

CADTH RAPID RESPONSE REPORT:  
SUMMARY WITH CRITICAL APPRAISAL

# Intermittent Pneumatic Compression Devices for the Management of Lymphedema: A Review of Clinical Effectiveness and Guidelines

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## Context and Policy Issues

In 2017, it was estimated that up to one million Canadians suffer from lymphedema, a chronic edema lasting more than three months and with little response to diuretics or limb elevation.<sup>1</sup> Lymphedema is defined as an abnormal swelling caused by the accumulation of protein-rich fluid in the interstitial spaces.<sup>2</sup> Although lymphedema frequently affects the limbs, it may occur in the head, neck torso, abdomen, and genitalia.<sup>3</sup> It affects people of all ages and gender, and can be classified as primary or secondary lymphedema.<sup>4</sup> Primary lymphedema is an inborn disorder caused by a faulty lymphatic system that may present at birth during puberty or later in life.<sup>4</sup> Secondary lymphedema occurs after the lymphatic system is damaged by cancer or non-cancer related surgery, radiation therapy, or other severe injuries.<sup>4</sup>

There is no cure for lymphedema.<sup>3</sup> The complex decongestive therapy (CDT) is a multimodal therapy, which is recognized as a conservative management of lymphedema and consists of compression therapy (i.e., multilayer bandaging), manual lymphatic drainage (MLD), exercise and skin care.<sup>3</sup> Intermittent pneumatic compression (IPC) can be used in the treatment of lymphedema as an adjunct to CDT, particularly in patients with compromised mobility or physical exercise.<sup>3</sup> Although lymphedema reduces after application, the use of IPC remains controversial due to its adverse effects, including the recurrence of edema due to residual proteins remaining in the interstitial space, and potential lymphatic structure damage due to high pressure application.<sup>3</sup>

The aim of this report is to review the clinical effectiveness and evidence-based guidelines on the use of IPC devices for adult patients with primary and secondary lymphedema in any setting.

## Research Questions

1. What is the clinical effectiveness of intermittent pneumatic compression devices for patients with primary and secondary lymphedema?
2. What is the comparative clinical effectiveness of single chamber intermittent pneumatic compression devices versus multi-chamber intermittent pneumatic compression devices for patients with primary and secondary lymphedema?
3. What are the evidence-based guidelines regarding the use of intermittent pneumatic compression devices for the management of primary and secondary lymphedema?

## Key Findings

The evidence suggested that intermittent pneumatic compression (IPC) may not provide additional benefits when used in combination with routine management of lymphedema. No literature for the comparative clinical effectiveness between single chamber and multi-chamber IPC devices was identified. A 2014 evidence-based guideline recommended the short-term use of IPC in combination with a lymphedema treatment program for reducing breast cancer-related lymphedema.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and April 17, 2017.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Adult patients with primary and secondary lymphedema in any setting
<b>Intervention</b>	Q1 & Q3: Intermittent pneumatic compression devices (single chamber or multi-chamber) Q2: Single chamber intermittent pneumatic compression devices
<b>Comparator</b>	Q1: Alternative interventions for the management of lymphedema or usual care (e.g., manual lymph drainage, compression garments); no treatment Q2: Multi-chamber intermittent pneumatic compression devices Q3: No comparator necessary
<b>Outcomes</b>	Q1 & Q2: Clinical effectiveness (e.g., effect on pain, swelling, cellulitis) and safety (e.g., fibrosis or fibrotic ring near site of device) Q3: Evidence-based guidelines, including recommendations for monitoring of patients using intermittent pneumatic compression devices
<b>Study Designs</b>	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized studies, and evidence-based guidelines

### Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, and if they were published prior to 2010. Conference abstracts, duplicates of publication of the same study, or SRs, in which their included studies were overlapped with another SR published at a later date, were excluded.

### Critical Appraisal of Individual Studies

The SIGN checklists were used to assess the quality of systematic reviews (SRs) and meta-analyses (MAs),<sup>5</sup> and randomized controlled trials (RCTs).<sup>6</sup> The Appraisal of Guidelines Research & Evaluation (AGREE II) instrument was used to evaluate the quality of the included guidelines.<sup>7</sup>

## Summary of Evidence

### Quantity of Research Available

A total of 143 citations were identified in the literature search. Following screening of titles and abstracts, 123 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. Eight potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 22 publications were excluded for various reasons, while six publications, including one SR and MA, three RCTs and two guidelines, met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

### Summary of Study Characteristics

The characteristics of the SR and MA,<sup>8</sup> RCTs<sup>9-11</sup> and guidelines<sup>12,13</sup> are summarized below and presented in Appendix 2.

#### SR and MA

##### *Study Design*

The SR<sup>8</sup> included seven RCTs involving the use of ICP pump for treatment of breast cancer-related lymphedema with a total population of 287 patients.

##### *Country of Origin*

The SR<sup>14</sup> was conducted by authors from China and was published in 2014.

##### *Population*

The overall population of the included studies was patients with a prior history of treatment of breast cancer and lymphedema. The latter was defined as an absolute increase in arm volume of at least 10% or 2 cm between the affected and unaffected arms.

##### *Interventions and Comparators*

The interventions included a combination of decongestive lymphatic therapy (DLT) and IPC or IPC alone. The comparators were DLT alone or manual lymphatic drainage or control. The pressure used in the IPC pump ranged from 40 to 60 mmHg, and the IPC treatment duration per session varied between 0.5 and 2.0 hours.

##### *Outcomes*

The clinical outcomes included the percentage of edema reduction, and subjective symptoms, such as heaviness, pain and tension, and joint mobility.

##### *Treatment and Follow-up Period*

The treatment period ranged from two to 15 weeks, and the follow-up period ranged from two weeks to three months.

##### *Data Analysis and Synthesis*

Of the included seven RCTs, three RCTs with 126 patients were available for meta-analysis on the percentage of volume reduction. The findings of the remaining RCTs were synthesized narratively.

### *Quality Appraisal*

The quality of the included RCTs was assessed using quality items, such as randomization process, allocation concealment, blinding, completeness of follow-up and intention-to-treat analysis.

### RCTs

#### *Study Design*

All RCTs were open-label and parallel, and they each enrolled patients from a single centre.<sup>9-11</sup>

#### *Country of Origin*

The RCTs were conducted in France,<sup>9</sup> Poland<sup>10</sup> and Turkey,<sup>11</sup> and published in 2016,<sup>9</sup> 2015,<sup>10</sup> and 2012,<sup>11</sup> respectively.

#### *Population*

All RCTs included adult patients with a mean age ranging from 51 to 64 years. Two RCTs<sup>9,10</sup> included male and female patients with primary or secondary lymphedema and with unilateral or bilateral lymphedema of the lower limbs. One RCT<sup>11</sup> included female patients with lymphedema of the upper limbs following surgery due to breast cancer. The mean BMI of patients in the RCTs ranged from 27 to 31 kg/m<sup>2</sup>.

#### *Interventions and Comparators*

The interventions were the combination of IPC and complex decongestive therapy (CDT) (i.e., manual lymphatic drainage [MLD] and bandaging),<sup>9,10</sup> or IPC and self-lymphatic drainage (SLD).<sup>11</sup> The comparators were a pulsating suit (i.e., Stando device)<sup>9</sup> or CDT alone.<sup>10,11</sup> One RCT<sup>10</sup> compared IPC set at 120 mmHg with IPC set at 60 mmHg pressure. The IPC pressures in the other two RCTs were 47 mmHg<sup>9</sup> and 25 mmHg.<sup>11</sup>

#### *Outcomes*

The clinical outcomes included a change in edema volume,<sup>9-11</sup> change in body weight,<sup>9</sup> change in limb circumference,<sup>11</sup> change in the quality of life,<sup>9,11</sup> patient appreciation,<sup>9</sup> global assessment of safety and tolerability<sup>9</sup> and adverse events.<sup>9</sup>

#### *Treatment Duration*

Treatment durations were five days,<sup>9</sup> four weeks<sup>10</sup> and six weeks.<sup>11</sup>

#### *Analysis*

The evaluations of study endpoints in all RCTs<sup>9-11</sup> were performed on an intention-to-treat basis. None of the studies presented a sample size calculation to obtain sufficient power for the primary outcome.

### Guidelines

#### *Country of Origin*

Two evidence-based guidelines published in 2011<sup>13</sup> and 2014<sup>12</sup> were included in this review. One guideline was from Australia (Queensland Health Lymphedema [QHL]) clinical practice guideline<sup>12</sup> and one from Japan (The Japan Lymphedema Study Group [JLSG]).<sup>13</sup>

## *Overall Objectives*

The main objective of the included guidelines was to provide recommendations for the management and treatment of established lymphedema based on the existing evidence.

## *Target Users of the Guidelines*

Both guidelines were targeted to health care professionals, including physicians, registered nurses, occupational therapists, and physiotherapists with lymphedema training.<sup>13</sup>

## *Methods Used to Formulate Recommendations*

One guideline<sup>12</sup> did not provide the grading of its recommendations. One guideline<sup>13</sup> graded its recommendations based on the level of evidence that was evaluated according to the standards in the *Handbook of Guidelines ver. 4.3*.

## Summary of Critical Appraisal

The summary of the quality assessment for the SR, RCTs, and guidelines are briefly described below, and presented in Appendix 3.

### SR and MA

The SR<sup>14</sup> was of high quality as most of the criteria were fulfilled, including an explicit research question, a comprehensive literature search, and at least two people were independently involved in the study selection and data extraction. Further, the publication status was not used as an inclusion criterion, and the relevant study characteristics, quality assessment of included studies and a declaration of the conflicts of interest were completed. Appropriate methods of meta-analysis were used in addition to a narrative synthesis. An assessment for publication bias was not applicable as there were three studies available for meta-analysis. A list of excluded studies was not provided.

### RCTs

All RCTs<sup>9-11</sup> were of low quality as few criteria were fulfilled, including an explicit question, a similarity in patient characteristic between treatment groups, relevant outcome measures and intention-to-treat analysis. While one RCT<sup>11</sup> briefly described the methodology on randomization, the other two<sup>9,10</sup> did not. None of the RCTs reported the method of concealment, used a blinding approach, or conducted a multi-centric trial.

### Guidelines

Both guidelines<sup>12,13</sup> were explicit in terms of scope and purpose, clarity of presentation, and editorial independence. They were also explicit in the rigour of development, except one guideline<sup>12</sup> did not explicitly describe the methods of formulating the recommendations and the procedure for updating the guideline. For stakeholder involvement, both guidelines<sup>12,13</sup> included relevant professional groups in the guideline development, defined the target users, but were not explicit in seeking the views and preferences of the target populations. Neither guideline<sup>12,13</sup> met all the criteria for applicability of guidelines, including facilitators and barriers to its application, advice or tools on how the recommendations can be put into practice, resource implications, and monitoring or auditing criteria.

## Summary of Findings

*Question 1: What is the clinical effectiveness of intermittent pneumatic compression devices for patients with primary and secondary lymphedema?*

The main findings and conclusions of the included SR and RCTs are presented in Appendix 4.

### *Volume (Edema) Reduction*

The findings from the SR<sup>14</sup> and two RCTs<sup>10,11</sup> showed that the combination of DLT and IPC had no significant difference in the volume reduction compared to DLT alone. The pressure inside the chambers of the IPC pumps operated in those studies ranged from 25 mmHg to 60 mmHg. One RCT<sup>10</sup> found that IPC with pressure of 120 mmHg significantly reduced the edema compared to control or to IPC with pressure of 60 mmHg. One RCT<sup>9</sup> found that IPC with pressure of 47 mmHg had similar effect in volume change compared to the Stendo pulsating suit in patients with leg lymphedema.

### *Subjective symptoms*

The SR<sup>14</sup> found that there were no significant differences in pain and paresthesia between DLT plus IPC group and DLT alone group. Patients in the DLT alone group felt a greater reduction of heaviness than those in the DLT plus IPC group. IPC in studies included in the SR was operated at pressure of 40 to 60 mmHg.

### *Joint Mobility*

The SR<sup>14</sup> found that there were no significant differences in joint mobility between DLT plus IPC group and DLT alone group, although both groups showed an improvement compared to baseline.

### *Quality of Life*

There were no statistically significant differences between SLD plus IPC and MLD plus bandaging in quality of life assessed by either the American Shoulder and Elbow Surgeons (ASES) tests or the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.<sup>11</sup> There was also no statistically significant difference between IPC and Stendo pulsating suit in quality of life assessed by the visual analog scale (VAS).

### *Adverse Events*

None of the studies reported adverse events associated with IPC.

*Question 2: What is the comparative clinical effectiveness of single chamber intermittent pneumatic compression devices versus multi-chamber intermittent pneumatic compression devices for patients with primary and secondary lymphedema?*

No literature was identified.

*Question 3: What are the evidence-based guidelines regarding the use of intermittent pneumatic compression devices for the management of primary and secondary lymphedema?*

The recommendations of the included guidelines<sup>12,13</sup> are presented in Appendix 4.



The JLSG guideline<sup>13</sup> found no evidence that IPC could reduce lymphedema of the limbs (Grade D)

The QHL guideline<sup>12</sup> suggested that IPC, irrespective to the number of chambers or cycle time, could be used in combination with other treatment program for a short term, up to two months, for reducing lymphedema related to breast cancer surgery.

### Limitations

The quality of RCTs included in the SR and RCTs identified in this review was relatively low as some studies did not explicitly report the method of randomization and allocation concealment. The sample sizes were fewer than 50 patients per group, and were not calculated to detect statistically significant differences of the primary endpoint. The long-term results of CDT were unclear since the treatment duration of the trials ranged from five days to nine weeks, and few trials included a follow-up period. Blinding was not possible in all trials due to the characteristics of the study protocols, where patients were either treated with or without IPC pump that may induce performance bias and measurement bias. Heterogeneity existed among trials in terms of study population because of the different inclusion criteria. As well, heterogeneity was present in the reported outcomes, chamber pressure of IPC pumps, duration of treatment, and length of follow-up. None of the trials reported any adverse events associated with IPC. In most trials, IPC was used in combination with decongestive lymphatic therapy (manual lymphatic and bandaging). Also, information on a direct comparison of IPC and alternative options for lymphedema management was limited. Literature for the comparative clinical effectiveness between single chamber IPC and multi chamber IPC devices was not identified, and the most recent guidelines identified were published in 2014.

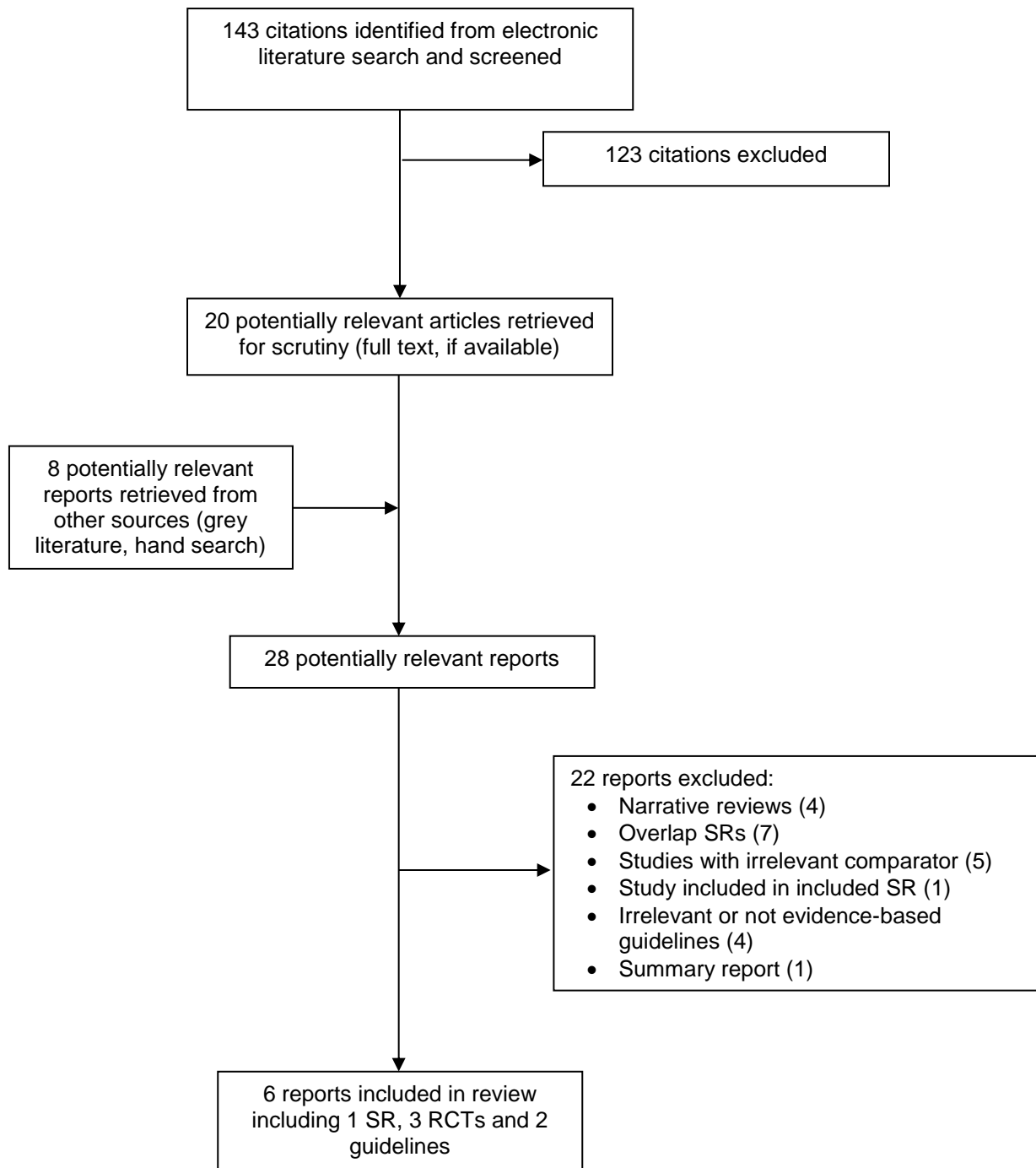
### Conclusions and Implications for Decision or Policy Making

The evidence from the included SR and RCTs suggested that IPC may not provide additional benefits when used in combination with the routine management of lymphedema. On the other hand, there is some evidence that IPC with higher pressure may reduce lymphedema effectively. The clinical effectiveness and safety of IPC operating at high pressure remain to be determined. Despite the lack of clinical effectiveness of IPC in reducing lymphedema as noted in the 2011 guideline, the 2014 guidelines recommended the short term use of IPC in combination with a lymphedema treatment program for reducing breast cancer-related lymphedema, irrespective to the number of chambers and cycle time. Given the low quality of evidence, the findings should be interpreted with caution. Multi-centre trials of high quality with uniform criteria, larger sample sizes, standard treatment protocols and outcome measures, and a new generation of pump devices are needed for future research.

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## Appendix 1: Selection of Included Studies



## Appendix 2: Characteristics of Included Studies

**Table A1: Characteristics of Included Systematic Reviews**

First Author, Publication Year, Country, Funding	Types and Numbers of Primary Studies Included	Population Characteristics	Interventions	Comparators	Clinical Outcomes, Length of Follow-up
Shao et al., 2014 <sup>14</sup> China  Source of funding: NR	SR of 7 RCTs on IPC pump for BCRL published between 1998 and 2013  Quality items assessed: randomization, allocation concealment, blinding, completeness of follow-up and intention-to-treat analysis	287 patients with prior history of breast cancer and lymphedema  Age: NR Gender: female	Management of BCRL with IPC	Management of BCRL without IPC	<ul style="list-style-type: none"> <li>• Primary outcome:                             <ul style="list-style-type: none"> <li>- Percent of volume (edema)reduction</li> </ul> </li> <li>• Secondary outcomes                             <ul style="list-style-type: none"> <li>- Subjective symptoms</li> <li>- Joint mobility</li> </ul> </li> </ul> <p>Treatment period: 2 weeks to 15 weeks Follow-up period: 2 weeks to 3 months</p>

BCRL = breast-cancer related lymphedema; IPC = intermittent pneumatic compression; NR = not reported; RCT = randomized controlled trial; SR = systematic review

**Table A2: Characteristics of Included Primary Studies**

First Author, Publication Year, Country, Study Name (if reported), Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Jonas et al., 2016 <sup>9</sup> France  Source of funding: Stendo Company	Open-label pilot RCT, single center, parallel, 1:1 ratio  Recruitment period: September 1, 2014 to February 23, 2015  Analysis: ITT  Sample size calculation: None  Treatment duration: 5 days	Adult patients (n=24) - Mean age: 64 years - Gender: 21 females, 3 males - Primary (63%) or secondary (38%) lymphedema of stage II or III - One (21%) leg or two (79%) legs with lymphedema - Mean BMI = 31 kg/m <sup>2</sup> - Mean systolic/diastolic BP = 128/76 - Mean total volume of the limb = 120 L - Mean QoL (VAS) = 7.4 - Both groups had similar in 5 of 6 QoL SF36 domains	CDT (MLD and bandaging) + IPC (multi chamber, TP05 or TP07 device from Euroduc Company)  IPC: one-hour sessions, 40 second inflate and 21 second deflate periods, mean pressure of 47 mmHg	CDP (MLD and bandaging) + Stendo device (pulsating suit from Stando company)  Stendo: 60-minute sessions, 65 mmHg inflation pressure (start with 50 mmHg during first 3 minutes, then 65 mmHg)	Primary outcome: - Total volume change  Secondary outcomes: - Quality of life (assessed by VAS and SF36) - Body weight change - Patient appreciation - Global assessment - Adverse events
Taradaj et al., 2015 <sup>10</sup> Poland  Source of funding: Polish Society of Lymphology	Open-label RCT, single center, parallel, 1:1:1 ratio  Recruitment period: July 1, 2013 to July 4, 2014  Analysis: Modified ITT  Sample size calculation: NR  Treatment duration: 4 weeks	Adult patients (n=24) - Mean age: 51 years - Gender: 60% females, 40% males - Chronic venous insufficiency with unilateral or bilateral lymphedema of lower limbs - Mean edema occurrence: 5.7 years - Mean BMI = 27 kg/m <sup>2</sup>	CDT (MLD and bandaging) + IPC (multi chamber, DL1200 from Technomex LLC) with 120 mmHg pressure  All patients receives pharmacotherapy (phlebotropic drug – Diosmin 500 mg tablets per day)	- CDT (MLD and bandaging) + IPC (multi chamber, DL1200 from Technomex LLC) with 60 mmHg pressure  - CDT (MLD and bandaging) alone  All patients receive pharmacotherapy (phlebotropic drug – Diosmin 500 mg tablets per day)	Percent volume (edema) reduction

First Author, Publication Year, Country, Study Name (if reported), Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Gurdal et al., 2012 <sup>11</sup> Turkey Source of funding: NR	Open-label RCT, single center, parallel, 1:1 ratio  Recruitment period: NR  Analysis: ITT  Sample size calculation: NR  Treatment duration: 6 weeks	Adult patients (n=30) - Mean age: 54 years - Gender: female - Unilateral lymphedema of upper limbs following surgery due to breast cancer - Mean edema occurrence: NR - Mean BMI = 30 kg/m <sup>2</sup>	SLD + IPC  IPC: 45-minute sessions, 25 mmHg pressure	CDT (MLD + bandaging)	- Change in limb volume - Limb circumference measurement - QoL (assessed by EORTC QLQ-C30 and ASES tests)

ASES = American Shoulder and Elbow Surgeons; BP = blood pressure; CDT = complex decongestive therapy; EORTC = European Organization for Research and Treatment of Cancer; IPC = intermittent pneumatic compression; ITT = intention to treat; MLD = manual lymph drainage; NR = not reported; QoL = quality of life; RCT = randomized controlled trial; SF36 = 36-item survey questionnaire; SLD = self-lymphatic drainage; VAS = visual analog scale

**Table A3: Characteristics of Included Guidelines**

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
<p>QHL<sup>12</sup></p> <p>2014</p> <p>Australia</p> <p>Source of funding: Allied Health Workforce Advice and Coordination Unit, Queensland Health</p>	<p><u>Intended users:</u> Occupational therapists, physiotherapists and registered nurses with lymphedema training</p> <p><u>Target population:</u> Adult patients with established lymphedema</p>	<p>Compression therapy for the treatment of established lymphedema (primary or secondary) in adults</p>	<p>Edema (volume) reduction</p>	<p>Systematic search for RCT published from 2000 to 2011 using Medline, Cochrane Database of Systematic Reviews, EMBASE, CINALL Plus with Full Text (EBSCO), PEDro and OT Seeker</p> <p>Synthesis based on evidence</p> <p>Quality assessment of RCTs was based on SIGN checklist</p>	<p>Recommendations were developed by a panel of multidisciplinary experts based on high quality evidence (level II)</p>	<p>The guideline was developed by the guidance of National Health and Medical Research council's handbook series on preparing clinical practice guidelines and Scottish Intercollegiate Guideline Network's (SIGN) Guideline Development Handbook</p>
<p>JLSG<sup>13</sup></p> <p>2011</p> <p>Japan</p> <p>Source of funding: 12<sup>th</sup> Japanese Society of Breast Cancer Group Research (Kitamura Research Group)</p>	<p><u>Intended users:</u> Physicians, nurses and healthcare professionals</p> <p><u>Target population:</u> Lymphedema patients</p>	<p>Management and treatment options for lymphedema</p>	<p>Clinical improvement, adverse events</p>	<p>Systematic search for evidence from PubMed and secondary references between 1980 and 2007 for clinical questions in the areas for the treatment of lymphedema.</p>	<p>Recommendations were developed by a panel of content experts in lymphedema based on scientific evidence</p>	<p>The guideline was developed in accordance with the <i>Handbook of Making Clinical Guidelines (Minds)</i> (Fukui, 2007)</p>

JLSG = Japan Lymphedema Study Group; QHL = Queensland Health Lymphedema

**Table A4: Grade of Recommendations and Level of Evidence**

Guideline Society or Institute, Year, Country	Grade of Recommendation	Level of Evidence
QHL <sup>12</sup> 2014 Australia	None	<p><b>I</b> Systematic review of Level II studies</p> <p><b>II</b> Randomized controlled trial</p> <p><b>III-1</b> Pseudo randomized controlled trial (i.e., alternate allocation or some other method)</p> <p><b>III-2</b> Comparative study with concurrent controls (i.e., non-randomized experimental trial, cohort study, case control study, interrupted time series with a control group)</p>
JLSG <sup>13</sup> 2011 Japan	<p><b>A</b> Definitive evidence of effectiveness and clinical agreement; this treatment is strongly recommended according to patient requests</p> <p><b>B</b> Sufficient evidence for clinical agreement; this treatment is recommended according to patient requests</p> <p><b>C</b> Insufficient evidence to develop clinical agreement; treatment recommended based on patient requests and clinical results</p> <p><b>D</b> There is no evidence of usefulness or clinical agreement; treatment requires both patient requests and clinical need</p> <p><b>E</b> Evidence of adverse effect or morbidity; treatment should not be performed</p>	<p>Each article's level of evidence was evaluated according to the standards in the <i>Handbook of Guidelines ver. 4.3</i> (<a href="http://www.cebm.net/levels-of-evidence.asp#level">www.cebm.net/levels-of-evidence.asp#level</a> )</p>

JLSG = Japan Lymphedema Study Group; QHL = Queensland Health Lymphedema



## Appendix 3: Quality Assessment of Included Studies

**Table A5: Quality Assessment of Systematic Reviews**

SIGN Checklist: Internal Validity <sup>5</sup>	Shao et al., 2014 <sup>14</sup>
1. The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper	Yes
2. A comprehensive literature search is carried out	Yes
3. At least two people should have selected studies	Yes
4. At least two people should have extracted data	Yes
5. The status of publication was not used as an inclusion criteria	Yes
6. The excluded studies are listed	No
7. The relevant characteristics of the included studies are provided	Yes
8. The scientific quality of the included studies was assessed and reported	Yes
9. Was the scientific quality of the included studies used appropriately?	Yes
10. Appropriate methods are used to combine the individual study findings	Yes
11. The likelihood of publication bias was assessed appropriately	NA
12. Conflicts of interest are declared	Yes
<b>Overall Assessment of the Study</b>	
High, Moderate, Low	High

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

**Table A6: Quality Assessment of Primary Studies**

<b>SIGN Checklist: Internal Validity<sup>6</sup></b>	<b>Jonas et al., 2016<sup>9</sup></b>	<b>Taradaj et al., 2015<sup>10</sup></b>	<b>Gurdal et al., 2012<sup>11</sup></b>
1. The study addresses an appropriate and clearly focused question.	Yes	Yes	Yes
2. The assignment of subjects to treatment groups is randomized.	Yes (method of randomization not reported)	Yes (method of randomization not reported)	Yes
3. An adequate concealment method is used.	Can't tell	Can't tell	Can't tell
4. Subjects and investigators are kept 'blind' about treatment allocation.	No	No	No
5. The treatment and control groups are similar at the start of trial.	Yes	Yes	Yes
6. The only difference between groups is the treatment under investigation.	Not clear	Not clear	Not clear
7. All relevant outcomes are measured in a standard, valid and reliable way.	Yes	Yes	Yes
8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	0%	0%	0%
9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes	Yes	Yes
10. Where the study is carried out more than one site, results are comparable for all sites.	No	No	No
<b>Overall Assessment of the Study</b>			
High, Moderate, Low	Low	Low	Low

For overall assessment of the study: *High* indicated that all or most criteria have been fulfilled; where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter. *Moderate* indicates that some of the criteria have been fulfilled; those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *Low* indicates that few or no criteria fulfilled; the conclusions of the study are thought likely or very likely to alter.

**Table A7: Quality Assessment of Guidelines**

AGREE II Checklist <sup>7</sup>	QHL, 2014 <sup>12</sup>	JLSG, 2011 <sup>13</sup>
<b>Scope and purpose</b>		
1. Objectives and target patients population were explicit	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes
3. The population to whom the guidelines is meant to apply is specifically described	Yes	Yes
<b>Stakeholder involvement</b>		
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes
5. The views and preferences of the target population have been sought	Not clear	Not clear
6. The target users of the guideline are clearly defined	Yes	Yes
<b>Rigour of development</b>		
7. Systematic methods were used to search for evidence	Yes	Yes
8. The criteria for selecting the evidence are clearly described	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Not clear	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Not clear	Yes
14. A procedure for updating the guideline is provided	Not clear	Yes
<b>Clarity of presentation</b>		
15. The recommendations are specific and unambiguous	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes
<b>Applicability</b>		
18. The guideline describes facilitators and barriers to its application	Not clear	Not clear
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Not clear	Not clear
20. The potential resource (cost) implications of applying the recommendations have been considered	Not clear	Not clear
21. The guideline presents monitoring and/or auditing criteria	Not clear	Not clear
<b>Editorial independence</b>		
22. The views of the funding body have not influenced the content of the guideline	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes

JLSG = Japan Lymphedema Study Group; QHL = Queensland Health Lymphedema

## Appendix 4: Main Study Findings and Author’s Conclusions

**Table A8: Summary of Findings of Included Systematic Reviews**

Main Study Findings	Author’s Conclusions
Shao et al., 2016 <sup>14</sup>	
<p>Included 7 RCTs; 3 RCTs were used in meta-analysis Quality grade: B (5 RCTs); C (2 RCTs)</p> <p><u>Volume Reduction:</u></p> <ul style="list-style-type: none"> <li>Percent volume reduction: DLT + IPC (40 to 60 mmHg) versus DLT: MD (95% CI): 4.51 (-7.01 to 16.03); <math>p=0.44</math>; <math>I^2 = 85\%</math>; 3 RCTs IPC versus MLD: 7% versus 15%, <math>p=0.36</math>; 1 RCT</li> <li>Median arm volume difference: DLT + IPC: 500 ml (range: 60 to 2,160 ml) versus DLT: 480 ml (range: 0 to 1,410 ml); NS; 1 RCT</li> <li>Number of patients achieving a <math>\geq 25\%</math> volume reduction in the 2 groups: IPC: 10 patients versus DLT: 8 patients; <math>p=0.59</math>; 1 RCT</li> </ul> <p><u>Subjective symptoms:</u></p> <ul style="list-style-type: none"> <li>Reduction of heaviness: Greater in DLT group than in DLT + IPC group (<math>p=0.04</math>); 1 RCT</li> <li>Pain: No significant difference between DLT and DLT + IPC groups (<math>p=0.389</math>); 1 RCT</li> <li>Paresthesia: No significant difference between DLT and DLT + IPC groups (<math>p=0.667</math>); 1 RCT</li> </ul> <p>Similar results (pain, tension, heaviness) were found in other 3 RCTs</p> <p><u>Joint mobility:</u> Improved compared to baseline, but there was no difference between groups; 2 RCTs Increased significantly in the DLT + IPC group, while it decreased significantly in the DLT group; 1 RCT</p>	<p><i>“Current trials failed to show the effectiveness of the addition of IPC to the routine management of BCRL.” (p170)<sup>14</sup></i></p>

BCRL = breast cancer-related lymphedema; DLT = decongestive lymphatic therapy; IPC = intermittent pneumatic compression; MLD = manual lymphatic drainage; NS = not significant difference; RCT=randomized controlled trial

**Table A9: Summary of Findings of Included Primary Studies**

Main Study Findings	Author’s Conclusions
Jonas et al., 2016 <sup>9</sup>	
<p><u>Efficacy</u></p> <ul style="list-style-type: none"> <li>Volume change: <ul style="list-style-type: none"> <li>Total volume change between Day 1 and Day 5 (mean [95% CI]): IPC (47 mmHg): -11.0 L (-8.8 to -13.3) versus Stendo (65 mmHg): -14.2 L (-12.0 to -16.5); <math>p=0.053</math></li> <li>Relative total volume change (mean [95% CI]): IPC: -8.8% (-6.2 to 10.8) versus Stendo: -11.2 L (-9.1 to 13.7); <math>p=0.081</math></li> </ul> </li> </ul>	<p><i>“The promising Stendo results open the way to larger clinical studies targeting CDP maintenance and moderate lymphedema in outpatient settings.” (p82)<sup>9</sup></i></p>

Main Study Findings	Author's Conclusions
<ul style="list-style-type: none"> <li>• Body weight change:               <ul style="list-style-type: none"> <li>○ Total body weight change between Day 1 and Day 5: IPC: -1.0 kg versus Stendo: -1.2 kg; <math>p=0.656</math></li> <li>○ Relative total body weight: IPC: -1.1 % versus Stendo: -1.2 %; <math>p=0.936</math></li> </ul> </li> <li>• QoL change:               <ul style="list-style-type: none"> <li>○ VAS change between Day 1 and Day 5 (mean [SD]): IPC: 0.3 cm (1.9) versus Stendo: 0.9 cm (1.7); <math>p=0.482</math></li> <li>○ Relative VAS change between Day 1 and Day 5 (mean [SD]): IPC: 6.7% (31.5) versus Stendo: 14.2 % (23.4); <math>p=0.517</math></li> </ul> </li> </ul> <p><u>Safety, tolerability and patient acceptability:</u></p> <ul style="list-style-type: none"> <li>• Patients' appreciation: excellent for both groups (9.3 in each group on VAS)</li> <li>• No adverse events</li> <li>• No blood pressure difference between groups</li> </ul>	
Taradaj et al., 2015 <sup>10</sup>	
<p><u>Efficacy</u></p> <ul style="list-style-type: none"> <li>• Percentage in edema reduction in right lower limb:               <ul style="list-style-type: none"> <li>○ Group A: CDT (MLD and bandaging) + IPC (120 mmHG): 38.45 %; <math>p=0.01</math> compared to group B or group C</li> <li>○ Group B: CDT (MLD and bandaging) + IPC (60 mmHG): 13.12 %</li> <li>○ Group C: CDT (MLD and bandaging) alone: 11.89 %</li> </ul> </li> <li>• Percentage in edema reduction in left lower limb:               <ul style="list-style-type: none"> <li>○ Group A: CDT (MLD and bandaging) + IPC (120 mmHG): 36.45 %; <math>p=0.01</math> compared to group B or group C</li> <li>○ Group B: CDT (MLD and bandaging) + IPC (60 mmHG): 11.78 %</li> <li>○ Group C: CDT (MLD and bandaging) alone: 12.21 %</li> </ul> </li> </ul> <p><u>Adverse events:</u> Not reported</p>	<p><i>"The IPC with the pressure of 120 mmHg inside the chambers effectively helps to reduce a phlebolympheoedema." (p1545)<sup>10</sup></i></p>
Gurdal et al., 2012 <sup>11</sup>	
<p><u>Efficacy</u></p> <ul style="list-style-type: none"> <li>• Decrease in total arm volume: SLD + IPC (25 mmHg): 529 ml (14.9%) versus MLD + bandaging: 439 ml (12.2%); <math>p=0.582</math></li> <li>• QoL: ASES test scores after treatment (mean ± SD): SLD + IPC: 19.20 ± 4.65 versus MLD + bandaging: 18.47 ± 6.93; <math>p=0.851</math></li> <li>• EORTC QLQ-C30: No statistically significant difference between groups for any items</li> </ul> <p><u>Adverse events:</u> Not reported</p>	<p><i>"Different treatment modalities consisting of MLD and compression bandage (complex decongestive therapy) or IPC and SLD appear to be effective in the treatment of lymphedema with similar therapeutic efficacy in patients with breast cancer." (p129)<sup>11</sup></i></p>

ASES = American Shoulder and Elbow Surgeons; CDP = complex decongestive physiotherapy; CDT = complex decongestive therapy; CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; IPC = intermittent pneumatic compression; MLD = manual lymphatic drainage; QoL = quality of life; SLD = self-lymphatic drainage; VAS = visual analog scale

**Table A10: Summary of Findings of Included Guidelines**

Recommendations
QHL, 2014 <sup>12</sup>
<ul style="list-style-type: none"> <li>• Recommendation: <i>“IPC can be effectively as part of a combined lymphedema treatment program for reducing BCRL in the short term, up to two months post treatment.”</i> (p11)<sup>12</sup></li> <li>• Recommendation: <i>“IPC can reduce limb volume in BCRL irrespective of the number of chambers and the cycle time used.”</i> (p11)<sup>12</sup></li> </ul>
JLSG, 2011 <sup>13</sup>
<ul style="list-style-type: none"> <li>• Recommendation: <i>“Currently, there is no evidence that IPC decreases the circumferential diameter of limbs with lymphedema (recommendation grade:D).”</i> (p65)<sup>13</sup></li> </ul>

BCRL = breast cancer-related lymphedema; IPC = intermittent pneumatic compression; JLSG = Japan Lymphedema Study Group; QHL = Queensland Health Lymphedema