JACC FOCUS SEMINAR: TROPICAL MEDICINE

JACC FOCUS SEMINAR

Rheumatic Heart Disease

JACC Focus Seminar 2/4

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ABSTRACT

It is a sad reality that although eminently preventable, and despite possessing such knowledge for >70 years, rheumatic heart disease (RHD) remains the most common cause of cardiovascular morbidity and early mortality in young people worldwide. A disease of the poor, RHD is one of the most neglected diseases. Several challenges are unique to the acute rheumatic fever/RHD continuum and contribute to its persistence, including its sequestration among the poorest, its protracted natural history, the erratic availability of penicillin, and the lack of a concerted effort in endemic regions. However, there is cause for optimism following a resurgence in scientific interest over the last 15 years. This review presents the latest advancements in epidemiology, diagnosis, and management. It also discusses pressing research questions on disease pathophysiology, the barriers to implementation of effective management strategies, and pragmatic policy solutions required for translation of current knowledge into meaningful action. (J Am Coll Cardiol 2023;81:81–94) © 2023 by the American College of Cardiology Foundation.

M uch has changed since Dr W.B. Cheadle first proposed the modern concept of the rheumatic state in his Harveian lectures in 1889 by opening with the words "There is perhaps no serious disease more familiar to us than acute articular rheumatism; it is one of the disorders most commonly seen in the wards of a general hospital; it is constantly encountered in private practice."[1] By the early part of the 20th century, Dr Cheadle's observations continued to ring true: acute rheumatic fever (ARF) had killed more 5- to 20-year-olds than any other illness in that era,[2] and children with ARF still occupied many of the beds in pediatric wards in high-income countries (HICs).

However, in the latter half of the 20th century, a dramatic epidemiologic shift unfolded: the disease had virtually disappeared in almost all HICs. Indeed, ARF has declined to such an extent in these populations that most physicians today are unlikely to ever encounter a case of ARF, and their experience with rheumatic heart disease (RHD) is usually restricted to older patients with advanced valvular lesions and its attendant complications.

This remarkable epidemiologic transformation probably owes much to the socioeconomic developments that HICs experienced over the last century, developments that have not been afforded to resource-limited populations which comprise >80% of the world's population and where ARF and RHD remain bigger problems than ever.

From a truly global disease in the 19th and 20th centuries, ARF has become a disease of crowding and poverty in the 21st century. Despite this stupendous advancement, the Global Burden of Disease estimates

that 40.5 million people currently live with RHD and 306,000 currently die of this disease each year.[3] A recent analysis has also shown that RHD receives the least funding relative to disease burden across a range of 16 tropical diseases. For example, the RHD funding/disability-adjusted life years is 100-fold less than for HIV/AIDS.[4] Over the last 15 years, however, a renaissance of innovative thinking has generated new optimism and brought the field closer to the forefront of scientific interest and international attention, driven in large part by a better understanding of the true disease burden (**Central Illustration**).

In 2005, a landmark study by Carapetis et al[5] estimated that RHD represents the greatest disease burden worldwide among diseases caused by group A *Streptococcus* (GAS). Another landmark study in 2007 on Cambodian schoolchildren found a 10-fold higher prevalence of RHD by echocardiographic screening compared with auscultation.[6] The first international evidence-based guidelines with well-defined echocardiographic criteria on the diagnosis of RHD emerged in 2012,[7] followed in 2015 by significant updates to the Jones criteria, including harnessing echocardiography in the diagnosis of rheumatic carditis, regardless of the presence or absence of a murmur.[8]

Effective advocacy, powered by these remarkable developments, has helped crystalize the calls to action and, gradually, the political agenda is beginning to align with the burden of RHD, as evidenced by the 2018 World Health Assembly resolution on RHD. Although this has helped generate a new urgency to critically review ARF/RHD control and priorities for fresh research, much work lies ahead.

As a result of the widespread use of evidence-based echocardiography, the entities subclinical carditis and latent RHD are now an established part of our lexicon (**Figure 1**). Although recent landmark data have emerged on the role of secondary penicillin prophylaxis in latent RHD,[9] its epidemiologic and clinical significance, and that of RHD screening in general, remain to be established.

Many mysteries of ARF also remain, including the very nature of its pathophysiology. Understanding ARF pathophysiology would address critical unmet needs but may also provide insights into one of the most perplexing issues in ARF/RHD: why was the ARF of Dr Cheadle's era much more conspicuous compared with today, where the pediatric beds in endemic regions are no longer filled with cases of ARF

HIGHLIGHTS

- Rheumatic heart disease is the most common cause of cardiovascular morbidity and early mortality in children and young adults worldwide.

- New data on disease burden have driven advancements in diagnosis and management of patients with rheumatic heart disease.

- Pragmatic policies are required to translate current knowledge into improved outcomes for patients with rheumatic heart disease.
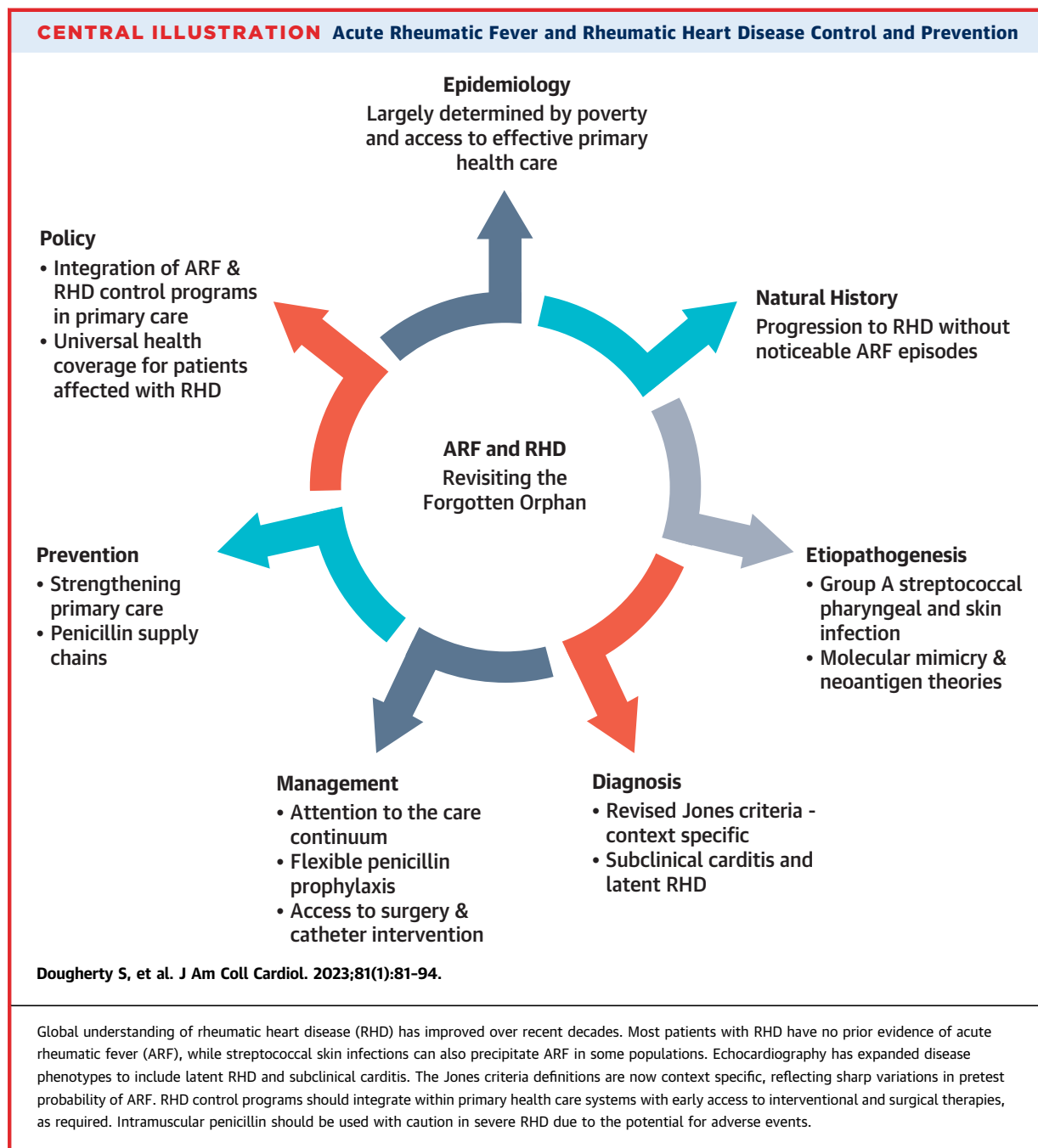
and more than two-thirds of patients with RHD report no history of ARF?[10]

CONCEPTUAL UPDATES ON DISEASE BIOLOGY

ARF is a postinfectious syndrome involving the heart, joints, subcutaneous tissues, and brain and while almost all symptoms resolve over weeks to months without any sequelae, ~60% of those with carditis develop residual valvular damage that is known as RHD. The greatest risk for a primary episode of ARF occurs in children and adolescents aged 5 to 15 years, whereas the peak prevalence of RHD occurs several decades later, between 25 and 45 years of age, reflecting the cumulative effects of recurrent episodes of ARF.

Although most data outside of Oceania indicate that ARF occurs only after nasopharyngeal infection with GAS, it is now accepted that GAS skin infections can also precipitate ARF. Aboriginal and Torres Strait Islander children experience among the highest rates of ARF globally, yet recent studies have found throat carriage of GAS was very low in these populations while impetigo due to GAS was very common, estimated to affect 45% at any one time.[11,12] These studies have also found a high incidence of group G streptococcal or group C streptococcal pharyngitis in those with RHD, potentially implicating these strains in the etiology of ARF.

The events that occur after GAS infection and that culminate in ARF remain incompletely understood. The observation that 3% to 6% of patients with GAS infection develop ARF suggests that pathogenesis likely involves socioeconomic risk factors, virulent strains of GAS, and a suspectable host, individually and collectively (**Figure 2,**[13] Supplemental Table 1).

CENTRAL ILLUSTRATION Acute Rheumatic Fever and Rheumatic Heart Disease Control and Prevention

Epidemiology
Largely determined by poverty and access to effective primary health care

Natural History
Progression to RHD without noticeable ARF episodes

Policy
• Integration of ARF & RHD control programs in primary care
• Universal health coverage for patients affected with RHD

ARF and RHD
Revisiting the Forgotten Orphan

Etiopathogenesis
• Group A streptococcal pharyngeal and skin infection
• Molecular mimicry & neoantigen theories

Prevention
• Strengthening primary care
• Penicillin supply chains

Management
• Attention to the care continuum
• Flexible penicillin prophylaxis
• Access to surgery & catheter intervention

Diagnosis
• Revised Jones criteria - context specific
• Subclinical carditis and latent RHD

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Global understanding of rheumatic heart disease (RHD) has improved over recent decades. Most patients with RHD have no prior evidence of acute rheumatic fever (ARF), while streptococcal skin infections can also precipitate ARF in some populations. Echocardiography has expanded disease phenotypes to include latent RHD and subclinical carditis. The Jones criteria definitions are now context specific, reflecting sharp variations in pretest probability of ARF. RHD control programs should integrate within primary health care systems with early access to interventional and surgical therapies, as required. Intramuscular penicillin should be used with caution in severe RHD due to the potential for adverse events.

The main driver of ARF is frequent untreated GAS infections; modifying environmental risk factors can therefore have a profound effect on the incidence of ARF. For example, data from the United States from 1910 to the 1970s show that ~85% of the deaths due to ARF decreased before 1940,[14] probably as a result of improved housing infrastructure and crowding, leading to reduced transmission of GAS. These changes predate the introduction of penicillin in 1942

and changes in the virulence of circulating GAS in the late 1960s.

GAS possesses several virulence factors. The M protein, a highly variable surface protein that is encoded by the emm gene, is essential for GAS virulence by providing antiphagocytic functions, among others. Epidemiologic studies of GAS strains initially relied on serotyping the M protein (M typing) in the 1950s, but this method has been superseded by

FIGURE 1   Taxonomy of ARF and RHD
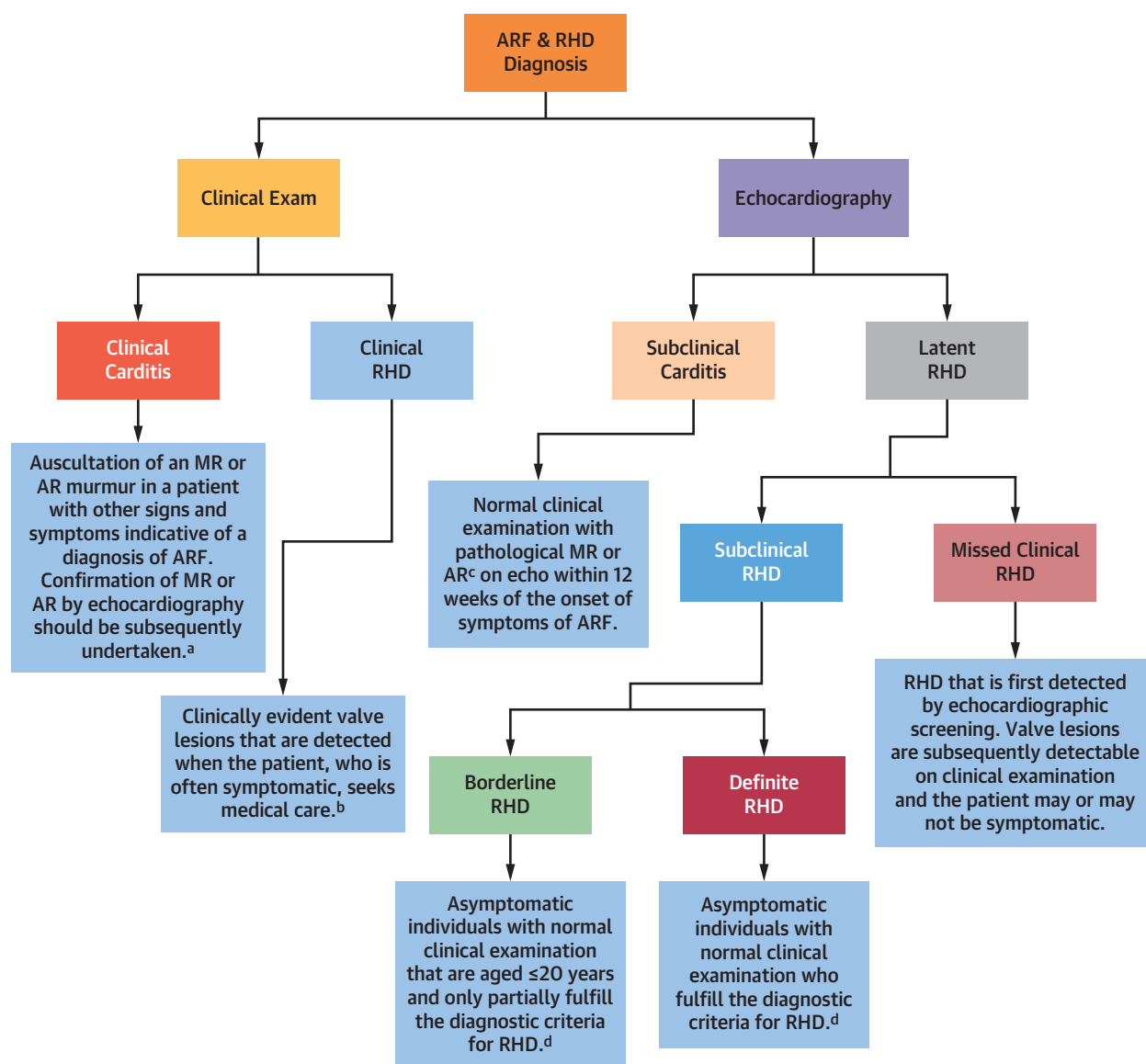
Proposed classification of rheumatic carditis and rheumatic heart disease (RHD), based on clinical examination and echocardiographic findings. [a]Isolated pericarditis or myocarditis are not sufficient for a diagnosis of rheumatic carditis. [b]Detection of a pathologic heart murmur without echocardiography is poorly sensitive and specific in echocardiographic screening studies for RHD. [c]As defined by the 2015 Jones criteria. [d]As defined by the 2012 World Heart Federation RHD diagnostic guidelines. AR = aortic regurgitation; ARF = acute rheumatic fever; MR = mitral regurgitation.

nucleotide sequencing of the hypervariable 5′ end of the emm gene (emm typing).

Experts have long postulated that various strains of GAS differ in the likelihood of subsequent ARF (so-called "rheumatogenic strains") because certain M types were implicated strongly and repetitively in outbreaks of ARF (eg, during the more recent up-surges in the United States in the 1980s and 1990s).

Such strains remain a hypothesis, however, because no rheumatogenic factor has ever been isolated. Epidemiologic studies over the last 2 decades have also failed to show any association of "rheumato-genic" emm types with ARF while revealing that strain diversity in endemic settings is significantly higher than in HICs, including that ARF is caused by GAS strains not traditionally associated with ARF.[15]

**FIGURE 2 Categorization of RHD Control and Prevention**
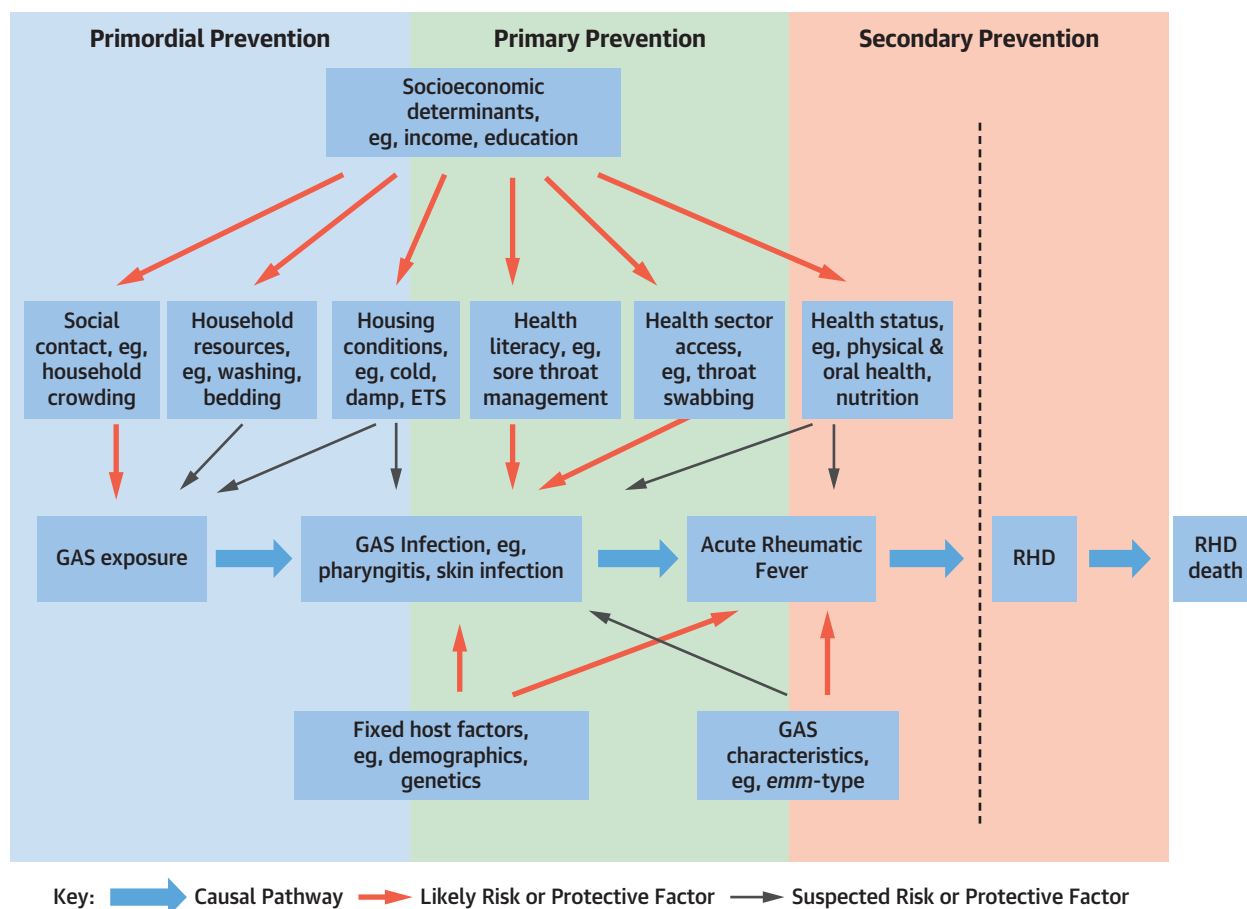
Primordial prevention targets societal-level factors contributing to RHD, namely improving living conditions and developing a vaccine against group A *Streptococcus* (GAS). Primary prevention targets early detection and treatment of GAS pharyngitis and impetigo. Secondary prevention involves preventing progression of ARF to RHD, including regular penicillin prophylaxis with the support of an RHD register. Reproduced with permission from Watkins et al.[13] ETS = environmental tobacco smoke; other abbreviations as in Figure 1.

Current evidence strongly implicates an immunologic mechanism in the pathophysiology of ARF. There is strong evidence that the initial damage to cardiac tissues is due to an abnormal humoral response to GAS infection, which then triggers a T cell-mediated response as the immune cascade evolves. Molecular mimicry is thought to underlie this process. A second and more recent notion is the "neo-antigen" theory, which suggests that the pathogenesis of ARF may not involve molecular mimicry with GAS antigens or a failure of the human immune system.[16] These theories are summarized in Figure 3 and the following text.

The first hypothesis is the molecular mimicry theory. After infection, GAS adheres to and invades the epithelial surface of the pharynx or skin, resulting in activation of both B and T cells in the peripheral blood. The activated B cells generate antibodies (antiendothelial cell antibodies) against the M protein or GAS group A carbohydrate antigen. Antiendothelial cell antibodies bind to the valve endothelium (endocardium), up-regulating vascular cell adhesion molecule-1. Up-regulated vascular cell adhesion molecule 1 allows activated T cells (primarily CD4$^+$ T cells) to infiltrate into the valve matrix, generating a T helper 1 response. The resulting cytokine-mediated damage results in valve breakdown and malformation. Valve breakdown also exposes type I collagen (present within the valve matrix), resulting in further immune-mediated valve damage.

FIGURE 3   Proposed Pathogenesis of ARF in the Heart
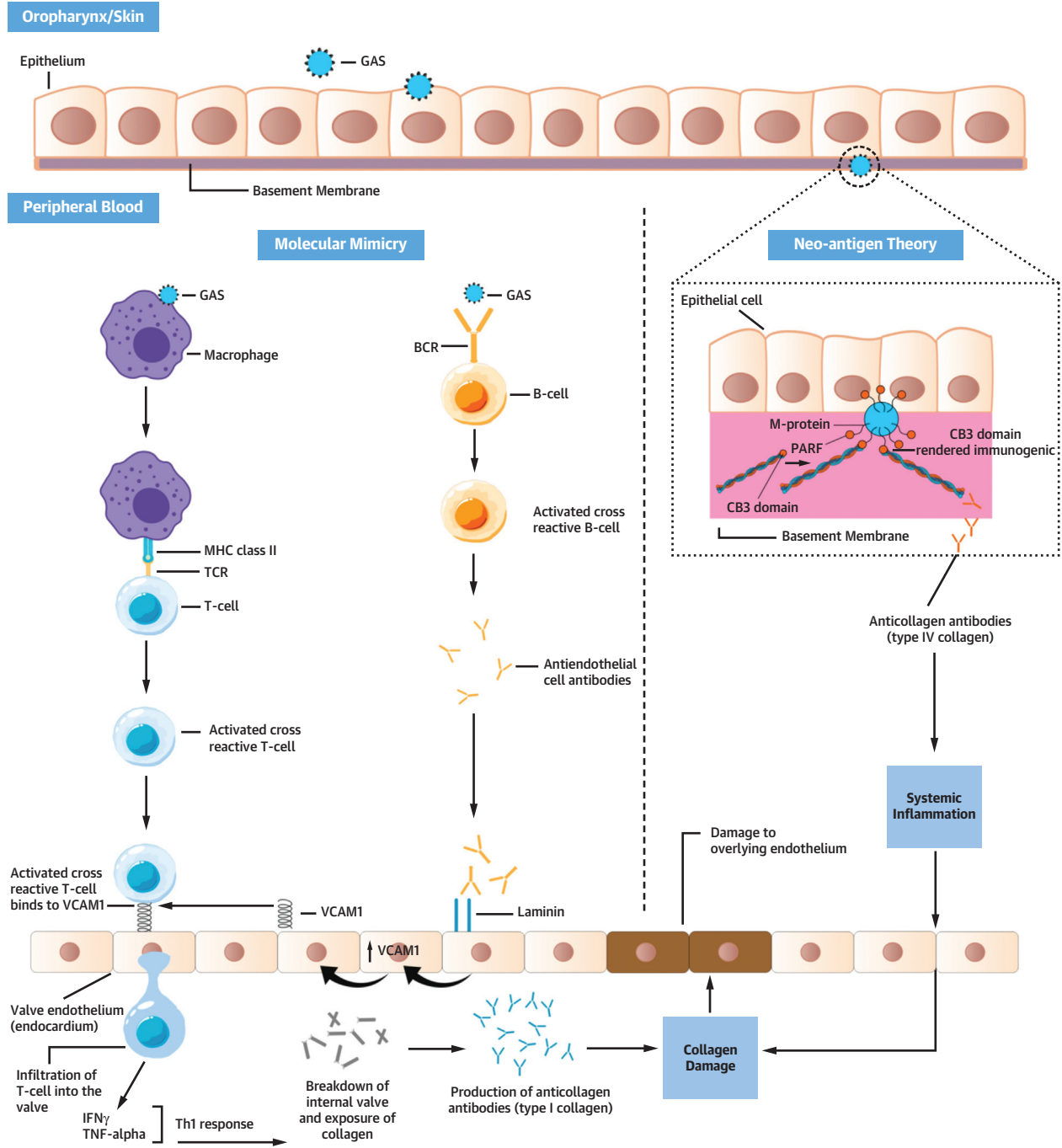
Molecular mimicry and the neo-antigen theory are both postulated to play a role in the pathophysiology of ARF, either independently or as interlinked processes (details are given in main text). BCR = B-cell receptor; IFN = interferon; MHC = major histocompatibility complex; TCR = T-cell receptor; TNF-alpha = tumor necrosis factor alpha; VCAM1 = vascular cell adhesion molecule 1; other abbreviations as in **Figures 1 and 2**.

TABLE 1   Priorities for Research and Unmet Needs in ARF Pathophysiology
There is a priority to bring NGS technologies to aid in the understanding of ARF pathophysiology. NGS technologies encompass a multi-omics approach (genomics, metabolomics, transcriptomics, and others) and have the potential to address important unmet needs in ARF prevention, presentation, diagnosis, and management.
1. **ARF prevention:** the fear of autoimmune complications induced by vaccines against GAS has perhaps been the greatest obstacle to vaccine development. NGS technologies, combined with a GAS human challenge model, would allow a clearer delineation of initial host–pathogen interactions and immune responses and help address these concerns.
2. **ARF presentation:** one of the most glaring unanswered questions in ARF and RHD research is, why is the incidence of ARF significantly less than the prevalence of RHD? Although the answer is likely multifactorial, one possibility is that ARF in endemic settings manifests as a distinct clinical phenotype, whereas progression to RHD tends to be subclinical, compared with low-risk populations that experience periodic epidemics.
3. **ARF diagnosis:** the Jones criteria have imperfect sensitivity and specificity and rely on accurate application by the clinician. Individual biomarkers have the potential to improve diagnostic accuracy of ARF. NGS technologies offer hope of identifying a biomarker, or range of biomarkers, that could be used as a gold standard diagnostic test, or at least as an additional test to improve the accuracy of the Jones criteria.
4. **ARF management:** no treatment for ARF (eg, penicillin, NSAIDs, corticosteroids) has been proven to slow the progression of valvular disease. Understanding ARF pathophysiology could pave the way to the development of immunomodulatory therapies that could prevent development or reduce progression of valve disease.
Another important challenge of using NGS technologies in ARF is to ensure they remain affordable in settings where the disease is most common: low- and middle-income countries. Recent experiences have suggested there is a need to adapt higher technology testing to resource-limited settings, such as via point-of-care testing, rather than relying on more traditional laboratory testing.
ARF = acute rheumatic fever; GAS = group A *Streptococcus*; NGS = next-generation sequencing; NSAID = nonsteroidal anti-inflammatory drug; RHD = rheumatic heart disease.

The second hypothesis is the neo-antigen theory. After infection, GAS enters the epithelial basement membrane in the pharynx or skin. An octapeptide motif on the GAS M protein called PARF binds to the CB3 region of type IV collagen (present in the basement membrane), which renders the CB3 domain immunogenic. Autoantibodies are then directed against type IV collagen, resulting in systemic inflammation. Owing to the similarities between various forms of collagen, these antibodies may then target type I collagen in the valve, resulting in damage to the overlying valvular endothelium, leading to valve breakdown and malformation.

These 2 hypotheses are important and both could be correct, with one hypothesis not excluding the other. Most autoimmune diseases involve more than one autoantigen, and given that anticardiac myosin/laminin antibodies and anticollagen antibodies are both found in acute rheumatic carditis, it is possible that one might precede the other.[17] Unravelling the mechanisms by which GAS infection leads to ARF can potentially revolutionize ARF and RHD prevention and control (**Table 1**).

CONTEMPORARY UNDERSTANDING OF RHD EPIDEMIOLOGY

In the past 2 to 3 decades, there have been important developments in our understanding of the epidemiology of RHD.

MEASURES OF DISEASE BURDEN. A variety of methods can be used to survey populations for RHD.[18] Their advantages and limitations are summarized in **Table 2**. The use of echocardiographic screening has uncovered the existence of clinically silent rheumatic valve disease in a relatively large number of individuals residing in regions that are endemic for RHD.[6] This entity is now widely recognized as latent (subclinical) RHD, and it is seldom seen in populations that are not at risk for RHD.[19] Latent (subclinical) RHD progresses to clinically manifest disease at rates that are determined by the severity of valve affliction and younger age at initial detection. Although the prevalence of latent RHD may be a useful surrogate for the overall disease burden in a population, the precise relationship between numbers identified through echocardiographic screening and those with clinically manifest RHD is unclear.

GLOBAL TRENDS. Today, RHD is largely confined to the world's poorest populations with limited access to primary health care. This includes low- and middle-income countries (LMICs) and pockets of marginalized populations in selected HICs. In large LMICs such as India, Brazil, and China, there are sharp regional variations in RHD burden that mirror human development and access to primary health. However, it is estimated that >40 million individuals are affected with RHD across the globe, and RHD remains among the leading causes of cardiovascular mortality in young adults worldwide.[3]

It is perhaps important to recognize that declines in RHD prevalence and mortality in most parts of the world have paralleled general improvements in health and access to primary care and not because of implementation of disease-specific prevention strategies. It has also been shown that the decline in access to primary care as a result of the break-up of the Soviet Union was associated with a sharp increase in ARF and RHD in Central Asia.[20] There are a few examples of control programs specifically targeted at

TABLE 2 Methods Used to Measure the Burden of Rheumatic Heart Disease in Populations

	What Is Measured?	Limitations	Advantages
Community-based echocardiographic surveys	Prevalence of both subclinical and missed clinical RHD	Logistics of selecting a representative population of a region can be challenging Regions with low prevalence require very large sample size.	Better suited for high-prevalence regions with a clearly defined denominator
Clinical registries	Identifies clinically manifest RHD Can be used to estimate disability and calculate disability-adjusted life years	Heavily dependent on referral pathways: health care infrastructure in the area and willingness of the potential sources of referral Underreporting: mild cases, missed diagnosis, and marginalized sections of the population may be missed Overreporting: sampling from outside the study area due to referral to specialist centers Denominator: dependent on census data, errors may result from underestimation or overestimation of the migrant population	Wide coverage Relatively easy to organize
School surveys	Prevalence of RHD in a school-aged population. Physical examination will only identify clinically manifest disease. Identifying subclinical RHD in schools requires mass echocardiographic screening.	Focus entirely on the 5- to 15-year-old age group Limited value in areas with poor school enrollment rates Affected children may not attend schools (absenteeism) School surveys may yield a much lower prevalence in regions where affected RHD patients are older	Clearly defined denominator allows systematic and well-organized survey Better suited for RHD than for ARF
Hospital statistics	Burden of clinically manifest RHD with relatively advanced disease	Outpatient clinic records and inpatient admissions: only those relatively sick will be represented Procedure records: likely to miss valve lesions that do not require a procedure	Diagnosis is likely to be accurate although usually dependent on clinical coding
Mortality statistics	Mortality from RHD	Underreporting in areas with poor health infrastructure Weak mortality statistics in some regions (eg, Africa) Misclassification of underlying cause of deaths (eg, coded as heart failure or stroke instead of RHD)	Premature mortality is a key measure for estimating disease burden

Abbreviations as in **Table 1**.

RHD that have been effective in relatively smaller populations such as in Cuba and Costa Rica, where they served to greatly accelerate the declining trend.[21] While developing strategies for RHD control, it is essential to recognize the critical importance of primary health care, which is vital for the maintenance of disease registries as well supporting the care continuum of RHD from management of a sore throat to enabling tertiary care.

UPDATES ON DIAGNOSIS, PREVENTION AND CONTROL, AND MANAGEMENT

DIAGNOSIS. The diagnosis of ARF remains dependent on clinical criteria first described by Dr T. Duckett Jones in 1944.[22] Given the shifting epidemiology of ARF in HICs over the last century, the criteria have undergone numerous revisions to maintain Dr Jones's original intention of maintaining high specificity for ARF in low-risk populations.

More recently, in 2015, the American Heart Association has supported a fundamental overhaul of the Jones criteria to account for the sharp contrast in disease burden between low-risk and medium/high-risk areas. This is important because the utility of a diagnostic test is influenced by background disease prevalence, and thus a single set of diagnostic criteria for ARF was no longer appropriate. Accordingly, the diagnostic thresholds for the Jones criteria are now relatively lenient for moderate/high-risk areas (prioritizing sensitivity) and relatively stringent for low-risk areas (prioritizing specificity).[8]

Medium/high-risk populations are defined as those where the incidence of ARF is >2 per 100,000 in 5- to 14-year-olds per year or an all-age RHD prevalence of >1 per 1,000 population per year. Within these populations, polyarthralgia, monoarthritis, and monoarthralgia have been added to the joint criterion; the temperature threshold has been lowered to ≥38 °C; and the erythrocyte sedimentation rate threshold has been lowered to ≥30 mm/h.

The second major shift in the guidelines has been the addition of echocardiography for the diagnosis of carditis. Although auscultation of a regurgitant murmur remains a major criterion for carditis,

TABLE 3 Management of ARF			
	Specific Treatment Modalities	**Rationale**	**Recommendations**
Elimination of GAS skin or throat infection	Penicillin and alternatives	To limit the repetitive exposure to GAS antigens	A single intramuscular dose of BPG is ideal. Oral penicillin V can also be used. Azithromycin can be used for those with penicillin allergy.
Suppression of inflammation	NSAIDs (naproxen safer than aspirin) and steroids	Relief from symptoms of fever and arthritis NSAIDs and steroids have not been shown to prevent the progression to RHD	Naproxen immediate release oral: adult 250-500 mg q12h; child 10-20 mg/kg/d, divided q12h (maximum 1,000 mg/d) until pain is relieved, then taper the dose. Steroids are a useful alternative to NSAIDs in those who continue to worsen and develop heart failure. They enable rapid relief of symptoms and reduce the duration of hospitalization. Prednisolone/prednisone (1-2 mg/kg/d, maximum 80 mg/d) is generally preferred. It can be tapered after 2-3 weeks. Intravenous methylprednisolone can be used in life-threatening situations
Prevention of recurrences	Secondary penicillin prophylaxis	Secondary prophylaxis prevents recurrences of ARF and progression of heart valve damage	3-4 weekly intramuscular BPG or daily oral penicillin V (2009 AHA guidelines): ARF without carditis: until age 21 years or for 5 years after last ARF episode (whichever is longer) ARF with carditis but no residual valve damage: until age 21 years or for 10 years after last ARF episode (whichever is longer) ARF with carditis and residual valve damage: until age 40 years or for 10 years after last ARF episode (whichever is longer); lifelong prophylaxis may be needed

AHA = American Heart Association; BPG = benzathine penicillin G; q12h = every 12 hours; other abbreviations as in Table 1.

detection of pathologic mitral and/or aortic regurgitation by echocardiography, regardless of the presence or absence of a murmur, is now also considered diagnostic of carditis (Figure 1).[8]

The application of artificial intelligence to echocardiography has the potential to improve RHD diagnosis and move toward more equitable access to echocardiography. One example would be through automated RHD detection by nonexperts during population-based screening programs.

PREVENTION AND CONTROL. The traditional categorization of RHD prevention into primordial, primary, and secondary prophylaxis is shown in Figure 2. Primordial prevention of GAS infections requires improvement in living conditions and an effective vaccine. Primary prevention is targeted at early detection and treatment of GAS pharyngitis and impetigo. When applied to large populations, primary prevention programs can be expensive.[23] Secondary prevention involves preventing progression of latent or clinical RHD.

Because RHD runs a protracted course over several years, attention must be given throughout the life course of the disease to facilitate optimal management in affected populations. RHD prevention and control programs should seek establishment of a continuum of care in the community for people affected by or at risk of ARF/RHD.[24] This approach seeks to integrate secondary prophylaxis, access to specialized care that includes appropriate medical therapy with strategies to improve adherence and retention, access to surgery and interventions in specialized centers, appropriate follow-up care that includes monitoring of anticoagulation, and which addresses special challenges during events such as pregnancy.

Maintaining a regional RHD register is a critical requirement for prevention and control of RHD as it enables attention to all the components of the care continuum. The regional registers should be integrated into national databases that would allow for real-time assessment of disease burden. Regions with a high burden of RHD should be targeted for intense community education and primary prevention efforts. Unfortunately, health systems in the most affected regions often do not have the wherewithal to support such a comprehensive approach.

LATENT (SUBCLINICAL) RHD. A large single-center trial in Uganda that assessed the impact of 4-weekly (every 4 weeks) intramuscular benzathine penicillin G (BPG) injections on the progression of latent RHD over 2 years showed that only 0.8% of children in the BPG arm progressed compared with 8% in the non-BPG arm, suggesting a strong protective effect of BPG.[9] Although it would be appropriate to recommend penicillin prophylaxis for latent RHD, there are significant practical challenges that relate to the acceptability of regular injections in asymptomatic individuals, availability of penicillin, and preparedness of health systems. For borderline RHD, current evidence does not support long-term penicillin prophylaxis.

EPISODES OF ARF. Table 3 summarizes the goals of management of ARF.

MANAGEMENT OF CLINICAL RHD

MEDICAL MANAGEMENT. Although timely surgery or catheter-based treatment is ideally needed for symptomatic severe valvular disease, their availability is severely limited in most LMICs. Therefore, medical management is often all that can be offered initially, and it is targeted at consequences of valvular regurgitation or stenosis, including heart failure and atrial fibrillation (AF). Diuretic agents are the mainstay of management for symptomatic patients. Additional therapy is dictated by the specific valve lesions.

Isolated mitral stenosis benefits significantly from reductions in heart rate, which improves diastolic filling and reduces the transvalvular gradient. This is achieved through either beta-blockers or digoxin for those with AF. There is a possible association of digoxin use with increased mortality in mitral stenosis, particularly among those without concomitant AF or heart failure.[25] For those with sinus rhythm, ivabradine is an additional option.[26]

For severe regurgitation of the mitral or aortic valves, afterload reduction with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers partially mitigates the physiological consequences; however, there is no evidence showing long-term benefits in terms of reduction of progression of valve regurgitation or need for surgery.[27,28] Beta-blockers have also been used in regurgitant lesions, with little evidence favoring long-term benefits. Tricuspid valve involvement results in systemic venous congestion and is largely managed with diuretic agents. Severe aortic stenosis is particularly challenging to treat medically, and most cases will require surgical intervention.

In a Ugandan series, AF was the most common complication of RHD, contributing to both heart failure and thromboembolic risk.[29] The need for frequent international normalized ratio (INR) testing is a major barrier to the use of vitamin K antagonists (VKAs). The recently published INVICTUS trial compared VKAs with rivaroxaban in AF patients with predominantly hemodynamically significant rheumatic mitral stenosis.[30] Surprisingly, rivaroxaban increased the risk of the primary outcome (stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes) by 25% compared to those taking VKAs, which was driven almost entirely by a reduction in death in the VKA arm. This may, in part, be explained by the more frequent physician interactions for INR monitoring, thus allowing for medical optimization. We believe that for patients with significant rheumatic mitral stenosis and AF,

VKAs should remain the oral anticoagulant of choice as per current guidelines; however, for RHD patients without significant mitral stenosis who develop AF, non-vitamin K antagonist oral anticoagulants should remain a potential option pending further evidence.
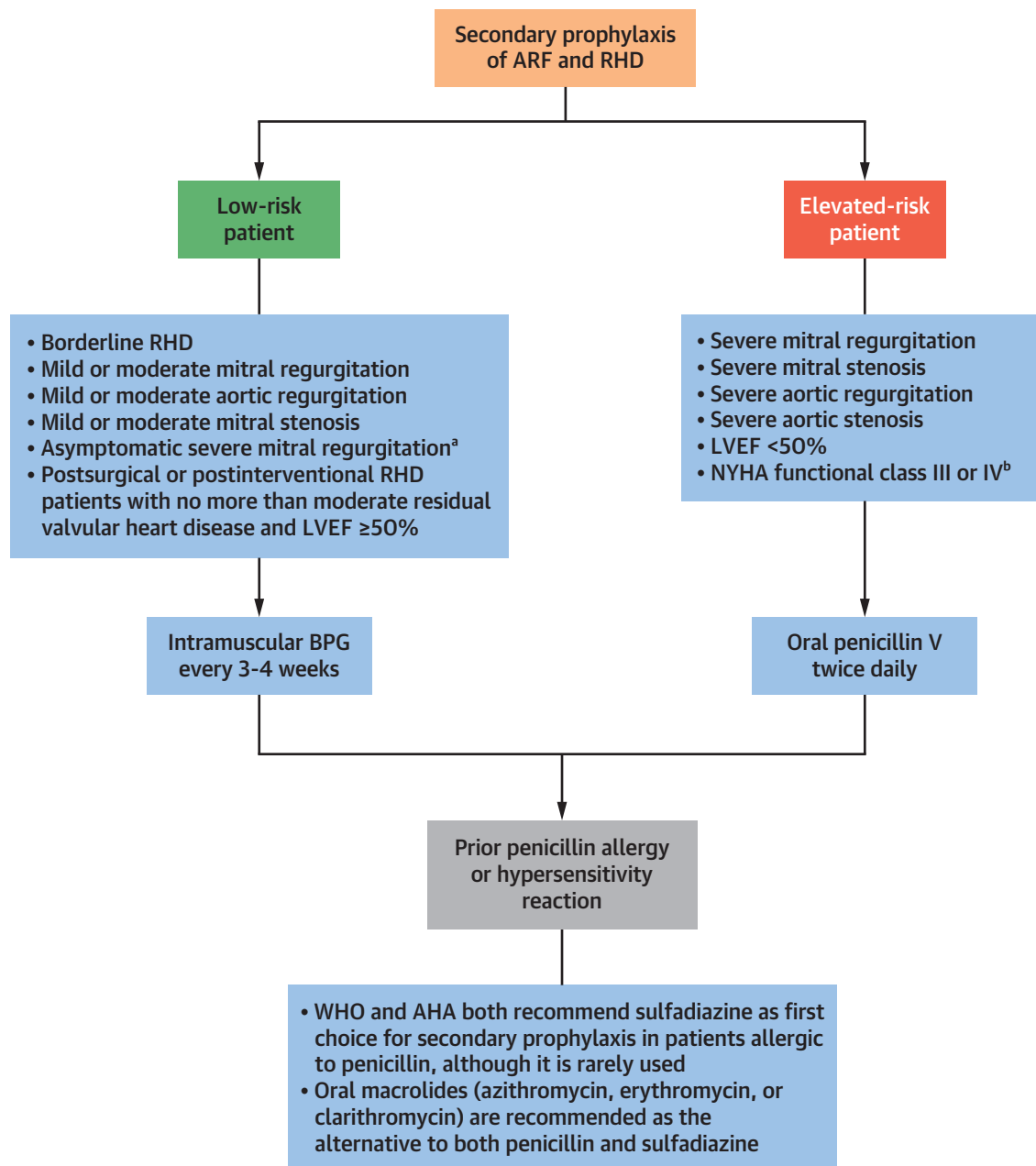
Patients with clinical RHD who have had surgery may need lifelong penicillin prophylaxis, or at least until age 40 years (Table 3). Three-to-four weekly BPG is the first-line choice for secondary prophylaxis of ARF and RHD. Fear of adverse events with BPG injections, however, is a barrier to effective treatment, and although serious events, including death and anaphylaxis, are rare, the evidence base for adverse BPG reactions among patients with RHD remains sparse. Nevertheless, there is concern that BPG injections may result in cardiac compromise in some patients with severe RHD (which may be misinterpreted as anaphylaxis), and the American Heart Association has recently advised that oral antibiotics be strongly considered in such patients (Figure 4).[31] Plans are underway to conduct clinical trials that compare oral penicillin as an alternative to injectable BPG.

CATHETER-BASED THERAPY. In patients with severe symptomatic mitral stenosis and favorable valve morphology, percutaneous mitral balloon commissurotomy (PMBC) is the treatment of choice, although this approach depends on the availability of relevant expertise. Outcomes after PMBC have been shown to be good, with symptom relief that can last as long as 20 years.[32] The best candidates for PMBC are those with isolated mitral stenosis and pliable, noncalcified valves that are predominantly fused at the commissures with limited subvalvular pathology and no left atrial thrombus.[33] The scope of PMBC has widened considerably over the years, including as an option for pregnant women with severe symptomatic mitral stenosis (which often presents for the first time during pregnancy), with success rates exceeding 95%.[34]

Isolated aortic stenosis is exceptional in RHD and is generally not suited for balloon dilation. Transcatheter aortic valve implantation, which is now an established therapy for severe calcific aortic stenosis, is unlikely to play a significant role in rheumatic aortic stenosis given the rarity of isolated rheumatic aortic stenosis, the relatively young age of these patients, and the relative lack of calcification of the rheumatic aortic valve.

SURGICAL INTERVENTIONS. Indications for surgery in RHD must be tailored to the individual patient based on a comprehensive assessment of the patient's condition, specifics of the valve lesion(s), surgical capabilities, and socioeconomic, cultural, and geographic background, as well as individual patient

FIGURE 4 AHA Presidential Advisory for Prophylaxis of ARF and RHD

Secondary prophylaxis of ARF and RHD

Low-risk patient

Elevated-risk patient

- Borderline RHD
- Mild or moderate mitral regurgitation
- Mild or moderate aortic regurgitation
- Mild or moderate mitral stenosis
- Asymptomatic severe mitral regurgitation[a]
- Postsurgical or postinterventional RHD patients with no more than moderate residual valvular heart disease and LVEF ≥50%

- Severe mitral regurgitation
- Severe mitral stenosis
- Severe aortic regurgitation
- Severe aortic stenosis
- LVEF <50%
- NYHA functional class III or IV[b]

Intramuscular BPG every 3-4 weeks

Oral penicillin V twice daily

Prior penicillin allergy or hypersensitivity reaction

- WHO and AHA both recommend sulfadiazine as first choice for secondary prophylaxis in patients allergic to penicillin, although it is rarely used
- Oral macrolides (azithromycin, erythromycin, or clarithromycin) are recommended as the alternative to both penicillin and sulfadiazine

This recent advisory states that patients with severe RHD may be at increased risk of cardiovascular compromise and death if they develop an adverse (nonanaphylactic) reaction while receiving intramuscular penicillin. This advisory is based on very limited evidence and has yet to be widely accepted internationally. [a]Patients with isolated severe MR often move back and forth between low-risk and high-risk categories. [b]Includes symptoms caused by nonstructural contributing factors such as atrial fibrillation and anemia. AHA = American Heart Association; BPG = benzathine penicillin G; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; WHO = World Health Organization; other abbreviations as in Figure 1.

TABLE 4 Indications for Surgery in RHD	
	Specific Recommendations

Mitral stenosis	Moderate to severe (≤1.5 cm^2) symptomatic mitral stenosis where PMBC is contraindicated or less favorable:
	    Calcific mitral stenosis with calcified commissures or extensive calcium deposits
	    Severe fusion of subvalvular apparatus
	    Associated mitral regurgitation: more than mild and/or at the commissures
	    Left atrial clot

Mitral regurgitation	Severe symptomatic chronic mitral regurgitation Acute mitral regurgitation resulting from chordal rupture during ARF that is unresponsive to therapy Asymptomatic mitral regurgitation with LVEF ≤60%, LVESD ≥40 mm, LA volume ≥60 mL/m^2 or diameter ≥55 mm, SPAP >50 mm Hg Atrial fibrillation
Aortic regurgitation	Severe symptomatic chronic aortic regurgitation Asymptomatic aortic regurgitation with LVESD ≥50 mm or 25 mm/m^2 BSA, or LVEF ≤50%
Tricuspid valve disease	Isolated tricuspid valve disease is rare in RHD. Any significant associated tricuspid valve disease must be addressed during valve repair or replacement of other valves. In general, tricuspid valves can be repaired in most patients.
Mixed heart valve disease	In general, symptomatic mixed or multivalve heart disease merits consideration for surgery. Approach should be individualized depending on the specifics of valve disease.

BSA = body surface area; LA = left atrial; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; MR = mitral regurgitation; PMBC = percutaneous mitral balloon commissurotomy; SPAP = systemic pulmonary artery pressure; other abbreviations as in Table 1.

preferences. Surgery is indicated for symptomatic valve regurgitation or valve stenosis not amenable to transcatheter management. As in nonrheumatic valvular disease, severe isolated or combined mitral and aortic regurgitation needs to be monitored regularly through serial echocardiography and requires consideration for surgery once chamber dimensions that predict a high risk of persistent ventricular dysfunction are reached (Table 4).

Multivalve and mixed valve lesions are common in RHD. They require a nuanced approach after careful assessment of relative severity of individual lesions. The threshold for surgery is often higher because double valve surgery carries significant additional risks and is often very expensive.

Surgical valve repair offers the prospect of avoiding dependence on long-term anticoagulation. The mitral valve is better suited for repair compared with the aortic valve. However, the thresholds and results of valve repair are dictated by surgical expertise and experience.[35] Mitral valve repair helps preserve ventricular function better than replacement. However, the specific challenges of mitral valve repair include the fact that it is technically challenging. There is also continued vulnerability to ongoing rheumatic valvulitis and the extremely limited feasibility of a second open heart surgery among affected patients because of resource constraints.

The rheumatic aortic valve is usually regurgitant and is generally not suited for repair. Mechanical aortic valve replacement also requires lifelong anticoagulation but is generally more forgiving when it comes to fluctuations in INR compared with mechanical mitral valve replacement.

CHALLENGES AND BARRIERS TO RHD PREVENTION AND MANAGEMENT IN AFFECTED POPULATIONS

The knowledge required to prevent ARF recurrence and progression of heart disease has been available for nearly 7 decades. However, RHD continues to be a major global challenge. A number of challenges are unique to RHD and they tend to get amplified in large populations. The disease runs a long and protracted course over many years, and affected individuals need close follow-up and lifelong attention in the form of penicillin prophylaxis and heart failure medications, as well as one or more surgical or catheter-based interventions. Special attention is required if the affected patient becomes pregnant or develops another illness. Because of the complexities of RHD prevention and management, competing public health priorities that are easier to manage appear as better targets for allocation of limited resources. Other important challenges are described in Table 5.

PUBLIC HEALTH APPROACHES TO RHD PREVENTION

Because of its overall complexity, perhaps RHD control cannot be accomplished as a vertical disease program that exists in relative isolation as a distinct entity. The care continuum of RHD is critically dependent on having a robust primary health care system. Countries or regions with a uniformly high burden of RHD can develop a national policy that deeply integrates RHD control with its primary care services.

TABLE 5	Key Challenges and Barriers for RHD Control and How They Can Be Addressed	
	Details	**Suggested Solutions**
Complexities of RHD prevention and management	Competing public health priorities that are easier to manage and appear as better targets for allocation of limited resources.	Presenting compelling economic arguments for RHD control and indicating the loss in terms of health care costs and productivity among young affected populations.
Magnitude	Large number of people affected that is well beyond the collective capacity of health infrastructure and resources in many nations.	Developing a targeted strategy that focuses on the most severely affected populations.
Data	Few data from regions that are likely to be worst affected because these regions have a very poor health infrastructure. Data collection and implementation of RHD control strategies require a reasonably functional health infrastructure. Registers not maintained or mandated for most LMICs.	Using echocardiographic prevalence of latent RHD in sample surveys as a surrogate of disease burden.
Awareness	Poor awareness of the magnitude of the problem and the distribution of disease among many health professionals, including cardiologists and policy makers. There is a mistaken perception that RHD is on a decline because of sequestration of disease in poorly served regions.	Curriculum revisions for undergraduate and postgraduate education, dedicated CME programs and interactive sessions, capsules of education material that summarize recent guidelines, dedicated sessions in major conferences. All these strategies can be implemented through close liaison with professional bodies.
Penicillin administration and availability	Penicillin supply chains are currently unable to cater to the demands in many parts of the world. Exaggerated fears regarding anaphylaxis.	Special efforts must be made in conjunction with the government on procurement of the active pharmaceutical ingredient, local formulation of injectable BPG, distribution through effective supply chains as dictated by regional demands. Global lack of availability of the active pharmaceutical ingredient. Sustained advocacy and international cooperation and involvement of agencies such as the World Health Organization.
Policy	ARF/RHD are not notifiable diseases in many nations. Significant challenges in formulating a uniform policy across large and diverse populations.	Sensitize health policy makers on the disease burden, regional variations and economic impact, as well as the opportunity to prevent RHD through public health interventions.
Implementation	Dysfunctional health systems can obstruct the implementation of RHD control efforts. RHD registries are seldom maintained. The care continuum is largely nonexistent for more regions.	RHD burden can be used as a barometer of effectiveness of primary health care. This will bring the focus of RHD control to primary care providers. RHD care must be integrated into models for universal health coverage.

CME = continuous medical education; LMIC = low- and middle-income countries; other abbreviations as in Tables 1 and 3.

For larger countries with regional diversity in RHD prevalence, such as India, a uniform national policy may not work. Here, it may be necessary to identify high prevalence regions and target them first. Sociodemographic indices are reasonable surrogates for RHD burden and may be used for the initial phases of disease control. Alterations and adjustments must be made once data on disease burden are obtained. Echocardiographic screening of sample populations may allow for rapid estimates of the likely disease burden. There is a need for sustained advocacy using innovative strategies to overcome the barriers that hinder RHD prevention (Table 5).

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APPENDIX For a supplemental table, please see the online version of this paper.