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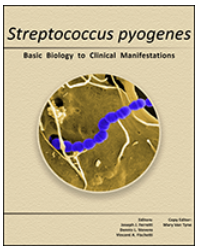

Acute Rheumatic Fever and Rheumatic Heart Disease

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Introduction

Acute rheumatic fever (ARF) results from the body's autoimmune response to a throat infection caused by Streptococcus pyogenes, also known as the group A Streptococcus bacteria. Rheumatic heart disease (RHD) refers to the long-term cardiac damage caused by either a single severe episode or multiple recurrent episodes of ARF. It is RHD that remains a significant worldwide cause of morbidity and mortality, particularly in resource-poor settings. While ARF and RHD were once common across all populations, improved living conditions and widespread treatment of superficial S. pyogenes infections have caused these diseases to become comparatively rare in wealthy areas (Carapetis, 2007). Currently, these diseases mainly affect those in low- and middle-income nations, as well as in indigenous populations in wealthy nations where initial S. pyogenes infections may not be treated, which allows for the development of harmful post-infectious sequelae (Carapetis, 2007).

The development of ARF occurs approximately two weeks after S. pyogenes infection (Gewitz, et al., 2015). The clinical manifestations and symptoms of ARF can be severe and are described in the Revised Jones Criteria (Gewitz, et al., 2015). Symptoms of ARF can include polyarthritis, carditis, chorea, the appearance of subcutaneous nodules, and erythema marginatum or a rash associated with ARF (Gewitz, et al., 2015; Martin, et al., 2015). These symptoms usually require patients to be hospitalized for two to three weeks, during which time the outward symptoms resolve, but the resultant cardiac damage may persist. With repeated S. pyogenes pharyngitis infections, ARF can recur and cause cumulative damage to the heart valves (Martin, et al., 2015).

This chapter will briefly cover the epidemiology and pathophysiology of ARF and RHD, and will also outline the clinical manifestations, diagnostic considerations, and recommended treatment and management options for both conditions. Finally this chapter will also highlight prevention strategies for ARF and RHD and will discuss current vaccination efforts against S. pyogenes.

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Epidemiology of ARF and RHD

Burden of Disease

The global burden of ARF and RHD is significant, and is predominantly found in populations living in low-resource settings (Carapetis, Steer, Mulholland, & Weber, 2005). Incidence rates of ARF are poorly documented in most low- and middle-income countries, including in populations with a high prevalence of RHD, where it is presumed that a high incidence of ARF also occurs. This relates both to the lack of infrastructure for disease surveillance in those settings, but also to a paucity of ARF cases that are presented for clinical care. It is not known if the latter issue is a result of health-seeking behavior (people with ARF who choose not to seek health care), or due to inadequate diagnosis of ARF by health staff. The latter may in turn be due to true misdiagnosis as a result of problems with training, a lack of access to diagnostic facilities (such as electrocardiography, streptococcal serology, acute phase reactant testing, and echocardiography); or possibly because many cases of ARF may be milder, or even sub-clinical, in highly endemic settings (Bishop, Currie, Carapetis, & Kilburn, 1996).

ARF incidence rates have been reported to be as high as 155 per 100,000 children aged 5 to 14 years in indigenous populations in North Queensland, Australia (Gray, Brown, & Thomson, 2012) with rates in the Northern Territory reported at 380.1 per 100,000 children in 2002 (Parnaby & Carapetis, 2010). In New Zealand, ARF affects mainly children and teens aged 4–19 years who are predominantly of Māori and Pasifika descent and are living in low socioeconomic regions of the North Island (Jack, et al., 2015). Between 1993 and 2009, the average incidence rates for ARF based on hospitalization data for children 5–14 years were 81.2 per 100,000 for Pasifika children, as compared with 40.2 per 100,000 for Māori children and 2.1 per 100,000 for non-Māori, non-Pasifika children (Milne, Lennon, Stewart, Vander Hoorn, & Scuffham, 2012a).

Global disease estimates in 2005 reported 471,000 ARF cases annually, which largely occurred in children and teens aged 5–15 years, with the prevalence of RHD cases ranging between 15.6–19.6 million (Carapetis, Steer, Mulholland, & Weber, 2005). Approximately 350,000 deaths occurred each year due to either ARF or RHD (Carapetis, Steer, Mulholland, & Weber, 2005). The number of new cases of RHD diagnosed was estimated at 282,000 per year, with approximately 233,000 deaths annually (Carapetis, Steer, Mulholland, & Weber, 2005). Global burden of disease estimates performed in 2010 calculated the number of individuals living with RHD was at least 34.2 million, with 10.1 million disability-adjusted life years lost (de Dassel, Ralph, & Carapetis, 2015). There are challenges in obtaining precise global figures concerning ARF and RHD, with one example being that the diagnosis of ARF remains difficult and problematic across many settings. Improved diagnostic tools and measures are vital, and such efforts would support enhanced global disease estimation efforts (Sheel, Moreland, Fraser, & Carapetis, 2016). It should also be noted that these figures concerning incidence and prevalence are likely to be underestimated, due to variable and insufficient data collection in resource-poor settings, where the rates of ARF and RHD are often highest (Zühlke, et al., 2014). More accurate estimates of RHD prevalence may result from the increased availability of echocardiography, which can detect cardiac damage that is due to RHD more accurately than auscultation (Roberts, et al., 2015).

Risk Factors

Risk factors for ARF and RHD include age, gender, and various environmental factors (Carapetis, et al., 2016). In terms of age, ARF largely affects children between the ages of 5 and 14 years, and initial cases of ARF can affect children even younger than this (Lawrence, Carapetis, Griffiths, Edwards, & Condon, 2013; Parnaby & Carapetis, 2010). Recurrent episodes generally affect older children and can occur into young adulthood. Because RHD often results from cumulative damage, the peak prevalence of RHD occurs in an individual's twenties and thirties, though the burden of RHD in children and adolescents remains substantial (Lawrence, Carapetis, Griffiths, Edwards, & Condon, 2013).

While ARF is equally common in both males and females, RHD tends to be more common in females (Lawrence, Carapetis, Griffiths, Edwards, & Condon, 2013; Parnaby & Carapetis, 2010). It is unclear whether this difference in RHD prevalence is due to greater susceptibility to developing autoimmune responses following *S. pyogenes* infection, or whether social factors such as involvement in child-raising, which may cause increased susceptibility and likelihood of *S. pyogenes* infections, may combine with reduced access to primary and secondary prevention regimens (Carapetis, et al., 2016). Furthermore, RHD often becomes apparent during pregnancy, because of its associated higher cardiac burden (Carapetis, et al., 2016).

Environmental factors affect the prevalence of ARF by increasing exposure to *S. pyogenes* infections. A major environmental factor that increases the likelihood of ARF is household crowding, which facilitates the spread of *S. pyogenes* infections (Quinn, 1982). In addition, it has been shown that ARF and RHD are more prevalent in rural and remote areas as well as in urban slums, but this likely reflects other risk factors, such as greater household crowding due to low socioeconomic status or limited access to medical resources (Carapetis, et al., 2016). There is also a potential link between insufficient nutrition in childhood and susceptibility to ARF, but it is unclear whether this occurs because insufficient nutrition can increase susceptibility to developing aggressive autoimmune responses to *S. pyogenes* infection, or whether poor nutrition is connected to household overcrowding and other factors associated with poverty that increase susceptibility to *S. pyogenes* infection (Steer, Carapetis, Nolan, & Shann, 2002).

Pathophysiology

The pathogenic mechanisms of ARF are not completely understood. Studies of the pathogenesis of ARF have been constrained by the lack of a highly suitable animal model, although a Lewis rat model of valvulitis and chorea has been used for some time (Quinn, Kosanke, Fischetti, Factor, & Cunningham, 2001; Brimberg, et al., 2012). In order for ARF to occur, it appears that a pharyngeal infection caused by *S. pyogenes* must occur in a host with a genetic susceptibility to the disease (Denny, Wannamaker, Brink, Rammelkamp, & Custer, 1950; Bryant, Robins-Browne, Carapetis, & Curtis, 2009).

Activation of the innate immune system begins with a pharyngeal infection that leads to the presentation of *S. pyogenes* antigens to T and B cells. $CD4^+$ T cells are activated and production of specific IgG and IgM antibody by B cells ensues (Cunningham, Pathogenesis of group A streptococcal infections, 2000). Tissue injury is mediated through an immune-mediated mechanism that is initiated via molecular mimicry (Guilherme, Kalil, & Cunningham, 2006). Structural similarity between the infectious agent and human proteins leads to the cross-activation of antibodies and/or T cells directed against human proteins (Cunningham, 2000). In ARF, this cross-reactive immune response results in the clinical features of rheumatic fever, including carditis, due to antibody binding and infiltration of T cells; transient arthritis, due to the formation of immune complexes; chorea, due to the binding of antibodies to basal ganglia; and skin manifestations, due to a delayed hypersensitivity reaction (Figure 1; Carapetis, et al., 2016).

Molecular mimicry

There are a number of lines of evidence that suggest molecular mimicry plays a role in the development of carditis by stimulating both humoral and cellular cross-reactive immune responses (Cunningham, 2000; Guilherme, Kalil, & Cunningham, 2006; Cunningham, et al., 1992). The alpha-helical protein structures found in M protein and N-acetyl-beta-D-glucosamine (the carbohydrate antigen of *S. pyogenes*) share epitopes with myosin, and antibodies against both of these antigens cross-react against human tissues (Galvin, Hemric, & Cunningham, 2000). Monoclonal antibodies generated from tonsillar or peripheral blood lymphocytes of patients infected with *S. pyogenes* cross-react with myosin (Cunningham, 2000; Cunningham, et al., 1988). Monoclonal antibodies directed against myosin and N-acetyl-beta-D-glucosamine isolated react against human valvular endothelium in patients with rheumatic fever (Cunningham, et al., 1988). In a Lewis rat model,

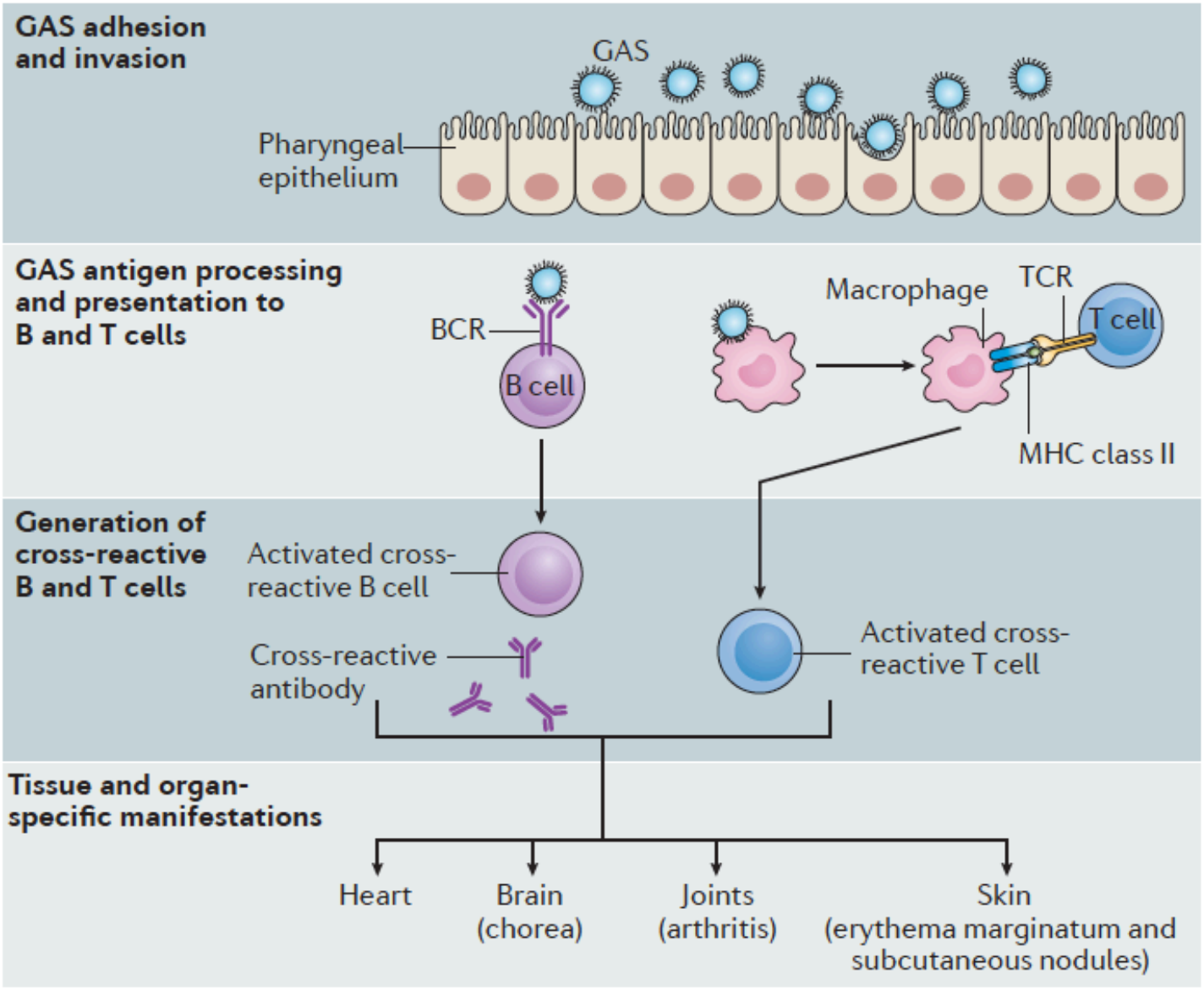

Figure 1. Overview of the pathogenesis of acute rheumatic fever (GAS: group A Streptococcus; BCR: B cell receptor; TCR: T cell receptor) Figure reproduced with permission from (Carapetis, et al., 2016).

immunization with recombinant streptococcal M protein type 6 led to development valvulitis (Quinn, Kosanke, Fischetti, Factor, & Cunningham, 2001).

Human heart intralesional T cell clones react against cardiac tissues, including myosin and valve-derived proteins (Faé, et al., 2006). Autoreactive T cells appear to play an important role in granulomatous inflammation in cardiac valves. Vascular cell adhesion molecule 1 may be the link between humoral and cellular immunity at the valve surface (Figure 2; Roberts, Kosanke, Terrence Dunn, Jankelow, Duran, & Cunningham, 2001). Vascular cell adhesion molecule 1 is upregulated at the valve endothelium surface as a result of binding of cross-reactive antibodies. This leads to adherence of $CD4^+$ T cells to the endothelium, with subsequent infiltration of these cells into the valve. The T-cells initiate a predominantly TH1 response with the release of γ -IFN. Inflammation leads to neovascularization, which allows further recruitment of T-cells. Epitope spreading may occur in the valve, where T-cells respond against other cardiac proteins such as vimentin and tropomyosin and lead to the formation of granulomatous lesions underneath the endocardium (Aschoff bodies) (Roberts, et al., 2001).

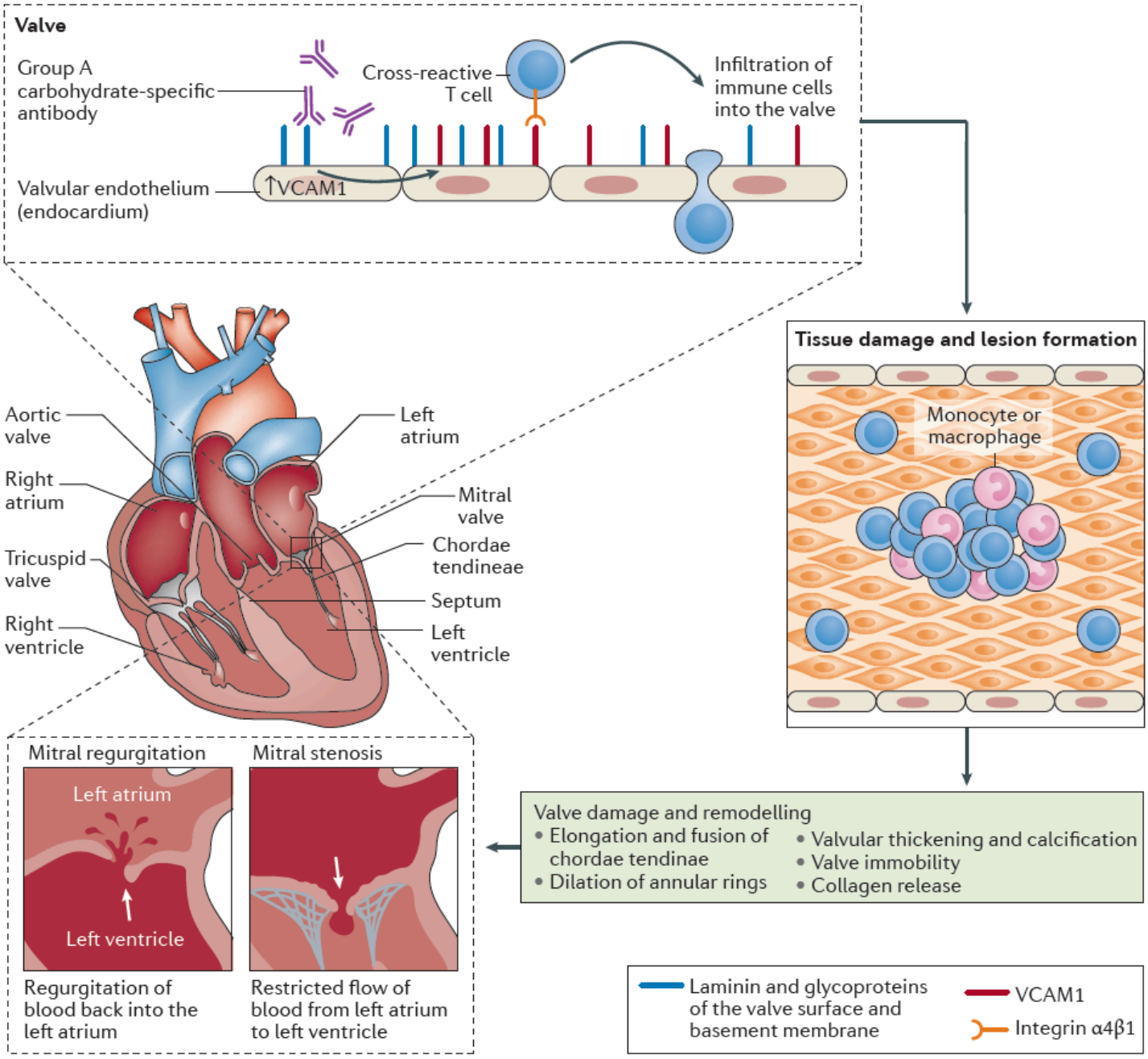

Figure 2. Pathogenesis of carditis in acute rheumatic fever (VCAM1: Vascular cell adhesion molecule 1). Figure reproduced with permission from (Carapetis, et al., 2016).

Genetic susceptibility

Acute rheumatic fever is a highly heritable disease, with frequent cases observed in family members, including twins (Bryant, Robins-Browne, Carapetis, & Curtis, 2009). A meta-analysis of twin studies found that the pooled probandwise concordance risk was 44% and 12% in monozygotic and dizygotic twins respectively, and the association between zygosity and concordance was strong, with an odds ratio of 6.4 (95% CI 3.4 to 12.1) (Engel, Stander, Vogel, Adeyemo, & Mayosi, 2011).

It is most likely that susceptibility to ARF is polygenic. Polymorphisms in several genes coding for immune proteins have been associated with ARF susceptibility. Several studies have reported genetic associations related

to class II human leukocyte (HLA) molecules (Anastasiou-Nana, Anderson, Carlquist, & Nanas, 1986; Ayoub, Barrett, Maclaren, & Krischer, 1986; Carlquist, et al., 1995; Hafez, et al., 1985), while others have reported associations with non-HLA related immune proteins (Bryant, Robins-Browne, Carapetis, & Curtis, 2009). Large-scale genome wide association studies of rheumatic heart disease in multiple populations in over 20 countries, including in Africa, the Pacific, and northern Australia are currently underway.

Acute Rheumatic Fever

Clinical Manifestations

ARF can present with several different clinical manifestations in the weeks following an episode of *S. pyogenes* pharyngitis (Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association, 1992; Gewitz, et al., 2015). The most common presenting features of ARF are fever (>90% of patients) and arthritis (75% of patients). The most serious manifestation is carditis (>50% of patients) because it can lead to chronic rheumatic heart disease—while all other clinical features fully resolve, often within weeks.

Arthritis

There are a large number of differential diagnoses of the arthritis of ARF, and as a result, it is the most diagnostically challenging manifestation (World Health Organisation, 2004). The arthritis of ARF most commonly affects the large joints, especially the knees, ankles, elbows, and wrists. Multiple joints are frequently involved, with the onset of arthritis in different joints either separated in time or overlapping, giving rise to the description of a "migratory" or "additive" polyarthritis (Jansen, Janssen, de Jong, & Jeurissen, 1999; Congeni, Rizzo, Congeni, & Sreenivasan, 1987; Veasy, Tani, & Hill, 1994). Each joint is affected for a few days to a week, with the entire episode resolving without treatment within one month. The joint pain can be quite severe, especially in older children and adolescents, and is often out of keeping with the clinical signs of inflammation (Feuer & Speira, 1997; Wallace, Garst, Papadimos, & Oldfield, 1989).

An important feature of the arthritis of ARF is its rapid response to anti-inflammatory therapy. If joint symptoms do not respond to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoid treatment within 48 hours, then the diagnosis of ARF should be reconsidered (ARF/RHD Writing Group, 2012). In patients presenting with a monoarthritis in whom ARF is suspected, some experts recommend withholding NSAID therapy and treating with acetaminophen or paracetamol until a second joint is affected, thus declaring the diagnosis of ARF. Although patients with ARF may present with only a monoarthritis (Carapetis & Currie, 2001; Wilson, Wilson, Voss, Morreau, & Lennon, 2007b), a consideration of septic arthritis as a differential diagnosis is needed in these patients, especially in younger children. Joint aspiration with synovial fluid white cell count and culture is indicated in these patients. The synovial fluid is sterile, with a lymphocyte predominance in patients with ARF (Harlan, Tani, & Byington, 2006; Mataika, Carapetis, Kado, & Steer, 200). The recently updated Jones criteria highlight that joint manifestations may include aseptic monoarthritis or polyarthralgia as major manifestations in high-risk populations, while in low-risk populations, only polyarthritis is acceptable as a major manifestation (Gewitz, et al., 2015).

Carditis

ARF can cause a pancarditis that involves the pericardium, epicardium, myocardium, and endocardium (Gewitz, et al., 2015). However, the main clinical manifestation of ARF carditis reflects involvement of the endocardium, which presents as valvulitis of the mitral valve (mitral regurgitation) and, less frequently, of the aortic valve (aortic regurgitation) (Abernethy, et al., 1994; Vasan, et al., 1996; Veasy, et al., 1987). In patients with mitral regurgitation, auscultation reveals the characteristic pansystolic murmur of mitral regurgitation, and if the mitral regurgitation is severe, then an additional diastolic murmur may be present (Carey-Coombs

murmur). Cardiomegaly may occur when there is more severe valvular regurgitation. A pericardial rub may be heard when there is extensive involvement of the pericardium (Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association, 1992).

Patients with suspected ARF should have an echocardiogram to confirm clinical findings and to grade severity of valvular regurgitation, to evaluate cardiac function and to diagnose any subclinical involvement (Gewitz, et al., 2015). Subclinical carditis refers to evidence of regurgitation on echocardiography in the absence of ausculatory findings (Tubridy-Clark & Carapetis, 2007; Minich, Tani, Pagotto, Shaddy, & Veasy, 1997; Figueroa, et al., 2001). As specific criteria for diagnosing sub-clinical carditis are lacking, the 2015 Jones Criteria suggest that the WHF criteria may be used to distinguish physiological from pathological regurgitation (Gewitz, et al., 2015), as shown in Table 2. Both clinical and subclinical carditis are considered a major manifestation of ARF in both low- and high-risk populations (Gewitz, et al., 2015).

Table 2: WHF Criteria for the Echocardiographic Diagnosis of RHD. Content reproduced and used with permission from (Reményi, et al., 2012).

2012 WHF Criteria for the Echocardiographic Diagnosis of RHD	
Definite (>20 years): Either A, B, C, or D	
A Pathologic MR and at least two morphologic features of RHD of the mitral valve	
B Mitral stenosis with mean gradient ≥4 mmHg*	
C Pathologic AR and at least two morphologic features of RHD of the aortic valve+	
D (Only in individuals <35 years)	
E D. Pathological AR and at least two morphological features of RHD of the mitral valve	
Definite (≤ 20 years): Either A, B, C, or D	
A Pathologic MR and at least two morphologic features of RHD of the mitral valve.	
B Mitral stenosis with mean gradient ≥4 mmHg*	
C Pathologic AR and at least two morphologic features of RHD of the aortic valve+	
D Borderline disease of both the aortic and mitral valves	
Borderline (≤ 20 years): Either A, B, or C	
A At least two morphologic features of RHD of the mitral valve	
B Pathologic MR	
C Pathologic AR	
Pathologic MR (all criteria must be met)	**Pathologic AR (all criteria must be met)**
Seen in two views	Seen in two views
Jet length ≥2 cm** (in at least one view)	Jet length ≥1 cm** (in at least one view)
Velocity ≥3 m/s for one complete envelope	Velocity ≥3 m/s for one complete envelope
Pansystolic jet in at least one envelope	Pandiastolic jet in at least one envelope
Morphologic features of the mitral valve	**Morphologic features of the aortic valve**
Anterior leaflet thickening ≥3 mm	Irregular or focal thickening
Chordal thickening	Coaptation defect
Restricted leaflet motion	Restricted leaflet motion

Table 2 continued from previous page.

2012 WHF Criteria for the Echocardiographic Diagnosis of RHD	
Excessive leaflet tip motion during systole	Prolapse

MR: mitral regurgitation; AR: Aortic regurgitation
*Must exclude congenital mitral valve anomalies and in adults non-rheumatic mitral annular calcification
✚Bicuspid aortic valve, dilated aortic root, and hypertension must be excluded
Combined MR and AR in high prevalence regions and in the absence of congenital heart disease is regarded as rheumatic

Chorea

The chorea of ARF, also referred to as Sydenham's chorea or St. Vitus's dance, occurs in up to 30% of patients with ARF. It is characterized by involuntary, non-rhythmic, and purposeless movements of the trunk and limbs, which are often more pronounced on one side of the body (al-Eissa, 1993). Rheumatic chorea frequently affects the face and is characterized by grimaces, grins, and frowns. Note that chorea disappears with sleep. Emotional lability is also a feature of rheumatic chorea, especially in older children and adolescents, and is characterized by restlessness and outbursts of inappropriate behavior, including crying (Wilcox & Nasrallah, 1988; Asbahr, et al., 1998).

Chorea may present on its own, without other features of ARF and without evidence of a recent streptococcal infection, because chorea can occur many months after the inciting streptococcal infection. If chorea has an isolated presentation, it is important to exclude other causes of chorea, such as systemic lupus erythematosus, Wilson disease, and drug reactions (World Health Organisation, 2004). In all cases of suspected rheumatic chorea, a careful cardiac examination and echocardiogram must be performed, because chorea is strongly associated with carditis (Elevli, Celebi, Tombul, & Gökalp, 1999).

Skin findings: erythema marginatum and subcutaneous nodules

The skin manifestations of ARF occur in less than 10% of patients, and rarely occur as the sole manifestation of ARF (Gewitz, et al., 2015). Erythema marginatum, also referred to as "erythema annulare," is characterized by bright pink, blanching, non-pruritic macules or papules that spread outwards in a serpiginous pattern, usually on the trunk and proximal limbs. Subcutaneous nodules are small (0.5–2 cm), painless, round nodules that develop over bony prominences (especially the elbows) or extensor tendons, and are usually symmetric. There are usually three to four nodules, and they are generally present for one to two weeks.

Other clinical features

There are four other clinical features that are considered minor manifestations of ARF: fever, arthralgia, elevated acute phase reactants, and prolonged PR interval on electrocardiogram (Gewitz, et al., 2015). The fever of ARF is usually ≥ 38.5 degrees Celsius, but may be lower grade (≥ 38°C) in high-risk populations (Carapetis & Currie, 2001). Arthralgia usually involves several joints in a pattern similar to that of polyarthritis (Cherian, 1979). The erythrocyte sedimentation rate (ESR) is often above >60 mm/hour, and levels of C reactive protein (CRP) are usually above >3.0 mg/dL in patients with ARF, although the ESR may be lower (>30 mm/hour) in high-risk populations.

A number of other clinical features are often observed in patients with ARF but are not included as manifestations in the Jones Criteria, including lethargy, abdominal pain, and epistaxis, as well as rapid sleeping pulse rate and tachycardia out of proportion to fever (Stollerman, Markowitz, Taranta, Wannamaker, & Whittemore, 1965; The Committee on Standards and Criteria for Programs of Care, 1956). Full blood examination frequently reveals a normochromic and normocytic anemia and leukocytosis.

Diagnosis of Acute Rheumatic Fever

There is no single confirmatory test for ARF. Instead, the diagnosis of initial or recurrent ARF relies on patients fulfilling a set of clinical criteria. The most famous of these, the Jones criteria, underwent its fifth revision in 2015 (Gewitz, et al., 2015; Table 1), which expands its applicability to both high and low-risk populations. The revisions also include the results of sub-clinical carditis as a major criterion, which is diagnosed through echocardiographic evaluation. Staying true to its original form, the diagnosis of initial ARF continues to require two major or one major and two minor Jones criteria, along with evidence of a preceding streptococcal infection (Table 1). Chorea and chronic indolent rheumatic carditis remain as exceptions to this requirement, and are considered in isolation as sufficient evidence of ARF. The Jones criteria continues to emphasize that ARF must be a disease of exclusion, with an active search for other systemic diseases (Gewitz, et al., 2015).

In low-risk populations, defined as an "ARF incidence < 2 per 100,000 school-aged children per year or an all-age prevalence of RHD of ≤ 1 per 1000 population per year" (Gewitz, et al., 2015), the Jones criteria continue to emphasize high specificity to avoid false positive diagnoses. Major criteria include carditis (clinical or sub-clinical), polyarthritis, chorea, erythema marginatum, and subcutaneous nodules. Minor criteria include polyarthralgia, fever (≥ 38.5°C), ESR ≥ 60mm in the first hour and/or CRP ≥ 3.0 mg/dL, and a prolonged PR interval (unless carditis is already counted as a major criteria, as shown in Table 1).

In moderate- to high-risk populations, which are defined as any population with a prevalence or incidence of infection outside the definition of low risk (see above), the criteria emphasize high sensitivity to avoid false negative diagnoses. Since the last revision (1992), data emerged from endemic regions that restricting joint involvement to the classic migratory polyarthritis led to an under-diagnosis of ARF (Carapetis & Currie, 2001; Cann, Sive, Norton, McBride, & Ketheesan, 2010; Parks, Kado, Colquhoun, Carapetis, & Steer, 2009; Noonan, et al., 2013). Polyarthritis, monoarthritis, or polyarthralgia can now fulfill a major criterion. Slight changes to minor criteria in moderate- to high-risk populations further improve sensitivity and include monoarthralgia, a lowered fever requirement of ≥ 38.0°C, and a lowered ESR cutoff of ≥ 30mm in the first hour (Table 1).

The 2015 Jones revision also provides specific diagnostic criteria for ARF reoccurrences, which have been vague in previous iterations. In patients with a reliable history of ARF or RHD and documentation of a recent streptococcal infection, a reoccurrence can be diagnosed through fulfilling two major, one major and two minor, or three minor criteria. There is also provision for the diagnosis of "possible ARF" both for initial and recurrent ARF, for cases where there is a high clinical suspicion of ARF but incomplete fulfillment of the criteria. Lack of criteria could occur secondary to the unavailability of laboratory or echocardiographic testing, poor clinical history, and/or late presentation. In these circumstances, the Jones criteria find it reasonable to offer secondary prophylaxis with clinical and echocardiographic re-evaluation after one year (Gewitz, et al., 2015).

Table 1: Jones Criteria; (ARF: Acute Rheumatic Fever, RHD: Rheumatic Heart Disease, ESR: Erythrocyte Sedimentation Rate, CRP: C - reactive protein; * Subclinical carditis: Seen only on echocardiography without ausculatory findings, **Accounting for age variability & only if carditis NOT counted as a major criteria). Content reproduced and used with permission from (Gewitz, et al., 2015).

2015 Jones Criteria for the Diagnosis of ARF		
	Low-Risk Population ARF incidence ≤ 2 per 100,000 school-aged children or all-age RHD prevalence of ≤ 1 per 1000 population year	Moderate/High Risk Population Children not clearly from a low-risk population.
Major Criteria		
Carditis	Clinical and/or Subclinical*	Clinical and/or Subclinical*
Arthritis	Polyarthritis	Monoarthritis, Polyarthritis, and/or Polyarthralgia
	Chorea	Chorea

Table 1 continued from previous page.

2015 Jones Criteria for the Diagnosis of ARF		
	Erythema Marginatum	Erythema Marginatum
	Subcutaneous Nodules	Subcutaneous Nodules
Minor Criteria		
Carditis	Prolonged PR interval**	Prolonged PR interval**
Arthralgia	Polyarthralgia	Monoarthralgia
Fever	≥ 38.5°C	≥ 38°C
Markers of Inflammation	Peak ESR ≥ 60mm in 1 hour and/or CRP ≥ 3.0 mg/dL	Peak ESR ≥ 30mm in 1 hour and/or CRP ≥ 3.0 mg/dL
Evidence of Preceding Streptococcal Infection (any one of the following)		
Increased or rising anti-streptolysin O titer or other streptococcal antibodies (anti-DNASE B)		
A positive throat culture for group A B-hemolytic streptococci		
A positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pre-test probability of streptococcal pharyngitis		

Medical Management of ARF

The first aim of management of ARF is to confirm the diagnosis, for which a high index of suspicion is needed, especially in patients presenting with acute arthritis in geographic settings where ARF is endemic. All patients with suspected ARF should be hospitalized so that the clinical course can be closely observed and so that key investigations can be undertaken (Box 1). Additional investigations, such as joint ultrasound, joint aspiration, tests for other causes of arthritis, and tests for other causes of chorea are directed by the clinical presentation and course. Hospitalization also provides an opportunity for education about ARF, especially the need for secondary prophylaxis.

Beyond diagnosis, the priorities in management of ARF are: eradication of the group A streptococcus from the throat and commencement of secondary prophylaxis; symptomatic treatment of arthritis and/or arthralgia; management of carditis and/or heart failure; management of chorea; and patient and family education.

BOX 1: Key investigations for the diagnosis of acute rheumatic fever.

Full blood count

Acute phase reactants: C-reactive protein and erythrocyte sedimentation rate

Echocardiogram

Electrocardiogram

Chest radiograph

Throat swab for bacterial culture

Streptococcal serology (anti-streptolysin O titer and anti-deoxyribonuclease B titer)

Eradication of the group A streptococcus and starting secondary prophylaxis

Patients with ARF are treated with an antibiotic to eradicate *S. pyogenes* (Shulman, et al., 2012). A pragmatic approach is to administer long-acting intramuscular benzathine penicillin G, which serves two purposes: 1) to eradicate *S. pyogenes* carriage; and 2) as the first dose of four-weekly secondary prophylaxis. The first dose of intramuscular BPG given in a hospital setting can begin the process of education about the importance of secondary prophylaxis. Secondary prophylaxis with benzathine penicillin G is the cornerstone of the long-term management of patients with ARF (Shulman, et al., 2012); see Table 3).

Table 3: Recommendations for dosing and duration of secondary prophylaxis. Content reproduced and used with permission from (Gerber, et al., 2009). (Rating indicated classification of recommendation and Level of Evidence (LOE) eg, IA indicates class I, LOE A).

Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)			
Agent	**Dosage**	**Route of Administration**	**Rating**
Benzathine Penicillin G	**Children (27kg / 60lb or less)** 600 000 U **Those (weighing more than 27kg / 60lb)** 1 200 000 U Every 4 weeks*	Intramuscular	IA
Penicillin V	250 mg twice daily	Oral	IB
Sulfadiazine	Patients (27kg / 60lb or less) 0.5 g once daily Patients (weighing more than 27kg / 60lb) 0.5 g once daily	Oral	IB
For patients allergic to penicillin and sulfadiazine			
Macrolide or Azalide	Variable	Oral	IC

* In high risk situations, administration every 3 weeks is justified and recommended.

Management of joint symptoms

Anti-inflammatory treatment is the mainstay of symptomatic management of the acute joint symptoms of ARF (Illingworth, Lorber, Holt, & Rendle-Short, 1957; Dorfman, Gross, & Lorincz, 1961). First-line therapy has traditionally been aspirin, which remains the most widely used anti-inflammatory medication for ARF. There is increasing experience in using newer NSAIDs, including naproxen for older patients and ibuprofen for younger children (Cilliers, 2003; Czoniczer, Amezcua, Pelargonio, & Massell, 1964; Hashkes, et al., 2003; Uziel, Hashkes, Kassem, Padeh, Goldman, & Wolach, 2000), which some prefer, because of their more convenient dosing frequency and the reduced risk of toxicity or Reye's syndrome, as compared to salicylates. A single small, randomized controlled trial supports the use of naproxen in ARF (Hashkes, et al., 2003). Ibuprofen has been used successfully in younger children with rheumatic fever. In patients with mild arthralgia, acetaminophen or paracetamol may provide adequate treatment.

Aspirin and NSAIDs quickly control joint symptoms, but should be continued until all symptoms have resolved (Dorfman, Gross, & Lorincz, 1961). Most patients require treatment for one to two weeks, although some patients require a longer course. Arthritis can recur when dosage of anti-inflammatory treatment is reduced—this phenomenon is known as "rebound" and means that a longer course of treatment is required (Holt, 1956). If corticosteroid treatment is used for management of carditis or for another reason, aspirin or NSAIDs can be ceased during the period of corticosteroid therapy, but should be re-started following the cessation of treatment.

Management of carditis

There is no evidence that anti-inflammatory therapy alters the long-term outcome of patients with ARF, although some experts recommend corticosteroids treatment in patients with severe carditis (ARF/RHD Writing Group, 2012; Bywaters & Thomas, 1961; Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Sub-Committee of the Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, 1965). Therefore, the management of carditis consists of treatment of heart failure in those with severe carditis. Valve surgery is rarely necessary in patients with rheumatic carditis, but can be life-saving in patients with acute rupture of a valve leaflet or with chordae tendinae (al Kasab, al Fagih, Shahid, Habbab, & al Zaibag, 1988).

All patients with severe carditis, including those with significant cardiomegaly, congestive heart failure, or a third-degree heart block, require an urgent echocardiogram and assessment by a cardiologist. Diuretics, fluid restriction, and bed rest are mainstays in the management of heart failure. Angiotensin-converting enzyme inhibitors are recommended for some patients with symptomatic aortic regurgitation and/or left ventricular dysfunction (Thatai & Turi, 1999). Many experts recommend the use of corticosteroids in severe acute carditis with heart failure, despite an absence of high-quality evidence. The side effects of corticosteroids, including gastrointestinal bleeding and fluid retention, can worsen cardiac failure.

Cardiac surgery is generally avoided until the acute inflammation has subsided, so that the repair is technically easier and so that a better long-term outcome can be achieved (Skoularigis, Sinovich, Joubert, & Sareli, 1994). The exception to this is torrential mitral or aortic regurgitation, which is often due to chordae tendinae rupture with a flail leaflet and requires urgent life-saving surgical repair (al Kasab, al Fagih, Shahid, Habbab, & al Zaibag, 1988). Where possible, valve repair rather than replacement is always the preferred surgery, in order to avoid the long-term anticoagulation treatment that is required for mechanical valves (Remenyi, et al., 2013b).

There are no reliable data to support the use of anti-inflammatory drugs (aspirin, NSAIDs, corticosteroids, intravenous immune globulin) in acute carditis, with regard to subsequent development of heart valve lesions and cardiac disease (Cilliers, Manyemba, & Saloojee, 2003; Voss, et al., 2001; Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Sub-Committee of the Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, 1965).

Management of chorea

Rheumatic chorea is usually benign and self-limiting with resolution within weeks to months, and as a result, treatment other than rest and a calm environment is often not necessary (Lessof & Bywaters, 1956), especially as medications used for chorea have potential serious adverse effects. However, if choreiform movements substantially interfere with normal activities of daily living, place the person at risk of injury, or are distressing to the patient and their family, then treatment should be considered (ARF/RHD Writing Group, 2012).

Valproic acid and carbamazepine are considered first-line treatments for chorea (Daoud, Zaki, Shakir, & al-Saleh, 1990; Genel, Arslanoglu, Uran, & Saylan, 2002; Peña, Mora, Cardozo, Molina, & Montiel, 2002). A small, prospective comparative study found that valproic acid was the more effective agent (Daoud, Zaki, Shakir, & al-Saleh, 1990). However, some experts recommend carbamazepine as initial therapy for severe chorea, because of the potential risk of liver toxicity with valproic acid (Heart Foundation, 2014). Valproic acid is contra-indicated in females of child-bearing age, due to the risk of teratogenicity. Short-course corticosteroid treatment can be also considered for severe or refractory chorea (Barash, Margalith, & Matitiau, 2005; Cardoso, Maia, Cunningham, & Valença, 2003; Paz, Silva, & Marques-Dias, 2006). Aspirin and NSAIDs have no significant effect on rheumatic chorea.

Education

Patients and their caregivers require adequate information and education about rheumatic fever and rheumatic heart disease, as well as the importance of adhering to secondary prophylaxis (Shulman, et al., 2012). In addition, it is important to educate patients about seeking treatment for sore throats, as well as emphasizing the role of dental care.

The transition to chronic rheumatic heart disease

Approximately 35–72% of patients that experience ARF will develop clinical carditis (Bland & Duckett Jones, 1951; Wilson & Lim, 1956; Ash, 1948; Lawrence, Carapetis, Griffiths, Edwards, & Condon, 2013; Meira, Goulart, Colosimo, & Mota, 2005), with an additional 18% showing evidence of sub-clinical cardiac involvement by echocardiography (Tubridy-Clark & Carapetis, 2007). However, resolution of acute carditis can occur, particularly with excellent compliance with prophylaxis, and not all of these patients will transition to chronic RHD. Resolution is seen most often in the first year following ARF, but has been documented as far out as 10 years following the initial cardiac insult (Bland & Duckett Jones, 1951). Acute carditis limited to pure mitral regurgitation is the most likely lesion to regress, with regression almost never seen with aortic valve involvement (Bland & Duckett Jones, 1951). Factors that consistently predispose patients to development of chronic RHD include a younger age at first episode of ARF, more severe carditis at first episode of ARF, and frequency and number of ARF reoccurrences (Bland & Duckett Jones, 1951; Wilson & Lim, 1956; Ash, 1948).

It is also possible for children who do not have clinical carditis during initial ARF presentation to develop chronic RHD. This may be due to subclinical recurrences, poor compliance with prophylaxis, or delayed development of clinically-apparent disease, and highlights the need for serial echo data.

In the pre-penicillin, pre-echocardiography era, 24% of patients at 10 years and 44% of patients at 20 years who had no clinical carditis at ARF presentation had ausculatory findings of chronic RHD, despite only one-third having documented ARF reoccurrences (Bland & Duckett Jones, 1951). Contemporary data from Australia supports this finding, with 35% of children demonstrating RHD at 1 year following ARF, a number that increased to 61% 10 years after the initial ARF presentation (Lawrence, Carapetis, Griffiths, Edwards, & Condon, 2013).

Rheumatic Heart Disease

Clinical Manifestations, Features and Diagnosis of RHD

Echocardiography is the primary evaluation tool for patients with suspected and confirmed RHD, as it delineates the distribution and severity of valvular involvement and excludes alternate pathology (Saxena, 2013). While the carditis associated with ARF is a pancarditis, valvular pathology almost exclusively dominates chronic RHD. Left-sided cardiac involvement is most commonly seen; it involves the mitral valve almost 100% of the time and involves the aortic valve in 20–30% of cases. The tricuspid valve is affected histologically in 15–40% of patients with RHD (Kitchin & Turner, 1964; Roguin, Rinkevich, Milo, Markiewicz, & Reisner, 1998; Chopra & Bhatia, 1992), but this finding is rarely of clinical importance except in the most severe cases (Kitchin & Turner, 1964; Carpentier, et al., 1974). The pulmonary valve is almost never affected, though there are reports of pulmonary autografts, which have been used in the aortic position during a Ross procedure, subsequently developing graft failure and showing signs of rheumatic carditis (Choudhary, et al., 1999).

Mitral Regurgitation

Mitral regurgitation is the most commonly seen valvular pathology in RHD (Tissier, et al., 2005; Chockalingam, Gnanavelu, Elangovan, & Chockalingam, 2003), particularly in children and young adults, where pure mitral regurgitation is the most common RHD presentation (Rheumatic Fever Working Party of the Medical Research

Council of Great Britain and the Sub-Committee of the Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, 1965; The Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, 1960). Rheumatic mitral regurgitation primarily results from morphological changes that reflect chronic scarring of the mitral valve and mitral valve apparatus. Morphological mitral valve features are well-visualized on standard 2D echocardiography, though emerging data suggests that 3D echocardiography may improve the sensitivity and specificity of RHD detection in cases of mild valvular involvement and facilitate improved surgical planning for those with advanced disease (Beniwal, Bhaya, Panwar, Panwar, & Singh, 2015).

Valvular thickening, which is seen in 56–100% of patients with rheumatic carditis, is the most common morphological feature on both echocardiography (Yuko-Jowi & Bakari, 2005; Vasan, et al., 1996; Atalay, Uçar, Ozçelik, Ekici, & Tutar, 2007; Câmara, Neubauer, Câmara, & Lopes, 2004) and direct visualization (Skoularigis, Sinovich, Joubert, & Sareli, 1994; Ungar & Ben-Ishay, 1965; van der Bel-Kahn & Becker, 1986). Such thickening is most commonly seen at the free edge of the leaflet, where the chordal structures can fuse with the leaflet tips (Ungar & Ben-Ishay, 1965); though nodularity, or beading, along the length of the leaflet can also be seen (Atalay, Uçar, Ozçelik, Ekici, & Tutar, 2007). The 2012 WHF criteria advise objective measurement of the mitral valve without harmonic imaging and set criteria for an abnormally thickened mitral valve based on age (Reményi, et al., 2012); see Table 2). Chordal thickening, a purely subjective measure on echocardiography (Reményi, et al., 2012), is also a common feature and results in the restricted movement of the anterior and/or posterior mitral leaflets, and the incomplete valvular coaptation characteristic of rheumatic mitral regurgitation (Vasan, et al., 1996; Atalay, Uçar, Ozçelik, Ekici, & Tutar, 2007; Câmara, Neubauer, Câmara, & Lopes, 2004). Another less common mechanism for chronic rheumatic mitral regurgitation and poor mitral coaptation involves excessive motion of the anterior mitral leaflet tip, which is sometimes referred to imprecisely as mitral prolapse. Though it is more commonly seen in acute rheumatic carditis, excessive anterior leaflet motion is defined as the displacement of the tip of the leaflet (rather than the leaflet body in classic mitral valve prolapse) towards the left atrium, and results from elongation of the primary mitral chords (Reményi, et al., 2012; Kalangos, et al., 2000; Chauvaud, et al., 2001).

Pure mitral regurgitation is generally well tolerated, and particularly that of mild to moderate severity. However, mitral regurgitation can progress over time (Enriquez-Sarano, et al., 1999) through continued scarring of the valve and valve apparatus and/or through compensatory left ventricular dilation, which further prevents proper coaptation by altering the size and position of the mitral annulus (Otsuji, et al., 1997). Patients with significant mitral regurgitation will show increased precordial activity with displacement of the ventricular impulse that is consistent with the degree of ventricular dilation. The classic murmur of mitral regurgitation is a holosystolic apical murmur, which can be best heard with the patient in the left lateral decubitus position. The intensity of the murmur generally correlates with the severity of regurgitation. A normal EKG and chest X-ray are most common with mild mitral regurgitation, but both will show left atrial and left ventricular dilation as the severity of regurgitation increases. Atrial fibrillation is uncommon with pure mitral regurgitation, particularly in the pediatric population, but occurs more commonly as left atrial size increases (Okello, et al., 2013). Except for those with severe acute mitral regurgitation, most patients will remain asymptomatic for years. Over time, mitral regurgitation can result in left ventricular dysfunction and symptomatic patients usually present with signs of left heart failure, decreased exercise tolerance, and shortness of breath with exertion (Nishimura, et al., 2014; Otto, 2003).

Mitral Stenosis

RHD is the most common etiology of mitral stenosis worldwide (Ratnakar, Rajagopal, & Somaraju, 1989; Waller, Howard, & Fess, 1994; Iung, et al., 2007). Development of mitral stenosis is associated with the number, though not necessarily with the severity, of carditis during ARF reoccurrences (Bland & Duckett Jones, 1951; Walsh &

Nestor, 1956), and is more common in women (Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Sub-Committee of the Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, 1965; Stollerman, 2001). Mitral stenosis was also commonly seen as a late complication of chorea in up to 25% of children in the pre-antibiotic era (Bland & Duckett Jones, 1951). Rheumatic mitral stenosis was classically thought to be a late presentation in RHD, occurring in the third to sixth decade of life (Horstkotte, Niehues, & Strauer, 1991). However, rheumatic mitral stenosis has a more aggressive course in sub-Saharan Africa and other low-resource settings. For example, in Ethiopia, cases have been documented in a child as young as five years, and mitral stenosis was found in one-third of children diagnosed with clinical RHD (Tadele, Mekonnen, & Tefera, 2013).

Rheumatic mitral stenosis occurs later on the continuum of valvular scarring, and shares many morphological features with rheumatic mitral regurgitation. Typically, the mitral valve leaflets are thick and relatively immobile. Restricted leaflet mobility generally results from shortening and fusion of the mitral valve chords (seen in 100% of patients with severe mitral stenosis) (Anwar, et al., 2010), calcification, and/or commissural fusion (Reményi, et al., 2012; Ratnakar, Rajagopal, & Somaraju, 1989; Carpentier, 1983), which results in a funnel-shaped mitral valve orifice.

Mild mitral stenosis is well tolerated and usually asymptomatic. However, with increasing stenosis, the left atrial pressure rises, which leads to increased pulmonary venous pressure and eventually to pulmonary hypertension. Early symptoms reflect decreased cardiac output and include fatigue and decreased exercise tolerance. Later, symptoms of pulmonary edema appear with shortness of breath, cough, wheeze, orthopnea, and paroxysmal nocturnal dyspnea. With development of pulmonary hypertension, patients can present in extremis with syncope, hemoptysis, and right heart failure (Nishimura, et al., 2014). Findings on physical examination reflect the severity of disease. The classical mitral stenosis murmur consists of a low-pitched rumbling apical diastolic murmur, which is best heard in the left lateral decubitus position (Nishimura, et al., 2014). Murmurs of longer duration reflect more severe stenosis. If the patient has developed pulmonary hypertension, P2 may be accentuated and patients can show an increased right ventricular impulse. Chest x-ray shows an enlarged left atrium, with or without pulmonary edema, and/or enlarged pulmonary arteries depending on disease severity. ECG evaluation is of critical importance, as patients with significant mitral stenosis are at high risk of atrial fibrillation.

Aortic Regurgitation

Rheumatic aortic regurgitation is most commonly seen in combination with rheumatic mitral valve pathology (Zühlke, et al., 2014). Pure aortic valve disease is uncommon (Zühlke, et al., 2014), occurring in only 4.5% of individuals < 18 and 2.8% of those >18 in a large series of patients from India (Chockalingam, Gnanavelu, Elangovan, & Chockalingam, 2003). If valve disease is suspected, a comprehensive search for other aortic pathologies should be undertaken (bicuspid aortic valve, sub-aortic membrane, infective endocarditis, and connective tissue diseases). The mechanism for rheumatic aortic regurgitation is most commonly restricted aortic leaflet motion, which occurs as a result of leaflet retraction and thickening (Cohen, et al., 1996). Surgical studies have demonstrated that between 41–100% of patients with rheumatic aortic regurgitation show aortic valve thickening, which is often irregular and nodular in appearance and results in a central coaptation defect (Myers, et al., 2010; Talwar, Saikrishna, Saxena, & Kumar, 2005b; Bernal, et al., 1998; Bozbuga, et al., 2004; Tekumit, et al., 2010; Grinda, et al., 2002). Prolapse of the aortic valve is a second, less common mechanism for rheumatic aortic regurgitation (Cohen, et al., 1996), but other primary causes of aortic prolapse are more common and should be ruled out.

Similar to chronic mitral regurgitation, patients with chronic aortic regurgitation can remain asymptomatic for years. However, aortic regurgitation creates both a volume and pressure load on the left ventricle and results in compensatory ventricular dilation (Nishimura, et al., 2014). Over time, ventricular dysfunction can occur and patients may present with symptoms of left heart failure, such as decreased exercise tolerance, fatigue, and

shortness of breath with exertion. On physical exam, patients with significant aortic regurgitation will show a widened pulse pressure, bounding pulses, and increased precordial activity with leftward deviation of the ventricular impulse secondary to left ventricular dilation. The classical aortic regurgitation murmur is a high-pitched diastolic murmur heard at the left lower sternal boarder most prominently when a patient is leaning forwards and at end-expiration. Severity of regurgitation correlates with duration of the murmur, with a shorter murmur associated with more severe disease. Chest x-ray and ECG will be normal with mild disease, but with more advanced disease, long-standing aortic regurgitation evidence of left ventricular dilation will present, along with ascending aortic enlargement by chest x-ray.

Aortic Stenosis

Aortic stenosis is a less common rheumatic valvular pathology that is found in only 9% of study subjects in a recent large prospective data collection across Africa (Zühlke, et al., 2014). Stenosis occurs secondary to progressive leaflet thickening, commissural fusion, fibrosis, and calcification. Rheumatic aortic stenosis almost never occurs in isolation, and most patients have mixed aortic valve disease and concurrent mitral valve pathology. The prevalence of aortic stenosis increases with age and most commonly comes to attention anywhere from 20 to 40 years after the initial appearance of ARF (Bland & Jones, 1936).

The development of rheumatic aortic stenosis is usually gradual, which allows time for cardiac compensation and an asymptomatic period. As stenosis worsens, symptoms of left heart failure, poor cardiac output, and poor coronary perfusion develop, including angina, syncope, and shortness of breath with exertion. Patients with aortic stenosis may demonstrate a palpable thrill at the right upper sternal border or suprasternal notch. The classic murmur is a systolic ejection murmur at the right upper sternal border, often with a diastolic decrescendo murmur if there is concurrent aortic regurgitation. In contrast to congenital aortic pathologies, there is rarely an associated opening click (Nishimura, et al., 2014).

Mixed Valve Disease

Except in the young, where pure mitral regurgitation dominates, mixed valvular pathology is the most common finding in chronic RHD (Zühlke, et al., 2014). Mitral regurgitation and mitral stenosis most often develop along a continuum of disease, and many patients have both important regurgitating and stenotic components (Bland & Duckett Jones, 1951). These changes reflect the ongoing valvular scarring and remodeling that occur in RHD, even when recurrent episodes of ARF are absent. Similarly, aortic valve pathology is rarely seen in isolation (Zühlke, et al., 2014), and most commonly has an associated mitral pathology. The right-sided heart valves are infrequently involved and are never involved in isolation. Rheumatic tricuspid involvement is more common than pulmonary involvement, with clinically apparent disease in 3–5% of patients (Kitchin & Turner, 1964; Carpentier, et al., 1974).

Screening for Rheumatic Heart Disease

Not all patients who develop chronic RHD have a clinical history of ARF (Sliwa, et al., 2010; Carapetis, Currie, & Mathews, 2000). Emerging data from low-resource nations suggest that, at least in some endemic regions, latent RHD, or RHD absent a history of ARF, may even be the most common presentation among those with advanced rheumatic cardiac disease (Zhang, et al., 2013). RHD also typically shows a relatively long period between the initial cardiac insult and presentation with symptomatic cardiac disease. While the highest risk of ARF is in childhood, symptomatic RHD most commonly presents in the third and fourth decade (Zühlke, et al., 2014). This clinically silent period presents an opportunity for early RHD detection, and active surveillance for RHD has been advocated for endemic regions since the 1970s (WHO Expert Committee on the Prevention of Rheumatic Fever World Health Organization, 1966).

RHD fulfills the four criteria outlined by the 1994 Council of Europe for determination of diseases suitable for screening (Roberts, Colquhoun, Steer, Reményi, & Carapetis, 2013b). Within endemic areas, RHD exerts an

enormous human and financial toll on individuals and communities (Günther, Asmera, & Parry, 2006; Kumar, Raizada, Aggarwal, & Ganguly, 2002; Carapetis & Currie, 1999; Milne, Lennon, Stewart, Vander Hoorn, & Scuffham, 2012b; Parks, et al., 2015), and also substantially contributes to the overall global burden of disease (Global Burden of Disease Study 2013 Collaborators, 2015). The natural history of untreated RHD is well documented, with progression of rheumatic valvular disease dependent on both the severity of the initial carditis and the number of ARF reoccurrences (Bland & Duckett Jones, 1951; Tompkins, Boxerbaum, & Liebman, 1972). Echocardiography, when interpreted through the 2012 World Heart Federation Criteria (WHF; Table 2) (Reményi, et al., 2012), appears to be highly sensitive (Roberts, Brown, Maguire, Atkinson, & Carapetis, 2013a; Beaton, et al., 2014; Colquhoun, et al., 2014; Engel, et al., 2015) and specific (Roberts, et al., 2014; Clark, Krishnan, McCarter, Scheel, Sable, & Beaton, 2016; McGlacken-Byrne, Parry, Currie, & Wilson, 2015) screening test, though the clinical significance of the category "borderline RHD" remains unclear (see more below). And finally, initiation and maintenance of regular intramuscular penicillin injections (secondary prophylaxis), at least in those with early RHD and a documented history of ARF, improves the long-term prognosis by preventing recurrent ARF episodes and halting the progression of valvular damage (Feinstein, et al., 1964b; Stollerman, Rusoff, & Hirschfeld, 1955; Feinstein, Stern, & Spagnuolo, 1964a; Lue, Tseng, Lin, Hsieh, & Chiou, 1983).

Echocardiographic screening for RHD has emerged over the last decade as the most sensitive test for early RHD detection. A systematic review of echocardiographic screening studies to date calculated a pooled prevalence of RHD of 2.9 per 1000 people by auscultation, as compared to 12.9 per 1000 people by echocardiography (Rothenbühler, et al., 2014). However, studies directly comparing auscultation to echocardiographic screening have demonstrated auscultation to be both poorly sensitive and poorly specific (Viali, Saena, & Futi, 2011; Mehta, et al., 2014), and auscultation is no longer recommended for RHD screening (Reményi, et al., 2012). In 2011, an expert working group was convened by the World Heart Federation to develop the first evidence-based set of criteria for the echocardiographic diagnosis of RHD (Reményi, et al., 2012). These criteria use morphological and functional features of the mitral and aortic valves to categorize individuals as having no RHD, borderline RHD, or definite RHD. These criteria are meant for use only in individuals who have no clinical history of ARF and who reside in RHD endemic regions. It was the hope that standardized diagnostic criteria would improve both the sensitivity and specificity of screening, (particularly in limiting false positive diagnoses) and would provide a platform for sharing and collation of data across studies and sites (Table 2; Reményi, et al., 2012).

Screening by echocardiography has revealed a large burden of "borderline RHD"; a diagnostic category in the 2012 WHF criteria, which includes isolated functional or isolated morphological changes to either the mitral or aortic valves (Reményi, et al., 2012). The clinical significance of borderline RHD is not yet known, and the need for and role of secondary prophylaxis in this population is uncertain. The majority of short-term natural history studies appear to show a relatively benign prognosis for borderline RHD, particularly when the initial lesion is isolated pathological mitral regurgitation (Beaton, et al., 2014; Paar, et al., 2010; Mirabel, et al., 2015c; Bhaya, Beniwal, Panwar, & Panwar, 2011; Saxena, et al., 2011). However, a single study from Australia (with a follow-up at 2.5–5 years) showed that children with borderline RHD were at a significantly greater risk of ARF and progression of valvular disease, as compared to their age- and gender-matched peers (Rémond, et al., 2015). Clearly, more research in this area is needed. Currently, the most common practice for children with borderline RHD is close clinical follow-up, with initiation of secondary prophylaxis only in cases of recurrent ARF or progression of valvular disease.

Echocardiographic screening also faces significant implementation barriers, and echocardiographic screening as a public health measure is not yet widely supported (Roberts, Colquhoun, Steer, Reményi, & Carapetis, 2013b; Zühlke & Mayosi, 2013). Financial resources and skilled healthcare providers are scarce in most regions where RHD is endemic. Task-shifting of RHD screening to non-experts and the use of less expensive handheld echocardiography for screening have shown promise (Beaton, et al., 2015; Lu, et al., 2015; Ploutz, et al., 2016; Mirabel, et al., 2015b; Mirabel, et al., 2012; Engelman, et al., 2015), but further research is needed.

Implementation research that examines the best screening strategies and environments is sparse, and the integration of screening into existing healthcare structures is only beginning. Additionally, in most RHD-endemic regions, an investment in infrastructure development will be needed prior to wide-spread screening, to ensure a reliable supply of penicillin and skilled care across the continuum of RHD severity. Finally, while there are preliminary data supporting the overall cost-effectiveness of echocardiographic RHD screening (Manji, et al., 2013; Zachariah & Samnaliev, 2015), these data are based largely on modeling. Future studies will need to include the direct costs from ongoing screening programs in a variety of clinical environments in order to justify investment in echocardiographic screening as a sustainable public health policy.

Medical Treatment and Management of Chronic RHD

Medical management for chronic RHD is largely based on the presence or absence of cardiovascular symptoms. Most patients with mild to moderate valvular involvement will remain asymptomatic for years. Strict adherence to secondary prophylaxis (see above) should be emphasized, as poor adherence and reoccurrence of ARF have independently been associated with an increased risk of RHD complications and death. Heart failure should be considered a surgical disease, with no long-term role for medical management, except in cases where surgery is unavailable or contraindicated (Nishimura, et al., 2014; Borer & Bonow, 2003). Exercise restrictions are based both on the severity of valvular disease and the intensity of the desired activity, and should be guided by the 2005 Bethesda Guidelines (Maron & Zipes, 2005). Emerging data suggests that statins may slow the progression of rheumatic mitral and aortic stenosis, but prospective adult trials have shown mixed results (Antonini-Canterin, et al., 2009; Antonini-Canterin, et al., 2010; Cowell, et al., 2005; Rossebø, et al., 2008). Statins are not currently recommended in patients with chronic RHD.

Mitral Regurgitation

There is no role for medical management in patients with severe mitral regurgitation and preserved left ventricular function (Nishimura, et al., 2014; Borer & Bonow, 2003). Data on the impact of afterload reduction on hemodynamics is mixed, with some studies reporting improvement (Gupta, Kapoor, Garg, Tewari, & Sinha, 2001; Sampaio, et al., 2005) and others reporting hemodynamic worsening (Wisenbaugh, Essop, Rothlisberger, & Sareli, 1992; Röthlisberger, Sareli, & Wisenbaugh, 1994). Importantly, afterload reduction has not been shown to slow symptom development, preserve left ventricular function, or improve survival rates; and as a result, it is not a recommended course of treatment (Nishimura, et al., 2014). Patients who develop symptoms or have decreased left ventricular function should be referred for surgical intervention (Nishimura, et al., 2014). Surgical intervention should also be considered in patients with severe left ventricular enlargement but preserved left ventricular function, if the chances of repair vs. replacement are high, the mortality risk is <1%, and if the surgery can be performed at a Heart Valve Center of Excellence (Nishimura, et al., 2014). Additionally for patients with severe mitral regurgitation and preserved function who have developed atrial fibrillation or resting systolic pulmonary artery hypertension (>50mmHg), surgical interventions should be considered if the chances of repair vs. replacement are high (Nishimura, et al., 2014). If surgical intervention is unavailable or contraindicated, medical therapy for systolic dysfunction is considered a reasonable course of treatment to manage symptoms (Nishimura, et al., 2014).

Mitral Stenosis

Medical management of mitral stenosis centers on the prevention of thromboembolic events. Anticoagulation is indicated for patients with mitral stenosis and atrial fibrillation, and/or a prior embolic event, and/or a left atrial thrombus (Nishimura, et al., 2014). Additional heart rate control can be beneficial in patients with mitral stenosis and atrial fibrillation with rapid ventricular response, or in those whom have mitral stenosis and symptoms that are associated with exercise (Nishimura, et al., 2014). A pilot study examining the utility of Bosentan, an endothelin receptor antagonist, has shown early promise in improving the functional status of patients with pulmonary hypertension secondary to rheumatic mitral stenosis (Vlachogeorgos, et al., 2015), but

larger studies are needed before a universal recommendation can be made. As with mitral regurgitation, the timing of intervention is based on development of cardiovascular symptoms, as well as the overall favorability of the valve for a percutaneous vs. a surgical intervention (Nishimura, et al., 2014).

Aortic Regurgitation

Medical therapy has a limited role in treating patients with rheumatic aortic regurgitation. Recent evidence on the role of afterload reduction in the asymptomatic patient with severe aortic insufficiency and preserved left ventricular function has been mixed (Evangelista, Tornos, Sambola, Permanyer-Miralda, & Soler-Soler, 2005; Scognamiglio, Rahimtoola, Fasoli, Nistri, & Dalla Volta, 1994), and afterload reduction is not currently recommended for these patients (Nishimura, et al., 2014). The asymptomatic patient with significant aortic regurgitation should be monitored for systemic hypertension (systolic BP >140 in an adult), and if present, appropriately treated with afterload reduction, such as calcium-channel blockers, ACE inhibitors, or angiotensin-receptor blockers (Nishimura, et al., 2014). Surgical intervention is indicated for all symptomatic patients with severe aortic insufficiency, even if the left ventricular function is preserved. Surgery should also be considered in asymptomatic patients with severe aortic insufficiency if there is decreased left ventricular function or severe left ventricular dilation (Nishimura, et al., 2014). If surgery is unavailable or otherwise contraindicated, it is reasonable to attempt symptom management with B-blockade and afterload reduction, such as ACE inhibitors or an angiotensin receptor blockade (Nishimura, et al., 2014).

Aortic Stenosis

There is no effective therapy for symptomatic rheumatic aortic valve stenosis (Nishimura, et al., 2014). Timing of surgical intervention is based both on the severity of the disease and the presence of cardiovascular symptoms. Unlike some congenital pathology, catheter-based balloon angioplasty has low efficacy in patients with rheumatic aortic stenosis, and should be reserved for symptomatic patients who are not surgical candidates (Nishimura, et al., 2014; Otto, et al., 1994; Lieberman, et al., 1995).

Endocarditis Prophylaxis

Endocarditis is an important co-morbidity in patients with chronic RHD, and a large percentage of endocarditis in low-and-middle income nations occurs in patients with RHD (Mirabel, et al., 2015a; Moges, et al., 2015; Watt, et al., 2015). However, prophylaxis antibiotics prior to dental and other high-risk procedures are not universally recommended. Current American Heart Association guidelines recommend the use of antibiotic prophylaxis only in patients with prosthetic cardiac valves, for the first six months in patients after placement of intracardiac or intravascular prosthetic material, and in patients with a previous history of endocarditis (Wilson, et al., 2007a). If endocarditis prophylaxis is prescribed for patients with chronic RHD who already receive regular secondary prophylaxis, oral flora should be assumed to be relatively penicillin/amoxicillin resistant and alternative therapies such as clindamycin, azithromycin, or clarithromycin should be utilized. Good oral hygiene should be emphasized for all patients with chronic RHD to decrease the lifetime risk of infective endocarditis (Wilson, et al., 2007a).

Atrial Fibrillation

Patients with mitral stenosis are at the greatest risk for developing atrial fibrillation, though it is also seen in patients with severe mitral regurgitation and significant left atrial dilation. Among patients with mitral stenosis, risk factors for development of atrial fibrillation include older age, higher right atrial pressure, and lower left ventricular ejection fraction (Pourafkari, Ghaffari, Bancroft, Tajlil, & Nader, 2015). Atrial fibrillation can initially present as episodic, but often becomes persistent as valvular disease progresses. Patients with rheumatic mitral and aortic disease have limited cardiovascular reserves, and the combination of decreased atrial contribution to cardiac output (up to one-third) and decreased ventricular filling time secondary to rapid ventricular rate may be poorly tolerated. Additionally, atrial fibrillation, even the transient sub-clinical form (Karthikevan, et al.,

2014), increases the risk of systemic embolism and requires anticoagulation to prevent thromboembolic events (Nishimura, et al., 2014).

Surgical and Catheter-Based Treatment of Chronic Rheumatic Heart Disease

As noted above, the primary indications for surgical or catheter-based intervention in chronic RHD are the development of cardiovascular symptoms and/or decreased left ventricular function. Additionally, if a patient with multivalvular disease meets the criteria for intervention on one valve, the team should consider concurrently addressing the other involved valves, even if the valves don't individually meet the criteria, in order to limit future additional surgeries (Nishimura, et al., 2014). The timing of surgery in children, especially asymptomatic children, is particularly challenging, as chronic RHD often exhibits a lifetime of progression, and the risk of recurrent ARF is highest during youth. Absent specific guidelines for children, most clinicians extrapolate from the adult guidelines (Nishimura, et al., 2014). Decisions on the type of surgical intervention and on surgery vs. catheter intervention are complex and cannot be covered here in full. More complete recommendations were published by the American Heart Association and American College of Cardiology in 2014 and should be consulted prior to making these decisions (Nishimura, et al., 2014).

Mitral Valve Repair vs. Mitral Valve Replacement

When a good result can be achieved, mitral valve repair is preferable to mitral valve replacement, particularly in children (Wang, Zhou, Gu, Zheng, & Hu, 2013). Techniques to repair the mitral valve include classical approaches such as thinning of the anterior mitral leaflet, commisuroplasty, and mitral annuloplasty (Talwar, Rajesh, Subramanian, Saxena, & Kumar, 2005a; Kitamura, Uemura, Kunitomo, Utoh, & Noji, 2000; Chauvaud, et al., 1986; Rumel, Vaughn, & Guibone, 1969), as well as newer techniques such as tricuspid autografts, neo-chordae, and pericardial patches (El Oumeiri, et al., 2009; Pomerantzeff, et al., 2009). A 2013 meta-analysis that compared mitral valve repair to mitral valve replacement found lower early and late mortality and fewer major adverse events in patients undergoing mitral valve repair. As compared to replacement, repair avoids the need for anticoagulation, and a decrease in hemorrhage and thromboembolic complications contributed to the reduction in risk. However, patients undergoing repair showed a higher rate of re-operation (Wang, Zhou, Gu, Zheng, & Hu, 2013). In most populations, the authors concluded that repair should be favored over replacement, though they have still accepted the potential need for re-operation (Wang, Zhou, Gu, Zheng, & Hu, 2013). However, in resource-limited settings (particularly those without self-sustained cardiovascular surgery programs), operative decisions need to account both for the risks of anticoagulation (which favors repair or the use of bioprosthetic valves) and the feasibility of re-operation (which favors replacement).

Surgical Mitral Valvotomy vs. Catheter-based Valvotomy

In selected patients and in the hands of a skilled operator, percutaneous mitral balloon valvotomy shows comparable results to open mitral commissurotomy, with high success rates. Percutaneous intervention is also highly effective in juvenile rheumatic mitral stenosis, and when possible, should be attempted as the primary procedure (Karur, Veerappa, & Nanjappa, 2014). Selection of patients with favorable mitral valves predicts success. Patients that are most likely to have immediate and lasting improvement have valves that are non-calcified, relatively mobile, and that lack severe leaflet thickening or subvalvular pathology (Wilkins, Weyman, Abascal, Block, & Palacios, 1988). Pre-existing left atrial thrombus and/or significant mitral regurgitation are relative contraindications to a percutaneous approach (Nishimura, et al., 2014). Current practice favors earlier intervention in patients who meet criteria for percutaneous intervention, with practitioners waiting longer to intervene if a surgical approach is needed (Nishimura, et al., 2014; Carabello, 2005).

Management of RHD during Pregnancy

Another aspect of management for RHD occurs during pregnancy, due to its associated increase in cardiac output. By monitoring pregnant women with RHD, healthcare providers can ensure that the extra cardiac output

during pregnancy does not lead to heart damage or failure in RHD patients—especially since in some cases, the presence or severity of RHD may only become apparent during pregnancy, and as a result, secondary prophylaxis would not have been previously administered (Sawhney, et al., 2003). This management involves careful family planning through use of contraceptives, education about the risks of pregnancy, and the use of an anticoagulant that ensures both maternal and fetal safety.

Prevention of ARF and RHD

Group A Streptococcus, Acute Rheumatic Fever, and Rheumatic Heart Disease

Streptococcus pyogenes, also known as group A Streptococcus, is a Gram-positive bacterial pathogen responsible for a range of human diseases (Walker, et al., 2014). Superficial *S. pyogenes* infections, such as pharyngitis and impetigo, do not require long-term care. Nevertheless, these diseases are significant due to their prevalence and the required use of antibiotics for treatment that may be scarce in low-resource settings. Furthermore, superficial infections can lead to serious invasive diseases, including toxic shock, necrotizing fasciitis, and cellulitis (Moreland, et al., 2014). *S. pyogenes* infections can also lead to post-infectious, immune-mediated sequelae, which require costly, long-term treatment.

The most significant sequelae to *S. pyogenes* infection are ARF and RHD, and there are many strategies available to prevent these diseases. The challenge is to ensure that they are available in all settings, including resource-constrained environments, and that novel strategies are explored to help eliminate or eradicate ARF and RHD.

Primordial Prevention

Primordial prevention for ARF refers to the reduction of risk factors for *S. pyogenes* exposure and infection in susceptible individuals, given that these factors and infections would normally precede ARF (ARF/RHD Writing Group, 2012). While often underemphasized, primordial prevention is the major explanation for the control of ARF and RHD that occurred in affluent settings during the 20th century (Gordis, 1985). Figure 3 demonstrates that the major reduction in RF deaths in the USA occurred prior to the availability of antibiotics—these reductions can be attributed to improved living conditions and reductions in poverty (Gordis, 1985).

One poverty-associated risk factor for *S. pyogenes* infection is household crowding (Maguire, Carapetis, Walsh, & Brown, 2012; Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Sub-Committee of the Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, 1965; Gordis, Lilienfeld, & Rodriguez, 1969). The effects of overcrowding were analysed in a study showing that when beds were moved closer to one another in military barracks, rates of *S. pyogenes* infection increased (Wannamaker, 1954). Another study in Australia found a strong association between overcrowded housing in Aboriginal communities and rates of streptococcal impetigo (McDonald, et al., 2006). The association is highly plausible because crowding allows for rapid *S. pyogenes* bacterial transmission. Thus, the improvement of housing is crucial to preventing the spread of *S. pyogenes* infections.

Another potential risk factor for *S. pyogenes* infection is poor nutrition in childhood (Steer, Carapetis, Nolan, & Shann, 2002). While this factor may merely be correlated with overcrowded housing, rather than being solely responsible for *S. pyogenes* infection susceptibility, insufficient nutrition can alter antibody responses, with evidence that poorly-nourished individuals may be more likely to develop ARF subsequent an *S. pyogenes* infection (Steer, Carapetis, Nolan, & Shann, 2002). Overall, risk factors resulting from poverty are associated with high rates of ARF and RHD, making it crucial to tackle these factors and avoid the requirement for expensive treatments and reductions in the quality of life once individuals have already contracted *S. pyogenes* infections, ARF, and RHD.

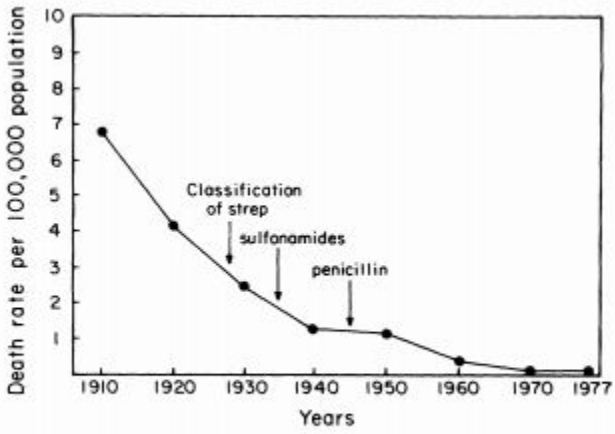

FIGURE 7. Crude death rates from rheumatic fever, United States, 1910–1977.

Figure 3. Crude death rates from rheumatic fever in the USA, 1910–1977. Figure reproduced from (Gordis, 1985) with permission.

Primary Prevention

While primordial prevention addresses the socioeconomic risk factors for *S. pyogenes* infection, primary prevention serves to prevent *S. pyogenes* colonization, infection, and transmission, as well as preventing the spread of *S. pyogenes* infections (ARF/RHD Writing Group, 2012).

The most desirable primary prevention method is vaccination against the *S. pyogenes* bacterium, which would prevent *S. pyogenes* colonization and infection, and thus prevent post-infectious sequelae, such as ARF and RHD (Sheel, Moreland, Fraser, & Carapetis, 2016). Based on the range of diseases caused by *S. pyogenes* that include superficial, invasive infections to post-infectious sequelae, a vaccine against *S. pyogenes* could effectively prevent all of these *S. pyogenes*-mediated diseases (Sheel, Moreland, Fraser, & Carapetis, 2016). However, few pharmaceutical companies have shown interest in developing an *S. pyogenes* vaccine until recently. This may be partially due to antibiotics being readily available to treat *S. pyogenes* pharyngitis in wealthy areas, which makes a vaccine potentially unnecessary. Until an effective, globally-relevant *S. pyogenes* vaccine reaches the market, other methods must be relied upon to prevent the development of invasive infection and post-infectious sequelae upon *S. pyogenes* infection.

The current mainstay of primary prevention of ARF and RHD is the administration of antibiotics for *S. pyogenes* pharyngitis (ARF/RHD Writing Group, 2012), which eliminates bacteria before they can trigger an autoimmune response. To treat pharyngitis and prevent ARF, healthcare providers may administer one dose of intramuscular BPG or a ten-day course of oral penicillin or amoxicillin, commencing within nine days of the onset of the *S. pyogenes* infection (Bass, Crast, Knowles, & Onufer, 1976; Lennon, Farrell, Martin, & Stewart, 2008; Clegg, et al., 2006; Robertson, Volmink, & Mayosi, 2005). This is known as primary prophylaxis.

There are two main strategies to the implementation of primary prophylaxis. The first involves the incorporation of primary prevention efforts, such as administering antibiotics following *S. pyogenes* infection, into primary health care delivery efforts, while another strategy could involve a systematic surveillance approach for identifying and treating *S. pyogenes* throat infections at the community level. In almost all settings, the more practical strategy would be the implementation of primary prophylaxis into primary care delivery efforts; however, in resource-poor settings, various challenges (such as poor health seeking behaviors in those who may have a sore throat), the logistics, cost, limited supply, availability and timely delivery of BPG may hinder this approach (Karthikeyan & Mayosi, 2009). For effective primary prophylaxis intervention, individuals with sore throats must present for health care; health staff must have awareness, the appropriate training and resources to

diagnose and treat *S. pyogenes* pharyngitis; and finally, the treatment must be delivered and the treatment schedule followed. Very few resource-poor countries are capable of providing these key elements in their entirety, in addition to the added cost and limited feasibility of obtaining a bacteriological diagnosis, leaving the diagnosis of *S. pyogenes* pharyngitis using imperfect clinical algorithms as the only practical option.

However, even under ideal circumstances, primary prophylaxis may potentially prevent a minority of ARF cases, since many ARF episodes do not follow a significant sore throat, with outbreaks of ARF documented over the past decades in Utah (Veasy, et al., 1987), Columbus (Hosier, Craenen, Teske, & Wheller, 1987), Ohio (Congeni, Rizzo, Congeni, & Sreenivasan, 1987), and Pennsylvania (Wald, Dashefsky, Feidt, Chiponis, & Byers, 1987). Although the cause of these particular outbreaks remains unknown and they affected mainly mid-socioeconomic family groups, there is a possibility that they may have been related to particularly virulent bacterial strains or other factors.

Discouraging as this may be, primary prophylaxis remains an important step for preventing new episodes of ARF and the subsequent development of RHD. Encouraging sore throat presentations along with the correct diagnosis and appropriate treatment of *S. pyogenes* infections remains a significant means of preventing new episodes of ARF; however, this may have a minimal impact on the incidence of ARF at the population level (Carapetis, 2010).

An alternative strategy that could be undertaken is active surveillance of at-risk children in an effort to diagnose and appropriately treat *S. pyogenes* pharyngitis. This has been attempted in different ways, although the more common approach is through the utilization of a school-based sore throat surveillance system (Lennon, Stewart, Farrell, Palmer, & Mason, 2009). The only rigorous study of this approach was a large randomized trial conducted in New Zealand that found a 22–28% non-significant reduction in ARF incidence in schools with sore-throat clinics (Lennon, Stewart, Farrell, Palmer, & Mason, 2009). Despite the lack of statistical significance found in this study, New Zealand has since embarked on a large implementation of school-based sore throat surveillance and treatment, combined with a number of other strategies to try to reduce the incidence of ARF. An interim evaluation found evidence of a significant reduction in ARF incidence that was confined to the region of the country with the highest incidence rate, but was not directly attributable to the sore throat clinics in schools (Jack, et al., 2015). Moreover, the approach that was undertaken in New Zealand was costly and expensive, and unlikely to be affordable in the vast majority of countries with a high incidence of ARF. At this stage, active sore throat surveillance and treatment remains a costly exercise and may not be routinely recommended.

There is some evidence that skin infection may play a role in the pathogenesis of ARF (Williamson, et al., 2015), which raises the prospect that control of skin infections may lead to subsequent reductions in ARF incidence. There is also considerable momentum currently in Australia around community-based interventions to control skin infections and underlying scabies (Andrews, McCarthy, Carapetis, & Currie, 2009; Steer, et al., 2016) but the potential for this to be a form of primary prevention for RF and RHD remains unproven. While primary prevention measures are necessary to ensure that *S. pyogenes* throat or possibly skin infections do not lead to ARF, the challenge remains for the implementation of these available strategies in resource-constrained settings. The development of a *S. pyogenes* vaccine would greatly facilitate primary prevention in these areas.

Secondary Prevention

The goal of secondary prevention of ARF and RHD (otherwise known as secondary prophylaxis), is to prevent recurrence of *S. pyogenes* infection in those previously diagnosed with ARF (Wyber, et al., 2014). The most effective approach to secondary prophylaxis involves the use of benzathine penicillin G (BPG), the long-acting depot form of penicillin G (Medsafe, 2012; Stollerman & Rusoff, 1952; Stollerman, Markowitz, Taranta, Wannamaker, & Whittemore, 1965). Once BPG is intramuscularly injected, the drug is slowly released from the muscle into the systemic circulation, where it is activated via *in-vivo* hydrolysis, and produces prolonged serum

concentrations of benzylpenicillin (Medsafe, 2012). This prolonged release BPG formulation is vital for the treatment and prevention of ARF and RHD, where serum concentrations of benzylpenicillin are expected to remain at or above 0.02 μg/ml, the accepted minimum inhibitory concentration (MIC) for preventing *S. pyogenes* colonization and preventing ARF recurrences (Gutmann & Tomasz, 1982; Currie B. , 2006; Medsafe, 2012).

The use of oral penicillin V is an alternative regimen, but even with 100% adherence, it is not as protective against recurrent *S. pyogenes* infection or ARF as BPG (Manyemba & Mayosi, 2003). Most patients who report an allergy to penicillin may not necessarily have experienced an allergic reaction to the drug, but since penicillin is the drug of choice for secondary prophylaxis, it is recommended that a thorough assessment of possible penicillin hypersensitivity be conducted before accepting that an ARF or RHD patient cannot receive penicillin prophylaxis. In these rare circumstances, the American Heart Association recommends sulfadiazine or sulfasoxazole, or an oral macrolide or azalide as a suitable alternative (Gerber, et al., 2009).

To maintain protective serum concentrations, the recommended regimen for secondary prophylaxis requires the injection of 1.2 million units of BPG once every four weeks for a minimum of 10 years, and in some cases, even for a lifetime (Wyber, et al., 2014). While current protocols for secondary prophylaxis suggest four-weekly BPG injections, pharmacokinetic studies show that serum penicillin G levels may be below the minimum inhibitory concentration (MIC) detection level of 0.02 μg/ml for *S. pyogenes* by 10–21 days after injection (Broderick, et al., 2011; Neely, Kaplan, Blumer, Faix, & Broderick, 2014). More frequent BPG dosing has been suggested (Broderick, et al., 2011; Neely, Kaplan, Blumer, Faix, & Broderick, 2014); however, adherence to such intensive injection schedules may be problematic. Despite the low serum penicillin G levels, current evidence suggests that dosing BPG every 28 days can prevent recurrences of ARF (ARF/RHD Writing Group, 2012). Therefore, the World Heart Federation recommends BPG injections every four weeks for those on secondary prophylaxis, unless the patient has a history of breakthrough ARF recurrence on prophylaxis or lives in a particularly high-risk setting. While more frequent administration may offer better protection, the recommendation for BPG injection every four weeks is also influenced by patient acceptability, adherence rates, logistical barriers, and costs involved with the delivery of secondary prophylaxis, as well as the supply of high quality penicillin. In New Zealand, where dosing once every four weeks has long been the standard of care, the recurrence rates of ARF remain low (Pennock, et al., 2014; Robin, Mills, Tuck, & Lennon, 2013; Siriett, Crengle, Lennon, Stonehouse, & Cramp, 2012; Spinetto, Lennon, & Horsburgh, 2011).

Even with the use of injections every four weeks, rather than more frequent BPG administration schedules, patient adherence to secondary prophylaxis is often low (Gasse, et al., 2013). While adherence to as few as 80% of BPG doses can significantly lower a patient's chances of contracting an *S. pyogenes* infection, in some regions with high rates of RHD, nearly half of all patients fail to meet this threshold (Spinetto, Lennon, & Horsburgh, 2011). Moreover, it is suspected that in low socioeconomic populations of many countries, access to and availability of BPG is so problematic that most ARF and RHD patients receive no secondary prophylaxis at all.

There are many community-specific barriers for the adherence of BPG secondary prophylaxis schedules, which can include poor healthcare delivery, a lack of relationships with local healthcare providers, limited availability of transportation, and fear of anaphylaxis (Gasse, et al., 2013; Huck, et al., 2015; Musoke, et al., 2013; Tullu, Gandhi, & Ghildiyal, 2010; Stewart, McDonald, & Currie, 2007). These barriers must be addressed by tailoring implementation of secondary prophylaxis to the needs of those receiving treatment. There are also secondary prophylaxis adherence barriers that are shared across ARF and RHD patients, which could potentially be addressed through BPG reformulation. One significant example that is responsible for lack of patient adherence to secondary prophylaxis is the frequency of injections. This is particularly problematic in remote and low-resource areas, where patients may not be able to access clinics every four weeks (Mincham, Toussaint, Mak, & Plant, 2003; Huck, et al., 2015). The pain associated with the monthly BPG intramuscular injections is also

another significant factor, as children in particular often comment on the pain they experience when receiving their injections (Gasse, et al., 2013; Stewart, McDonald, & Currie, 2007; Huck, et al., 2015).

Difficulties with the administration of BPG injections are exacerbated by the use of a powdered BPG formulation, which often crystallizes and causes needle blockage after resuspension in diluent (Public Health Agency of Canada, 2013). The alternate, premixed formulation of BPG requires refrigeration and is very expensive, making it impractical for use in remote locations (Currie B. , 2006). Therefore, the pain and inconvenience of secondary prophylaxis remains inevitable whenever the premixed formulation of BPG cannot be used.

There are also concerns that even those who adhere to treatment schedules may not be receiving high-quality BPG (Wyber, Taubert, Marko, & Kaplan, 2013). The issue of needle-blockage has raised concerns about the quality of BPG, since it is unclear whether this problem is caused by the active ingredient or by contaminants and by-products, which may also cause allergic reactions and anaphylaxis. Furthermore, concerns have also been raised as to whether available formulations of BPG contain enough of the active ingredient to protect patients for the expected drug-release period (Currie, 1996; Currie, Burt, & Kaplan, 1994; Lue, Wu, Hsieh, Lin, Hsieh, & Chiou, 1986; Lue, Wu, Wang, Wu, & Wu, 1994; Lue, Wu, Wang, Wu, & Wu, 1996; Broderick, Hansen, Russell, Kaplan, Blumer, & Faix, 2011). Limited global data are available on the quality of BPG, and there are few quality control guidelines in place for BPG manufacturing (Wyber, Taubert, Marko, & Kaplan, 2013). Thus, secondary prophylaxis patients may not be receiving high-quality BPG, which increases their risk of contracting *S. pyogenes* infections. In the long term, concerns regarding BPG quality and low secondary prophylaxis adherence must be addressed through the development of a safe, effective and less painful BPG reformulation that supports adherence. The preferred characteristics of a long-acting BPG reformulation that could improve adherence to secondary prophylaxis schedules were recently published (Wyber, et al., 2016). These characteristics included a BPG reformulation that was less painful and featured an extended dose interval, therefore reducing dose frequency, was heat stable, and is cheaper than currently available products (Wyber, et al., 2016). Secondary prophylaxis for ARF and RHD is crucial in preventing cardiac damage in patients, often children, with a history of ARF. Thus, it is important to improve the delivery and effectiveness of secondary prophylaxis.

Tertiary Prevention

Tertiary prevention refers to the provision of medical and surgical interventions to prevent morbidity and mortality from cardiac damage that has resulted from ARF (ARF/RHD Writing Group, 2012; World Health Organization). These interventions include management of heart failure, anticoagulation, arrhythmia, prevention of endocarditis and pregnancy-related complications, along with surgical interventions (Remenyi, Carapetis, Wyber, Taubert, & Mayosi, 2013a)—these are covered in previous sections.

Tools for the Prevention of ARF and RHD: Register-Based Control of RHD

The purpose of a register-based approach to RHD control is to improve the delivery of secondary prophylaxis by keeping track of those who are receiving treatment (Carapetis & Zühlke, Global research priorities in rheumatic fever and rheumatic heart disease, 2011). The use of registers as a tool to improve delivery of secondary prevention for ARF and RHD was first established across the USA in the 1950s, and while the significant decreased prevalence of ARF and RHD in the USA cannot be solely attributed to these programs, the register-based approach is still considered to be an effective tool (McDonald, Brown, Noonan, & Carapetis, 2005). Due to the success of registers in the USA, the WHO launched a register for ARF and RHD control in 1972 (McDonald, Brown, Noonan, & Carapetis, 2005). These WHO-coordinated registers were established in various locations, and while the use of these registers differed based on location, the proportion of individuals receiving ten or more doses of BPG per year increased for patients on the register (Strasser, et al., 1981). This study revealed that

a register-based approach could significantly improve the delivery of secondary prophylaxis, though the registers in this study did have lower coverage rates (McDonald, Brown, Noonan, & Carapetis, 2005).

The WHO-coordinated registers were replaced in 1990 with a global program that helped establish registers in 16 countries, but funding for this program ended in 2001 (Thornley, McNicholas, Baker, & Lennon, 2001). Since then, few countries have been able to establish significant regional or national registers.

It is important to distinguish between a register, which is a database used to monitor and improve patient care, and a control program, which may use a register as its core data collection tool, but which also incorporates broader strategies around patient care, disease control, and education. The most successful RHD control programs currently in use are based in New Zealand and Australia (Thornley, McNicholas, Baker, & Lennon, 2001). The New Zealand approach includes management and surveillance programs, where management programs coordinate delivery of secondary prophylaxis through nursing services, while surveillance programs keep track of those receiving prophylaxis without providing the treatment themselves (Thornley, McNicholas, Baker, & Lennon, 2001). Overall, these two types of registers are effective because they both help track RHD prevalence and centralize treatment delivery (Thornley, McNicholas, Baker, & Lennon, 2001). Overall, a register-based approach may help ensure consistent delivery of secondary prophylaxis as well as medical and surgical care to ARF and RHD patients, which will help lower the recurrence of ARF and morbidity and mortality from RHD. This approach can help prevent cardiac damage, which is costly and detracts from patients' quality of life.

Conclusion

The progression of RHD, beginning with *S. pyogenes* infection and continuing through ARF and subsequent cardiac valve damage, offers many opportunities for the prevention of "the next step" in disease prognosis. Thus, it is important to ensure that areas with high rates of ARF and RHD have adequate resources for all of these stages of prevention. These include programs to improve housing and sanitation, antibiotics to treat *S. pyogenes* infection and an *S. pyogenes* vaccine (once developed), a stable supply of high-quality BPG for those diagnosed with ARF, and access to appropriate medical and surgical treatments to treat cardiac damage.

These strategies are not equally effective in preventing ARF and RHD, nor have they been assigned equal focus. While efforts have been directed towards improving access to secondary prophylaxis, fewer resources have been dedicated to preventing the initial attack of ARF through vaccine development, and even more fundamentally, through the improvement of housing and sanitation in resource-poor areas. While it is crucial to improve the delivery of secondary prophylaxis by ensuring that BPG is available and that dosing strategies are effective in those receiving this treatment, and while secondary prophylaxis has been determined to be cost-effective, this does not mean efforts should only be directed at this prevention effort (Steer & Carapetis, 2009). While cardiac surgery would ideally be made accessible to those who have been impacted by RHD, this strategy is costly and may not necessarily ensure a high quality of life for those affected. It is crucial that investment also be directed at primordial and primary prevention of *S. pyogenes* infection; for, as observed through the rarity of ARF and RHD in wealthy communities, the prevention and treatment of initial infection through less crowded housing, vaccination, and the treatment of *S. pyogenes* pharyngitis (and possibly skin infection), can prevent ARF and RHD (Steer & Carapetis, Prevention and treatment of rheumatic heart disease in the developing world, 2009). Secondary and tertiary prevention strategies certainly prevent cardiac damage and death from ARF and RHD, but primordial and primary prevention strategies can prevent the onset of these conditions in the first place, which will ultimately help eliminate (or ideally, eradicate) ARF and RHD.

Vaccine Development

The Development of a Vaccine for *Streptococcus pyogenes*

Please refer to the following chapter article in this series:

Ferretti, J. J., Stevens, D. L., & Fischetti, V. A. (2016). Current Approaches to Group A Streptococcal Vaccine Development--Streptococcus pyogenes: Basic Biology to Clinical Manifestations.

The CANVAS Initiative to Facilitate *S. pyogenes* Vaccine Development

To make a safe and effective *S. pyogenes* vaccine available for use, vaccine development efforts must be complemented by projects that facilitate the development and distribution of this vaccine. One such project is the trans-Tasman CANVAS (Coalition to Advance New Vaccines for Group A *Streptococcus*) initiative, which offers three deliverables to accelerate *S. pyogenes* vaccine development (Steer, et al., 2016). One deliverable is an economic evaluation, which will help determine whether investment in a *S. pyogenes* vaccine is economically viable (Steer, et al., 2016). Based on the high costs of treatment for *S. pyogenes*-mediated diseases such as ARF and RHD, it is likely that vaccination against *S. pyogenes* will be cost-effective, particularly in developing nations with high rates of ARF and RHD (Steer & Carapetis, 2009; Steer, et al., 2016). Furthermore, pharmaceutical companies, including Merck and GSK, as well as governmental organizations have supported *S. pyogenes* vaccine development in the past (Steer, et al., 2016). Overall, while a rigorous economic evaluation of a potential *S. pyogenes* vaccine has yet to be published, it is likely that the development of a *S. pyogenes* vaccine will be economically efficient, due to the high duration of treatment for *S. pyogenes*-mediated diseases, such as ARF and RHD, and the loss of productivity that is due to the severity of these diseases (Sheel, Moreland, Fraser, & Carapetis, 2016).

The CANVAS initiative seeks to create a panel composed of a selection of the most common strains of *S. pyogenes*, which would help determine which strains should be covered by a vaccine. Current vaccine candidates will be tested against this panel (Sheel, Moreland, Fraser, & Carapetis, 2016). These CANVAS initiative projects aim to facilitate the rapid development and availability of a *S. pyogenes* vaccine.

Conclusions

The need for a vaccine against *S. pyogenes* is evident, given the high rates of *S. pyogenes* infection globally and the severity of some *S. pyogenes*-mediated diseases, particularly in low-resource areas. Unfortunately, efforts to develop a *S. pyogenes* vaccine have been hindered by safety concerns and by lingering perceptions that *S. pyogenes* infections are harmless or easily treatable, since invasive infections and post-infectious sequelae are rare in wealthy regions, which are where vaccine development will likely take place. The development of a safe and effective vaccine against *S. pyogenes* will help prevent severe diseases that often affect children, and will improve the quality of life for individuals susceptible to *S. pyogenes* infections, particularly in developing countries and in indigenous populations in wealthy nations.

References

Abernethy M., Bass N., Sharpe N., Grant C., Neutze J., Clarkson P., et al. Doppler echocardiography and the early diagnosis of carditis in acute rheumatic fever. Australian and New Zealand Journal of Medicine. 1994;24(5):530–535. PubMed PMID: 7848157.

al Kasab S., al Fagih M. R., Shahid M., Habbab M., al Zaibag M. Valve surgery in acute rheumatic heart disease. One- to four-year follow-up. Chest. 1988;94(4):830–833. PubMed PMID: 3168577.

al-Eissa A. Sydenham's chorea: a new look at an old disease. The British Journal of Clinical Practice. 1993;47(1):14–16. PubMed PMID: 8461241.

Anastasiou-Nana M. I., Anderson J. L., Carlquist J. F., Nanas J. N. HLA-DR typing and lymphocyte subset evaluation in rheumatic heart disease: a search for immune response factors. American Heart Journal. 1986;112(5):992–997. PubMed PMID: 3490780.

Andrews R. M., McCarthy J., Carapetis J. R., Currie B. J. Skin disorders, including pyoderma, scabies, and tinea infections. Pediatric Clinics of North America. 2009;56(6):1421–1440. PubMed PMID: 19962029.

Antonini-Canterin F., Leiballi E., Enache R., Popescu B. A., Roşca M., Cervesato E., et al. Hydroxymethylglutaryl coenzyme-a reductase inhibitors delay the progression of rheumatic aortic valve stenosis a long-term echocardiographic study. Journal of the American College of Cardiology. 2009;53(20):1874–1879. PubMed PMID: 19442887.

Antonini-Canterin F., Moura L. M., Enache R., Leiballi E., Pavan D., Piazza R., et al. Effect of hydroxymethylglutaryl coenzyme-a reductase inhibitors on the long-term progression of rheumatic mitral valve disease. Circulation. 2010;121(19):2130–2136. PubMed PMID: 20439789.

Anwar A. M., Attia W. M., Nosir Y. F., Soliman O. L., Mosad M. A., Othman M., et al. Validation of a new score for the assessment of mitral stenosis using real-time three-dimensional echocardiography. Journal of the American Society of Echocardiography. 2010;23(1):13–22. PubMed PMID: 19926444.

ARF/RHD Writing Group. (2012). *The Australian guideline for prevention, diagnosis, and management of acute rheumatic fever and rheumatic heart disease (2nd edition)*. Darwin: Menzies School of Health Research.

Asbahr F. R., Negrão A. B., Gentil V., Zanetta D. M., da Paz J. A., Marques-Dias M. J., et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. The American Journal of Psychiatry. 1998;155(8):1122–1124. PubMed PMID: 9699708.

Ash R. The first ten years of rheumatic infection in childhood. American Heart Journal. 1948;36(1):89–97. PubMed PMID: 18860032.

Atalay S., Uçar T., Ozçelik N., Ekici F., Tutar E. Echocardiographic evaluation of mitral valve in patients with pure rheumatic mitral regurgitation. The Turkish Journal of Pediatrics. 2007;49(2):148–153. PubMed PMID: 17907513.

Ayoub E. M., Barrett D. J., Maclaren N. K., Krischer J. P. Association of class II human histocompatibility leukocyte antigens with rheumatic fever. The Journal of Clinical Investigation. 1986;77(6):2019–2026. PubMed PMID: 3486889.

Barash J., Margalith D., Matitiau A. Corticosteroid treatment in patients with Sydenham's chorea. Pediatric Neurology. 2005;32(3):205–207. PubMed PMID: 15730904.

Bass J. W., Crast F. W., Knowles C. R., Onufer C. N. Streptococcal pharyngitis in children. A comparison of four treatment schedules with intramuscular penicillin G benzathine. JAMA. 1976;235(11):1112–1116. PubMed PMID: 765515.

Beaton A., Lu J. C., Aliku T., Dean P., Gaur L., Weinberg J., et al. The utility of handheld echocardiography for early rheumatic heart disease diagnosis: a field study. European Heart Journal Cardiovascular Imaging. 2015;16(5):475–482. PubMed PMID: 25564396.

Beaton A., Okello E., Aliku T., Lubega S., Lwabi P., Mondo C., et al. Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection. Pediatric Cardiology. 2014;35(7):1259–1267. PubMed PMID: 24827080.

Beniwal R., Bhaya M., Panwar R. B., Panwar S., Singh A. Diagnostic criteria in rheumatic heart disease. Global Heart. 2015;10(1):81–82. PubMed PMID: 25754572.

Bernal J. M., Fernández-Vals M., Rabasa J. M., Gutiérrez-García F., Morales C., Revuelta J. M. Repair of nonsevere rheumatic aortic valve disease during other valvular procedures: is it safe? The Journal of Thoracic and Cardiovascular Surgery. 1998;115(5):1130–1135. PubMed PMID: 9605083.

Bhaya M., Beniwal R., Panwar S., Panwar R. B. Two years of follow-up validates the echocardiographic criteria for the diagnosis and screening of rheumatic heart disease in asymptomatic populations. Echocardiography. 2011;28(9):929–933. PubMed PMID: 21854437.

Bishop W., Currie B., Carapetis J., Kilburn C. A subtle presentation of acute rheumatic fever in remote northern Australia. Australian and New Zealand Journal of Medicine. 1996;26(2):214–242. PubMed PMID: 8744631.

Bland E. F., Duckett Jones T. Rheumatic fever and rheumatic heart disease; a twenty year report on 1000 patients followed since childhood. Circulation. 1951;4(6):836–843. PubMed PMID: 14879491.

Bland E. F., Jones T. D. The Natural History of Rheumatic Fever and Rheumatic Heart Disease. Transactions of the American Clinical and Climatological Association. 1936;52:85–87. PubMed PMID: 21407521.

Borer J. S., Bonow R. O. Contemporary approach to aortic and mitral regurgitation. Circulation. 2003;108:2432–2438. PubMed PMID: 14623790.

Bozbuga N., Erentug V., Kirali K., Akinci E., Isik O., Yakut C. Midterm results of aortic valve repair with the pericardial cusp extension technique in rheumatic valve disease. The Annals of Thoracic Surgery. 2004;77(4):1272–1276. PubMed PMID: 15063250.

Brimberg L., Benhar I., Mascaro-Blanco A., Alvarez K., Lotan D., Winter C., et al. Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders. Neuropsychopharmacology. 2012;37(9):2076–2087. PubMed PMID: 22534626.

Broderick M. P., Hansen C. J., Russell K. L., Kaplan E. L., Blumer J. L., Faix D. J. Serum Penicillin G Levels Are Lower Than Expected in Adults within Two Weeks of Administration of 1.2 Million Units. PLoS One. 2011;6(10):e25308. PubMed PMID: 21991307.

Bryant P. A., Robins-Browne R., Carapetis J. R., Curtis N. Some of the people, some of the time: susceptibility to acute rheumatic fever. Circulation. 2009;119(5):742–753. PubMed PMID: 19204317.

Bywaters E. G., Thomas G. T. Bed rest, salicylates and steroid in rheumatic fever. British Medical Journal. 1961;1(5240):1628–1634. PubMed PMID: 13689614.

Câmara E. J., Neubauer C., Câmara G. F., Lopes A. A. Mechanisms of mitral valvar insufficiency in children and adolescents with severe rheumatic heart disease: an echocardiographic study with clinical and epidemiological correlations. Cardiology in the Young. 2004;14(5):527–532. PubMed PMID: 15680075.

Cann M. P., Sive A. A., Norton R. E., McBride W. J., Ketheesan N. Clinical presentation of rheumatic fever in an endemic area. Archives of Disease in Childhood. 2010;95(6):455–457. PubMed PMID: 19880393.

Carabello B. A. Modern management of mitral stenosis. Circulation. 2005;112(3):432–437. PubMed PMID: 16027271.

Carapetis J. R. Rheumatic Heart Disease in Developing Countries. The New England Journal of Medicine. 2007;357:439–441. PubMed PMID: 17671252.

Carapetis J. R. Letter by Carapetis regarding article, "Is primary prevention of rheumatic fever the missing link in the control of rheumatic heart disease in Africa? Circulation. 2010;121(15):e384. PubMed PMID: 20404265.

Carapetis J. R., Currie B. J. Mortality due to acute rheumatic fever and rheumatic heart disease in the Northern Territory: a preventable cause of death in aboriginal people. Australian and New Zealand Journal of Public Health. 1999;23(2):159–163. PubMed PMID: 10330730.

Carapetis J. R., Currie B. J. Rheumatic fever in a high incidence population: the importance of monoarthritis and low grade fever. Archives of Disease in Childhood. 2001;85:223–227. PubMed PMID: 11517105.

Carapetis J. R., Zühlke L. J. Global research priorities in rheumatic fever and rheumatic heart disease. Annals of Pediatric Cardiology. 2011;4(1):4–12. PubMed PMID: 21677798.

Carapetis J. R., Beaton A., Cunningham M. W., Guilherme L., Karthikeyan G., Mayosi B. M., et al. Acute rheumatic fever and rheumatic heart disease. Nature Reviews Disease Primers. 2016;2:15084. PubMed PMID: 27188830.

Carapetis J. R., Currie B. J., Mathews J. D. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? Epidemiology and Infection. 2000;124(2):239–244. PubMed PMID: 10813149.

Carapetis J. R., Steer A. C., Mulholland E. K., Weber M. The global burden of group A streptococcal diseases. The Lancet Infectious Diseases. 2005;5(11):685–694. PubMed PMID: 16253886.

Cardoso, F., Maia, D., Cunningham, M. C., & Valença, G. (2003). Treatment of Sydenham chorea with corticosteroids. *Movement Disorders: official journal of the Movement Disorders society, 18*(11), 1374-1377.

Carlquist J. F., Ward R. H., Meyer K. J., Husebye D., Feolo M., Anderson J. L. Immune response factors in rheumatic heart disease: meta-analysis of HLA-DR associations and evaluation of additional class II alleles. Journal of the American College of Cardiology. 1995;26(2):452–457. PubMed PMID: 7608450.

Carpentier A. Cardiac valve surgery--the "French correction". The Journal of Thoracic and Cardiovascular Surgery. 1983;86(3):323–337. PubMed PMID: 6887954.

Carpentier A., Deloche A., Hanania G., Forman J., Sellier P., Piwnica A., et al. Surgical management of acquired tricuspid valve disease. The Journal of Thoracic and Cardiovascular Surgery. 1974;67(1):53–65. PubMed PMID: 4587627.

Chauvaud S., Fuzellier J.-F., Berrebi A., Deloche A., Fabiani J.-N., Carpentier A. Long-Term (29 Years) Results of Reconstructive Surgery in Rheumatic Mitral Valve Insufficiency. Circulation. 2001;104 Suppl 1:I12–I15. PubMed PMID: 11568022.

Chauvaud S., Perier P., Touati G., Relland J., Kara S. M., Benomar M., et al. Long-term results of valve repair in children with acquired mitral valve incompetence. Circulation. 1986;74(3 Pt 2):1104–1109. PubMed PMID: 3742766.

Cherian G. Acute rheumatic fever--the Jones criteria: a review and a case for polyarthralgia. The Journal of the Association of Physicians of India. 1979;27(5):453–457. PubMed PMID: 528500.

Chockalingam A., Gnanavelu G., Elangovan S., Chockalingam V. Clinical spectrum of chronic rheumatic heart disease in India. The Journal of Heart Valve Disease. 2003;12(5):577–581. PubMed PMID: 14565709.

Chopra P., Bhatia M. L. Chronic rheumatic heart disease in India: a reappraisal of pathologic changes. The Journal of Heart Valve Disease. 1992;1(1):92–101. PubMed PMID: 1341228.

Choudhary S. K., Mathur A., Sharma R., Saxena A., Chopra P., Roy R., et al. Pulmonary autograft: should it be used in young patients with rheumatic disease? The Journal of Thoracic and Cardiovascular Surgery. 1999;118(3):483–490discussion 490-491. PubMed PMID: 10469964.

Cilliers A. Treating acute rheumatic fever. BMJ. 2003;327(7416):631–632. PubMed PMID: 14500407.

Cilliers A. M., Manyemba J., Saloojee H. Anti-inflammatory treatment for carditis in acute rheumatic fever. The Cochrane Database of Systematic Reviews. 2003;2:CD003176. PubMed PMID: 12804454.

Clark B. C., Krishnan A., McCarter R., Scheel J., Sable C., Beaton A. Using a Low-Risk Population to Estimate the Specificity of the World Heart Federation Criteria for the Diagnosis of Rheumatic Heart Disease. Journal of the American Society of Echocardiography. 2016;29(3):253–258. PubMed PMID: 26725186.

Clegg H. W., Ryan A. G., Dallas S. D., Kaplan E. L., Johnson D. R., Norton H. J., et al. Treatment of streptococcal pharyngitis with once-daily compared with twice-daily amoxicillin: a noninferiority trial. The Pediatric Infectious Disease Journal. 2006;25(9):761–767. PubMed PMID: 16940830.

Cohen G. I., Duffy C. I., Klein A. L., Miller D. P., Cosgrove D. M., Stewart W. J. Color Doppler and two-dimensional echocardiographic determination of the mechanism of aortic regurgitation with surgical correlation. Journal of the American Society of Echocardiography. 1996;9(4):508–515. PubMed PMID: 8827634.

Colquhoun S. M., Kado J. H., Remenyi B., Wilson N. J., Carapetis J. R., Steer A. C. Echocardiographic screening in a resource poor setting: borderline rheumatic heart disease could be a normal variant. International Journal of Cardiology. 2014;173(2):284–289. PubMed PMID: 24655549.

Congeni B., Rizzo C., Congeni J., Sreenivasan V. V. Outbreak of acute rheumatic fever in northeast Ohio. The Journal of Pediatrics. 1987;111(2):176–179. PubMed PMID: 3302191.

Cowell S. J., Newby D. E., Prescott R. J., Bloomfield P., Reid J., Northridge D. B., et al. A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis. The New England Journal of Medicine. 2005;352:2389–2397. PubMed PMID: 15944423.

Cunningham M. W. Pathogenesis of group A streptococcal infections. Clinical Microbiology Reviews. 2000;13(3):470–511. PubMed PMID: 10885988.

Cunningham M. W., Antone S. M., Gulizia J. M., McManus B. M., Fischetti V. A., Gauntt C. J. Cytotoxic and viral neutralizing antibodies crossreact with streptococcal M protein, enteroviruses, and human cardiac myosin. Proceedings of the National Academy of Sciences of the United States of America. 1992;89(4):1320–1324. PubMed PMID: 1311095.

Cunningham M. W., McCormack J. M., Talaber L. R., Harley J. B., Ayoub E. M., Muneer R. S., et al. Human monoclonal antibodies reactive with antigens of the group A Streptococcus and human heart. Journal of Immunology. 1988;141(8):2760–2766. PubMed PMID: 3049816.

Currie B. Benzathine penicillin — down but not out. Northern Territory Disease Control Bulletin. 2006;13:1–3.

Currie B. J. Are the Currently Recommended Doses of Benzathine Penicillin G Adequate for Secondary Prophylaxis of Rheumatic Fever? Pediatrics. 1996;97(6):989–991. PubMed PMID: 8637788.

Currie B. J., Burt T., Kaplan E. L. Penicillin concentrations after increased doses of benzathine penicillin G for prevention of secondary rheumatic fever. Antimicrobial Agents and Chemotherapy. 1994;38(5):1203–1204. PubMed PMID: 8067767.

Czoniczer G., Amezcua F., Pelargonio S., Massell B. F. Therapy of Severe Rheumatic Carditis. Comparison of Adrenocortical Steroids and Aspirin. Circulation. 1964;29:813–819. PubMed PMID: 14172089.

Daoud A. S., Zaki M., Shakir R., al-Saleh Q. Effectiveness of sodium valproate in the treatment of Sydenham's chorea. Neurology. 1990;40(7):1140–1141. PubMed PMID: 2113207.

de Dassel J. L., Ralph A. P., Carapetis J. R. Controlling acute rheumatic fever and rheumatic heart disease in developing countries: are we getting closer? Current Opinion in Pediatrics. 2015;27(1):116–123. PubMed PMID: 25490689.

Denny F. W., Wannamaker L. W., Brink W. R., Rammelkamp C. H., Custer E. A. Prevention of rheumatic fever; treatment of the preceding streptococcic infection. Journal of the American Medical Association. 1950;143(2):151–153. PubMed PMID: 15415234.

Dorfman A., Gross J. I., Lorincz A. E. The treatment of acute rheumatic fever. Pediatrics. 1961;27(5):692–706. PubMed PMID: 13723875.

El Oumeiri B., Boodhwani M., Glineur D., De Kerchove L., Poncelet A., Astarci P., et al. Extending the scope of mitral valve repair in rheumatic disease. The Annals of Thoracic Surgery. 2009;87(6):1735–1740. PubMed PMID: 19463587.

Elevli M., Celebi A., Tombul T., Gökalp A. S. Cardiac involvement in Sydenham's chorea: clinical and Doppler echocardiographic findings. Acta Paediatrica. 1999;88(10):1074–1077. PubMed PMID: 10565452.

Engel M. E., Haileamlak A., Zühlke L., Lemmer C. E., Nkepu S., van de Wall M., et al. Prevalence of rheumatic heart disease in 4720 asymptomatic scholars from South Africa and Ethiopia. Heart. 2015;101(17):1389–1394. PubMed PMID: 26076935.

Engel M. E., Stander R., Vogel J., Adeyemo A. A., Mayosi B. M. Genetic susceptibility to acute rheumatic fever: a systematic review and meta-analysis of twin studies. PLoS One. 2011;6(9):e25326. PubMed PMID: 21980428.

Engelman D., Kado J. H., Reményi B., Colquhoun S., Watson C., Rayasidamu S. C., et al. Teaching focused echocardiography for rheumatic heart disease screening. Annals of Pediatric Cardiology. 2015;8(2):118–121. PubMed PMID: 26085762.

Enriquez-Sarano M., Basmadjian A. J., Rossi A., Bailey K. R., Seward J. B., Tajik A. J. Progression of mitral regurgitation: a prospective Doppler echocardiographic study. Journal of the American College of Cardiology. 1999;34(4):1137–1144. PubMed PMID: 10520803.

Evangelista A., Tornos P., Sambola A., Permanyer-Miralda G., Soler-Soler J. Long-Term Vasodilator Therapy in Patients with Severe Aortic Regurgitation. The New England Journal of Medicine. 2005;353:1342–1349. PubMed PMID: 16192479.

Faé K. C., da Silva D. D., Oshiro S. E., Tanaka A. C., Pomerantzeff P. M., Douay C., et al. Mimicry in recognition of cardiac myosin peptides by heart-intralesional T cell clones from rheumatic heart disease. Journal of Immunology. 2006;176(9):5662–5670. PubMed PMID: 16622036.

Feinstein A. R., Stern E. K., Spagnuolo M. The prognosis of acute rheumatic fever. American Heart Journal. 1964a;68(6):817–834. PubMed PMID: 14235961.

Feinstein A. R., Wood H. F., Spagnuolo M., Taranta A., Jonas S., Kleinberg E., et al. Rheumatic Fever in Children and Adolescents. A Long-Term Epidemiologic Study of Subsequent Prophylaxis, Streptococcal Infections, and Clinical Sequelae. Vii. Cardiac Changes and Sequelae. Annals of Internal Medicine. 1964b;60 Suppl 5:87–123. PubMed PMID: 14118551.

Feuer J., Speira H. Acute rheumatic fever in adults: a resurgence in the Hasidic Jewish community. The Journal of Rheumatology. 1997;24(2):337–340. PubMed PMID: 9034994.

Figueroa F. E., Fernández M. S., Valdés P., Wilson C., Lanas F., Carrión F., et al. Prospective comparison of clinical and echocardiographic diagnosis of rheumatic carditis: long term follow up of patients with subclinical disease. Heart. 2001;85(4):407–410. PubMed PMID: 11250966.

Galvin J. E., Hemric M. E., Cunningham M. W. Cytotoxic mAb from rheumatic carditis recognizes heart valves and laminin. The Journal of Clinical Investigation. 2000;106(2):217–224. PubMed PMID: 10903337.

Gasse B., Baroux N., Rouchon B., Meunier J.-M., De Frémicourt I., D'Ortenzio E. Determinants of poor adherence to secondary antibiotic prophylaxis for rheumatic fever recurrence on Lifou, New Caledonia: a retrospective cohort study. BMC Public Health. 2013;13:131. PubMed PMID: 23402561.

Genel F., Arslanoglu S., Uran N., Saylan B. Sydenham's chorea: clinical findings and comparison of the efficacies of sodium valproate and carbamazepine regimens. Brain & Development. 2002;24(2):73–76. PubMed PMID: 11891095.

Gerber M. A., Baltimore R. S., Eaton C. B., Gewitz M., Rowley A. H., Shulman S. T., et al. Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease. Circulation. 2009;119:1541–1551. PubMed PMID: 19246689.

Gewitz M. H., Baltimore R. S., Tani L. Y., Sable C. A., Shulman S. T., Carapetis J., et al. Revision of the Jones Criteria for the Diagnosis of Acute Rheumatic Fever in the Era of Doppler Echocardiography: A Scientific Statement From the American Heart Association. Circulation. 2015;131:1806. PubMed PMID: 25908771.

Global Burden of Disease Study 2013 Collaborators. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet, 386*(9995), 743-800.

Gordis L. The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T. Duckett Jones memorial lecture. Circulation. 1985;72(6):1155–1162. PubMed PMID: 4064266.

Gordis L., Lilienfeld A., Rodriguez R. Studies in the epidemiology and preventability of rheumatic fever. I. Demographic factors and the incidence of acute attacks. Journal of Chronic Diseases. 1969;21(9):645–654. PubMed PMID: 5770431.

Gray, C., Brown, A., & Thomson, N. (2012). *Review of cardiovascular health among Indigenous Australians.* Retrieved February 6, 2017, from Australian Indigenous HealthInfoNet: http://www.healthinfonet.ecu.edu.au/chronic-conditions/cvd/reviews/heart_review

Grinda J. M., Latremouille C., Berrebi A. J., Zegdi R., Chauvaud S., Carpentier A. F., et al. Aortic cusp extension valvuloplasty for rheumatic aortic valve disease: midterm results. The Annals of Thoracic Surgery. 2002;74(2):438–443. PubMed PMID: 12173826.

Guilherme L., Kalil J., Cunningham M. Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease. Autoimmunity. 2006;39(1):31–39. PubMed PMID: 16455580.

Günther G., Asmera J., Parry E. Death from rheumatic heart disease in rural Ethiopia. The Lancet. 2006;367(9508):391. PubMed PMID: 16458755.

Gupta D. K., Kapoor A., Garg N., Tewari S., Sinha N. Beneficial effects of nicorandil versus enalapril in chronic rheumatic severe mitral regurgitation: six months follow up echocardiographic study. The Journal of Heart Valve Disease. 2001;10(2):158–165. PubMed PMID: 11297201.

Gutmann L., Tomasz A. Penicillin-resistant and penicillin-tolerant mutants of group A Streptococci. Antimicrobial Agents and Chemotherapy. 1982;22(1):128–136. PubMed PMID: 6181734.

Hafez M., Chakravarti A., el-Shennawy F., el-Morsi Z., el-Sallab S. H., Al-Tonbary Y. HLA antigens and acute rheumatic fever: evidence for a recessive susceptibility gene linked to HLA. Genetic Epidemiology. 1985;2(3):273–282. PubMed PMID: 4054602.

Harlan G. A., Tani L. Y., Byington C. L. Rheumatic fever presenting as monoarticular arthritis. The Pediatric Infectious Disease Journal. 2006;25(8):743–746. PubMed PMID: 16874177.

Hashkes P. J., Tauber T., Somekh E., Brik R., Barash J., Mukamel M., et al. Naproxen as an alternative to aspirin for the treatment of arthritis of rheumatic fever: a randomized trial. The Journal of Pediatrics. 2003;143(3):399–401. PubMed PMID: 14517527.

Heart Foundation. (2014). *Acute rheumatic fever and rheumatic heart disease - guideline.* Retrieved February 7, 2017, from Heart Foundation: https://www.heartfoundation.org.nz/resources/diagnosis-management-and-secondary-prevention-of-acute-rheumatic-fever-and

Holt K. S. The rebound phenomenon in acute rheumatic fever. Archives of Disease in Childhood. 1956;31(160):444–451. PubMed PMID: 13395571.

Horstkotte, D., Niehues, R., & Strauer, B. E. (1991). Pathomorphological aspects, aetiology and natural history of acquired mitral valve stenosis. *European Heart Journal, 12 Suppl B*, 55-60.

Hosier D. M., Craenen J. M., Teske D. W., Wheller J. J. Resurgence of acute rheumatic fever. American Journal of Diseases in Children. 1987;141(7):730–733. PubMed PMID: 3591761.

Huck D. M., Nalubwama H., Longenecker C. T., Frank S. H., Okello E., Webel A. R. A qualitative examination of secondary prophylaxis in rheumatic heart disease: factors influencing adherence to secondary prophylaxis in Uganda. Global Heart. 2015;10(1):63–69. PubMed PMID: 25754568.

Illingworth R. S., Lorber J., Holt K. S., Rendle-Short J. Acute rheumatic fever in children: a comparison of six forms of treatment in 200 cases. Lancet. 1957;273(6997):653–659. PubMed PMID: 13476677.

Iung B., Baron G., Tornos P., Gohlke-Bärwolf C., Butchart E. G., Vahanian A. Valvular heart disease in the community: a European experience. Current Problems in Cardiology. 2007;32(11):609–661. PubMed PMID: 17976510.

Jack, S., Williamson, D., Galloway, Y., Pierse, N., Milne, R., Mackereth, G., et al. (2015, November 13). *Interim Evaluation of the Sore Throat Management Component of the New Zealand Rheumatic Fever Prevention Programme.* Retrieved February 6, 2017, from Ministry of Health: http://www.health.govt.nz/publication/interim-evaluation-sore-throat-management-component-new-zealand-rheumatic-fever-prevention-programme

Jansen T. L., Janssen M., de Jong A. J., Jeurissen M. E. Post-streptococcal reactive arthritis: a clinical and serological description, revealing its distinction from acute rheumatic fever. Journal of Internal Medicine. 1999;245(3):261–267. PubMed PMID: 10205588.

Kalangos A., Beghetti M., Vala D., Jaeggi E., Kaya G., Karpuz V., et al. Anterior mitral leaflet prolapse as a primary cause of pure rheumatic mitral insufficiency. The Annals of Thoracic Surgery. 2000;69(3):755–761. PubMed PMID: 10750756.

Karthikevan G., Ananthakrishnan R., Devasenapathy N., Narang R., Yadav R., Seth S., et al. Transient, subclinical atrial fibrillation and risk of systemic embolism in patients with rheumatic mitral stenosis in sinus rhythm. The American Journal of Cardiology. 2014;114(6):869–874. PubMed PMID: 25086468.

Karthikeyan G., Mayosi B. M. Is primary prevention of rheumatic fever the missing link in the control of rheumatic heart disease in Africa? Circulation. 2009;120(8):709–713. PubMed PMID: 19667233.

Karur S., Veerappa V., Nanjappa M. C. Balloon mitral valvotomy in juvenile rheumatic mitral stenosis: comparison of immediate results with adults. Heart, Lung & Circulation. 2014;23(12):1165–1168. PubMed PMID: 24972510.

Kitamura N., Uemura S., Kunitomo R., Utoh J., Noji S. A new technique for debridement in rheumatic valvular disease: the rasping procedure. The Annals of Thoracic Surgery. 2000;69(1):121–125. PubMed PMID: 10654499.

Kitchin A., Turner R. Diagnosis and Treatment of Tricuspid Stenosis. British Heart Journal. 1964;26(3):354–379. PubMed PMID: 14156086.

Kumar R., Raizada A., Aggarwal A. K., Ganguly N. K. A community-based rheumatic fever/rheumatic heart disease cohort: twelve-year experience. Indian Heart Journal. 2002;54(1):54–58. PubMed PMID: 11999089.

Lawrence J. G., Carapetis J. R., Griffiths K., Edwards K., Condon J. R. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. Circulation. 2013;128(5):492–501. PubMed PMID: 23794730.

Lennon D. R., Farrell E., Martin D. R., Stewart J. M. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. Archives of Disease in Childhood. 2008;93(6):474–478. PubMed PMID: 18337284.

Lennon D., Stewart J., Farrell E., Palmer A., Mason H. School-based prevention of acute rheumatic fever: a group randomized trial in New Zealand. The Pediatric Infectious Disease Journal. 2009;28(9):787–794. PubMed PMID: 19710585.

Lessof M. H., Bywaters E. G. The duration of chorea. The BMJ. 1956;1(4982):1520–1523. PubMed PMID: 13316200.

Lieberman E. B., Bashore T. M., Hermiller J. B., Wilson J. S., Pieper K. S., Keeler G. P., et al. Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. Journal of the American College of Cardiology. 1995;26(6):1522–1528. PubMed PMID: 7594080.

Lu J. C., Sable C., Ensing G. J., Webb C., Scheel J., Aliku T., et al. Simplified rheumatic heart disease screening criteria for handheld echocardiography. Journal of the American Society of Echocardiography. 2015;28(4):463–469. PubMed PMID: 25660669.

Lue H. C., Tseng W. P., Lin G. J., Hsieh K. H., Chiou J. F. Clinical and epidemiological features of rheumatic fever and rheumatic heart disease in Taiwan and the Far East. Indian Heart Journal. 1983;35(3):139–146. PubMed PMID: 6629385.

Lue H. C., Wu M. H., Hsieh K. H., Lin G. J., Hsieh R. P., Chiou J. F. Rheumatic fever recurrences: controlled study of 3-week versus 4-week benzathine penicillin prevention programs. The Journal of Pediatrics. 1986;108(2):299–304. PubMed PMID: 3511209.

Lue H. C., Wu M. H., Wang J. K., Wu F. F., Wu Y. N. Long-term outcome of patients with rheumatic fever receiving benzathine penicillin G prophylaxis every three weeks versus every four weeks. The Journal of Pediatrics. 1994;125(5 Pt 1):812–816. PubMed PMID: 7965439.

Lue H. C., Wu M. H., Wang J. K., Wu F. F., Wu Y. N. Three- versus four-week administration of benzathine penicillin G: effects on incidence of streptococcal infections and recurrences of rheumatic fever. Pediatrics. 1996;97(6 Pt 2):984–988. PubMed PMID: 8637787.

Maguire G. P., Carapetis J. R., Walsh W. F., Brown A. D. The future of acute rheumatic fever and rheumatic heart disease in Australia. The Medical Journal of Australia. 2012;197(3):133–134. PubMed PMID: 22860775.

Manji R. A., Witt J., Tappia P. S., Jung Y., Menkis A. H., Ramjiawan B. Cost-effectiveness analysis of rheumatic heart disease prevention strategies. Expert Review of Pharmacoeconomics & Outcomes Research. 2013;13(6):715–724. PubMed PMID: 24219047.

Manyemba J., Mayosi B. M. Intramuscular penicillin is more effective than oral penicillin in secondary prevention of rheumatic fever--a systematic review. South African Medical Journal. 2003;93(3):212–218. PubMed PMID: 12768947.

Maron B. J., Zipes D. P. Introduction: Eligibility recommendations for competitive athletes with cardiovascular abnormalities—general considerations. Journal of the American College of Cardiology. 2005;45(8):1318–1321. PubMed PMID: 15837280.

Martin W. J., Steer A. C., Smeesters P. R., Keeble J., Inouye M., Carapetis J., et al. Post-infectious group A streptococcal autoimmune syndromes and the heart. Autoimmunity Reviews. 2015;14(8):710–725. PubMed PMID: 25891492.

Mataika R., Carapetis J. R., Kado J., Steer A. C. (200). Acute rheumatic fever: an important differential diagnosis of septic arthritis. Journal of Tropical Pediatrics.54(3):205–207. PubMed PMID: 18208843.

McDonald M. I., Towers R. J., Andrews R. M., Benger N., Currie B. J., Carapetis J. R. Low rates of streptococcal pharyngitis and high rates of pyoderma in Australian aboriginal communities where acute rheumatic fever is hyperendemic. Clinical Infectious Diseases. 2006;43(6):683–689. PubMed PMID: 16912939.

McDonald M., Brown A., Noonan S., Carapetis J. R. Preventing recurrent rheumatic fever: the role of register based programmes. Heart. 2005;91(9):1131–1133. PubMed PMID: 16103536.

McGlacken-Byrne S. M., Parry H. M., Currie P. F., Wilson N. J. Failure of oral penicillin as secondary prophylaxis for rheumatic heart disease: a lesson from a low-prevalence rheumatic fever region. BMJ Case Reports. 2015;3:2015. PubMed PMID: 26531741.

Medsafe. (2012). *Benzathine Benzylpenicillin Injection for deep IM injection only.* Retrieved March 9, 2017, from Available at: http://www.medsafe.govt.nz/profs/datasheet/b/BicillinLAinj.pdf

Mehta M., Jacobson T., Peters D., Le E., Chadderdon S., Allen A. J., et al. Handheld ultrasound versus physical examination in patients referred for transthoracic echocardiography for a suspected cardiac condition. JACC Cardiovascular Imaging. 2014;7(10):983–990. PubMed PMID: 25240450.

Meira Z. M., Goulart E. M., Colosimo E. A., Mota C. C. Long term follow up of rheumatic fever and predictors of severe rheumatic valvar disease in Brazilian children and adolescents. Heart. 2005;91(8):1019–1022. PubMed PMID: 16020588.

Milne R. J., Lennon D. R., Stewart J. M., Vander Hoorn S., Scuffham P. A. Incidence of acute rheumatic fever in New Zealand children and youth. Journal of Paediatrics and Child Health. 2012a;48(8):685–691. PubMed PMID: 22494483.

Milne R. J., Lennon D., Stewart J. M., Vander Hoorn S., Scuffham P. A. Mortality and hospitalisation costs of rheumatic fever and rheumatic heart disease in New Zealand. Journal of Paediatrics and Child Health. 2012b;48(8):692–697. PubMed PMID: 22494452.

Mincham C. M., Toussaint S., Mak D. B., Plant A. J. Patient views on the management of rheumatic fever and rheumatic heart disease in the Kimberley: a qualitative study. The Australian Journal of Rural Health. 2003;11(6):260–265. PubMed PMID: 14678407.

Minich L. L., Tani L. Y., Pagotto L. T., Shaddy R. E., Veasy L. G. Doppler echocardiography distinguishes between physiologic and pathologic "silent" mitral regurgitation in patients with rheumatic fever. Clinical Cardiology. 1997;20(11):924–926. PubMed PMID: 9383585.

Mirabel M., André R., Mikhail P. B., Colboc H., Lacassin F., Noël B., et al. Infective endocarditis in the Pacific: clinical characteristics, treatment and long-term outcomes. Open Heart. 2015a;2:e000183. PubMed PMID: 25973211.

Mirabel M., Bacquelin R., Tafflet M., Robillard C., Huon B., Corsenac P., et al. Screening for rheumatic heart disease: evaluation of a focused cardiac ultrasound approach. Circulation Cardiovascular Imaging. 2015b;8(1):e002324. PubMed PMID: 25567654.

Mirabel M., Celermajer D. S., Ferreira B., Tafflet M., Perier M.-C., Karam N., et al. Screening for rheumatic heart disease: evaluation of a simplified echocardiography-based approach. European Heart Journal Cardiovascular Imaging. 2012;13(12):1024–1029. PubMed PMID: 22518053.

Mirabel M., Fauchier T., Bacquelin R., Tafflet M., Germain A., Robillard C., et al. Echocardiography screening to detect rheumatic heart disease: A cohort study of schoolchildren in French Pacific Islands. International Journal of Cardiology. 2015c;188:89–95. PubMed PMID: 25889336.

Moges T., Gedlu E., Isaakidis P., Kumar A., Van Den Berge R., Khogali M., et al. Infective endocarditis in Ethiopian children: a hospital based review of cases in Addis Ababa. The Pan African Medical Journal. 2015;20:75. PubMed PMID: 26090033.

Moreland N. J., Waddington C. S., Williamson D. A., Sriskandan S., Smeesters P. R., Proft T., et al. Working towards a group A streptococcal vaccine: report of a collaborative Trans-Tasman workshop. Vaccine. 2014;32(30):3713–3720. PubMed PMID: 24837510.

Musoke C., Mondo C. K., Okello E., Zhang W., Kakande B., Nyakoojo W., et al. Benzathine penicillin adherence for secondary prophylaxis among patients affected with rheumatic heart disease attending Mulago Hospital. Cardiovascular Journal of Africa. 2013;24(4):124–129. PubMed PMID: 24217043.

Myers P. O., Tissot C., Christenson J. T., Cikirikcioglu M., Aggoun Y., Kalangos A. Aortic valve repair by cusp extension for rheumatic aortic insufficiency in children: Long-term results and impact of extension material. The Journal of Thoracic and Cardiovascular Surgery. 2010;140(4):836–844. PubMed PMID: 20659746.

Neely M., Kaplan E. L., Blumer J. L., Faix D. J., Broderick M. P. A population pharmacokinetic modeling approach shows that serum penicillin G concentrations are below inhibitory concentrations by two weeks after benzathine penicillin G injection in the majority of young adults. Antimicrobial Agents and Chemotherapy. 2014;58(11):6735–6741. PubMed PMID: 25182635.

Nishimura, R. A., Otto, C. M., Bonow, R. O., Carabello, B. A., Erwin, J. P., Guyton, R. A., et al. (2014). *2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.*

Noonan S., Zurynski Y. A., Currie B. J., McDonald M., Wheaton G., Nissen M., et al. A national prospective surveillance study of acute rheumatic fever in Australian children. The Pediatric Infectious Disease Journal. 2013;32(1):e26–e32. PubMed PMID: 22926211.

Okello E., Wanzhu Z., Musoke C., Kakande B., Mondo C. K., Freers J., et al. Cardiovascular complications in newly diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda. Cardiovascular Journal of Africa. 2013;24(3):82–87. PubMed PMID: 23736132.

Otsuji Y., Handschumacher M. D., Schwammenthal E., Jiang L., Song J.-K., Guerrero J. L., et al. Insights From Three-Dimensional Echocardiography Into the Mechanism of Functional Mitral Regurgitation: Direct In

Vivo Demonstration of Altered Leaflet Tethering Geometry. Circulation. 1997;96(6):1999–2008. PubMed PMID: 9323092.

Otto C. M. Timing of surgery in mitral regurgitation. Heart. 2003;89(1):100–105. PubMed PMID: 12482807.

Otto C. M., Mickel M. C., Kennedy J. M., Alderman E. L., Bashore T. M., Block P. C., et al. Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. Circulation. 1994;89(2):642–650. PubMed PMID: 8313553.

Paar J. A., Berrios N. M., Rose J. D., Cáceres M., Peña R., Pérez W., et al. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. The American Journal of Cardiology. 2010;105(12):1809–1814. PubMed PMID: 20538135.

Parks T., Kado J., Colquhoun S., Carapetis J., Steer A. Underdiagnosis of acute rheumatic fever in primary care settings in a developing country. Tropical Medicine & International Health. 2009;14(11):1407–1413. PubMed PMID: 19735369.

Parks T., Kado J., Miller A. E., Ward B., Heenan R., Colquhoun S. M., et al. Rheumatic Heart Disease-Attributable Mortality at Ages 5-69 Years in Fiji: A Five-Year, National, Population-Based Record-Linkage Cohort Study. PloS Neglected Tropical Diseases. 2015;9(9):e0004033. PubMed PMID: 26371755.

Parnaby M. G., Carapetis J. R. Rheumatic fever in indigenous Australian children. Journal of Paediatrics and Child Health. 2010;46(9):527–533. PubMed PMID: 20854325.

Paz J. A., Silva C. A., Marques-Dias M. J. Randomized double-blind study with prednisone in Sydenham's chorea. Pediatric Neurology. 2006;34(4):264–269. PubMed PMID: 16638499.

Peña J., Mora E., Cardozo J., Molina O., Montiel C. Comparison of the efficacy of carbamazepine, haloperidol and valproic acid in the treatment of children with Sydenham's chorea: Clinical follow-up of 18 patients. Arquivos de Neuro-Psiquatria. 2002;60(2B):374–377. PubMed PMID: 12131934.

Pennock V., Bell A., Moxon T., Reed P., Maxwell F., Lennon D. Retrospective epidemiology of acute rheumatic fever: a 10-year review in the Waikato District Health Board area of New Zealand. The New Zealand Medical Journal. 2014;127(1393):26–37. PubMed PMID: 24816954.

Ploutz M., Lu J. C., Scheel J., Webb C., Ensing G. J., Aliku T., et al. Handheld echocardiographic screening for rheumatic heart disease by non-experts. Heart. 2016;102:35–39. PubMed PMID: 26438784.

Pomerantzeff P. M., Brandão C. M., Filho O. A., Guedes M. A., da Silva M. F., Grinberg M., et al. Mitral valve repair in patients with rheumatic mitral insufficiency. Twenty years of techniques and results. Brazilian Journal of Cardiovascular Surgery. 2009;24(4):485–489. PubMed PMID: 20305921.

Pourafkari L., Ghaffari S., Bancroft G. R., Tajlil A., Nader N. D. Factors associated with atrial fibrillation in rheumatic mitral stenosis. Asian Cardiovascular & Thoracic Annals. 2015;23(1):17–23. PubMed PMID: 24696100.

Public Health Agency of Canada. (2013, December 13). *Protocol for the Preparation of Benzathine Penicillin*. Retrieved March 9, 2017, from Available at: http://www.collectionscanada.gc.ca/webarchives/20071213033429/http://www.phac-aspc.gc.ca/std-mts/protocol_e.html

Quinn A., Kosanke S., Fischetti V. A., Factor S. M., Cunningham M. W. Induction of Autoimmune Valvular Heart Disease by Recombinant Streptococcal M Protein. Infection and Immunity. 2001;69(6):4072–4078. PubMed PMID: 11349078.

Quinn R. W. Epidemiology of group A streptococcal infections — their changing frequency and severity. Yale Journal of Biology and Medicine. 1982;55(3-4):265–270. PubMed PMID: 6758372.

Ratnakar K. S., Rajagopal P., Somaraju B. Surgical pathology of mitral valves--the Indian scene. International Journal of Cardiology. 1989;24(1):124–126. PubMed PMID: 2759751.

Remenyi B., Carapetis J., Wyber R., Taubert K., Mayosi B. M. Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. Nature Reviews Cardiology. 2013a;10:284–292. PubMed PMID: 23546444.

Remenyi B., Webb R., Gentles T., Russell P., Finucane K., Lee M., et al. Improved Long-Term Survival for Rheumatic Mitral Valve Repair Compared to Replacement in the Young. World Journal for Pediatric and Congenital Heart Surgery. 2013b;4(2):155–164. PubMed PMID: 23799728.

Reményi B., Wilson N., Steer A., Ferreira B., Kado J., Kumar K., et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease--an evidence-based guideline. Nature Reviews Cardiology. 2012;9(5):297–309. PubMed PMID: 22371105.

Rémond M., Atkinson D., White A., Brown A., Carapetis J., Remenyi B., et al. Are minor echocardiographic changes associated with an increased risk of acute rheumatic fever or progression to rheumatic heart disease? International Journal of Cardiology. 2015;198:117–122. PubMed PMID: 26163902.

Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Sub-Committee of the Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association. The Natural History of Rheumatic Fever and Rheumatic Heart Disease: Ten-Year Report of a Co-operative Clinical Trial of ACTH, Cortisone and Aspirin. Circulation. 1965;32(3):457–476. PubMed PMID: 4284068.

Roberts K. V., Brown A. D., Maguire G. P., Atkinson D. N., Carapetis J. R. Utility of auscultatory screening for detecting rheumatic heart disease in high-risk children in Australia's Northern Territory. The Medical Journal of Australia. 2013a;199(3):196–199. PubMed PMID: 23909543.

Roberts K. V., Maguire G. P., Brown A., Atkinson D. N., Remenyi B., Wheaton G., et al. Rheumatic heart disease in Indigenous children in northern Australia: differences in prevalence and the challenges of screening. The Medical Journal of Australia. 2015;203(5):221. PubMed PMID: 26852054.

Roberts K., Colquhoun S., Steer A., Reményi B., Carapetis J. Screening for rheumatic heart disease: current approaches and controversies. Nature Reviews Cardiology. 2013b;10(1):49–58. PubMed PMID: 23149830.

Roberts K., Maguire G., Brown A., Atkinson D., Reményi B., Wheaton G., et al. Echocardiographic screening for rheumatic heart disease in high and low risk Australian children. Circulation. 2014;129(19):1953–1961. PubMed PMID: 24622384.

Roberts S., Kosanke S., Terrence Dunn S., Jankelow D., Duran C. M., Cunningham M. W. Pathogenic mechanisms in rheumatic carditis: focus on valvular endothelium. The Journal of Infectious Diseases. 2001;183(3):507–511. PubMed PMID: 11133385.

Robertson K. A., Volmink J. A., Mayosi B. M. Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis. BMC Cardiovascular Disorders. 2005;5:11. PubMed PMID: 15927077.

Robin A., Mills C., Tuck R., Lennon D. The epidemiology of acute rheumatic fever in Northland, 2002–2011. The New Zealand Medical Journal. 2013;126(1373):46–52. PubMed PMID: 23797076.

Roguin A., Rinkevich D., Milo S., Markiewicz W., Reisner S. Long-term follow-up of patients with severe rheumatic tricuspid stenosis. American Heart Journal. 1998;136(1):103–108. PubMed PMID: 9665226.

Rossebø A. B., Pedersen T. R., Boman K., Brudi P., Chambers J. B., Egstrup K., et al. Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. The New England Journal of Medicine. 2008;359:1343–1356. PubMed PMID: 18765433.

Rothenbühler M., O'Sullivan C. J., Stortecky S., Stefanini G. G., Spitzer E., Estill J., et al. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. The Lancet Global Health. 2014;2(12):e717–e726. PubMed PMID: 25433627.

Röthlisberger C., Sareli P., Wisenbaugh T. Comparison of single dose nifedipine and captopril for chronic severe mitral regurgitation. The American Journal of Cardiology. 1994;73(13):978–981. PubMed PMID: 8184862.

Rumel W. R., Vaughn C. C., Guibone R. A. Surgical reconstruction of the mitral valve. The Annals of Thoracic Surgery. 1969;8(4):289–296. PubMed PMID: 5343732.

Sampaio R. O., Grinberg M., Leite J. J., Tarasoutchi F., Chalela W. A., Izaki M., et al. Effect of enalapril on left ventricular diameters and exercise capacity in asymptomatic or mildly symptomatic patients with regurgitation secondary to mitral valve prolapse or rheumatic heart disease. The American Journal of Cardiology. 2005;96(1):117–121. PubMed PMID: 15979448.

Sawhney H., Aggarwal N., Suri V., Vasishta K., Sharma Y., Grover A. Maternal and perinatal outcome in rheumatic heart disease. International Journal of Gynaecology and Obstetrics. 2003;80(1):9–14. PubMed PMID: 12527454.

Saxena A. Echocardiographic diagnosis of chronic rheumatic valvular lesions. Global Heart. 2013;8(3):203–212. PubMed PMID: 25690497.

Saxena A., Ramakrishnan S., Roy A., Seth S., Krishnan A., Misra P., et al. Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (Rheumatic Heart Echo Utilisation and Monitoring Actuarial Trends in Indian Children) study. Heart. 2011;97(24):2018–2022. PubMed PMID: 22076022.

Scognamiglio R., Rahimtoola S. H., Fasoli G., Nistri S., Dalla Volta S. Nifedipine in Asymptomatic Patients with Severe Aortic Regurgitation and Normal Left Ventricular Function. The New England Journal of Medicine. 1994;331:689–694. PubMed PMID: 8058074.

Sheel M., Moreland N. J., Fraser J. D., Carapetis J. Development of Group A streptococcal vaccines: an unmet global health need. Expert Review of Vaccines. 2016;15(2):227–238. PubMed PMID: 26559880.

Shulman S. T., Bisno A. L., Clegg H. W., Gerber M. A., Kaplan E. L., Lee G., et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2012;55(10):1279–1282. PubMed PMID: 23091044.

Siriett V., Crengle S., Lennon D., Stonehouse M., Cramp G. The epidemiology of rheumatic fever in the Tairāwhiti/Gisborne region of New Zealand: 1997–2009. The New Zealand Medical Journal. 2012;125(1365):42. PubMed PMID: 23254495.

Skoularigis J., Sinovich V., Joubert G., Sareli P. Evaluation of the long-term results of mitral valve repair in 254 young patients with rheumatic mitral regurgitation. Circulation. 1994;90(5 Pt 2):167–174. PubMed PMID: 7955247.

Sliwa K., Carrington M., Mayosi B. M., Zigiriadis E., Mvungi R., Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. European Heart Journal. 2010;31(6):719–727. PubMed PMID: 19995873.

Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. (1992). Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. *JAMA, 268*(15), 2069-2073.

Spinetto H., Lennon D., Horsburgh M. Rheumatic fever recurrence prevention: a nurse-led programme of 28-day penicillin in an area of high endemnicity. Journal of Paediatrics and Child Health. 2011;47(4):228–234. PubMed PMID: 21470327.

Steer A. C., Carapetis J. R. Prevention and treatment of rheumatic heart disease in the developing world. Nature Reviews Cardiology. 2009;6(11):689–698. PubMed PMID: 19752868.

Steer A. C., Carapetis J. R., Dale J. B., Fraser J. D., Good M. F., Guilherme L., et al. Status of research and development of vaccines for Streptococcus pyogenes. Vaccine. 2016;34(26):2953–2958. PubMed PMID: 27032515.

Steer A. C., Carapetis J. R., Nolan T. M., Shann F. Systematic review of rheumatic heart disease prevalence in children in developing countries: the role of environmental factors. Journal of Paediatrics and Child Health. 2002;38(3):229–234. PubMed PMID: 12047688.

Stewart T., McDonald R., Currie B. Acute rheumatic fever: adherence to secondary prophylaxis and follow up of Indigenous patients in the Katherine region of the Northern Territory. The Australian Journal of Rural Health. 2007;15(4):234–240. PubMed PMID: 17617086.

Stollerman G. H. Rheumatic fever in the 21st century. Clinical Infectious Diseases. 2001;33(6):806–814. PubMed PMID: 11512086.

Stollerman G. H., Rusoff J. H. Prophylaxis Against Group A Streptococccal Infections in Rheumatic Fever Patients: Use of new repository penicillin preparation. JAMA. 1952;150(16):1571–1575. PubMed PMID: 12990472.

Stollerman G. H., Markowitz M., Taranta A., Wannamaker L. W., Whittemore R. Committee report: Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. Circulation. 1965;32:664–668. PubMed PMID: 5825556.

Stollerman G. H., Rusoff J. H., Hirschfeld I. Prophylaxis against Group A Streptococci in Rheumatic Fever — The Use of Single Monthly Injections of Benzathine Penicillin G. The New England Journal of Medicine. 1955;252:787–792. PubMed PMID: 14370428.

Strasser T., Dondog N., El Kholy A., Gharagozloo R., Kalbian V. V., Ogunbi O., et al. The community control of rheumatic fever and rheumatic heart disease: report of a WHO international cooperative project. Bulletin of the World Health Organization. 1981;59(2):285–294. PubMed PMID: 6972819.

Tadele H., Mekonnen W., Tefera E. Rheumatic mitral stenosis in children: more accelerated course in sub-Saharan patients. BMC Cardiovascular Disorders. 2013;13:95. PubMed PMID: 24180350.

Talwar S., Rajesh M. R., Subramanian A., Saxena A., Kumar A. S. Mitral valve repair in children with rheumatic heart disease. The Journal of Thoracic and Cardiovascular Surgery. 2005a;129(4):875–879. PubMed PMID: 15821657.

Talwar S., Saikrishna C., Saxena A., Kumar A. S. Aortic valve repair for rheumatic aortic valve disease. The Annals of Thoracic Surgery. 2005b;79(6):1921–1925. PubMed PMID: 15919285.

Tekumit H., Cenal A. R., Tataroglu C., Uzun K., Polat A., Akinci E. Cusp shaving for concomitant mild to moderate rheumatic aortic insufficiency. Journal of Cardiac Surgery. 2010;25(1):16–22. PubMed PMID: 19874414.

Thatai D., Turi Z. G. Current guidelines for the treatment of patients with rheumatic fever. Drugs. 1999;57(4):545–555. PubMed PMID: 10235692.

The Committee on Standards and Criteria for Programs of Care. JONES CRITERIA (modified) for guidance in the diagnosis of rheumatic fever; report of the Committee on Standards and Criteria for programs of care. Circulation. 1956;13(4):617–620. PubMed PMID: 13356420.

The Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association. (1960). The Evolution of Rheumatic Heart Disease in Children: Five-Year Report of a Co-operative Clinical Trial of ACTH, Cortisone and Aspirin. *The Canadian Medical Association Journal / Le Journal de L'Association Médicale Canadienne, 83*(15), 781-789.

Thornley C., McNicholas A., Baker M., Lennon D. Rheumatic Fever Registers in New Zealand. Public Health Report. 2001;8(6):41–44.

Tissier R., Chetboul V., Moraillon R., Nicolle A., Carlos C., Enriquez B., et al. Increased mitral valve regurgitation and myocardial hypertrophy in two dogs with long-term pimobendan therapy. Cardiovascular Toxicology. 2005;5(1):43–51. PubMed PMID: 15738584.

Tompkins D. G., Boxerbaum B., Liebman J. Long-term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin. Circulation. 1972;45(3):543–551. PubMed PMID: 5012243.

Tubridy-Clark M., Carapetis J. R. Subclinical carditis in rheumatic fever: a systematic review. International Journal of Cardiology. 2007;119(1):54–58. PubMed PMID: 17034886.

Tullu M. S., Gandhi A., Ghildiyal R. G. Benzathine Penicillin Prophylaxis in Children with Rheumatic Fever (RF)/ Rheumatic Heart Disease (RHD): A Study of Compliance. Al Ameen Journal of Medical Sciences. 2010;3(2):140–145.

Ungar H., Ben-Ishay Z. Rheumatic and Age Changes of the Heart in Israel: Pathological and Statistical Study. Israel Journal of Medical Sciences. 1965;1:50–61. PubMed PMID: 14252799.

Uziel Y., Hashkes P. J., Kassem E., Padeh S., Goldman R., Wolach B. The use of naproxen in the treatment of children with rheumatic fever. The Journal of Pediatrics. 2000;137(2):269–271. PubMed PMID: 10931426.

van der Bel-Kahn J., Becker A. E. The surgical pathology of rheumatic and floppy mitral valves. Distinctive morphologic features upon gross examination. The American Journal of Surgical Pathology. 1986;10(4):282–292. PubMed PMID: 3706614.

Vasan R. S., Shrivastava S., Vijaykumar M., Narang R., Lister B., Narula J. Echocardiographic evaluation of patients with acute rheumatic fever and rheumatic carditis. Circulation. 1996;94(1):73–82. PubMed PMID: 8964121.

Veasy L. G., Tani L. Y., Hill H. R. Persistence of acute rheumatic fever in the intermountain area of the United States. The Journal of Pediatrics. 1994;124(1):9–16. PubMed PMID: 7802743.

Veasy L. G., Wiedmeier S. E., Orsmond G. S., Ruttenberg H. D., Boucek M. M., Roth S. J., et al. Resurgence of Acute Rheumatic Fever in the Intermountain Area of the United States. The New England Journal of Medicine. 1987;316:421–427. PubMed PMID: 3807984.

Viali S., Saena P., Futi V. Rheumatic Fever Programme in Samoa. The New Zealand Medical Journal. 2011;124(1329):26–35. PubMed PMID: 21475357.

Vlachogeorgos G. S., Daskalopoulos N., Blatsiotis P., Kourbeti I. S., Mantas I., Stathopoulos G. T. Bosentan for patients with echocardiographic evidence of pulmonary hypertension due to long-standing rheumatic mitral stenosis. Hellenic Journal of Cardiology. 2015;56(1):36–43. PubMed PMID: 25701970.

Voss L. M., Wilson N. J., Neutze J. M., Whitlock R. M., Ameratunga R. V., Cairns L. M., et al. Intravenous Immunoglobulin in Acute Rheumatic Fever: A Randomized Controlled Trial. Circulation. 2001;103:401–406. PubMed PMID: 11157692.

Wald E. R., Dashefsky B., Feidt C., Chiponis D., Byers C. Acute rheumatic fever in western Pennsylvania and the tristate area. Pediatrics. 1987;80(3):371–374. PubMed PMID: 3627888.

Walker M. J., Barnett T. C., McArthur J. D., Cole J. N., Gillen C. M., Henningham A., et al. Disease manifestations and pathogenic mechanisms of Group A Streptococcus. Clinical Microbiology Reviews. 2014;27(2):264–301. PubMed PMID: 24696436.

Wallace M. R., Garst P. D., Papadimos T. J., Oldfield E. C. The return of acute rheumatic fever in young adults. JAMA. 1989;262(18):2557–2561. PubMed PMID: 2681847.

Waller B. F., Howard J., Fess S. Pathology of mitral valve stenosis and pure mitral regurgitation--Part I. Clinical Cardiology. 1994;17(6):330–336. PubMed PMID: 8070151.

Walsh B. J., Nestor J. O. Rheumatic fever with heart disease. Clinical Proceedings - Children's Hospital of the District of Columbia. 1956;12(4):68–74. PubMed PMID: 13330227.

Wang Z., Zhou C., Gu H., Zheng Z., Hu S. Mitral valve repair versus replacement in patients with rheumatic heart disease. The Journal of Heart Valve Disease. 2013;22(3):333–339. PubMed PMID: 24151759.

Wannamaker, L. (1954). The epidemiology of streptococcal infections. In M. McCarty (Ed.), *Streptococcal Infections.* New York: Columbia Press.

Watt G., Lacroix A., Pachirat O., Baggett H. C., Raoult D., Fournier P.-E., et al. Prospective Comparison of Infective Endocarditis in Khon Kaen, Thailand and Rennes, France. The American Journal of Tropical Medicine and Hygiene. 2015;92(4):871–874. PubMed PMID: 25646262.

WHO Expert Committee on the Prevention of Rheumatic Fever World Health Organization. (1966). *Prevention of rheumatic fever : report of a WHO Expert Committee.* Geneva: World Health Organization.

Wilcox J. A., Nasrallah H. Sydenham's chorea and psychopathology. Neuropsychobiology. 1988;19(1):6–8. PubMed PMID: 3185898.

Wilkins G. T., Weyman A. E., Abascal V. M., Block P. C., Palacios I. F. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. British Heart Journal. 1988;60(4):299–308. PubMed PMID: 3190958.

Williamson D. A., Smeesters P. R., Steer A. C., Steemson J. D., Ng A. C., Proft T., et al. M-Protein Analysis of Streptococcus pyogenes Isolates Associated with Acute Rheumatic Fever in New Zealand. Journal of Clinical Microbiology. 2015;53(11):3618–3620. PubMed PMID: 26292296.

Wilson E., Wilson N., Voss L., Morreau J., Lennon D. Monoarthritis in rheumatic fever? The Pediatric Infectious Disease Journal. 2007b;26(4):369–370. PubMed PMID: 17414410.

Wilson M. G., Lim W. N. Natural course of active rheumatic carditis and evaluation of hormone therapy. JAMA. 1956;160(17):1457–1460. PubMed PMID: 13306576.

Wilson W., Taubert K. A., Gewitz M., Lockhart P. B., Baddour L. M., Levison M., et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young... Circulation. 2007a;116(15):1736–1754. PubMed PMID: 17446442.

Wisenbaugh T., Essop R., Rothlisberger C., Sareli P. Effects of a single oral dose of captopril on left ventricular performance in severe mitral regurgitation. The American Journal of Cardiology. 1992;69(4):348–353. PubMed PMID: 1734647.

World Health Organisation. (2004). Rheumatic fever and rheumatic heart disease: report of a WHO Expert Consultation Geneva. Geneva, Switzerland.

World Health Organization. (n.d.). *Rheumatic fever and rheumatic heart disease.* Retrieved March 9, 2017, from Cardiovascular Disease: http://www.who.int/cardiovascular_diseases/publications/trs923/en/

Wyber R., Boyd B. J., Colquhoun S., Currie B. J., Engel M., Kado J., et al. Preliminary consultation on preferred product characteristics of benzathine penicillin G for secondary prophylaxis of rheumatic fever. Drug Delivery and Translational Research. 2016;6(5):572–578. PubMed PMID: 27465618.

Wyber, R., Grainger Gasser, A., Thompson, D., Kennedy, D., Johnson, T., Taubert, K., et al. (2014). *TIPS Handbook: Tools for implementing rheumatic heart disease control programmes.* Retrieved March 9, 2017, from RHD Action: http://rhdaction.org/sites/default/files/TIPS-HANDBOOK_World-Heart-Federation_RhEACH.pdf

Wyber R., Taubert K., Marko S., Kaplan E. L. Benzathine Penicillin G for the Management of RHD: Concerns About Quality and Access, and Opportunities for Intervention and Improvement. Global Heart. 2013;8(3):227–234. PubMed PMID: 25690500.

Yuko-Jowi C., Bakari M. Echocardiographic patterns of juvenile rheumatic heart disease at the Kenyatta National Hospital, Nairobi. East African Medical Journal. 2005;82(10):514–519. PubMed PMID: 16450679.

Zachariah J. P., Samnaliev M. Echo-based screening of rheumatic heart disease in children: a cost-effectiveness Markov model. Journal of Medical Economics. 2015;18(6):410–419. PubMed PMID: 25629653.

Zhang W., Mondo C., Okello E., Musoke C., Kakande B., Nyakoojo W., et al. Presenting features of newly diagnosed rheumatic heart disease patients in Mulago Hospital: a pilot study. Cardiovascular Journal of Africa. 2013;24(2):28–33. PubMed PMID: 23612950.

Zühlke L., Mayosi B. M. Echocardiographic screening for subclinical rheumatic heart disease remains a research tool pending studies of impact on prognosis. Current Cardiology Reports. 2013;15(3):343. PubMed PMID: 23338725.

Zühlke L., Engel M. E., Karthikeyan G., Rangarajan S., Mackie P., Cupido B., et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). European Heart Journal. 2014;36(18):1115–1122. PubMed PMID: 25425448.

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