Structural Heart 7 (2023) 100219

Articles and Issues Available at ScienceDirect

Structural Heart

journal homepage: www.structuralheartjournal.org

Review Article

Rheumatic Heart Disease in the Developing World

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ARTICLE INFO

Article history:
Submitted 27 May 2022
Revised 1 August 2023
Accepted 3 August 2023
Available online 19 September 2023
Guest Editor: Zoltan Turi, MD

Keywords:
Mitral valve repair
Mitral valve replacement
Rheumatic heart disease

ABSTRACT

Despite recent public policy initiatives, rheumatic heart disease (RHD) remains a major source of morbidity worldwide. Rheumatic heart disease occurs as a sequela of *Streptococcus pyogenes* (group A streptococcal [GAS]) infection in patients with genetic susceptibility. Strategies for prevention of RHD or progression of RHD include prevention of GAS infection with community initiatives, effective treatment of GAS infection, and secondary prophylaxis with intramuscular penicillin. The cardiac surgical community has attempted to improve the availability of surgery in RHD-endemic areas with some success, and operative techniques and outcomes of valve repair continue to improve, potentially offering patients a safer, more durable operation. Innovation offers hope for a more scalable solution with improved biomaterials and transcatheter delivery technology; however, cost remains a barrier.

ABBREVIATIONS

ARF, acute rheumatic fever; BMV, balloon mitral valvuloplasty; BPG, benzathine penicillin G; CHF, congestive heart failure; CMC, closed mitral commissurotomy; GAS, group A streptococcus; LMIC, lower- and middle-income countries; RHD, rheumatic heart disease.

Introduction

Rheumatic heart disease (RHD) remains an underrecognized health issue globally, despite initiatives introduced over the last several decades that have helped decrease the global number of cases during this time. This is in part due to the highly effective public health policies put forth in industrialized nations in the last half-century to prevent, recognize, and treat group A streptococcal (GAS) infections. However, worldwide RHD cases number over 15 million and contribute to over two hundred thousand deaths per year.[1] Progress has been made over the last 2 decades as several nations in the developing world with high disease prevalence have prioritized its treatment and global health organizations have pursued the elimination of RHD with renewed vigor. While significant attention has rightfully been paid to screening primary and secondary prevention of RHD, there has been less focus on broadening access to cardiac care and surgical care for those patients already with established RHD. In this review, we describe pathophysiology, primary and secondary prophylaxis, and variety of therapies available for RHD in developing countries.

Epidemiology

Endemic patterns of RHD are seen in lower- and middle-income countries (LMIC), especially in Southeast Asia, sub-Saharan Africa, and Oceania.[1] China, India, Pakistan, and Indonesia were the countries with the highest number of RHD cases in 2015; however, age-adjusted prevalence and death rates are highest in Oceania, sub-Saharan Africa, and

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https://doi.org/10.1016/j.shj.2023.100219

South Asia. Notably, the worldwide prevalence of heart failure due to RHD increased from 1990 to 2015 (Figure 1).[1]

Pathophysiology

RHD occurs as an autoimmune sequela of acute rheumatic fever (ARF), which usually occurs after GAS pharyngitis, although there is more recent data suggesting that GAS skin and soft tissue infection may play a larger role in the developing world than in industrialized countries.[2] The pathophysiology of ARF is not completely understood but is thought to involve cross-reactivity between GAS and host proteins in a genetically susceptible host.[2] Rheumatic fever is diagnosed based on the Jones criteria, which include a combination of major and minor clinical symptoms of ARF with or without evidence of a prior GAS infection. The most common presenting symptoms are arthritis and fever; chorea may be considered pathognomonic for ARF but occurs less frequently. Importantly, these criteria have more recently been revised to include population risk in order to increase the detection of ARF in endemic areas. Importantly, there is some suggestion that the presentation of ARF may differ between the developing world and industrialized countries; reasons for this are unclear but may be due to decreased suspicion in industrialized nations, leading to delayed diagnosis.[3]

While ARF symptoms resolve, damage done to valves remains and progresses with subsequent GAS infections, leading to progressive valvular fibrosis seen in RHD. The mitral valve is most frequently involved and can be affected by both mitral stenosis and regurgitation. 50% to 80% of patients with carditis during an initial ARF episode will progress to chronic RHD.

ARF primarily affects school-aged children, likely related to GAS transmission among students. The low incidence of ARF relative to that of GAS infection is not fully explained.[4] Some studies point to the possibility of genetic disposition, implicating immune-related genes such as human leukocyte antigen, toll-like receptor, and cytokines.[5] The pathophysiology of RHD development is shown in Figure 2.

Economic Impact

The effects of RHD are disproportionately felt by school-aged children and young adults in their most economically productive years. The cost of premature deaths due to RHD is estimated to be on the order of trillions of US dollars annually.[6] Effects on children and adolescents include increased school absence and rates of dropout, which have a downstream impact on the ability of children to eventually support their own families independently. At the same time, young adults sick with RHD will have decreased capacity to work, impairing their ability to provide for themselves and their families. The impact of disability caused by RHD accounts for nearly 0.5% of worldwide disability adjusted life years.[1] Additionally, RHD affects many women of childbearing age and has implications for maternal health in LMICs. Severe and symptomatic mitral stenosis are independent predictors of adverse fetal and maternal outcomes.[7] Together, these effects on those who are typically society's most productive workers have a profound socioeconomic impact.

Prevention/Primary Prophylaxis

Success in essentially eradicating RHD from the industrialized world was a result of a multipronged effort to improve public health infrastructure and access to primary care. Often overlooked in the prevention of RHD is so-called "primordial prophylaxis". Such social determinants of health are poverty-related and include overcrowding and poor nutrition. Household crowding, defined as in-home population of greater than 2 persons per habitable room[8] has been shown to increase transmission of GAS infection.[9] Additionally, poor nutrition has been associated with increased susceptibility to ARF.[10] These socioeconomic factors represent potential targets for intervention for both governments and nongovernmental organizations.

The core of primary prevention for RHD is the effective diagnosis and treatment of GAS infection with antimicrobial agents. Considerations here include symptom recognition, health care literacy, and

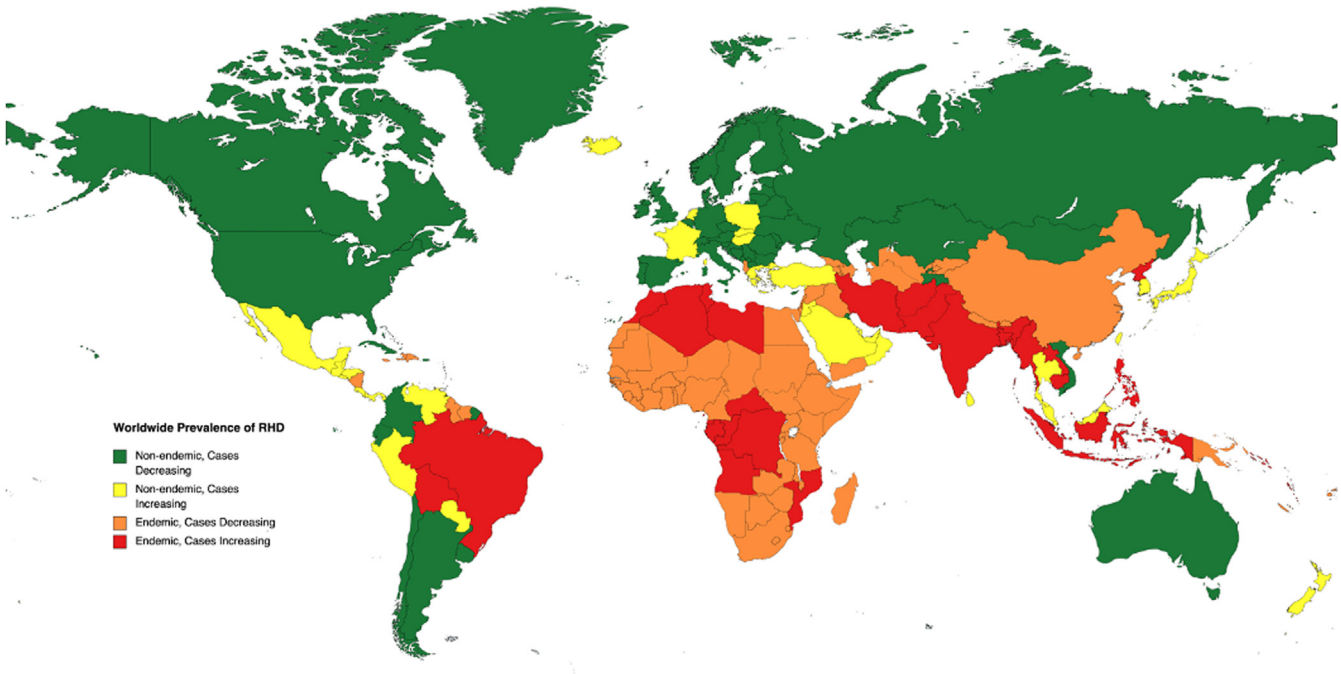

Figure 1. Global Impact of RHD. Countries with endemic patterns of RHD are commonly seen to have increasing number of cases over the previous decade; however, cases are rising in some middle- and upper-income countries, likely as a result of recent immigration patterns.
Abbreviation: RHD, rheumatic heart disease.

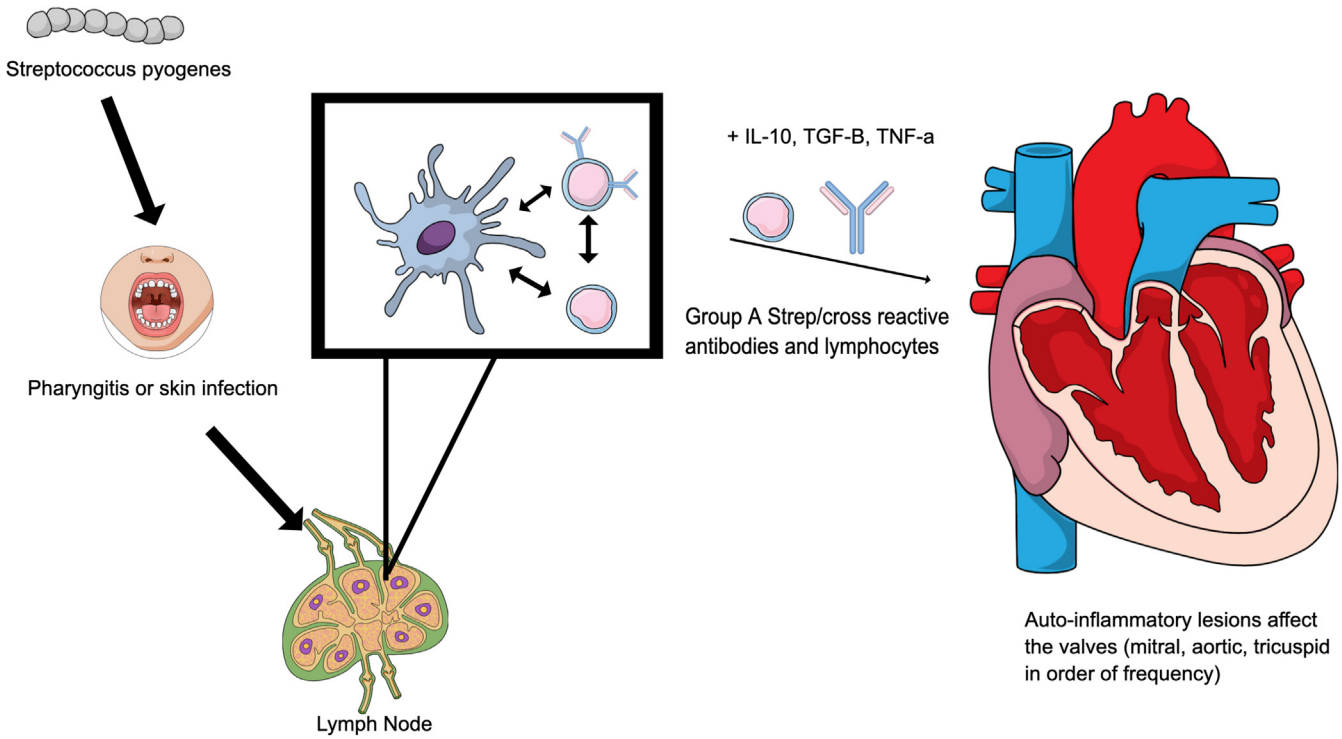

Figure 2. Pathophysiology of RHD. RHD occurs as a sequela of GAS infection, especially pharyngitis. Social determinants of health and genetic predisposition play a role in repeated infection as well as in the progression to RHD. Cross-reactive antibodies and immune cells form in response to GAS infection and attack endothelial cells throughout the body; however, damage to the endothelial surface of the valves is not repaired effectively.
Abbreviations: GAS, group A streptococcal; RHD, rheumatic heart disease.

willingness to present for primary care. Upon presentation, the availability of accurate and expedient diagnostic testing and accessibility to treatment are critical factors that affect disease progression and long-term sequelae. As part of a comprehensive RHD program, the World Health Organzation recommends a community-based approach focusing on awareness of GAS and its link with RHD, and such programs have shown good results.[11]

Microbiologic testing is the gold standard for the diagnosis of GAS infection; however, access in the developing world is limited, and this may not be cost-effective.[12] Rapid tests may be deployed in these areas with high sensitivity and specificity.[13] Clinical decision-making algorithms also play a role in the developing world due to supply chain difficulties in obtaining rapid tests. Clinical decision rules have been shown in Egypt to be highly sensitive while also limiting unnecessary antibiotic use.[14] Algorithms may be applied to other communities; however, likely require validation studies and modifications prior to use.

GAS infections are exquisitely sensitive to penicillin, and a single shot of benzathine penicillin G (BPG) administered intramuscularly effectively treats both pharyngitis and impetigo. Early treatment of GAS infections mitigates the molecular mimicry that causes ARF and has been shown to prevent up to 70% of ARF cases.[15] BPG is listed as a World Health Organization Essential Medication for Children.[16] Despite this, reports from providers in the developing world suggest widespread BPG shortages, with some reporting no access to BPG at all.[17] This is clearly problematic for strategies of both primary and secondary prophylaxis. Problems with supply aside, BPG, when available, is affordable; it is sold at a median price of $0.31 per dose.[17] Despite the low price, questions remain concerning the cost-effectiveness of primary prevention as a RHD strategy at the population level. Data from the early 2000s reports the average per-person cost of microbiologic GAS infection confirmation followed by BPG administration to be $50, while the number needed to treat was 50 in order to prevent one case of ARF.[15,17–19]

Lastly, GAS vaccine development represents a major opportunity to reduce ARF and RHD in the developing world. Vaccination for GAS has been difficult for several reasons: complex epidemiology, lack of surrogate markers for protection in humans, genetic diversity of the most common vaccine target, and perceived safety concerns that a vaccine could precipitate ARF. Momentum toward vaccination slowed as ARF and RHD cases plummeted in the industrialized world and investment decreased. However, with new data showing that indigenous populations in Australia and New Zealand deal with high rates of ARF, there is renewed interest. Several vaccines are currently in the early stages of development.[20,21]

Screening

Despite the proven link between ARF and RHD, it is common in the developing world for RHD to present without an antecedent history of ARF.[22] Latency between ARF and the development of RHD may contribute to this. The highest incidence of ARF is in children, while RHD presents most commonly in the third and fourth decades of life.[23] This period represents an opportunity for surveillance and identification of early RHD as well as initiation of secondary prophylactic treatment. Screening for RHD has been recommended since at least the 1960s.[24]

Broadly speaking, there are 2 types of screening for RHD used in the developing world: auscultation and echocardiography. While it has largely fallen out of favor in the last several decades, auscultation does offer the advantage of being readily available and translatable in remote rural communities. Compared with echocardiography, however, auscultation is significantly less sensitive and specific for the detection of RHD. One systematic review found that echocardiography detects greater than 4 times the number of cases as auscultation.[25] In fact, the increase in utilization of echocardiography for the detection of RHD was an important part of the renewed interest in treating RHD as a global scourge. It also led to the creation of a unified set of echocardiographic criteria to diagnose RHD.[26] Three categories of RHD were created based

on the morphological features of the aortic and mitral valves: definite RHD, borderline RHD, and normal. Echocardiography enabled the detection of previously undetected cases of borderline RHD. The natural history of this category is less clear but has implications with regards to potential therapies; studies in India, Africa, and the Pacific provide evidence that children diagnosed with borderline RHD[27–31] have minimal disease progression at medium-term follow-up, while other studies from rural Australia and Nepal showed the opposite.[32,33] Another large prospective screening program of pregnant women in India identified multiple at-risk women with RHD and other structural heart abnormalities and allowed for medical and procedural care of the women and fetuses in the high-risk peripartum period. As a result, controversy exists as to whether or not to initiate secondary prophylaxis in this group. Answering this key question will be central to the continued development of RHD screening programs.[34]

Other problems exist with the implementation of echocardiographic screening programs. Echocardiographic screening requires equipment, a reliable source of electricity, as well as expertise to perform and interpret the exam. RHD-endemic areas tend to be resource-poor and lack access to skilled health care workers. In response, initiatives to train nonexpert health care workers have been implemented and have shown promise.[35] Nurses attending an 8-week training course providing echocardiographic screening were 85% specific and 84% sensitive relative to examination by a pediatric cardiologist. Concerns about the cost of echocardiography equipment have been addressed with the use of less expensive handheld echocardiography, which has been shown to be an effective screening tool in RHD-endemic regions.[36–38]

Secondary Prophylaxis

Secondary prophylaxis refers to the strategy of preventing recurrent GAS infections and ARF episodes in order to limit the progression of valvular disease. After an initial bout of ARF, recurrence rates may be as high as 50%,[39] with each attack causing further valvular damage and the progression of RHD. A systematic review summarized the effects of secondary prophylaxis in preventing further ARF episodes, showing a relative risk reduction of 55% with penicillin compared to observation.[40] Prevention of recurrent ARF has been associated with less valvular damage and mortality.[41,42] BPG is the first-line antibiotic for secondary prophylaxis; the recommended regimen is 1.2 million units every 4 weeks for a minimum of 10 years and sometimes longer.[43] With adherence to this regimen, ARF recurrence is acceptably low.[44,45] However, data indicates that patient adherence, especially in low socioeconomic countries and populations, is low.[46] The factors that affect adherence to secondary prophylactic regimens are similar to those for primary prophylaxis. Potential areas for improvement include longer-lasting depot injections to allow for less frequent dosing and mitigating the impact of low provider access, especially in remote communities. Administration of BPG with lidocaine can improve postinjection pain. The formulation of BPG that is premixed without the requirement for refrigeration may also aid with distribution.[47] However, there is benefit to secondary prophylaxis even without full adherence. Current guidelines target at least 80% regimen adherence, but data indicates that benefits start as low as 40% and increase with each 10% increase.[48]

There is also evidence that suggests that secondary prophylaxis can be associated with regression of RHD based on echocardiographic criteria. Several studies have reported this; however, low patient numbers preclude further analysis. This is an important question to address to justify more resources for secondary prophylaxis programs.

Some controversy exists regarding the duration of secondary prophylaxis, as rates of GAS infection decrease substantially as patients enter adulthood.[49,50] Data comparing the effectiveness of different durations of secondary prophylaxis are lacking. As a result, most nations rely on guidance from expert opinion. Generally speaking, the duration of secondary prophylaxis depends on the age of the most recent ARF episode and the presence of rheumatic valvular heart disease as seen on echocardiography. For example, Australian guidelines dictate that patients without evidence of carditis be treated until they are 18 years old or for 5 years after the most recent ARF episode, while those patients with severe RHD warrant prophylaxis up to the age of 40.[51] Importantly, variations in national policies must also reflect the availability of resources. This includes not only the availability of BPG but also the ability of a national health care system to provide comprehensive surgical and medical treatment to those patients who develop severe RHD. In many developing nations, it is likely more cost-effective to divert resources to improve an existing secondary prophylaxis program as opposed to trying to improve access to cardiac surgical care, at least in the short term. More data to address this important question is a research priority.

Availability of Cardiac Surgery

In recognition of the global problem RHD presents, cardiac surgeons and cardiologists issued the Drakensburg declaration 15 years ago in a call to action for the development of prevention and screening programs with the lofty goal of eradicating RHD. Despite this, RHD continues to be a major challenge. Access to open heart surgery, currently the only definitive treatment for advanced RHD, is severely limited in the developing world. In 2018, there was a renewed push to increase access to cardiac surgical care globally.[1,27,52] There is an estimated need to perform 300 cardiac surgical operations per 1 million people in RHD-endemic regions of lower income countries. This is in stark contrast to the number of available centers in sub-Saharan Africa, where 22 centers serve approximately 1 billion people.

Prior efforts to increase access have focused on mission trips from high-income countries and training pathways to fund surgeons from low-income countries to train in high-income countries. Neither is ideal for a number of reasons. Mission trips cannot fully fill the need gap as they do not provide incentives for local investment in infrastructure or centers and fail to provide a sustainable solution. Additionally, they do not address issues with postoperative follow-up for patients who undergo mitral valve repair or replacement. Funding trainees from low-income regions solves some of these issues, but may not provide adequate exposure to pathology and operations they will perform in their home countries. Moreover, this option does not provide training in the resource-limited environments that are most in need. Historically, 1 unintended consequence of such advanced training is the potential low return rate of specialists to their country of origin.[53]

A more recent initiative has been to identify and invest in local centers that have demonstrated the capacity to provide quality care as well as quality training.[54] At the same time, longer-term embedding of experienced surgeons at these centers and other more fledgling centers have demonstrated a quickening of institutional learning curves. Aswan Heart Center in Egypt is one such success story.[55]

The delivery of cardiac surgical care in developing nations poses challenges beyond the availability of surgical personnel. Prior to establishing an open-heart surgery program, a full needs assessment is paramount to ensuring good patient outcomes. Hospital sites must be evaluated for energy reliability, ventilators, echocardiography, radiography, functional cardiopulmonary bypass machines, ability to check activated clotting times, and well-stocked pharmacies and blood banks. While some of these needs overlap significantly with other clinical areas, there are multiple cardiac surgery-specific fixed and variable costs that can be cost-prohibitive without significant investment by the government or charity.[56] Essential personnel include full-time nurses with open-heart experience, anesthesiologists, perfusionists, and critical care providers, if available. Procuring sufficient valves, conduits, and pacemaker implants can pose a significant logistical challenge for new programs, but charity funds and donation programs are available through

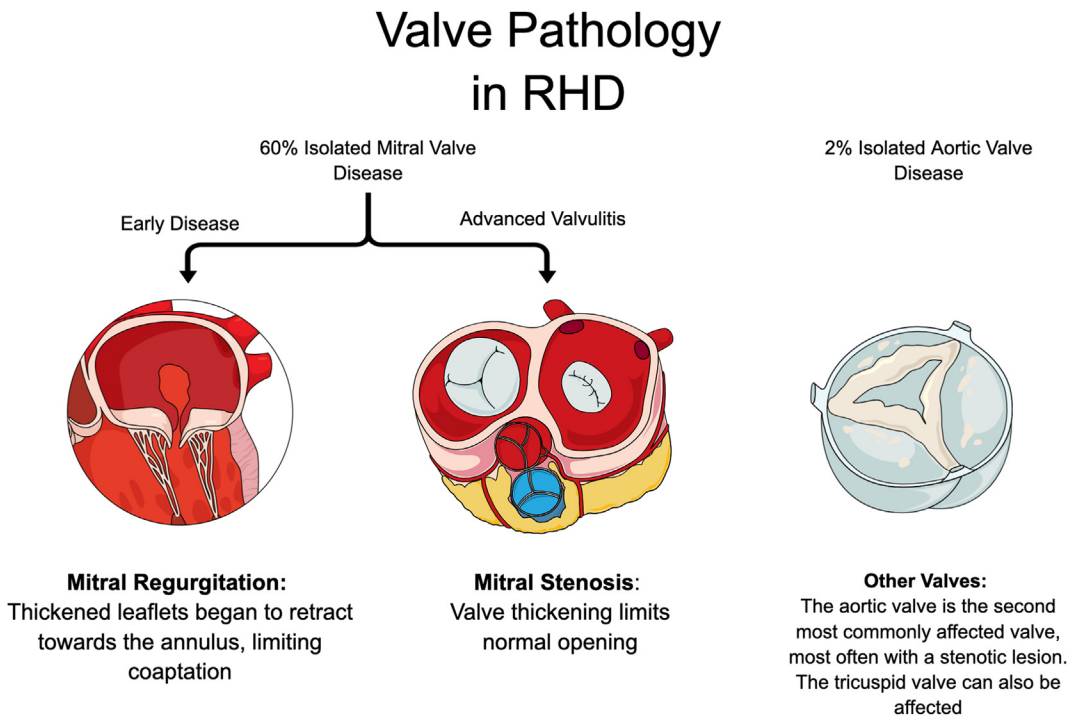

Figure 3. Valvular Pathology in RHD. The mitral valve is most commonly affected in RHD. Mitral valve lesions generally begin as predominant regurgitant lesions; however, as valve damage progresses, stenosis occurs. The aortic and tricuspid valves can also be affected by the RHD disease process; the tricuspid valve can also be affected as a sequelae of mitral disease and pulmonary hypertension.
Abbreviation: RHD, rheumatic heart disease.

most of the major device companies. The availability of such resources can impact patient case selection.

There are similar infrastructural issues in terms of postoperative follow-up as with screening and prophylaxis. Patients undergoing valve repair or bioprosthetic replacement require monitoring for repair failure and structural valve degeneration. Mechanical valve replacement is a long-term solution but requires lifelong anticoagulation and periodic blood work in order to mitigate the risk of severe bleeding or valve thrombosis. The management of anticoagulation in this setting is especially problematic given the prevalence of young women affected in childbearing years. In summary, efforts to improve global access to cardiac surgical care must address a myriad of infrastructural needs.

Rheumatic Mitral Valve Interventions

Patients with RHD should be assessed for severity of symptoms with intervention based on the affected valves and specific pathology, as summarized in Figure 3. Mitral stenosis occurs in progressive RHD and is common at the time of presentation or intervention. Once symptoms develop, the valve should be assessed echocardiographically and a Wilkins score calculated. The Wilkins score is a semiquantitative rubric used to assess the severity of valvular disease and is correlated with the outcome after balloon mitral valvuloplasty (BMV). Components of the Wilkins score are leaflet mobility, leaflet thickening, subvalvar thickening, and calcification.[57]

Closed mitral commissurotomy (CMC) was the first operation described to relieve mitral stenosis in RHD. This operation requires a thoracotomy and is traditionally done without cardiopulmonary bypass. The method offered a cheap and relatively safe solution to treating patients with RHD, in which the surgeon's finger provides both tactile assessment and guides the dilator. The main limitation of CMC was the presence of calcified leaflets and/or diseased subvalvular apparatus.[58] It was largely replaced by open mitral commissurotomy after the development of cardiopulmonary bypass due to direct visualization and the ability of open commissurotomy to also address the abovementioned limitations.[58] Open surgery achieved a larger mitral valve area and a greater increase in cardiac index compared to CMC.[59] Furthermore, it was reported that both the incidence of reoperation as well as valve-related morbidity and mortality were significantly lower after open commissurotomy. However, long-term survival was similar for both.[60] BMV overtook surgical commissurotomy as the first-line therapy for symptomatic mitral RHD with favorable anatomy given its equivalent-or-better success and restenosis rates and lesser invasiveness.[61,62] Nevertheless, CMC may still offer some utility in particularly resource-scarce locations.[58] The above is further supported by the more recent study showing comparable long-term results of CMC compared with BMV.[63]

BMV optimal short- and long-term outcomes are associated with a Wilkins score of 8 or less.[57,64] In the original analysis, all patients with a Wilkins score greater than 11 had suboptimal outcomes, while scores between 9 and 11 were not predictive of outcome. Patients with a score of 9 to 11 without other risk variables such as age and New York Heart Association class IV heart failure may be considered for BMV as there is reasonable immediate success and 5-year event-free survival.[57,64] Broadly speaking, there are 2 techniques of BMV: the double-balloon technique and the Inoue balloon technique. The Inoue balloon technique is widely preferred today as it has demonstrated similar efficacy with less risk of procedural complications.[65]

For those patients in whom BMV is contraindicated, including those with a Wilkins score >11, grade 2 or more mitral regurgitation, extensive commissural calcification, left atrial thrombus, or other significant valvular disease, surgical intervention should be recommended.[66] The options for surgical intervention on the mitral valve include mitral valve repair and mitral valve replacement. Experience with degenerative mitral valve disease in industrialized countries has demonstrated the superiority of valve repair; however, the complexity of valve pathology seen in rheumatic mitral valve disease prevents extrapolation of this finding to the RHD population.[67] Given the aforementioned issues with follow-up

after mitral valve replacement along with the younger population presenting with RHD, there has been a recent effort to improve techniques for rheumatic mitral valve repair.

Mitral valve repair for RHD is not straightforward due to the involvement of both the leaflets and the subvalvular apparatus. The principles of repair are based on individual leaflet morphology and dysfunction. Commissures are split with a knife; fused primary chords are separated and debulked without causing a flail. Anterior and posterior leaflet shaving and/or elongation are also employed to increase mobility and coaptation. If pathology affects the full thickness of the leaflet, resection may be required, followed by augmentation with glutaraldehyde-fixed autologous pericardium. Bulky calcification may pose similar problems for leaflet thinning and necessitate resection.[68] Gortex neochords can be employed if resection of abnormal chords has led to unsupported leaflet edges. Due to complexity and need for significant experience, mitral valve repair has not been widely adopted in LMICs, and more research is needed on outcomes. A center in Thailand has published reasonable results with a mean 42-month follow-up of 563 patients; however, longer-term follow-up is required in order to make meaningful comparisons between valve repair and valve replacement.[69]

Mitral valve replacement can be performed with either bioprosthetic valves or mechanical valves. Commercially available bioprosthetic valves are constructed from glutaraldehyde-fixed porcine aortic valve leaflets or bovine pericardium. These valves have limited durability, especially in younger patients typical of RHD, but avoid the complications of requisite lifetime anticoagulation for mechanical prostheses. In Rwanda, where a surgical outcomes registry has been created, early structural valve degeneration is documented at 11%,[70] making mechanical valves preferable. However, in patients for whom anticoagulation with warfarin is contraindicated, such as women who plan to become pregnant, bioprosthetic valve replacement is acceptable. Patients should be counseled that they will likely require further intervention in this case, and redo mitral valve replacement is associated with relatively high mortality.[71] While mechanical valve replacement does offer benefits in terms of longevity, it is important to note that anticoagulation management is challenging in LMICs, leading to higher rates of valve thrombosis, thromboembolism, and bleeding complications than in industrialized nations.[72] Surgical options for rheumatic mitral valve disease are summarized in Figure 4.

While the mitral valve is most affected in RHD, lesions on the aortic valve (2% isolated) and less commonly the tricuspid valve do occur. Lesion severity impacts the efficacy of BMV in improving patient symptoms. Concomitant lesions should therefore be addressed surgically. Tricuspid valve disease occurs most frequently secondary to severe left-sided heart disease. Tricuspid regurgitation in this setting should be addressed at the time of mitral valve surgery if is it severe or if there is significant annular dilatation even in the setting of mild or moderate tricuspid regurgitation. The most common intervention is annuloplasty reinforced with a band or ring. With primary tricuspid valve disease, other techniques such as leaflet augmentation or valve replacement with a biologic prosthetic should be employed.

In aortic valve disease, the most common intervention is valve replacement with a mechanical or biologic prosthesis. The benefits and pitfalls of each type are similar, as in mitral valve replacement. Aortic valve repair is challenging as there is often significant tissue loss and calcification by the time there is severe valvular dysfunction. There may be a role for valve repair of mild to moderate stenotic or regurgitant

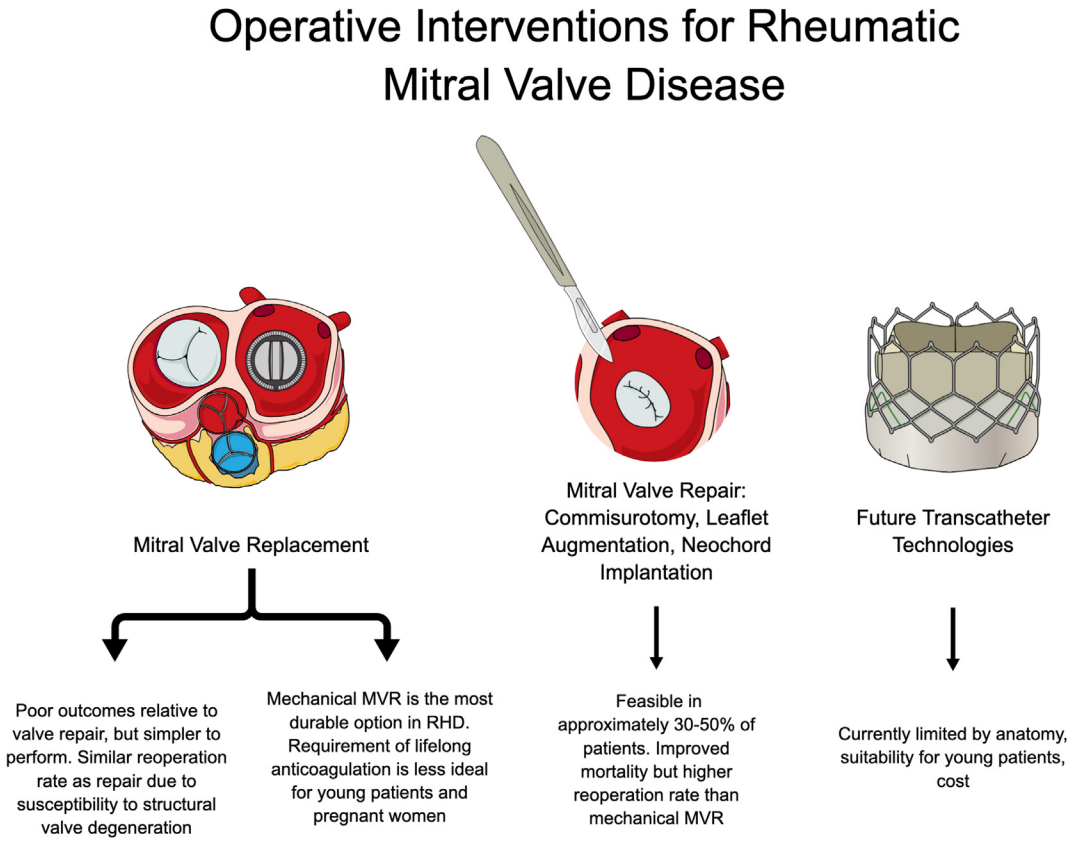

Figure 4. Operative Interventions for RHD. Mitral valve replacement with a mechanical prosthesis is the most durable operation for RHD; however, it requires lifelong anticoagulation, which may affect the labor force and women of childbearing age. Mitral repair for RHD has expanded in recent years and has shown good short- and midterm outcomes. Future innovation will likely focus on biomaterials and transcatheter technologies that can safely improve symptoms in young patients without the requirement for anticoagulation.
Abbreviations: MVR, mitral valve disease; RHD, rheumatic heart disease.

lesions at the time of mitral valve repair.[73] In these mildly or moderately affected valves, enough tissue remains to support a repair. Repair is an especially good option for children, where the benefit of avoiding a prosthesis is multiplied. Techniques are similar to those in mitral valve repair, involving peeling of the leaflets in order to improve height and sharp dissection for commissurotomy or decalcification. As in mitral valve repair, longitudinal study is required in order to better determine the best candidates for aortic valve repair and its long-term efficacy.

There are other options for young patients with rheumatic aortic valve disease. Recently, the Ross procedure has regained popularity to treat aortic valve disease in appropriately selected patients in North America and Europe. There is limited data available on the application of this operation in rheumatic disease, but there may be a role for its use in young adults.[74] However, it does seem that the pulmonary autograft is subject to recurrent valvulitis which may ultimately limit its durability relative to what is seen in industrialized nations. The Ozaki procedure is another option available in young patients with aortic valve disease, and has been used to treat rheumatic disease.[75] Both the Ross and Ozaki operations are technically demanding and should be applied only at specialized centers with highly trained surgeons.

Management of Atrial Fibrillation

Atrial fibrillation is common in patients with rheumatic mitral valve disease and may be a source of major morbidity in this population due to its association with stroke. Stroke risk may be mitigated with anticoagulation; however, anticoagulation use in LMICs is overall lower than expected. Systemic issues exist with anticoagulation control; a systematic review of anticoagulation control and outcomes in African nations shows suboptimal time in the therapeutic window and a high risk of thromboembolic or bleeding complications. There are not clear data demonstrating the prevalence of atrial fibrillation and LMICs; however, evidence suggests there is under-reporting, especially throughout sub-Saharan Africa.[76] Multiple studies have described the feasibility and efficacy of the Cox Maze procedure at the time of mitral valve intervention. This procedure is safe; however, may be less effective in patients with rheumatic disease due to the chronicity of arrhythmias and atrial size. Other complicating factors are the technical difficulty of the cut-and-sew maze and the availability of contemporary energy sources used for ablation. Even so, closure or ligation of the left atrial appendage has proven to significantly reduce the stroke risk associated with atrial fibrillation.[77] Contemporary epicardial or endocardial devices available in North America and Europe may be difficult or costly to distribute to areas of need; however, surgical oversewing is a simple and scalable technique that can be done easily at the time of a mitral valve operation. Arrhythmia associated with valvular disease in LMICs is a field that requires significantly more study and may represent an area in which cardiologists and cardiac surgeons can collaborate to significantly reduce morbidity.

Advanced Presentation

Despite improvements in screening and treatment, many RHD patients in LMICs will develop congestive heart failure (CHF) as a result of their advanced valvular disease. While these patients may benefit from intervention, advanced disease makes the likelihood of successful percutaneous intervention less likely and increases the operative risk for surgical intervention, which is also more likely to be a valve replacement as opposed to a repair.

The standard medications used to treat heart failure in developed countries may be employed in LMICs, namely beta blockade, angiotensin blockade, and diuretics. These medications may improve symptoms, but will not change the natural history of advanced rheumatic disease. A cross-sectional study evaluating heart failure across a spectrum of LMIC regions found relatively low utilization of proven heart failure medications.[78] These medications may be available in LMICs, especially in urban areas; however, lack of health insurance and health literacy may result in patients not seeking necessary treatment. As a result, the outcomes of patients with CHF in LMIC lag behind those of their developed counterparts. Additionally, the LMIC CHF population is significantly younger than that of developed countries, resulting in a major social and economic impact.

Transcatheter Valve Replacement

Over the last decade in industrialized nations, transcatheter aortic valve replacement has revolutionized the delivery of care for valvular heart disease. Although these technologies are promising for the treatment of RHD, their cost is currently prohibitive for low- and middle-income countries. Additionally, commercially available transcatheter valves in the United States and Europe are constructed of the same materials as surgically implanted valve replacements, making them susceptible to structural valve degeneration. The durability of these valves is of real concern, especially in the young patients often presenting for surgery for RHD. Several institutions and companies are evaluating biopolymeric compounds for the construction of leaflets in transcatheter implantation. Some show promise in terms of long-term durability and thrombogenic potential compared to current technology.[79] Other issues for the application of transcatheter aortic valve replacement to rheumatic disease include variable amounts of calcification in rheumatic valves that make current devices difficult to deploy accurately. There is improving technology on this front as well, with the development of homing devices.

Current designs are limited to use in the aortic valve position, which somewhat limits its potential in RHD. These valves could be used for valve-in-valve procedures in failing mitral bioprostheses; however, this requires careful preoperative patient selection, intraoperative imaging capacity, and operator technical expertise.

Although these technologies remain in the preclinical phase, they are promising for specific populations where delaying an open operation would be advantageous or where an open operation is contraindicated. If the aforementioned barriers are overcome, it is likely that transcatheter operations will significantly change how RHD is treated in LMICs.

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Funding

The authors have no funding to report.

Disclosure Statement

The authors report no conflict of interest.

Review Statement

Given his role as an editor, Isaac George, MD, had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Zoltan Turi, MD.

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