



RHEUMATIC HEART DISEASE FROM VALVULAR FIBROSIS TO EMERGING PHARMACOLOGICAL STRATEGIES

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Abstract:

Rheumatic heart disease (RHD) is a chronic, progressive valvular disorder and an important cause of cardiovascular morbidity and premature mortality, particularly in low- and middle-income countries. It develops as a long-term consequence of acute rheumatic fever following group A Streptococcus infection and involves recurrent inflammation and progressive structural damage to cardiac valves. Despite effective antibiotic treatment and secondary prophylaxis, established valvular disease may progress to leaflet thickening, commissural fusion, chordal shortening, fibrosis, stenosis, and regurgitation. Current management focuses mainly on preventing recurrent infection, controlling cardiac complications, and correcting advanced valvular lesions. However, no established pharmacological therapy specifically prevents or reverses rheumatic valvular fibrosis. Emerging understanding of inflammatory and fibrotic valve remodeling has stimulated interest in disease-modifying approaches targeting profibrotic signaling, inflammatory mediators, oxidative stress, extracellular-matrix remodeling, valvular interstitial cells, endothelial-to-mesenchymal transition, calcification, and regulatory microRNAs. This review highlights current management and emerging pharmacological strategies aimed at limiting progressive valvular damage and improving long-term outcomes in RHD.

Keywords: Rheumatic heart disease; Acute rheumatic fever; Valvular fibrosis; Antifibrotic therapy; Pharmacological strategies; Disease-modifying therapy

1. INTRODUCTION

Rheumatic heart disease (RHD) is a chronic acquired cardiovascular disorder characterized by permanent structural and functional damage to the heart valves following acute rheumatic fever (ARF). It represents the long-term cardiac consequence of an abnormal immune response that develops after infection with group A Streptococcus (GAS), particularly following streptococcal pharyngitis. RHD is considered the most serious cardiac complication of rheumatic fever and primarily affects the cardiac valves, with the mitral valve being most frequently involved, followed by the aortic and, less commonly, tricuspid valves. [1]

The disease may develop following a single severe episode of ARF or, more commonly, through recurrent inflammatory episodes that progressively damage the valvular apparatus. During the acute phase, rheumatic carditis may involve the endocardium, myocardium, and pericardium, with valvulitis representing the most clinically important component. Persistent or recurrent inflammation can subsequently result in permanent valvular abnormalities, including leaflet thickening, commissural fusion, chordal shortening, fibrosis, stenosis, and regurgitation. Chronic rheumatic valvular disease most commonly manifests as mitral stenosis with varying degrees of mitral regurgitation and may be accompanied by atrial dilatation, arrhythmias, ventricular dysfunction, and heart failure. [2]

RHD remains an important cause of cardiovascular morbidity and premature mortality, particularly in low- and middle-income countries. Its progression is influenced by recurrent GAS infections, inadequate secondary prophylaxis, socioeconomic conditions, and limited access to healthcare. Although antibiotic treatment and secondary

prophylaxis can prevent recurrent rheumatic fever and reduce further valve injury, established valvular damage may continue to progress. Advanced RHD can ultimately require percutaneous or surgical valve intervention.

From a therapeutic perspective, progressive valvular fibrosis represents a major determinant of irreversible structural damage and an important unmet clinical need. Current treatment primarily focuses on infection prevention, secondary prophylaxis, management of cardiac complications, and correction of advanced valve disease. This review deals with the clinical progression, diagnosis, current management, and emerging pharmacological strategies for preventing or limiting progressive rheumatic heart disease.

2. SIGNS AND SYMPTOMS

Rheumatic fever is a systemic inflammatory disease that typically develops 2–4 weeks after a group A β -hemolytic streptococcal pharyngeal infection. Clinical manifestations are variable and may include constitutional, musculoskeletal, neurological, dermatological, and cardiac features. A history of preceding sore throat may be reported in approximately 70% of older children and young adults, whereas it is less frequently recalled by younger children. [3,4]

Common systemic manifestations include fever, fatigue, malaise, headache, diaphoresis, pallor, weight loss, and epistaxis. Patients may also experience abdominal pain, nausea, vomiting, and chest discomfort. Musculoskeletal involvement is characterized predominantly by migratory polyarthritides or joint pain, in which pain and inflammation move sequentially between large joints.

Neurological manifestations may include Sydenham chorea, characterized by involuntary, purposeless movements, impaired motor coordination, emotional lability, irritability, personality changes, and reduced attention span. Dermatological manifestations are less frequent and include erythema marginatum, a characteristic non-pruritic, transient rash, and subcutaneous nodules.

Carditis is the most clinically important manifestation and may involve the endocardium, myocardium, or pericardium. Clinical features include exertional or resting dyspnea, orthopnea, peripheral edema, abdominal distension, and other manifestations of congestive heart failure. A pericardial friction rub may indicate pericardial involvement. Valvular involvement is particularly important, with mitral regurgitation being the most common lesion, typically producing an apical pansystolic murmur. Aortic regurgitation occurs less frequently. Rheumatic heart disease predominantly affects the left-sided cardiac valves, whereas tricuspid and pulmonary valve involvement is uncommon and generally occurs in association with mitral valve disease.

In established rheumatic heart disease, progressive valvular damage may produce dyspnea, exercise intolerance, fatigue, palpitations, chest discomfort, and symptoms of heart failure. Chronic valvular disease may also predispose patients to atrial fibrillation and other cardiovascular complications. Thus, the clinical spectrum ranges from nonspecific systemic symptoms during acute rheumatic fever to progressive cardiac manifestations associated with chronic rheumatic valvular disease.

EPIDEMIOLOGY

RHD remains a major cause of acquired cardiovascular disease among children and young adults, particularly in low- and middle-income countries. Although its incidence has declined substantially in high-income countries, RHD continues to cause considerable morbidity, premature mortality, and disability in South Asia, sub-Saharan Africa, Oceania, and parts of Latin America. Global estimates suggest that more than 30 million people are affected by RHD, with over 300,000 deaths annually, although estimates vary according to case definitions and the inclusion of subclinical disease. [5,6]

The geographical distribution of RHD is highly unequal, with the highest burden reported in central and sub-Saharan Africa, South Asia, and Oceania. India, Pakistan, Bangladesh, Indonesia, and several African countries account for a substantial proportion of the global burden. In endemic regions, echocardiographic screening detects considerably more disease than clinical examination alone, demonstrating that clinically silent or latent RHD represents an important and frequently overlooked component of the disease burden.

RHD predominantly originates during childhood. Acute rheumatic fever (ARF) occurs most frequently between 5 and 15 years of age following GAS infection, whereas established RHD often becomes clinically apparent during adolescence or adulthood after cumulative valvular injury. Recurrent episodes of ARF markedly increase the risk of

progressive valve damage. Women may experience a particularly important burden of RHD because significant valvular disease during pregnancy can increase maternal and fetal complications.

Socioeconomic deprivation is a major determinant of RHD. Overcrowded housing, poor living conditions, inadequate access to healthcare, delayed treatment of GAS infection, and inadequate adherence to secondary antibiotic prophylaxis facilitate recurrent infections and disease progression. The burden is especially pronounced among Indigenous populations, including Aboriginal and Torres Strait Islander Australians, Māori, and Pacific Island communities, where geographical isolation and healthcare inequalities further contribute to disease persistence.

In contrast, RHD has become uncommon in most Western countries following improvements in living conditions, access to healthcare, and widespread antibiotic treatment of streptococcal infections. Nevertheless, sporadic outbreaks and persistent disparities among disadvantaged populations demonstrate that RHD has not been completely eliminated.

A major epidemiological challenge is the substantial burden of subclinical disease. Echocardiographic studies indicate that latent RHD is several-fold more common than clinically detected disease, highlighting the limitations of conventional auscultation-based surveillance. Early identification of valvular abnormalities, followed by appropriate secondary prophylaxis and longitudinal monitoring, may therefore provide an opportunity to prevent progression to advanced RHD.

3. PATHOPHYSIOLOGY OF RHEUMATIC HEART DISEASE

RHD is a chronic, progressive valvular disorder that develops as a consequence of an abnormal immune response following infection with group A *Streptococcus* (GAS), principally *Streptococcus pyogenes*. The disease represents the chronic cardiac manifestation of acute rheumatic fever (ARF), in which recurrent or severe inflammatory episodes can progressively transform an initially reversible valvulitis into permanent valvular fibrosis, commissural fusion, leaflet thickening, chordal shortening and, ultimately, stenosis or regurgitation. Although the pathogenesis of RHD is not completely understood, current evidence supports an interaction between streptococcal virulence factors, molecular mimicry, genetic susceptibility, dysregulated adaptive and innate immunity, endothelial dysfunction, inflammatory cytokines and progressive extracellular-matrix remodeling. [7-9]

The initiating event is usually pharyngeal infection with GAS. The organism is a Gram-positive, β -hemolytic coccus whose major virulence determinants include the M protein, streptococcal pyrogenic exotoxins, streptolysins and other surface-associated molecules. The M protein is particularly important because some rheumatogenic GAS strains possess antigenic epitopes that resemble proteins present in human cardiac tissues. Following infection, antigen-presenting cells process streptococcal antigens and present them to T lymphocytes. In genetically susceptible individuals, this immune response may become directed against structurally similar host antigens, initiating the autoimmune cascade characteristic of ARF and RHD.

The classical explanation for this phenomenon is the molecular mimicry theory. Streptococcal antigens, particularly components associated with M proteins and cell-wall carbohydrates, share structural similarities with cardiac proteins and valvular components. Consequently, antibodies and T cells generated against GAS may cross-react with cardiac myosin, laminin, sarcolemmal proteins, valvular glycoproteins and other host structures. This phenomenon allows an immune response initially directed against the pathogen to become redirected toward host tissue. The molecular mimicry hypothesis is supported by the demonstration of cross-reactive antibodies and T-cell responses against streptococcal and cardiac antigens. However, molecular mimicry alone does not completely explain the heterogeneity of RHD, and additional mechanisms, including neoantigen formation and altered immune tolerance, may contribute.

The neoantigen hypothesis proposes that tissue injury produced during infection may expose or generate previously inaccessible host antigens. These modified self-antigens can subsequently be recognized by the immune system, producing an autoimmune response independent of direct structural similarity between streptococcal and host antigens. Thus, molecular mimicry and neoantigen formation may represent complementary rather than mutually exclusive mechanisms. The development of RHD is likely dependent on the interaction between the initiating infection, tissue injury, host genetic susceptibility and the intensity and duration of the immune response.

Both humoral and cellular immunity participate in the development of rheumatic valvular injury. Streptococcal infection activates B cells and promotes the generation of antibodies against bacterial antigens. Some of these antibodies can recognize cardiac and valvular structures. However, chronic rheumatic valvular lesions are

characterized predominantly by cellular immune responses, particularly infiltration by CD4⁺ T lymphocytes and macrophages. Streptococcal-primed CD4⁺ T cells recognize cross-reactive antigens presented by antigen-presenting cells within cardiac tissue and release inflammatory cytokines, including interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and interleukin-6 (IL-6). These mediators amplify local inflammation, activate endothelial cells and promote recruitment of additional immune cells.

Valvular endothelial dysfunction is an important early event in the development of chronic RHD. The valvular endothelium normally regulates leukocyte trafficking and maintains extracellular-matrix homeostasis. Inflammatory cytokines and cross-reactive antibodies can activate valvular endothelial cells, resulting in increased expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Increased endothelial adhesiveness facilitates the migration of activated lymphocytes and macrophages into the valve. Once these cells enter the valvular interstitium, they release inflammatory and profibrotic mediators that alter the behavior of resident valvular cells.

An imbalance between proinflammatory and regulatory immune responses may contribute to persistence of valvular inflammation. Increased expression of IFN- γ and TNF- α and reduced regulatory cytokine activity have been reported in rheumatic valve tissue. In particular, reduced representation or activity of IL-4-producing regulatory cells has been proposed to contribute to persistent inflammation and tissue injury. Decreased regulatory T-cell activity may further impair immune tolerance and permit continued activation of autoreactive lymphocytes. Therefore, the severity of valvular damage is likely influenced not only by the magnitude of the immune response but also by the capacity of regulatory mechanisms to terminate inflammation.

The acute cardiac manifestation of ARF is rheumatic carditis, which can involve the endocardium, myocardium and pericardium. Valvular involvement is particularly important because it determines the long-term consequences of RHD. The mitral valve is most frequently and severely affected, followed by the aortic valve. The tricuspid valve can also be involved, whereas pulmonary valve involvement is uncommon. During acute valvulitis, inflammation may produce edema, endothelial injury and small sterile vegetations along the lines of valve closure. Histologically, rheumatic carditis may demonstrate characteristic Aschoff bodies, consisting of areas of fibrinoid necrosis surrounded by lymphocytes, macrophages and characteristic activated macrophages known as Anitschkow cells. Subendocardial lesions may produce MacCallum plaques, particularly in the left atrium. Although acute inflammation may resolve, repeated episodes produce cumulative structural injury.

The transition from acute inflammation to chronic RHD is critically dependent on fibrotic remodeling. Persistent cytokine stimulation activates valvular interstitial cells (VICs), which normally maintain the structural integrity of the valve. Under pathological conditions, TGF- β and other profibrotic mediators induce VIC differentiation into activated myofibroblast-like cells. These cells express α -smooth muscle actin and synthesize excessive amounts of collagen and other extracellular-matrix proteins. TGF- β /Smad signaling is particularly important because it promotes collagen production, fibroblast activation and extracellular-matrix accumulation. Non-canonical pathways involving mitogen-activated protein kinases and Rho-associated signaling may further reinforce the activated phenotype.

Inflammation and fibrosis are therefore closely interconnected. Cytokines such as IL-1 β , TNF- α and IL-6 can stimulate fibroblast and VIC activity, while tissue injury and oxidative stress may activate the NLRP3 inflammasome. NLRP3 activation promotes caspase-1-dependent maturation of IL-1 β and IL-18, potentially creating a positive feedback loop between inflammation and fibrosis. Simultaneously, altered matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) activity disrupts normal extracellular-matrix turnover. Excessive collagen deposition and abnormal matrix organization progressively increase leaflet stiffness and thickness.

Repeated inflammatory injury produces characteristic chronic anatomical changes, including leaflet thickening, commissural fusion, shortening and thickening of chordae tendineae, and fusion of the valve apparatus. These changes may produce either stenosis, regurgitation or a combination of both. In the mitral valve, progressive fibrosis and commissural fusion can produce rheumatic mitral stenosis, whereas leaflet and chordal distortion may result in mitral regurgitation. Aortic involvement can similarly lead to progressive regurgitation or stenosis. As the structural abnormality progresses, altered hemodynamic forces may further stimulate endothelial and interstitial-cell signaling, thereby perpetuating the fibrotic process even after the initial infectious trigger has disappeared.

Genetic susceptibility contributes substantially to the variability in disease development and progression. Associations have been reported between RHD and specific human leukocyte antigen (HLA) class II alleles, particularly HLA-DR

and HLA-DQ variants involved in antigen presentation. Polymorphisms in inflammatory genes, including *TNFA* and *MBL2*, have also been associated with susceptibility or disease phenotype in some populations. These genetic factors may influence the strength of antigen presentation, complement activation and cytokine production, thereby modifying the intensity of the autoimmune response.

4. DIAGNOSIS

The diagnosis of RHD requires integration of clinical findings, evidence of preceding group A *Streptococcus* (GAS) infection, inflammatory markers, electrocardiography, and cardiac imaging. Because clinical manifestations and disease severity vary considerably across populations, diagnostic assessment should consider the epidemiological risk of the affected population. The World Health Organization recommends the use of the revised Jones criteria for diagnosing ARF, the principal precursor of RHD. [10-12]

Evidence of recent GAS infection is an important component of ARF diagnosis. Throat culture and rapid antigen detection testing can identify GAS infection, although throat cultures are frequently negative by the time ARF or RHD becomes clinically apparent. Therefore, serological evidence is often more useful, particularly measurement of antistreptolysin O (ASO) and anti-DNase B antibodies. A rising or elevated antibody titre supports recent streptococcal infection, with anti-DNase B generally providing greater sensitivity than ASO alone.

The revised Jones criteria combine major and minor clinical manifestations with evidence of preceding GAS infection. Major manifestations include carditis, arthritis, Sydenham chorea, erythema marginatum, and subcutaneous nodules. The classification of joint manifestations differs according to population risk, with broader joint criteria applied in moderate- and high-risk populations. Minor manifestations include fever, arthralgia, elevated inflammatory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and prolonged PR interval on electrocardiography when other criteria are appropriately considered. Carditis may be clinical or subclinical, with echocardiographic evidence increasingly recognized as an important component of diagnosis.

Inflammatory markers such as ESR and CRP are commonly elevated during acute rheumatic fever. Although these markers are sensitive indicators of inflammation, they are not specific for ARF or RHD and are therefore primarily useful as supportive investigations and for monitoring inflammatory activity. Electrocardiography may demonstrate sinus tachycardia, PR-interval prolongation, chamber enlargement, atrial fibrillation, or other conduction abnormalities. However, first-degree atrioventricular block is nonspecific and should not be interpreted in isolation as evidence of RHD.

Echocardiography with Doppler is the principal imaging modality for detecting and characterizing RHD and is substantially more sensitive than auscultation for identifying valvular disease, including subclinical carditis. It provides information regarding valvular morphology, regurgitation, stenosis, ventricular function, and disease progression. Typical rheumatic changes include leaflet and chordal thickening, restricted leaflet motion, commissural fusion, and pathological mitral or aortic regurgitation. The 2023 World Heart Federation (WHF) criteria introduced a staged approach to echocardiographic diagnosis, replacing the earlier categories of definite, borderline, and normal RHD with stages A–D according to disease severity and risk of progression. The revised framework also distinguishes screening criteria for non-experts from confirmatory criteria for expert assessment.

Handheld echocardiography may provide a useful screening approach in settings where conventional echocardiography is unavailable, particularly among children and adolescents in populations with moderate or high RHD prevalence. Chest radiography may demonstrate cardiomegaly or pulmonary congestion in patients with advanced disease or heart failure, whereas cardiac magnetic resonance imaging remains primarily an investigational tool and may provide additional information regarding myocardial fibrosis.

At the pathological level, chronic RHD is characterized by fibrotic thickening of the valve leaflets, commissural fusion, chordal shortening and fusion, and variable calcification. Histological examination may demonstrate chronic neovascularization and, during active rheumatic carditis, characteristic Aschoff bodies containing macrophages, lymphocytes, and areas of fibrinoid necrosis.

The WHF staging system further categorizes RHD from Stage A, representing minimal echocardiographic abnormalities, through Stage B, mild disease, Stage C, advanced disease at high risk of complications, and Stage D, advanced disease with established clinical complications such as heart failure, arrhythmia, stroke, or previous cardiac

surgery. This staged approach facilitates early detection, risk stratification, longitudinal monitoring, and timely therapeutic intervention.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of rheumatic heart disease includes a range of infectious, inflammatory, autoimmune, structural, and myocardial disorders that can produce similar clinical or echocardiographic findings. Infective endocarditis should be considered in patients with fever and valvular insufficiency, while viral or nonviral myocarditis may present with myocardial dysfunction and functional mitral regurgitation. Mitral valve prolapse associated with degenerative myxomatous disease is another important structural differential, particularly in children and young adults. Other valvular disorders, including aortic stenosis and aortic regurgitation, as well as congenital abnormalities such as a bicuspid aortic valve, may mimic rheumatic valvular disease. In the pediatric population, more than trace mitral or aortic regurgitation may be considered potentially pathological after nonrheumatic causes have been excluded. Other conditions that may enter the differential diagnosis include Kawasaki disease, systemic lupus erythematosus, acute or chronic pericarditis, dilated cardiomyopathy, heart failure, cardiac tumors, and malignant pericardial effusion. In patients presenting with arthritis, septic arthritis and transient synovitis should also be considered, while glomerulonephritis and systemic infections such as histoplasmosis or coccidioidomycosis may produce overlapping systemic manifestations. Careful clinical assessment, laboratory investigations, and echocardiographic evaluation are therefore essential to distinguish rheumatic cardiac involvement from these alternative conditions. [13]

TREATMENT AND MANAGEMENT

Management of RHD involves primary prevention, treatment of acute rheumatic fever, secondary antibiotic prophylaxis, management of cardiac complications, and intervention for advanced valvular disease. Primary prevention depends on prompt recognition and treatment of GAS pharyngitis. Penicillin remains the preferred therapy, with oral penicillin V, amoxicillin, or intramuscular benzathine penicillin G used according to clinical circumstances and adherence considerations. Appropriate treatment of GAS infection reduces the risk of subsequent ARF. [14-16]

In patients with established ARF or RHD, residual GAS infection should be eradicated when present, while treatment of acute manifestations is directed toward symptom control and prevention of complications. Although salicylates, nonsteroidal anti-inflammatory drugs, corticosteroids, and intravenous immunoglobulin have historically been used for inflammatory manifestations, evidence has not demonstrated consistent improvement in long-term cardiac outcomes with anti-inflammatory therapy. NSAIDs may be useful for arthritis, whereas glucocorticoids may be considered in selected patients with severe carditis.

Secondary antibiotic prophylaxis is the cornerstone of preventing recurrent ARF and progressive valvular damage. Intramuscular benzathine penicillin G administered at regular intervals is the preferred strategy, with administration every 4 weeks and, in selected high-risk or endemic settings, every 3 weeks. Oral penicillin or appropriate alternatives may be considered when intramuscular therapy is unsuitable or contraindicated. Prophylaxis is particularly important because recurrent ARF accelerates the progression of valve damage. The duration of prophylaxis should be individualized according to the presence and severity of carditis, residual valve disease, age, and risk of recurrent GAS exposure.

Cardiac complications require appropriate supportive and pharmacological management. Patients who develop heart failure may require diuretics, afterload reduction with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), digoxin in selected cases, oxygen, and appropriate fluid and sodium restriction. Loop diuretics are commonly used for congestion, while mineralocorticoid receptor antagonists may be added when clinically indicated. ACE inhibitors may be particularly useful in patients with significant mitral or aortic regurgitation and ventricular dysfunction.

In advanced valvular disease, pharmacological therapy cannot reverse established anatomical damage. Percutaneous mitral balloon valvuloplasty is an important therapeutic option for appropriately selected patients with rheumatic mitral stenosis, while surgical valve repair or replacement may be required for severe stenotic or regurgitant lesions. Progressive or refractory heart failure caused by severe valve dysfunction may necessitate cardiothoracic intervention.

COMPLICATIONS

Rheumatic heart disease may remain clinically silent for several years before progressive valvular damage produces significant cardiovascular complications. The major complications are primarily related to severe valvular stenosis or regurgitation and the resulting hemodynamic burden. Heart failure may develop because of chronic valvular dysfunction, particularly advanced mitral or aortic valve disease. Atrial fibrillation and other atrial arrhythmias may occur secondary to atrial enlargement, especially in patients with severe mitral stenosis or regurgitation. Progressive disease can also lead to pulmonary hypertension and pulmonary edema. Intracardiac thrombus formation associated with atrial fibrillation or marked atrial dilation may result in systemic thromboembolism and stroke. Other important complications include recurrent pulmonary embolic events and infective endocarditis involving damaged valves. In advanced disease, persistent pressure and volume overload may result in progressive ventricular dysfunction and worsening functional capacity. These complications substantially contribute to morbidity and premature mortality and highlight the importance of early diagnosis, regular echocardiographic monitoring, secondary antibiotic prophylaxis, and timely intervention for severe valvular disease. [17]

PROGNOSIS

The prognosis of RHD is primarily determined by the risk of recurrent rheumatic fever, the severity of valvular damage, and the extent of cardiac involvement. Acute manifestations of rheumatic fever generally resolve within 12 weeks in approximately 80% of patients, although recovery may extend to 15 weeks in others. Residual valvular disease is substantially more frequent among patients with recurrent episodes, with reported 10-year rates of approximately 34% without recurrence compared with 60% following recurrent rheumatic fever. Valvular abnormalities may continue to regress over several years, particularly when secondary antibiotic prophylaxis is maintained. Historically, 60–70% of patients developed chronic valvular disease following acute rheumatic fever, whereas this proportion declined to approximately 9–39% after the introduction of penicillin. Prognosis is poorer with recurrent disease, severe initial carditis, and delayed recognition or inadequate follow-up. Advanced RHD may ultimately result in heart failure, arrhythmias, thromboembolic complications, and premature mortality. Regular clinical and echocardiographic monitoring, together with effective secondary prophylaxis, is therefore essential for improving long-term outcomes. [18]

EMERGING THERAPEUTIC STRATEGIES

Despite advances in antibiotic prophylaxis and management of valvular complications, there is currently no established pharmacological therapy capable of reversing or specifically preventing rheumatic valvular fibrosis. Emerging therapeutic strategies therefore focus on interrupting the inflammatory and profibrotic pathways that link recurrent immune-mediated injury to progressive valve remodeling. Potential targets include TGF- β /Smad signaling, angiotensin II pathways, NLRP3 inflammasome activation, IL-6/IL-17 signaling, NF- κ B, oxidative stress, MMP/TIMP imbalance, valvular interstitial cell activation, endothelial-to-mesenchymal transition, fibroblast growth factor signaling, microRNAs, and pathological valvular calcification. [19-21]

Among these, TGF- β signaling represents a particularly attractive antifibrotic target because of its central role in myofibroblast activation and extracellular-matrix deposition. However, systemic inhibition may interfere with immune regulation and tissue repair, suggesting that tissue-selective or downstream modulation may be more feasible. Similarly, angiotensin II signaling may contribute to TGF- β activation, oxidative stress, inflammation, and matrix deposition. However, ACE inhibitors and ARBs should currently be used in RHD according to established cardiovascular indications rather than as proven antifibrotic therapies.

Inflammatory pathways such as NLRP3/IL-1 β , IL-6/IL-17, and NF- κ B represent additional potential targets. Their inhibition could theoretically reduce inflammatory amplification and subsequent fibroproliferative remodeling; however, clinical evidence supporting their use in RHD remains insufficient. Direct modulation of valvular interstitial cell activation, EndMT, and MMP/TIMP imbalance may offer more disease-specific approaches by targeting cellular and extracellular mechanisms directly involved in valve fibrosis.

Metabolic and molecular approaches are also emerging. SGLT2 inhibitors have been proposed as hypothesis-generating candidates because of their potential effects on oxidative stress, mitochondrial function, inflammation, and TGF- β -associated fibrosis, although RHD-specific evidence remains inadequate. Likewise, microRNA-based therapeutics could potentially regulate multiple inflammatory and fibrotic pathways simultaneously, while modulation of fibroblast growth factor signaling and pathological calcification represents additional areas for investigation.

Future therapeutic development should adopt a stage-specific and biomarker-guided approach. Immune modulation may be most relevant during active rheumatic inflammation, whereas antifibrotic strategies could be more beneficial during early progressive valve remodeling, before irreversible anatomical distortion occurs. Biomarkers of collagen turnover and fibrosis, integrated with echocardiographic, imaging, and molecular data, may eventually facilitate identification of patients most likely to benefit from disease-modifying therapy.

5. CONCLUSION

Rheumatic heart disease remains a major cause of preventable valvular morbidity, with progressive fibrosis and structural remodeling contributing to irreversible cardiac dysfunction. Emerging pharmacological strategies targeting inflammation, fibrosis, extracellular-matrix remodeling, and valvular disease progression may provide new opportunities for disease modification and improved long-term outcomes

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