Circulation

AHA SCIENTIFIC STATEMENT

Contemporary Diagnosis and Management of Rheumatic Heart Disease: Implications for Closing the Gap

A Scientific Statement From the American Heart Association

ABSTRACT: The global burden of rheumatic heart disease continues to be significant although it is largely limited to poor and marginalized populations. In most endemic regions, affected patients present with heart failure. This statement will seek to examine the current state-of-the-art recommendations and to identify gaps in diagnosis and treatment globally that can inform strategies for reducing disease burden. Echocardiography screening based on World Heart Federation echocardiographic criteria holds promise to identify patients earlier, when prophylaxis is more likely to be effective; however, several important questions need to be answered before this can translate into public policy. Population-based registries effectively enable optimal care and secondary penicillin prophylaxis within available resources. Benzathine penicillin injections remain the cornerstone of secondary prevention. Challenges with penicillin procurement and concern with adverse reactions in patients with advanced disease remain important issues. Heart failure management, prevention, early diagnosis and treatment of endocarditis, oral anticoagulation for atrial fibrillation, and prosthetic valves are vital therapeutic adjuncts. Management of health of women with unoperated and operated rheumatic heart disease before, during, and after pregnancy is a significant challenge that requires a multidisciplinary team effort. Patients with isolated mitral stenosis often benefit from percutaneous balloon mitral valvuloplasty. Timely heart valve surgery can mitigate the progression to heart failure, disability, and death. Valve repair is preferable over replacement for rheumatic mitral regurgitation but is not available to the vast majority of patients in endemic regions. This body of work forms a foundation on which a companion document on advocacy for rheumatic heart disease has been developed. Ultimately, the combination of expanded treatment options, research, and advocacy built on existing knowledge and science provides the best opportunity to address the burden of rheumatic heart disease.

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Rheumatic heart disease (RHD) has declined sharply in most industrialized, high-income nations and many other parts of the world that have had improvements in human development indices and health systems. The disease persists among the rural poor and marginalized populations with little or no access to primary health care.[1,2]

There are many complex reasons for this ongoing global disparity, including inadequate and inaccurate data on disease burden, ineffective advocacy, ongoing poverty and inequality, and weak health systems, most of which predominantly affect large populations in most low- and middle- income countries (LMICs).[3] Numerous barriers and gaps continue to exist in implementation of RHD prevention strategies and effective care of affected patients that falls short of recommendations.[4] As a result, RHD continues to have a devastating impact, with estimates of nearly 300 000 deaths globally and loss of >10 million disability-adjusted life-years.[1]

This statement will seek to examine the current state-of-the-art management and identify gaps in diagnosis and treatment globally that can inform strategies for reducing disease burden. Additionally, the challenges in providing tertiary care, including access to heart valve surgery and balloon mitral valvuloplasty (BMV) in low-resource environments, will be examined, with a view to developing pragmatic strategies toward addressing the challenges faced by those with established RHD.

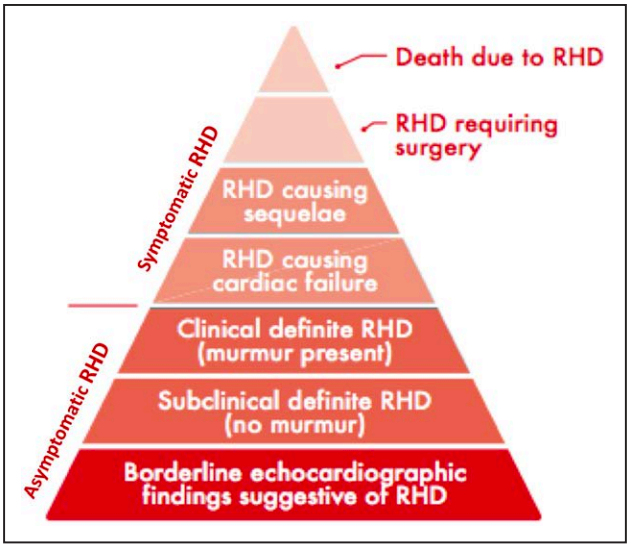

Figure 1. Progression of rheumatic heart disease (RHD).
This cartoon depicts burden and progression of RHD from latent to clinical to heart failure to death.

EPIDEMIOLOGY AND NATURAL HISTORY OF RHD

Epidemiology

The global, regional, and national burden of RHD from 1990 to 2015, as part of the 2015 Global Burden of Disease study, was reported in a 2017 publication[1] and is updated annually on the Global Burden of Disease Study website.[5] Although a worldwide decline in health-related burden of RHD was noted, the study found persistence of high rates of RHD in poor regions of the world where RHD remains endemic (defined as having high RHD-related mortality exceeding 0.15 deaths per 100 000 population among children 5–9 years of age). Overall, there were an estimated 38.0 million to 40.8 million cases of RHD globally in 2017, with the highest prevalence, disability, and mortality in Oceania, South Asia, and sub-Saharan Africa (SSA; Supplemental Figure 1). The prevalence ranged from 3.4 cases per 100 000 population in nonendemic countries to >1000 cases per 100 000 in endemic countries.[1] There are a few reports of sporadic outbreaks of acute rheumatic fever (ARF) in the United States in the 1980s and 1990s and more recent reports from Australia and Italy.[6–8]

The data on morbidity and mortality attributable to RHD are less robust than prevalence estimates.[1] Healthcare information systems in LMICs are scarce, thereby making the current estimates questionable. There were an estimated 266 200 to 303 300 deaths attributable to RHD in 2017.[5] In nonendemic regions, the mortality from RHD is shifted toward those from poor socioeconomic background (Supplemental Figure 2). Better-quality epidemiological data are still needed to address the burden of RHD in terms of mortality, morbidity, and economic impact.[9]

Natural History of RHD

Rheumatic carditis includes a spectrum of lesions, including pericarditis and valvulitis during clinical or subclinical ARF; there is a transition from rheumatic carditis to RHD, with chronic valvular lesions that evolve over years after ≥1 episodes of ARF (Figure 1). Progressive valvular disease commonly develops in the years after ≥1 episodes of ARF, although ARF is usually only recognized in 30% to 50% of cases. A prospective study of children with ARF followed up for 2 to 15 years in Brazil found that 72% of the 258 subjects developed chronic valvular disease, and 16% progressed to severe aortic or mitral disease.[10] Although chronic RHD occurs only as a sequel to ARF, the majority of patients with RHD lack a history of past ARF[2], which suggests that the diagnosis of ARF is frequently missed, with the initial or recurrent insults being subclinical or not detected.

In Australia, it was noted that ARF recurrence was highest (incidence, 3.7 per 100 person-years) in the first year after the initial ARF episode, but low-level risk persisted for >10 years. Progression to RHD was also highest (incidence, 35.9/100 person-years) in the first year, almost 10 times higher than ARF recurrence.[11] In an elegant study, Cannon et al[12] used Northern Territory

(Australia) data to identify and follow those diagnosed with RHD between the ages of 5 to 24 years. Disease severity, surgery, and deaths were then recorded. Of the 16.2% of patients with severe RHD at diagnosis, 50% had proceeded to valve surgery by 2 years, and 10% were dead within 6 years. Although patients with mild RHD at diagnosis were the most stable, with 64% continuing to have mild RHD after 10 years, 11.4% progressed to severe RHD, and half of these required surgery.[12] Those with severe disease at presentation had rapid disease progression and outcomes.

Contemporary articles considering risk factors for progression (deterioration) or regression (improvement or stabilization) have largely focused on the subclinical or latent RHD phenotype found on echocardiography screening, as discussed in more detail here in the Echocardiography section. However, these studies do not reflect the natural history of established RHD, and no data exist to demonstrate the quantifiable effect of recurrent ARF on established disease and to explain the differing patterns of RHD in endemic and nonendemic countries. Juvenile mitral stenosis (MS) has long been a manifestation of the disease, having been reported in Ethiopia and India. Similarly, no data exist to explain how risk factors such as sex, age at initial clinical presentation, coexisting morbidities at presentation (such as heart failure), or additional streptococcal infections (throat infections or skin sores) can affect progression to RHD or affect deterioration of existing valve lesions. In early longitudinal studies, the clear role of initial carditis in ARF, followed by recurrences of carditis leading to established RHD, predominantly mitral regurgitation (MR) and aortic regurgitation (AR), was identified, and consideration of the indolent or subclinical carditis episodes leading to MS was described.[13]

RHD DIAGNOSIS

General Features

RHD typically affects left-sided valves, with greater affinity and consequence for the mitral valve. Characteristic acute mitral valvulitis shows mitral annulus dilatation, chordal elongation, and anterior leaflet prolapse, with varying degrees of MR and rarely chordal rupture. Isolated aortic disease occurs in 2% of cases.[14] Right-sided valve disease is not infrequent, typically affects the tricuspid valve (as primary valvulitis or as the result of deleterious hemodynamic consequences of left-sided valve disease), and rarely affects the pulmonic valve. Acute rheumatic valvulitis manifests as valvular regurgitation, but over time, chronic inflammation leads to valve stenosis from commissural fusion with or without associated regurgitation in a subset of patients. MS from commissural fusion, with variable degrees of involvement of other parts of the mitral valve apparatus, is the hallmark lesion of the later stages of RHD.[15] The more malignant fulminant course of RHD, linked to recurrent bouts of ARF, occurs in the most endemic regions of the world.

Clinical Features

Precise and comprehensive evaluation of the patient's history and symptomatic status, thorough physical examination, auscultation, and a search for heart failure signs are crucial for the diagnostic evaluation of RHD (Supplemental Table 1). The initial symptom is often exertional dyspnea, which worsens gradually. Heart failure symptoms develop with progressive heart valve damage. It should also be considered that because of the slow, progressive nature of many valve lesions, patients may not recognize symptoms because they may have gradually limited their daily activity levels.[16] Although chronic heart valve disease is often manifested in adolescents and young adults, advanced valve damage happens earlier in life in the most endemic regions. Patients may be diagnosed after a known ARF attack; however, a significant portion of RHD patients, well over 50% in LMICs, may present without any prior symptoms or memory of ARF.[17] In these settings, RHD may present for the first time during pregnancy or after a complication such as acute heart failure, atrial arrhythmia, an embolic event, or infective endocarditis (IE). Most patients have heart failure symptoms at the time of clinical diagnosis through auscultation of pathological heart murmurs.

An electrocardiogram and chest radiograph can be helpful in the initial assessment of RHD patients. Although electrocardiography findings are not specific for RHD, they may demonstrate left atrial or left ventricular enlargement and ventricular strain. In more severe degrees of mitral valve damage, especially in older patients, atrial fibrillation may be present. The chest radiograph may show an enlarged left atrium or left ventricle and radiological signs of pulmonary venous congestion in more advanced cases (Supplemental Figure 3).[18]

Echocardiography

Echocardiography is vital to establishing a diagnosis of RHD, ascertaining the severity of the individual valve afflictions, determining the physiological consequences (chamber enlargement and function, pulmonary artery hypertension), and planning surgical or interventional therapy. The vast majority of patients have either isolated MR, mixed mitral valve disease (MR and MS), or mitral and aortic valve disease.[2] The minimal echocardiographic criteria to establish a diagnosis of RHD in this context are described in the 2012 World Heart Federation (WHF) guidelines.[19] Morphological and Doppler findings for ARF and RHD and a differential diagnosis

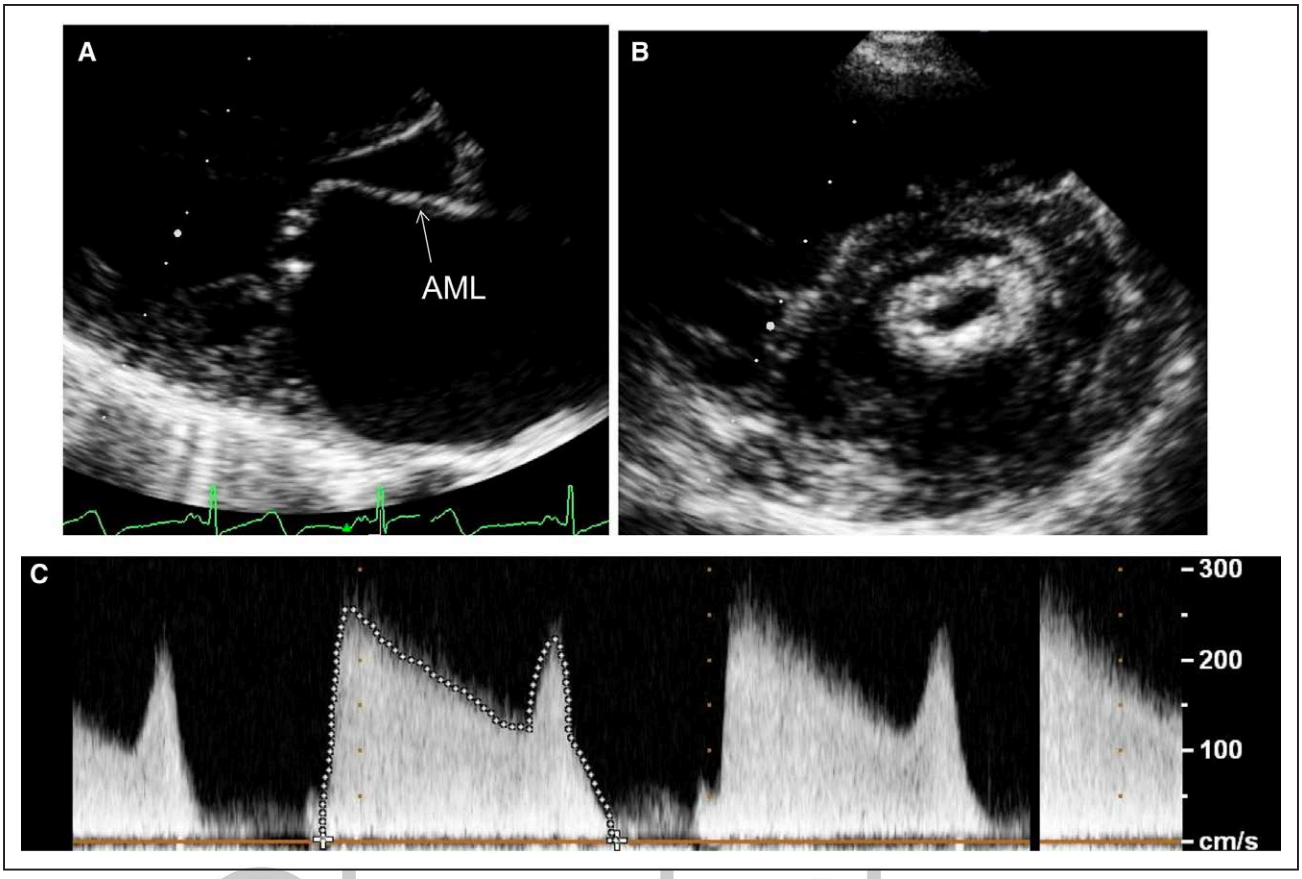

Figure 2. Two-dimensional echocardiography for rheumatic heart disease and mitral stenosis.
A, Diastolic frame from parasternal long-axis view. The characteristic "dog leg" or "elbow" deformity is shown in the anterior mitral valve leaflet (AML). The tips of the AML are thickened. The thick and shortened chordae attached to the posterior mitral leaflet are also shown in this frame. **B**, Picture obtained from parasternal short-axis view. This view captures the mitral valve orifice in mid diastole and allows accurate estimation of the mitral valve area. This view is also very useful in planning balloon mitral valvotomy. In this patient, for instance, it can be anticipated that the commissures would split favorably after balloon mitral valvotomy. **C**, Doppler tracing from the same patient showing the characteristic M-shaped flow acceleration across the stenotic valve that is seen in patient with mitral stenosis and sinus rhythm. The second peak results from atrial contraction and is responsible for the presystolic accentuation of the mid-diastolic murmur.

for aortic and mitral valve changes are provided in Supplemental Tables 2 through 4, modified from the 2012 WHF guidelines and the 2015 Jones Criteria update.[19,20] Supplemental Figure 4 and Figure 2 show echocardiographic images from patients with severe MR and MS, respectively. Supplemental Videos 1 through 4 show images from patients with ARF, moderate MR, severe MR, and mixed mitral valve disease, respectively. Supplemental Video 5 shows images of borderline RHD.

Quantification of MR includes several parameters described in the American Society of Echocardiography[21] and American College of Cardiology/American Heart Association[16] guidelines. Assessment includes a combination of chamber size, vena contracta width on color Doppler, pulsed- and continuous-wave Doppler characteristics of mitral inflow and regurgitation, and use of proximal isovelocity surface area to calculate effective regurgitant orifice, regurgitant volume, and regurgitant fraction. Additional findings of severe MR, more often in longstanding disease, include left atrial enlargement, pulmonary hypertension, and left ventricular systolic dysfunction. There are limitations in using these criteria to differentiate between trivial and mild disease, as well as in grading the severity of rheumatic MR with an eccentric jet.

MS in RHD results from thickening and deformity of the valve apparatus, which includes the commissures, cusps, and chordae. MS can be isolated or occur with MR, which is referred to as mixed mitral valve disease. The degree of narrowing of the mitral valve in MS is classified according to the mitral valve area determined on echocardiography using direct planimetry in the parasternal short-axis view or indirect measurements using pressure half-time taken in the apical 4-chamber view. The morphological features of the mitral valve apparatus (leaflet mobility, valve thickening, subvalvular thickening, valvular calcification, commissural morphology, and leaflet displacement) can be graded to determine the suitability for BMV.[22] Supplemental Figure 5 shows 3-dimensional echocardiography images before and after BMV.

A number of echocardiography parameters are recommended for use to determine the severity of AR.[21] Quantitative approaches for assessment of AR include jet width and the presence of diastolic flow reversal in

the descending aorta, whereas qualitative measures include the pressure half-time method, vena contracta width, and regurgitant volume/fraction.

ECHOCARDIOGRAPHY SCREENING

Rationale for Screening

Timely diagnosis and treatment of group A streptococcal (GAS) infections will not prevent all cases of ARF. Up to one-third of patients with ARF report no history of a sore throat.[23] Similarly, improved recognition and timely initiation of secondary prophylaxis will not prevent all RHD.[2] Despite the existence of international diagnostic guidelines, the diagnosis of ARF remains challenging in tropical and subtropical climates where the differential diagnoses for a febrile illness with sore joints are broad, awareness is low, and laboratory facilities are limited.[20] In these settings, for the millions of young people in the world who already have established RHD, echocardiographic active case finding for mild to moderate disease appears to hold the most tangible hope for a longer and healthy life by detecting RHD at a stage when secondary prophylaxis may have a greater chance of success.[24] Earlier detection of severe RHD may allow for timing of cardiac surgery at a stage in illness when short- and long-term outcomes of cardiac surgery are reported to be better.[18,25]

The reality is that today, many patients living with RHD are unaware of their diagnosis and the sore throat/ARF that preceded RHD. In many RHD-endemic areas, the majority of patients seek help once severe RHD develops and present with complications of RHD, which include heart failure, arrhythmias, pulmonary hypertension, stroke, systemic embolic events, IE, and pregnancy-related complications.[26,27] Severe RHD carries a high risk of morbidity and mortality, with a 2-year case fatality rate as high as 16.9%.[26] Access to life-saving surgical or catheter-based interventions is often limited or cost prohibitive.[26] The cumulative nature of repetitive cases of ARF that lead to RHD means there is typically a latent period between the initial ARF episode and the development of advanced cardiac disease.[28] Screening, or active case finding, aims to identify individuals with RHD during this latent period. Proposed definitions in relation to echocardiographically and clinically detected RHD are detailed in Table 1.

Table 1. Proposed RHD Definitions

Latent RHD	All cases of RHD diagnosed through echocardiographic screening, to include previously unrecognized clinical RHD and subclinical RHD
Clinical RHD	All cases of RHD that have clinical signs or symptoms including pathological heart murmur* diagnosed either through echocardiographic screening or clinical evaluation. Clinical RHD is typically more advanced than subclinical RHD.
Subclinical RHD	All cases of RHD that do not have clinical signs or symptoms including heart murmur.* Subclinical RHD is only diagnosed by echocardiography and is typically less advanced than clinical RHD.

RHD indicates rheumatic heart disease.

*Detection of a pathological heart murmur without echocardiography has been shown to be poorly sensitive and specific in echocardiographic screening studies for RHD.

Screening-Based Data

With the advent of the HIV epidemics in the 1990s, RHD became less of a priority for policy makers, and auscultation-based World Health Organization (WHO) screening programs were abandoned because of lack of funding.[4] Subsequent research studies addressed the suitability of the stethoscope as a screening tool and found that auscultation is neither sensitive nor specific for RHD and hence not a suitable screening tool.[29] Simultaneously, research studies addressed the lack of prevalence data that were necessary for advocacy by means of echocardiography-based screening from 2007 onward. The majority of these studies focused on schoolchildren aged 5 to 15 years in countries where RHD is thought to be endemic.[30] Technical aspects differed from one study to another, using different devices and slightly different echocardiographic criteria until the publication of the 2012 WHF evidence-based echocardiographic guidelines, which are now considered to be the standard for the diagnosis of RHD.[19] Overall, the pooled prevalence of subclinical RHD (21.1 per 1000 people [95% CI, 14.1–31.4]) was about 7 times higher than that of clinically manifest disease (2.7 per 1000 people [95% CI, 1.6–4.4]).[31,32]

Role of Active Case Detection and Screening

Active case detection and echocardiography-based screening for RHD can occur in several different settings, including clinical, systematic population-based screening; epidemiological studies; other research studies; and advocacy projects. The most suitable target populations are school-aged children and pregnant women. The incidence of primary episodes of ARF is highest in the 5- to 15-year-old age group, and the incidence of recurrent episodes of ARF is highest within 5 years of original presentation.[28] Therefore, it is school-aged children who remain at the highest risk of ARF recurrences and most likely to benefit from secondary prophylaxis. However, the highest prevalence of RHD is in the 20- to 30-year-old age group as a result of cumulative episodes of ARF that have gone unrecognized or undertreated.[2] Previously undetected latent RHD poses a special risk during pregnancy; if the

disease is severe, it could compromise the life of the mother and the baby.[33] Clinical detection of RHD is especially challenging during pregnancy, because signs and symptoms of RHD overlap with pregnancy and cardiac flow murmurs are prevalent.[33] Although research studies have performed echocardiographic screening in adult populations to gather epidemiological data, adult populations are much less likely to benefit from secondary prophylaxis because of the inherent lower risk of ARF recurrences.[28,34]

To date, screening and active case finding have been almost exclusively performed in the research arena and have focused predominantly on school-aged children. The key focus has been to (1) establish the disease burden, thereby demonstrating the need for active case finding; (2) use prevalence data for regional and global advocacy; (3) ascertain the short- and medium-term outcomes of echocardiographically detected latent RHD, thereby demonstrating its clinical significance; and (4) develop models to make echocardiographic screening practical and affordable in resource-poor settings, by evaluating task-shifting and the use of cheaper handheld machines.

The demonstration of the prevalence of RHD has probably been the most significant outcome of echocardiography screening to date. Advocacy as a result of this information contributed significantly to the landmark event of a global resolution on RHD at the 71st WHO Assembly. Regionally, in a number of countries such as Uganda and Timor-Leste, advocacy as a result of active case finding led to the development of local RHD registries and led to secure supplies of benzathine penicillin (BPG).[30,35]

Researchers have demonstrated that borderline RHD findings are not always benign.[36,37] Those with subclinical mild definite RHD have various long-term outcomes: some improve, others remain stable, and some progress to clinical disease. In the largest study to date (227 children with median follow-up of 2.4 years; range, 1.1–5.9 years), children with mild definite and borderline RHD showed 26% and 9.8% echocardiographic progression and 45.2% and 46.3% echocardiographic improvement, respectively.[36] More advanced disease category, younger age, and morphological mitral valve features were risk factors for an unfavorable outcome. In another study, a 5-year follow-up demonstrated variable long-term outcomes, with latent RHD resolving to normal in nearly half of school pupils.[37] Those with echocardiographically detected latent moderate or severe RHD are more likely missed clinical cases and have very poor prognosis when secondary prevention strategies are not adequately implemented and when access to cardiac surgery is limited.[36,38,39] Researchers have developed simplified echocardiographic criteria that could be implemented on cheaper handheld machines and performed by less skilled or minimally trained health workers.[40,41]

Significant work has been done to resolve how to make echocardiographic screening more practical and cost-effective. However, many unanswered questions remain, and as a result, very few countries (aside from Egypt, Western Samoa, and Tonga) have implemented systematic echocardiographic screening public health programs. In countries such as Australia, annual auscultation of the hearts of high-risk children occurs, which preselects patients who require an echocardiogram, although this model has shown to be an inappropriate public health model for early detection of RHD.[42]

Clinical screening, which implies that a child presents to a clinic and undergoes opportunistic cardiac auscultation or echocardiography, remains challenging in resource-poor settings. Even in remote parts of Australia, children have limited access to doctors and are often seen by nurses or health workers with minimal skills in cardiac auscultation and echocardiography.

Research Priorities

It is unquestionable that those with echocardiographically detected latent RHD have worse outcomes than those with normal echocardiograms, but many important unanswered questions remain. The role of echocardiographic screening as a public health strategy for global reduction of the burden of RHD, its related morbidity and mortality, and estimates of number needed to treat are still unknown. One study found that antistreptolysin O titers were elevated in children with definite RHD detected during echocardiographic screening,[30] but no data are available on the role of antistreptolysin O titers in diagnosis of borderline RHD or to monitor efficacy of prophylaxis in subclinical RHD. Other nonechocardiographic risk factors such as background incidences of ARF, prevalence of RHD, biomarkers, family history, living conditions, and the impact of secondary prophylaxis have not been evaluated satisfactorily to date and require attention.[36,39,43] It has been hypothesized that active case finding followed by diagnosis of RHD and the delivery of penicillin at an early stage of the disease should provide a better prognosis than intervention after spontaneously sought treatment; however, there are few data to support this statement.[19] To the contrary, 2 observational studies showed paradoxical increased severity of heart valve disease in children treated by penicillin for subclinical RHD.[36,44] However, children with more significant echocardiographic features might have been deemed suitable for penicillin, leading to selection bias. In addition, in both of these studies, patients prescribed penicillin did not reach the minimum therapeutic compliance rate of 80% that is required to substantially reduce the risk of ARF recurrences.[45]

A randomized controlled trial is currently under way to determine the absolute benefit of secondary

prophylaxis in the setting of subclinical mild RHD (the GOAL [Gwoko Adunu pa Lutino] trial; URL: ClinicalTrials.gov. Unique identifier: NCT03346525).[46] Children with borderline and mild definite RHD are randomized to receive monthly BPG or no BPG (458 in each group). The primary outcome is echocardiographic progression and the secondary outcome is echocardiographic regression at 24 months from time of enrollment, as determined by an expert review panel. The study will also track adverse reactions to BPG. The results of this trial will hopefully provide the most definitive data to date to inform recommendations for follow-up and whether or not BPG prophylaxis in indicated in patients with borderline and mild definite RHD. Further research is also needed to develop methods of systematically improving the delivery of secondary prophylaxis.[47]

Beyond clinical and translational research, cost-effectiveness of echocardiography screening needs to be further assessed. There have been 4 studies to date assessing the cost-effectiveness, all using broad assumptions and restricted to specific healthcare systems but all suggesting that echocardiographic screening is at least cost neutral.[48] If secondary prophylaxis proves to impact latent RHD, then feasibility studies will become urgent before scaling up echocardiography screening to a population level. Making echocardiography a tool that is available to the entire world's population will have benefits beyond RHD.

RHD MANAGEMENT

Registry-Based Care

The WHO recommends RHD registries as a vital adjunct for prevention and control of RHD. Registries are being used in many parts of the world, at global (eg, REMEDY [the Global Rheumatic Heart Disease Registry]),[2] regional or subregional (eg, VALVAFRIC [Registry of Rheumatic Heart Disease in Western and Central Africa]),[49] and national or subnational levels in many countries. However, it is quite likely that current registries cover only a small fraction of the affected populations. Although global registries are useful in studying disease burden, improved management of affected patients is best facilitated by regional registries with close follow-up of affected patients. Primary care providers will need to be involved in the maintenance of RHD registries.

The purpose of establishing registries is to ensure optimal clinical care is provided to patients within available resources. Data from the registry on treatment practices can help in formulating strategies to improve adherence to treatments, thereby improving patient outcomes. Registries are highly useful to support longitudinal treatment programs for patients diagnosed with RHD. Evidence suggests that community-based registries enable more effective secondary prophylaxis services. A contemporary study from New Zealand demonstrated the incremental value of registry-based care.[50] The VALVAFRIC registry has provided important information on in-hospital patient care.[49]

Registries should include information on demographic characteristics; risk factors; details such as clinical presentation of patients, type and severity of valvular lesions, complications, key treatments including surgery and catheterization, and hospital admissions; and details on prophylaxis, including a comprehensive record of penicillin administration. Registries should enable healthcare workers to identify and manage complications on time. Electronic registries with standardized formats have the potential of simplifying data collection using mobile devices such as tablets. Supplemental Figure 6 shows an example of an RHD registry form. Additionally, registries from multiple local sites can be combined to generate national or multinational data. The WHF database collection format developed in 2000 and a recent electronic patient register for RHD (eRegister) can be useful tools for developing RHD registry-based services.[51]

The effectiveness of registry-based care depends on the accuracy of the database, how well it is maintained, and how well the information is disseminated. Challenges in registry-based care include underreporting of cases, requirements for informed consent, and privacy. Maintaining a registry is a complex and relatively expensive process that requires adequate and sustained financial resources.[52] Paper-based registries are further limited by lack of consistency, clarity, data safety, and protection against damage and loss. Computer-based registries require maintenance of hardware and software, training of staff, and reliable internet connectivity. For practical purposes, registries should be user-friendly for local health workers, with minimal data requirements, only those needed to fulfill essential goals (eg, for clinical management or research activities). A fundamental challenge with registry-based care is in countries or regions with large diverse populations, geographic challenges, and a poorly developed primary healthcare network. A practical strategy would be to target the most endemic regions for registry-based care.

Although the utility of registries in RHD management is largely beyond question, their integration into the mainstream health system remains a daunting task.[53] Keeping up with rapid advances in technology is another area that needs attention. Innovative approaches to data collection using mobile phones and tablets need to be considered. Coupling research activities with a comprehensive service delivery program with an aim to maintain a rigorous evidence base for disease management and control should be a priority for all registry-based services.[54] Future research should include utilization of the RHD registry to deliver effective care and improve adherence and tracking of secondary prophylaxis.

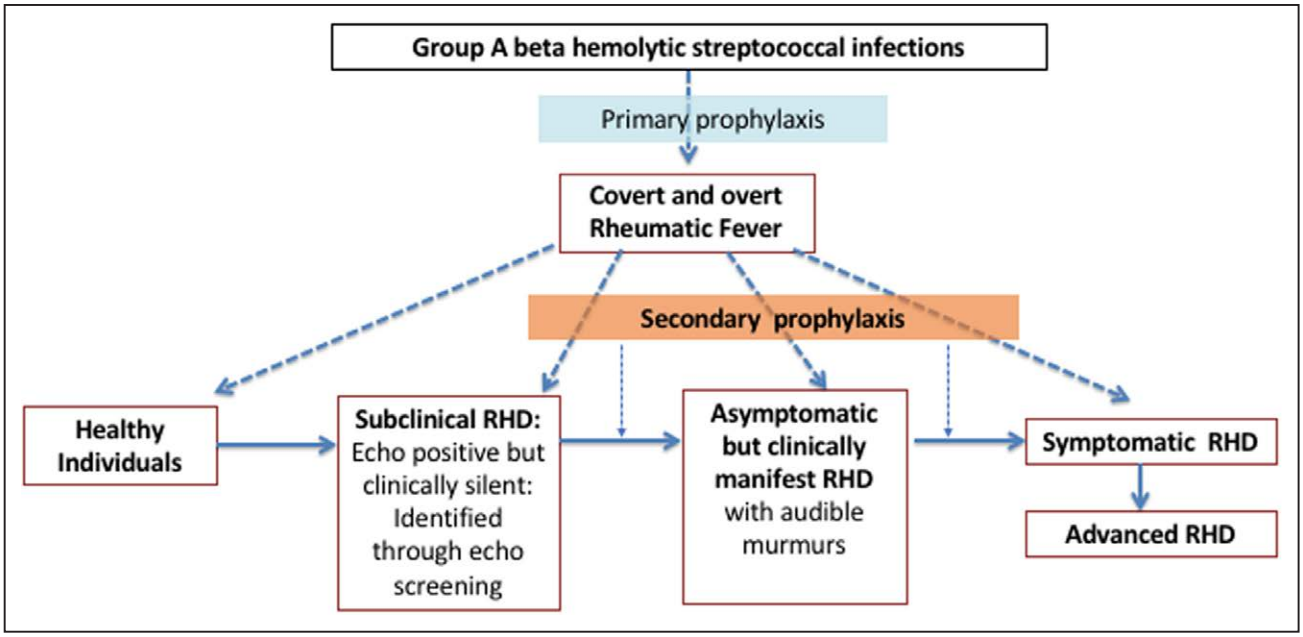

Figure 3. Progression of rheumatic heart disease (RHD): role of penicillin prophylaxis in prevention of RHD and mitigating its progression to advanced heart valve disease.

This flow diagram summarizes the progression to advanced RHD and indicates the role of primary and secondary penicillin prophylaxis based on the currently accepted paradigm of progression of RHD. Primary prophylaxis is used to prevent acute rheumatic fever after identifiable episodes of infection with group A beta hemolytic streptococcus. Secondary prophylaxis seeks to prevent progression of RHD after an episode of acute rheumatic fever or in those with established clinical or subclinical RHD. It may not be possible to prevent the development of subclinical RHD in vulnerable healthy individuals who do not have acute rheumatic fever. Echo indicates echocardiography.

Secondary Penicillin Prophylaxis

Individuals who have had a sentinel episode of ARF are at higher risk for recurrent ARF. ARF becomes less common after 25 years of age and is rarely seen in those >30 years old.[55] Recurrent ARF can cause RHD in those whose hearts were not initially affected and can worsen existing RHD. Treatment of symptomatic streptococcal infections is not adequate to prevent ARF, because asymptomatic GAS can trigger ARF, and recurrent ARF can occur even in the setting of adequate GAS treatment. Thus, secondary prevention (the protection from recurrent episodes of GAS and ARF through continuous antibiotic chemoprophylaxis) is the cornerstone of ARF/RHD management.[56] Figure 3 presents the framework for penicillin prophylaxis in the context of the prevailing understanding of development and progression of RHD.

BPG is the most effective formulation for GAS eradication[57] and is superior to oral penicillin prophylaxis in preventing GAS pharyngitis and recurrent ARF. Of 4 studies directly comparing BPG to oral penicillin, 3 showed children receiving BPG had fewer intercurrent GAS pharyngeal infections (78 versus 313; relative risk, 0.09–0.29) and all 4 showed fewer recurrent episodes of ARF (7 versus 89; relative risk, 0.04–0.13).[58] Every-4-week, or 28-day, dosing of BPG is used in most settings. There are limited data that more frequent dosing, every 2 or 3 weeks, may provide superior protection and more stable penicillin levels,[59] but contemporary data from New Zealand have also shown that ARF recurrences are rare among people fully adherent to a 4-week regimen (0.07 cases per 100 patient years).[55] Current American Heart Association guidelines recommend intramuscular BPG as the preferred agent for secondary prophylaxis, with an every-4-week schedule for most individuals, although an every-3-week schedule can be considered for those at high risk or those who experience recurrent ARF despite high adherence to a 4-week schedule.[60] The pain of BPG injection can be reduced significantly when reconstituted with 1% lidocaine, recommended as best practice.[61] Additional pain relief may be achieved with the addition of a locally applied vibratory device, when available.

High-quality research on the appropriate duration of secondary prophylaxis is lacking, and current recommendations are based mainly on expert opinion. Current national and international recommendations are detailed in Table 2.[60,62–65] The most heavily weighed considerations are the characteristics of initial ARF presentation (age, time since last ARF, rheumatic carditis at presentation) and the presence and severity of chronic RHD. Current American Heart Association recommendations advise secondary prophylaxis for the longer of 5 years or until the age of 21 for those with ARF without carditis, the longer of 10 years or until the age of 21 for those with ARF and resolved carditis, and the longer of 10 years or until the age of 40 (or life) for those with ARF and severe chronic RHD, including after surgical

Table 2. Recommended Durations of Secondary Prophylaxis According to International Guidelines

Guideline	Secondary Prophylaxis Duration Recommended
American (AHA 2009)[60]	ARF with carditis and residual heart disease: until age 40 y or for 10 y after last ARF (whichever is longer); lifetime prophylaxis may be needed
	ARF with carditis but no residual heart disease: until age 21 y or for 10 y after last ARF (whichever is longer)
	ARF without carditis: until age 21 y or for 5 y after last ARF (whichever is longer)
WHO Expert Consultation Geneva (2004)[63]	Lifelong if severe valvular disease or after valve surgery
	For 10 y after last ARF or until age 25 y in patients with previous diagnosis of carditis
	For 5 y after last ARF or until age 18 y in patients without proven carditis
Indian (2008)[64]	Lifelong in severe disease or postintervention patients; may opt for secondary prophylaxis until age 40 y
	ARF with healed, mild, or moderate carditis: until age 25 y or for 10 y after last ARF (whichever is longer)
	ARF without carditis: until age 18 y or for 5 y after last ARF (whichever is longer)
New Zealand (2014)[65]	After definite/probable ARF, continue prophylaxis for at least 10 y; consider 5 y of prophylaxis after ARF in patients with mild or no carditis >21 y of age or in patients with ARF classified as "possible"
	Severe RHD generally until age 40 y, with review at age 30 y
	Moderate RHD until age 30 y
	Mild RHD or ARF without RHD diagnosis, until age 21 y or for 10 y after last ARF (whichever is longer)
Australian (2020)[62]	Possible ARF: 12 mo
	Probable or definite ARF without carditis: minimum of 5 y or until age 21 y (whichever is longer)
	Borderline RHD: not usually recommended but can be considered for 1–3 y based on risk factors
	Mild RHD: If documented history of ARF, then a minimum of 10 y after the most recent episode of ARF or until age 21 y (whichever is longer) If no documented history of ARF and aged <35 y, then a minimum of 5 y after diagnosis of RHD or until age 21 y (whichever is longer)
	Moderate RHD: If documented history of ARF, then a minimum of 10 y after the most recent episode of ARF or until age 35 y (whichever is longer) If no documented history of ARF and aged <35 y, then a minimum of 5 y after diagnosis of RHD or until age 35 y (whichever is longer)
	Severe RHD: If documented history of ARF, then a minimum of 10 y after the most recent episode of ARF or until age 40 y (whichever is longer) If no documented history of ARF, then a minimum of 5 y after diagnosis of RHD or until age 40 y (whichever is longer)

AHA indicates American Heart Association; ARF, acute rheumatic fever; RHD, rheumatic heart disease; and WHO, World Health Organization.

repair or valve replacement.[60] The national guidelines in New Zealand recommend a slightly longer minimum course: the longer of 10 years or until the age of 21 as a minimum for all RF, with longer duration for those with moderate (until 30 years of age) and severe (until 40 years of age or life) RHD. Before stopping prophylaxis, an individual's risk of GAS exposure, including high-risk status (teachers, parents, healthcare providers, etc) and high-risk GAS transmission environments (poor housing conditions, overcrowding, etc), should be considered.

The majority of patients with clinically or echocardiographically detected RHD do not have a documented history of ARF, and hence, current guidelines on duration of secondary prophylaxis may not directly apply.[60] Although the WHF guidelines clearly state that secondary prophylaxis should be begun in those with echocardiographically detected definite RHD, whether clinical or subclinical, they do not specify duration.[19] There is an urgent need to update existing management guidelines and to address this gap in recommendations that apply to the majority of patients in the world with RHD. Table 3 outlines priorities for defining secondary prevention in many groups of patients that do not fall within current published guidelines. This table is not meant to be prescriptive; more data are needed before specific recommendations for use and duration of secondary prophylaxis in these groups can be formulated.

Historic data from the early and mid-20th century provide unequivocal evidence that secondary prevention improves cardiac outcomes after ARF. In a comparison of 2 longitudinal ARF cohorts, 1 with and 1 without secondary prevention, 70% of children in whom secondary prevention was used showed auscultatory regression compared with only 20% of those who did not receive secondary prevention.[13] Data from contemporary global cohorts also suggest high BPG adherence reduces ARF risk and improves outcomes.[66] However, there are limited data supporting the widely used target

Table 3. Priorities for Defining Minimum Duration of Secondary Prophylaxis

Category	Definition	Comments
Possible (uncertain) ARF	Normal echocardiogram	Reassess in 12 mo. If ARF remains uncertain, consider ceasing; if highly suspected or definite ARF, continue as indicated
Probable (highly suspected) and definite ARF	Normal echocardiogram	Abbreviated prophylaxis (5 y after last episode or 21 y of age) as per standard recommendation
Borderline RHD	Borderline RHD detected on echocardiography without a history of ARF	In some cases, based on nonechocardiographic risk factors such as family history of RHD, individuals may opt to commence secondary prophylaxis to reduce risk of ARF; in these cases, it should be prescribed as per mild RHD
Mild RHD	May or may not be associated with a cardiac murmur	Risk of recurrence is extremely low in people aged >40 y. In some cases (eg, when the patient decides they want to reduce even a minimal risk of recurrence), prophylaxis may be continued beyond the age of 40 y, or even for life. Lifelong prophylaxis is preferable for patients who have had cardiac valve surgery
Moderate RHD	Moderate RHD (asymptomatic) with normal left ventricular function	
Severe RHD	Severe RHD, previous valve repairs or prosthetic valves, or symptomatic moderate RHD	

ARF indicates acute rheumatic fever; and RHD, rheumatic heart disease

of ≥80% to define "good" or "high" adherence and inconsistent ways this figure is calculated (total injections received versus continuous data on days of adequate coverage). Recently, data from an Australian Northern Territory RHD register showed the risk of recurrent ARF decreased once a person had received at least 40% of BPG doses, after which there was a further 17% decreased risk for every 10% increase in adherence.[45] This cohort also showed an all-cause survival benefit of higher adherence (12% lower risk for each 10% increase in adherence),[45] although a large multinational study did not show this benefit.[26]

Maintaining high BPG adherence remains a global challenge, and more research is needed to explore and enable improved delivery, update, and adherence to BPG.[67] Data across populations suggest the pain of injections, difficulty attending injection clinics, and financial constraints are barriers to receipt of BPG, whereas strong patient-nurse relationships, dedicated staff for BPG injections, patient education, and an individual sense of responsibility for injections are enablers.[68] In Uganda, a cascade-of-care analysis demonstrated retention in care was the most powerful driver of adherence, with those retained showing 92% adherence to BPG.[36] This model could be useful in other settings to assess and monitor health system performance for BPG delivery. Registry-based care with recall systems may improve uptake and is currently recommended as best practice for the delivery of secondary prophylaxis.[67] Incentivizing BPG through mobile phone money was assessed in a single study.[69] BPG uptake, in particular for partially adherent patients, increased, although the intervention was costly ($989 for each successful injection; costs included phones, visits, and medical staff resources), and efficacy of the intervention decreased with time.[69] Adherence to secondary prophylaxis did not improve in a community-based approach stepped-wedge randomized trial in Australia.[47]

Adverse reactions to BPG further limit compliance and can have a devastating impact on regional control efforts. Until recently, deaths in the minutes and hours after BPG injection have been presumed to be anaphylactic. However, a growing number of anecdotal reports of immediate or nearly immediate BPG-related deaths do not have features of classic anaphylaxis. In a recent case review of 10 cases from 5 countries, 7 cases showed remarkable similarity: patients with severe valvular RHD who lost consciousness shortly after BPG injection and could not be resuscitated.[70] These deaths appear predominantly hemodynamic: a painful BPG injection leading to hypotension, decreased coronary perfusion, ventricular arrhythmias, and death in a patient with significant existing cardiovascular compromise. These reactions are likely exacerbated by conditions common in LMICs: dehydrated and hungry patients who have travelled long distances and waited hours for injections. Formal guidance focused on precautions for high-risk patients, including adequate hydration and staying supine after injections, should be disseminated to frontline healthcare workers delivering BPG. Additional research is needed, but these cases have led to a growing global dialogue questioning whether the benefits of BPG over oral penicillin outweigh the risks in all patients or in all contexts, although BPG prophylaxis provides superior ARF prevention.

Historical data from the 1930s, 1940s, 1950s, and 1960s provide no supporting evidence for the role of tonsillectomy in prevention of ARF and RHD. The New Zealand rheumatic fever guidelines 2019 update on GAS sore throat management provides a comprehensive review of this subject.[71]

Medical Management of Heart Failure

Management principles for RHD in the young are often extrapolated from published guidelines for adult

patients. Guidelines for valvular heart disease stress the overall strong evidence-based support for surgical and catheter-based intervention for severe or symptomatic valvular heart disease.[16] In contrast, the guidelines describe little evidence-based support for pharmacological management of severe valvular heart disease to alter outcomes. Unfortunately, the majority of the global burden of symptomatic RHD exists in regions of the world where definitive surgical or catheter-based treatment may not be available.[1,3] For such patients, pharmacological management is often the only option that may allow for symptomatic improvement.[72] The REMEDY study and a single-country report from Uganda highlight the large gap between patients in need of surgery and those who actually receive it in LMICs.[2,27]

Symptomatic medical management of moderate to severe MR includes diuretic agents (loop diuretic agents and spironolactone) and afterload reduction with vasodilator therapy, most often angiotensin-converting enzyme inhibition and angiotensin II receptor blockers. Additionally, digoxin and β-blockade may be considered. There are a few small studies specifically focused on medical management of RHD. Treatment with enalapril resulted in a significant reduction in left ventricular diameter and volume relative to placebo in 47 patients with MR, 26 with RHD.[73] A Turkish study reported similarly that the addition of angiotensin-converting enzyme inhibition lowered left ventricular end-diastolic volume and atrial natriuretic peptide levels after 20 days of treatment.[74] Both enalapril and nicorandil (a balanced vasodilator) resulted in decreased left ventricular systolic volume and increased ejection fraction in 87 patients with RHD with severe MR over 6 months; nicorandil had a greater effect.[75] The management of RHD must also include differentiation between primary and secondary RHD (from ischemia or other causes of cardiomyopathy).

The only proven effective treatment for MS is catheter or surgical intervention. Diuretic agents are indicated to reduce preload. Loop diuretic agents are useful in acute pulmonary edema and for long-term management; however, overdiuresis can reduce preload and compromise cardiac output. Other diuretic agents such as aldosterone blockers (spironolactone and eplerenone) and thiazide diuretic drugs (metolazone and chlorthalidone) are also used. β-Blockers reduce the heart rate through their negative chronotropic effect, allowing for greater diastolic filling into the left ventricle, and this can help reduce left atrial pressure and provide symptom relief.

As yet, no medical therapy has been shown to slow the progression of AR, and so treatment is predominantly targeted at symptom relief and treatment of underlying left ventricular dysfunction and heart failure. Treatment with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and β-blockers has been shown to be beneficial in large population cohort studies in patients with AR, particularly those with left ventricular dysfunction.[76] Treatment of other associated comorbidities, such as hypertension, should also be considered.

There are no scientific data to guide medical management of mixed valve disease, and surgery is often indicated. In the most common scenario of multivalve disease with MR and AR, medical therapy with afterload reduction, diuretic agents, and possibly β-blockade may be complementary. Conversely, in mixed mitral valve disease, diuretic agents may be the only medical therapy available.

Atrial Fibrillation

Atrial fibrillation is a common complication of RHD. The prevalence of atrial fibrillation is dependent on the type of valvular involvement,[77] and its presence in any form is associated with a poor prognosis with or without valve intervention.[26,78] The highest frequency of atrial fibrillation was found in patients with a combination of mixed mitral valve disease and tricuspid regurgitation (70%) versus isolated MS (29%) or isolated MR (16%).[77] Factors associated with atrial fibrillation include age, left ventricular ejection fraction, left atrial size, left atrial strain, and right atrial pressure.[79] Complications of atrial fibrillation include heart failure, stroke, peripheral thromboembolism, and premature death.[26] Efficacy and superiority of rhythm control over rate control with nondihydropyridine calcium channel blockers or β-blockers for treatment of symptomatic atrial fibrillation and maintenance of sinus rhythm have been demonstrated in small, single-center randomized trials using either electric and pharmacological (usually amiodarone) cardioversion or catheter ablation[80] in addition to valvular interventions when indicated, but these strategies are not generalizable to all patients and may not be readily available or affordable in LMICs.

Anticoagulation with oral vitamin K antagonists or direct thrombin or factor Xa inhibitors (direct-acting oral anticoagulants) is recommended for stroke prevention when there is atrial fibrillation or atrial flutter.[81] However, it is unknown whether direct-acting oral anticoagulants are efficacious in patients with moderate to severe rheumatic mitral valve stenosis because these patients were excluded from the randomized clinical trials of direct-acting oral anticoagulants.[81] The INVICTUS-VKA (Investigation of Rheumatic Atrial Fibrillation Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies, Non-Inferiority) noninferiority trial is currently enrolling participants to evaluate the noninferiority of a direct-acting oral anticoagulant (rivaroxaban) versus standard vitamin K antagonist therapy in patients with RHD and atrial fibrillation/flutter. The role for percutaneous approaches to occlude the left atrial appendage[81] in young patients

with RHD and atrial fibrillation is unknown; however, cost considerations and the fact that left atrial clots in RHD are not limited to the left atrial appendage alone may limit their application.

Endocarditis

IE is a relatively uncommon but severe disease that still carries high mortality rates, approaching 30% at 1 year.[82] The epidemiology and management of IE has drastically changed over the past 2 decades in Western countries, where IE has become a healthcare-related disease in elderly patients early after heart valve surgery. The true burden of IE remains unknown, mainly because of the scarcity of data from low-income countries. In the few studies from LMICs, RHD was found to be the underlying valve disease in 5.4% to 77% of cases.[83] In New Caledonia, a French Pacific island, Oceanic Islanders had a significantly higher incidence of IE than non-Oceanic (mainly European) populations. RHD was the most common underlying valve condition among Oceanic islanders, with a proportion of ≈35% *Streptococcus spp* (ie, oral streptococci) IE.[84] Therefore, the characteristics of IE may differ between countries where RHD has nearly been eradicated and those where RHD is still endemic.

Guidelines have considerably reduced the role of antibiotic prophylaxis before dental procedures because of the lack of scientific evidence of the reduction of IE burden when using prophylaxis.[85] The guidelines have then been reinforced by the absence of peak incidence of *Streptococcus sp* IE in high-income countries after their publication.[86] There is uncertainty whether these Western guidelines are valid for LMICs, where dental hygiene is much poorer.

The higher incidence of IE caused by *Streptococcus sp* among endemic RHD populations raises several questions around the indication of prophylaxis before dental procedures. Need for prophylaxis before dental procedures has not been established in settings where *Streptococcus spp* remain a leading pathogen. Poor access to oral health services in low- and lower-middle-income settings may render the question of prophylaxis hypothetical. Clustered randomized intervention studies at regional or national levels could help to answer the question. Dental health policies should, however, be promoted as a general recommendation for all RHD patients.

Pregnancy

Medical management of women before, during, and after pregnancy with unoperated and operated RHD is a challenge and requires a multidisciplinary team of physicians, cardiologists, obstetricians, anesthesiologists, and sometimes cardiothoracic surgeons.

Unoperated RHD is most commonly diagnosed in pregnancy when the increase in cardiac output and drop in vascular resistance unmask moderate or severe valve lesions, and it contributes to maternal mortality (within 42 days after delivery) and late maternal death (up to 1 year postpartum).[87,88] Therefore, all women with RHD have an increased risk of poor maternal and fetal outcomes, which increases further in the presence of left or right ventricular dysfunction, pulmonary hypertension, atrial fibrillation, and any signs of heart failure. Stenotic lesions are less well tolerated than regurgitant lesions and occasionally require interventions that include BMV, cardiothoracic surgery, or termination of pregnancy.[88]

Appropriate preconception counseling, including advice on contraception, should be the goal but is unfortunately not the reality. The REMEDY study showed that only 5% of women with prosthetic heart valves and 2% of those with severe MS were on contraception. A recent study of 3506 pregnant women (who underwent echocardiography screening in the second or third trimester) in Uganda found that 1.7% had cardiac disease, 88% of which was RHD. Additionally, the study found that <5% of women were aware of their diagnosis, 50% required intervention or change in delivery planning, and the attributable risk of heart disease on maternal mortality was 11%.[33] Maternal and infant mortality were higher in women with heart disease.

Women with mechanical valve replacement require anticoagulation throughout the pregnancy, which can include warfarin, unfractionated heparin, or low-molecular-weight heparin.[89] Management of these women is complex, and maternal and fetal risk differ according to treatment regimen. In women needing warfarin ≤5 mg/d, the medication should be continued until the end of the pregnancy, whereas in others a more complex treatment algorithm needs to be instituted.[89]

Percutaneous Interventions

In symptomatic patients with severe isolated rheumatic MS, the low cost and rapid turnaround time associated with BMV compared with open heart surgery make it an attractive option. Moreover, studies have shown that long-term outcomes are comparable between BMV and open mitral commissurotomy.[90] BMV is often the preferred option in younger patients who have an absolute or relative contraindication to anticoagulation, severe MS that manifests during pregnancy, and selected patients with restenosis after surgical valvotomy. It can be repeated for those who develop restenosis after previous BMV. Almost 80% of symptomatic patients with severe RHD MS are candidates for BMV, leaving only 20% to undergo surgery because of unfavorable anatomy and high Wilkins score.[91] Although balloon dilation is traditionally reserved for pure mitral valve

Table 4. Case Selection for Balloon Mitral Valvuloplasty

Criterion	Key Considerations	Key References
Age	Extremes of age; in the very young (juvenile MS), the procedure may be technically challenging, and smaller sizes of the Inoue balloon may be needed; older patients have a higher likelihood of atrial fibrillation, atrial thrombi, and calcified valves	95
PH and right-sided heart failure	Severe PH does not preclude BMV. PH tends to resolve over time if severe.	99
Previous BMV/surgical valvotomy	BMV can be successfully performed in those who have had a previous BMV or surgical valvotomy; results are dependent on the mitral valve anatomy.	92
Atrial fibrillation, LA or atrial appendage thrombus	Atrial fibrillation mandates careful imaging (often through TEE) to rule out a thrombus in the LA or atrial appendage; although an LA clot is considered a contraindication for BMV, selected patients with a small organized clot in the atrial appendage may undergo BMV by an experienced operator.	96
Associated aortic valve disease	BMV can be performed in presence of mild or moderate aortic valve regurgitation; careful preprocedural echocardiography is mandatory.	93
Associated tricuspid valve disease	TR resulting from PH often resolves after BMV, but TR resulting from organic involvement of the tricuspid valve by RHD may not. Additionally, dilation of right atrium makes transseptal puncture challenging. Results of BMV are sometimes suboptimal in the presence of severe TR.	98
Associated MR	Mild central mitral valve regurgitation ("fixed orifice") does not constitute a contraindication for BMV; however, commissural MR is likely to progress after BMV. Echocardiography should be performed with care to distinguish between these 2 forms of MR.	94
Mitral valve morphology	The critical elements that constitute the Wilkins score include leaflet mobility, valve thickness, subvalvular thickening, and calcification. Good immediate and long-term results can be expected for scores under 8. Additionally, specific echocardiographic characteristics of the mitral valve may predict a higher than usual likelihood of MR after BMV; these include localized calcification of the leaflet margin at commissure.	97

BMV indicates balloon mitral valvuloplasty; LA, left atrium; MR, mitral regurgitation; MS, mitral stenosis; PH, pulmonary hypertension; RHD, rheumatic heart disease; TEE, transesophageal echocardiography; and TR, tricuspid regurgitation.

stenosis, selected patients with mild central MR can also undergo BMV (Table 4).[92–99] For pregnant women with severe MS, BMV can be lifesaving and can be accomplished with minimal complication rates and low fluoroscopy times.

The equipment, infrastructure, and expertise for BMV are easier to organize than open-heart surgery. The procedure can be performed expeditiously with a short turnaround time. Although the costs of BMV are much lower that open heart surgery, most of the affected patients still cannot afford the procedure. The requirements needed to perform BMV are listed in Supplemental Table 5. With careful case selection and attention to detail in individual steps, excellent results can be expected, and 80% of patients achieve valve areas in excess of 1.5 cm^2.

Immediate catastrophic complications after BMV occur in 2% to 5% of procedures and include cardiac tamponade, stroke, and acute MR. A ruptured valve leaflet requires urgent surgery. Rarely, surgery is needed to rescue a patient from cardiac tamponade after attempted transseptal puncture. The need for surgery, although infrequent, is unavoidable as more and more cases are performed, but with increasing expertise and refined case selection, the need for emergency surgery declines considerably. However, there is a need for surgical backup to be available in the same institution in which BMV is performed. Centers without the possibility of surgical backup may need to limit BMV to a small number of carefully selected cases.

Given the fact that BMV is much less resource intensive than surgery, it is necessary to develop a sustainable, low-cost model for BMV in environments that need it the most. Acquiring the skill set for BMV may initially necessitate a steep learning curve, but the procedure subsequently becomes routine. Initial equipment and logistics may be challenging but become manageable as well. A BMV center that performs the Inoue technique with conscious sedation, transthoracic echocardiography guidance, and the possibility of resterilization and reuse of the balloon can make it relatively affordable. Low-cost options are available as alternatives to the Inoue balloon. The most significant barrier to widespread application of BMV is the prospect of emergency surgery in a small number of patients. It is necessary to overcome this barrier through collective efforts and advocacy.

Percutaneous valve implantation holds promise,[100] especially if this work can be expanded to the mitral valve as a treatment for severe MR or mixed mitral disease. However, the application of these technologies in young rheumatic patients appears less probable in the foreseeable future, primarily because current techniques and devices are less appropriate for rheumatic MR that requires valves with annulus sizes well over 3 cm.

Surgery

When there is severe valvular dysfunction, especially if the patient is symptomatic, surgery is indicated. The

exception is for isolated severe MS, for which BMV may be the procedure of choice. Indications for surgery are similar to those of nonrheumatic pathologies, both for the mitral and the aortic valves. Accompanying tricuspid regurgitation is frequent, especially in chronic rheumatic mitral valve disease, and often requires simultaneous surgery. There is evidence to support removal of the left atrial appendage during surgery in patients with atrial fibrillation, but indications are less clear in patients in sinus rhythm, although the left atrial appendage is a potential substrate for thromboembolic events.[101]

When surgery is undertaken, the question of the type of procedure—repair versus replacement—arises and is especially relevant in young patients from underprivileged regions of the globe, who face significant challenges to be compliant with any form of medical therapy, including secondary prophylaxis of ARF and anticoagulation therapy. In these cases, the importance of repair, especially of the mitral valve, is therefore unquestionable. Global survival and survival free from prosthetic valve complications are lower after valve replacement with either mechanical or biological prostheses, because of higher rates of thromboembolism in the former and a faster degenerative process in the latter. The lower incidence of these complications with aortic prostheses and the greater difficulty with aortic valve repair makes aortic valve replacement more acceptable.

Rheumatic mitral valve repair has evolved significantly since the first reports by Carpentier, Duran, and others in the 1970s. Several aspects of the technique have been perfected, and new procedures, such as artificial chordal implantation, have made rheumatic mitral valve repair more standardized and reproducible. Recent reports have shown better early and late results, including in children. The majority of surgeons with experience in these cases have recently reported feasibility of the repair in 75% to 80% of the patients and long-term survival superior to those after valve replacement.[102] However, the durability of repair of the rheumatic mitral valve is generally poorer than in nonrheumatic valves.[103] Additionally, in RHD-endemic regions with emerging surgery programs, the most important considerations may be the risk of needing reoperation given limited resources (and low probability of being able to get a second operation) and the surgical team having more expertise in valve replacement than repair. As a result, valve replacement is often the practice of choice in many settings, especially for double-valve surgery, despite the need for lifetime anticoagulation.

When aortic valve repair is not possible, there remains the question of the choice of valve substitute, essentially between mechanical prostheses and bioprostheses. As mentioned, both types of prostheses have a higher incidence of complications, especially in young patients, and there is no clear evidence of superiority of either one. Poor compliance with anticoagulation remains an important factor in the decision against a mechanical valve, but degeneration of bioprostheses may progress so fast that death may occur before reoperation can be undertaken.

Access to surgery remains one of the most important problems in LMICs where RHD is endemic. Only a few of these countries have cardiac surgical facilities, and only infrequently do their rheumatic patients have access to surgery elsewhere. Open heart surgery is expensive, and other priorities, in health and otherwise, render eventual hopes for creating such facilities an elusive goal. That is what happens especially in SSA countries.[104] With the exception of South Africa, cardiac surgery is performed independently, without visiting mission teams, in only a few countries. Continued efforts to reduce costs of care are needed. The TTK Chitra prosthetic heart valve is an example of a low-cost solution that was developed in an LMIC and offers an affordable alternative.[105] Low-cost valve rings and open heart surgery disposables need to be explored urgently to bring down costs.

In a study reported by Yankah et al in 2014,[106] it was found that there were 3 cardiothoracic surgeons per 1 million inhabitants in North Africa and 1 cardiothoracic surgeon per 3.3 million people in SSA. The identified 156 cardiothoracic surgeons in Africa (South Africa excluded) represented a surgeon to population ratio of 1:5.9 million people. In SSA, the ratio was 1 surgeon per 14.3 million. Open heart operations were performed at a rate of ≈12 per million inhabitants in Africa, 92 per million in North Africa, and 2 per million in SSA. By comparison, the European median is 500 to 600 per million (>1250 per million in Germany) and ≈1300 per million in the United States (Supplemental Figure 7).

In other LMICs, the existing facilities fall very short of an adequate response to the burden of the disease, which is estimated at millions of potential surgical candidates. Fewer than 10% of patients with RHD living in Africa who need a mitral valve operation actually undergo surgery. Although we have witnessed some progress in the past few decades in most countries of Central and South America, North Africa, and South and East Asia, this is far from satisfying the needs. In sites with limited resources, there is frequently competition from congenital heart diseases that may receive preferential case selection by the surgical teams. It is estimated that severe congenital heart diseases requiring surgical care occur in 2.5 to 3 per 1000 live births. Surgery for congenital heart diseases tends to be offered to children originating from better off population groups who have better access to health care, whereas patients with RHD more often originate from poorer sectors of the population with lesser access to health care. However, there is an opportunity to leverage the need for congenital heart disease and RHD surgery together to advocate for expanded resources.

OUTCOMES

Mortality and Morbidity: Lessons Learned From REMEDY

The Global Rheumatic Heart Disease Registry (the REMEDY study) assembled a contemporary cohort of 3343 RHD patients from 14 LMICs to document patient characteristics and treatment patterns with particular reference to valvular involvement, the prevalence of adverse cardiac events, and the use of key interventions.[2,26] Patients with RHD were young (median age 28 years), mainly female (66.2%), and largely unemployed (75.3%). The majority (63.9%) of patients had moderate to severe multivalvular disease, complicated by congestive heart failure (33.4%), pulmonary hypertension (28.8%), atrial fibrillation (21.8%), stroke (7.1%), IE (4%), and major bleeding (2.7%).

The pattern of native disease showed multivalvar disease across the entire age spectrum, indicative of severity of disease in patients enrolled and demonstrating a clear need for advanced surgical and medical intervention, lacking in most of these countries (Supplemental Figure 8).

Two studies focusing on RHD incidence, both from Africa, demonstrated the predominance and the high burden of morbidity in older populations. In the Heart of Soweto study, Sliwa et al[17] reviewed all new cases (n=4005) of RHD within a 24-month enrollment period and found that 68% were women, with 16% in higher New York Heart Association functional class, 17% with renal dysfunction, and 9% with atrial fibrillation at presentation. Within 30 months of diagnosis, 26% of the total cohort were admitted to hospital, and 225 underwent surgery.[17] In Tunisia, a study of 676 patients newly admitted for RHD estimated the standardized incidence rate for RHD. The standardized incidence rate per 100 000 person-years was 10.97, 9.3 in men and 19.1 in women, respectively. Hospitalizations for women were also significantly higher, with 728 hospitalizations for RHD, representing 2.5% of all cardiology hospitalizations (95% CI, 2.3%–2.7%), with a prevalence of 13.3% for women aged 15 to 29 years.[107] Among patients hospitalized for acute heart failure in a multicenter study,[108] women were younger and more likely to have atrial fibrillation and RHD despite similar outcomes. The outcomes for patients with RHD presenting with acute heart failure were dismal. In REMEDY, the 2-year case fatality rate was high (500 deaths, 16.9%). The mortality rate was 116.3 per 1000 patient-years in the first year and 65.4 per 1000 patient-years in the second year. Median age at death was 28.7 years. Independent predictors of death were severe valve disease (hazard ratio [HR], 2.36 [95% CI, 1.80–3.11]), congestive heart failure (HR, 2.16 [95% CI, 1.70–2.72]), New York Heart Association functional class III/IV (HR, 1.67 [95% CI, 1.32–2.10]), atrial fibrillation (HR, 1.40 [95% CI, 1.10–1.78]), and older age (HR, 1.02 [95% CI, 1.01–1.02] per year increase) at enrollment. In addition, low-income countries showed a significantly higher mortality after adjustment for age and sex.[26]

REMEDY also demonstrated significant morbidity. Two hundred four patients (6.9%) had new congestive heart failure (incidence, 38.42/1000 patient-years), 46 (1.6%) had a stroke or transient ischemic attack (8.45/1000 patient-years), 19 (0.6%) had recurrent ARF (3.49/1000 patient-years), and 20 (0.7%) had IE (3.65/1000 patient-years). More than 1 in 5 patients, 22.1% (657/2960) of those with follow-up, experienced a significant adverse medical event in the 24 months after enrollment in the study.[26] The contribution of advanced disease, poor resources, and lack of surgical and medical interventions to mortality and morbidity, as well as suboptimal use of evidenced-based interventions such as secondary prophylaxis, warfarin, and reproductive health care in women of child-bearing age, in these LMICS is starkly apparent.

Impact of Surgery and Catheterization

Long-term results after BMV suggest a sustained benefit in ≈75% of patients. During long-term follow-up, mortality is relatively uncommon, but a variable proportion of patients (8%–10%) require repeat balloon valvuloplasty or surgery because of fibrous stenosis. Advanced disease as suggested by functional class II, III, or IV status at presentation, an echocardiographic Wilkins score >8, advanced age, and residual valve area <1.75 cm^2 are all predictive of poor long-term results.[109]

Although long-term results after surgical closed mitral commissurotomy are comparable if not superior to balloon procedure, this procedure is seldom performed these days, presumably because the required surgical expertise is uncommon among modern cardiac surgeons. Although the long-term results of open mitral commissurotomy are similar to BMV, surgical outcomes are consistently superior in patients with Wilkins score >8.[90]

Because atrial fibrillation can continue to occur even after successful BMV or surgical commissurotomy, with the attendant risk of stroke, monitoring of rhythm during follow-up is important, and anticoagulation is indicated for those with intermittent or persistent atrial fibrillation. The challenges of compliance and the requirement of monitoring after long-term oral anticoagulation after mitral valve replacement have been the impetus for acceptance of mitral valve repair as standard of care for RHD.[25,102] These challenges are especially relevant in women in the reproductive age group. On the other hand, the durability of heart valve repair is determined by compliance with secondary penicillin prophylaxis, especially among younger patients. These are significant considerations in most low-resource

environments and often influence the decision at the time of initial operation. The long-term results of isolated aortic valve replacement are generally superior to those of mitral valve replacement.

Repair of the tricuspid valve is required at the time of initial mitral or aortic valve surgery in selected patients with organic rheumatic involvement of the tricuspid valve. However, tricuspid valve dysfunction does progress over time, and there is a need for reoperation during late follow-up.[110]

Palliative Care

Unfortunately, most children and young adults in the world with RHD do not have access to life-saving cardiac surgical intervention.[2,26] Prognostication is difficult, and young patients often decompensate gradually over the course of weeks, months, or years as the result of congestive cardiac failure, pulmonary hypertension, and atrial arrhythmias.[2,26] It is the terrible reality that patients from remote and resource-poor settings often receive no formal counseling or palliative care support.[111] Diuretic drugs and morphine are proven to reduce respiratory distress and improve the quality of end-of-life care, yet these are not currently available to the majority of the world's population.[111] While awaiting socioeconomic and political changes to rid the world of RHD,[4] children and young adults should have the right access to basic and culturally appropriate palliative care, which has been shown to reduce depression and anxiety and to improve quality of life scores.[111]

CONCLUSIONS

The WHF has called for a 25% reduction in the burden of RHD by 2025. Achieving this goal and ultimately reaching near-elimination of RHD in LMICs is one of the most critical challenges facing the global cardiovascular community today.[67] The 71st WHO Assembly adopted a resolution on RHD in June 2018. Representatives of 26 member states and 6 nongovernmental organizations spoke in support of the resolution, recognizing that RHD remains a significant public health concern in many countries.

The diagnosis and current management of RHD described in this statement highlight many of the gaps that need to be addressed to meet the WHF mandate and operationalize the WHO resolution. Increased funding for research to expand scientific discovery and update what was learned in the 20th century is critical. Early diagnosis, including echocardiography screening, holds promise for both raising awareness and developing prevention strategies that can decrease the need for intervention. However, many research questions need to be answered before this can become public policy.

Treatment of advanced RHD remains a major problem with no solution in sight. Medical treatment provides limited symptomatic relief, but advanced RHD and its complications can only be addressed by interventional catheterization and surgery. Missions by humanitarian teams provide invaluable life-changing care for the small number of patients treated, but these do not constitute a sustainable solution. Building local capacity is the only true solution for this serious public health problem.

The Cape Town declaration on access to cardiac surgery in the developing world,[112] signed in 2018, proposes "a framework structure to create a coordinated and transparent international alliance to address this inequality." The declaration defines 2 aims: (1) "to establish an international working group (coalition) of individuals from cardiac surgery societies and representatives from industry, cardiology, and government to evaluate and endorse the development of cardiac care in low- to middle-income countries"; and (2) "to advocate for the training of cardiac surgeons and other key specialized caregivers at identified and endorsed centers in low- to middle-income countries."

This body of work forms a foundation on which a companion document on advocacy for RHD (Beaton et al[113]) has been developed. Ultimately, the combination of expanded treatment options, research, and advocacy built on existing knowledge and science provides the best opportunity to address the 21st century humanitarian crisis of RHD.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

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†Significant.

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