/S- 159
Modified all-treated - 150

MAT-population comprised of all patients who received at least one dose of study drug and did not have any osteomyelitis.

Standard wound care, including off-loading, sharp debridement of devitalized tissue, and moist dressings, were followed during the study, and the one-time use of a topical antiseptic was allowed after a surgical procedure or debridement.

<u>Baseline characteristics:</u>

Overall, patients' demographic characteristics, baseline diagnoses, wound classes and ulcer locations, and concomitant diseases were similarly distributed in the two treatment groups.

<u>Setting:</u>
Regional areas in United States</td>
<td><u>Inclusion:</u>
Adult patients with diabetes mellitus and open infected foot ulcers that met the University of Texas Grade IB, ID, IIB, or IID classification of foot ulcers , have at least one full- or partial-thickness infected ulcer at or below the ankle. Patients were also required to have purulent drainage or two of the following: Erythema, local edema, fluctuance, induration, increased local warmth, or fever.

<u>Exclusion:</u>

Pregnancy or lactation; anticipated amputation of the infected area within two months; conditions requiring concurrent topical antibiotics to the ulcer site or any other systemic antibacterials during the study period; creatinine clearance less than 40 mL/min; conditions requiring immunosuppressive drug treatments; gangrene or severely</td>
<td>I.V. piperacillin /tazobactam (P/T) (4 g/0.5 g q8h).

Doses adjusted in patients with renal function in both groups.</td>
<td>I.V. ampicillin/ sulbactam (A/S- 2 g/1 g q6h).

Patients with MRSA or methicillin-resistant Staphylococcus epidermidis (MRSE) present as part of a polymicrobial infection were also given vancomycin at 1 g ql2h</td>
<td>Day 4, day 7, at the end of treatment visit, and at the test-of-cure visit (occurred within 14-21 days of completion of therapy)</td>
<td>The rates of clinical success(defined as cure or improvement for the patient-level clinical response) in the MAT population between treatment groups were: 71.2% of the patients in the piperacillin/tazobactam group and 66.7% of the patients in the ampicillin/sulbactam group.

<table>
<tr><td></td><td>Clinical success</td><td>No clinical success</td><td>Total</td></tr>
<tr><td>P/T</td><td>99</td><td>40</td><td>139</td></tr>
<tr><td>A/S</td><td>100</td><td>50</td><td>150</td></tr>
<tr><td>Total</td><td>199</td><td>90</td><td>289</td></tr>
</table>
Relative Risk- 99/139 ÷ 100/150 = 1.07

There were no substantial differences in clinical success rates when results were compared by age, gender, race, or smoking status.

Eradication of Gram Positive and Negative organisms

<table>
<tr><td>P/T</td><td>Ampicillin/sulbactam</td><td></td></tr>
<tr><td>51/65</td><td>46/64</td><td>Gram positive</td></tr>
<tr><td>6/7</td><td>0/0</td><td>Gram negative</td></tr>
</table>
Adverse events:

<table>
<tr><td>Adverse event</td><td>P/T (n=155)</td><td>A/S (n=159)</td></tr>
<tr><td>With at least 1 adverse event</td><td>117</td><td>105</td></tr>
<tr><td>With at least 1 treatment related adverse event</td><td>29</td><td>21</td></tr>
</table>
</td>
</tr>
</table>

		impaired arterial supply to any portion of the affected foot; hypersensitivity to penicillins, /S-lactamase inhibitors, or vancomycin; presence of organisms known or suspected to be resistant to either study drug; renal insufficiency requiring renal replacement therapy; osteomyelitis; or thrombocytopenia. A patient could be withdrawn from the study for noncompli-ance, adverse events, investigator belief that withdrawal was in the best interest of the patient, patient choice, lack of efficacy, patient loss to follow-up, or death. Additionally, patients who had infections caused by organisms resistant to randomized treatment were withdrawn from the study.				<table><tr><td>With at least 1 serious adverse event</td><td>42</td><td>46</td></tr></table> **Relative Risk- 29/155 ÷ 21/159 = 1.41** The majority of adverse events were mild-to-moderate in severity, and the incidence and severity of all adverse events and treatment-related adverse events were comparable between the two groups.
Additional comments: Randomisation was performed. Open-labelled. Power calculation used. Allocation concealment not mentioned. Confounding mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Harkless, L, Boghossian, J, Pollak, R, Caputo, W, Dana, A, Gray, S, Wu, D An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. *Surgical Infections* 2005; **6:** 27-40.

<table>
<tr><td colspan="7">Title: Treatment of hospitalised patients with complicated skin and structure infections: double-blind, randomised, multicentre study of piperacillin-tazobactam versus ticarcillin-clavulanate</td></tr>
<tr><td>Level of Evidence</td><td>Patient Population/ Characteristics</td><td>Selection/Inclusion criteria</td><td>Intervention</td><td>Comparison</td><td>Follow-up</td><td>Outcome and Results</td></tr>
<tr><td>ID: 10637

Level of evidence: ()

Study type: RCT

Authors: Tan et al. (1993)</td><td><u>Total no. of patients:</u>

A patient was considered evaluable if each of the following criteria was met: a pretherapy pathogen susceptible to either study drug was present, susceptibility data for at least one pathogen were available, no other antibacterial agents were administered concomitantly during the study, there were at least 5 days of treatment with the study medication (to qualify for a favourable outcome), and the patient underwent at least one post-therapy follow-up (to qualify for a favourable outcome). For an unfavourable outcome, at least 3 days of therapy were required.

Surgical debridement or drainage was allowed and was accepted as an integral part of patient management.

<u>Baseline characteristics:</u>

The distribution of patients by race and sex was comparable between the two treatment arms and the mean ages among all treated patients were similar. Differences in the distributions of clinical diagnoses were not significant between the two treatment</td><td><u>Inclusion:</u>
Patients 16 years of age and older with complicated skin or skin structure infections like ischemic or diabetic foot infec-tions, present with purulent drainage or collection and at least three of the following: temperature greater than 38°C, peripheral leukocyte count greater than 10,000/mm^3 with greater than 5% immature neutrophils, local erythema, local swelling, tenderness, pain, or fluctuance.

<u>Exclusion:</u>

Known or suspected hypersensitivity to beta-lactam antibiotics or {3-lactamasc inhibitors; moderate to severe renal dysfunction; evidence of active liver disease; peripheral granulocyte counts of <l,000/mm^3 or platelet counts of <50,000/mm^3; receipt of more than two doses of another antibacterial agent within 72 h prior to enrolment; receipt of another investiga-tional drug within 1 month prior to enrolment; active or treated leukaemia; AIDS; the need for haemodialysis, peritoneal dialysis, plasmapheresis, or haemoperfusion; osteomyelitis contiguous with a skin or skin</td><td>Dosed every 6 h with pipcracillin-tazobactam (P/T), 3 g and 375 mg, respectively for 5 days and at least 48h after resolution of signs and symptoms.</td><td>Dosed every 6 h with ticarcillin-clavuianatc (T/C), 3 g and 100 mg, respectively for 5 days and at least 48h after resolution of signs and symptoms.</td><td>Patients were evaluated for their clinical responses to therapy daily for the duration of treatment in the hospital, at 24 to 72 h after the completion of therapy (early follow-up), and at 10 to 14 days after the completion of therapy (late follow-up).</td><td>Table: Clinical responses at endpoint for evaluable patients.

<table><tr><td>Outcome</td><td>P/T</td><td>T/C</td><td>p value</td></tr><tr><td>Cured/improved</td><td>12</td><td>7</td><td>0.90</td></tr><tr><td>Unfavourable</td><td>6</td><td>10</td><td></td></tr><tr><td>total</td><td>18</td><td>17</td><td></td></tr></table>
Relative Risk- 12/18 ÷ 7/17 = 1.62

Adverse Events:

Data not extractable for patients with diabetic foot infection.</td></tr>
</table>

	arms. Setting: 20 centers	structure infection; potential requirement for amputation of the infected area; pressure ulcer infections of greater than 2 weeks' duration {because of the. known difficulty in eradicating organisms from chronic decubitus ulcers); and a concomitant infection other than the skin and skin structure infection.				
Additional comments: Randomisation was performed. Blinding performed. Power calculation used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Tan, JS, Wishnow, RM, Talan, DA, Duncanson, FP, Norden, CW Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin-tazobactam versus ticarcillin-clavulanate. The Piperacillin/Tazobactam Skin and Skin Structure Study Group. *Antimicrobial Agents & Chemotherapy* 1993; **37:** 1580-1586.

Title: Treatment of diabetic foot infection: an open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 1702 Level of evidence: () Study type: RCT Authors: Bouter et	Total no. of patients: Baseline = 46 I/C- 22 (1 excluded due to being included twice) I/C-21 P/LC- 24 The minimum length of treatment required for evaluability was at least 10 days. Antibiotic therapy was discontinued if the patient's	Inclusion: Diabetic foot lesions, Wagner Stages II, III or IV, and have an ankle/brachial index (AB1) of at least 0.45. Exclusion: Patients known to be hypersensitive to any of	Piperacillin 3000 mg QID in combination with clindamycin 600 mg (P/CL)- TID Dosages reduced in patients with renal or liver	Imipenem/cilastatin (I/C)- 500 mg QID Dosages reduced in patients with renal or liver function impairment.	Every 3 days and after completion of antibiotic therapy.	Efficacy: Table: Assessment of clinical response to treatment with imipcncm/cilastalin or the combination of piperacillin with clindamycin

Clinical outcome	Imipenem/ cilastatin (n-21)	Piperacillin/ clindamycin (n-24)
Cured	4	6
Improved	16	12
Failed	0	2

<table>
<tr>
<td>al. (1996)</td>
<td>clinical condition worsened after 72 h and questions were raised about the appropriateness of therapy.

In case of chronic osteomyelitis, antibiotic therapy was continued with oral quinolone (ciprofloxacin 500 mg BID or ofloxacin 400 mg BID) and/or clindamycin 600 mg TID depending on culture results.

<u>Baseline characteristics:</u>

The two study populations were similar with regard to age, sex, type of diabetes mellitus and associated conditions.
The two study groups were comparable in terms of baseline severity.

<u>Setting:</u>
Bosch McdiCentre, Den Bosch and the Eemland Hospital, Amersfoort, The Netherlands.</td>
<td>the study drugs or who had received antimicrobial therapy known or presumed effective against the infecting pathogens within 48 h preceding initiation of treatment were excluded from the study. Patients with a high probability of death within 48 h were also excluded from the study as were patients known to be infected with Xanthomonas maltophilia other microorganisms known or presumed resistant to the study drugs.</td>
<td>function impairment.</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Died</td><td>1</td><td>4</td></tr>
</table>

In the IC study population, four (19.0%) patients were considered to be clinically cured, 16 (76.2%) improved. No patients were classified as a clinical failure.

In the PCL study population, six (25.0%) patients were considered to be clinically cured, 12 (50.0%) improved. Two patients (8.3%) were classified as a clinical failure due to persistence or aggravation of clinical signs of infection

Relative Risk$_{cured}$- 6/24 ÷ 4/21 = 1.31

Relative Risk$_{cured\ and\ improved}$ -18/24 ÷ 20/21 = 0.79

Bacteriological response:

Table 2: Assessment of bacteriological response to treatment with imipenem/ cilastatin or the combination of piperacillin with clindamycin

<table>
<tr><td>Bacteriological outcome</td><td>Imipenem/ cilastatin (n = 20)</td><td>Piperacillin/ clindamycin (n = 23)</td></tr>
<tr><td>Eradication</td><td>9</td><td>16</td></tr>
<tr><td>Partial eradication</td><td>3</td><td>1</td></tr>
<tr><td>Failure</td><td>1</td><td>3</td></tr>
<tr><td>Superinfection</td><td>4</td><td>3</td></tr>
<tr><td>Relapse</td><td>3</td><td>0</td></tr>
</table>

In the IC treatment group eradication of baseline pathogens was in 9 and partial eradication in 3 patients. 1patient was considered to be a bacteriological failure.

In the PCL patient group antibiotic treatment resulted in eradication of baseline pathogens in 16 patients. 3 patients were classified as a</td>
</tr>
</table>

<table>
<tr>
<td></td><td></td><td></td><td></td><td></td><td></td>
<td>bacteriological failure.

Relative Risk- 16/24 ÷ 9/21 = 1.56

Adverse Events:

Table: Adverse events reported during treatment with miipcnem/cilastatin or the combination of piperacillin with clindamycin
<table>
<tr><th>Adverse event</th><th>Imipenem/ cilastatin (n-21)</th><th>Piperacillin/ clindamycin (n-24)</th></tr>
<tr><td>Yes</td><td>3</td><td>12</td></tr>
<tr><td>No</td><td>18</td><td>12</td></tr>
</table>
Significantly more patients treated with PCL than patients treated with IC experienced side effects that were probably related to the study drugs (P < 0.05).
Relative Risk- 12/24 ÷ 3/21 = 3.50</td>
</tr>
<tr>
<td colspan="6">Additional comments:
Randomisation was performed. Blinding performed. Power calculation not mentioned. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.</td>
</tr>
</table>

Reference: Bouter, KP, Visseren, FLJ, Van Loenhout, RMM, Bartelink, AKM, Erkelens, DW, Diepersloot, RJA Treatment of diabetic foot infection: An open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy. *International Journal of Antimicrobial Agents* 1996; 7: 143-47.

Title: *Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-Clavulanate.*

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6518 Level of evidence: () Study type: RCT Authors: Lipsky et al. (2007)	<u>Total no. of patients:</u> Baseline = 607 306 randomised to moxifloxacin 311 to P/T-A/C ITT (intention-to treat)-127 63 to moxifloxacin 64 to P/T-A/C Efficacy valid population(EVP)-78 37- moxifloxacin 41- P/T-A/C ITT- and safety populations were defined as all randomized patients who received at least one dose of study medication The efficacy-valid population consisted of patients who met the entry criteria, had an investigator-defined DFI, received study medication for the minimum duration (2 days if a clinical failure and >5 days if a clinical cure), received no non-study systemic or topical antibiotic agent for >72h prior to enrolment and had no protocol violations that would have influenced treatment efficacy. Patients in the microbiologically-valid population consisted of those in the efficacy-valid population with one or more causative organism(s) identified at enrolment.	<u>Inclusion:</u> At least 18 years of age, with a cSSSI (complicated skin and skin structure infections). Each enrolled patient had to have al least three of the following signs or symptoms of wound infection: drainage or discharge, erythema, fluctuance, localized heat or warmth, pain or tenderness, swelling or induration, fever, leucocyiosis or >15% immature neutrophils on peripheral blood smear. The investigators only enrolled patients with an infection of sufficient severity to require hospitalization and iv antimicrobial therapy. <u>Exclusion:</u> Excluded patients who had received antibiotic therapy for >24h within 3 days prior to study enrolment or those who needed concomitant systemic antibiotic therapy for treatment of other infections. We also excluded patients with a DFI who had suspected or documented osteomyelitis, unless the infected bone was fully or partially resected and any residual soft tissue infection could be adequately treated with study drug for < 14 days.	IV therapy for at least 3 days with moxifioxacin (400 mg/day). Then switched to oral therapy with moxifloxacin 400 mg/day	piperacillin-tazobactam (P/T) (3.0 g/0.375 g every 6 h) for at least 3 days. Then switched to amoxicillin-clavulanate (A/C)suspension 800 mg every 12 h	Patients were evaluated regularly until 10-42 after completing the study therapy.	Efficacy Table 1: Clinical cure rates at the TOC (test-of cure) visit (10-42 days post-therapy) in the efficacy-valid population DFI definition / Moxifloxacin / P/T-A/C / p-value Per investigator (efficacy valid population) / 25/37 / 25/41 / 0.54 ITT / 28/63 / 25/64 / 0.54 Relative Risk (EVP)- 25/37 ÷ 25/41 = 1.10 Relative Risk (ITT)- 28/63 ÷ 25/64 = 1.14 Bacteriologic response Bacteriologic eradication rates for the microbiologically-valid population at TOC for patients in the moxifloxacin(n-29) and comparator (n-32)treatment arms were not statistically significantly different overall (69% versus 66%, P = 1.00). Relative Risk (EVP)- 20/29 ÷ 21/32 = 1.05 Eradication of Gram positive and Negative organisms / Moxifioxacin / P/T Gram positive aerobes / 24/27 / 27/42 Gram positive anerobes / 0/1 / ¾ Gram negative aerobes / 2/7 / 8/12

	Baseline characteristics: There were no statistically significant differences between patients in the two treatment groups in their demographic or clinical characteristics at baseline for all variables Setting: 68 centres in 6 countries.					

Gram negative anerobes	1/3	3/6

Adverse events:

Table 2: Adverse events by treatment group

	Moxifloxacin N= 63	P/T-A/C N= 64
Any adverse event	52	42
Drug-related adverse event	20	8
Serious adverse effect	15	15
Study drug discontinued due to adverse event	8	7

Almost a quarter of patients experienced a serious adverse event, and in ~11% this led to their study drug being discontinued prematurely.

More patients in the moxifioxacingroup than in the comparator group experienced a drug-related adverse event (28 versus 8).

No severe drug-related adverse events occurred in any patient in the moxifioxacin group, compared with two that occurred in patients in the comparator group.

Relative Risk (ITT)- 52/63 ÷ 42/64 = 1.26

Additional comments:
Randomisation was performed. Blinding performed. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.

Reference: Lipsky, BA, Giordano, P, Choudhri, S, Song, J Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-clavulanate. *Journal of Antimicrobial Chemotherapy* 2007; **60:** 370-376.

Title: Topical versus Systemic Antimicrobial Therapy for Treating Mildly Infected Diabetic Foot Ulcers: A Randomized, Controlled, Double-Blinded, Multicenter Trial of Pexiganan Cream.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6523 Level of evidence: () Study type: RCT Authors: Lipsky et al. (2008)	<u>Total no. of patients:</u> Study 303 Baseline = 493 ITT (intention-to treat)-Pexiganan= 247 ITTM(intention-to treat microbiological)= 189 ITT-Ofloxacin= 246 ITTM= 198 Study 304 Baseline = 342 ITT -Pexiganan= 171 ITTM= 138 ITT-Ofloxacin= 171 ITTM= 140 This study involved 2 groups: study 303 and 304. Investigators performed appropriate local wound care, including any necessary debridement	<u>Inclusion:</u> Men or women aged ≥18 years who had diabetes mellitus (according to American Diabetes Association definitions), had an infected wound below the malleoli that exceeded 0.5 cm2 in area after appropriate debridement, wounds had to be full thickness, the DFI had to be severe enough to require antibiotic therapy, but it had to be amenable to outpatient treatment. <u>Exclusion:</u> If they had an abscess, extensive gangrene, an imminently limb-threatening infection, evidence of systemic infec-tion (e.g., fever, chills, or hypotension), plain radiograph findings suggestive of osteomyelitis, no palpable dorsalis pedis or posterior tibial pulse or a pedal systolic pressure (by Doppler) of ≤40 mm Hg on the affected limb,	Pexiganan cream-twice daily Or Placebo cream-twice daily	Ofloxacin tablets-200mg-orally-twice daily Or Placebo tablets-200mg-orally-twice daily	Patients were evaluated at 3, 10, 14, and 21 days after enrollment; at end of treatment (EOT); and at follow-up (2 weeks after EOT).	Clinical Outcome Table 1: Clinical outcomes (cured or improvement) at end of treatment (EOT) and follow-up visits for patients who received either pexiganan or ofloxacin in the intention-to-treat populations. Visit and study / Pexiganan treatment group / Ofloxacin treatment group EOT 303: 210/247 / 224/246 304: 153/171 / 153/171 Follow-up 303: 186/243 / 201/240 304: 134/163 / 137/163 The difference in the rates of clinical cure or improvement in study 304 was within the 95% CIs for equivalence at both EOT (89% for both the ofloxacin group and the pexiganan group) and follow-up (84% for the ofloxacin group and 82% for the pexiganan group). Relative Risk (304-EOT)- 153/171 ÷ 153/171 = 1 Relative Risk (304-Follow up)- 134/163 ÷ 137/163 = 0.98 In study 303, however, pexiganan did not demonstrate equivalence to ofloxacin either at EOT (rates of clinical cure or improvement were

<table>
<tr>
<td></td>
<td>and pressure off-loading of the infected she, and they obtained wound tissue specimens for aerobic and anaerobic culture al enrolment. Nonstudy systemic or topical anti-infective agents were not allowed after enrolment.

<u>Baseline characteristics:</u>

Baseline characteristics of patients randomized to the 2 treatment groups in each of the 2 studies were not statistically different.

<u>Setting:</u>
Various centres in United States.</td>
<td>requirement for renal dialysis, need for immunosuppressive medication, or hyper-sensitivity to either study medication.</td>
<td></td>
<td></td>
<td></td>
<td>85% and 91%, respectively) or follow-up (77% and 84%, respectively).

Relative Risk (303-EOT))- 210/247 ÷ 224/246 = 0.93

Relative Risk (303-Follow up)- 186/243 ÷ 201/240 = 0.91

Microbiological Outcome:

Table 2: Microbiological outcomes* at end of treatment (EOT) and follow-up visits for patients who received either pexiganan or ofloxacin in the intention-to-treat populations.

*- in whom some or all of the initially isolated pathogens were eradicated, in whom there were no new pathogens isolated, and who experienced clinical cure or improvement.

<table>
<tr><th>Visit and study</th><th>Pexiganan treatment group</th><th>Ofloxacin treatment group</th></tr>
<tr><td>EOT</td><td></td><td></td></tr>
<tr><td>303</td><td>91/189</td><td>94/198</td></tr>
<tr><td>304</td><td>63/138</td><td>66/140</td></tr>
<tr><td>Follow-up</td><td></td><td></td></tr>
<tr><td>303</td><td>78/185</td><td>90/194</td></tr>
<tr><td>304</td><td>55/130</td><td>62/134</td></tr>
</table>

The percentages of patients who were microbiological responders in both trials were not significantly different between the ofloxacin and pexiganan arms at both the EOT (~47% for each) and follow-up (46% and 42%, respectively) time points.

Rates of microbiological failure at follow-up were</td>
</tr>
</table>

low, and similar rates were noted for the pexiganan and ofloxacin groups in studies 303 (8% and 6%, respectively) and 304 (10% and 8%, respectively).

Relative Risk (303-EOT))- 91/189 ÷ 94/198 = 1.01

Relative Risk (303-Follow up)- 78/185 ÷ 90/194 = 0.91

Relative Risk (304-EOT)- 63/138 ÷ 66/140 = 0.97

Relative Risk (304-Follow up)- 55/130 ÷ 62/134 = 0.91

Eradication of Gram positive and Negative organisms

	Pexiganan	Ofloxacin
Gram positive	209/383	243/396
Gram negative	82/119	77/110

Wound Assessments:

There were no statistically significant differences between the ofloxacin- and pexiganan-treated patients al baseline in the mean total wound score or wound infection score or in median wound area or depth. The wound assessment scores decreased at the EOT visit for all measurements in both studies for both treatment arms, and they decreased further for each measurement at the follow-up visit. The magnitude of the decrease in score was similar for the 2 treatment groups.

Adverse events:

The overall incidence and types of systemic and cutaneous adverse events were comparable in the 2 treatment arms of both studies.

In study 303, adverse events were experienced

						by 98 (39.8%) of the pexiganan-treated patients and by 109 (44.3%) of the ofioxacin-lrealed patients. Relative Risk (303)- 98/247 ÷ 109/246 = 0.9 In study 304, they occurred in 76 (44.4%) of the pexiganan-treated patients and 84 (49.1%) of the ofloxacin-treated patients. Relative Risk (304)- 76/171 ÷ 84/171 = 0.9
Additional comments: Randomisation was performed. Blinding performed (not sue). Power calculation used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Lipsky, BA, Holroyd, KJ, Zasloff, M Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. *Clinical Infectious Diseases* 2008; **47:** 1537-45.

Title: Treating Foot Infections in Diabetic Patients: A Randomized, Multicenter, Open-Label Trial of Linezolid versus Ampidllm-Sulbactam/ Amoxicillin-Clavulanate.

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6504 Level of evidence: () Study type: RCT Authors: Lipsky et al. (2004)	Total no. of patients: Baseline = 371 Linezolid- 241 After exclusion Linezolid- 203 A/S and A/C- 120 After exclusion A/S and A/C- 108 Patients with presumed osteomyelitis were allowed to be enrolled if the in-vestigator believed 4 weeks of antibiotic therapy was sufficient for treatment. Patients received twice-daily dressing changes (which consisted of any sterile nonadherent type selected	Inclusion: Men and women (age, ≥18 years) with diabetes mellitus, a foot infection (cellulitis, paronychia, infected ulcer, deep soft-tissue infection, septic arthritis, abscess, or osteomyelitis) were potentially eligible. Exclusion: If they had critical ischemia of the affected limb, if they had a wound with prosthetic materials or devices; if they had an infection requiring >28 days of antibiotic	Linezolid (600 mg ql2 h either iv or per oral)	ampicillin-sulbaclam (A/S, 1.5-3 g q6h iv}, or amoxicillin-clavulanate (A/C, 500-875 mg every 8-12 h per oral).	The test-of-cure evaluation was conducted 15-21 days after treatment was completed	Efficacy Table 1: Clinical cure rates for the intent-to-treat population, by selected parameters. No. of patients cured/ No. of patients assessed(%)* Linezolid (n- 241) / Aminopenicillin / β lactamase inhibitor (n-=120) Overall: 165/203 (81) / 77/108 (71) Type of infection** Infected ulcer: 131/161 (81) / 57/84 (68) Cellulitis: 68/86 (79) / 40/54 (74)

	by the investigator) and periodic debridement, as needed throughout the study. Baseline characteristics: There were no significant differences between the 2 treatment groups at baseline with respect to demographic characteristics, medical histories, findings of physical examination, and results of laboratory tests. Setting: 45 sites in 8 countries.	treatment; or if they had a wound with extensive gangrene. Patients were also excluded if they had received potentially effective antibiotic therapy for >72 h in the week before enrollment, if they needed additional treatment with antibiotics not tested in our study, if they had an absolute neutrophil count of <500 cells/mm^3, if they were pregnant or lactating, or if they had a history of hypersensitivity to linezolid, penicillin, or vancomycin.				<table><tr><td>Deep soft-tissue infection</td><td>20/32 (63)</td><td>8/14 (57)</td></tr><tr><td>Paronychia</td><td>11/12 (92)</td><td>9/11 (82)</td></tr><tr><td>Abscess</td><td>5/5 (100)</td><td>1/1 (100)</td></tr><tr><td>Osteomyelitis</td><td>27/44 (61)</td><td>11/16(69)</td></tr><tr><td>Route of initial treatment</td><td></td><td></td></tr><tr><td>Intravenous</td><td>41/53 (77)</td><td>15/22 (68)</td></tr><tr><td>Oral</td><td>124/150 (83)</td><td>62/86 (72)</td></tr></table> *- Excludes patients with indeterminate and missing outcomes **- Patients could have had >1 baseline diagnosis. There was no statistically significant difference between the treatment groups in the overall clinical cure rate. When analyzed by primary diagnosis, however, statistically significantly more patients with an infected ulcer in the linezolid arm were clinically cured than in the aminopenicillin//3-lactamase inhibitor arm (81% vs. 68%, respectively; 95% CI, 1.9-25.2; P = .018). Clinical outcomes were similar between treatment groups among patients with cellulitis, deep soft-tissue infection, paronychia, abscess, and osteomyelitis. Relative Risk (overall)- 165/203 ÷ 77/108 = 1.14 Relative Risk (infected ulcer)- 131/161 ÷ 57/84 = 1.20 Relative Risk (Osteomyelitis)- 27/44 ÷ 11/16 = 0.89 Adverse events:

						Linezolid group No. of patients- 64 Patients who discontinued therapy- 18 Aminopenicillin / β lactamase inhibitor No. of patients- 12 Patients who discontinued therapy- 4 Overall, significantly fewer patients experienced a drug-related adverse event in the aminopenicillin/β-laclamase inhibitor groups than in the linezolid group (12 [10%] of 120 patients vs. 64 [27%] of 241 patients, respectively; P = .001), but the frequencies of drug-related events leading to drug discontinuation were comparable (4 [3%] of 120 patients vs. 18 [8%] of 241 patients, respectively; P - 0.16) Treatment-related adverse events occurred in 55% and 53% of patients in the linezolid and aminopenkillin/ /J-lactamase inhibitor groups, respectively (P = .82) Events were generally mild to moderate in intensity and of limited duration. Relative Risk- 64/241 ÷ 12/120 = 2.65
Additional comments: Randomisation (ratio 2:1) was performed. Open-labelled. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Lipsky, BA, Itani, K, Norden, C, Linezolid Diabetic Foot Infections Study Group Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate. *Clinical Infectious Diseases* 2004; **38:** 17-24.

<table>
<tr><th colspan="7">Title: Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections.</th></tr>
<tr><th>Level of Evidence</th><th>Patient Population/ Characteristics</th><th>Selection/Inclusion criteria</th><th>Intervention</th><th>Comparison</th><th>Follow-up</th><th>Outcome and Results</th></tr>
<tr>
<td>ID: 6512

Level of evidence: ()

Study type: RCT

Authors: Lipsky et al. (2005)</td>
<td><u>Total no. of patients:</u>
Baseline = 133
103-clinically evaluable
47-Daptomycin
56-comparator

For suspected or proven polymicrobial infection, the investigator was allowed to add aztreonam to cover gram-negative bacteria or metronidazole lo cover obligate anaerobic bacteria, at his or her discretion.

<u>Baseline characteristics:</u>

Patients in the daptomycin and comparator groups were statistically equiv-alent with respect to all noted baseline variables, including mean age (60 and 63 years), sex (54% and 54% male) and race (80% and 78% white), respectively.

<u>Setting:</u>
134 sites in the United States, Europe. South Africa, Australia, and Israel</td>
<td><u>Inclusion:</u>
Eligible patients were those with diabetes between the ages of 18 and 85 years who required hospitalization for an infected ulcer that was known or suspected (based on a Gram-stained smear) to be caused by a Gram-positive organism.
<u>Exclusion:</u>

Patients with minor or superficial skin infections, uncomplicated cellulitis, myositis, multiple infected ulcers at distant sites, infected third-degree burn wounds, osteomyelitis, known bacleraemic shock, hypotension, or any disorder that could interfere with the treatment evaluation were excluded. Other exclusions were pregnancy, infection due to an organism known to be resistant lo any study drug before study entry, body weight less than 40kg, history of hypersensitivity reaction lo any study drug, need for haemodialysis or peritoneal dialysis, impaired renal function (creatinine clearance less than 30ml7min). immunosuppression, serum creatine phosphoki-nase (CPK) more than 50% above the upper limit of normal, or</td>
<td>Daptomycin [4mg/kg every 24h intravenously (iv) over 30min]</td>
<td>Vancomycin 1 g every 12h iv over 60min or a semi-synthetic penicillin (nafcillin. oxacillin, cloxacillin or llucloxa-cillin, per the investigator's choice) given in equally divided doses totalling 4-12g/day iv].</td>
<td>Patients were assessed at 'end-of-therapy' (i.e. within 3 days of the last dose of study drug); 'test-of-cure' (i.e. within 6-20 days after completing the study drug); and 'post-study' (i.e. within 20-28 days after completing the study drug).</td>
<td>Table 1: Clinical success rates for patients with infected diabetic ulcers by antibiotic treatment group (clinically evaluable population).

<table>
<tr><th>Comparator group</th><th>Daplomycin* (n=47)</th><th>Comparator (n= 56)</th></tr>
<tr><td>Pooled</td><td>66.0 (31/47)</td><td>70.0 (39/56)</td></tr>
<tr><td>Semi-synthetic penicillin</td><td>64.0 (16/25)</td><td>70.4 (19/27)</td></tr>
<tr><td>Vancomycin</td><td>71.4 (10/14)</td><td>69.0 (20/29)</td></tr>
</table>
*- Pre-randomization assignment unavailable in 8 subjects

The overall clinical success rate was 66% for patients treated with daptomycin and 70% for patients treated with a comparator agent (95% CI, -14.4-21.8).

Relative Risk(? Methodology)- 31/47 ÷ 39/56 = 0.95

Looking at individual comparators, the clinical success rates for patients randomized to daptomycin versus a semi-synthetic penicillin were 64.0% and 70.4%, respectively.

Relative Risk- 16/25 ÷ 19/27 = 0.91

Whereas for those randomized to daptomycin versus vancomycin rates were 71.4% and 69.0%, respectively. None of these differences was statistically significant.
Relative Risk- 10/14 ÷ 20/29 = 1.03

Adverse events:</td>
</tr>
</table>

		the use of any 3-hydroxy-3-metlwlghitaryl coenzyme reductase inhibitor (statin) drugs. Patients were also excluded if they had received more than 24h of systemic antibiotic therapy for the infected ulcer within the previous 48 h.				The most common events in both groups were gastrointestinal; most adverse events were deemed unrelated to the study medications, were of mild to moderate intensity, and rarely required that the drug be discontinued. Of the 56 adverse events that were possibly or probably related to treatment, 37 (66%) occurred in the 72 patients in the comparator group, and 19 (34%) occurred in the 61 patients in the dapto-mycin group. **Relative Risk(? Methodology)- 19/61 ÷ 37/72 = 0.60**
Additional comments: Randomisation was performed but partially.. Blinding performed. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Lipsky, BA, Stoutenburgh, U Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. *Journal of Antimicrobial Chemotherapy* 2005; **55:** 240-245.

Title: *Ertapenem Versus Piperacillin/Tazobactam for Diabetic Foot Infections (SIDESTEP):* Prospective/Randomized, Controlled, Double-Blinded, Multicentre Trial						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6511 Level of evidence: () Study type: RCT Authors: Lipsky et al. (2005)	Total no. of patients: Baseline = 586 295- ertapenem 289- clinical MITT (modified-intention-to-treat) 244- microbiological MITT 226 DCIV clinically evaluable 206-FUA clinically evaluable 151-microbiologically evaluable 291-P/T 285-clinical MITT 226-mocrobiological MITT	Inclusion: Presented with diabetes mellitus (type 1 or type 2, controlled by diet or medications) and a foot infection that did not extend above the knee and required intravenous antibiotics. All patients had purulent drainage or at least three other indicators of infection. Exclusion: Patients who had infections that	Intravenous ertapenem (1 g bolus, followed by a saline placebo every 6 h for three additional doses).	Intravenous piperacillin/tazobac tam (P/T-3-375 g every 6 h).	Day 5 of intravenous therapy, at the time of discontinuation of intravenous therapy (DCIV), at the time of discontinuation of any subsequent oral antibiotic therapy, and at the follow-up assessment (FUA) 10 days after the	The proportion of patients with a favourable clinical response at the DCIV timepoint, adjusted for baseline severity, was 94% (213 of 226) for the ertapenem group and 92% (202 of 219) for the piperaciliin/lazobaclam group. Relative Risk- 213/226 ÷ 202/219 = 1.02 At the 10-day FUA timepoint, the clinical response rate, adjusted for baseline severity, was 87% (180 of 206) in the ertapenem group and 83% (162 of 196) in the piperacillin/tazobactam group. Relative Risk- 180/206 ÷ 162/196 = 1.06

	219-DCIV clinically evaluable 196-FUA clinically evaluable 135-microbiologically evaluable Investigators sharply debrided any wounds that had callus or devitalized tissue at baseline, and whenever necessary during the study. To ensure adequate antibiotic coverage for potentially antibiotic resistant Enlerococcus spp and meticillin-resistant S aureus (MRSA), investigators could administer vancomycin to patients in either treatment group if these organisms were known or suspected pathogens. After 5 days of intravenous therapy, the investigator could elect to switch patients in either group to oral antibiotic therapy with amoxicillin/ clavulanic acid (875/125 mg every 12 h). <u>Baseline characteristics:</u> The baseline characteristics—including details of peripheral neuro-pathy, palpable pedal pulses, and wound severity—of those randomized, which were similar between groups. At baseline, we stratified patients with the University of Texas Diabetic Wound Classification. Stratum I patients had a relatively superficial wound with	were: mild and did not require parenteral antibiotic therapy; known at entry to be caused by pathogens resistant to either study drug; predominantly caused by thermal bums; categorised as necrotising fasciitis; known or suspected to be associated with underlying osteomyelitis, complicated by indwelling foreign or prosthetic material; or associated with gangrenous tissue that could not be adequately removed by surgical debridement. We also excluded women who were pregnant, nursing, or fertile and not using contraception, as well as patients with: a history of a serious reaction to any β lactam antibiotic; a need for any additional concomitant systemic antibacterial agent other than the study drug(s) or vancomycin; diabetes or impaired glucose tolerance that was secondary; arterial perfusion insufficiency of the affected limb, requiring a revascularisation procedure; any rapidly progressive or terminal illness; a requirement for dialysis; immunosuppression of any cause; or receiving corticosteroid therapy {2=40 mg prednisone daily or its equivalent). Laboratory variables for which patients were excluded were: markedly abnormal liver function tests; haemalocril of less than 25%, haemoglobin of less than 8 g/L, platelet count of less than 75 OOO/mm^1; or coagulation test results more than 1.5 times the upper limit of normal (unless on anticoagulant therapy). Finally, we			last dose of study antibiotic therapy (intravenous or oral).	Among the 574 patients in the more conservative MITT analysis (those who received at least one dose of study drug, with patients with missing or indeterminate outcomes considered treatment failures), the proportion with a favourable clinical response at the 10-day FUA was 71% (206 of 289) and 66% {188 of 285), respectively (treatment difference 5%, 95% CI —2-6 to 12-5). Relative Risk- 206/289 ÷ 188/285 = 1.08 None of these differences between treatment groups is significant. Table1: Rate of favourable clinical response at 10-day FUA, by baseline stratum and wound classification {| | | Ertapenem (n=206) | P/T (n=196) |- | Moderate | 127/142 | 129/135 |- | Severe | 53/64 | 43/61 |- | Grade 0 | 2/2 | 5/5(|- | Grade 1 | 125/140 | 114/130 |- | Grade 2 | 43/51 | 33/48 |- | Grade 3 | 10/13 | 10/l3 |- | Stage B | 172/195 | 156/187 |- | Stage D | 8/11 | 6/9 |} Clinical cure rates were generally similar between treatment groups for patients with either moderate or severe infections, and for every stage and grade. There was a trend towards lower success rates with deeper wounds (moving from grade 0 to grade 3}, and patients with an ischemic limb (stage D) generally had lower clinical success rates than patients with adequate perfusion (stage B). Microbiological outcome: Among individuals with a positive wound culture, 358 of 384 (93%) isolates were known or presumed to be

	or without ischemia (grade 0 or 1, stages B or D), and Stratum II patients had a deeper wound (grades 2 or 3, stages B or D). <u>Setting:</u> USA	excluded patients who had been treated for more than 24 h with systemic antibiotic therapy likely to be effective for their infection within the 72 h before study screening, unless there was clinical evidence of treatment failure with an associated deep-tissue culture that yielded pathogen(s).				eradicated in those in the ertapenem group compared with 271 of 336 (81%) in the piperacillin/tazobactam group (difference 12-5%, 95% CI 7-2-18-8). Relative Risk- 358/384 ÷ 271/336 = 1.16 Adverse Events: Most adverse events were unrelated to the study drugs. 137 (47%) patients on ertapenem and 136 (47%) on piperacillin/tazobactam had at least one adverse event during parenteral therapy. There were no significant differences between treatment groups in drug-related adverse events (n=44 [15%] for ertapenem; n=57 [20%] for piperacillin/tazobactam) Relative Risk- 44/295 ÷ 57/291 = 0.76
<u>Additional comments:</u> Randomisation was performed. Open-labelled. Power calculation used. Allocation concealment mentioned. Confounding mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Lipsky, BA, Armstrong, DG, Citron, DM, Tice, AD, Morgenstern, DE, Abramson, MA Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. *Lancet* 2005; **366:** 1695-703

Title: ***Treatment and Long-Term Follow-Up of Foot Infections in Patients with Diabetes or Ischemia: A Randomized, Prospective, Double-Blind Comparison of Cefoxitin and Ceftizoxime***

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 4914 Level of evidence: () Study type: RCT Authors: Hughes et al.	<u>Total no. of patients:</u> Baseline = 63 Ceftizoxime **–** 33 (5 unevaluable) Cefoxitin- 30 (5-unevaluable) Some patients, after completing the study, received oral antibiotics for variable lengths of time at the discretion of their	<u>Inclusion:</u> (1) a history or clinical evidence of peripheral arterial insufficiency or diabetes mellitus; (2) isolation of bacterial organisms from wound, soft tissue, or bone; (3) two or more signs of infection, including local heat, drainage, erythema, or temperature greater than 38 °C.	Ceftizoxime, up to 4 gm IV every eight hours. Dosages of study medication were reduced for patients with renal dysfunction.	Cefoxitin, up to2 gm IV every four hours. Dosages of study medication were reduced for patients with renal dysfunction.	Every 3 days. Subsequent follow-up evaluations were made after 3, 6, 9, and 12 months.	**Table 1: Clinical responses** Number with Satisfactory Clinical Response/ Total Number Treated Ceftizoxime / Cefoxitin All evaluable patients: 23/28 / 17/25 Osteomyelitis: 10/14 / 8/12 Soft tissue infections: 13/14 / 9/13 Infections associated: 0/1 / 1/4

(1987)	physician. Baseline characteristics: Evaluable patients were similar with regard to age, sex, duration of therapy, and associated conditions. Setting: 2 Veterans Administration medical centers (VAMC)	Exclusion: Excluded for previous penicillin or cephalosporin allergy, rapidly progressive underlying disease, concomitant infection, or antibiotic therapy effective against the bacterial isolates within three days preceding initiation of-the study.	Placebo infusions were given at appropriate intervals to patients in the ceftizoxime group to maintain double-blind conditions.			with bacteremia Satisfactory clinical responses were observed in 82% of patients treated with ceftizoxime and 68% of patients treated with cefoxitin. **Relative Risk- 23/28 ÷ 17/25 = 1.20** Treatment of osteomyelitis with either agent was particularly encouraging, being only slightly less successful than treatment of soft tissue infections. Infections associated with bacteremia frequently were clinically unsatisfactory. There was no significant difference between responses of patients with peripheral vascular disease alone and responses of diabetics with or without apparent peripheral vascular disease. The in vitro susceptibilities of selected bacterial isolates are 161 of 185 (87%) isolates tested were susceptible to ceftizoxime and 148 of 183 (81%) were susceptible to cefoxitin. **Long term Follow up** **3 months** After three months of follow-up, six patients in each group had relapses of infection at the same site, which required parenteral antibiotics. **12 months** After 12 months, of 23 patients who initially had satisfactory clinical responses to ceftizoxime, eight were free of infection (at the same site), nine had relapsed, two had died of unknown causes, and four had failed to return for follow-up. Seventeen patients had initially satisfactory clinical responses to cefoxitin. After 12 months, seven remained free of infection, eight had relapsed, and

						two had not returned for follow-up. Five of 12 patients with soft tissue infections and two of 11 with osteomyelitis were known to have satisfactory long-term outcomes. **Adverse events** Adverse effects were observed in 16/33 (48%) patients receiving ceftizoxime and in 19/30 (63%) patients receiving cefoxitin. These consisted mostly of minor laboratory abnormalities, which resolved with discontinuation of therapy. **Relative Risk- 16/33 ÷ 19/30 = 0.76**
Additional comments: Randomisation (Computer-generated Code) was performed. Blinding performed. Power calculation not used. Allocation concealment not mentioned. Confounding not mentioned. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Hughes, CE, Johnson, CC, Bamberger, DM, Reinhardt, JF, Peterson, LR, Mulligan, ME, Gerding, DN, George, WL, Finegold, SM Treatment and long-term follow-up of foot infections in patients with diabetes or ischemia: a randomized, prospective, double-blind comparison of cefoxitin and ceftizoxime. *Clinical Therapeutics* 1987; **10:** Suppl-49.

Title: Outpatient management of uncomplicated lower-extremity infections in diabetic patients.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: HTA paper Level of evidence: () Study type: RCT Authors: Lipsky et al. (1990)	Total no. of patients: Baseline = 56 I= 27 C= 29 At the initial evaluation, lesions were cleaned with half-strength hydrogen peroxide, debrided mechanically and covered with a gauze dressing. Baseline characteristics: Mean ± SEM age: I: 59.4 ± 2.3 years C: 62.7 ± 2.4 years Patients with an ulcerated lesion: I: 24/27 (89%) C: 27/29 (93%) Setting: Washington State Veterans Affairs Medical Centre	Inclusion: non-limbthreatening lower extremity infections. Clinically infected lesions were defined as the recent development of purulence or at least two of the following: erythema, warmth, tenderness, induration, fluctuance, drainage Exclusion: Systemic or topical antimicrobial therapy within the preceding 2 weeks, presence of systemic toxicity, an infection that was immediately threatening to life or limb, patient unable to perform daily wound care, history of nonadherence with outpatient treatment, unwilling to return for outpatient visits, allergy to study drugs.	I (n = 27 patients): Clindamycin 300 mg orally, four times daily for 2 weeks.	C (n = 29 patients): Cephalexin 500 mg orally, four times daily for 2 weeks	**Not mentioned.**	**Results at 2 weeks** **Complete healing:** I: 10/25 (40%) C: 9/27 (33%) **Relative Risk- 10/25 ÷ 9/27 = 1.21** **Improved lesions:** I: 14/25 (56%) C: 18/27 (67%) **Relative Risk- 14/25 ÷ 18/27 = 0.83** **Lesions not improved:** I: 1/25 (4%) C: 0/27 (0%) **Adverse effects:** I: 1 patient had mild Diarrhoea C: 2 patients had mild nausea and diarrhoea No tests of statistical significance reported
Additional comments: Randomisation was performed (method not stated). Blinding performed. Power calculation not used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Lipsky BA, Pecoraro RE, Larson SA et al. (1990) Outpatient management of uncomplicated lower-extremity infections in diabetic patients. Archives of Internal Medicine 150: 790-7.

Review question 5: What is the clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems, for example, dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy, and electrical stimulation?

Vac (Negative Wound Pressure) Therapy

Evidence table

Title: ***The use of negative pressure wound therapy on diabetic foot ulcers: a preliminary controlled trial.***						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 3195 Level of evidence: () Study type: RCT Authors: Etoz et al. (2004)	<u>Total no. of patients:</u> Baseline = 24 NPWT-12 Control-12 In this study, wound closure was to be achieved by lesser surgical procedures. <u>Baseline characteristics:</u> Mean age: NPWT: 66.2 (54-77) years Control: 64.7 (56-74) years Mean Diabetic wound surface area NPWT: 109cm^2 Control: 94.8cm^2 There was no significant difference in groups regarding the initial wound surface area and ages (p>0.05) <u>Setting:</u>	<u>Inclusion:</u> Not mentioned <u>Exclusion:</u> Not mentioned	Negative pressure wound therapy (NPWT)(n=12) The diabetic foot ulcers were surgically debrided prior to initiation of treatment. During the healing process, the patients ambulated using walking sticks and/or wheelchairs.	Control-saline-moistened gauze dressing, (n- 12). Changed twice a day. The diabetic foot ulcers were surgically debrided prior to initiation of treatment. During the healing process, the patients ambulated using walking sticks and/or wheelchairs.	Every 48 hour until the wound beds approached nearly total coverage with granulation tissue without any inflammatory signs.	NPWT Mean diabetic wound surface area decreased from 109cm^2 to 88.6 cm^2 (20.4 cm^2, SD-11.7) Control Mean diabetic wound surface area decreased from 94.8cm^2 to 85.3 cm^2 (9.5 cm^2, SD-4.11) There was a significant difference in decrease rates. NPWT reduced the wound surface areas more effectively than moist gauze dressing (p- 0.032). Adverse events: No negative impact was seen on extremity functions and psychology of patients.

	Not mentioned					

Additional comments:

Randomisation was performed (method not stated). Blinding performed. Power calculation not used. Patients lost to follow up and excluded after randomisation was not mentioned. All parameters were not analysed as intention to treat.

Reference: Etoz, A, Kahveci, R Negative pressure wound therapy on diabetic foot ulcers. *Wounds: A Compendium of Clinical Research & Practice* 2007; 19: 250-255.

Title: ***Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers. A multicenter randomised controlled trial..***

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 1559 Level of evidence: () Study type: RCT Authors: Blume et al. (2008)	Total no. of patients: Baseline = 384 42 excluded 342-enrolled 335-analysed(7 –no treatment received) NPWT-169 AMWT- 166 Baseline characteristics: No statistically significant demographic differences existed between treatment arms. Setting: 37 diabetic foot and wound clinics and hospitals.	Inclusion: Diabetic adults ≥18 years with a stage 2 or 3 (Wagner's scale), calcaneal, dorsal, or plantar foot ulceration ≥2cm^2 in area after debridement, adequate blood perfusion. Exclusion: Patients with recognised active Charcot disease or ulcers resulting from electrical, chemical, or radiation burns and those with collagen vascular disease, ulcer malignancy, untreated osteomyelitis, or cellulitis, uncontrolled hyperglycaemia (AIC >12%) or inadequate lower extremity perfusion, ulcer with normothermic or hyperbaric oxygen therapy, concomitant medications such as corticosteroids, immunosuppressive	Negative pressure wound therapy using vacuum-assisted closure (NPWT, n= 169) Dressings changed every 48-72h All patients received off-loading as deemed necessary.	Control- advanced ,moist wound therapy (AMWT, n- 166) All patients received off-loading as deemed necessary.	Weekly for first 4 weeks (day 28), then every other week until day 112 or ulcer closure by any means. Patients achieving ulcer closure were followed at 3 and 9 months.	Efficacy Complete ulcer closure during ATP(active treatment phase) NPWT- 73/169 AMWT-48/166 The NPWT group proportion was significantly (p-0.007) greater for complete closure than the AMWT group. Relative risk- 73/169 ÷ 48/166 = 1.5 Complete ulcer closure after ATP NPWT- 73/120 AMWT-48/120 For patients completing the ATP, analysis significantly (p- 0.001) confirmed that a greater percentage of NPWT-treated ulcers achieved ulcer closure than AMWT-treated ulcers. Relative risk- 73/120 ÷ 48/120 = 1.52 Kaplan Meier median time to complete ulcer closure: NPWT- 96 days (95% CI 75-114, p- 0.001) AMWT- could not be estimated.

<table>
<tr>
<td></td>
<td></td>
<td>medications, or chemotherapy; recombinant or autologous growth factors products; skin and dermal substitutes within 30 days of study start; or use of any enzymatic debridement, pregnant or nursing mothers.</td>
<td></td>
<td></td>
<td></td>
<td>
>75% Ulcer closure (p- 0.044)

NPWT-106/161
AMWT- 85/166

Relative risk- 106/161 ÷ 85/166 = 1.21

Kaplan Meier median time to 75% ulcer closure:

NPWT- 58 days (95% CI 53-78, p- 0.014)
AMWT- 84 days (95% CI 58-89)

Ulcer area

NPWT= -4.32cm^2
AMWT= -2.53cm^2

Safety

Table 1: Results of safety analysis (6 months)

<table>
<tr><td></td><td>NPWT</td><td>AMWT</td></tr>
<tr><td>n</td><td>169</td><td>166</td></tr>
<tr><td>Secondary amputation</td><td>7</td><td>17</td></tr>
<tr><td>Oedema</td><td>5</td><td>7</td></tr>
<tr><td>Wound infection</td><td>4</td><td>1</td></tr>
<tr><td>Cellulitis</td><td>4</td><td>1</td></tr>
<tr><td>Osteomyelitis</td><td>1</td><td>0</td></tr>
<tr><td>Infected skin ulcer</td><td>1</td><td>2</td></tr>
</table>

Significantly (p-0.035) fewer amputations were observed in the NPWT patients compared with AMWT patients. In all other categories, no significant differences were observed.
</td>
</tr>
<tr>
<td colspan="7">Additional comments:</td>
</tr>
</table>

Randomisation was performed (method not stated). Blinding performed. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.

Reference: Blume, PA, Walters, J, Payne, W, Ayala, J, Lantis, J Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008; 31: 631-36.

Title: ***Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial..***						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 11715 Level of evidence: () Study type: RCT Authors: Williams et al. (2005)	<u>Total no. of patients:</u> Baseline = 162 NPWT-77 Control-85 All patients received off-loading therapy, preventatively and therapeutically, as indicated. <u>Baseline characteristics:</u> There were no statistically significant differences in the demographic char-acteristics of the patients. <u>Setting:</u> 18 centres (diabetic foot and wound clinics in private and academic health-science centres)-USA	<u>Inclusion:</u> People aged 18 years or older, presence of a wound from a diabetic foot amputation to the transmetatarsal level of the foot, evidence of adequate perfusion, and wounds with University of Texas grade 2 or 3 in depth. <u>Exclusion:</u> Patients with active Charcot arthropathy of the foot, wounds resulting from burns, venous insufficiency, untreated cellulitis, or osteomyelitis (after amputation), collagen vascular disease, malignant disease in the wound, or uncontrolled hyperglycaemia, treatment with corticosteroids, immunosuppressive drugs, or chemotherapy, previous VAC therapy in the past 30 days, present or previous treatment with growth factors, normothermic therapy, hyperbaric	Negative pressure wound therapy (NPWT)(n=77) Delivered through the VAC system and dressings changed every 48 h	Control- moist wound therapy with alginates, hydrocolloids, foams, or hydrogels. Dressing changes occurred every day.	Day 0, 7, 14, 28, 42, 56, 84, and 112	Wound closure (16 weeks) NPWT-43/77 Control-33/85 A greater proportion of patients had healed achieved complete closure during the 16 week assessment in the NPWT group compared to the control group (p-0.040). Relative risk- 43/77 ÷ 33/85 = 1.43 Time (median) to achieve 75-100% granulation in patients with 0-10% granulation at baseline NPWT- 42 days (40-56) Control-84 days (57-112), p-0.002. Time (median) to achieve 75-100% granulation in patients with 0-25% granulation at baseline NPWT- 42 days (14-56) Control-82 days (28-112), p-0.010 Relative risk ratio for second amputation was 0.244 (95% CI, 0.05-1.1) indicating that patients treated with NPWT were only a quarter as likely as control patients to need a second amputation. Adverse events: 40 (52%) patients assigned to receive NPWT and 46 (54%) patients assigned to receive control

		medicine, or bioengineered tissue products in the past 30 days.				treatment had one or more adverse event during the study but this was not significant (p- 0.875). Relative risk- 40/77 ÷ 46/85 = 0.96 9 in NPWT had a treatment-related adverse event 11 in control group had a treatment-related adverse event Relative risk- 9/77 ÷ 11/85 = 0.90
Additional comments: Randomisation was performed (neither patients nor investigators were masked to the randomised treatment assignment). Blinding performed. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Williams, DT, Maegele, M, Gregor, S, Peinemann, F, Sauerland, S, Chantelau, E, Armstrong, DG, Lavery, LA Negative pressure therapy in diabetic foot wounds... Armstrong DG, Lavery LA et al. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet 2005;366:1704-10. *Lancet* 2006; 367: 725-28.

Skin Grafts

<table>
<tr><td colspan="7">Title: Evaluation of a human skin equivalent for the treatment of diabetic foot ulcers in a prospective randomised, clinical trial.</td></tr>
<tr><td>Level of Evidence</td><td>Patient Population/ Characteristics</td><td>Selection/Inclusion criteria</td><td>Intervention</td><td>Comparison</td><td>Follow-up</td><td>Outcome and Results</td></tr>
<tr>
<td>ID: 8456

Level of evidence: ()

Study type: RCT

Authors: Pham et al. (1999)</td>
<td><u>Total no. of patients:</u>
Baseline = 33
Skin equivalent-16
Control-17

Ulcers in both groups that did not heal by study week 5 were covered with a layer of saline-moistened gauze and a layer of conforming gauze bandage for weeks 6-12.

<u>Baseline characteristics:</u>
Demographic data were comparable between the two groups with no significant differences.
Baseline observations were generally similar between skin equivalent and control groups.

<u>Setting:</u>
Deaconess-Joslin Foot Centre</td>
<td><u>Inclusion:</u>
Patients with diabetes with full thickness (>1cm^2 but <16cm^2) ulcers on the foot, 18-80 years old, without active Charcot's disease, had dorsalis pedis and posterior tibial pulses, HbA1C >6% but <12%.

<u>Exclusion:</u>
Patients with clinical infection at the study ulcer site, clinically significant lower-extremity ischemia, ulcer of a non-diabetic pathophysiology, patients with significant medical conditions that wound impair wound healing, and patients whose ulcers responded to saline-moistened gauze during the screening period.</td>
<td>Skin equivalent (n- 16) treatment for 12 weeks

Proper wound care, including extensive debridement and weight offloading was provided to all participants.</td>
<td>Control-woven gauze kept moist by saline (n-17)for 12 weeks.

Proper wound care, including extensive debridement and weight offloading was provided to all participants.</td>
<td>Weekly from study 0 to week 12.</td>
<td>Efficacy analysis

Table 1: Complete wound closure (at 12 weeks)

<table>
<tr><td colspan="4">Frequency of complete closure</td></tr>
<tr><td>Treatment</td><td colspan="2">% healed</td><td>P value</td></tr>
<tr><td>Graft skin</td><td colspan="2">75 (12/16)</td><td><0.05</td></tr>
<tr><td>control</td><td colspan="2">41 (7/17)</td><td></td></tr>
<tr><td colspan="4">Kaplan-Meier estimate of time (days) to complete closure</td></tr>
<tr><td></td><td>Minimum</td><td>Medium</td><td>Maximum</td></tr>
<tr><td>Graft skin</td><td>7</td><td>38.5</td><td>85</td></tr>
<tr><td>control</td><td>14</td><td>91</td><td>91</td></tr>
</table>

The difference in median time to healing was shown to be significantly in favour of the skin equivalent-treated group (p-0.01).

Relative Risk - 12/16 ÷ 7/17 = 1.83</td>
</tr>
<tr><td colspan="7"><u>Additional comments:</u>
Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.</td></tr>
</table>

Reference: Pham, HT, Rosenblum, BI, Lyons, TE, Giurini, JM, Chrzan, JS, Habershaw GM, ea Evaluation of a human skin equivalent for the treatment of diabetic foot ulcers in a prospective, randomized, clinical trial. *Wounds: A Compendium of Clinical Research and Practice* 1999; 11: 79-86.

Title: ***Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage.***

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 8753 Level of evidence: () Study type: RCT Authors: Puttirutvong et al. (2004)	Total no. of patients: Baseline = 80 Meshed skin graft-36 Ordinary split thickness skin graft-17 The thighs were used for donor site of skin graft. Dressing changed every day. Baseline characteristics: Demographic data were comparable between the two groups with no significant differences. Baseline observations were generally similar between skin equivalent and control groups. Setting: Deaconess-Joslin Foot Centre	Inclusion: Patients with FBS 150-200 mg%, haematocrit ≥30% and rare bacterial colonisation ($<10^5$ micro-organisms/g tissue) Exclusion: Patients with clinical infection at the study ulcer site, clinically significant lower-extremity ischemia, ulcer of a non-diabetic pathophysiology, patients with significant medical conditions that wound impair wound healing, and patients whose ulcers responded to saline-moistened gauze during the screening period.	Meshed skin graft (n- 38)	Control-Ordinary split thickness skin graft (n- 42)	Weekly for 6 months.	Complete healing duration Meshed skin graft – 19.84 ± 7.37 days Ordinary split thickness skin graft- 20.36 ± 7.21 days (p-0.282) Table 1:the efficacy of treatment Excellent- skin grafts epithelised or healed 95% within 14 days with a smooth scar Good- skin grafts epithelised or healed 95% within 21days/hypertrophic scar subsided within 6 months Fair- skin grafts epithelised or healed 95% within 21days/prone to abrasion from minor trauma/minor infected wounds/obvious hypertrophic scar after 6 months Poor- skin grafts epithelised or healed 95% within 28days/keloid/contracture of toes or joints/recurrent ulcer. Relative Risk (excellent) - 19/38 ÷ 17/42 = 1.23 Relative Risk (excellent and good) - 31/38 ÷ 35/42 = 0.98 Relative Risk (excellent, good, and fair) - 38/38 ÷ 40/42 = 1.05 Adverse events: The cosmetic results in both groups were very satisfactory at 6 months.

	Meshed skin graft		Ordinary split thickness skin graft	
	Cases	%	Cases	%
Excellent	19	50	17	40.5
Good	12	31.6	18	42.9
Fair	7	18.4	5	11.9
Poor	0	0	2	4.8

Additional comments:
Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was not mentioned. All parameters were not analysed as intention to treat.

Reference: Puttirutvong, P Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage. *Journal of the Medical Association of Thailand* 2004; 87: 66-72.

Title: Grafts Skin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers . A prospective randomized multicenter clinical trial.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 11258 Level of evidence: () Study type: RCT Authors: Veves et al. (2001)	<u>Total no. of patients:</u> Baseline = 277 69 excluded Graftskin-112 Control- 96 Ulcers in both groups that did not heal by study week 5 were covered with a layer of saline-moistened gauze and a layer of petrolatum and wrapped with a layer of Kling for study weeks 6-12. <u>Baseline characteristics:</u> At baseline, the two groups were similar regarding demographics, type and dura-tion of diabetes, and ulcer size and duration. <u>Setting:</u> 24 centres-USA	<u>Inclusion:</u> Type 1. or 2 diabetes, age 18-80 years, HbA_{1c} between 6 and 12%, and full-thickness neuropathic ulcers (excluding the dorsum of the foot and the calcaneus). The ulcer was required to be of ≥2 weeks duration and the post-debridement ulcer size had to be between 1 and 16 cm^2-. All patients were also required to have dorsalis pedis and posterior tibial pulses. <u>Exclusion:</u> Clinical infection at the studied ulcer site, clinically significant lower-extremity ischemia, active Charcot's disease, and an ulcer that was of a non-diabetic pathophysiology (e.g., rheumatoid, radiation-related, and vasculitis-relaied ulcers). Patients with significant medical conditions that would impair wound healing were also excluded from the study. These conditions included liver disease, aplastic anaemia, scleroderma, malignancy, and treatment with immunosuppressive agents or steroids. Patients whose ulcere responded lo saline-	Graftskin (n-112, its a living human skin equivalent) Standard state-of-the-art adjunctive therapy, which included extensive surgical debridement and adequate fool off-loading, was provided in both groups.	Control- saline moistened gauze (n-96). Standard state-of-the-art adjunctive therapy, which included extensive surgical debridement and adequate fool off-loading, was provided in both groups.	Weekly from study day 0 until 12weeks. Then once a month for 3 months for safety evaluations.	By the end of the study, complete wound healing was achieved in 63 (56%) Graftskin-treated patients—a significantly higher rate when compared with 36 (38%) control subjects (P = 0.0042). Relative Risk- 63/112 ÷ 36/96 = 1.50 The odds ratio for complete healing for a Graftskin-treated ulcer compared with a control-treated ulcer was 2.14 (95% CI 1.23-3.74). The Kaplan-Meier median time to complete closure was 65 days for Graftskin—significantly lower than the 90 days observed in the control group (P = 0.0026). The estimated hazard ratio indicated that an average patient treated with Graftskin had a 1.59-fold better chance for closure per unit lime than a patient treated with the active control (95% CI 1.26-2.00). Secondary end points Between study day 0 and study week 12, both Graftskin and active control groups showed statistically significant improve-ment in undermining, maceration, exu-date, granulation, eschar, and fibrin slough. A statistically significant difference was seen between the two treatment groups

		moistened gauze during the screening period, as defined by a 30% decrease in the size of the ulcer, were not entered into the study.				with regard lo maceration (P < 0.05), exudate (P < 0.05), and eschar (P < 0.05). Ulcer recurrence At 6 months, the incidence of ulcer recurrence was similar in the two groups, with 5.9% (3 of 51) in the Graflskin group and 12.9% (4 of 31) in the active control group (NS). Relative Risk- 3/51 ÷ 4/31 = 0.45 Adverse events Because of adverse events, six Graftskin-treated and nine control-treated patients withdrew before completion of the study. Relative Risk (non specific adverse events)- 35/112 ÷ 46/96 = 0.65 Relative Risk (withdrawal due to adverse events-non specific) = 6/112 ÷ 9/96 = 0.57
Additional comments: Randomisation was performed. Blinding not performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Veves, A, Falanga, V, Armstrong, DG, Sabolinski, ML Graftskin, a human skin equivalent, is effective in the management of neuropathic diabetic foot ulcers. *Diabetes Care* 2001; 24: 290-295.

Title: Use of Dermagraft, a Cultured Human Dermis, to Treat Diabetic Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 3855 Level of evidence: () Study type: RCT Authors: Gentzkow et al. (1996)	<u>Total no. of patients:</u> Baseline = 25 Dermagraft- 12 Control-13 <u>Baseline characteristics:</u> No significant differences were observed in any of these factors <u>Setting:</u> 5 institutions	<u>Inclusion:</u> The patients had IDDM or NIDDM under reasonable control. HbA_{Ic} was measured, and patients could not have had more than one episode of hospitalization during the previous 6 months due to hyperglycemia, hypoglycemia, or ketoacidosis. 2) Diabetic ulcers of the plantar surface or heel were included; ulcers of nondiabetic origin were excluded. 3) The ulcer had to be a full-thickness defect >1 cm^2. 4) The foot had to have circulation adequate for healing. 5) The patient had to be able to complete a 12-week trial and could not be pregnant. <u>Exclusion:</u> Medications known to interfere with healing (e.g., corticosteroids, immunosuppressives, or cytotoxic agents) were excluded.	Dermagraft Group A (n-12) One piece of Dermagraft applied weekly for a total of eight pieces and eight applications, plus control treatment. Group B (n-14) Two pieces of Dermagraft applied every 2 weeks for a total of eight pieces and four applications, plus control treatment. Group C(n-11) One piece of Dcrmagraft applied every 2 weeks for a total of four pieces and four applications, plus control treatment. All patients received debridement, dressings, and pressure relief.	Group D (n-13) (Control group): conventional therapy and wound-dressing techniques using saline moistened gauze All patients received debridement, dressings, and pressure relief.	Weekly for 12weeks.	Percentage of wounds achieving complete closure and 50% closure The percentage of patients who achieved complete wound closure by week 12 was significantly higher in group A than in the control group (50.0, 21.4, 18.2, and 7.7% in groups A, B, C, and D, respectively; P = 0.03 for group A vs. D). Relative Risk (A vs. D)- 6/12 ÷ 1/13 = 6.5 A dose response was observed; that is, the percentage of patients achieving complete wound closure by week 12 increased with increasing Dermagraft dosage (group A > group B > group C). Time to complete wound closure Median time to complete wound closure was 12 weeks in group A and >12 weeks in the remaining groups. Percentage of wounds achieving 50% closure In group A, 75% of patients achieved 50% wound closure by week 12, compared with 50.0, 18.2, and 23.1% in groups B, C, and D, respectively. Relative Risk (A vs. D)- 9/12 ÷ 3/13 = 3.24 For group A, the difference was statistically significant compared with the control group (P« 0.017). Time to 50% closure Median time to 50% closure was significantly faster, 2.5 weeks in group A, compared with >12 weeks in the control group (P = 0.0047). Wound volume In group A, the median percentage decrease in volume was 88.9% at week 12 versus no decrease in group D (P = 0.017). Adverse events No patients in this study experienced an adverse device effect. Incidences of specific intercurrent

						events were low. Relative Risk - 2/12 ÷ 3/13 = 0.72
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Gentzkow, GD, Iwasaki, SD, Hershon, KS, Mengel, M, Prendergast, JJ, Ricotta, JJ, Steed, DP, Lipkin, S Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 1996; 19: 350-354.

Title: HYAFF 11 -Based Autologous Dermal and Epidermal Grafts in the Treatment of Noninfected Diabetic Plantar and Dorsal Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 2034 Level of evidence: () Study type: RCT Authors: Caravaggi et al. (1996)	Total no. of patients: Baseline = 82 3 excluded Hyalograft-43 Control- 36 In case of wound infection during the study period, an appropriate antibiotic therapy was prescribed. Baseline characteristics: At baseline the two groups were similar in regard to clinical characteristics. Setting: 6 centres-Italy	Inclusion: Type 1 or type 2 diabetes, an ulcer >2 cm^2 on plantar surface or dorsum of the foot without signs of healing for 1 month, Wagner score 1-2, $TcPO_2$ ≥30 mmHg, and ankle brachial pressure index (ABPI) ≥ 0.5. Exclusion: Ulcers with clinical infection, exposed bone, osteomyelitis, inability to tolerate an off-loading cast, and poor-prognosis diseases. After 15 days of screening (application of standard dressing, i.e., at visit 1) all patients with an ulcer area <1 cm' were excluded from the study.	The treatment group with autologous fibroblasts on Hyalograft 3D grafts (n = 43). All ulcers were subjected to an aggressive and extensive debridement to remove ne-crotic tissue and to control infection.	Control group with non-adherent paraffin gauze (n = 36) All ulcers were subjected to an aggressive and extensive debridement to remove ne-crotic tissue and to control infection.	Weekly until ulcer healed or 11 weeks, whichever came first.	Complete wound healing (ITT analysis) Complete wound healing was achieved in 65.3% of the treatment group ulcers versus 49.6% of the control group ulcers (P = 0.191, log-rank test). Relative Risk- 28/43 ÷ 18/36 = 1.31 The Kaplan-Meier median time for complete ulcer healing was 57 and 77 days for the treatment and control groups, respectively. Complete wound healing (per-protocol analysis to assess robustness of the outcomes) Complete wound healing was achieved in 63.7% (n- 35)of the treatment group ulcers versus 50% (n- 26) of the control group ulcers (P = 0.332, log-rank test) with a medium time for complete ulcer healing of 59 days for the treatment group and >77 days for the control group. Relative Risk- 22/35 ÷ 13/26 = 1.27 Secondary efficacy parameters: Secondary efficacy parameters (presence of

						FIBROUS SLOUGH, NECROTIC TISSUE, GRANULATION TISSUE, MACERATION, EXUDATE, ODOUR, INFECTION, AND PAIN SYMPTOMATOLOGY) WERE ANALYZED, AND BOTH groups showed an improvement in these parameters, the treatment group showed greater improvement than the control group as far as exudate presence. Adverse events TWENTY-TWO ADVERSE EVENTS WERE REPORTED FROM THE 82 RANDOMIZED PATIENTS (26.8%). THESE EVENTS WERE EQUALLY DISTRIBUTED BETWEEN THE TWO GROUPS. OF THESE, 17 (10 IN THE CONTROL GROUP AND 7 IN THE TREATMENT GROUP) WERE CLASSIFIED AS SERIOUS ADVERSE EVENTS. WITHDRAWAL DUE TO ADVERSE EVENTS (ULCER RELATED) Relative Risk- 3/43 ÷ 6/36 = 0.41
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Caravaggi, C, De, GR, Pritelli, C, Sommaria, M, Dalla, NS, Faglia, E, Mantero, M, Clerici, G, Fratino, P, Dalla, PL, Mariani, G, Mingardi, R, Morabito, A HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial. *Diabetes Care* 2003; 26: 2853-59.

Title: The Efficacy and Safely of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers. Results of a prospective randomized trial.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 6909 Level of evidence: () Study type: RCT Authors: Marston et al. (2003)	Total no. of patients: Baseline = 245 Dermagraft- 130 Control- 115 Study ulcers were stratified into one of two groups according to ulcer size: group 1, ≥1 to ≤2 cm^2; group 2, >2 to ≤20 cm^2 Baseline characteristics: There were no statistically significant differences with respect to any demographic characteristics between the two groups. Setting: 35 centres-USA	Inclusion: • Patient is >18 years old • Patient has type I or II diabetes • Patient's ulcer has been present for a minimum of 2 weeks under the current investigator's care • Patient's fool ulcer is on the plantar surface of ihe forefoot or heel and 2=1,0 cm^2 in size at day 0 • Patient's ulcer extends through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone, or joinl capsule • Patient's wound is free of necrotic debris and appears lo be made up of healthy vascularized tissue • Patient has adqequale circulation lo the foot as evidenced by a palpable pulse Exclusion: • Gangrene is present on any part of the affected fool • Patient's ulcer is over a Charcot deformity • Ulcer total surface area is >20 cm^2 • Patient's ulcer has decreased or increased in size by 50% or more during	Dermagraft (a bioengineered dermal substitute, n-130) Study ulcers received sharp debridement and saline-moistened gauze dressings. In addition, patients received off-weight bearing instructions.	Control group Conventional therapy (n- 115) It consisted of wound dressings (consisted of a nonadherent interface, saline-moistened gauze to fill the ulcer) dry gauze, and adhesive fixation sheets (Hypafix). Study ulcers received sharp debridement and saline-moistened gauze dressings. In addition, patients received off-weight bearing instructions.	Weekly until complete wound closure or the patient reached the week 12 visit without healing.	Efficacy: Complete Wound Closure at 12 weeks The results showed that treatment with Dermagrafl produced a significantly greater proportion (30%) of healed ulcers compared with the control group (18%) (P-0.023). Relative Risk- 39/130 ÷ 21/115 = 1.66 The Dermagraft-treated group had a significantly faster time to complete wound closure than the control group (P — 0.04). By week 12, the median percent wound closure for the Dermagraft group was 91% compared with 78% for the control group (p = 0.044). Adverse events The overall incidence of adverse events was comparable between the Dermagraft group (67%) and the control group (73%). Relative Risk- 87/130 ÷ 84/115 = 0.92 The number of patients who developed study ulcer-related adverse events (i.e., local wound infection, osteomyelitis, and cellulitis) was significantly lower in the Dermagraft-treated patients (19%) than in the control patients (32%; P = 0.007) Relative Risk (ulcer related)- 31/130 ÷ 49/115 = 0.56 Surgical Interventions in Ulcers

		THE SCREENING PERIOD • SEVERE MALNUTRITION IS PRESENT AS EVIDENCED BY ALBUMIN <2.0 • PATIENT'S RANDOM BLOOD SUGAR READING IS >450 MG/DL • URINE KETONES ARE NOTED LO BE "SMALL, MODERATE, OR LARGE" • PATIENT HAS A NONSTUDY ULCER ON THE STUDY FOOT THAT IS LOCATED WITHIN 7.0 CM OF THE STUDY ULCER AT DAY 0 • PATIENT IS RECEIVING ORAL OR PARENTERAL CORTICOSTEROIDS, IMMUNOSUPPRESSIVE OR CYTOTOXIC AGENTS, COUMADIN, OR HEPARIN • PATIENT HAS A HISTORY OF BLEEDING DISORDER • PATIENT HAS AIDS OR IS HIV-POSITIVE • CELLULITIS, OSTEOMYELITIS, OR OTHER EVIDENCE OF INFECTION IS PRESENT EXCLUDED FROM THE STUDY.				Relative Risk (ulcer related)- 13/163 ÷ 22/151 = 0.54
Additional comments: Randomisation was performed. Blinding performed (single). Allocation concealment not mentioned. Confounding mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Marston, W, Foushee, K, Farber, M Prospective randomized study of a cryopreserved, human fibroblast-derived dermis in the treatment of chronic plantar foot ulcers associated with diabetes mellitus. *14th Annual Symposium on Advances Wound Care and Medical Research Forum on Wound Repair* 2001.

Title: A Metabolically Active Human Derma! Replacement for the Treatment of Diabetic Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: Level of evidence: () Study type: RCT Authors: Naughton et al. (1997)	Total no. of patients: Baseline = 281 Group 1- 142 Group 2- 139 All patients were screened. Baseline characteristics: Not mentioned Setting: 20 investigational centres-USA	Inclusion: PATIENTS WITH NEUROPATHIC FULL-THICKNESS PLANTAR SURFACE FOOT ULCERS OF THE FOREFOOT OR HEEL, ≥1.0CM^2 IN SIZE. Exclusion: Initial rapid healing in response to standard care during the screening period.	Group 2(n-139) Treated with conventional therapy plus applications of Dermagraft on day 0 and weeks 1,2,3,4,5,6, and 7.	GROUP 1(N-142) TREATED WITH CONVENTIONAL THERAPY WHICH INCLUDED DEBRIDEMENT, INFECTION CONTROL, SALINE MOISTENED GAUZE DRESSINGS AND STANDARDISED OFF WEIGHTING.	Weekly until week 12 and then 4 weekly until week 32	Efficacy: Healing at week 12 Group 1- 31.7% Group 2- 38.5% Relative Risk- 54/139 ÷ 45/142= 1.21 Time to healing (mean) Group 1- 28 weeks Group 2- 13 weeks Recurrence of ulcers Ulcers recurred in a comparable minority of both groups, it is noteworthy that Dermagraft tended to delay recurrence Medial time to recurrence Dermagraft- 12 weeks Control-7 weeks Adverse events No safety problems were identified, and no significant differences were found between Dermagraft and control patients in the occurrence of wound infections or other intercurrent events.
Additional comments: Randomisation was performed. Single Blinding performed. Allocation concealment not mentioned. Confounding not mentioned. Power calculation not used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were not analysed as intention to treat.						

Reference: Naughton, G, Mansbridge, J, Gentzkow, G A metabolically active human dermal replacement for the treatment of diabetic foot ulcers. *Artificial Organs* 1997; 21: 1203-10.

Growth Factors

Section 1: Granulocyte-colony stimulating factors (G-CSF)

Title: Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections (Cochrane review)					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: Study type: Systematic review Authors: Cruciani et al. (2009)	People with diabetes who have a foot infection, including infected ulcers, cellulitis, osteomyelitis, deep abscess. Where possible, wound severity was reported according to the Wagner classification system The studies varied considerably in design and quality. For instance, de Lalla (2001) included only patients with limb-threatening infections, all of whom had osteomyelitis, whilst Yonem (2001) enrolled only patients with mild infections. Most of the studies included patients with foot cellulitis; Viswanathan (2003) and Kastenbauer (2003) enrolled patients with foot ulcers graded 2 or 3 on the Wagner scale, while Yonem (2001) included only patients with grade 1 or 2, and de Lalla (2001) patients with grade 3 or 4.	All randomised controlled trials (RCTs) that investigated the therapeutic effects of G-CSF in people with a diabetic foot infection. Studies were included only if they compared the effects of treatment as usual (e.g. antibiotic treatment for infection, surgery, pressure relief, wound care) with that of treatment as usual plus adjunctive G-CSF therapy, such that the G-CSF therapy is the only systematic treatment difference between trial arms. Review content assessed as up-to-date: 15 March 2009. The methodological strength of each study was appraised using a standard risk of bias checklist for the following criteria: • sequence generation; • allocation concealment; • blinding; • incomplete outcome data/completeness of follow-up • selective reporting of outcomes; • ITT analysis • other bias. The clinical characteristics of the diabetic foot infections varied, but the level of severity described among the	Intervention: G-CSF given subcutaneously, intramuscularly or intravenously plus treatment as usual. Control: treatment as usual with or without placebo. One study (de Lalla 2001) used lenograstim, the glycosylate human recombinant G-CSF, while the other studies used filgrastim, a non-glycosylate. Studies with filgastrim used a daily dose of 5 µg/kg, with dose reduction based on neutrophil count. Lenogastrin was administered at a daily dose of 263 µg (one vial). By contrast, the duration of G-CSF administration varied from 7 to 21 days, thus accounting for a wide range (from 2114 to 5523 µg) in the total G-CSF dose administered . Systemic antibiotics were administered in all the trials. A combination of intravenous clindamycin and ciprofloxacin (followed by oral route if necessary) was given in three trials (de Lalla 2001; Yonem 2001; Kastenbauer 2003); a combination of four intravenous antibiotics (ceftazidime, amoxicillin,	Range from 10 days to 6 months. <u>*5 studies:*</u> Gough (1997): unclear de Lalla (2001): 6 months Yonem (2001): unclear Kastenbauer (2003): 10 days Viswanathan (2003): unclear	Meta-analyses were carried out where there are two studies or more. *Resolution of infection* (2 studies; study period: unclear; total 80 participants): RR = 2.75 (95%CI: 1.05 to 7.20) *Infection status - improvement*[a] (4 studies; study period: range 10 days to 6 moths; total 140 participants): RR = 1.40 (95%CI: 1.06 to 1.85) [a]*improvement = eradication or some eradication of pathogen (through swab or tissue culture) but still have persistent signs (pain, swelling, erythema).* *Healing of wounds* (2 studies; study period: unclear; total 79 participants): RR = 9.45 (95%CI: 0.54 to 164.49) *Overall surgical interventions* (5 studies; study period: range 10 days to 6 moths; total 164 participants): RR = 0.37 (95%CI: 0.20 to 0.68) *Number of amputation* (5 studies; study period: range 10 days to 6 moths; total 167 participants): RR = 0.41 (95%CI: 0.18 to 0.95)

		studies varied from relatively mild (Yonem 2001; Viswanathan 2003) to severe (de Lalla 2001). Initial antibiotic therapy was apparently uniformly parenteral, but regimens and duration of therapy also varied considerably. The inclusion and exclusion criteria, clinical characteristics monitored, and end-points for therapy also differed.	flucloxacillin, and metronidazole) was given in one study (Gough 1997); the antibiotic regimen consisted of intravenous ofloxacin andmetronidazole in the remaining study (Viswanathan 2003). The studies employed different G-CSF preparations, at different dosages, and for different durations. Even the several studies that gave filgrastim used products made in different laboratories.		*Adverse events (side effects of G-CSF)* (3 studies; study period: range 10 days to 6 moths; total 117 participants): RR = 5.59 (95%CI: 0.71 to 44.05) *Days with systemic antibiotics* (3 studies; study period: range 10 days to 6 moths; total 107 participants): MD = -0.27 (95%CI: -1.30 to 0.77) *Days of hospital stay* (2 studies; study period: unclear; total 50 participants): MD = 2.75 (95%CI: 1.05 to 7.20)
Additional comments: Good quality systematic review. The generation of the randomisation process was unclear in 3 studies. Allocation concealment was unclear in 3 studies. There were 3 blinded placebo-controlled studies and 2 open-labelled studies. 2 studies were reported to be patient-blinded; blinding of investigators was reported in 3 other placebo-controlled studies; blinding of the outcome assessor was reported in 1 study and not stated or unclear in the remaining studies. No information about the blinding of the data analyst were available from any of the studies.					

Reference: Cruciani Mario AU: Lipsky Benjamin Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. *Cochrane Database of Systematic Reviews: Reviews* 2009; Issue 3.

Section 2: Recombinant Human Platelet-Derived Growth Factor (rhPDGF)

Title: Efficacy of Recombinant Human Platelet-Derived Growth Factor (rhPDGF) Based Gel in Diabetic Foot Ulcers: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study in India					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 4435 Study type: RCT Authors: Hardikar et al. (2005)	Total no. of patients = 113 Treatment = 58 Control = 55 <u>Mean age (SD)</u> Control = 54.5 (9.9) Treatment = 54.7 (9.0) <u>Males/females</u> Control = 40 (69%)/18 (31%) Treatment = 40(73%)/15 (27%) <u>Target ulcer surface area (mean cm^2) (SD)</u> Control = 13.7 (11.2) Treatment = 11.9 (9.9) <u>Duration of ulceration (mean weeks) (SD)</u> Control = 19.8 (39.8) Treatment = 25.5 (31.9) <u>Setting:</u> 8 sites, mostly public	<u>Inclusion:</u> Patients either with type 1 or 2 diabetes mellitus, were aged > 18 years but < 80 years and had at least 1 but less than 3 full-thickness chronic neuropathic ulcers of at least 4 weeks duration on the lower extremity. Only ulcers categorized as stage III or stage IV, as defined by the Wound, Ostomy, and Continence Nurses Society," and those with infection control as determined by a wound evaluation score were considered for inclusion. If multiple ulcers were present, the largest ulcer was taken as the target ulcer, and the size of ulcer was restricted to an area of 1-4Ocm1 <u>Exclusion:</u> Patients with arterial venous ulcers or those with ulcers caused by osteomyelitis or burns; if they had poor nutritional status (serum total proteins <6.5g/dL), persistent infection, life-threatening concomitant diseases, deformities like Charcot foot, chronic renal insufficiency (serum creatinine >3mg/dL), uncontrolled hyperglycemia (HbAlc >12%), history of corticosteroids or	<u>Treatment:</u> A 0.01% gel containing 100ng of rhPDGF-BB/g + standard wound care <u>Control:</u> Standard wound care only. The wounds were covered with thin 1.5mm layers of gel and covered with moist saline gauze. Standard wound care = regimen consisting of appropriate sharp surgical debridement, daily ulcer cleaning and dressing, and offloading (eg, crutches or wheelchair) or, in cases where possible, complete bed rest. Treatment group = 5 withdrawn due to concomitant illness and lost to follow-up Control group = 13 withdrawn	10 weeks and 20 weeks	Complete healing of ulcers: At 10 weeks: Treatment = 39/55; Control = 18/58 At 20 weeks: Treatment = 47/55; Control = 31/58 Mean healing time (days): At 10 weeks: Treatment = 46 days; Control = 61 days $p < 0.001$ At 20 weeks: Treatment = 57 days; Control = 96 days $p < 0.01$ The use of systemic antibiotics was found to contribute to increased healing percentages. In the treatment group, use of antibiotics increased the healing rate from 59% to 78%, while in the control group, antibiotic use increased the healing rate from 22.7% to 36%. Withdrawal due to adverse events was also similar at about 4% in the treatment group

	hospitals, in India.	immunosuppressant use, or any known hypersensitivity to the gel components. Women of childbearing age and pregnant or nursing women who were not taking contraceptives or not willing to use them were also excluded.	due to concomitant illness and lost to follow-up		and 5% in the control group. Nearly half of the adverse events were due to ulcer-related events, such as infection and osteomyelitis. No erythematous rashes or hypersensitivity to the gel or excipients was noted in any of the patients.
Additional comments: No details on randomisation methods; no mention of allocation concealment; no mention of blinding methods					

Reference: Hardikar, JV, Reddy, YC, Bung, DD, Varma, N, Shilotri, PP, Prasad ED, ea Efficacy of recombinant human platelet-derived growth factor (rhPDGF) based gel in diabetic foot ulcers: a randomized, multicenter, double-blind, placebo-controlled study in India. *Wounds: A Compendium of Clinical Research and Practice* 2005; 17: 141-52.

Title: Integrating the Results of Phase IV (Postmarketing) Clinical Trial With Four Previous Trials Reinforces the Position that Regranex (Becaplermin) Gel 0.01% Is an Effective Adjunct to the Treatment of Diabetic Foot Ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 9181 Study type: RCT Authors: Robson et al. (2005)	Total no. of patients = 146 Treatment = 74 Control = 72 Baseline characteristics were generally comparable between groups. The mean duration of diabetes mellitus in the Regranex Gel 0.01% group (17.9 years) was slightly longer than that in the standardized therapy group (14.7 years). The median ulcer at baseline was similar in the two treatment groups (1.5 and 1.6 cm2).	Inclusion: • Be 18 years of age or older; if female, must be practicing birth control. • Have documented wound etiology resulting from complications of diabetes mellitus. • Have at least one chronic nonhealing cutaneous full thickness diabetic neuropathic foot ulcer between 1.7-12 cm2area, 4-52 weeks duration, on the plantar aspect of the forefoot (midarch forward) and free of necrotic and infected tissue postdebridement. • Have a supine TcP02 > 30 mmHg on the dorsum of the target ulcer foot; an ulcer tissue biopsy with < 1 x 105organisms/g of tissue and no beta hemolytic streptococci. • Be willing and able to comply with the protocol. Exclusion: • Have the target ulcer other than on the plantar surface forward of the mid-arch; and a known hypersensitivity to any of the study drug components; have a malignant disease at the ulcer site; osteomyelitis confirmed by bone biopsy • Have a target ulcer < 1.7 or > 12 cm2 post-debridement. • Have more than one diabetic ulcer on the same foot as the target ulcer; more than three chronic wounds on the same extremity as the target ulcer; have thermal, electrical, chemical, or radiation wounds at the site of the target ulcer. • Have wounds resulting from large vessel arterial insufficiency, venous insufficiency, or necrobiosis lipoidica.	Treatment: Regranex Gel 0.01% with the Adaptic dressing + standardized good wound care Control: Adaptic dressing + standardized good wound care. The dosage of Regranex Gel 0.01% was determined by study personnel on a weekly basis by multiplying the greatest length of the target ulcer by the greatest width. In addition to the once daily dressing changes, standardized good	20 weeks	Complete wound healing at 20 weeks: Treatment = 31/74 Control = 25/72 p = 0.316 Of the patients who achieved complete healing, there was evidence for preferential healing of target ulcers with baseline areas less than 1.46 cm2 in favour of patients treated with Regranex Gel 0.01% (p = 0.0286).

		• Have significant metabolic, rheumatic, collagen vascular disease, chronic renal insufficiency, or chronic severe liver disease. • Have received any investigational drug, Procuren solution, or prior Regranex Gel 0.01% usage within the past 30 days. • Have a preexisting disease or condition that could interfere with evaluation of the effectiveness of Regranex Gel 0.01% or be adversely affected by Regranex Gel 0.01%. • Be receiving any systemic corticosteroids, immunosuppressive agents, radiation, or chemotherapy or revascularization surgery in the past 6 weeks; exposed bone or tendon, or presence of Charcot foot; or severe pitting limb edema.	wound care procedures (maintenance of a clean moist environment, infection control, non-weightbearing regimen, and debridement) were followed.		
Additional comments: No details on randomisation methods; no mention of allocation concealment; only sing-blinded (investigator).					

Reference: Robson, MC, Payne, WG, Garner, WL, Biundo, J, Giacalone, VF, Cooper, DM, Ouyang, P Integrating the results of phase IV (postmarketing) clinical trial with four previous trials reinforces the position that Regranex (becaplermin) Gel 0.01% is an effective adjunct to the treatment of diabetic foot ulcers. *Journal of Applied Research* 2005; 5: 35-45.

Title: Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (Becaplermin) in patients with chronic neuropathic diabetic ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 11667 Study type: RCT Authors: Wieman et al. (1998)	Total no. of patients = 382 Treatment 100ug/g = 124 Treatment 30ug/g = 132 Control (placebo gel) = 127 <u>Treatment 100ug/g</u> Male/female = 82/41 Mean age (SD) = 57 (11.5) Mean ulcer duration (wks) (SD) = 46 (54.7) Mean ulcer size (cm^2) (SD) = 2.6 (3.41) <u>Treatment 30ug/g</u> Male/female = 82/50 Mean age (SD) = 58 (11.3) Mean ulcer duration (wks) (SD) = 56 (80.3) Mean ulcer size (cm^2) (SD) = 2.6 (2.69)	<u>Inclusion:</u> Patients > 19 years of age with type 1 or type 2 diabetes. Patients had at least one full thickness (stage III or IV, as defined in the International Association of Enterostomal Therapy guide to chronic wound staging, chronic ulcer of the lower extremities. Target ulcers had to be present for at least 8 weeks despite previous treatment. <u>Exclusion:</u> Patients were excluded if 1) osteomyelitis affecting the area of the target ulcer was present, 2) after debridement, the target ulcer area (estimated by multiplying length by width) was <1 cm2 or >40 cm2, or 3) the sum of the areas of all ulcers present exceeded 100 cm2. Patients with ulcers resulting from any cause other than	<u>Treatment:</u> (Regranex Gel 0.01%) Becaplermin gel 100 ug/g or Becaplermin gel 30 ug/g, plus standard wound care <u>Control:</u> Placebo gel plus standard wound care Patients were instructed to apply a continuous thin layer of gel to the entire ulcer area once daily, preferably when the dressing was changed in the evening. Standardized regimen of good wound care = complete sharp debridement of ulcers to remove callus, fibrin, and	20 weeks then 3 months	Complete wound healing at 20 weeks: Treatment 100ug/g = 61/124 Treatment 30ug/g = 48/132 Control (placebo gel) = 44/127 Discontinuation because of treatment related adverse effects: Treatment 100ug/g = 11/124 Treatment 30ug/g = 13/132 Control (placebo gel) = 10/127 Discontinuation: Placebo gel 30 100

	Control (placebo gel) Male/female = 91/36 Mean age (SD) = 58 (11.8) Mean ulcer duration (wks) (SD) = 46 (52.1) Mean ulcer size (cm^2) (SD) = 2.8 (4.14) Before randomization, the target ulcer was sharply debrided to remove all nonviable tissue and callus. Any infection or cellulitis present before debridement had to be well controlled before randomization. Setting: Multicentres (23 sites in the U.S.)	diabetes (e.g., electrical, chemical, or radiation insult) and patients with cancer were excluded. Additional exclusion criteria included concomitant diseases (e.g., connective tissue disease), treatment (e.g., radiation therapy), or medication (e.g., corticosteroids, chemotherapy, or immunosuppressive agents) that would present safety hazards or interfere with evaluation of the study medication. Women who were pregnant, nursing, or of childbearing potential and not using either an intrauterine device or oral contraception were excluded. All patients gave their written informed consent before study entry.	necrotic tissue was an important component of good wound care and was performed by investigators during clinic visits if necessary. Good wound care also consisted of twice-daily dressing changes (moist saline), off-loading of pressure from the affected area, and adequate control of infection if present		Reason for discontinuation Lost 10 follow up: 2 / 1 / 1 AE: 13 / 17 / 13 Noncompliance: 3 / 4 / 3 Protocol violation: 3 / 2 / 2 Other: 3 / 4 / 2 Total discontinuations: 24 / 28 / 21 Patients completing study*: 103 / 104 / 102 Treatment failures: 7 / 17 / 10
Additional comments: No details on randomisation methods; no mention of allocation concealment; no mention of blinding methods					

Reference: Wieman, TJ, Smiell, JM, Su, Y Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998; 21: 822-27.

Title: Sodium Carboxymethylcellulose Aqueous-Based Gel vs. Becaplermin Gel in Patients with Non-healing Lower Extremity Diabetic Ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 2584 Study type: RCT Authors: D'Hemecourt et al. (2005)	Total no. of patients = 172 NaCMC gel = 70 Becaplermin gel 100 ug/g = 34 Control = 68 <u>Treatment NaCMC gel</u> Male/female = 49/21 Mean age (SD) = 59 (13.02) Mean ulcer duration (wks) (SD) = 52.8 (60.92) Mean ulcer size (cm^2) (SD) = 3.2 (2.75) <u>Treatment 100ug/g</u> Male/female = 24/10 Mean age (SD) = 58.5 (11.9) Mean ulcer duration (wks) (SD) = 20 (14.39) Mean ulcer size (cm^2) (SD) = 2.4 (2.02) <u>Control (good wound care)</u> Male/female = 54/14 Mean age (SD) = 59 (11.29) Mean ulcer duration (wks) (SD) = 42 (42) Mean ulcer size (cm^2) (SD) = 3.5 (3.53) <u>Setting:</u> Multicentres (10 sites), US.	<u>Inclusion:</u> Patients 19 years of age or older with type 1 or type 2 diabetes mellitus. Patients had at least one full-thickness (Stage 3 or 4), chronic diabetic ulcer of the lower extremity that had been present for at least eight weeks prior to the study. A target area between 1.0 and 10.0 cm2 post-debridement was required. <u>Exclusion:</u> Patients were excluded if (1) osteomyelitis affecting the area of the target ulcer was present, (2) after debridement, the target ulcer area (measured by multiplying length by width) was < 1 cm2 or > 10 cm3, or (3) they had more than three chronic ulcers present at baseline. Patients with ulcers resulting from any cause other than diabetes (e.g. electrical, chemical, or radiation insult), or patients with cancer at the time of enrolment were excluded. Additional exclusion criteria included use of concomitant medications known to affect wound healing (e.g. corticosteroids, chemotherapy, or immunosuppressive agents). Women who were pregnant or nursing, or of childbearing potential and not using an acceptable method of birth control were excluded.	<u>Treatment:</u> NaCMC gel plus good wound care Becaplermin gel 100 ug/g plus good wound care <u>Control:</u> Good wound care alone In the treatment groups, a thin layer of the corresponding gel was applied once daily at the morning dressing change for a maximum of 20 weeks or until the target ulcer was completely healed. Good wound care = included sharp debridement of ulcers to remove calluses, fibrin, and necrotic tissue. Debridement was performed by investigators at Visit 2 and throughout the study as necessary; and also included wet-to-moist saline-soaked gauze dressing changes every 12 hours, off-loading of pressure, and systemic control of infection if present.	20 weeks	Complete wound healing at 20 weeks: NaCMC gel = 25/70 Becaplermin gel 100 ug/g = 15/34 Control = 15/68 Discontinuation because of treatment related adverse effects: NaCMC gel = 8/70 Becaplermin gel 100 ug/g = 5/34 Control = 16/68 At least 1 treatment related adverse effect: NaCMC gel = 57/70 Becaplermin gel 100 ug/g = 22/34 Control = 48/68 Good wound care alone (n = 68) / NaCMC gel (n = 70) / Becaplermin gel 100 ug/g (n = 34) Withdrew: 21 (31) / 11(16) / 9(26) AE: 16(24) / 8(11) / 5(15) Lost to follow-up: 1(1) / 2(3) / 2(6) Patient choice: 3(4) / 0(0) / 1(3) Other: 1(1) / 1(1) / 1(3) A treatment-emergent AE was defined as an adverse event not present at baseline or if present at baseline, one which worsened in frequency or severity as the study progressed.

Additional comments:
No details on randomisation methods; no mention of allocation concealment; only evaluator-blinded.

Reference: d'Hemecourt, PA, Smiell, JM, Karim, MR Sodium carboxymethylcellulose aqueous-based gel vs. becaplermin gel in patients with nonhealing lower extremity diabetic ulcers. *Wounds: A Compendium of Clinical Research & Practice* 1998; 10: 69-76.

Section 3: Human Epidermal Growth Factor

Title: Human Epidermal Growth Factor Enhances Healing of Diabetic Foot Ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 10951 Study type: RCT Authors: Tsang et al. (2003)	127 patients were screened Total no. of patients randomised = 61 0.02% [wt/wt] hEGF = 21 0.04% [wt/wt] hEGF = 21 Control =19 <u>Treatment 0.02% [wt/wt] hEGF</u> Male/female = 13/8 Mean age (SD) = 68.76 (10.45) Mean ulcer duration (wks) (SD) = 8.24 (5.55) Mean ulcer size (cm^2) (SD) = 2.78 (0.82) <u>Treatment 0.04% [wt/wt] hEGF</u> Male/female = 6/15 Mean age (SD) = 62.24 (13.68) Mean ulcer duration (wks) (SD) = 11.48 (14.68) Mean ulcer size (cm^2) (SD) = 3.4 (1.1) <u>Control</u> Male/female = 10/9 Mean age (SD) = 64.37 (11.67) Mean ulcer duration (wks) (SD) = 12 (15.47) Mean ulcer size (cm^2) (SD) = 3.48 (0.82) Between September 2000 and August	<u>Inclusion:</u> 1) ulcer with grade I or 13, as defined by the Wagner Classification; 2) ulcer located below the ankle, and 3) ulcer with adequate perfusion, as indicated by an ankle-brachial index (ABI) ≥ 0.7. <u>Exclusion:</u> Patients were excluded if they had very poor sugar control (HbA, c > 12%) or had ulcers with severity equal to or greater than grade III. In the second consultation, we excluded patients whose ulcers healed >25% with conventional foot ulcer care.	<u>Treatment:</u> • 0.02% [wt/wt] hEGF plus Actovegin 5%cream plus standard wound care • 0.04% [wt/wt] hEGF plus Actovegin 5%cream plus standard wound care <u>Control:</u> Actovegin 5% cream plus standard wound care Actovegin is a protein free calf blood extract manufactured by NYCOMED Austria The cream under study was applied locally and covered with sterile gauze. Patients were instructed to continue with the normal daily saline dressing, combined with local application of the cream. Standard wound care consisted of debridement of necrotic tissue and reduction of callus. Antibiotics were prescribed	12 weeks and 24 weeks	<u>Wound completely healed (12 weeks):</u> Treatment 0.02% [wt/wt] hEGF = 12/19 Treatment 0.04% [wt/wt] hEGF = 20/21 Control = 8/19 <u>Wound completely healed (24 weeks):</u> Treatment 0.02% [wt/wt] hEGF = 17/19 Treatment 0.04% [wt/wt] hEGF = 20/21 Control = 17/19 <u>Amputation (24 weeks):</u> Treatment 0.02% [wt/wt] hEGF = 2/19 Treatment 0.04% [wt/wt] hEGF = 0/21 Control = 2/19

	2002 Diabetes Ambulatory Care centre, China		based on clinical judgment or on positive wound bacterial cultures.		
Additional comments: No mention of allocation concealment; no mention of blinding methods; no report of adverse events.					

Reference: Tsang, MW, Wong, WK, Hung, CS, Lai, KM, Tang, W, Cheung, EY, Kam, G, Leung, L, Chan, CW, Chu, CM, Lam, EK Human epidermal growth factor enhances healing of diabetic foot ulcers. *Diabetes Care* 2003; 26: 1856-61.

Title: Efficacy of topical epidermal growth factor in healing diabetic foot ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 579 Study type: RCT Authors: Afshari et al. (2005)	Total no. of patients = 50 Treatment ECF = 30 Control = 20 Treatment ECF Male (%) = 72.7% Mean age (SD) = 56.9 (12.7) Mean ulcer duration (days) (SD) = 42.9 (38.4) Mean ulcer size (mm^2) (SD) = 87.5 (103.2) Infection = 21/30 Control Male (%) = 53.3% Mean age (SD) = 59.7 (12.3) Mean ulcer duration (days) (SD) = 59.7 (55.5) Mean ulcer size (mm^2) (SD) = 103.4 (147.8) Infection = 12/20 Between October 1998 and September 2001 Tehran's Doctor Shariati University Hospital	Inclusion: Ulcer with Grade I or II, as defined by the Wagner Classification Ulcer with adequate perfusion, as indicated by an ankle-brachlal index (ABI) and ultrasound. Exclusion criteria not reported.	Treatment: 1 mg EGF plus 1000 mg of 1 % silver sulfadiazine in a hydrophilic base plus standard wound care Control: 1000 mg of 1 % silver sulfadiazine in a hydrophilic base plus standard wound care Patients in both the EGF and placebo groups had their wounds washed with normal saline and dressed every day Wound dressing consisted of sterile gau/e and adhesive tape only No disinfecting solution, such asbetadine, was used. EGF or placebo was applied once a day, every day, for 28 consecutive days, at the time of wound dressing.	4 weeks	Treatment = 7/30 Control = 2/20 Mean hospital stay (days, SD): Treatment = 29.6 (20.95) Control = 28.9 (15.1)
Additional comments:					

No details on randomisation methods; no mention of allocation concealment; assessor blinded only; no report of adverse events exclusion criteria not reported.

Reference: Afshari, M, Larijani, B, Fadayee, M, Darvishzadeh, F, Ghahary, A, Pajouhi, M, Bastanhagh, MH, Baradar-Jalili, R, Vassigh, AR Efficacy of topical epidermal growth factor in healing diabetic foot ulcers. *Therapy* 2005; 2: 759-65.

Title: Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 3327 Study type: RCT Authors: Fernandez-Monntequin et al. (2009)	Total no. of patients = 149 rhEGF 75 ug = 53 rhEGF 25 ug = 48 Control = 48 Treatment rhEGF 75 ug: Male/female = 28/25 Median age (IQR) = 63 (55-69) Median duration of ulcer (wks) (IQR) = 4.3 (2.9-10.3) Median ulcer size (cm^2) (IQR) after initial debridement = 28.5 (10.4-42.8) Treatment rhEGF 25 ug: Male/female = 21/27 Median age (IQR) = 65.5 (56-72) Median duration of ulcer (wks) (IQR) = 4.3 (2.6-8.3) Median ulcer size (cm^2) (IQR) after initial debridement = 20.1 (11-34) Control: Male/female = 27/21 Median age (IQR) = 64 (51-70) Median duration of ulcer (wks) (IQR) = 4.9 (3.3-12.9) Median ulcer size (cm^2) (IQR) after initial debridement = 21.8 (8.8-34.6)	Inclusion: Patients (type 1 or 2 diabetes) >18 years old were included if they had a Wagner's grade 3 or 4 DFU, >1 cm^2 Exclusion: Revascularisation surgery possibility (for ischaemic ulcers), haemoglobin <100 g/l, uncompensated chronic diseases such as heart failure signs, diabetic coma or ketoacidosis and renal failure (creatinine >200mg/dl), malignancies, psychiatric or neurological diseases that could impair proper reasoning for consent, immune-suppressor drugs or corticosteroids use, pregnancy and nursing.	Treatment (injection): rhEGF 75 ug plus standard wound care rhEGF 25 ug plus standard wound care Control: Standard wound care Treatment injected intralesionally, 3 times per week on alternate days. rhEGF was presented as a lyophilised powder containing 75 or 25 u,g per vial (Heberprot-P*, Heber Biotec, Havana). Both doses and placebo vials (containing all components of the formulation except EGF) were indistinguishable. Standard good wound care = ulcers were sharply debrided, gangrenous and necrotic tissue removed (toe disarticulation or transmeta tarsal amputation if necessary) and saline-moistened gauze dressing used. The affected area was pressure off-loaded by bed rest during the hospital period and appropriate footwear afterwards. Metabolic control was strictly followed. Broad-spectrum antibiotics were used if	2 weeks	More than 50% wound reduction (2 weeks): rhEGF 75 ug = 44/53 rhEGF 25 ug = 34/48 Control = 19/48 Adverse events: *Pain at the administration site:* rhEGF 75 ug = 13/53 rhEGF 25 ug = 13/48 Control = 20/48 *Burning sensation:* rhEGF 75 ug = 12/53 rhEGF 25 ug = 10/48 Control = 14/48 *Shivering:* rhEGF 75 ug = 17/53 rhEGF 25 ug = 8/48 Control = 2/48 Lost to follow-up: rhEGF 75 ug = 2/53 rhEGF 25 ug = 3/48 Control = 2/48

	20 centres throughout all Cuban provinces		needed to clear infections before intra-lesional injections started.		

Additional comments:
No details on randomisation methods; no mention of allocation concealment; code was opened after 2 weeks, if no response, patients on placebo or 25 ug EGF were offered to continue treatment unblinded with 25 or 75 ug.

Reference: Fernandez-Montequin, JI, Valenzuela-Silva, CM, Diaz, OG, Savigne, W, Sancho-Soutelo, N, Rivero-Fernandez, F, Sanchez-Penton, P, Morejon-Vega, L, Artaza-Sanz, H, Garcia-Herrera, A, Gonzalez-Benavides, C, Hernandez-Canete, CM, Vazquez-Proenza, A, Berlanga-Acosta, J, Lopez-Saura, PA, Cuban Diabetic Foot Study Group Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study. *International Wound Journal* 2009; 6: 432-43.

Title: A Phase III Study to Evaluate the Safety and Efficacy of Recombinant Human Epidermal Growth Factor (REGEN-D™ 150) in Healing Diabetic Foot Ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 11327 Study type: RCT Authors: Viswanathan et al. (2006)	Total no. of patients = 57 Treatment = 29 Control = 28 *Patients' baseline characteristics not reported.* Multicenter (3 centres) in India.	Inclusion: Target ulcers were no less than 2 cm^2 and no more than 50 cm^2 in area. Healthy men or women between the ages of 18 and 65 years at the time of consent were included. Women had to be of non-child bearing potential (eg, surgically sterilized) or, if of child bearing potential, must have had a negative pregnancy test, must have used adequate contraceptive precautions and must have agreed to continue such precautions up to Week 15. Included patients had controlled diabetes mellitus (type 1 and 2) and foot ulcers. Ulcers that remained open without healing for more than 2-3 weeks (irrespective of the ambulatory treatment administered) were included. Patients had to have ankle brachial index (ABI) readings of ≤ 0.75. Exclusion: Patients with ≥ Grade III Wagner classification diabetic foot ulcers; with life-threatening or serious cardiac failure, gastrointestinal, hepatic, renal, endocrine, hematological, or immunologic disorder; hypertension Grade III; known case of hypersensitivity to the incipient(s); uncontrolled diabetes mellitus (type 1 or 2), diabetic ketoacidosis or coma; past history of current acute or chronic autoimmune disease; chronic alcohol abuse; those who were receiving or had received within 1 month prior to the initial visit any treatment known to impair wound healing including but not limited to corticosteroids, immunosuppressive drugs, cytotoxic agents, radiation therapy, and chemotherapy; use of any marketed,	Treatment: Topical rhEGF gel Control: Placebo gel (water base) No mention of standard good wound care The visit at Day 0 constituted the study medication administration day. The study drug was provided in a gel base to allow for even application (topically) on the ulcer using a sterile cotton swab. This was done twice daily until the wound healed or until the end of Week 15, whichever was earlier Patients were also given oral and intravenous antibiotics	15 weeks	Complete wound healing (15 weeks): Treatment = 25/29 Control = 14/28

		investigational, or herbal medicine or non-registered drug for wounds or burns in the past 6 months; clinically relevant abnormal hematology or biochemistry values; evidence of systemic or local infection; treatment with a dressing containing any other growth factors or other biological dressings within 30 days prior to the screening visit; or participation in another clinical study within 30 days prior to the screening visit or during the study.	for prevention of infection. The antibiotics used were regular antibiotics prescribed for patients with diabetes and foot ulcers		
Additional comments: Randomisation method and allocation concealment were reported; double-blinded (patients and investigators); but no ITT and baseline characteristics not reported.					

Reference: Viswanathan, V, Pendsey, S, Sekar, N, Murthy, GSR A phase III study to evaluate the safety and efficacy of recombinant human epidermal growth factor (REGEN-D 150) in healing diabetic foot ulcers. *Wounds: A Compendium of Clinical Research and Practice* 2006; 18: 186-96.

Section 4: Transforming Growth Factor β2

Title: Effects of Transforming Growth Factor β2 on Wound Healing in Diabetic Foot Ulcers: A Randomized Controlled Safety and Dose-Ranging Trial					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 9180 Study type: RCT Authors: Robson et al. (2002)	Total no. of patients = 177 TGF-β2 0.05 ug/cm^2 = 43 TGF-β2 0.5 ug/cm^2 = 44 TGF-β2 5.0 ug/cm^2 = 44 Placebo = 22 Standard care alone = 24 *TGF-β2 0.05 ug/cm^2:* Male/female (%) = 77/23 Mean age (SD) = 56 (11) Mean ulcer duration (wks) (SD) = 51 (64) Mean ulcer size (cm^2) (SD) = 2.1 (3.1) *TGF-β2 0.5 ug/cm^2:* Male/female (%) = 77/23 Mean age (SD) = 56 (12) Mean ulcer duration (wks) (SD) = 59 (74) Mean ulcer size (cm^2) (SD) = 2.7 (3.6) *TGF-β2 5.0 ug/cm^2:* Male/female (%) = 77/23 Mean age (SD) = 56 (8) Mean ulcer duration (wks) (SD) = 54 (72) Mean ulcer size (cm^2) (SD) = 2.7 (3.5) *Placebo:* Male/female (%) = 82/18 Mean age (SD) = 60 (10) Mean ulcer duration (wks) (SD) = 41 (47) Mean ulcer size (cm^2) (SD) = 2.7 (3.0) *Standard care alone:* Male/female (%) = 92/8 Mean age (SD) = 55 (9) Mean ulcer duration (wks) (SD) = 59 (103) Mean ulcer size (cm^2) (SD) = 2.1 (1.9) Between December 1995 and October 1998	Inclusion: Patients who were at least 18 years of age, had diabetes mellitus and a neuropathic ulcer present for at least 8 weeks on the plantar surface of the forefoot, toes, metatarsals, or dorsum of the fool. After debridement, the ulcer must have been between 1 cm^2 and 20 cm^2 in area and full thickness without exposed bone or tendon; have had adequate peripheral arterial circulation as determined by an ankle/brachial index between 0.7 and 1.3, or a transcutaneous oxygen pressure measurement on the foot of 30 mm Hg or more. Exclusion: Those who had radiographically documented osteomyelitis, clinical infection of the ulcer, use of systemic steroids within the previous 30 days, HgAc greater than 13%, serum creatinine greater than 2.5 mg/dL or serum albumin less than 2 mg/dL.	Treatments: TGF-β2 0.05 ug/cm^2 sponge TGF-β2 0.5 ug/cm^2 sponge TGF-β2 5.0 ug/cm^2 sponge Controls: Placebo collagen sponge Standard care alone All patients who received sponges also received standard care. Standard care = sharp debridement, coverage with non-adherent dressing, and weight off-loading from the affected fool Dressing changes and additional sponge placements were required twice weekly. If, however, clinical infection of the ulcer or osteomyelitis was observed, treatment was suspended and the infection was treated according to best judgment of the physician. If the infection resolved within the 20 week intervention period, treatment could be resumed.	21 weeks	Complete wound healing (week 21): TGF-β2 0.05 ug/cm^2 = 25/43 TGF-β2 0.5 ug/cm^2 = 25/44 TGF-β2 5.0 ug/cm^2 = 27/44 Placebo = 7/22 Standard care alone = 17/24 Median time to wound closure (weeks)[compared to placebo]: TGF-β2 0.05 ug/cm^2 = 16, p = 0.133 TGF-β2 0.5 ug/cm^2 = 12, p = 0.085 TGF-β2 5.0 ug/cm^2 = 13, p = 0.03 Placebo = not reported Standard care alone = 9, p = 0.009 **IQR not reported.* *Uncertainty regarding the report on adverse events (the figures did not match)* 38 patients lost to follow-up.

	15 centres in the United States				
Additional comments: Randomisation method and allocation concealment were reported; double-blinded (patients and investigators).					

Reference: Robson, MC, Steed, DL, McPherson, JM, Pratt, BM Effects of transforming growth factor ÇY2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. *Journal of Applied Research* 2002; 2: 133-46.

Hyperbaric Oxygen Therapy

Title: Hyperbaric oxygen therapy for chronic wounds (Cochrane review)					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: Study type: Systematic review Authors: Kranke et al. (2003)	The baseline characteristics of patients entering these trials varied. 2 trials measured and reported Wagner Grades of the ulcers at baseline, but included different subsets of patients: 1 trial included people with Wagner grade 2, 3, 4; 1 trial included only patients with grade 0, 1, 2. Of the other 2 trials, 1 included any diabetic patient with a chronic foot lesion; whilst 1included patients with lesions present for more than 6 weeks where the ulcers were between 1 and 10 cm in diameter. Both these trials are likely to have included patients with a broad range of Wagner grades and in such cases, particularly where trials are small, imbalance across treatment arms for wound size or severity is highly likely	<u>Inclusion:</u> RCTs that compared the effect on chronic wound healing of treatment with HBOT with no HBOT: Any person in any health care setting with a chronic wound associated with diabetes mellitus. Chronic wounds were defined as described in the retrieved papers (prolonged healing or healing by secondary intention), but must have had some attempt at treatment by other means prior to the application of HBOT. Compared wound care regimens which included HBOT with similar regimens that excluded HBOT. <u>Exclusion criteria:</u> 1 trial specifically excluded patients for whom vascular surgical procedures were planned. Review content assessed as up-to-date: 13 October 2003. <u>Quality assessment by the five-point Oxford-Scale (Jadad 1996):</u> Randomisation Double-blinding Description of withdrawals Each of which, if present, is given a score of 1. Further points are available for description of a reliable randomisation method and use of a placebo (modified for our analysis to include a sham HBOT session). The scores are totalled as an estimate of overall quality of reporting. <u>Missing data</u>	4 trials were included in the systematic review. <u>Treatment:</u> HBOT + standard care HBOT administered in a compression chamber between pressures of 1.5ATA and 3.0ATA and treatment times between 30 minutes and 120 minutes daily or twice daily. Treatment periods ranged from 2 weeks to 6 weeks. <u>Control:</u> Standard care alone 2 trials employed a sham treatment in the control group, on the same schedule as the HBOT group. The other 2 trials did not employ a sham therapy. The comparator group was diverse, any standard treatment regimen designed to promote wound healing was accepted. The salient feature of the comparison group was that these measures had failed before enrolment in the studies. 1 trial did not specify any comparator, 2 trials described a comprehensive and specialised multidisciplinary wound management program to which HBOT was added for the active arm of the trial, and 1 specified a	<u>Treatment period:</u> Doctor (1992) = 4 wks Faglia (1996) = 6 wks Lin (2001) = 30 days Abidia (2003) = 6 wks <u>The follow-up periods varied between trials:</u> Doctor (1992) = *followed patients to discharge from hospital* Faglia (1996) = *followed patients to discharge from hospital* Lin (2001) = 30 days Abidia (2003) = 1 year Faglia (1996) and Abidia (2003) = both had 2 lost to follow-up.	<u>Complete wound healing (end of treatment – 6 weeks):</u> Treatment = 7/9; Control = 4/9 RR = 1.75 (95%CI: 0.78 to 3.93) <u>Complete wound healing (at 6 months follow-up):</u> Treatment = 6/9; Control = 4/9 RR = 1.50 (95%CI: 0.63 to 3.56) <u>Complete wound healing (at 1 year follow-up):</u> Treatment = 8/9; Control = 4/9 RR = 2.00 (95%CI: 0.93 to 4.30) <u>Major amputation:</u> Treatment = 8/60; Control = 19/58 RR = 0.41 (95%CI: 0.19 to 0.86) <u>Minor amputation:</u> Treatment = 6/24; Control = 2/24 RR = 2.60 (95%CI: 0.68 to 10.01) 2 trials (Doctor 1992; Abidia 2003) stated explicitly that there were no complications or adverse events as a result of HBOT. The other 2 trials simply did not report on adverse events or complications of therapy in either arm.

	at entry into the trial.	As ITT was not conducted in some of the trials, missing data was imputed using the worst-case scenario.	surgical and dressing regimen common to both arms.		

Additional comments:
Good quality systematic review.
The study samples were small and the quality of the studies varied. Allocation concealment was unclear in 3 studies.
Standard care was not clearly described in some studies. Also, it is not clear if the surgical decision to amputate was made while blinded to treatment allocation, and this is an important potential source of bias and thus a threat to validity of these results.
No report of adverse events.

Reference: Kranke Peter AU: Bennett Michael Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database of Systematic Reviews: Reviews* 2004; Issue 1.

Title: Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 5583 Study type: RCT Authors: Kessler et al. (2003)	Total no. of patients = 28 (1 withdrawn with no ITT) Treatment = 14; Control = 13 Treatment: Male/female = 10/4 Mean age (SD) = 60.2 (9.7) Mean diabetes duration (years) (SD) = 18.2 (13.2) Mean ulcer size (cm^2) (SD) = 2.31 (2.18) Control: Male/female = 9/4 Mean age (SD) = 67.6 (10.5) Mean diabetes duration (years) (SD) = 22.1 (13.1) Mean ulcer size (cm^2) (SD) = 2.82 (2.43) January 1999 to January 2000 Hospital in France.	Inclusion: Type 1 and 2 diabetic patients admitted to the ward for chronic foot ulcers (Wagner grade 1, 2 and 3). Ulcers depth <2mmfor at least 3 months despite the stabilization of glycemia, the absence of clinical local infection, and satisfactory off-loading measures. Exclusion: Gangrenous ulcers with severe sepsis; severe arteriopathy; emphysema, proliferating retinopathy, claustrophobia.	Treatment: HBOT + standard care Control: Standard care alone Treatment = two 90min daily session of 100% O_2 breathing in a multi-place hyperbaric chamber pressurized at 2.5 ATA; for 5 days a week for 2 consecutive weeks. Standard care = each patient was asked to keep weight off the affected foot. Each patient was provided with an orthopaedic device to remove mechanical stress and pressure at the site of the ulcer during walking; the optimization of metabolic control required subcutaneous insulin administration. Antibiotics were given to patients with chronic infection.	2 weeks treatment with 1 month follow-up (2 weeks in hospital; 2 weeks as outpatient)	Complete wound healing (4 weeks): Treatment = 2/14; Control = 0/13 Reduction of ulcer surface area (4 weeks)(% with SD): Treatment = 61.9% (23.3%) Control = 55.1% (21.5%), p > 0.05.

Additional comments:
No mention of allocation concealment; only investigator-blinded; no ITT.

Reference: Kessler, L, Bilbault, P, Ortega, F, Grasso, C, Passemard, R, Stephan, D, Pinget, M, Schneider, F Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care* 2003; 26: 2378-82.

Title: Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 2982 Study type: RCT Authors: Duzgun et al. (2008)	Total no. of patients = 100 Treatment = 50 Control = 50 Treatment: Male/female = 37/13 Mean age (SD) = 58.1 (11.03) Mean diabetes duration (years) (SD) = 16.9 (6.24) Control: Male/female = 27/23 Mean age (SD) = 63.3 (9.15) Mean diabetes duration (years) (SD) = 15.88 (5.56) January 2002 to December 2003 A teaching and research hospital, Turkey.	Inclusion: Consecutive diabetes patients who were admitted to the emergency surgical department; at least 18 years of age; had a foot wound that had been present for at least 4 weeks despite appropriate local and systemic wound care. Exclusion: Those considered would have contraindications to HBOT such as untreated pneumothorax; COPD; history of otic surgery; URTI; febrile state; history of idiopathic convulsion; hypoglycaemia; current use of corticosteroid, amphetamine, catecholamine or thyroid hormone.	Treatment: HBOT + standard care Control: Standard care alone Treatment = administered at a maximum working pressure of 20 ATA, using a unichamber pressure room employing a volume of $10m^3$ at 2 to 3 ATA for 90mins. Treatment was administered as 2 session per day, alternating throughout the course of therapy, which typically extended for a period of 20 to 30 days. Standard care = daily wound care including dressing changes and local debridement at bedside or in the operating room, as well as amputation when indicated. Infection controls were carried out by clinical follow-up and by performing culture-antibiograms of surgically obtained specimens to determine appropriate antibiotic therapy.	20 to 30 days	Complete wound healing (without any surgical interventions) (30 days): Treatment = 33/50; control = 0/50 Required surgical interventions to achieve wound coverage (surgical debridement, amputation, use of a flap or skin graft): Treatment = 8/50; control = 50/50 Amputation (all): Treatment = 4/50; control = 41/50 Amputation (distal): Treatment = 4/50; control = 24/50 Amputation (proximal): Treatment = 0/50; control = 17/50
Additional comments: No mention of lost to follow-up or ITT.					

Reference: Duzgun, AP, Satir, HZ, Ozozan, O, Saylam, B, Kulah, B, Coskun, F Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. *Journal of Foot & Ankle Surgery* 2008; 47: 515-19.

Title: Randomised controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcer					
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention/ Comparison	Follow-up	Outcome/ Results
ID: 6307 Study type: RCT Authors: Leslie et al. (1988)	Total no. of patients = 28 Treatment = 12; control = 16 <u>Treatment:</u> Male/female = 6/6 Mean age (SD) = 52.8 (8.6) Mean ulcer duration (weeks) (SD) = 6.4 (6.2) Previous amputation = 7/12 <u>Control:</u> Male/female = 10/6 Mean age (SD) = 46.2 (8.5) Mean ulcer duration (weeks) (SD) = 6.2 (7.8) Previous amputation = 5/16 1 April 1983 to 31 July 1985 Rancho Los Amigos Medical Centre Ortho-Diabetes Service, US.	<u>Inclusion:</u> A diagnosis of diabetes; a well demarcated foot ulcer, circular or elliptical in shape; located at or below the level of the ankle, and with no visible bone exposure; the patient was considered to be a candidate for a 2-week trial of conservative therapy and was not deemed to require urgent surgical amputation, according to the attending physician; there was absence of gangrene, crepitation, severe ischemia, and persistent fever > 100^{o}F. <u>Exclusion:</u> None reported.	<u>Treatment:</u> THO + standard care <u>Control:</u> Standard care alone Treatment = two daily 90mins sessions with the topical hyperbaric leg chamber; provided 100% oxygen at pressures that cycled between 0 and 30 mmHg every 20 second. Standard care = treated for 2 weeks with intravenous antibiotics, wet to dry local dressings, and bed rest.	2 weeks	<u>Reduction in ulcer size (at 2 weeks) from baseline:</u> Treatment = 45.6% (SD: 23.4%) Control = 35.6% (SD: 23%) p > 0.05 <u>Reduction in ulcer depth (at 2 weeks) from baseline:</u> Treatment = 75.8% (SD: 23.4%) Control = 67.3% (SD: 23.5%) p > 0.05
<u>Additional comments:</u> No mention of allocation concealment; only investigator-blinded; no mention of lost to follow-up or ITT.					

Reference: Leslie, CA, Sapico, FL, Ginunas, VJ, Adkins, RH Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. *Diabetes Care* 1988; 11: 111-15.

Other Adjunctive Therapies

Evidence table

Title: A Prospective, Randomized, Controlled Trial of Autologous Platelet-Rich Plasma Gel for the Treatment of Diabetic Foot Ulcers.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 2933 Level of evidence: () Study type: RCT Authors: Driver et al. (2006)	Total no. of patients: Baseline = 129 57-excluded Intention to treat-72 PRP-40 Control-32 Because the results of the ITT analyses did not seem to reflect previous clinical outcomes, the study sponsor commissioned an independent audit to ensure study compliance with Good Clinical Practices (GCP) at the investigative sites. Excluded from both groups-32 PRP per protocol-19 Control per protocol- 21 Baseline characteristics: In the intent-to-treat (ITT) population, the mean and standard deviations (SD) for age, HgA_{1c}, wound area, and volume in the two treatments were not significantly different. No significant differences in patient demographics, wound distribution, or ulcer location were observed between the two treatment groups. Setting: 14 investigative sites-USA	Inclusion: Persons with type 1 or type 2 diabetes between the ages of 18 and 95 with an ulcer of at least 4-weeks* duration, hemoglobin AlC <12, index foot ulcer located on the plantar, medial, or lateral aspect of the foot (including all toe surfaces), and wound area (length x width) measurement between 0.5 cm^3 and 20 cm^2, inclusive, wounds located under a Charcot deformity had to be free of acute changes and must have undergone appropriate structural consolidation. The index ulcer had to be clinically noninfected and full-thickness without exposure of bone, muscle, ligaments, or tendons (University of Texas Treatment-Based Diabetic Foot Classification System: Grade 1 A), the limb had to have adequate perfusion. Exclusion: Patient currently enrolled in another investigational device or drug trial or previously enrolled (within last 30 days) in investigative research of a	Platelet rich plasma gel (PRP, n- 40) All patients completed a 7-day screening-period. This included initial excision/debridement, baseline wound measurements and evaluation, and appli-cation of the control saline gel to the wound.	Control- Normal saline gel (n-32) All patients completed a 7-day screening-period. This included initial excision/debridement, baseline wound measurements and evaluation, and application of the control saline gel to the wound.	Weekly up to week 12.	ITT group In the ITT group, 13 out of 40 patients (32.5%) in the PRP gel and nine out of 32 patients (28.1%) in the control group had completely healed wounds after 12 weeks (*P* = 0.79). Relative risk- 13/40 ÷ 9/32 = 1.16 (0.57-2.35) Efficacy outcomes: Healed In the PP dataset, 13 of 19 (68.4%) patients in PRP gel and 9 out of 21 (42.9%) patients in the control group healed (P- 0.125). Relative risk- 13/19 ÷ 9/21 = 1.59 Time to healing: The Kaplan-Meier median time to complete closure was 45 days for PRP gel compared to 85 days for control (log-rank test, *P* - 0.126). Follow-up Of the 40 patients in the PP dataset, 22 with healed wounds participated in the 12-week follow-up phase; of those, 1 in the PRP gel group had a wound that reopened.

	(wound care physicians' and podiatrists' offices, outpatient wound care centres, a university-based college of podiatric medicine clinic, Veteran's Administration wound care clinics, and an Army hospital limb preservation program).	device or pharmaceutical agent Ulcer decreased >50% in area during 7-day screening period; Ulcer is due to non-diabetic aetiology; Patient's blood vessels are non-compressible for ABI testing; Evidence of gangrene in ulcer or on any part of the foot; Patient has radiographic evidence consistent with diagnosis of acute Charcot foot; Patient is currently receiving or has received radiation or chemotherapy within 3 months of randomization; Topical, oral, or IV antibiotic/antimicrobial agents or medications have been used within 2 days (48 hours) of randomization; Patient has received growth factor therapy (e.g., autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, extracellular matrix) within 7 days of randomization; Screening serum albumin level <2.5 g/dL; Screening haemoglobin <10.5 mg/dl Screening platelet count < 100 x 109/L; Patient is undergoing renal dialysis, has known immune insufficiency, known abnormal platelet activation disorders -i.e., gray platelet syndrome, liver disease, active cancer (except remote basal cell of the skin), eating/nutritional, hematologic, collagen vascular disease, rheumatic disease, or bleeding				None of the control-treated patients' wounds re-opened; this difference was not statistically significant. Adverse events 122 adverse events occurring after randomization, 60 (49%) were in the PRP gel group and 62 (51%) in the control group. Relative risk- 0.96 Of the 122 adverse events after randomization, 23 were classified as serious adverse events; 6 occurred in the PRP gel group and 17 in the control group. All serious adverse events were unlikely or unrelated to device usage as defined by the investigators

		disorders; History of peripheral vascular repair within the 30 days of randomization; Patient has known or suspected osteomyelitis; Surgical correction (other than debridement) required for ulcer to heal; Index ulcer has exposed tendons, ligaments, muscle, or bone; Patient is known to have a psychological, developmental, physical, emotional, or social disorder, or any other situation that may interfere with compliance with study requirements and/or healing of the ulcer; History of alcohol or drug abuse within the last year prior to randomization; Patient has inadequate venous access for blood draw ; Patient has a religious or cultural conflict with the use of platelet gel treatment; Patients whose wounds reduced in area by >50% during the screening period were not randomized to treatment and discontinued from any further study participation because they appeared to be able to heal without more advanced intervention.				
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. Confounding mentioned. Power calculation used. Patients lost to follow up and excluded after randomisation was mentioned. All parameters were analysed as intention to treat.						

Reference: Driver, VR, Hanft, J, Fylling, CP, Beriou, JM, Autologel Diabetic Foot Ulcer Study Group A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy/wound management* 2006; 52: 68-70, 72, 74.

Title: Electric Stimulation as an Adjunct to Heal Diabetic Foot Ulcers: A Randomized Clinical Trial.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 8394 Level of evidence: () Study type: RCT Authors: Peters et al. (2001)	Total no. of patients: Baseline = 40 *Electrical stimulation-20* *2 withdrew* *Control-20* *3 withdrew* Baseline characteristics: No significant differences were noted between the treatment and the placebo groups as far as age, gender, glycosylated hemoglobin, peak plantar pressure, duration of diabetes, initial wound area, and neuropathy were concerned. Setting: University medical centre.	Inclusion: All wounds were classified as grades 1A-2A using the University of Texas Diabetic Wound Classification System. All patients had a transcutaneous oxygen tension greater than 30mmHg Exclusion: Soft tissue or bone infection, malignancy, or any cardiac conductivity disorder.	Electrical stimulation (n-20) It was delivered via the Micro-Z$^{TM\,c}$, a small 5.5 x 6cm electric simulation device, that delivers current via a microcomputer to a Dacron-mesh silver nylon stocking. A dose of 50V with 80 twin peak monophase pulses per second was delivered for 10 minutes. This was followed by 10 minutes of 8 pulses per second of current. Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	Placebo-used an active electric stimulation unit but did not deliver any current (n-20) Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	Weekly until week 12	Healed 13 (65%) of the patients healed in the electric stimulation treatment group, 7 (35%) healed in the group that received a sham unit (p-0.058). Relative risk- 13/20 ÷ 7/20 = 1.86 (0.94- 3.7) Rate of Wound Healing and the Average time until wounds healed There was no significant difference in the rate of wound healing and the average time until wounds healed among treatment and placebo groups. The total change in ulcer cross-sectional area was 86.2%versus 71.4% in treatment and control groups, respectively, over the 12-week duration of the study. Among patients who healed, the average healing times for patients with an electric stimulation unit and a placebo unit were 6.8 ± 3.4 weeks and 6.9 ± 2.8 weeks, respectively.
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Peters, EJ, Lavery, LA, Armstrong, DG, Fleischli, JG Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. *Archives of Physical Medicine & Rehabilitation* 2001; 82: 721-25.

Title: The management of neuropathic ulcers of the foot in diabetes by shock wave therapy.						
Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 7455 Level of evidence: () Study type: RCT Authors: Moretti et al. (2009)	Total no. of patients: Baseline = 30 *ESWT-15* *Control-15* Baseline characteristics: There were no significant differences between the two groups in terms of demographics and clinical data. Setting: Diabetic ambulatory of endocrinology unit of university of Bari-Italy.	Inclusion: Neuropathic foot plantar ulceration below the malleoli for a period of at least 6 months with an area wider than 1 cm^2, age 30-70 years, a diameter of the lesion between 0.5 and 5 cm and type 1 diabetes mellitus with insulin treatment for at least 5 years prior. Patients also should have had peripheral neuropathy, ankle-brachial index > 0.7 and palpation of the dorsalis pedis and posterior tibial arteries. Exclusion: Peripheral vascular disease, coronary bypass, pregnancy, coagulation diseases or history of neoplasia or other conditions, based on the principal investigator's clinical judgment.	External shock wave therapy (ESWT) plus standard therapy (n-15) The treatment lasted just 1 or 2 minutes. The protocol consisted of 3 sessions (every 72 hours), with 100 pulses per 1 cm^2 of wound delivered at each session at a flux density of 0.03mJ/mm^2 using a electromagnetic lithotripter (MINILITH SL1). Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	Control-standard therapy consisting of therapeutic footwear, debridement and dressing and treatment of infection (n-15). Both the treatment and placebo group received traditional wound care consisting of debridement, NU-GFI collagen wound gel, and pressure reduction at the site of the ulceration.	For 20 weeks	Healing The proportions of ulcers that healed in 20 weeks in the A and B groups were 53.33% and 33.33%, respectively. Relative risk- 8/15 ÷ 5/15 = 1.60 (0.68-3.77) Healing times For the ulcers that healed during the 20-week period, the healing times were 60.8 +/- 4.7 days (mean +/- DS) in group ESWT and 82.2 +/- 4.7 days (mean +/- DS) in control group patients ($p < 0.001$). Re-epithelisation A significant difference was observed in the index of the re-epithelization between the two groups, with values of 2.97 +/- 0.34 mm^2/die (mean +/- DS) in the ESWT group and 1.30 +/- 0.26 mm^2/die (mean +/- DS) in the control-group ($p < 0.001$). Adverse events All patients of both groups completed the study and attended all control visits. No significant differences emerged between the two groups with regard to treatment complications. One patient in each group developed local signs of infection
Additional comments: Randomisation was performed. Blinding not performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Moretti, B, Notarnicola, A, Maggio, G, Moretti, L, Pascone, M, Tafuri, S, Patella, V The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC Musculoskeletal Disorders* 2009; 10: 54.

<table>
<tr><td colspan="7">Title: Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study.</td></tr>
<tr><td>Level of Evidence</td><td>Patient Population/ Characteristics</td><td>Selection/Inclusion criteria</td><td>Intervention</td><td>Comparison</td><td>Follow-up</td><td>Outcome and Results</td></tr>
<tr><td>ID: 9032

Level of evidence: ()

Study type: RCT

Authors: Reyzelman et al. (2009)</td><td><u>Total no. of patients:</u>
Baseline = 93
7 excluded
Am therapy-47
1 patient withdrew
Control-39

<u>Baseline characteristics:</u>

No statistically significant differences in demographic, ulcer location and pre-treatment ulcer variables were observed between treatment groups.

<u>Setting:</u>
Multicentre-11 sites</td><td><u>Inclusion:</u>
Patients who were 18 years of age or older, with a diagnosis of type 1 ortype 2 diabetes, a University of Texas (UT) grade 1 or 2 diabetic foot ulcer ranging in size from 1 to 25 cm^2, absence of infection, adequate circulation.

<u>Exclusion:</u>
Patients who were in poor metabolic control (HgAlc greater than 12%; within the previous 90 days) were excluded, as were patients with serum creatinine levels of 3-0 mg/ dl or greater. Patients with sensitivity to gentamycin, cefoxilin, linocmycin, polymyxin B or vancomycin also were excluded because of the broth composition in which the AM is processed. Additional exclusion criteria included non re-vascuiarable surgical sites, ulcers probing to bone (UT grades 3A to D), and wounds treated with biomedical or topical growth factors within the</td><td>Study group received a single application of a human acel-lular dermal regenerative tissue matrix graft (n-46)

All patients underwent debridement and off loading.</td><td>Control group received standard-of-care wound management consisting of moist-wound therapy with alginates, foams, hydrocolloids or hydrogels at the discretion of the treating physician (n-39)

All patients underwent debridement and off loading.</td><td>Weekly until complete epithcli-alisation occurred or 12 weeks</td><td>Complete healing:
Of the patients completing the clinical trial, complete healing occurred in 32 (69.6%) of the 46 patients in the study group and 18(46.2%) of the 39 patients in the control group.

Relative risk- 32/46 ÷ 18/39 = 1.50 (1.02-2.22)

There was a statistically significant difference in proportion of healed ulcers between the treatment groups (P = 0.0289, OR – 2.7). Based on the odds ratio, the odds of healing in the study group were 2.7 times higher than in the control group.

Table1: Comparison of time to complete healing of ulcers that healed on or before 12 weeks between treatment groups

<table>
<tr><td></td><td colspan="2">Time to complete healing</td></tr>
<tr><td></td><td>Study group (n-32)</td><td>Control group (n-18)</td></tr>
<tr><td>Mean</td><td>5.7</td><td>6.8</td></tr>
<tr><td>Median</td><td>4.5</td><td>7.0</td></tr>
<tr><td>Standard deviation</td><td>3.5</td><td>3.3</td></tr>
<tr><td>Range</td><td>1.0-12.0</td><td>2.0-12.0</td></tr>
</table>
No statistically significant difference in mean time to wound healing was observed between treatment groups.

A statistically significant difference in non healing rate was calculated between treatment groups (P = 0.0075). At the 12-week endpoint, the non healing rate of 53.8% in the control group was</td></tr>
</table>

		previous 30 days.				significantly higher than the 30.4% non healing rate observed in the study group. After adjusting for ulcer size at presentation (following Cox proportional hazards model), there was a statistically significant difference in non healing rate between treatment groups (P — 0-0233). The corresponding adjusted hazard ratio of 2-0 (95% CI, 1-0-3-5) indicated that the probability of healing is approximately two times greater in the study group than in the control group. Adverse events: A total of 6 occurred in both groups (3-study group, 3-control)
Additional comments: Randomisation was performed. Blinding not performed. Allocation concealment not mentioned. All parameters were analysed as intention to treat. Confounding not mentioned. Power calculation mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Reyzelman, A, Crews, RT, Moore, JC, Moore, L, Mukker, JS, Offutt, S, Tallis, A, Turner, WB, Vayser, D, Winters, C, Armstrong, DG Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *International Wound Journal* 2009; 6: 196-208.

Title: Randomized Clinical Trial Comparing OASIS Wound Matrix to Regranex Gel for Diabetic Ulcers**.**

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 7857 Level of evidence: () Study type: RCT Authors: Niezgoda et al. (2005)	Total no. of patients: Baseline = 98 73 completed treatment assigned OASIS-50 37 completed treatment Regranex-48 36 completed treatment. Patients whose wounds were not healing by the 12th week were given the option to cross over to the other treatment arm; in other words, OASIS-	Inclusion: Patients were age 18 or older Type 1 or type 2 diabetes, 1 to 48 cm^2 in ulcer size, Extends through both the epidermis and dermis, Grade I, Stage A {University of Texas classification), month and nonhealing Viable wound bed with granulation tissue. Exclusion: Exposed bone, tendon, or fascia, clinically defined	OASIS wound matrix (n-50) with standard care *All patients underwent debridement, off loading and regularly cleansed.*	Regranex gel (Growth factor-PDGF, n-48) with standard care *All patients underwent debridement, off loading and regularly cleansed.*	Weekly for 12 weeks and then final 6 month visit.	Healing At the end of the 12-week treatment period, 49% (I8/37) of patients receiving OASIS Wound Matrix were considered healed versus 28% (10/36) of patients receiving daily treatment with Regranex Gel (P- 0.055) Relative risk- 18/37 ÷ 10/36 = 1.75 (0.94-3.26) Subgroup analysis Table 1: INCIDENCE OF HEALING AT 12 WEEKS

		Healed (%)	Not healed (%)
Alt patients	OASIS	18 (49)	19

	treated patients could receive Regranex Gel and vice versa. <u>Baseline characteristics:</u> Patient demographics and baseline values were similar for both groups on all values measured. <u>Setting:</u> *9 outpatient institutions- USA and Canada*	and documented severe arterial disease, history of radiation therapy to ulcer site, Ulcer of nondiabetic pathophysiology, Receiving corticosteroids or immune suppressive, History of collagen vascular disease, Malnutrition (albumin <2.5 g/dl), Known allergy to porcine-derived products, Known hypersensitivity to any component of Regranex Gel (e.g. parabens), Religious or cultural objection to the use of porcine products, Uncontrolled diabetes (A1C>12%, Previous organ transplant, Ulcer clinically infected, Signs of cellulitis, osteomyelitis, necrotic or avascular ulcer bed, Undergoing haemodialysis, Insufficient blood supply to the ulcer ($TcPO_2$ <30 mm Hg or toe-brachial index <0.70), Active Charcot or sickle cell disease, Received treatment with any other investigational drug or device within the last 30 days, Unable to comply with the procedures described in the protocol, Enrolled in a clinical evaluation for another investigational wound care device or drug				<table><tr><td>*(p- 0* .055)</td><td></td><td></td><td>(51)</td></tr><tr><td></td><td>Regranex</td><td>10 (28)</td><td>26 (72)</td></tr><tr><td>Planter ulcers (P- 0.014)</td><td>OASIS</td><td>14 (52)</td><td>13 (48)</td></tr><tr><td></td><td>Regranex</td><td>3 (14)</td><td>18 (86)</td></tr><tr><td>Type 1 diabetes (P- 1.000)</td><td>OASIS</td><td>6 (33)</td><td>12 (67)</td></tr><tr><td></td><td>Regranex</td><td>2 (25)</td><td>6 (75)</td></tr><tr><td>Type *2* diabetes *(P- 0* .034)</td><td>OASIS</td><td>12 (63)</td><td>7 (37)</td></tr><tr><td></td><td>Regranex</td><td>8 (29)</td><td>20 (71)</td></tr></table> Of the patients with type 1 diabetes, 33% (6/18) of OASIS-treated patients healed versus 25% (2/8) of Regranex Gel-treated patients (P = 1). Of the patients with type 2 diabetes, 63% (12/19) of patients treated with OASIS healed versus 29% (8/28) of patients treated with Regranex Gel (P = .034). Of the patients with plantar ulcers, 52% (14/27) of OASIS-treated patients healed versus 14% (3/21) of Regranex Gel-treated patients (P- 0.014) Time to healing No significant difference was found in the mean time to healing between treatment groups (67 days for the OASIS group and 73 days for the Regranex Gel group, P- 0.245)

A Cox proportional hazards regression model showed an improved trend of healing for the OASIS group. This model indicates that at 7 weeks, patients in the OASIS group were approximately twice as likely to heal as those in the Regranex group.

Covariate analysis
Covariate analyses of interest revealed significant differences in healing proportions between treatment group after adjusting for type 1 and type 2 diabetes (P-0.030) and ulcer location (P-0.026).

Recurrence of ulcers
Table 2: RESULTS AT 6-MONTH FOLLOW-UP (n = 37)

	OASIS	Regranex
Total patients seen at follow up	19	18
Patients healed at 12 weeks	8	6
Patients remaining healed at 6 months	6	4
% Recurrence-	25%	33%

Approximately half (37) of the 73 patients were seen at a 6-month or later follow-up visit. Ulcers from 14 of these 37 patients had healed within the 12-week study period; 10 remained healed at the follow-up visit.
Relative risk- 0.79 (0.29-2.12)

Adverse events
A total of 27 study-relevant events were reported for all patients, 17 for the OASIS group and 10 for the Regranex Gel group.
Relative risk- 17/50 ÷ 10/48 = 1.63

Between the 2 treatment groups, no significant

						differences were found in the proportion of patients experiencing complications/adverse events.
Additional comments: Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.						

Reference: Niezgoda, JA, Van Gils, CC, Frykberg, RG, Hodde, JP Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Advances in Skin & Wound Care* 2005; 18: t-66.

Title: Effect of Dalteparin on Healing of Chronic Foot Ulcers in Diabetic Patients With Peripheral Arterial Occlusive Disease. **A prospective, randomized, double-blind, placebo-controlled study.**

Level of Evidence	Patient Population/ Characteristics	Selection/Inclusion criteria	Intervention	Comparison	Follow-up	Outcome and Results
ID: 5365 Level of evidence: () Study type: RCT Authors: Kalani et al. (2003)	Total no. of patients: Baseline = 87 2 dropped out *Delteparin-43* *Placebo-42* *All patients underwent debridement, off loading. Dressings and antibiotic treatment as and when required.* Baseline characteristics: Baseline characteristics of the treatment groups were compa-rable. Setting: Department of Endocrinology and Diabe-tology, Karolinska Hospital ; the Department of Medicine, University Hospital, Lund ; the Diabetes Center, Sahlgrenska University Hospital, Goteborg; and the	Inclusion: Patient with diabetes, chronic foot ulcers and PAOD (peripheral arterial occlusive disease), foot ulcer duration of more than 2 months, ulcer stage 1 and 11 according to the Wagner classification (7), toe/arm blood pressure index ≤0.6, and treatment with a daily dose of *75* mg aspirin for at least four weeks before randomization. Exclusion: Vascular reconstruction or angioplasty performed less than 3 months before randomization, renal insufficiency defined as a serum creatinine level ≥200 p.mol/1, and treatment with anticoagulants.	Dalteparin-0.2 ml (fragmin, 25,000 units/ml) for maximum of 6 months (n-43)	Placebo-0.2ml of physiologic saline for maximum of 6 months (n-42)	For 6 months	Table 1: Ulcer outcome in 85 diabetic patients with PAOD and chronic foot ulcers, randomly assigned lo treatment with dalteparin or placebo See table below The ulcer outcome—including healing with intact

	Dalteparin	Placebo
n	43	42
Healed (with intact skin)	14 (33)	9(21)
Improved (ulcer area decreased ≥50%)	15(35)	11 (26)
Unchanged (decreased or increased ulcer area <50%)	7(16)	9(21)
Impaired (increased ulcer area ≥50%)	5(12)	5(12)
Amputation (above/below ankle)	2(5)	8(19)

	Department of Medicine, University Hospital, Umea, Sweden.					skin; improved, unchanged, or impaired ulcer area; and amputation— was significantly (P = 0.042) improved by Dalteparin treatment compared with placebo. More patients healed with intact skin in the Dalteparin group (n -14) compared with the placebo group (n = 9; NS). Relative risk- 14/43 ÷ 9/42 = 1.57 Reduced ulcer ≥50% in area A total of 15 patients reduced the ulcer area ≥50% in the dalteparin group compared with 11 in the placebo group (NS). Relative risk- 15/43 ÷ 11/42 = 1.35 The percentage decrease in ulcer area was the same in the dalteparin group (73%) as in the placebo group (75%). Healing times There was no significant difference in mean healing time between the dalteparin group (17 ± 8; 8-26 weeks |min-max) and the placebo group (16 ± 7; 8-26 weeks [min-max). Biochemical variables There were no significant differences in haemoglobin concentration, leukocyte count, and serum concentrations of hsCRP, S-AA, albumin, and creatinine between the treatment groups at cither baseline or study termination, respectively, nor were there any significant changes within the treatment groups between study termination and baseline Amputations There were four times more amputations in the placebo group (n= 8) than in the Dalteparin group (n = 2; NS)

						Relative risk- 2/43 ÷ 8/42 = 0.24

Additional comments:
Randomisation was performed. Blinding performed. Allocation concealment not mentioned. All parameters were not analysed as intention to treat. Confounding not mentioned. Power calculation not mentioned. Patients lost to follow up and excluded after randomisation was justified.

Reference: Kalani, M, Apelqvist, J, Blomback, M, Brismar, K, Eliasson, B, Eriksson, JW, Fagrell, B, Hamsten, A, Torffvit, O, Jorneskog, G Effect of dalteparin on healing of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease: a prospective, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2003; 26: 2575-80.

Review question 6: When is the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems?

No study identified met the inclusion/exclusion criteria, therefore no study was included.

Appendix L List of excluded studies

Excluded studies

Review question 1 and review question 2

A guide to new classifications for diabetic foot infections... includes discussion. Wounds: A Compendium of Clinical Research & Practice 2005; 6-12.
Ref ID: 323
Reason for Exclusion: general background

Diabetic foot. Diabetes Research and Clinical Practice 1986; 2: 236-39.
Ref ID: 13
Reason for Exclusion: general background

Dopplers and the diabetic foot. Diabetic Foot 1999; 2: 16-26.
Ref ID: 154
Reason for Exclusion: general background

Guideline to improve foot care in type 2 diabetes patients. Practice Nurse 2004; 27: 6-7.
Ref ID: 297
Reason for Exclusion: not a study

Managing foot ulcers in patients with diabetes. [Review] [29 refs][Erratum appears in Drug Ther Bull 2002 Mar;40(3):24]. Drug & Therapeutics Bulletin 2002; 40: 11-14.
Ref ID: 207
Reason for Exclusion: general background

Managing leg ulcers: A careful history is paramount. *Modern Medicine* 1995; **63:** 22-24.

Ref ID: 44

Reason for exclusion: not a study

Peripheral arterial disease in people with diabetes. Diabetes Care 2003; 26: 3333-42.
Ref ID: 240
Reason for Exclusion: general background

Prevention of diabetic foot complications. World of Irish Nursing 2003; 11: 42-43.
Ref ID: 244
Reason for Exclusion: not a study

Treat NIDDM/osteomyelitis empirically; noninvasive testing is not necessary. *Modern Medicine* 1995; **63:** 37.
Ref ID: 46

Reason for exclusion: not a study

Achari, V Management of diabetic foot. Journal of Internal Medicine of India 2000; 3: 30-36.
Ref ID: 553
Reason for Exclusion: general background

Al Zahrani, HA, Saban, SA, Merdad, HT Management of diabetic foot ulcer. Asian Journal of Surgery 1991; 14: 24-27.
Ref ID: 669
Reason for Exclusion: general background

Alexandrescu, V, Hubermont, G, Philips, Y, Guillaumie, B, Ngongang, C, Coessens, V, Vandenbossche, P, Coulon, M, Ledent, G, Donnay, JC Combined primary subintimal and endoluminal angioplasty for ischaemic inferior-limb ulcers in diabetic patients: 5-year practice in a multidisciplinary 'diabetic-foot' service. European Journal of Vascular & Endovascular Surgery 2009; 37: 448-56.
Ref ID: 699
Reason for exclusion: looks at strategies to aid in healing of ulcers

Alexandrescu, VA, Hubermont, G, Philips, Y, Guillaumie, B, Ngongang, C, Vandenbossche, P, Azdad, K, Ledent, G, Horion, J Selective primary angioplasty following an angiosome model of reperfusion in the treatment of Wagner 1-4 diabetic foot lesions:

Practice in a multidisciplinary diabetic limb service. Journal of Endovascular Therapy 2008; 15: 580-593.
Ref ID: 700
Reason for Exclusion: for q3-4

American Diabetes Association Peripheral arterial disease in people with diabetes. [Review] [37 refs]. Diabetes Care 2003; 26: 3333-41.
Ref ID: 739
Reason for exclusion: general background

Andersen, CA, Roukis, TS The diabetic foot. Surgical Clinics of North America 2007; 87: 1149-78.
Ref ID: 756
Reason for Exclusion: not a study

Andros, G Diagnostic and therapeutic arterial interventions in the ulcerated diabetic foot. [Review] [31 refs]. Diabetes/Metabolism Research Reviews 2004; 20: Suppl-33.
Ref ID: 777
Reason for Exclusion: general background

Apelqvist, J, Agardh, CD The association between clinical risk factors and outcome of diabetic foot ulcers. Diabetes Research & Clinical Practice 1992; 18: 43-53.
Ref ID: 798
Reason for Exclusion: looks at predicting outcome of DFU using clinical risk factors

Apelqvist, J, Larsson, J, Agardh, CD The importance of peripheral pulses, peripheral oedema and local pain for the outcome of diabetic foot ulcers. Diabetic Medicine 1990; 7: 590-594.
Ref ID: 793
Reason for Exclusion: looks at predicting outcome of ulcers using clinical signs and symptoms

Aragon-Sanchez, J, Lazaro-Martinez, JL, Quintana-Marrero, Y, Hernandez-Herrero, MJ, Garcia-Morales, E, Cabrera-Galvan, JJ, Beneit-Montesinos, JV Are diabetic foot ulcers complicated by MRSA osteomyelitis associated with worse prognosis? Outcomes of a surgical series. Diabetic Medicine 2009; 26: 552-55.

Ref ID: 832
Reason for Exclusion: background for MRSA

Armstrong, DG, Lavery, LA, Harkless, LB Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care* 1998; **21:** 855-59.

Ref ID: 900

Reason for exclusion: looks at markers for amputation

Becker, W Imaging osteomyelitis and the diabetic foot. [Review] [48 refs]. *Quarterly Journal of Nuclear Medicine* 1999; **43:** 9-20.
Ref ID: 1306
Reason for Exclusion: narrative review

Benbow, M Diabetic foot ulcers: managing patient care. *Practice Nurse* 2005; **29**.
Ref ID: 1358
Reason for Exclusion: Case Report

Benbow, M Diagnosing and assessing wounds. *Journal of Community Nursing* 2007; **21:** 26-NaN.
Ref ID: 1362
Reason for Exclusion: general background

Benbow, ME Care of a patient with an infected ulcer of the foot. *Journal of Wound Care* 1993; **2:** 142-45.
Ref ID: 1364
Reason for Exclusion: Case Report

Bentley, J, Foster, A Multidisciplinary management of the diabetic foot ulcer. [Review] [25 refs]. *British Journal of Community Nursing* 2008; **12:** S6.
Ref ID: 1398
Reason for Exclusion: general background
Berendt, AR, Peters, EJ, Bakker, K, Embil, JM, Eneroth, M, Hinchliffe, RJ, Jeffcoate, WJ, Lipsky, BA, Senneville, E, Teh, J, Valk, GD Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment (Provisional abstract). *Diabetes/Metabolism Research and Reviews* 2008; **24:** S145-S161.
Ref ID: 1406
Reason for exclusion: general background

Brem, H, Sheehan, P, Rosenberg, HJ, Schneider, JS, Boulton, AJM Evidence-based protocol for diabetic foot ulcers. *Plastic and Reconstructive Surgery* 2006; **117:** 193S-209S.

Ref ID: 1789
Reason for exclusion: narrative review

Bevilacqua, NJ, Rogers, LC Update on MRSA in the diabetic foot. *Podiatry Management* 2007; **26:** 83-89.
Ref ID: 1451
Reason for Exclusion: MRSA background

Blasinska-Przerwa, K, Swiatkowski, J, Michalowska, I, Poltorak, D, Kotapski, J The diabetic foot - diagnostic difficulties. *Ortopedia Traumatologia Rehabilitacja* 2002; **4:** 590-596.
Ref ID: 1530
Reason for Exclusion: not in English
Boike, AM, Hall, JO A practical guide for examining and treating the diabetic foot. [Review] [1 refs]. *Cleveland Clinic Journal of Medicine* 2002; **69:** 342-48.
Ref ID: 1576
Reason for Exclusion: general background

Brash, PD, Foster, J, Vennart, W, Anthony, P, Tooke, JE Magnetic resonance imaging techniques demonstrate soft tissue damage in the diabetic foot. *Diabetic Medicine* 1999; **16:** 55-61.
Ref ID: 1770
Reason for Exclusion: not relevant-assessing neuropathy

Bridges, J, Deitch, EA Diabetic foot infections: Pathophysiology and treatment. *Surgical Clinics of North America* 1994; **74:** 537-55.
Ref ID: 1798
Reason for Exclusion: not a study

Brocklesby, S MRSA, macrophages and maggots. *Diabetic Foot* 2002; **5:** 16-NaN.
Ref ID: 1833
Reason for Exclusion: general background

Brookes, S, O'leary, B Feet first: a guide to diabetic foot services. *British Journal of Nursing* 2006; **15:** S4-10.
Ref ID: 1848
Reason for Exclusion: not a study and a guideline

Brower, AC Diagnosing osteomyelitis in the foot of a patient with diabetes. *American Journal of Roentgenology* 1994; **163:** 471-72.
Ref ID: 1862
Reason for Exclusion: expert opinion

Brower, AC What is the preferred method for diagnosing osteomyelitis in the foot of a patient with diabetes? *AJR* 1994; **American:** 471-72.
Ref ID: 1861
Reason for exclusion: expert opinion

Caballero, E, Frykberg, RG Literature review. Diabetic foot infections. *Journal of Foot & Ankle Surgery* 1998; **37:** 248-59.
Ref ID: 1957
Reason for Exclusion: general background

Canade, A, Savino, G, Porcelli, A, Troia, A, Cina, A, Pedicelli, A, Campioni, P Diagnostic imaging of the diabetic foot. What the clinician expects to know from the radiologist.. *Rays* 2003; **28:** 433-42.
Ref ID: 2006
Reason for Exclusion: Case Report

Ciavarella, A, Silletti, A, Mustacchio, A, Gargiulo, M, Galaverni, MC, Stella, A, Vannini, P Angiographic evaluation of the anatomic pattern of arterial obstructions in diabetic patients with critical limb ischaemia. *Diabete et Metabolisme* 1993; **19:** 586-89.
Ref ID: 2335
Reason for Exclusion: /tests used to outline the anatomic pattern rather than diagnose

Classen, JN, Rolley, RT, Carneiro, R, Martire, JR Management of foot conditions of the diabetic patient. *American Surgeon* 1976; **42:** 81-88.
Ref ID: 2358
Reason for exclusion: not a study

Cobb, J, Claremont, D Noninvasive measurement techniques for monitoring of microvascular function in the diabetic foot. *International Journal of Lower Extremity Wounds* 2002; **1:** 161-69.
Ref ID: 2380
Reason for Exclusion: general background

Collins, R, Cranny, G, Burch, J, Aguiar-Ibanez, R, Craig, D, Wright, K, Berry, E, Gough, M, Kleijnen, J, Westwood, M A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. *Health Technology Assessment* 2007; **11(20):** 1-202.
Ref ID: 2425
Reason for Exclusion: unable to get a copy due to copyright law

Commean, PK, Mueller, MJ, Smith, KE, Hastings, M, Klaesner, J, Pilgram, T, Robertson, DD Reliability and validity of combined imaging and pressures assessment methods for diabetic feet. *Archives of Physical Medicine & Rehabilitation* 2002; **83:** 497-505.
Ref ID: 2429
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Cook, TA, Rahim, N, Simpson, HC, Galland, RB Magnetic resonance imaging in the management of diabetic foot infection. *British Journal of Surgery* 1996; **83:** 245-48.
Ref ID: 2455
Reason for exclusion: not clear what the reference standard was

Corson, JD, Jacobs, RL, Karmody, AM, Leather, RP, Shah, DM The diabetic foot. *Current Problems in Surgery* 1986; **23:** 721-88.
Ref ID: 2482
Reason for exclusion: it's a textbook and not a study

Craig, JG, Amin, MB, Wu, K, Eyler, WR, van Holsbeeck, MT, Bouffard, JA, Shirazi, K Osteomyelitis of the diabetic foot: MR imaging-pathologic correlation. *Radiology* 1997; **203:** 849-55.
Ref ID: 2503
Reason for Exclusion: descriptive of pathology rather than diagnostic accuracy or assessment

Crane, M, Werber, B, Lavery, LA Critical pathway approach to diabetic pedal infections in a multidisciplinary setting. *Journal of Foot and Ankle Surgery* 1999; **38:** 82-83.
Ref ID: 2508
Reason for Exclusion: comment

Crerand, S, Dolan, M, Laing, P, Bird, M, Smith, ML, Klenerman, L Diagnosis of osteomyelitis in neuropathic foot ulcers. *Journal of Bone & Joint Surgery - British Volume* 1996; **78:** 51-55.
Ref ID: 2515
Reason for exclusion: sequential scanning, flaw in methodology

Crim, JR, Seeger, LL Imaging evaluation of osteomyelitis. [Review] [81 refs]. *Critical Reviews in Diagnostic Imaging* 1994; **35:** 201-56.
Ref ID: 2522
Reason for Exclusion: general background

Cuzzell, J Wound assessment and evaluation: diabetic ulcer protocol. *Dermatology Nursing* 2003; **15:** 153.
Ref ID: 2570
Reason for Exclusion: general background

Dante, A, Checchi, A Implementation of clinical pathway in the management of patients with diabetic foot [Italian]. *International Nursing Perspectives* 2008; **8:** 109-13.
Ref ID: 2623
Reason for Exclusion: not in English

De, P, Scarpello, JHB What is the evidence for effective treatment of diabetic foot ulceration? *Practical Diabetes International* 1999; **16:** 179-84.
Ref ID: 2715
Reason for exclusion: general background

Di, GF, Bray, A, Pedicelli, A, Settecasi, C, Priolo, F Diagnostic imaging of the diabetic foot. [Review] [10 refs]. *Rays* 1997; **22:** 550-561.
Ref ID: 2793
Reason for Exclusion: general background

Di, SC, Di, GF, Cina, A, Pedicelli, A, Cotroneo, AR The diabetic foot: role of color-Doppler US. [Review] [19 refs]. *Rays* 1997; **22:** 562-78.
Ref ID: 2795
Reason for Exclusion: general background

Dinh, MT, Abad, CL, Safdar, N Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clinical Infectious Diseases* 2008; **47:** 519-27.
Ref ID: 2827
Reason for Exclusion: general background

Doupis, J, Veves, A Classification, diagnosis, and treatment of diabetic foot ulcers. *Wounds: A Compendium of Clinical Research & Practice* 2008; **20:** 117-27.
Ref ID: 2911
Reason for Exclusion: general background

Dumarey, N, Egrise, D, Blocklet, D, Stallenberg, B, Remmelink, M, del, M, V, Van, SG, Jacobs, F, Goldman, S Imaging infection with 18F-FDG-labeled leukocyte PET/CT: initial experience in 21 patients. *Journal of Nuclear Medicine* 2006; **47:** 625-32.
Ref ID: 2960
Reason for Exclusion: mixed study sample

Durham, JR, Lukens, ML, Campanini, DS, Wright, JG, Smead, WL Impact of magnetic resonance imaging on the management of diabetic foot infections. *American Journal of Surgery* 1991; **162:** 150-154.
Ref ID: 2976
Reason for Exclusion: no reference standard used in the study

Dutta, P, Bhansali, A, Mittal, BR, Singh, B, Masoodi, SR Instant 99mTc-ciprofloxacin scintigraphy for the diagnosis of osteomyelitis in the diabetic foot. *Foot & Ankle International* 2006; **27:** 716-22.
Ref ID: 2980
Reason for exclusion: sequential scanning, selective sampling

Edwards, V A multidisciplinary approach to foot care in diabetes. *Community Nurse* 1998; **4:** 53-55.
Ref ID: 3084
Reason for Exclusion: general background

Fard, AS, Esmaelzadeh, M, Larijani, B Assessment and treatment of diabetic foot ulcer. [Review] [90 refs]. *International Journal of Clinical Practice* 2007; **61:** 1931-38.

Ref ID: 3273
Reason for Exclusion: literature review

Fishman, TD Wound assessment and evaluation. Diabetic neuropathic ulcer. *Dermatology Nursing* 1999; **11:** 116.
Ref ID: 3402
Reason for Exclusion: general background

Fishman, TD Wound assessment and evaluation. Gangrene. *Dermatology Nursing* 2000; **12:** 55-56.
Ref ID: 3407
Reason for Exclusion: general background

Fitzgerald, RH, Mills, JL, Joseph, W, Armstrong, DG The diabetic rapid response acute foot team: 7 essential skills for targeted limb salvage. *Eplasty [Electronic Resource]* 2009; **9:** e15.
Ref ID: 3413
Reason for Exclusion: general background

Foster, A Assessment of diabetic foot ulcers. *Podiatry Now* 2005; **8:** S1-NaN.
Ref ID: 3532
Reason for Exclusion: general background

Foster, A, Edmonds, ME Examination of the diabetic foot. *Practical Diabetes* 1987; **4:** 105-6.
Ref ID: 3507
Reason for Exclusion: general background

Foster, A Changes in the care of the diabetic foot: Part two. *Practical Diabetes International* 2001; **18:** 165-69.
Ref ID: 3524
Reason for exclusion: not a study

Foster, A, Edmonds, ME Examination of the diabetic foot - Part II. *Practical Diabetes* 1987; **4:** 153-54.
Ref ID: 3508
Reason for Exclusion: general background

Fowler, AL, Mitchell, DC Assessment of the vascular status of the diabetic foot. *Diabetic Foot* 1998; **1:** 105-8.
Ref ID: 3558
Reason for Exclusion: general background

Fowler, E, Vesely, N, Pelfrey, M, Jordan, S, Amberry, T Managing diabetic foot ulcers. [Review] [15 refs]. *Home Healthcare Nurse* 65 A.D.; **17:** 357-64.
Ref ID: 3562
Reason for Exclusion: general background

Frykberg, RG Diabetic foot infections: evaluation and management. [Review] [33 refs]. *Advances in Wound Care* 1998; **11:** 329-31.
Ref ID: 3644
Reason for Exclusion: general background

Frykberg, RG The team approach in diabetic foot management. [Review] [46 refs]. *Advances in Wound Care* 1998; **11:** 71-77.
Ref ID: 3648
Reason for exclusion: Not a study and general background.

Gentry, LO Diagnosis and management of the diabetic foot ulcer. *Journal of Antimicrobial Chemotherapy* 1993; **32:** 77-89.
Ref ID: 3848
Reason for Exclusion: general background

Game, F, Jeffcoate, W MRSA and osteomyelitis of the foot in diabetes. *Diabetic Medicine, Supplement* 2004; **21:** 16-19.
Ref ID: 3753
Reason for exclusion: general background

Gershater, MA, Londahl, M, Nyberg, P, Larsson, J, Thorne, J, Eneroth, M, Apelqvist, J Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. *Diabetologia* 2009; **52:** 398-407.
Ref ID: 3875
Reason for Exclusion: looks at monitoring ulcer healing rather than diagnostics

Ghirlanda, G, Mancini, L, Castagneto, M, Citterio, F, Serra, F, Cotroneo, AR, Marano, P The foot clinic. Multidisciplinary management of the patient with diabetic foot. [Review] [5 refs]. *Rays* 1997; **22:** 638-43.
Ref ID: 3889
Reason for Exclusion: general background

Gil, HC, Morrison, WB MR imaging of diabetic foot infection. [Review] [52 refs]. *Seminars in Musculoskeletal Radiology* 2004; **8:** 189-98.
Ref ID: 3938
Reason for Exclusion: not a study

Giurini, JM, Chrzan, JS, Gibbons, GW, Habershaw, GM Charcot's disease in diabetic patients. Correct diagnosis can prevent progressive deformity. [Review] [14 refs]. *Postgraduate Medicine* 1991; **89:** 163-69.
Ref ID: 3973
Reason for Exclusion: general background

Giurini, JM, Lyons, TE Diabetic foot complications: diagnosis and management. [Review] [84 refs]. *International Journal of Lower Extremity Wounds* 2005; **4:** 171-82.

Ref ID: 3980
Reason for Exclusion: general background

Gnanasegaran, G, Chicklore, S, Vijayanathan, S, O'Doherty, MJ, Fogelman, I Diabetes and bone: advantages and limitations of radiological, radionuclide and hybrid techniques in the assessment of diabetic foot. *Minerva Endocrinologica* 2009; **34:** 237-54.
Ref ID: 4006
Reason for Exclusion: general background

Gold, RH, Tong, DJ, Crim, JR, Seeger, LL Imaging the diabetic foot. [Review] [30 refs]. *Skeletal Radiology* 1995; **24:** 563-71.
Ref ID: 4015
Reason for Exclusion: general background

Goldstein, DR, Vogel, KM, Mureebe, L, Kerstein, MD Differential diagnosis: assessment of the lower-extremity ulcer -- is it arterial, venous, neuropathic? *Wounds: A Compendium of Clinical Research & Practice* 1998; **10:** 125-32.
Ref ID: 4037
Reason for Exclusion: general background

Golinko, MS, Clark, S, Rennert, R, Flattau, A, Boulton, AJ, Brem, H Wound emergencies: the importance of assessment, documentation, and early treatment using a wound electronic medical record. *Ostomy Wound Management* 2009; **55:** 54-61.
Ref ID: 4052
Reason for Exclusion: Case Report

Graham, S, Morley, M What "foot care" really means. *American Journal of Nursing* 1984; **84:** 889-92.
Ref ID: 4117
Reason for Exclusion: general background

Grasty, MS Dopplers and the diabetic foot. Use of the hand-held Doppler to detect peripheral vascular disease. *Diabetic Foot* 1999; **2:** 18-22.
Ref ID: 4136
Reason for Exclusion: general background

Gratama, JWC, Bloem, JL, Pope, TL, Jr. Imaging in the diagnosis of osteomyelitis. *Journal of Musculoskeletal Medicine* 1996; **13:** 46-54.
Ref ID: 4137
Reason for Exclusion: narrative review

Green, MF, Aliabadi, Z, Green, BT Diabetic foot: evaluation and management. [Review] [81 refs]. *Southern Medical Journal* 2002; **95:** 95-101.
Ref ID: 4168
Reason for Exclusion: general background

Greenspan, A Advanced imaging of the foot and ankle. *Current Opinion in Orthopaedics* 1998; **9:** 18-23.
Ref ID: 4192
Reason for Exclusion: not a study

Greenspan, A Imaging of the foot and ankle. *Current Opinion in Orthopaedics* 1995; **6:** 72-77.
Ref ID: 4189
Reason for Exclusion: not a study

Hall, M Diagnosis of Charcot foot: an overlooked diabetic consequence. *Journal for Nurse Practitioners* 2009; **5:** 380-382.
Ref ID: 4359
Reason for Exclusion: general background

Halperin, JL Evaluation of patients with peripheral vascular disease. [Review] [34 refs]. *Thrombosis Research* 2002; **106:** V303-V311.
Ref ID: 4364
Reason for Exclusion: /background for PVD

Harris, SB, Stewart, M, Brown, JB, Wetmore, S, Faulds, C, Webster-Bogaert, S, Porter, S Type 2 diabetes in family practice. Room for improvement. *Canadian Family Physician* 2003; **49:** 778-85.
Ref ID: 4466
Reason for Exclusion: /looks at improving knowledge in the family

Hess, CT Management of a diabetic foot ulcer. *Advances in Skin & Wound Care* 2006; **14:** 18-Feb.
Ref ID: 4655
Reason for Exclusion: general background

Hicks, L Correctly assessing diabetic foot ulceration. *Nursing in Practice: The Journal for Today's Primary Care Nurse* 2005; 28-33.
Ref ID: 4673
Reason for Exclusion: general background

Hietala, SO, Lithner, F Diabetic foot angiography. *Acta Endocrinologica, Supplement* 1982; **100:** 29.
Ref ID: 4678
Reason for Exclusion: expert opinion

Hjelm, K, Nyberg, P, Apelqvist, J The diabetic foot: multidisciplinary management from the patient's perspective. *Clinical Effectiveness in Nursing* 2002; **6**.
Ref ID: 4731
Reason for exclusion: foreign setting, not valid as qualitative evidence

Horowitz, JD, Durham, JR, Nease, DB, Lukens, ML, Wright, JG, Smead, WL Prospective evaluation of magnetic resonance imaging in the management of acute diabetic foot infections. *Annals of Vascular Surgery* 1993; **7:** 44-50.

Ref ID: 4841
Reason for exclusion: general background

Howell, M, Thirlaway, S Integrating foot care into the everyday clinical practice of nurses. [Review] [25 refs]. *British Journal of Nursing* 2004; **13:** 470-473.
Ref ID: 4871
Reason for Exclusion: literature review

Jeffcoate, WJ, Lipsky, BA Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. *Clinical Infectious Diseases* 2004; **39:** S115-S122.
Ref ID: 5160
Reason for Exclusion: general background

Johnson, KM Diabetic foot assessment. *Orthoscope* 1996; **2:** 8-11.
Ref ID: 5240
Reason for Exclusion: British library don't have it in their collection

Kalker, AJ, Kolodny, HD, Cavuoto, JW The evaluation and treatment of diabetic foot ulcers. *Journal of the American Podiatry Association* 1982; **72:** 491-96.
Ref ID: 5378
Reason for Exclusion: general background

Kapoor, A, Page, S, Lavalley, M, Gale, DR, Felson, DT Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis. [Review] [38 refs]. *Archives of Internal Medicine* 2007; **167:** 125-32.
Ref ID: 5419
Reason for Exclusion: the population being studies is not purely diabetic foot ulcer patients and unable to extract data

Kesselman, P The comprehensive diabetic foot examination revisited. *Podiatry Management* 2009; **28:** 65-NaN.
Ref ID: 5582
Reason for Exclusion: general background

Khammash, MR, Obeidat, KA, El-Qarqas, EA Screening of hospitalised diabetic patients for lower limb ischaemia: is it necessary? *Singapore Medical Journal* 2008; **49:** 110-113.
Ref ID: 5595
Reason for exclusion: flawed statistical methods

Knight, K, Badamgarav, E, Henning, JM, Hasselblad, V, Gano, AD, Jr., Ofman, JJ, Weingarten, SR A systematic review of diabetes disease management programs. [Review] [57 refs]. *American Journal of Managed Care* 2005; **11:** 242-50.
Ref ID: 5730
Reason for Exclusion: literature review

Kosinski, MA, Joseph, WS Update on the treatment of diabetic foot infections. [Review] [32 refs]. *Clinics in Podiatric Medicine & Surgery* 2007; **24:** 383-96.
Ref ID: 5821
Reason for Exclusion: general background

Kraft, GH The dysvascular and diabetic patient: Update in diagnosis, treatment and rehabilitation. Foreword. *Physical Medicine & Rehabilitation Clinics of North America* 2009; **20:** ix.
Ref ID: 5835
Reason for Exclusion: not a study

Krasner, D Diabetic ulcers of the lower extremity: a review of comprehensive management. [Review] [41 refs]. *Ostomy Wound Management* 1998; **44:** 56-58.
Ref ID: 5842
Reason for Exclusion: narrative review

Kravitz, SR, McGuire, J, Shanahan, SD Physical assessment of the diabetic foot. [Review] [23 refs][Erratum appears in Adv Skin Wound Care. 2003 May-Jun;16(3):145]. *Advances in Skin & Wound Care* 2009; **16:** 68-75.
Ref ID: 5854
Reason for Exclusion: general background

Krishnan, S, Nash, F, Baker, N, Fowler, D, Rayman, G Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. *Diabetes Care* 2008; **31:** 99-101.
Ref ID: 5874
Reason for Exclusion: looks at preventing amputation rates

Krishnan, STM, Baker, NR, Carrington, AL, Rayman, G Comparative roles of microvascular and nerve function in foot ulceration in type 2 diabetes. *Diabetes Care* 2004; **27:** 1343-48.
Ref ID: 5877
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Kruse, I, Edelman, S Evaluation and treatment of diabetic foot ulcers. *Clinical Diabetes* 2006; **24:** 91-93.
Ref ID: 5885
Reason for Exclusion: general background

Krysiak-Zielonka, I Is it possible to predict places of occurrence of diabetic ulceration? *Diabetologia Doswiadczalna i Kliniczna* 2008; **8:** 110-114.
Ref ID: 5891
Reason for Exclusion: risk identification

Kumar, S, Ashe, HA, Parnell, LN, Fernando, DJ, Tsigos, C, Young, RJ, Ward, JD, Boulton, AJ The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. *Diabetic Medicine* 1994; **11:** 480-484.
Ref ID: 5914

Reason for Exclusion: not relevant

Laing, P Diabetic foot ulcers. [Review] [54 refs]. *American Journal of Surgery* 1994; **167:** 31S-6S.
Ref ID: 5985
Reason for Exclusion: general background

Laji, K, Kumar, J, Bishop, J, Page, M Locally developed digital image archive for diabetic foot clinic: A DGH experience. *Practical Diabetes International* 2001; **18:** 231-34.
Ref ID: 5992
Reason for Exclusion: looks at monitoring patients with diabetic foot ulcers and creating a database

Lam, WH, Chao, DVK Diabetic foot - A review in clinical assessment. *Hong Kong Practitioner* 2006; **28:** 301-7.
Ref ID: 6001
Reason for Exclusion: general background

Larsson, J, Agardh, CD, Apelqvist, J, Stenstrom, A Local signs and symptoms in relation to final amputation level in diabetic patients. A prospective study of 187 patients with foot ulcers. *Acta Orthopaedica Scandinavica* 1994; **65:** 387-93.
Ref ID: 6064
Reason for Exclusion: looks at predictors for amputation

Lavery, LA, Armstrong, DG, Harkless, LB Classification of diabetic foot wounds. *Ostomy Wound Management* 1950; **43:** 44-48.
Ref ID: 6095
Reason for Exclusion: general background

Lavery, LA, Armstrong, DG, Harkless, LB Classification of diabetic foot wounds. *Journal of Foot & Ankle Surgery* 1996; **35:** 528-31.
Ref ID: 6108
Reason for Exclusion: general background

Lavery, LA, Armstrong, DG, Harkless, LB Classification of diabetic foot wounds ... reprinted with permission from The Journal of Foot & Ankle Surgery 1996;35(6):528-531... including commentary by Saye DE. *Ostomy Wound Management* 1997; **43:** 44-NaN.
Ref ID: 6122
Reason for Exclusion: general background

Lavery, LA, Armstrong, DG, Vela, SA, Quebedeaux, TL, Fleischli, JG Practical criteria for screening patients at high risk for diabetic foot ulceration. *Archives of Internal Medicine* 1998; **158:** 157-62.
Ref ID: 6123
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Lavery, LA, Armstrong, DG, Peters, EJ, Lipsky, BA Probe-to-bone test for diagnosing diabetic foot osteomyelitis: reliable or relic? *Diabetes Care* 2007; **30:** 270-274.
Ref ID: 6141
Reason for Exclusion: patients recruited from primary care and study in primary care setting

Lavery, LA, Peters, EJ, Williams, JR, Murdoch, DP, Hudson, A, Lavery, DC, International Working Group on the Diabetic Foot Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. *Diabetes Care* 2008; **31:** 154-56.
Ref ID: 6148
Reason for Exclusion: assessing effectiveness of international working group classification system for diabetic foot ulcers

Lavery, LA, Peters, EJ, Armstrong, DG, Wendel, CS, Murdoch, DP, Lipsky, BA Risk factors for developing osteomyelitis in patients with diabetic foot wounds. *Diabetes Research & Clinical Practice* 2009; **83:** 347-52.
Ref ID: 6149
Reason for Exclusion: primary care screening programme

Lavery, LA, Armstrong, DG Temperature monitoring to assess, predict, and prevent diabetic foot complications. *Current Diabetes Reports* 2007; **7:** 416-19.
Ref ID: 6139
Reason for Exclusion: narrative review

Lavery, LA, Armstrong, DG, Murdoch, DP, Peters, EJ, Lipsky, BA Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. *Clinical Infectious Diseases* 2007; **44:** 562-65.
Ref ID: 6142
Reason for Exclusion: looks at infection classification system to grade diabetic foot infections

Lawrence, S, Wraight, P, Campbell, D, Colman, P Current assessment, investigation and management practices of diabetes related foot complications requiring admission to hospital. *Australasian Journal of Podiatric Medicine* 2002; **36:** 95-100.
Ref ID: 6161
Reason for Exclusion: general background and prevalence study of admission

Lawrence, SM, Wraight, PR, Campbell, DA, Colman, PG Assessment and management of inpatients with acute diabetes-related foot complications: Room for improvement. *Internal Medicine Journal* 2004; **34:** 229-33.
Ref ID: 6163
Reason for Exclusion: only reported variations

Ledermann, HP, Morrison, WB Differential diagnosis of pedal osteomyelitis and diabetic neuroarthropathy: MR Imaging. [Review] [70 refs]. *Seminars in Musculoskeletal Radiology* 2005; **9:** 272-83.
Ref ID: 6202
Reason for Exclusion: not a study

Ledermann, HP, Morrison, WB, Schweitzer, ME MR image analysis of pedal osteomyelitis: distribution, patterns of spread, and frequency of associated ulceration and septic arthritis. *Radiology* 2002; **223:** 747-55.
Ref ID: 6196
Reason for Exclusion: 18% of the study sample not diabetic foot, also narrative/descriptive study, no clear analysis

Lee, L, Blume, PA, Sumpio, B Charcot joint disease in diabetes mellitus. [Review] [39 refs]. *Annals of Vascular Surgery* 2003; **17:** 571-80.
Ref ID: 6228
Reason for Exclusion: background for Charcot's

Levin, ME Preventing amputation in the patient with diabetes. [Review] [117 refs]. *Diabetes Care* 1995; **18:** 1383-94.
Ref ID: 6337
Reason for Exclusion: general background

Lipman, BT, Collier, BD, Carrera, GF, Timins, ME, Erickson, SJ, Johnson, JE, Mitchell, JR, Hoffmann, RG, Finger, WA, Krasnow, AZ, Hellman, RS Detection of osteomyelitis in the neuropathic foot: nuclear medicine, MRI and conventional radiography. *Clinical Nuclear Medicine* 1998; **23:** 77-82.
Ref ID: 6474
Reason for exclusion: mixed populations with patients without diabetes, can't extract subgroup

Lipsky, BA Bone of contention: Diagnosing diabetic foot osteomyelitis. *Clinical Infectious Diseases* 2008; **47:** 528-30.
Ref ID: 6525
Reason for Exclusion: narrative review

Lipsky, BA Diabetic foot infections. Pathophysiology, diagnosis, and treatment. [Review] [5 refs]. *International Journal of Dermatology* 1991; **30:** 560-562.
Ref ID: 6487
Reason for Exclusion: general background

Lipsky, BA, Berendt, AR, Deery, HG, Embil, JM, Joseph, WS, Karchmer, AW, LeFrock, JL, Lew, DP, Mader, JT, Norden, C, Tan, JS Diagnosis and treatment of diabetic foot infections. *Journal - American Podiatric Medical Association* 2005; **95:** 183-210.
Ref ID: 6513
Reason for Exclusion: consensus guideline

Lipsky, BA, Berendt, AR, Deery, HG, Embil, JM, Joseph, WS, Karchmer, AW, LeFrock, JL, Lew, DP, Mader, JT, Norden, C, Tan, JS Diagnosis and treatment of diabetic foot infections. *Plastic and Reconstructive Surgery* 2006; **117:** 212S-38S.
Ref ID: 6516
Reason for Exclusion: general background

Lipsky, BA, Berendt, AR, Deery, HG, Embil, JM, Joseph, WS, Karchmer, AW, LeFrock, JL, Lew, DP, Mader, JT, Norden, C, Tan, JS, Infectious Diseases Society of America Diagnosis and treatment of diabetic foot infections.[Reprint in Plast Reconstr Surg. 2006 Jun;117(7 Suppl):212S-238S; PMID: 16799390]. *Clinical Infectious Diseases* 2004; **39:** 885-910.
Ref ID: 6501
Reason for Exclusion: general background
Lipsky, BA New developments in diagnosing and treating diabetic foot infections. *Diabetes/Metabolism Research and Reviews* 2008; **24:** S66-S71.
Ref ID: 6526
Reason for Exclusion: general background

Liu, PT, Dorsey, ML MRI of the foot for suspected osteomyelitis: Improving radiology reports for orthopaedic surgeons. *Seminars in Musculoskeletal Radiology* 2007; **11:** 28-35.
Ref ID: 6562
Reason for Exclusion: narrative review

Loredo, RA, Garcia, G, Chhaya, S Medical imaging of the diabetic foot. [Review] [42 refs]. *Clinics in Podiatric Medicine & Surgery* 2007; **24:** 397-424.
Ref ID: 6649
Reason for Exclusion: general background

Luther, M Critical limb ischaemia in diabetes: Definition, assessment, prognosis. *Vasa - Journal of Vascular Diseases* 2001; **30:** 21-27.
Ref ID: 6706
Reason for Exclusion: consensus guideline and statements

Macfarlane, RM, Jeffcoate, WJ Classification of diabetic foot ulcers: the S(AD) SAD system. *Diabetic Foot* 1999; **2:** 123-30.
Ref ID: 6724
Reason for Exclusion: British library don't have it in their collection

Mader, JT, Ortiz, M, Calhoun, JH Update on the diagnosis and management of osteomyelitis. [Review] [87 refs]. *Clinics in Podiatric Medicine & Surgery* 1996; **13:** 701-24.
Ref ID: 6741
Reason for Exclusion: general background

Marcus, CD, Ladam-Marcus, VJ, Leone, J, Malgrange, D, Bonnet-Gausserand, FM, Menanteau, BP MR imaging of osteomyelitis and neuropathic osteoarthropathy in the feet of diabetics. *Radiographics* 1996; **16:** 1337-48.
Ref ID: 6853
Reason for Exclusion: narrative of cases, no analysis

Margolis, DJ, Allen-Taylor, L, Hoffstad, O, Berlin, JA Diabetic neuropathic foot ulcers: predicting which ones will not heal. *American Journal of Medicine* 2003; **115:** 627-31.

Ref ID: 6862
Reason for Exclusion: not relevant

Margolis, DJ, Gelfand, JM, Hoffstad, O, Berlin, JA Surrogate end points for the treatment of diabetic neuropathic foot ulcers. *Diabetes Care* 2003; **26:** 1696-700.
Ref ID: 6863
Reason for Exclusion: looks at markers to identify healing time of ulcers

Matthews, PC, Berendt, AR, Lipsky, BA Clinical management of diabetic foot infection: diagnostics, therapeutics and the future. [Review] [84 refs]. *Expert Review of Antiinfective Therapy* 2007; **5:** 117-27.
Ref ID: 6989
Reason for Exclusion: general background

McAleese, J Diabetic foot care in the secondary care setting. *Journal of Diabetes Nursing* 2006; **10:** -NaN.
Ref ID: 7041
Reason for Exclusion: not a study

McDermott, JE The diabetic foot: diagnosis and prevention. [Review] [17 refs]. *Instructional Course Lectures* 1993; **42:** 117-20.
Ref ID: 7115
Reason for Exclusion: general background

McInnes, A, Booth, J, Birch, I Multidisciplinary diabetic foot care teams: professional education. *Diabetic Foot* 1998; **1:** 109-15.
Ref ID: 7141
Reason for Exclusion: general background

McInnes, A, Booth, J, Birch, I Multidisciplinary diabetic foot care teams: skills and knowledge. *Diabetic Foot* 1999; **2:** 67-71.
Ref ID: 7146
Reason for Exclusion: general background

Medical Services Advisory Committee LeukoScan(R). For use in diagnostic imaging of the long bones and feet in patients with suspected osteomyelitis, including those with diabetic foot ulcers (Structured abstract). *Canberra: Medical Services Advisory Committee (MSAC)* 2003; 118.
Ref ID: 7217
Reason for Exclusion: British library don't have it in their collection

Mekkes, JR, Loots, MA, Van Der Wal, AC, Bos, JD Causes, investigation and treatment of leg ulceration. [Review] [104 refs]. *British Journal of Dermatology* 2003; **148:** 388-401.
Ref ID: 7250
Reason for Exclusion: narrative review

Miller, AO, Henry, M Update in diagnosis and treatment of diabetic foot infections. [Review] [65 refs]. *Physical Medicine & Rehabilitation Clinics of North America* 2009; **20:** 611-25.
Ref ID: 7307
Reason for Exclusion: consensus guideline

Morrison, WB, Ledermann, HP, Schweitzer, ME MR imaging of the diabetic foot. *Magnetic Resonance Imaging Clinics of North America* 2001; **9:** 603-13.
Ref ID: 7477
Reason for Exclusion: general background

Morrison, WB, Schweitzer, ME, Batte, WG, Radack, DP, Russel, KM Osteomyelitis of the foot: relative importance of primary and secondary MR imaging signs. *Radiology* 1998; **207:** 625-32.
Ref ID: 7475
Reason for Exclusion: 15% of the study sample not diabetic foot, unable to extract data

Mueller, MJ, Smith, KE, Commean, PK, Robertson, DD, Johnson, JE Use of computed tomography and plantar pressure measurement for management of neuropathic ulcers in patients with diabetes. *Physical Therapy* 1999; **79:** 296-307.
Ref ID: 7549
Reason for Exclusion: Case Report

Naheed, T, Akbar, N, Shehzad, M, Jamil, S, Ali, T Skin manifestations amongst diabetic patients admitted in a general medical ward for various other medical problems. *Pakistan Journal of Medical Sciences* 2002; **18:** 291-96.
Ref ID: 7691
Reason for exclusion: general background

Ndip, A, Jude, EB, Whitehouse, R, Prescott, M, Boulton, AJ Charcot neuroarthropathy triggered by osteomyelitis and/or surgery. *Diabetic Medicine* 2008; **25:** 1469-72.
Ref ID: 7744
Reason for Exclusion: Case Report

Newman, LG Imaging techniques in the diabetic foot. [Review] [41 refs]. *Clinics in Podiatric Medicine & Surgery* 1995; **12:** 75-86.
Ref ID: 7808
Reason for exclusion: systematic review

Nigro, ND, Bartynski, WS, Grossman, SJ, Kruljac, S Clinical impact of magnetic resonance imaging in foot osteomyelitis.[Erratum appears in J Am Podiatr Med Assoc 1993 Feb;83(2):86]. *Journal of the American Podiatric Medical Association* 1992; **82:** 603-15.
Ref ID: 7858
Reason for Exclusion: population is not purely diabetic foot ulcers and its not possible to extract data only for diabetic patients

Nube, VL, McGill, M, Molyneaux, L, Yue, DK From acute to chronic: monitoring the progress of Charcot's arthropathy. *Journal of the American Podiatric Medical Association* 2002; **92:** 384-89.
Ref ID: 7911
Reason for Exclusion: general background

O'Hanlon, JM, Keating, SE Osteomyelitis of the foot in diabetic patients: evaluation with magnetic resonance imaging. *Journal of Foot Surgery* 1991; **30:** 137-42.
Ref ID: 7946
Reason for Exclusion: Case Report

O'Meara, S, Nelson, EA, Golder, S, Dalton, JE, Craig, D, Iglesias, C, DASIDU Steering Group Systematic review of methods to diagnose infection in foot ulcers in diabetes. [Review] [23 refs]. *Diabetic Medicine* 2006; **23:** 341-47.
Ref ID: 7953
Reason for exclusion: general background

Orsted, HL, Searles, GE, Trowell, H, Shapera, L, Miller, P, Rahman, J Best practice recommendations for the prevention, diagnosis, and treatment of diabetic foot ulcers: update 2006... reprinted with permission from Wound Care Canada, the Official Publication of the Canadian Association of Wound Care (2006; 4[1]: 57-71). *Advances in Skin & Wound Care* 2007; **20:** 655-69.
Ref ID: 8055
Reason for exclusion: general background

Pakarinen, TK, Laine, HJ, Honkonen, SE, Peltonen, J, Oksala, H, Lahtela, J Charcot arthropathy of the diabetic foot. Current concepts and review of 36 cases. [Review] [39 refs]. *Scandinavian Journal of Surgery: SJS* 2002; **91:** 195-201.
Ref ID: 8145
Reason for Exclusion: descriptive/narrative of cases, no analysis

Parsons, LM Pitfalls in the diagnosis of chronic osteomyelitis in the presence of a contiguous neuropathic ulcer. *Journal of Cutaneous Medicine & Surgery* 2009; **13:** Suppl-7.
Ref ID: 8244
Reason for Exclusion: expert opinion

Patout, CA, Jr., Birke, JA, Wilbright, WA, Coleman, WC, Mathews, RE A decision pathway for the staged management of foot problems in diabetes mellitus. [Review] [42 refs]. *Archives of Physical Medicine & Rehabilitation* 2001; **82:** 1724-28.
Ref ID: 8281
Reason for Exclusion: general background

Payne, C Regional variations of diabetic foot complications and podiatric services. *Australasian Journal of Podiatric Medicine* 1999; **33:** 51-55.
Ref ID: 8298
Reason for Exclusion: general background for q1

Payne, CB Health services planning and the diabetic foot. *Foot* 1997; **7:** 159-65.
Ref ID: 8301
Reason for Exclusion: general background

Penny, HL, Webster, N, Sullivan, R, Spinazzola, J A multidisciplinary approach to a possible limb-threatening infection. *Advances in Skin & Wound Care* 2008; **21:** 564-67.
Ref ID: 8337
Reason for Exclusion: Case Report

Peters, EJ, Lavery, LA, International Working Group on the Diabetic Foot Effectiveness of the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. *Diabetes Care* 2001; **24:** 1442-47.
Ref ID: 8393
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Petre, M, Erdemir, A, Cavanagh, PR An MRI-compatible foot-loading device for assessment of internal tissue deformation. *Journal of Biomechanics* 2008; **41:** 470-474.
Ref ID: 8422
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Pham, H, Armstrong, DG, Harvey, C, Harkless, LB, Giurini, JM, Veves, A Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. *Diabetes Care* 2000; **23:** 606-11.
Ref ID: 8450
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Piaggesi, A, Palumbo, F, Tedeschi, A, Ambrosini, L, Macchiarini, S, Scatena, A, Goretti, C, Campi, F, Rizzo, L Measurements in the diabetic foot. *Wounds: A Compendium of Clinical Research & Practice* 2005; **17:** 247-55.
Ref ID: 8505
Reason for Exclusion: general background

Pinzur, MS, Shields, N, Trepman, E, Dawson, P, Evans, A Current practice patterns in the treatment of Charcot foot. [Review] [6 refs]. *Foot & Ankle International* 2000; **21:** 916-20.
Ref ID: 8571
Reason for Exclusion: looks at current treatment patterns in patients with Charcot's

Pinzur, MS, Slovenkai, MP, Trepman, E Guidelines for diabetic foot care. The Diabetes Committee of the American Orthopaedic Foot and Ankle Society. *Foot & Ankle International* 1999; **20:** 695-702.
Ref ID: 8563
Reason for Exclusion: general background

Pinzur, MS, Slovenkai, MP, Trepman, E, Shields, NN, Diabetes Committee of American Orthopaedic Foot and Ankle Society Guidelines for diabetic foot care: recommendations endorsed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society. *Foot & Ankle International* 2005; **26:** 113-19.
Ref ID: 8591
Reason for exclusion: general background

Prompers, L, Schaper, N, Apelqvist, J, Edmonds, M, Jude, E, Mauricio, D, Uccioli, L, Urbancic, V, Bakker, K, Holstein, P, Jirkovska, A, Piaggesi, A, Ragnarson-Tennvall, G, Reike, H, Spraul, M, Van, AK, Van, BJ, Van, MF, Ferreira, I, Huijberts, M Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia* 2008; **51:** 747-55.
Ref ID: 8730
Reason for Exclusion: looks at predictors of ulcer healing in patients with diabetic foot

Prompers, L, Huijberts, M, Apelqvist, J, Jude, E, Piaggesi, A, Bakker, K, Edmonds, M, Holstein, P, Jirkovska, A, Mauricio, D, Tennvall, GR, Reike, H, Spraul, M, Uccioli, L, Urbancic, V, Van, AK, Van, BJ, Van, MF, Schaper, N Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. *Diabetic Medicine* 2008; **25:** 700-707.
Ref ID: 8729
Reason for exclusion: general background

Rahman, A, Moizuddin, M, Ahmad, M, Salim, M Vasculopathy in patients with diabetic foot using Doppler ultrasound. *Pakistan Journal of Medical Sciences* 2009; **25:** 428-33.
Ref ID: 8802
Reason for Exclusion: narrative of cases, no analysis

Rajbhandari, SM, Harris, ND, Sutton, M, Lockett, C, Eaton, S, Gadour, M, Tesfaye, S, Ward, JD Digital imaging: an accurate and easy method of measuring foot ulcers. *Diabetic Medicine* 1999; **16:** 339-42.
Ref ID: 8825
Reason for Exclusion: monitoring measurement of foot ulcers rather than diagnostics

Rajbhandari, SM, Sutton, M, Davies, C, Tesfaye, S, Ward, JD 'Sausage toe': a reliable sign of underlying osteomyelitis. *Diabetic Medicine* 2000; **17:** 74-77.
Ref ID: 8827
Reason for exclusion: case reports

Rajbhandari, SM, Harris, ND, Tesfaye, S, Ward, JD Early identification of diabetic foot ulcers that may require intervention using the micro lightguide spectrophotometer. *Diabetes Care* 1999; **22:** 1292-95.
Ref ID: 8824
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Ramsey, DE, Manke, DA, Sumner, DS Toe blood pressure. A valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. *Journal of Cardiovascular Surgery* 1983; **24:** 43-48.

Ref ID: 8852
Reason for Exclusion: monitoring ulcer healing rather than diagnostics

Reinherz, RP, Cheleuitte, ER, Fleischli, JG, Hill, M Identification and treatment of the diabetic neuropathic foot. [Review] [28 refs]. *Journal of Foot & Ankle Surgery* 1995; **34:** 74-78.
Ref ID: 9004
Reason for Exclusion: general background

Rogers, LC, Bevilacqua, NJ Imaging of the Charcot foot. [Review] [36 refs]. *Clinics in Podiatric Medicine & Surgery* 2006; **25:** 263-74.
Ref ID: 9201
Reason for Exclusion: general background

Rooh, UM, Ahmed, M, Griffin, S Evaluation and management of diabetic foot according to Wagner's classification. A study of 100 cases. *Journal of Ayub Medical College, Abbottabad: JAMC* 2003; **15:** 39-42.
Ref ID: 9245
Reason for Exclusion: general background

Russell, JM, Peterson, JJ, Bancroft, LW MR Imaging of the Diabetic Foot. *Magnetic Resonance Imaging Clinics of North America* 2008; **16:** 59-70.
Ref ID: 9350
Reason for Exclusion: general background

Saleem, TFM, Caputo, GM, Juliano, PJ, Ulbrecht, JS Recognizing and managing Charcot foot. *Emergency Medicine (00136654)* 2003; **35:** 43-49.
Ref ID: 9431
Reason for Exclusion: general background
Santilli, JD, Santilli, SM Chronic critical limb ischemia: diagnosis, treatment and prognosis. [Review] [21 refs]. *American Family Physician* 1999; **59:** 1899-908.
Ref ID: 9506
Reason for Exclusion: general background

Santos, D, Carline, T Examination of the lower limb in high risk patients. [Review] [60 refs]. *Journal of Tissue Viability* 2000; **10:** 97-105.
Ref ID: 9511
Reason for Exclusion: general background

Sapico, FL, Witte, JL, Canawati, HN, Montgomerie, JZ, Bessman, AN The infected foot of the diabetic patient: quantitative microbiology and analysis of clinical features. *Reviews of Infectious Diseases* 1984; **6:** Suppl-6.
Ref ID: 9516
Reason for Exclusion: general background

Saraogi, RK Diabetic foot ulcer: Assessment and management. *Journal of the Indian Medical Association* 2008; **106:** 112-19.
Ref ID: 9519
Reason for Exclusion: general background

Schaper, NC, Apelqvist, J, Bakker, K The international consensus and practical guidelines on the management and prevention of the diabetic foot. *Current Diabetes Reports* 2003; **3:** 475-79.
Ref ID: 9586
Reason for Exclusion: consensus guideline

Schinabeck, MK, Johnson, JL Osteomyelitis in diabetic foot ulcers. Prompt diagnosis can avert amputation. *Postgraduate Medicine* 2005; **118:** 11-15.
Ref ID: 9624
Reason for Exclusion: general background

Schlossbauer, T, Mioc, T, Sommerey, S, Kessler, SB, Reiser, MF, Pfeifer, KJ Magnetic resonance imaging in early stage charcot arthropathy: correlation of imaging findings and clinical symptoms. *European Journal of Medical Research* 2008; **13:** 409-14.
Ref ID: 9635
Reason for Exclusion: mixed population and unable to extract data only on diabetic population

Schofield, CJ, Stang, D, Jones, GC, Leese, GP The foot in practice... The 6th Biennial Practical Diabetes Foot Conference in Scotland held in Dundee on 16 May 2007. *Practical Diabetes International* 2007; **24:** 416-17.
Ref ID: 9652
Reason for Exclusion: British library don't have it in their collection

Schweitzer, ME, Morrison, WB MR imaging of the diabetic foot. *Radiologic Clinics of North America* 2004; **42:** 61-71.
Ref ID: 9693
Reason for Exclusion: general background

Sehati, F Raising the standards for diabetic foot care. *Podiatry Management* 1997; **16:** 49-53.
Ref ID: 9743
Reason for Exclusion: expert interview

Sella, EJ Current concepts review: diagnostic imaging of the diabetic foot. [Review] [42 refs]. *Foot & Ankle International* 2009; **30:** 568-76.
Ref ID: 9759
Reason for Exclusion: general background

Sella, EJ, Grosser, DM Imaging modalities of the diabetic foot. [Review] [38 refs]. *Clinics in Podiatric Medicine & Surgery* 2003; **20:** 729-40.
Ref ID: 9756
Reason for Exclusion: narrative review

Sella, EJ, Barrette, C Staging of Charcot neuroarthropathy along the medial column of the foot in the diabetic patient. *Journal of Foot & Ankle Surgery* 1999; **38:** 34-40.
Ref ID: 9754
Reason for Exclusion: no analysis, no indicator for what treatment

Senior, C Assessment of infection in diabetic foot ulcers. [Review] [56 refs]. *Journal of Wound Care* 2000; **9:** 313-17.
Ref ID: 9769
Reason for exclusion: not a study

Shank, CF, Feibel, JB Osteomyelitis in the diabetic foot: diagnosis and management. [Review] [59 refs]. *Foot & Ankle Clinics* 2006; **11:** 775-89.
Ref ID: 9817
Reason for Exclusion: general background

Siller, TA, Calhoun, JH, Mader, JT Diabetic foot infections: active intervention to preserve function. *Journal of Musculoskeletal Medicine* 1996; **13:** 43-51.
Ref ID: 9992
Reason for Exclusion: narrative review

Silver, K, Sollitto, RJ, Jamil, Z Digital subtraction angiography versus noninvasive testing in the vascular assessment of the ischemic foot. *Journal of Foot Surgery* 1987; **26:** 217-21.
Ref ID: 9998
Reason for Exclusion: Case Report

Sinacore, DR, Withrington, NC Recognition and management of acute neuropathic (Charcot) arthropathies of the foot and ankle. [Review] [47 refs]. *Journal of Orthopaedic & Sports Physical Therapy* 1999; **29:** 736-46.
Ref ID: 10049
Reason for Exclusion: narrative review of Charcot

Slater, R, Ramot, Y, Rapoport, M Diabetic foot ulcers: principles of assessment and treatment. [Review] [27 refs]. *Israel Medical Association Journal: Imaj* 2001; **3:** 59-62.
Ref ID: 10102
Reason for Exclusion: general background

Slater, RA, Ramot, Y, Buchs, A, Rapoport, MJ The diabetic Charcot foot. [Review] [25 refs]. *Israel Medical Association Journal: Imaj* 2004; **6:** 280-283.
Ref ID: 10104
Reason for Exclusion: general background

Smieja, M, Hunt, DL, Edelman, D, Etchells, E, Cornuz, J, Simel, DL Clinical examination for the detection of protective sensation in the feet of diabetic patients. *Journal of General Internal Medicine* 1999; **14:** 418-24.

Ref ID: 10130
Reason for Exclusion: risk classification

Smith, RG Validation of Wagner's classification: a literature review. [Review] [52 refs]. *Ostomy Wound Management* 2003; **49:** 54-62.
Ref ID: 10177
Reason for Exclusion: general background

Snyder, RJ, Cohen, MM, Sun, C, Livingston, J Osteomyelitis in the diabetic patient: diagnosis and treatment. Part 1: Overview, diagnosis, and microbiology. [Review] [67 refs]. *Ostomy Wound Management* 1925; **47:** 18-22.
Ref ID: 10195
Reason for Exclusion: general background

Sommer, TC, Lee, TH Charcot foot: the diagnostic dilemma. [Review] [21 refs][Erratum appears in Am Fam Physician 2002 Jun 15;65(12):2436-8]. *American Family Physician* 2001; **64:** 1591-98.
Ref ID: 10252
Reason for Exclusion: general background

Spaeth, HJ, Jr., Dardani, M Magnetic resonance imaging of the diabetic foot. [Review] [28 refs]. *Magnetic Resonance Imaging Clinics of North America* 1994; **2:** 123-30.
Ref ID: 10278
Reason for Exclusion: general background

Spollett, GR Preventing amputations in the diabetic population. [Review] [44 refs]. *Nursing Clinics of North America* 1998; **33:** 629-41.
Ref ID: 10305
Reason for Exclusion: general background

Springett, K Foot ulceration in diabetic patients. [Review] [33 refs]. *Nursing Standard* 1970; **14:** 65-68.
Ref ID: 10308
Reason for Exclusion: British library don't have it in their collection

Stanley, S, Turner, L A collaborative care approach to complex diabetic foot ulceration. [Review] [41 refs]. *British Journal of Nursing* 2004; **13:** 788-93.
Ref ID: 10359
Reason for Exclusion: not a study

Strauss, M, Barry, DD Vascular assessment of the neuropathic foot. *Journal of Prosthetics & Orthotics (JPO)* 2005; **17:** S35-NaN.
Ref ID: 10467
Reason for Exclusion: not a study

Stuart, L, Baker, N Diabetes foot care services: location, location, and location? *Practical Diabetes International* 2007; **24:** 289-91.
Ref ID: 10511
Reason for Exclusion: general background

Stuart, L, Wiles, P, Chadwick, P, Smith, P Improving peripheral arterial assessment of people with diabetes. *Diabetic Foot* 2004; **7:** 183-86.
Ref ID: 10506
Reason for Exclusion: general background

Sykes, MT, Godsey, JB Vascular evaluation of the problem diabetic foot. [Review] [228 refs]. *Clinics in Podiatric Medicine & Surgery* 1998; **15:** 49-83.
Ref ID: 10595
Reason for Exclusion: general background

The diabetic foot. *Clinics in Podiatric Medicine & Surgery* 1987; **4:** 315-522.
Ref ID: 14
Reason for Exclusion: general background

Takahashi, T, Nishizawa, Y, Emoto, M, Kawagishi, T, Matsumoto, N, Ishimura, E, Inaba, M, Okuno, Y, Shimada, H, Morii, H Sympathetic function test of vasoconstrictor changes in foot arteries in diabetic patients. *Diabetes Care* 1998; **21:** 1495-501.
Ref ID: 10614
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Takolander, R, Rauwerda, JA The use of non-invasive vascular assessment in diabetic patients with foot lesions. *Diabetic Medicine* 1996; **13:** S39-S42.
Ref ID: 10618
Reason for Exclusion: general background

Tan, JS Current management recommendations for patients with diabetic foot infections. *Infectious Diseases in Clinical Practice* 2005; **13:** 216-23.
Ref ID: 10647
Reason for Exclusion: narrative review

Tan, JS, File, TM, Jr. Diagnosis and treatment of diabetic foot infections. [Review] [18 refs]. *Comprehensive Therapy* 1988; **14:** 57-62.
Ref ID: 10635
Reason for Exclusion: general background

Tan, JS, File, TM, Jr. Diagnosis and treatment of diabetic foot infections. [Review] [62 refs]. *Best Practice & Research in Clinical Rheumatology* 1999; **13:** 149-61.
Ref ID: 10641
Reason for Exclusion: general background

Tan, JS, Flanagan, PJ, Donovan, DL, File, TM Team approach in the management of diabetic foot infections. *Journal of Foot Surgery* 1987; **26:** Suppl-6.
Ref ID: 10634
Reason for Exclusion: general background

Tan, MJ, Tan, JS Managing foot infections in patients with diabetes. *Infections in Medicine* 2006; **23:** 168-73.
Ref ID: 10649
Reason for Exclusion: narrative review

Tan, PL, Teh, J MRI of the diabetic foot: differentiation of infection from neuropathic change. [Review] [39 refs]. *British Journal of Radiology* 2007; **80:** 939-48.
Ref ID: 10652
Reason for Exclusion: general background

Tassler, PL, Dellon, AL, Scheffler, NM Computer-assisted measurement in diabetic patients with and without foot ulceration. *Journal of the American Podiatric Medical Association* 1995; **85:** 679-84.
Ref ID: 10683
Reason for Exclusion: not relevant

Tec-Hock, CJ, Tan, SB, Sivathasan, C, Pavanni, R, Tan, SK Vascular assessment in the neuropathic diabetic foot. *Clinical Orthopaedics and Related Research* 1995; **320:** 95-100.
Ref ID: 10697
Reason for exclusion: highly selective patients, not relevant analysis

Teh, J, Berendt, T, Lipsky, BA Rational Imaging . Investigating suspected bone infection in the diabetic foot. *BMJ* 2009; **339:** b4690.
Ref ID: 10703
Reason for Exclusion: expert opinion

Temar, K, Warren, W, Kyramarios, C, Williams, A, Hanft, JR Diabetic foot infections: identification and treatment. *Podiatry Management* 2003; **22:** 83-NaN.
Ref ID: 10708
Reason for Exclusion: not a study

Tennvall, GR, Apelqvist, J, Eneroth, M The inpatient care of patients with diabetes mellitus and foot ulcers. A validation study of the correspondence between medical records and the Swedish Inpatient Registry with the consequences for cost estimations. *Journal of Internal Medicine* 2000; **248:** 397-405.
Ref ID: 10718
Reason for Exclusion: general background

Thivolet, C, el, FJ, Petiot, A, Simonet, C, Tourniaire, J Measuring vibration sensations with graduated tuning fork. Simple and reliable means to detect diabetic patients at risk of neuropathic foot ulceration. *Diabetes Care* 1990; **13:** 1077-80.

Ref ID: 10752
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

Thompson, C, McWilliams, T, Scott, D, Simmons, D Importance of diabetic foot admissions at Middlemore Hospital. *New Zealand Medical Journal* 1993; **106:** 178-80.
Ref ID: 10781
Reason for Exclusion: looks at how long patients are admitted in hospital and how much it costs

Thomson, FJ, Boulton, AJM Guidelines to diabetic foot care in the elderly. (Review article). *Care of the Elderly* 1990; **2**.
Ref ID: 10798
Reason for Exclusion: general background

Thurston, R, Beattie, C Diabetes. Four. Foot lesions in diabetics. Care of a patient. *Nursing Times* 1984; **80:** 48-50.
Ref ID: 10814
Reason for Exclusion: general background

Tonnesen, KH, Noer, I, Paaske, W, Sager, P Classification of peripheral occlusive arterial diseases based on symptoms, signs and distal blood pressure measurements. *Acta Chirurgica Scandinavica* 1980; **146:** 101-4.
Ref ID: 10860
Reason for Exclusion: monitoring peripheral occlusive arterial disease rather than diagnostics

Trepanier, E, Pavlovich-Danis, SJ Taking the right steps for diabetic feet. *NurseWeek (15475131)* 2009; **16:** 22-28.
Ref ID: 10918
Reason for Exclusion: general background

Treece, KA, Macfarlane, RM, Pound, N, Game, FL, Jeffcoate, WJ Validation of a system of foot ulcer classification in diabetes mellitus. *Diabetic Medicine* 2004; **21:** 987-91.
Ref ID: 10911
Reason for Exclusion: no indication for treatments, scoring only associated with healed vs. Unhealed

Tseng, CL, Helmer, D, Rajan, M, Tiwari, A, Miller, D, Crystal, S, Safford, M, Greenberg, J, Pogach, L Evaluation of regional variation in total, major, and minor amputation rates in a national health-care system. *International Journal for Quality in Health Care* 2007; **19:** 368-76.
Ref ID: 10961
Reason for Exclusion: general background

Umeh, L Preventing amputation in older adults with diabetes. [Review] [17 refs]. *Advance for Nurse Practitioners* 2007; **14:** 41-43.
Ref ID: 11026
Reason for Exclusion: general background

Umeh, L, Wallhagen, M, Nicoloff, N Identifying diabetic patients at high risk for amputation. [Review] [29 refs]. *Nurse Practitioner* 1970; **24:** 56.
Ref ID: 11027
Reason for Exclusion: general background

Uzun, G, Solmazgul, E, Curuksulu, H, Turhan, V, Ardic, N, Top, C, Yildiz, S, Cimsit, M Procalcitonin as a diagnostic aid in diabetic foot infections. *Tohoku Journal of Experimental Medicine* 2007; **213:** 305-12.
Ref ID: 11068
Reason for exclusion: flawed methodology, analysis only run on patients already sifted out as having infections by clinical examination

Valente, LA, Caughy, M, Fischbach, L A validation study of a self-administered questionnaire to identify increased risk for foot ulceration or amputation among people with diabetes. *Diabetes Educator* 2004; **30:** 932-38.
Ref ID: 11090
Reason for Exclusion: looks at identifying patients at high risk of developing diabetic foot ulcers

van, d, V, Chapman, CB, Bowker, JH Charcot neuroarthropathy of the foot and ankle. [Review] [73 refs]. *Journal of the American Academy of Orthopaedic Surgeons* 2009; **17:** 562-71.
Ref ID: 11177
Reason for Exclusion: general background

van Houtum, WH, Lavery, LA Outcomes associated with diabetes-related amputations in The Netherlands and in the state of California, USA. *Journal of Internal Medicine* 1996; **240:** 227-31.
Ref ID: 11138
Reason for exclusion: general background

Vella, S, Cachia, MJ Charcot neuroarthropathy: Pathogenesis diagnosis and medical management. *Malta Medical Journal* 2008; **20:** 13-19.
Ref ID: 11222
Reason for Exclusion: general background

Wall, B Assessment of ischaemic feet in diabetes. *Journal of Wound Care* 1997; **6:** 32-38.
Ref ID: 11401
Reason for Exclusion: monitoring ischemic feet rather than diagnostics

Ward, MM, Yankey, JW, Vaughn, TE, BootsMiller, BJ, Flach, SD, Welke, KF, Pendergast, JF, Perlin, J, Doebbeling, BN Physician process and patient outcome measures for diabetes care: relationships to organizational characteristics. *Medical Care* 2004; **42:** 840-850.
Ref ID: 11472
Reason for Exclusion: looking at adherence to guidelines by practitioners

Wegener, WA, Alavi, A Diagnostic imaging of musculoskeletal infection. Roentgenography; gallium, indium-labeled white blood cell, gammaglobulin, bone scintigraphy; and MRI. [Review] [84 refs]. *Orthopedic Clinics of North America* 1991; **22:** 401-18.

Ref ID: 11541
Reason for Exclusion: general background

Wendelken, ME, Markowitz, L, Patel, M, Alvarez, OM Objective, noninvasive wound assessment using B-mode ultrasonography. *Wounds: A Compendium of Clinical Research & Practice* 2003; **15:** 351-61.
Ref ID: 11581
Reason for exclusion: not a pure diabetic foot ulcer patient sample

Wheat, J Diagnostic strategies in osteomyelitis. [Review] [33 refs]. *American Journal of Medicine* 1985; **78:** 218-24.
Ref ID: 11611
Reason for Exclusion: literature review

Whelan, CT Development and implementation of a hospital pathway for patients with diabetic foot lesions. *Journal of Clinical Outcomes Management* 2003; **10:** 267-73.
Ref ID: 11620
Reason for Exclusion: general background

Wilczynski, R Diagnosis of diabetic wound infections: leading to optimal patient treatment. *Podiatry Management* 1999; **18:** 67-NaN.
Ref ID: 11681
Reason for Exclusion: not a study

Williams, DT, Hilton, JR, Harding, KG Diagnosing foot infection in diabetes. *Clinical Infectious Diseases* 2004; **39:** S83-S86.
Ref ID: 11710
Reason for Exclusion: general background

Worley, CA Neuropathic ulcers: diabetes and wounds, part I. Etiology and assessment. *Dermatology Nursing* 1959; **18:** 52.
Ref ID: 11830
Reason for Exclusion: not a study

Worley, CA Neuropathic ulcers: diabetes and wounds, part II. Differential diagnosis and treatment. *Dermatology Nursing* 2006; **18:** 163-64.
Ref ID: 11831
Reason for Exclusion: general background

Wraight, PR, Lawrence, SM, Campbell, DA, Colman, PG Creation of a multidisciplinary, evidence based, clinical guideline for the assessment, investigation and management of acute diabetes related foot complications. [Review] [59 refs]. *Diabetic Medicine* 2005; **22:** 127-36.
Ref ID: 11835
Reason for Exclusion: a literature search and good general background

Wright, DG, Sammarco, GJ Imaging: diabetic foot disease. *Foot Ankle* 1995; **16:** 105-6.
Ref ID: 11842
Reason for Exclusion: Case Report

Wrobel, JS, Connolly, JE Making the diagnosis of osteomyelitis. The role of prevalence. *Journal of the American Podiatric Medical Association* 1998; **88:** 337-43.
Ref ID: 11846
Reason for Exclusion: literature review

Wrobel, JS, Robbins, JM, Charns, MP, Bonacker, KM, Reiber, GE, Pogach, L Diabetes-related foot care at 10 Veterans Affairs medical centers: must do's associated with successful microsystems. *Joint Commission Journal on Quality & Patient Safety* 2006; **32:** 206-13.
Ref ID: 11853
Reason for Exclusion: foreign setting, not valid as qualitative evidence

Wu, S, Armstrong, DG Risk assessment of the diabetic foot and wound. [Review] [63 refs]. *International Wound Journal* 2005; **2:** 17-24.
Ref ID: 11870
Reason for Exclusion: narrative review

Wu, SC, Driver, VR, Armstrong, DG Vascular problems in the diabetic foot. *Journal for Vascular Ultrasound* 2006; **30:** 203-12.
Ref ID: 11876
Reason for Exclusion: general background

Younes, NA, Bakri, FG Diabetic foot infection. [Review] [81 refs]. *Saudi Medical Journal* 2006; **27:** 596-603.
Ref ID: 11998
Reason for Exclusion: narrative overview

Younes, NA, Albsoul, AM The DEPA scoring system and its correlation with the healing rate of diabetic foot ulcers. *Journal of Foot & Ankle Surgery* 2004; **43:** 209-13.
Ref ID: 11993
Reason for Exclusion: outcomes only reflect which categories heal quicker-no indication for what treatment

YOUNG, AJ, Boulton, AJM Guidelines for identifying the at-risk foot. (Foot ulceration and gangrene in diabetics). *Practical Diabetes* 1991; **8**.
Ref ID: 12001
Reason for Exclusion: general background

Young, MJ Management of the diabetic foot: a guide to the assessment and management of diabetic foot ulcers. *Diabetic Foot* 2002; **5:** S1-NaN.
Ref ID: 12044
Reason for Exclusion: not a study

Young, MJ, Breddy, JL, Veves, A, Boulton, AJ The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. *Diabetes Care* 1994; **17:** 557-60.
Ref ID: 12041
Reason for Exclusion: about risk identification

Yu, JS Diabetic foot and neuroarthropathy: magnetic resonance imaging evaluation. [Review] [96 refs]. *Topics in Magnetic Resonance Imaging* 1998; **9:** 295-310.
Ref ID: 12064
Reason for Exclusion: not a study

Zimmerman, BR Neurologic evaluation and treatment of the diabetic foot. *Clinics in Podiatric Medicine & Surgery* 1987; **4:** 341-50.
Ref ID: 12187
Reason for Exclusion: general background

Zimny, S, Dessel, F, Ehren, M, Pfohl, M, Schatz, H Early detection of microcirculatory impairment in diabetic patients with foot at risk. *Diabetes Care* 2001; **24:** 1810-1814.
Ref ID: 12191
Reason for Exclusion: looking at risk assessment of foots at high risk

Review question 3, 4 and 5

Advanced Tissue Sciences and Smith & Nephew present Dermagraft data. *Ostomy Wound Management* 1980; **43:** 77-78.
Ref ID: 8
Reason for Exclusion: not a RCT

Clinical trials and experience with Apligraf in diabetic foot ulceration... Diabetic Foot Study Group meeting 7-9 September, Crieff, Scotland. *Diabetic Foot* 2001; **4:** 148-50.
Ref ID: 195
Reason for Exclusion: not a RCT/Study

Dermagraft promotes the healing of diabetic foot ulcers. *Modern Medicine* 1996; **64:** 40-41.
Ref ID: 56
Reason for Exclusion: $$Health Business Elite/abstract/Dermis/Diabetic Foot/Foot/Foot Ulcer/Healing/Human/Research/Ulcer
Erratum: Oral clindamycin and ciprofloxacin therapy for diabetic foot infections (Pharmacotherapy 1990; 10: 154-156). *Pharmacotherapy* 1990; **10:** 261.
Ref ID: 22
Reason for Exclusion: abstract

Foam dressing "superior" for diabetic ulcers. *Australian Nursing Journal* 1994; **2:** 17-18.
Ref ID: 35
Reason for Exclusion: commentary

Growth factor may help restore nerve function in diabetic feet. *Joint Letter* 1998; **4:** 115-16.
Ref ID: 116
Reason for Exclusion: $$Cinahl/cant find in BL

Hyperbaric oxygen therapy for diabetic foot wounds. 2008. USA, Lansdale, PA: HAYES, Inc. Directory Publication.
Ref Type: Report
Ref ID: 453
Reason for Exclusion: not available in the BL

Living skin substitute can heal diabetic foot ulcer wounds. *FDA Consumer* 9 A.D.; **34:** 6-Oct.
Ref ID: 5
Reason for Exclusion: not a RCT

New dressing helps heal diabetic foot ulcers. *Modern Medicine* 1994; **62:** 64-66.
Ref ID: 37
Reason for Exclusion: not a RCT

New treatments for the diabetic foot: who to treat, which one and when to use... Diabetic Foot Study Group meeting 7-9 September, Crieff, Scotland. *Diabetic Foot* 2001; **4:** 149-51.
Ref ID: 196
Reason for Exclusion: not a RCT

Study finds new antibiotic effective for diabetes foot infections. *Diabetes Educator* 2008; **30:** 395-Jun.
Ref ID: 1
Reason for Exclusion: not a RCT

Study finds new antibiotic effective for diabetic foot infections. *Nephrology News & Issues* 2004; **18:** 19-20.
Ref ID: 294
Reason for Exclusion: duplicate

Sulesomab. *Australian Prescriber* 2002; **25:** 74.
Ref ID: 216
Reason for Exclusion: abstract

Tissue engineering for wound care... Diabetic Foot Study Group meeting 7-9 September, Crieff, Scotland. *Diabetic Foot* 2001; **4:** 147-49.
Ref ID: 194
Reason for Exclusion: not a RCT

Topical gel for diabetic foot ulcers. *Modern Medicine* 1998; **66:** 55.
Ref ID: 112
Reason for Exclusion: abstract

Topical negative pressure for chronic wounds?. [Review] [25 refs]. *Drug & Therapeutics Bulletin* 2007; **45:** 57-61.
Ref ID: 397
Reason for Exclusion: not a RCT

Two parenteral-to-oral regimens are effective for diabetic foot infections. *Modern Medicine* 1997; **65:** 61.
Ref ID: 80
Reason for Exclusion: abstract

Vacuum-assisted closure for chronic wound healing. *Tecnologica MAP Supplement* 2000; 19-20.
Ref ID: 157
Reason for Exclusion: can't find in BL

Abbott, CA, Vileikyte, L, Williamson, S, Carrington, AL, Boulton, AJM, ALCAR Foot Ulcer Study Group Effect of treatment with acetyl-l-carnitine on diabetic foot ulceration in patients with peripheral neuropathy: a 1 year prospective multi-centre study. *Diabetologia* 1997; **40:** A556.
Ref ID: 527
Reason for Exclusion: not a RCT

Abdelatif, M, Yakoot, M, Etmaan, M Safety and efficacy of a new honey ointment on diabetic foot ulcers: a prospective pilot study. *Journal of Wound Care* 2008; **17:** 108-10.
Ref ID: 533
Reason for Exclusion: not a RCT

Abidia, A, Laden, G, Kuhan, G, Johnson, BF, Wilkinson, AR, Renwick, PM, Masson, EA, McCollum, PT The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular & Endovascular Surgery* 2003; **25:** 513-18.
Ref ID: 541
Reason for Exclusion: In Cochrane review

Abramson, MA The Sidestep study of diabetic foot infections (DFI): A multicenter, double-blinded, randomized, controlled trial (RCT) of ertapenem (E) vs. piperacillin/tazobactam (P/T). *Diabetologia* 2005; **48:** A81-A82.
Ref ID: 547
Reason for Exclusion: abstract

Acosta, JB, Savigne, W, Valdez, C, Franco, N, Alba, JS, del, RA, Lopez-Saura, P, Guillen, G, Lopez, E, Herrera, L, Fernandez-Montequin, J Epidermal growth factor intralesional infiltrations can prevent amputation in patients with advanced diabetic foot wounds. *International Wound Journal* 2006; **3:** 232-39.
Ref ID: 556
Reason for Exclusion: not a RCT

Adler, PF Assessing the effects of pentoxifylline (Trental) on diabetic neurotrophic foot ulcers. *Journal of Foot Surgery* 1991; **30:** 300-303.
Ref ID: 577
Reason for Exclusion: not a RCT

Agrawal, RP, Agrawal, S, Beniwal, S, Joshi, CP, Kochar, DK Granulocyte-macrophage colony-stimulating factor in foot ulcers. *Diabetic Foot* 2003; **6:** 93-98.
Ref ID: 589
Reason for Exclusion: not a RCT

Akalin, HE The role of beta-lactam/beta-lactamase inhibitors in the management of mixed infections. *International Journal of Antimicrobial Agents* 1999; **12:** S15-S20.
Ref ID: 623
Reason for Exclusion: literature review

Akova, M, Ozcebe, O, Gullu, I, Unal, S, Gur, D, Akalin, S, Tokgozoglu, M, Telatar, F, Akalin, HE Efficacy of sulbactam-ampicillin for the treatment of severe diabetic foot infections. *Journal of Chemotherapy* 1996; **8:** 284-89.
Ref ID: 645
Reason for Exclusion: not a RCT

Amery, CM Growth factors and the management of the diabetic foot. [Review] [10 refs]. *Diabetic Medicine* 2005; **22:** Suppl-4.
Ref ID: 741
Reason for Exclusion: expert opinion

Andros, G, Armstrong, DG, Attinger, CE, Boulton, AJ, Frykberg, RG, Joseph, WS, Lavery, LA, Morbach, S, Niezgoda, JA, Toursarkissian, B, Tucson Expert Consensus Conference Consensus statement on negative pressure wound therapy (V.A.C. Therapy) for the management of diabetic foot wounds. [145 refs]. *Ostomy Wound Management* 2006; **Suppl:** 1-32.
Ref ID: 778
Reason for Exclusion: expert opinion

Apelqvist, J, Armstrong, DG, Lavery, LA, Boulton, AJM Diabetic foot ulcer and VAC resource utilization and economic cost based on a randomized trial. *20th Annual Symposium on Advanced Wounds Care and the Wound Healing Society Meeting; 2007, 28 April - 1 May; Tampa, FL* 2007; C64.
Ref ID: 813
Reason for Exclusion: abstract

Apelqvist, J, Castenfors, J, Larsson, J, Stenstrom, A, Persson, G Ketanserin in the treatment of diabetic foot ulcer with severe peripheral vascular disease. *International Angiology* 1990; **9:** 120-124.
Ref ID: 792
Reason for Exclusion: not licensed in the UK

Apelqvist, J, Armstrong, DG, Augustin, M, Baharestani, M, Banwell, P, Dalla, PL, Deva, A, Ennis, W, Fish, J, Fleischmann, W, Gupta, S, Gustafsson, R, Harding, K, Horch, RE, Ingemansson, R, Jukema, G, Mahoney, J, MouÇ®s, C, Price, P, Soldevilla, Ç, Song, C, TÇ¸ot, L, Trueman, P, Vowden, K, Vowden, P, Wild, T Vacuum assisted closure - recommendations for use: a consensus document... reprinted courtesy of the World Union of Wound Healing Societies Principles of Best Practice ¶¸MEP Ltd, 2008. *World Council of Enterostomal Therapists Journal* 2009; **29:** 8-20.
Ref ID: 824
Reason for Exclusion: can't find in BL

Apelqvist, J, Armstrong, DG, Augustin, M, Baharestani, M, Banwell, P, Dalla, PL, Deva, A, Ennis, W, Fish, J, Fleischmann, W, Gupta, S, Gustafsson, R, Harding, K, Horch, RE, Ingemansson, R, Jukema, G, Mahoney, J, Moues, C, Price, P, Agreda, JS, Song, C, Teot, L, Trueman, P, Vowden, K, Vowden, P, Wild, T Vacuum assisted closure: Recommendations for use - A consensus document. *International Wound Journal* 2008; **5:** iii-19.
Ref ID: 819
Reason for Exclusion: a guideline

Argenta, LC, Morykwas, MJ, Marks, MW, DeFranzo, AJ, Molnar, JA, David, LR Vacuum-assisted closure: state of clinic art. *Plastic & Reconstructive Surgery* 2006; **117:** Suppl-142S.
Ref ID: 848
Reason for Exclusion: not a RCT

Armstrong, DG, Lavery, LA Evidence-based options for off-loading diabetic wounds. [Review] [23 refs]. *Clinics in Podiatric Medicine & Surgery* 1998; **15:** 95-104.
Ref ID: 907
Reason for Exclusion: systematic review

Armstrong, DG, Attinger, CE, Boulton, AJ, Frykberg, RG, Kirsner, RS, Lavery, LA, Mills, JL Guidelines regarding negative wound therapy (NPWT) in the diabetic foot. [Review] [64 refs]. *Ostomy Wound Management* 2004; **50:** Suppl-27S.
Ref ID: 974
Reason for Exclusion: not a RCT, a guideline

Armstrong, DG, Mossel, J, Short, B, Nixon, BP, Knowles, EA, Boulton, AJ Maggot debridement therapy: a primer. *Journal of the American Podiatric Medical Association* 2002; **92:** 398-401.
Ref ID: 958
Reason for Exclusion: not a RCT

Armstrong, DG, Boulton, AJ, Banwell, P Negative pressure wound therapy in treatment of diabetic foot wounds: a marriage of modalities. [Review] [21 refs]. *Ostomy Wound Management* 2004; **50:** Suppl-12.
Ref ID: 973
Reason for Exclusion: not a RCT

Armstrong, DG, Boulton, AJM, Banwell, P Negative pressure wound therapy in treatment of diabetic foot wounds: a marriage of modalities... Proceedings from the 2003 National V.A.C. Education Conference. *Wounds: A Compendium of Clinical Research & Practice* 2004; 9-13.
Ref ID: 984
Reason for Exclusion: not a RCT

Ayala, J, Payne, W, Keith, MS Time to 50% reduction in wound area as a significant predictor of complete wound closure in patients with partial diabetic foot amputations: results from a randomized controlled trial comparing vacuum assisted closure to standard therapy (ST). *SAWC 2006; April 30 - May 3, 2006; San Antonio, Texas* 2006; **Poster 9**.
Ref ID: 1088
Reason for Exclusion: can't find in BL and poster presentation

Bahrami, A, Kamali, K, Ali-Asgharzadeh, A, Hosseini, P, Heshmat, R, Khorram Khorshid, HR, Gharibdoust, F, Madani, SH, Larijani, B Clinical application of oral form of ANGIPARS[trademark] and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial. *Daru* 2008; **16:** 41-48.
Ref ID: 1115
Reason for Exclusion: complementary herbal extract

Baker, LL, Chambers, R, DeMuth, SK, Villar, F Effects of electrical stimulation on wound healing in patients with diabetic ulcers. *Diabetes Care* 1997; **20:** 405-12.
Ref ID: 1130
Reason for Exclusion: semi cross-over trial with contaminated end point results

Baker, NR A randomised comparative pilot study to evaluate Allevyn hydrocellular dressings and Sorbsan calcium alginate dressings in the treatment of diabetic foot ulcers. *3rd European Conference on Advances in Wound Management; 1993, 19-22 October; Harrogate, UK* 1994; 170.
Ref ID: 1142
Reason for Exclusion: abstract

Barnett, SJ A literature review looking at contempory developments in antimicrobial agents, with special reference to applications in the field of podiatry. *Foot* 1996; **6:** 51-57.
Ref ID: 1248
Reason for Exclusion: literature review

Baroni, G, Porro, T, Faglia, E, Pizzi, G, Mastropasqua, A, Oriani, G, Pedesini, G, Favales, F Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care* 1987; **10:** 81-86.

Ref ID: 1249
Reason for Exclusion: not a RCT

Bennett, SP, Griffiths, GD, Schor, AM, Leese, GP, Schor, SL Growth factors in the treatment of diabetic foot ulcers. [Review] [130 refs]. *British Journal of Surgery* 2003; **90:** 133-46.
Ref ID: 1385
Reason for Exclusion: systematic review

Berendt, AR Counterpoint: Hyperbaric oxygen for diabetic foot wounds is not effective. *Clinical Infectious Diseases* 2006; **43:** 193-98.
Ref ID: 1403
Reason for Exclusion: systematic review

Birke, JA, Pavich, MA, Patout Jr, CA, Horswell, R Comparison of forefoot ulcer healing using alternative off-loading methods in patients with diabetes mellitus. *Advances in Skin & Wound Care* 2002; **15:** 210-215.
Ref ID: 1495
Reason for Exclusion: not a RCT

Black, JR Management of diabetic plantar ulcers with a walking brace. A clinical trial. *Journal of the American Podiatric Medical Association* 1990; **80:** 156-57.
Ref ID: 1518
Reason for Exclusion: not a RCT

Blozik, E, Scherer, M Skin replacement therapies for diabetic foot ulcers: systematic review and meta-analysis. *Diabetes Care* 2008; **31:** 693-94.
Ref ID: 1553
Reason for Exclusion: systematic review

Blume, PA Interim results of a randomized, controlled multicenter trial of vacuum-assisted closure therapy* in the treatment and blinded evaluation of diabetic foot ulcers. *20th Annual Symposium on Advanced Wounds Care and the Wound Healing Society Meeting; 2007, 28 April - 1 May; Tampa, FL* 2007; C126.
Ref ID: 1558
Reason for Exclusion: abstract only

Bolton, LL Evidence corner. Debriding pressure ulcers with maggot versus conventional therapy. *Wounds: A Compendium of Clinical Research & Practice* 2006; **18:** A19-NaN.
Ref ID: 1588
Reason for Exclusion: not a RCT

Bowering, CK Dermagraft in the treatment of diabetic foot ulcers. [Review] [33 refs]. *Journal of Cutaneous Medicine & Surgery* 1998; **3:** Suppl-32.
Ref ID: 1708
Reason for Exclusion: can't find in BL

Bowling, FL, Gautam, V, Salgami, EV, McCardle, M, Boulton, AJM Larval therapy in the treatment of diabetic foot wounds -- a review of the literature. *EWMA Journal* 2008; **8:** 10-NaN.
Ref ID: 1720
Reason for Exclusion: can't find in BL

Bowling, FL, Salgami, EV, Boulton, AJ Larval therapy: a novel treatment in eliminating methicillin-resistant Staphylococcus aureus from diabetic foot ulcers. *Diabetes Care* 2007; **30:** 370-371.
Ref ID: 1719
Reason for Exclusion: not a RCT

Brakora, MJ, Sheffield, PJ Hyperbaric oxygen therapy for diabetic wounds. [Review] [48 refs]. *Clinics in Podiatric Medicine & Surgery* 1995; **12:** 105-17.
Ref ID: 1759
Reason for Exclusion: general background

Brockenbrough, G Negative pressure wound therapy shows a 97.8% limb-salvage rate for diabetic feet. *Orthopedics Today* 2009; **29:** 42-43.
Ref ID: 1830
Reason for Exclusion: not a RCT

Burns, J, Wegener, C, Begg, L, Vicaretti, M, Fletcher, J Randomized trial of custom orthoses and footwear on foot pain and plantar pressure in diabetic peripheral arterial disease. *Diabetic Medicine* 2009; **26:** 893-99.
Ref ID: 1923
Reason for Exclusion: not looking at treatment of PAD rather looking at prevention

Burrell, NA [Commentary on] Reducing dynamic foot pressures in high-risk diabetic subjects with foot ulcerations: a comparison of treatments [original article by Lavery LA, Lavery DC, Vela SA, and Quebedeaux TL appears in DIABETES CARE 1996;19(8):818-821]. *Foot & Ankle Quarterly--The Seminar Journal* 1998; **11:** 100-105.
Ref ID: 1928
Reason for Exclusion: not a RCT and not relevant

Canawati, HN Comparative in vitro activity of cefoxitin, cefotaxime alone, and in combination with desacetylcefotaxime against the Bacteroides species. *Diagnostic Microbiology & Infectious Disease* 1989; **12:** 33-37.
Ref ID: 2009
Reason for Exclusion: not a RCT

Caputo, WJ, Beggs, DJ, DeFede, JL, Simm, L, Dharma, H A prospective randomised controlled clinical trial comparing hydrosurgery debridement with conventional surgical debridement in lower extremity ulcers. *International Wound Journal* 2008; **5:** 288-94.
Ref ID: 2030
Reason for Exclusion: mixed population, can't extract DF population data

Caravaggi, C, De, GR, Faglia, E A multicenter, randomized controlled clinical trial to evaluate the efficacy of hyaluronan based dermal and epidermal autologous grafts in the treatment of diabetic foot ulcers. *Diabetic Foot Study Group of the EASD* 2001; A30.
Ref ID: 2033
Reason for Exclusion: abstract only

Caravaggi, C, Sganzaroli, AB, Pogliaghi, I, Cavaiani, P, Fabbi, M, Ferraresi, R Safety and efficacy of a dermal substitute in the coverage of cancellous bone after surgical debridement for severe diabetic foot ulceration. *EWMA Journal* 2009; **9:** 11-15.
Ref ID: 2037
Reason for Exclusion: can't find in BL

Catanzariti, AR, Haverstock, BD, Grossman, JP, Mendicino, RW Off-loading techniques in the treatment of diabetic plantar neuropathic foot ulceration. [Review] [41 refs]. *Advances in Wound Care* 1999; **12:** 452-58.
Ref ID: 2086
Reason for Exclusion: not a RCT

Cavallini, M Autologous fibroblasts to treat deep and complicated leg ulcers in diabetic patients. *Wound Repair & Regeneration* 2007; **15:** 35-38.
Ref ID: 2098
Reason for Exclusion: not a RCT

Cetin, M, Ocak, S, Kuvandik, G, Aslan, B Comparison of bacterial isolates cultured from hemodialysis patients and other patients with diabetic foot and their antimicrobial resistance. *Renal Failure* 2007; **29:** 973-78.
Ref ID: 2141
Reason for Exclusion: not relevant

Chadwick, P The use of negative pressure wound therapy in the diabetic foot. *British Journal of Nursing (BJN)* 2009; **18:** S12-S25.
Ref ID: 2156
Reason for Exclusion: not a RCT

Chantelau, E, Tanudjaja, T, Altenhofer, F, Ersanli, Z, Lacigova, S, Metzger, C Antibiotic treatment for uncomplicated neuropathic forefoot ulcers in diabetes: a controlled trial. *Diabetic Medicine* 1996; **13:** 156-59.
Ref ID: 2199
Reason for Exclusion: In HTA report

Chen, SJ, Yu, CT, Cheng, YL, Yu, SY, Lo, HC Effects of hyperbaric oxygen therapy on circulating interleukin-8, nitric oxide, and insulin-like growth factors in patients with type 2 diabetes mellitus. *Clinical Biochemistry* 2007; **40:** 30-36.
Ref ID: 2247
Reason for Exclusion: not looking at effects on DFU population

Cianci, P Adjunctive hyperbaric oxygen therapy in the treatment of the diabetic foot. [Review] [90 refs]. *Journal of the American Podiatric Medical Association* 1994; **84:** 448-55.
Ref ID: 2328
Reason for Exclusion: not a RCT

Cianci, P Advances in the treatment of the diabetic foot: Is there a role for adjunctive hyperbaric oxygen therapy?. [Review] [88 refs]. *Wound Repair & Regeneration* 2004; **12:** 2-10.
Ref ID: 2331
Reason for Exclusion: general background

Cianci, P Consensus development conference on diabetic foot wound care: A randomized controlled trial does exist supporting use of adjunctive hyperbaric oxygen therapy. *Diabetes Care* 2000; **23:** 873.
Ref ID: 2330
Reason for Exclusion: not a RCT

Clare, MP, Fitzgibbons, TC, McMullen, ST, Stice, RC, Hayes, DF, Henkel, L Experience with the vacuum assisted closure negative pressure technique in the treatment of non-healing diabetic and dysvascular wounds. *Foot & Ankle International* 2002; **23:** 896-901.
Ref ID: 2350
Reason for Exclusion: not a RCT

Cordrey, R Light therapy and advanced wound care on a neuropathic plantar ulcer on a Charcot foot. *Journal of Wound, Ostomy & Continence Nursing* 2008; **35:** 116-18.
Ref ID: 2476
Reason for Exclusion: case study

Cruciani, M, Lipsky, BA, Mengoli, C, de, LF Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections?: A meta-analysis. *Diabetes Care* 2005; **28:** 454-60.
Ref ID: 2532
Reason for Exclusion: general background

Cunha, BA Antibiotic selection for diabetic foot infections: a review. [Review] [31 refs]. *Journal of Foot & Ankle Surgery* 2000; **39:** 253-57.
Ref ID: 2555
Reason for Exclusion: general background

Dalla, PL, Brocco, E, Senesi, A, Merico, M, De, VD, Assaloni, R, DaRos, R Super-oxidized solution (SOS) therapy for infected diabetic foot ulcers. *Wounds: A Compendium of Clinical Research & Practice* 2006; **18:** 262-71.
Ref ID: 2600
Reason for Exclusion: not a RCT

Davis, JC The use of adjuvant hyperbaric oxygen in treatment of the diabetic foot. *Clinics in Podiatric Medicine & Surgery* 1987; **4:** 429-37.
Ref ID: 2659
Reason for Exclusion: Case Report

de, LF, Pellizzer, G, Strazzabosco, M, Martini, Z, Du, JG, Lora, L, Fabris, P, Benedetti, P, Erle, G Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection. *Antimicrobial Agents & Chemotherapy* 2001; **45:** 1094-98.
Ref ID: 2711
Reason for Exclusion: In Cochrane review

de, LJ, Miller, E, Keith, M A cost-effectiveness evaluating of vacuum-assisted closure treatment for hospitalized diabetic foot ulcer wound patient. *Journal of Wound, Ostomy & Continence Nursing* 2006; **33:** S52-NaN.
Ref ID: 2713
Reason for Exclusion: abstract

Doctor, N, Pandya, S, Supe, A Hyperbaric oxygen therapy in diabetic foot. *Journal of Postgraduate Medicine* 1992; **38:** 112-14.
Ref ID: 2853
Reason for Exclusion: In Cochrane review

Dodson WW, III, Kalns, J, Scruggs, J, Kiel, J, Wolf, EG 3-nitrotyrosine predicts healing in chronic diabetic foot wounds treated with hyperbaric oxygen. *Wounds: A Compendium of Clinical Research & Practice* 1999; **11:** 129-36.
Ref ID: 2854
Reason for Exclusion: not a RCT

Dolynchuk, K The use of collagenase in the debridement of diabetic foot ulcers: a double-blind prospective randomized study. *7th Annual Conference of the Canadian Association of Wound Care; 2001, 1-3 November; London, Ontario, Canada* 2001; 56.
Ref ID: 2856
Reason for Exclusion: can't find in BL

Driver, V, Andersen, C, Taneja, C, Oster, G Evaluation of health-care utilization and costs for hospitalizations and surgical procedures in patients with diabetic foot ulcers treated with negative pressure wound therapy using open cell foam versus advanced moist wound therapy. *3rd Congress of the World Union of Wound Healing Societies Meeting; 2008, 4-8 June; Toronto, Canada* 2008; Abstract.
Ref ID: 2928
Reason for Exclusion: abstract

Driver, VR, Anderson, C, Oster, G, Taneja, C Evaluation of healthcare utilization and costs for hospitalizations and surgical procedures in patients with diabetic foot ulcers treated with V.A.C. Therapy versus advanced moist wound therapy. *Ostomy Wound Management* 2009; **55:** 82-83.
Ref ID: 2935
Reason for Exclusion: abstract

Efrati, S, Gall, N, Bergan, J, Fishlev, G, Bass, A, Berman, S, Hamad-Abu, R, Feigenzon, M, Weissgarten, J Hyperbaric oxygen, oxidative stress, NO bioavailability and ulcer oxygenation in diabetic patients. *Undersea & Hyperbaric Medicine* 2009; **36:** 1-12.
Ref ID: 3088
Reason for Exclusion: looking at effects of HO on ulcer oxygenation

Eginton, MT, Brown, KR, Seabrook, GR, Towne, JB, Cambria, RA A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Annals of Vascular Surgery* 2003; **17:** 645-49.
Ref ID: 3091
Reason for Exclusion: less than 10 patients per arm

El-Nahas, M, Gawish, H, Tarshoby, M, State, O The impact of topical phenytoin on recalcitrant neuropathic diabetic foot ulceration. *Journal of Wound Care* 2009; **18:** 33-37.
Ref ID: 3106
Reason for Exclusion: not a RCT

Embil, JM Becaplermin (Regranex Gel 0.01%): Recombinant platelet-derived growth factor (rh-PDGF-BB) for healing diabetic foot ulcers. *Today's Therapeutic Trends* 2000; **18:** 131-48.
Ref ID: 3139
Reason for Exclusion: general background

Embil, JM, Rose, G, Trepman, E, Math, MC, Duerksen, F, Simonsen, JN, Nicolle, LE Oral antimicrobial therapy for diabetic foot osteomyelitis. *Foot & Ankle International* 2006; **27:** 771-79.
Ref ID: 3141
Reason for Exclusion: not a RCT

Embil, JM, Papp, K, Sibbald, G, Tousignant, J, Smiell, JM, Wong, B, Lau, CY Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy. *Wound Repair & Regeneration* 2000; **8:** 162-68.
Ref ID: 3138
Reason for Exclusion: not a RCT

Eneroth, M, van Houtum, WH The value of debridement and Vacuum-Assisted Closure (V.A.C.) Therapy in diabetic foot ulcers. [Review] [34 refs]. *Diabetes/Metabolism Research Reviews* 2008; **24:** Suppl-80.
Ref ID: 3151
Reason for Exclusion: can't find in BL

Faglia, E, Favales, F, Quarantiello, A, Calia, P, Brambilla, G, Rampoldi, A, Morabito, A Feasibility and effectiveness of peripheral percutaneous transluminal balloon angioplasty in diabetic subjects with foot ulcers. *Diabetes Care* 1996; **19:** 1261-64.

Ref ID: 3232
Reason for Exclusion: for question 6

Faglia, E, Clerici, G, Caminiti, M, Quarantiello, A, Gino, M, Morabito, A The role of early surgical debridement and revascularization in patients with diabetes and deep foot space abscess: retrospective review of 106 patients with diabetes. *Journal of Foot & Ankle Surgery* 2006; **45:** 220-226.
Ref ID: 3241
Reason for Exclusion: not a RCT

Faglia, E, Favales, F, Aldeghi, A, Calia, P, Quarantiello, A, Oriani, Gea Adjunctive systemic hyperbaric oxygen therapy in treatment of diabetic foot ulcer A randomized study. *Proceedings of the International Joint Meeting on Hyperbaric and Underwater Medicine; 1996; Grafica Victoria, Bologna* 1996; 391-99.
Ref ID: 3233
Reason for Exclusion: In Cochrane review

Faglia, E, Favales, F, Aldeghi, A, Calia, P, Quarantiello, A, Oriani, G, Michael, M, Campagnoli, P, Morabito, A Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care* 1996; **19:** 1338-43.
Ref ID: 3231
DUPLICATE
Reason for Exclusion: In Cochrane review

Fang, RC, Galiano, RD A review of becaplermin gel in the treatment of diabetic neuropathic foot ulcers. *Biologics* 2008; **2:** 1-12.
Ref ID: 3267
Reason for Exclusion: general background

Feldman, R Antimicrobial foam dressing used in the treatment of a diabetic foot ulcer. *Wounds: A Compendium of Clinical Research & Practice* 2009; 16-18.
Ref ID: 3310
Reason for Exclusion: Case Report

Fernandez-Montequin, JI, Betancourt, BY, Leyva-Gonzalez, G, Mola, EL, Galan-Naranjo, K, Ramirez-Navas, M, Bermudez-Rojas, S, Rosales, F, Garcia-Iglesias, E, Berlanga-Acosta, J, Silva-Rodriguez, R, Garcia-Siverio, M, Martinez, LH Intralesional administration of epidermal growth factor-based formulation (Heberprot-P) in chronic diabetic foot ulcer: treatment up to complete wound closure. *International Wound Journal* 2009; **6:** 67-72.
Ref ID: 3326
Reason for Exclusion: not a RCT

Fernandez-Montequin, JI, Infante-Cristia, E, Valenzuela-Silva, C, Franco-Perez, N, Savigne-Gutierrez, W, Artaza-Sanz, H, Morejon-Vega, L, Gonzalez-Benavides, C, Eliseo-Musenden, O, Garcia-Iglesias, E, Berlanga-Acosta, J, Silva-Rodriguez, R, Betancourt, BY, Lopez-Saura, PA, Cuban, C Intralesional injections of Citoprot-P (recombinant human epidermal growth factor) in advanced diabetic foot ulcers with risk of amputation. *International Wound Journal* 2007; **4:** 333-43.

Ref ID: 3325
Reason for Exclusion: dose dependent study

Flack, S, Apelqvist, J, Keith, M, Trueman, P, Williams, D An economic evaluation of VAC therapy compared with wound dressings in the treatment of diabetic foot ulcers. *Journal of Wound Care* 2008; **17:** 71-78.
Ref ID: 3418
Reason for Exclusion: health economics

Foo, LSS, Chua, BSY, Chia, GT, Tan, SB, Howe, TS Vacuum assisted closure vs moist gauze dressing in post-operative diabetic foot wounds: Early results from a randomised controlled trial. *2nd World Union of Wound Healing Societies Meeting; 2004 ,8-13 July; Paris* 2004; 8-9.
Ref ID: 3481
Reason for Exclusion: can't find in BL

Foster, AVM, Greenhill, MT, Edmonds, ME A randomised comparative study to compare Allevyn hydrocellular dressings and Kaltostat calcium-sodium alginate dressings in the treatment of diabetic foot ulcers. *5th Annual Symposium on Advanced Wound Care; 1992, 23-25 April; New Orleans, Lousiana* 1992; 146.
Ref ID: 3542
Reason for Exclusion: can't find in BL

Foster, AVM, Greenhill, MT, Edmonds, ME A randomised comparative study to compatre Allevyn hydrocellular dressings and Kaltostat calcium-sodium alginate dressings in the treatment of diabetic foot ulcers. *2nd European Conference on Advances in Wound Management; 1992, 20-23 October; Harrogate, UK* 1993; 77.
Ref ID: 3543
Reason for Exclusion: can't find in BL

Fung, B, Fang, D, Remedios, ID The use of ofloxacin in the treatment of diabetic foot infections: Preliminary findings. Journal of the Hong Kong Medical Association 1992; 44: 107-9.Ref ID: 3697
Reason for Exclusion: pilot study, poor quality on outcome data.

Fylling, CP, Dougherty, EJ Evidence-based cost-effectiveness of platelet-rich plasma (PRP) gel versus alternative therapies for the treatment of diabetic foot ulcers... 41st Annual Wound, Ostomy and Continence Nurses Annual Conference, St. Louis, Missouri, June 6-10, 2009. *Journal of Wound, Ostomy & Continence Nursing* 2009; **36:** S53-NaN.
Ref ID: 3708
Reason for Exclusion: not a RCT

Gater, L Hyperbaric oxygen therapy's role in treating chronic foot wounds. *Podiatry Management* 2007; **26:** 189-92.
Ref ID: 3808
Reason for Exclusion: not a RCT

Gentzkow, G, Iwasaki, S, Gupta, S, Hershon, K, Lipkin, S, Steed, Dea Cultured human dermal replacement tissue for the treatment of diabetic foot ulcers. *4th Annual Meeting of the European Tissue Repair Society; 1994, 25-28 August; Oxford, England* 1994; 166.
Ref ID: 3849
Reason for Exclusion: abstract

Gentzkow, G, Iwasaki, S, Gupta, S, Hershon, K, Lipkin, S, Steed, Dea Cultured human dermis for the treatment of diabetic foot ulcers. *4th Annual Meeting of the Wound Healing Society; 1994, 18-24 May; San Francisco, USA* 1994; 65.
Ref ID: 3850
Reason for Exclusion: abstract

Gentzkow, GD, Jensen, JL, Pollak, RA, Kroeker, RO, Lerner, JM, Lerner, M, Iwasaki, SD Improved healing of diabetic foot ulcers after grafting with a living human dermal replacement. *Wounds: A Compendium of Clinical Research & Practice* 1999; **11:** 77-85.
Ref ID: 3857
Reason for Exclusion: not a RCT

Gorman, DF, Harding, PE, Roberts, AP, Gilligan, JE, Capps, RA, Parsons, DW Topical hyperbaric oxygen for treatment of diabetic foot ulcers. *Diabetes Care* 3 A.D.; **11:** 819-Dec.
Ref ID: 4088
Reason for Exclusion: not a RCT

Gough, A, Clapperton, M, Rolando, N, Foster, AV, Philpott-Howard, J, Edmonds, ME Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. *Lancet* 1997; **350:** 855-59.
Ref ID: 4102
Reason for Exclusion: In Cochrane review

Gough, A, Clapperton, M, Rolando, N, Foster, AVM, Philpott-Howard, J Early report: Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. *British Journal of Podiatry* 1998; **1:** 53-58.
Ref ID: 4104
DUPLICATE
Reason for Exclusion: In Cochrane review

Gray, M Is total contact casting effective for treating diabetic foot ulcers? *Journal of Wound, Ostomy, & Continence Nursing* 2006; **33:** 359-62.
Ref ID: 4143
Reason for Exclusion: narrative review

Grayson, ML Erratum: Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients (Clinical Infectious Diseases (1994) 18 (683-693)). *Clinical Infectious Diseases* 1994; **19:** 820.
Ref ID: 4152
Reason for Exclusion: abstract

Gu, YQ, Zhang, J, Qi, LX, Yu, HX, Li, JX, Li, XF, Guo, LR, Luo, T, Cui, SJ, Wang, ZG Surgical treatment of 82 patients with diabetic lower limb ischemia by distal arterial bypass. *Chinese Medical Journal* 2007; **120:** 106-9.
Ref ID: 4251
Reason for Exclusion: not a RCT

Guo, S, Counte, MA, Gillespie, KN, Schmitz, H Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. *International Journal of Technology Assessment in Health Care* 2003; **19:** 731-37.
Ref ID: 4290
Reason for Exclusion: health economics

Harvima, IT, Virnes, S, Kauppinen, L, Huttunen, M, Kivinen, P, Niskanen, L, Horsmanheimo, M Cultured allogeneic skin cells are effective in the treatment of chronic diabetic leg and foot ulcers. *Acta Dermato-Venereologica* 1999; **79:** 217-20.
Ref ID: 4497
Reason for Exclusion: control group is not DFU population

Helm, PA, Walker, SC, Pullium, G Total contact casting in diabetic patients with neuropathic foot ulcerations. *Archives of Physical Medicine & Rehabilitation* 1984; **65:** 691-93.
Ref ID: 4615
Reason for Exclusion: not a RCT

Hemkens, LG, Waltering, A, Blume, PA Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial... Blume PA, Walters J, Payne W, Ayala J, Lantis J: Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care 31:631-6, 2008. *Diabetes Care* 2008; **31:** e76-NaN.
Ref ID: 4624
Reason for Exclusion: expert opinion

Heyneman, CA, Lawless-Liday, C Using hyperbaric oxygen to treat diabetic foot ulcers: safety and effectiveness. [Review] [43 refs]. *Critical Care Nurse* 2002; **22:** 52-60.
Ref ID: 4669
Reason for Exclusion: general background

Hong, JP, Jung, HD, Kim, YW Recombinant human epidermal growth factor (EGF) to enhance healing for diabetic foot ulcers. *Annals of Plastic Surgery* 399; **56:** 394-98.
Ref ID: 4819
Reason for Exclusion: Case Report

Hunt, DL Review: debridement using hydrogel seems to be better than standard wound care for healing diabetic foot ulcer. *ACP Journal Club* 3 A.D.; **139:** 16-Aug.
Ref ID: 4939
Reason for Exclusion: abstract only

Jeffery, S A honey-based dressing for diabetic foot ulcers: A controlled study. *The Diabetic Foot Journal* 2008; **11:** 87-91.
Ref ID: 5178
Reason for Exclusion: no. of events and patients <10 and patients not randomised

Jensen, JL, Seeley, J, Gillin, B Diabetic foot ulcerations. A controlled, randomized comparison of two moist wound healing protocols: Carrasyn Hydrogel Wound dressing and wet-to-moist saline gauze. *Advances in Wound Care* 1998; **11:** Suppl-4.
Ref ID: 5193
Reason for Exclusion: in Cochrane review

Joon, PH, Heun, DJ, Yun, WK Recombinant human epidermal growth factor (EGF) to enhance healing for diabetic foot ulcers. *Annals of Plastic Surgery* 2006; **56:** 394-98.
Ref ID: 5293
Reason for Exclusion: can't find in BL

Jude, E, Apelqvist, Spraul, M, Martini, J Randomized controlled study of diabetic foot ulcers dressed with hydrofiber© containing ionic silver or calcium alginate dressings. *European Wound Management Association Conference; 2005, 15-17 September; Stuttgart, Germany* 2005; **Thur 1730-1900; V33-4:** 106.
Ref ID: 5321
Reason for Exclusion: can't find in BL

Jude, EB, Selby, PL, Burgess, J, Lilleystone, P, Mawer, EB, Page, SR, Donohoe, M, Foster, AV, Edmonds, ME, Boulton, AJ Bisphosphonates in the treatment of Charcot neuroarthropathy: a double-blind randomised controlled trial. *Diabetologia* 2001; **44:** 2032-37.
Ref ID: 5331
Reason for Exclusion: for question 6

Kalani, M, Silveira, A, Blomback, M, Apelqvist, J, Eliasson, B, Eriksson, JW, Fagrell, B, Torffvit, O, Hamsten, A, Jorneskog, G Beneficial effects of dalteparin on haemostatic function and local tissue oxygenation in patients with diabetes, severe vascular disease and foot ulcers. *Thrombosis Research* 2007; **120:** 653-61.
Ref ID: 5368
Reason for Exclusion: not looking at effects on DFU

Kalani, M, Jorneskog, G, Naderi, N, Lind, F, Brismar, K Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. *Journal of Diabetes & its Complications* 2002; **16:** 153-58.

Ref ID: 5363
Reason for Exclusion: not a RCT

Kastenbauer, T, Hornlein, B, Sokol, G, Irsigler, K Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers. *Diabetologia* 2003; **46:** 27-30.
Ref ID: 5462
Reason for Exclusion: In Cochrane review

Kosinski, MA [Commentary on] Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomized, controlled, double-blinded, multicentre trial. *Foot & Ankle Quarterly--The Seminar Journal* 2007; **19:** 17-20.
Ref ID: 5824
Reason for Exclusion: comment on a RCT

Kwon, P, Breen, TJ, Gray, S, Lynch, CJ, Semba, CP, Hanft, JR, Pollak, RA, Barbul, A, Gils, CV Results of a phase I, randomized, double-blind, placebo-controlled trial of topical rhVEGF (telbermin) for the treatment of diabetic foot ulcers. *Ostomy Wound Management* 2006; **52:** 102-3.
Ref ID: 5947
Reason for Exclusion: abstract

L”ndahl, M, Katzman, P, Nilsson, A, Apelqvist, J, Sellman, A, Hammarlund, C Hyperbaric oxygen therapy as adjunctive treatment of chronic diabetic foot ulcers. *EWMA Journal* 2009; **9:** 83, Abstract.
Ref ID: 6679
Reason for Exclusion: abstract only

Lalau, JD Algoderm dressing versus Vaseline gauze for the treatment of diabetic foot lesions. *First World Wound Healing Congress; 2000, 10-13 September; Melbourne, Australia* 2000; 96.
Ref ID: 5997
Reason for Exclusion: can’t find in BL

Landau, Z Topical hyperbaric oxygen and low energy laser for the treatment of diabetic foot ulcers. *Archives of Orthopaedic & Trauma Surgery* 1998; **117:** 156-58.
Ref ID: 6008
Reason for Exclusion: not a RCT

Landau, Z, Schattner, A Topical hyperbaric oxygen and low energy laser therapy for chronic diabetic foot ulcers resistant to conventional treatment. *Yale Journal of Biology & Medicine* 2001; **74:** 95-100.
Ref ID: 6013
Reason for Exclusion: not a RCT

Lavery, LA, Boulton, AJ, Niezgoda, JA, Sheehan, P A comparison of diabetic foot ulcer outcomes using negative pressure wound therapy versus historical standard of care. *International Wound Journal* 2007; **4:** 103-13.
Ref ID: 6140
Reason for Exclusion: not a RCT

Lazaro-Martinez, JL, Garcia-Morales, E, Aragon-Sanchez, FJ Randomized comparative trial of a collagen/oxidised regenerated cellulose dressing in the treatment of the neuropathic diabetic foot ulcer. *EWMA Journal* 2008; **8:** 289, Abstract.
Ref ID: 6172
Reason for Exclusion: abstract only

Lee, SS, Chen, CY, Chan, YS, Yen, CY, Chao, EK, Ueng, SW Hyperbaric oxygen in the treatment of diabetic foot infection. *Changgeng Yi Xue Za Zhi* 1997; **20:** 17-22.
Ref ID: 6235
Reason for Exclusion: not a RCT

Lee, TH, Lin, SS, Wapner, KL Tendo-Achilles lengthening and total contact casting for plantar forefoot ulceration in diabetic patients with equinus deformity of the ankle. *Operative Techniques in Orthopaedics* 1996; **6:** 222-26.
Ref ID: 6236
Reason for Exclusion: not a RCT

Lin, SS, Bono, CM, Lee, TH Total contact casting and Keller arthoplasty for diabetic great toe ulceration under the interphalangeal joint. *Foot & Ankle International* 2000; **21:** 588-93.
Ref ID: 6454
Reason for Exclusion: not a RCT-a retrospective review

Lin, TF, Chen, SB, Niu, KC The vascular effects of hyperbaric oxygen therapy in treatment of early diabetic foot. *Undersea and Hyperbaric Medicine* 2001; **28:** 67, Abstract.
Ref ID: 6456
Reason for Exclusion: abstract

Lo, SF, Chang, CJ, Hu, WY, Hayter, M, Chang, YT The effectiveness of silver-releasing dressings in the management of non-healing chronic wounds: a meta-analysis. *Journal of Clinical Nursing* 2009; **18(5):** 716-28.
Ref ID: 6578
Reason for Exclusion: a meta analysis

Lodge, A, Jones, M, Thomas, S Maggots 'n' chips: a novel approach to the treatment of diabetic ulcers. [Review] [16 refs]. *British Journal of Community Nursing* 2006; **11:** S23-6.
Ref ID: 6603
Reason for Exclusion: case Report

Londahl, M, Katzman, P, Nilsson, A, Hammarlund, C, Sellman, A, Wykman, A, Hugo-Persson, M, Apelqvist, J A prospective study: hyperbaric oxygen therapy in diabetics with chronic foot ulcers. *Journal of Wound Care* 2006; **15:** 457-59.
Ref ID: 6620
Reason for Exclusion: not a completed study

Mahmoud, SM, Mohamed, AA, Mahdi, SE, Ahmed, ME Split-skin graft in the management of diabetic foot ulcers. *Journal of Wound Care* 2008; **17:** 303-6.
Ref ID: 6760
Reason for Exclusion: case control study

Markevich, YO, McLeod-Roberts, J, Mousley, M, Melloy, E Maggot therapy for diabetic neuropathic foot wounds. *Diabetologia* 2000; **43:** A15.
Ref ID: 6878
Reason for Exclusion: not a RCT

Marston, W, Foushee, K, Farber, M Prospective randomized study of a cryopreserved, human fibroblast-derived dermis in the treatment of chronic plantar foot ulcers associated with diabetes mellitus. *14th Annual Symposium on Advances Wound Care and Medical Research Forum on Wound Repair* 2001.
Ref ID: 6907
Reason for Exclusion: abstract only

Martin, BR, Sangalang, M, Wu, S, Armstrong, DG Outcomes of allogenic acellular matrix therapy in treatment of diabetic foot wounds: an initial experience. *International Wound Journal* 2005; **2:** 161-65.
Ref ID: 6918
Reason for Exclusion: not a RCT

Martinez-De Jesus, FR, Morales-Guzman, M, Castaneda, M, Perez-Morales, A, Garcia-Alonso, J, Mendiola-Segura, I Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers. *Archives of Medical Research* 1997; **28:** 95-99.
Ref ID: 6933
Reason for Exclusion: not licensed in the UK

Mazzone, T Evaluation of a new loaded foam membrane on the healing rate of diabetic foot ulcers. *1st Joint Meeting of the Wound Healing Society and the European Tissue Repair Society; 1993, August; Amsterdam, The Netherlands* 1993; 88.
Ref ID: 7031
Reason for Exclusion: can't find in BL

Mazzurco, S, Goretti, C, Rizzo, L, Piaggesi, A Efficacy and safety of a novel antiseptic super-oxidized solution in the management of wide post-surgical lesions in the infected diabetic foot [Poster no: 189]. *17th Conference of the European Wound Management Association; 2007, 2-4 May; Glasgow, Scotland* 2007; 186.
Ref ID: 7033
Reason for Exclusion: not a RCT

McCallon, SK, Knight, CA, Valiulus, JP, Cunningham, MW, McCulloch, JM, Farinas, LP Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. *Ostomy Wound Management* 2000; **46:** 28-32.
Ref ID: 7049
Reason for Exclusion: patients less than 10 per arm

McKinnon, PS, Paladino, JA, Grayson, ML, Gibbons, GW, Karchmer, AW Cost-effectiveness of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients. *Clinical Infectious Diseases* 1997; **24:** 57-63.
Ref ID: 7166
Reason for Exclusion: health economics

McLigeyo, Otieno, LS Diabetic ulcers--a clinical and bacteriological study. *East African Medical Journal* 1991; **68:** 204-10.
Ref ID: 7180
Reason for Exclusion: not a RCT

MÇ¬nter, KC, Beele, H, Russell, L, Crespi, A, GrÇôchenig, E, Basse, P, Alikadic, N, Fraulin, F, Dahl, C, Jemma, AP Effect of a sustained silver-releasing dressing on ulcers with delayed healing: the CONTOP study. *Journal of Wound Care* 2006; **15:** 199-207.
Ref ID: 7034
Reason for Exclusion: cant find in BL

Medical Advisory Secretariat. Hyperbaric oxygen therapy for non-healing ulcers in diabetes mellitus: an evidence-based analysis. 26. 2005. Canada, Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS).
Ref Type: Report
Ref ID: 318
Reason for Exclusion: literature review

Mendes, P, Carvalho, R, Dores, J, Serra, MB, Calado, E, Ramos, H, Amorim, J Efficacy of antibiotic regimens in severe diabetic foot infections. *Diabetic Foot* 2004; **7:** 138-NaN.
Ref ID: 7263
Reason for Exclusion: not a RCT

Mendicino, RW, Catanzariti, AR, Saltrick, KR, Dombek, MF, Tullis, BL, Statler, TK, Johnson, BM Tibiotalocalcaneal arthrodesis with retrograde intramedullary nailing. *Journal of Foot & Ankle Surgery* 2004; **43:** 82-86.
Ref ID: 7264
Reason for Exclusion: control patients not DFU population

Mendonca, DA, Cosker, T, Makwana, NK Vacuum-assisted closure to aid wound healing in foot and ankle surgery. *Foot & Ankle International* 2005; **26:** 761-66.

Ref ID: 7266
Reason for Exclusion: not a RCT

Meuleneire, F Management of diabetic foot ulcers using dressings with Safetac: A review of case studies. *Wounds UK* 2008; **4:** 16-30.
Ref ID: 7282
Reason for Exclusion: cases studies

Miller, MC, Nanchahal, J Advances in the modulation of cutaneous wound healing and scarring. [Review] [191 refs]. *Biodrugs* 2005; **19:** 363-81.
Ref ID: 7317
Reason for Exclusion: not a RCT

Miller, MS Use of topical recombinant human platelet-derived growth factor-BB (becaplermin) in healing of chronic mixed arteriovenous lower extremity diabetic ulcers. *Journal of Foot & Ankle Surgery* 1999; **38:** 227-31.
Ref ID: 7318
Reason for Exclusion: case study

Mills, CR, Harding, S Re: The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* 2004; **27:** 108.
Ref ID: 7342
Reason for Exclusion: abstract only

Misso, S, D'Onofrio, M, Paesano, L, Fratellanza, G, D'Agostino, E, Feola, B, Minerva, A, Formisano, S Our experience in the treatment of refractory ulcers with platelet gel. [Italian, English]. *Blood Transfusion* 2006; **4:** 196-205.
Ref ID: 7364
Reason for Exclusion: can't find in BL

Mody, GN, Nirmal, IA, Duraisamy, S, Perakath, B A blinded, prospective, randomized controlled trial of topical negative pressure wound closure in India. *Ostomy Wound Management* 2008; **54:** 36-46.
Ref ID: 7386
Reason for Exclusion: not a pure DFU population and unable to extract data for DFU population

Mohan, VK Recombinant human epidermal growth factor (REGEN-D 150): effect on healing of diabetic foot ulcers. *Diabetes Research & Clinical Practice* 2007; **78:** 405-11.
Ref ID: 7398
Reason for Exclusion: not a RCT

Mohr, P, Stegmann, W, Breitbart, EW Low-frequency ultrasound treatment of chronic venous ulcers. *Wound Repair & Regeneration* 1997; **5:** 18-22.
Ref ID: 7403
Reason for Exclusion: population unclear

Motta, GJ, Milne, CT, Corbett, LQ Impact of antimicrobial gauze on bacterial colonies in wounds that require packing. *Ostomy Wound Management* 2004; **50:** 48-62.
Ref ID: 7492
Reason for Exclusion: case series

Moustafa, M, Bullock, AJ, Creagh, FM, Heller, S, Jeffcoate, W, Game, F, Amery, C, Tesfaye, S, Ince, Z, Haddow, DB, MacNeil, S Randomized, controlled, single-blind study on use of autologous keratinocytes on a transfer dressing to treat nonhealing diabetic ulcers. *Regenerative Medicine* 2007; **2:** 887-902.
Ref ID: 7515
Reason for Exclusion: can't find in BL

Mueller, MJ, Sinacore, DR, Hastings, MK, Strube, MJ, Johnson, JE Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial. *Journal of Bone & Joint Surgery - American Volume* 2003; **85-A:** 1436-45.
Ref ID: 7554
Reason for Exclusion: not looking at Achilles tendon lengthening as a treatment option

Mueller, MJ, Sinacore, DR, Hastings, MK, Lott, DJ, Strube, MJ, Johnson, JE Impact of achilles tendon lengthening on functional limitations and perceived disability in people with a neuropathic plantar ulcer. *Diabetes Care* 2004; **27:** 1559-65.
Ref ID: 7558
Reason for Exclusion: for question 6

Mulder, G, Tallis, AJ, Marshall, VT, Mozingo, D, Phillips, L, Pierce, GF, Chandler, LA, Sosnowski, BK Treatment of nonhealing diabetic foot ulcers with a platelet-derived growth factor gene-activated matrix (GAM501): results of a phase 1/2 trial. *Wound Repair & Regeneration* 2009; **17:** 772-79.
Ref ID: 7577
Reason for Exclusion: not a RCT

Mulder, GD, Patt, LM, Sanders, L, Rosenstock, J, Altman, MI, Hanley, ME, Duncan, GW Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. *Wound Repair & Regeneration* 1994; **2:** 259-69.
Ref ID: 7580
Reason for Exclusion: can't find in BL

Munter, K, Beele, H, Russell, L Effect of a sustained silver-releasing dressing on ulcers with delayed healing: the CONTOP study. *J Wound Care* 2006; **15**.
Ref ID: 7606
Reason for Exclusion: can't extract data for DFU population

Muthukumarasamy, MG, Sivakumar, G, Manoharan, G Topical phenytoin in diabetic foot ulcers. *Diabetes Care* 1991; **14:** 909-11.
Ref ID: 7652
Reason for Exclusion: not a RCT

Narozny, W, Sicko, Z, Stankiewicz, CZ, Przewozny, T, Pegiel-Sicko, E The effect of hyperbaric oxygen on nasal mucociliary transport. *Clinical Otolaryngology and Allied Sciences* 2002; **27:** 140-146.
Ref ID: 7716
Reason for Exclusion: not relevant

Nedeljkovic-Beleslin, B, Beleslin, D Becaplermin: A new effective and safe adjuvant topical therapy in patients with chronic neuropathic diabetic foot ulcer. *Medicus* 2005; **6:** 25-29.
Ref ID: 7752
Reason for Exclusion: can't find in BL

Niinikoski, J Hyperbaric oxygen therapy of diabetic foot ulcers, transcutaneous oxymetry in clinical decision making. *Wound Repair & Regeneration* 2003; **11:** 458-61.
Ref ID: 7860
Reason for Exclusion: not a study

Nishimoto, GS, Attinger, CE, Cooper, PS Lengthening the Achilles tendon for the treatment of diabetic plantar forefoot ulceration. [Review] [31 refs]. *Surgical Clinics of North America* 2003; **83:** 707-26.
Ref ID: 7868
Reason for Exclusion: general background

Noel, GJ, Bush, K, Bagchi, P, Ianus, J, Strauss, RS A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clinical Infectious Diseases* 2008; **46:** 647-55.
Ref ID: 7882
Reason for Exclusion: not a pure DFU population

Nordmyr, J, Svensson, S, Bjorck, M, Acosta, S Vacuum assisted wound closure in patients with lower extremity arterial disease: The experience from tertiary referral-centres. *International Angiology* 2009; **28:** 26-31.
Ref ID: 7888
Reason for Exclusion: not a DFU population

Nouvong, A, Hoogwerf, B, Mohler, E, Davis, B, Tajaddini, A, Medenilla, E Evaluation of diabetic foot ulcer healing with hyperspectral imaging of oxyhemoglobin and deoxyhemoglobin. *Diabetes Care* 2009; **32:** 2056-61.
Ref ID: 7900
Reason for Exclusion: use oxygenation to predict healing

Oyibo, SO, Jude, EB, Tarawneh, I, Nguyen, HC, Harkless, LB, Boulton, AJ A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care* 2001; **24:** 84-88.
Ref ID: 8096
Reason for Exclusion: for question 2

Page, AV, Liles, WC Granulocyte colony-stimulating factor, granulocyteg[euro]" macrophage colony-stimulating factor, and other immunomodulatory therapies for the treatment of infectious diseases in solid organ transplant recipients. *Current Opinion in Organ Transplantation* 2008; **13:** 575-80.
Ref ID: 8119
Reason for Exclusion: literature review

Pai, MR, Sitaraman, N, Kotian, MS Topical phenytoin in diabetic ulcers: a double blind controlled trial. *Indian Journal of Medical Sciences* 2001; **55:** 593-99.
Ref ID: 8137
Reason for Exclusion: lack of data

Parish, L, Routh, H, Parish, J Diabetic foot ulcers: A randomized multicenter study comparing a moisture-controlling dressing with a topical growth factor. *Journal of the American Academy of Dermatology* 2009; **60:** AB202.
Ref ID: 8221
Reason for Exclusion: can't find in BL

Pathare, NA, Sathe, SR Antibiotic combinations in polymicrobic diabetic foot infections. *Indian Journal of Medical Sciences* 2001; **55:** 655-62.
Ref ID: 8271
Reason for Exclusion: not a RCT

Payne, E Vac Therapy vs Moist Wound Therapy in the Treatment of Diabetic Foot Amputation Wounds: Preliminary Results of a Mulitcenter Trial. *2nd World Union of Wound Healing Societies Meeting; 2004 ,8-13 July; Paris* 2004; 19.
Ref ID: 8309
Reason for Exclusion: can't find in BL

Peck, KR, Son, DW, Song, JH, Kim, S, Oh, MD, Choe, KW Enhanced neutrophil functions by recombinant human granulocyte colony-stimulating factor in diabetic patients with foot infections in vitro. *Journal of Korean Medical Science* 2001; **16:** 39-44.
Ref ID: 8312
Reason for Exclusion: not a RCT

Pham, C, Middleton, P, and Maddern, G. Vacuum-assisted closure for the management of wounds: an accelerated systematic review. 53. 2003. Australia, Stepney, SA: Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S). Report no. 37.
Ref Type: Report
Ref ID: 8446
Reason for Exclusion: systematic review

Pham, CT, Middleton, PF, Maddern, GJ The safety and efficacy of topical negative pressure in non-healing wounds: a systematic review. *Journal of Wound Care* 2006; **15:** 240-251.
Ref ID: 8448
Reason for Exclusion: systematic review

Piaggesi, A, Goretti, C, Mazzurco, S, Scatena, A, Tedeschi, A, Rizzo, L Efficacy and safety of a novel super-oxidized solution (SOS) in managing post-surgical lesions of the diabetic foot- a prospective, randomised clinical trial. *EWMA Journal* 2008; **8:** 57, Abstract.
Ref ID: 8507
Reason for Exclusion: abstract only

Piaggesi, A, Goretti, C, Mazzurco, S, Scatena, A, Tedeschi, A, Rizzo, L Efficacy and safety of a novel super-oxidized solution (sos) in managing post-surgical lesions of the diabetic foot: A prospective, randomized clinical trial. *3rd Congress of the World Union of Wound Healing Societies Meeting; 2008, 4-8 June; Toronto, Canada* 2008; Abstract.
Ref ID: 8508
Reason for Exclusion: abstract only

Piaggesi, A, Rizzo, L, Campi, F, Schipani, E Conservative surgical approach versus non-operative treatment for diabetic neuropathic foot ulcers: a randomized trial. *Journal of Endocrinological Investigation* 1998; **21:** 193.
Ref ID: 8491
Reason for Exclusion: In Cochrane review

Piaggesi, A, Schipani, E, Campi, F, Romanelli, M, Baccetti, F, Arvia, C, Navalesi, R Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. *Diabetic Medicine* 1998; **15:** 412-17.
Ref ID: 8490
DUPLICATE
Reason for Exclusion: In Cochrane review

Pinzur, M Surgical versus accommodative treatment for Charcot arthropathy of the midfoot. *Foot & Ankle International* 2004; **25:** 545-49.
Ref ID: 8533
Reason for Exclusion: for question 6

Pirayesh, A, Dessy, LA, Rogge, FJ, Hoeksema, HJ, Sinove, YM, Dall', AA, Jawad, MA, Gilbert, PM, Rubino, C, Scuderi, N, Blondeel, R, Monstrey, S The efficacy of a polyhydrated ionogen impregnated dressing in the treatment of recalcitrant diabetic foot ulcers: a multi-centre pilot study. *Acta Chirurgica Belgica* 2007; **107:** 675-81.
Ref ID: 8604
Reason for Exclusion: not a RCT and no control arm

Quatresooz, P, Pierard-Franchimont, C, Szepetiuk, G, Devillers, C, Pierard, GE Fungal chitin-glucan scaffold for managing diabetic xerosis of the feet in menopausal women. *Expert Opinion on Pharmacotherapy* 2009; **10:** 2221-29.
Ref ID: 8767
Reason for Exclusion: not relevant

Quatresooz, P, Kharfi, M, Paquet, P, Vroome, V, Cauwenbergh, G, Pierard, GE Healing effect of ketanserin on chronic leg ulcers in patients with diabetes. *Journal of the European Academy of Dermatology & Venereology* 2006; **20:** 277-81.
Ref ID: 8765
Reason for Exclusion: not licensed in the UK

Ramaswami, G, D'Ayala, M, Hollier, LH, Deutsch, R, McElhinney, AJ Rapid foot and calf compression increases walking distance in patients with intermittent claudication: results of a randomized study. *Journal of Vascular Surgery* 2005; **41:** 794-801.
Ref ID: 8844
Reason for Exclusion: not studying DFU population

Randall, KL, Booth, BA, Miller, AJ, Russell, CB, Laughlin, RT Use of an acellular regenerative tissue matrix in combination with vacuum-assisted closure therapy for treatment of a diabetic foot wound. *Journal of Foot & Ankle Surgery* 2008; **47:** 430-433.
Ref ID: 8860
Reason for Exclusion: Case Report

Reiber, GE, Smith, DG, Wallace, C, Sullivan, K, Hayes, S, Vath, C, Maciejewski, ML, Yu, O, Heagerty, PJ, LeMaster, J Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. *JAMA* 2002; **287:** 2552-58.
Ref ID: 8988
Reason for Exclusion: about prevention

Reiber, GE, Smith, DG, Wallace, CM, Vath, CA, Sullivan, K, Hayes, S, Yu, O, Martin, D, Maciejewski, M Footwear used by individuals with diabetes and a history of foot ulcer. *Journal of Rehabilitation Research & Development* 2002; **39:** 615-22.
Ref ID: 8987
Reason for Exclusion: not a RCT

Rhaiem, BB, Ftouhi, B, Brahim, SB, Mekaouer, A, Kanoun, F, Abde'nnebi, A, Khalifa, FB A comparative study of saccharose use in the treatment of cutaneous lesions in diabetic patients: About 80 cases: <ORIGINAL> ESSAI COMPARATIF DE L'UTILISATION DU SACCHAROSE DANS LE TRAITEMENT DES LESIONS CUTANEES CHEZ LE DIABETIQUE A PROPOS DE 80 CAS. *Tunisie Medicale* 1998; **76:** 19-23.
Ref ID: 9040
Reason for Exclusion: not in English

Ritchie, K, Baxter, S, Craig, J, Macpherson, K, Mandava, L, McIntosh, H, and Wilson, S. The clinical and cost effectiveness of hyperbaric oxygen therapy (HBOT). 282. 2008. Glasgow: NHS Quality Improvement Scotland (NHS QIS). HTA Systematic Review 2.
Ref Type: Report
Ref ID: 4571
Reason for Exclusion: health economics

Robson, MC, Mustoe, TA, Hunt, TK The future of recombinant growth factors in wound healing. *American Journal of Surgery* 1998; **176:** Suppl-82S.
Ref ID: 9176
Reason for Exclusion: not a RCT

Roeder, B, Van Gils, CC, Maling, S Antibiotic beads in the treatment of diabetic pedal osteomyelitis. *Journal of Foot and Ankle Surgery* 2000; **39:** 124-30.
Ref ID: 9198
Reason for Exclusion: case study

Rogers, LC, Lear, E The potential of gene therapy in podiatric medicine: several new bio-engineered products hold great promise for the treatment of diabetic ulcers. *Podiatry Management* 2009; **28:** 89-92.
Ref ID: 9220
Reason for Exclusion: not a RCT

Romanelli, M, Dini, V, Vowden, P, Agren, MS Amelogenin, an extracellular matrix protein, in the treatment of venous leg ulcers and other hard-to-heal wounds: experimental and clinical evidence. [Review] [43 refs]. *Clinical Interventions In Aging* 2008; **3:** 263-72.
Ref ID: 9237
Reason for Exclusion: not a study

Ropper, AH, Gorson, KC, Gooch, CL, Weinberg, DH, Pieczek, A, Ware, JH, Kershen, J, Rogers, A, Simovic, D, Schratzberger, P, Kirchmair, R, Losordo, D Vascular Endothelial Growth Factor Gene Transfer for Diabetic Polyneuropathy: A Randomized, Double-Blinded Trial. *Annals of Neurology* 2009; **65:** 386-93.
Ref ID: 9251
Reason for Exclusion: not studying DFU population

Ruffini, I, Belcaro, G, Cesarone, MR, Geroulakos, G, Di, RA, Milani, M, Coen, L, Ricci, A, Brandolini, R, Dugall, M, Pomante, P, Cornelli, U, Acerbi, G, Corsi, M, Griffin, M, Ippolito, E, Bavera, P Evaluation of the local effects of vitamin E (E-Mousse) on free radicals in diabetic microangiopathy: a randomized, controlled trial. *Angiology* 2003; **54:** 415-21.
Ref ID: 9335
Reason for Exclusion: looks at effects on free radicals rather than DFU healing

Rullan, M, Cerda, L, Frontera, G, Masmiquel, L, Llobera, J Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple-blind, placebo-controlled, clinical trial.[Erratum appears in Diabet Med. 2008 Oct;25(10):1257]. *Diabetic Medicine* 2008; **25:** 1090-1095.
Ref ID: 9341
Reason for Exclusion: study in primary care

Russo, G, Crippa, M, Lorenzi, G, Motolese, A Bioengineered skin grafts after revascularization in the treatment of ischemic ulcers. *Chirurgia* 2006; **19:** 253-56.
Ref ID: 9354
Reason for Exclusion: not a RCT

Saap, LJ, Falanga, V Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Repair & Regeneration* 2002; **10:** 354-59.
Ref ID: 9376
Reason for Exclusion: looking at index scores to define time to heal

Sabolinski, ML, Alvarez, O, Auletta, M, Mulder, G, Parenteau, NL Cultured skin as a 'smart material' for healing wounds: experience in venous ulcers. *Biomaterials* 1996; **17:** 311-20.
Ref ID: 9390
Reason for Exclusion: not a DFU population

Sacco, IC, Bacarin, TA, Canettieri, MG, Hennig, EM Plantar pressures during shod gait in diabetic neuropathic patients with and without a history of plantar ulceration. *Journal of the American Podiatric Medical Association* 2009; **99:** 285-94.
Ref ID: 9395
Reason for Exclusion: not relevant

Sacco, IC, Hamamoto, AN, Gomes, AA, Onodera, AN, Hirata, RP, Hennig, EM Role of ankle mobility in foot rollover during gait in individuals with diabetic neuropathy. *Clinical Biomechanics* 2009; **24:** 687-92.
Ref ID: 9394
Reason for Exclusion: not a RCT

Sadat, U, Chang, G, Noorani, A, Walsh, SR, Hayes, PD, Varty, K Efficacy of TNP on lower limb wounds: a meta-analysis. *Journal of Wound Care* 2008; **17(1):** 45-48.
Ref ID: 9400
Reason for Exclusion: a meta analysis

Saldalamacchia, G, Lapice, E, Cuomo, V, De, FE, D'Agostino, E, Rivellese, AA, Vaccaro, O A controlled study of the use of autologous platelet gel for the treatment of diabetic foot ulcers. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2004; **14:** 395-96.
Ref ID: 9428
Reason for Exclusion: not a study format

Salsich, GB, Mueller, MJ, Hastings, MK, Sinacore, DR, Strube, MJ, Johnson, JE Effect of Achilles tendon lengthening on ankle muscle performance in people with diabetes mellitus and a neuropathic plantar ulcer. *Physical Therapy* 2005; **85:** 34-43.
Ref ID: 9443
Reason for Exclusion: for question 6

Saltzman, CL, Zimmerman, MB, Holdsworth, RL, Beck, S, Hartsell, HD, Frantz, RA Effect of initial weight-bearing in a total contact cast on healing of diabetic foot ulcers. *Journal of Bone & Joint Surgery - American Volume* 2004; **86-A:** 2714-19.

Ref ID: 9448
Reason for Exclusion: not a RCT

Samoilova, KA, Zhevago, NA, Menshutina, MA, Grigorieva, NB Role of nitric oxide in the visible light-induced rapid increase of human skin microcirculation at the local and systemic level: I. diabetic patients. *Photomedicine and Laser Surgery* 2008; **26:** 433-42.
Ref ID: 9471
Reason for Exclusion: not looking at DFU population

Sams, HH, Chen, J, King, LE Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. *Dermatologic Surgery* 2002; **28:** 698-703.
Ref ID: 9476
Reason for Exclusion: less than 10 patients per arm

Sanders, CV Treatment of polymicrobial gynecologic and skin and skin-structure infections: Worldwide clinical trials. *Infectious Diseases in Clinical Practice* 1995; **4:** S26-S32.
Ref ID: 9486
Reason for Exclusion: not studying DFU population

Schindl, A, Schindl, M, Schon, H, Knobler, R, Havelec, L, Schindl, L Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. *Diabetes Care* 1998; **21:** 580-584.
Ref ID: 9625
Reason for Exclusion: for question 6

Schindl, A, Heinze, G, Schindl, M, Pernerstorfer-Schon, H, Schindl, L Systemic effects of low-intensity laser irradiation on skin microcirculation in patients with diabetic microangiopathy. *Microvascular Research* 2002; **64:** 240-246.
Ref ID: 9627
Reason for Exclusion: not a RCT

Schirmer, PL, Deresinski, SC Ceftobiprole: A new cephalosporin for the treatment of skin and skin structure infections. *Expert Review of Anti-Infective Therapy* 2009; **7:** 777-91.
Ref ID: 9630
Reason for Exclusion: general background

Schneider, SH, Tendler, M, Apelian, A, Jageneau, AH, Khachadurian, AK Effects of ketanserin, a 5-HT2-receptor antagonist, on the blood flow response to temperature changes in the diabetic foot. *Journal of Clinical Pharmacology* 1985; **25:** 413-17.
Ref ID: 9642
Reason for Exclusion: not licensed in the UK

Sherman, RA Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy. *Diabetes Care* 2003; **26:** 446-51.
Ref ID: 9894
Reason for Exclusion: not a RCT

Shirakawa, M, Isseroff, RR Topical negative pressure devices: Use for enhancement of healing chronic wounds. *Archives of Dermatology* 2005; **141:** 1449-53.
Ref ID: 9920
Reason for Exclusion: not pure DFU population

Sigala, F, Menenakos, C, Sigalas, P, Baunach, C, Langer, S, Papalambros, E, Hepp, W Transluminal angioplasty of isolated crural arterial lesions in diabetics with critical limb ischemia. *Vasa* 2005; **34:** 186-91.
Ref ID: 9988
Reason for Exclusion: for question 6

Silva, SY, Rueda, LC, Marquez, GA, Lopez, M, Smith, DJ, Calderon, CA, Castillo, JC, Matute, J, Rueda-Clausen, CF, Orduz, A, Silva, FA, Kampeerapappun, P, Bhide, M, Lopez-Jaramillo, P Double blind, randomized, placebo controlled clinical trial for the treatment of diabetic foot ulcers, using a nitric oxide releasing patch: PATHON. *Trials* 2007; **8, 2007. Article Number: 26. Date of Publication: 26 Sep 2007.** .
Ref ID: 9996
Reason for Exclusion: abstract only

Smiell, JM Clinical safety of becaplermin (rhPDGF-BB) gel. *American Journal of Surgery* 1998; **176:** 68S-73S.
Ref ID: 10132
Reason for Exclusion: can't extract data for individual studies

Smiell, JM, Wieman, TJ, Steed, DL, Perry, BH, Sampson, AR, Schwab, BH Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB)in patients with nonhealing, lower extremity diabetic ulcers: A combined analysis of four randomized studies. *Wound Repair and Regeneration* 1999; **7:** 335-46.
Ref ID: 10133
Reason for Exclusion: systematic review

Snyder, RJ, Hanft, JR Diabetic foot ulcers - effects on quality of life, costs, and mortality and the role of standard wound care and advanced-care therapies in healing: a review. *Ostomy Wound Management* 2009; **55:** 28-38.
Ref ID: 10218
Reason for Exclusion: a review

Steed, D, Donohoe, D, Webster, M, Lindsley, L, PDGF Study Group Extensive debridement of human diabetic foot ulcers is a vital adjunct to healing. *5th Annual Meeting of the European Tissue Repair Society; 1995, August 30-September 2; Padova, Italy* 1995; 371.
Ref ID: 10372
Reason for Exclusion: abstract

Steed, DL, Edington, HD, Webster, MW Recurrence rate of diabetic neurotrophic foot ulcers healed using topical application of growth factors released from platelets. *Wound Repair & Regeneration* 1996; **4:** 230-233.
Ref ID: 10383
Reason for Exclusion: can't find in BL

Steed, DL, Donohoe, D, Webster, MW, Lindsley, L Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. *Journal of the American College of Surgeons* 1996; **183:** 61-64.
Ref ID: 10382
Keywords: looked at effect of growth factors and no control arm for debridement

Steed, DL, Goslen, JB, Holloway, GA, Malone, JM, Bunt, TJ, Webster, MW Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. *Diabetes Care* 1992; **15:** 1598-604.
Ref ID: 10376
Keywords: less than 10 patients per arm

Stone, JA, Cianci, P The adjunctive role of hyperbaric oxygen therapy in the treatment of lower extremity wounds in patients with diabetes. *Diabetes Spectrum* 1997; **10:** 118-24.
Ref ID: 10460
Reason for Exclusion: not a RCT

Summers, JB, Kaminski, J, Frykberg, RG Maggot debridement therapy for diabetic necrotic foot... Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Physician 2002;66:1655-62. *American Family Physician* 2003; **68:** 2327-29.
Ref ID: 10542
Reason for Exclusion: not a RCT

Tuyet, HL, Nguyen Quynh, TT, Vo Hoang, MH, Thi Bich, DN, Do, DT, Le, TD, Van, HL, Le, HT, Doan, HH, Tran Trong, TN The efficacy and safety of epidermal growth factor in treatment of diabetic foot ulcers: the preliminary results. *International Wound Journal* 2009; **6:** 159-66.
Ref ID: 10989
Reason for Exclusion: not a RCT

Udell, E Negative-Pressure Wound Therapy and Diabetic Foot Amputations: A Retrospective Study of Payer Claims Data. *Journal - American Podiatric Medical Association* 2008; **98:** 164-65.
Ref ID: 11012
Reason for Exclusion: letter to editor

Unger, HD, Lucca, M The role of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers and refractory osteomyelitis. [Review] [36 refs]. *Clinics in Podiatric Medicine & Surgery* 1990; **7:** 483-92.
Ref ID: 11034
Reason for Exclusion: not a study

Vandeputte, J Clinical trial on the control of diabetic foot infection by an immunomodulating hydrogel containing 65% glycerine. *Proceedings of the 6th European Conference on Advances in Wound Management; 1995, 21-24 November; Harrogate, UK* 1997; 50-53.
Ref ID: 11191
Reason for Exclusion: in Cochrane review

Veves, A, Falango, V, Armstrong, DG, Sabolinski, ML Graftskin (Apligraf) a human skin equivalent, promotes wound healing in diabetic foot ulcers in a prospective, randomized, multicenter clinical trial. *Tenth Annual Meeting of the European Tissue Repair Society; 2000, 24-27 May; Brussels, Belgium* 2000; A436.
Ref ID: 11257
Reason for Exclusion: abstract

Viswanathan, V, Mahesh, U, Jayaraman, M, Shina, K, Ramachandram, A Beneficial role of granulocyte colony stimulating factor in foot infection in diabetic patients. *Journal of the Association of Physicians of India* 2003; **51:** 90-91.
Ref ID: 11321
Reason for Exclusion: abstract

Wallace, GF [Commentary on] A metabolically active human dermal replacement for the treatment of diabetic foot ulcers. *Foot & Ankle Quarterly--The Seminar Journal* 2002; **15:** -NaN.
Ref ID: 11407
Reason for Exclusion: expert opinion on a RCT

Wang, F Twenty-eight cases of diabetic foot ulcer and gangrene treated with the Chinese herbal medicine combined with injection of ahylsantinfarctase. *Journal of Traditional Chinese Medicine* 2002; **22:** 3-4.
Ref ID: 11442
Reason for Exclusion: case study

Whalley, A, Boulton, AJM, Dargis, V, Harding, K, Van, AK, Capillas, R Performance characteristics and safety of purilon gel versus intrasite using biatain non-adhesive dressing as secondary dressing in the treatment of diabetic foot ulcers. *11th European Tissue Repair Society Annual Conference; 2001 5-8 September; Cardiff, Wales* 2001; 49.
Ref ID: 11609
Reason for Exclusion: can't find in BL

Winters, CL, Brigido, SA, Liden, BA, Simmons, M, Hartman, JF, Wright, ML A multicenter study involving the use of a human acellular dermal regenerative tissue matrix for the treatment of diabetic lower extremity wounds. *Advances in Skin & Wound Care* 2008; **21:** 375-81.
Ref ID: 11771
Reason for Exclusion: not a RCT

Y”nem, A, Cakir, B, G□ ler, S, Azal, OO, Corak‡i, A Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. *Diabetes, Obesity & Metabolism* 2001; **3:** 332-37.
Ref ID: 12053
Reason for Exclusion: In Cochrane review

Yonem, A, Cakir, B, Guler, S, Azal, OO, Corakci, A Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. *Diabetes, Obesity & Metabolism* 2001; **3:** 332-37.
Ref ID: 11979
DUPLICATE
Reason for Exclusion: In Cochrane review

Zamboni, WA, Wong, HP, Stephenson, LL, Pfeifer, MA Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. *Undersea & Hyperbaric Medicine* 1997; **24:** 175-79.
Ref ID: 12083
Reason for Exclusion: not a RCT

Review question 6

Adam, DJ, Raptis, S, Fitridge, RA Trends in the presentation and surgical management of the acute diabetic foot. *European Journal of Vascular & Endovascular Surgery* 2006; **31:** 151-56.
Ref ID: 564
Reason for Exclusion: not relevant

Allie, DE, Patlola, RR, Herbert, CJ, Walker, CM Critical limb ischemia and diabetes: creative limb salvage revascularization strategies. *Journal for Vascular Ultrasound* 2008; **32:** 27-34.
Ref ID: 716
Reason for Exclusion: not a study and general background

Apelqvist, J, Agardh, CD The association between clinical risk factors and outcome of diabetic foot ulcers. *Diabetes Research & Clinical Practice* 1992; **18:** 43-53.
Ref ID: 798
Reason for Exclusion: looks at predicting outcome of DFU using clinical risk factors

Armstrong, DG Effect of Achilles tendon lengthening on neuropathic plantar ulcers: a randomized clinical trial. *Foot & Ankle Quarterly--The Seminar Journal* 2005; **17:** 36-41.

Ref ID: 1001
Reason for Exclusion: head to head comparison of ACL vs.TCC

Armstrong, DG, Stacpoole-Shea, S, Nguyen, H, Harkless, LB Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot.[Erratum appears in J Bone Joint Surg Am. 2000 Oct;82-A(10):1510; PMID: 11057482]. *Journal of Bone & Joint Surgery - American Volume* 1999; **81:** 535-38.
Ref ID: 938
Reason for Exclusion: looks at effectiveness of ACL

Arora, S, Pomposelli, F, LoGerfo, FW, Veves, A Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely after successful lower extremity revascularization. *Journal of Vascular Surgery* 2002; **35:** 501-5.
Ref ID: 1034
Reason for Exclusion: looks at effectiveness of revascularalisation

Batista, F, Nery, C, Pinzur, M, Monteiro, AC, de Souza, EF, Felippe, FH, Alcantara, MC, Campos, RS Achilles tendinopathy in diabetes mellitus. *Foot & Ankle International* 2008; **29:** 498-501.
Ref ID: 1281
Reason for Exclusion: looks at predictors for developing DFU

Biancari, F, Salenius, JP, Heikkinen, M, Luther, M, Ylonen, K, Lepantalo, M Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: A finnvasc registry study. *World Journal of Surgery* 2007; **31:** 217-25.
Ref ID: 1470
Reason for Exclusion: not relevant

Calle-Pascual, AL, Duran, A, Diaz, A, Monux, G, Serrano, FJ, de la Torre, NG, Moraga, I, Calle, JR, Charro, A, Maranes, JP Comparison of peripheral arterial reconstruction in diabetic and non-diabetic patients: a prospective clinic-based study. *Diabetes Research & Clinical Practice* 2001; **53:** 129-36.
Ref ID: 1983
Reason for Exclusion: control arm not DFU population

Campbell, WB, Ponette, D, Sugiono, M Long-term results following operation for diabetic foot problems: arterial disease confers a poor prognosis. *European Journal of Vascular & Endovascular Surgery* 2000; **19:** 174-77.
Ref ID: 2005
Reason for Exclusion: case series

Caputo, WJ Surgical management of the diabetic foot. *Wounds: A Compendium of Clinical Research & Practice* 2008; **20:** 74-84.
Ref ID: 2031
Reason for Exclusion: not a study

Cavallini, M, Caterino, S, Murante, G Revascularization of the ischemic diabetic foot by popliteal-to-distal bypass. *Minerva Cardioangiologica* 1999; **47:** 7-13.
Ref ID: 2097
Reason for Exclusion: case series

Citterio, F, Castagneto, M Lower limb revascularization in diabetics. [Review] [10 refs]. *Rays* 1997; **22:** 603-11.
Ref ID: 2344
Reason for Exclusion: not in English

Cnotliwy, M, Szumilowicz, J, Safranow, K, Petriczko, W, Wiernicki, I, Gutowski, P The role of isolated profundaplasty in attempts to lower the level of amputation in critical limb ischemia. [Polish, English]. *Polski Przeglad Chirurgiczny* 2007; **79:** 1398-405.
Ref ID: 2376
Reason for Exclusion: can't find in BL

Coerper, S, Schaffer, M, Witte, M, Deutschle, G, Wicke, C, Koveker, G, Becker, HD Impact of local surgery on the healing of refractory diabetic foot ulcerations. *Foot and Ankle Surgery* 2001; **7:** 103-8.
Ref ID: 2389
Reason for Exclusion: looks at healing of ulcers

Collins, R, Cranny, G, Burch, J, Aguiar-Ibanez, R, Craig, D, Wright, K, Berry, E, Gough, M, Kleijnen, J, Westwood, M A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. *Health Technology Assessment* 2007; **11(20):** 1-202.
Ref ID: 2425
Reason for Exclusion: population studied in not purely DFU and a systematic review

Conrad, MF, Kang, J, Cambria, RP, Brewster, DC, Watkins, MT, Kwolek, CJ, LaMuraglia, GM Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease. *Journal of Vascular Surgery* 2009; **50:** 799-805.
Ref ID: 2444
Reason for Exclusion: not a DFU population

Daniels, T, Tamir, E Surgical treatment of diabetic foot complications. *Geriatrics and Aging* 2006; **9:** 499-504.
Ref ID: 2616
Reason for Exclusion: not a study

Dellon, AL Neurosurgical prevention of ulceration and amputation by decompression of lower extremity peripheral nerves in diabetic neuropathy: update 2006. *Acta Neurochirurgica - Supplement* 2007; **100:** 149-51.
Ref ID: 2763
Reason for Exclusion: a literature review

DeNamur, C, Pupp, G Diabetic limb salvage. A team approach at a teaching institution. *Journal of the American Podiatric Medical Association* 2002; **92:** 457-62.
Ref ID: 2775
Reason for Exclusion: looking at effectiveness of team approach

DePalma, RG, Talieh, YJ Infrainguinal reconstruction in diabetes. *Diabetes* 1996; **45:** Suppl-8.
Ref ID: 2778
Reason for Exclusion: not a study

Duarte, PM, Young, RJ, Clarke, BF Clinic screening for peripheral vascular disease in diabetes mellitus: Reliability of history, palpation of pulses and Doppler ultrasound examination. *Practical Diabetes* 1988; **5:** 101-2.
Ref ID: 2943
Reason for Exclusion: general background.

Dudkiewicz, I, Schwarz, O, Heim, M, Herman, A, Siev-Ner, I Trans-metatarsal amputation in patients with a diabetic foot: Reviewing 10 years experience. *Foot* 2009; **19:** 201-4.
Ref ID: 2949
Reason for Exclusion: not relevant

Dunn, K Preventing amputation in patients with diabetes. *Wounds UK* 2007; **3:** 22-30.
Ref ID: 2968
Reason for Exclusion: literature search

Durham, JR, Horowitz, JD, Wright, JG, Smead, WL Percutaneous transluminal angioplasty of tibial arteries for limb salvage in the high-risk diabetic patient. *Annals of Vascular Surgery* 1994; **8:** 48-53.
Ref ID: 2977
Reason for Exclusion: case series

Early, JS, Hansen, ST Surgical reconstruction of the diabetic foot: a salvage approach for midfoot collapse. *Foot & Ankle International* 1996; **17:** 325-30.
Ref ID: 2994
Reason for Exclusion: looks at effectiveness of surgical reconstruction

Edmonds, ME, Foster, AVM Reduction of major amputations in the diabetic ischaemic foot: A strategy to "take control" with conservative care as well as revascularisation. *Vasa - Journal of Vascular Diseases* 2001; **30:** 6-14.
Ref ID: 3068
Reason for Exclusion: general background

Embil, JM Amputation prevention and rehabilitation in diabetes. *Advances in Experimental Medicine & Biology* 2001; **498:** 349-58.
Ref ID: 3140
Reason for Exclusion: not a study and general background

Estes, JM, Pomposelli, FB, Jr. Lower extremity arterial reconstruction in patients with diabetes mellitus. [Review] [17 refs]. *Diabetic Medicine* 1996; **13:** Suppl-7.
Ref ID: 3193
Reason for Exclusion: not a study

Faglia, E, Clerici, G, Clerissi, J, Gabrielli, L, Losa, S, Mantero, M, Caminiti, M, Curci, V, Lupattelli, T, Morabito, A Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. *European Journal of Vascular & Endovascular Surgery* 2006; **32:** 484-90.
Ref ID: 3240
Reason for Exclusion: no information on optimal timing for revascularisation

Faglia, E, Favales, F, Quarantiello, A, Calia, P, Brambilla, G, Rampoldi, A, Morabito, A Feasibility and effectiveness of peripheral percutaneous transluminal balloon angioplasty in diabetic subjects with foot ulcers. *Diabetes Care* 1996; **19:** 1261-64.
Ref ID: 3232
Reason for Exclusion: looks at effectiveness of angioplasty

Faglia, E, Mantero, M, Caminiti, M, Caravaggi, C, De, GR, Pritelli, C, Clerici, G, Fratino, P, De, CP, Dalla, PL, Mariani, G, Poli, M, Settembrini, PG, Sciangula, L, Morabito, A, Graziani, L Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. *Journal of Internal Medicine* 2002; **252:** 225-32.
Ref ID: 3237
Reason for Exclusion: looks at effectiveness of angioplasty

Faglia, E, Dalla, PL, Clerici, G, Clerissi, J, Graziani, L, Fusaro, M, Gabrielli, L, Losa, S, Stella, A, Gargiulo, M, Mantero, M, Caminiti, M, Ninkovic, S, Curci, V, Morabito, A Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. *European Journal of Vascular & Endovascular Surgery* 2005; **29:** 620-627.
Ref ID: 3239
Reason for Exclusion: no control arm and looks at effectiveness of angioplasty in patients with CLI

Faglia, E, Clerici, G, Caminiti, M, Quarantiello, A, Curci, V, Morabito, A Predictive values of transcutaneous oxygen tension for above-the-ankle amputation in diabetic patients with critical limb ischemia. *European Journal of Vascular & Endovascular Surgery* 2007; **33:** 731-36.
Ref ID: 3244
Reason for Exclusion: use of TcPO2 to predict major amputation after revascularisation and not before and when should revascularisation should happen

Faglia, E, Clerici, G, Clerissi, J, Mantero, M, Caminiti, M, Quarantiello, A, Curci, V, Lupattelli, T, Morabito, A When is a technically successful peripheral angioplasty effective in preventing above-the-ankle amputation in diabetic patients with critical limb ischaemia? *Diabetic Medicine* 2007; **24:** 823-29.
Ref ID: 3243
Reason for Exclusion: looks at procedures and not markers to prevent amputation

Faries, PL, Teodorescu, VJ, Morrissey, NJ, Hollier, LH, Marin, ML The role of surgical revascularization in the management of diabetic foot wounds. [Review] [26 refs]. *American Journal of Surgery* 2004; **187:** 34S-7S.
Ref ID: 3275
Reason for Exclusion: general background

Garapati, R, Weinfeld, SB Complex reconstruction of the diabetic foot and ankle. [Review] [38 refs]. *American Journal of Surgery* 2004; **187:** 81S-6S.
Ref ID: 3769
Reason for Exclusion: not a study and general background

Ger, R Prevention of major amputations in the diabetic patient. *Archives of Surgery* 1985; **120:** 1317-20.
Ref ID: 3865
Reason for Exclusion: expert opinion

Gerstein, H, Hunt, D Foot ulcers and amputations in diabetes. [Review] [25 refs][Update in Clin Evid. 2002 Dec;(8):569-77; PMID: 12603900]. *Clinical Evidence* 2002; 521-28.
Ref ID: 3876
Reason for Exclusion: not a study

Gibbons, GW, Freeman, D Vascular evaluation and treatment of the diabetic. *Clinics in Podiatric Medicine & Surgery* 1987; **4:** 377-81.
Ref ID: 3921
Reason for Exclusion: not a study and general background

Heis, HA, Shatanawi, NJ, Bani-Hani, KE, Elheis, MA, Balas, HA, Habboub, HK Critical limb ischemia: Revascularization options and clinical outcome. *Jordan Medical Journal* 2008; **42:** 20-27.
Ref ID: 4590
Reason for Exclusion: not a pure DFU population

Jonasson, JM, Ye, W, Sparen, P, Apelqvist, J, Nyren, O, Brismar, K Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care* 2008; **31:** 1536-40.
Ref ID: 5261
Reason for Exclusion: control arm not DFU population

Jude, EB, Selby, PL, Burgess, J, Lilleystone, P, Mawer, EB, Page, SR, Donohoe, M, Foster, AV, Edmonds, ME, Boulton, AJ Bisphosphonates in the treatment of Charcot neuroarthropathy: a double-blind randomised controlled trial. *Diabetologia* 2001; **44:** 2032-37.

Ref ID: 5331
Reason for Exclusion: looking at specific treatment of Charcot

Khalil, UR, Atif, UR Lower extrimity amputation in diabetic patient. *Medical Forum Monthly* 2006; **17:** 14-18.
Ref ID: 5593
Reason for Exclusion: can't find in BL

Krentz, AJ, Mani, R, Shearman, CP Peripheral arterial disease in diabetes: Time for a co-ordinated approach to management. *British Journal of Diabetes and Vascular Disease* 2003; **3:** 92-96.
Ref ID: 5865
Reason for Exclusion: not a study and general background

Krishnan, S, Nash, F, Baker, N, Fowler, D, Rayman, G Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. *Diabetes Care* 2008; **31:** 99-101.
Ref ID: 5874
Reason for Exclusion: looking at effectiveness of MDT to reduce amputation

Kugel, RD, Pereyra, R Combined femorotibial bypass and distal intraoperative transluminal angioplasty. *Journal of Vascular Surgery* 1986; **4:** 533-35.
Ref ID: 5898
Reason for Exclusion: case reports

La, FJ, Reyzelman, A, Rothenberg, G, Husain, K, Harkless, LB The role of revascularization in transmetatarsal amputations. *Journal of the American Podiatric Medical Association* 2001; **91:** 533-35.
Ref ID: 5951
Reason for Exclusion: looks at effectiveness of revascularaisation

Labbe, R, Douville, Y, Noel, HP Arterial reconstruction to the foot vessels: is it worth the trouble? *Canadian Journal of Surgery* 1989; **32:** 424-27.
Ref ID: 5958
Reason for Exclusion: not a pure DFU population

Laborde, JM Tendon lengthenings for forefoot ulcers. *Wounds: A Compendium of Clinical Research & Practice* 2005; **17:** 122-31.
Ref ID: 5961
Reason for Exclusion: looks at clinical effectiveness of ACL

Larsson, J, Agardh, CD, Apelqvist, J, Stenstrom, A Clinical characteristics in relation to final amputation level in diabetic patients with foot ulcers: a prospective study of healing below or above the ankle in 187 patients. *Foot & Ankle International* 1995; **16:** 69-74.
Ref ID: 6066
Reason for Exclusion: looks at relationship between level of amputation and clinical characterstics

Larsson, J, Apelqvist, J, Castenfors, J, Agardh, CD, Stenstrom, A Distal blood pressure as a predictor for the level of amputation in diabetic patients with foot ulcer. *Foot & Ankle* 1993; **14:** 247-53.
Ref ID: 6062
Reason for Exclusion: looks at distal BP to predict outcome of amputation

Larsson, J, Apelqvist, J Towards less amputations in diabetic patients. Incidence, causes, cost, treatment, and prevention--a review. [Review] [117 refs]. *Acta Orthopaedica Scandinavica* 1995; **66:** 181-92.
Ref ID: 6067
Reason for Exclusion: not a study and general background

Lee, CS, Sariego, J, Matsumoto, T Changing patterns in the predisposition for amputation of the lower extremities. *American Surgeon* 1992; **58:** 474-77.
Ref ID: 6213
Reason for Exclusion: not a pure DFU population

Lepore, G, Maglio, ML, Cuni, C, Dodesini, AR, Nosari, I, Minetti, B, Trevisan, R Poor glucose control in the year before admission as a powerful predictor of amputation in hospitalized patients with diabetic foot ulceration. *Diabetes Care* 2006; **29:** 1985-86.
Ref ID: 6301
Reason for Exclusion: not relevant

Levin, ME Preventing amputation in the patient with diabetes. [Review] [117 refs]. *Diabetes Care* 1995; **18:** 1383-94.
Ref ID: 6337
Reason for Exclusion: general background

Luther, B, Pillny, M, Muller, B, Lance, M, Sandmann, W Is the revascularisation of pedal arteries worthwhile in diabetic gangrene? *Vasa - Journal of Vascular Diseases* 2001; **30:** 34-39.
Ref ID: 6704
Reason for Exclusion: looks at effectiveness of revascularalisation

Luther, M, Lepantalo, M Arterial reconstruction to the foot arteries--a viable option? *European Journal of Surgery* 1997; **163:** 659-65.
Ref ID: 6705
Reason for Exclusion: still awaited from BL

Mills, S Open bypass and endoluminal therapy: Complementary techniques for revascularization in diabetic patients with critical limb ischaemia. *Diabetes/Metabolism Research and Reviews* 2008; **24:** S34-S39.
Ref ID: 7344
Reason for Exclusion: not a study and general background

Mohan, CR, Hoballah, JJ, Martinasevic, M, Chalmers, RT, Sharp, WJ, Kresowik, TF, Corson, JD Revascularization of the ischemic diabetic foot using popliteal artery inflow. *International Angiology* 1996; **15:** 138-43.

Ref ID: 7397
Reason for Exclusion: looks at effectiveness of revascularalisation

Moini, M, Rasouli, MR, Heidari, P, Mahmoudi, HR, Rasouli, M Role of early surgical revascularization in the management of refractory diabetic foot ulcers in patients without overt ischemic limbs. *Journal of Foot & Ankle Surgery* 2010; **16:** 50.
Ref ID: 7404
Reason for Exclusion: expert opinion

Morris, AD, McAlpine, R, Steinke, D, Boyle, DI, Ebrahim, AR, Vasudev, N, Stewart, CP, Jung, RT, Leese, GP, MacDonald, TM, Newton, RW Diabetes and lower-limb amputations in the community. A retrospective cohort study. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit. *Diabetes Care* 1998; **21:** 738-43.
Ref ID: 7468
Reason for Exclusion: comparing amputation rates between diabetic and non-diabetic population

Mueller, MJ, Sinacore, DR, Hastings, MK, Lott, DJ, Strube, MJ, Johnson, JE Impact of achilles tendon lengthening on functional limitations and perceived disability in people with a neuropathic plantar ulcer. *Diabetes Care* 2004; **27:** 1559-65.
Ref ID: 7558
Reason for Exclusion: looks at effectiveness of ACL compared to TCC

Neville, RF Diabetic revascularization: improving limb salvage in the absence of autogenous vein. [Review] [30 refs]. *Seminars in Vascular Surgery* 2003; **16:** 19-26.
Ref ID: 7796
Reason for Exclusion: not a study and general background

Peters, J Preventing chronic diabetic foot pathology from progressing to amputation: a podiatric case study. *Primary Intention: the Australian Journal of Wound Management* 2004; **12:** 155-61.
Ref ID: 8404
Reason for Exclusion: case study

Pinzur, M Surgical versus accommodative treatment for Charcot arthropathy of the midfoot. *Foot & Ankle International* 2004; **25:** 545-49.
Ref ID: 8533
Reason for Exclusion: head to head comparison of 2 different treatment options for Charcot's

Prompers, L, Schaper, N, Apelqvist, J, Edmonds, M, Jude, E, Mauricio, D, Uccioli, L, Urbancic, V, Bakker, K, Holstein, P, Jirkovska, A, Piaggesi, A, Ragnarson-Tennvall, G, Reike, H, Spraul, M, Van, AK, Van, BJ, Van, MF, Ferreira, I, Huijberts, M Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia* 2008; **51:** 747-55.
Ref ID: 8730
Reason for Exclusion: looks at predictors of ulcer healing in patients with diabetic foot

Poredos, P, Rakovec, S, Guzic-Salobir, B Determination of amputation level in ischaemic limbs using tcPO2 measurement. *Vasa* 2005; **34:** 108-12.
Ref ID: 8672
Reason for Exclusion: looks at level of amputation based on PO2 values

Rehm, KB Addressing PVD as a way of saving limbs: prevention of lower extremity amputations... peripheral vascular disease. *Podiatry Management* 2002; **21:** 123-32.
Ref ID: 8966
Reason for Exclusion: not a study and general background

Reiber, GE, Raugi, GJ Preventing foot ulcers and amputations in diabetes. [Review] [15 refs]. *Lancet* 2005; **366:** 1676-77.
Ref ID: 8995
Reason for Exclusion: expert opinion

Reiber, GE Who is at risk of limb loss and what to do about it? *Journal of Rehabilitation Research & Development* 1994; **31:** 357-62.
Ref ID: 8974
Reason for Exclusion: expert opinion

Rerkasem, K, Kosachunhanun, N, Tongprasert, S, Khwanngern, K, Matanasarawoot, A, Thongchai, C, Chimplee, K, Buranapin, S, Chaisrisawadisuk, S, Mangklabruks, A Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. *International Journal of Lower Extremity Wounds* 2008; **7:** 88-92.
Ref ID: 9017
Reason for Exclusion: looks at strategies to prevent amputation

Rivers, SP, Scher, L, Veith, FJ Indications for distal arterial reconstruction in the presence of palpable pedal pulses. *Journal of Vascular Surgery* 1990; **12:** 552-57.
Ref ID: 9127
Reason for Exclusion: case series

Rivolta, N, Piffaretti, G, Tozzi, M, Lomazzi, C, Maida, S, Riva, F, Buscarini, E, Castelli, P Two-stage treatment for diabetic foot: surgical peripheral revascularization and minor amputation in day-surgery admission. *International Journal Of Surgery* 2008; **6:** Suppl-7.
Ref ID: 9128
Reason for Exclusion: case reports

Rollins, DL, Kalakuntla, V, Wilson, A Arterial revascularization in patients with diabetes: An overview. *Journal for Vascular Ultrasound* 2006; **30:** 221-27.
Ref ID: 9230
Reason for Exclusion: general background

Sadikot, SM, Sathe, SR Peripheral vascular disease and foot problems; the use of a point based-protocol to categorise risk in patients and reduce the development of foot problems. *Journal of the Diabetic Association of India* 1990; **30:** 32-35.

Ref ID: 9403
Reason for Exclusion: looks at risk of developing foot problem and not amputation

Sathe, SR, Sadikot, SM Neuropathy and foot problems; the use of a point based protocol to categorise risk in patients and reduce the development of foot problems. *Journal of the Diabetic Association of India* 1990; **30:** 47-50.
Ref ID: 9535
Reason for Exclusion: looks at risk of developing foot problem and not amputation

Salsich, GB, Mueller, MJ, Hastings, MK, Sinacore, DR, Strube, MJ, Johnson, JE Effect of Achilles tendon lengthening on ankle muscle performance in people with diabetes mellitus and a neuropathic plantar ulcer. *Physical Therapy* 2005; **85:** 34-43.
Ref ID: 9443
Reason for Exclusion: looks at effectiveness of TAL on ankle muscle performance

Satterfield, K Amputation considerations and energy expenditures in the diabetic patient. *Clinics in Podiatric Medicine & Surgery* 2003; **20:** 793-801.
Ref ID: 9539
Reason for Exclusion: not a study and general background
Schindl, A, Schindl, M, Schon, H, Knobler, R, Havelec, L, Schindl, L Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. *Diabetes Care* 1998; **21:** 580-584.
Ref ID: 9625
Reason for Exclusion: **looks at effectiveness of low intensity laser irradiation on would healing**

Sheahan, MG, Hamdan, AD, Veraldi, JR, McArthur, CS, Skillman, JJ, Campbell, DR, Scovell, SD, LoGerfo, FW, Pomposelli, FB, Jr. Lower extremity minor amputations: the roles of diabetes mellitus and timing of revascularization. *Journal of Vascular Surgery* 2005; **42:** 476-80.
Ref ID: 9861
Reason for Exclusion: looking at effectiveness of revascularisation

Sheehan, P Early change in wound area as a predictor of healing in diabetic foot ulcers: knowing "when to say when". *Plastic & Reconstructive Surgery* 2006; **117:** Suppl-247S.
Ref ID: 9870
Reason for Exclusion: expert opinion

Shojaiefard, A, Khorgami, Z, Larijani, B Septic diabetic foot is not necessarily an indication for amputation. *Journal of Foot & Ankle Surgery* 2008; **47:** 419-23.
Ref ID: 9924
Reason for Exclusion: not relevant

Sigala, F, Menenakos, C, Sigalas, P, Baunach, C, Langer, S, Papalambros, E, Hepp, W Transluminal angioplasty of isolated crural arterial lesions in diabetics with critical limb ischemia. *Vasa* 2005; **34:** 186-91.
Ref ID: 9988
Reason for Exclusion: looks at effectiveness of angioplasty

Snyder, DC, Salameh, JR, Clericuzio, CP Retrospective review of forefoot amputations at a Veterans Affairs hospital and evaluation of post-amputation follow-up. *American Journal of Surgery* 2006; **192:** e51-e54.
Ref ID: 10193
Reason for Exclusion: looks at patients who already have had an amputation

Standing, P Prevent amputations with high-quality assessment. *GP: General Practitioner* 2002; 70.
Ref ID: 10351
Reason for Exclusion: can't find in BL

Stonebridge, PA, Murie, JA Infrainguinal revascularization in the diabetic patient. [Review] [94 refs]. *British Journal of Surgery* 1993; **80:** 1237-41.
Ref ID: 10463
Reason for Exclusion: not a study

Sutton, G, Wolfe, J Distal revascularisation and the diabetic foot. *Practical Diabetes* 1994; **11:** 95-96.
Ref ID: 10580
Reason for Exclusion: not a study and general background/surgery

Tan, SG, Ong, HS, Teoh, MK Early experience of limb salvage in critical leg ischaemia. *Singapore Medical Journal* 1998; **39:** 406-11.
Ref ID: 10654
Reason for Exclusion: looks at outcome of bypass surgery in patients who had CLI

Toursarkissian, B, D'Ayala, M, Stefanidis, D, Shireman, PK, Harrison, A, Schoolfield, J, Sykes, MT Angiographic scoring of vascular occlusive disease in the diabetic foot: relevance to bypass graft patency and limb salvage. *Journal of Vascular Surgery* 2002; **35:** 494-500.
Ref ID: 10891
Reason for Exclusion: looks at outcome of bypass graft surgery

Toursarkissian, B, Hassoun, HT, Smilanich, RP, Godsey, JB, Sykes, MT Efficacy of infrainguinal bypass for limb salvage in young diabetic patients. *Journal of Diabetes & its Complications* 2000; **14:** 255-58.
Ref ID: 10888
Reason for Exclusion: looks at efficacy of bypass surgery

Van Gils, CC, Wheeler, LA, Mellstrom, M, Brinton, EA, Mason, S, Wheeler, CG Amputation prevention by vascular surgery and podiatry collaboration in high-risk diabetic and nondiabetic patients. The Operation Desert Foot experience. *Diabetes Care* 1999; **22:** 678-83.
Ref ID: 11130
Reason for Exclusion: looks at effect of MDT to prevent amputation

Van, DH, Rorive, M, Martens De Noorthout, BM, Quaniers, J, Scheen, A, Limet, R Amputations in diabetic patients: a plea for footsparing surgery. *Acta Chirurgica Belgica* 2001; **101:** 123-29.

Ref ID: 11175
Reason for Exclusion: looks at causes for foot ulcers

Valente, LA, Caughy, M, Fischbach, L A validation study of a self-administered questionnaire to identify increased risk for foot ulceration or amputation among people with diabetes. *Diabetes Educator* 2004; **30:** 932-38.
Ref ID: 11090
Reason for Exclusion: looks at identifying patients with high risk of developing an ulcer ad not an amputation

Wilson, DJ Amputation and the diabetic foot: learning from a case study. *British Journal of Community Nursing* 2005; **10:** S18-S24.
Ref ID: 11751
Reason for Exclusion: case study

Yii, MK, Liew, NC Revascularization for foot salvage in diabetic critical foot ischaemia. *Medical Journal of Malaysia* 1999; **54:** 325-28.
Ref ID: 11968
Reason for Exclusion: case series

Younes, NA, Albsoul, AM, Awad, H Diabetic heel ulcers: a major risk factor for lower extremity amputation. [Review] [36 refs]. *Ostomy Wound Management* 2004; **50:** 50-60.
Ref ID: 11994
Reason for Exclusion: not a study and general background

Yusof, MI, Sulaiman, AR, Muslim, DA Diabetic foot complications: a two-year review of limb amputation in a Kelantanese population.[Erratum appears in Singapore Med J. 2008 Jun;49(6):518]. *Singapore Medical Journal* 2007; **48:** 729-32.
Ref ID: 12074
Reason for Exclusion: not a pure DFU population

Zimny, S, Dessel, F, Ehren, M, Pfohl, M, Schatz, H Early detection of microcirculatory impairment in diabetic patients with foot at risk. *Diabetes Care* 2001; **24:** 1810-1814.
Ref ID: 12191
Reason for Exclusion: control arm not DFU and looking at risk assessment of foots at high risk

Appendix M Glossary and abbreviations

Charcot arthropathy

Charcot arthropathy is a progressive musculoskeletal condition characterised by joint dislocation, fractures and deformities. It results in progressive destruction of bone and soft tissue of weight-bearing joints, most commonly in the foot and ankle. It is most commonly due to diabetes.

Clinical utilities

Utility literally means usefulness, so clinical utility could mean the usefulness of an intervention for, or in, clinical practice. Utility is also associated with utilitarianism – that is, the ethical doctrine of achieving the greatest good for the greatest number. In this sense, a clinical outcome, judgement or practice might be justified according to a balance of benefits and drawbacks. Pertinent questions for judgements about clinical utility would therefore be: (i) what are the components of usefulness, benefits, and drawbacks?; (ii) how might we define and measure these factors?; (iii) how should they be weighed against one another?; and (iv) usefulness and relative benefit for whom?

Cost-effectiveness model

An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Deterministic sensitivity analysis

Tests the impact of potential bias resulting from the selection of data sources for key model parameters.

False negative

A negative result in a diagnostic test when the person being tested does possess the attribute for which the test is conducted.

False positive

A positive result in a diagnostic result when the person being tested does not possess the attribute for which the test is conducted.

Incremental cost effectiveness ratio (ICER)

The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

Negative predictive value

The proportion of people with negative test results who do not have the disease.

Osteomyelitis

An infection of the bone or bone marrow. It can be usefully subclassified on the basis of the causative organism (pyogenic bacteria or mycobacteria), the route, duration and anatomic location of the infection.

Post-test probability (+ve)

The probability of having the disease in people who are tested positive

Post-test probability (despite [-ve])

The probability of having the disease in people who are tested negative

Pre-test probability

The probability of disease before the test result is known (also called prevalence)

Probabilistic sensitivity analysis

Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques.

Reference standard

An agreed standard, for example for a test or treatment, against which other interventions can be compared.

Abbreviation	
DSA	Digital subtraction angiography.
EGF	Epidermal growth factor
ESR	Erythrocyte sedimentation rate
G-CSF	Granulocyte colony-stimulating factor
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IV	Intravenous
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NNTB	Number needed to treat to benefit
NNTH	Number needed to treat to harm
PDGF	Platelet-derived growth factor
RCT	Randomised control trial
RR	Relative risk
TGF-beta	Transforming growth factor beta
UT wound	University of Texas wound scores

scores	

Appendix N Declaration of interests

GDG Member	Interest Declared	**Type of Interest**	Decisions Taken
Nirupam Goenka	Research Studies with pharmacological sponsorship:- 1. Solostar observational research study (Sanofi Aventis) 2. LANSCAPE study (Sanofi-Aventis) 3. BEGIN study (Novo-Nordisk) 4. IRIS study (Takeda) no individual payment is made as a result of this work, any payments as a result of these studies are always to departmental research funds.	**Non-personal pecuniary interest**	Declare and can participate in discussions on all topics
	Our department is receiving support from Eli Lilly for development of our diabetes website – this involves permission to use the basic IT structure and design of the website & the provision of project management training to the project team. No payments are being made to any member of our team as part of this project.	**Non-personal pecuniary interest**	Declare and can participate in discussions on all topics
	have given lectures, attended and chaired meetings sponsored by MSD, Eli Lilly, Takeda, and Novartis. These have been non-	**Non-personal pecuniary interest**	Declare and can participate in discussions on all topics

	promotional and non-product related. In addition any honoraria from these meetings (or any advisory board meetings that I have attended) are paid to our departmental diabetes education and research trust fund, or other registered charities		
	I organised the North Wales and Chester Endocrine meeting on Mersey (sponsored by Sanofi-Aventis), and organised/chaired the Cheshire Diabetes and Endocrine Group meeting on 3/9/09 (sponsored by Sanofi-Aventis and Eli Lilly). However I did not receive any payment for my participation in these meetings.	**Non-personal pecuniary interest**	Declare and can participate in discussions on all topics
	29/09/09 – 02/10/09 "EASD 2009 in Vienna" – Travel grant from Novo Nordisk to attend this meeting. The grant paid for economy class flights, accommodation and registration for the meeting. I was not required to attend symposium or meeting as a condition of this. I also received no personal payment (flights, accommodation and meeting registration were arranged by Novo Nordisk within ABPI guidelines – I did not actually receive any money).	**Non-personal pecuniary interest**	Declare and can participate in discussions on all topics
	IDF 2009 in Montreal" – Travel grant from BMS to attend this meeting. The grant paid for	**Non-personal pecuniary interest**	Declare and can participate in discussions on all topics

	economy class flights, accommodation and registration for the meeting. I was not required to attend symposium or meeting as a condition of this. I also received no personal payment (flights, accommodation and meeting registration were arranged by BMS within ABPI guidelines – I did not actually receive any money)		
	I am a committee member of ABCD	**Personal non-pecuniary interest**	Declare and can participate in discussions on all topics
Tony Berendt	I was awarded a Pfizer Visiting Professorship in Infectious Diseases to visit the Department of Allergy and Infectious Diseases at the University of Washington in Seattle. This is a competitive award made to the Department in response to a bid they submitted for an academic programme devised in collaboration with me to give a series of lectures and seminars on bone and joint infection, diabetic foot infection, and infection control. There are no honoraria paid to me though my expenses are paid. I will be taking up this award in March 2011. The specific description of the award is:'United Kingdom perspective of the prevention and management of MRSA infections, in the difficult context of orthopaedic infections, covering aspects of hospital infection	**Non-personal non-specific**	Declare and can participate in discussions

	control and epidemiology.' To emphasise the award is made to the host (University of Washington), not directly to me, and covers reasonable travel and susbsistence costs for the period of the Visiting Professorship The award is made on the recommendation of an independent academic committee, and is not linked to or dependent upon any activities for Pfizer.		

Appendix O Authorship and citation

Authorship of this document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

The guideline should be cited as:

National Institute for Health and Clinical Excellence (2011). Diabetic foot problems: Inpatient management of diabetic foot problems. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidance/CG119