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Review Article

Rheumatic Heart Disease: An In-Depth Review of Prevention, Pathophysiology, and Treatment Options

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Abstract

Rheumatic Heart Disease (RHD) is a major global health problem, particularly affecting populations in low- and middle-income countries. This disease results from an autoimmune response triggered by Group A *Streptococcus* (GAS) infection. The aim of this review is to thoroughly examine the complex pathophysiology of RHD, emphasizing the important role of molecular mimicry, which leads to autoimmune reactions, chronic inflammation of the heart valves, and subsequent long-term damage.

Key etiologic factors contributing to RHD include inflammatory processes characterized by immune cell infiltration. This infiltration stimulates the production of proinflammatory cytokines, which further exacerbate inflammation and tissue damage. Furthermore, Matrix Metalloproteinases (MMPs) play a vital role in heart valve remodeling, exacerbating the structural degeneration associated with this disease. Genetics also plays a crucial role in the risk of developing RHD, as specific polymorphisms in the Human Leukocyte Antigen (HLA) system and other immune-related genes indicate increased susceptibility to this serious disease.

Effective treatment for RHD is aimed at preventing Acute Rheumatic Fever (ARF) through timely administration of antibiotics. Furthermore, secondary prevention strategies are crucial for preventing relapses of ARF. Current treatment options include both drug therapy and surgical interventions aimed at resolving significant valvular dysfunction. Public health initiatives aimed at improving access to healthcare and educating the public about the risks associated with infections caused by GAV are crucial. Overall, this review highlights the need for integrated approaches combining clinical management with comprehensive preventive public health strategies to reduce the prevalence and consequences of RHD.

Keywords: Rheumatic heart disease; Leukocyte antigen; Public health; Autoimmune

Introduction

RHD is a chronic condition resulting from inflammation of the heart due to one or multiple episodes of Acute Rheumatic Fever (ARF). This fever is an autoimmune response triggered by infections with GAS bacteria, commonly associated with strep throat or scarlet fever [1,2]. During an episode of rheumatic fever, the immune system mistakenly attacks the body's own tissues, particularly affecting the heart, joints, skin, and brain. If the resulting inflammation is not promptly and effectively treated, it can cause lasting damage to the heart valves, especially the mitral and aortic valves [3]. Over time, this damage can lead to stenosis (narrowing) of the valve or regurgitation (leakage), which reduces the heart's ability to pump blood effectively and leads to various complications [4].

The pathophysiology of RHD involves progressive scarring and deformation of the heart valves due to chronic inflammation, initially caused by the immune response to a *streptococcal* infection [5]. In severe cases, the inflammation can spread to other areas of the heart, including the myocardium (heart muscle) and pericardium (the outer lining of the heart), leading to a condition known as pancarditis [6]. However, the heart valves are most seriously affected. As the inflammation subsides, the healing process often results in thickening, calcification, and decreased flexibility of the valves [7,8]. It is important to understand that RHD is the end result of a complex autoimmune reaction triggered by primary infection with group A *streptococcus*. This process involves molecular mimicry, in which the immune system's response to *streptococcal* antigens inadvertently cross-reacts with human tissue antigens, particularly those present in the heart [9-12]. Key *streptococcal* antigens involved in this mechanism include the M protein, which has structural similarities to several cardiac proteins, such as myosin, laminin, and tropomyosin. When the immune

system defends against *streptococcal* infection, it produces antibodies and activates T cells that mistakenly attack these autoantigens, leading to inflammation and tissue damage in the heart valves, myocardium, and other structures [13-16]. The inflammatory process in RHD is characterized by the infiltration of immune cells, including T-lymphocytes and macrophages, into the cardiac tissue. These cells release pro-inflammatory cytokines and enzymes that contribute to the degradation of the extracellular matrix and the destruction of valve tissue [17-19]. As the acute inflammatory phase resolves, it gives way to fibrosis and calcification, resulting in the characteristic thickening and scarring of the heart valves associated with chronic RHD. This scarring impairs the normal function of the valves, resulting in stenosis, where valve leaflets become narrowed and stiff, or regurgitation, where the valve does not close properly, allowing backward blood flow [20,21]. Over time, these valve dysfunctions place increasing strain on the heart, eventually leading to heart failure, arrhythmias, and other serious complications [22,23].

The biochemistry underlying RHD also includes persistent activation of certain signaling pathways and the production of MMPs, Enzymes involved in extracellular matrix degradation promote valve remodeling. The ongoing cycle of chronic inflammation and tissue repair in RHD exacerbates this condition [24-26]. Furthermore, genetic predisposition remains an area of active research, as certain genetic factors may influence an individual's susceptibility to the autoimmune response induced by *streptococcal* infection, although the exact genetic mechanisms are not yet fully understood [27,28].

RHD continues to pose a significant public health problem worldwide, particularly in low and middle-income countries, where it remains a leading cause of cardiovascular morbidity and mortality, particularly among children and young adults [29,30]. The prevalence of RHD varies significantly depending on geographic, socioeconomic, and health factors, with the highest rates observed in sub-Saharan Africa, South Asia, and the Pacific Islands. In these regions, prevalence can range from 1 to 10 per 1000 persons, with some regions reporting even higher rates [31,32]. These elevated rates are largely attributed to the persistence of *streptococcal* infections, poor access to health care, and limited availability of antibiotics, which are crucial for preventing initial episodes of ARF, the precursor to RHD [33]. In contrast, in high-income countries, the prevalence of RHD has decreased significantly in recent decades, primarily due to improved access to health care, widespread use of antibiotics, and better living conditions that help contain the spread of *streptococcal* infections. However, RHD still persists among marginalized populations, including indigenous communities and immigrants from high-prevalence regions, highlighting persistent socioeconomic and health inequalities [34-36] (Table 1).

Table 1: Pathophysiology and key factors of Rheumatic Heart Disease (RHD).

Component	Description	Role	Effects	Markers/Indicators
Group A *Streptococcus* (GAS)	Bacteria causing infections like strep throat	Trigger for autoimmune response	Can lead to rheumatic fever if untreated	-
Molecular mimicry	Immune response mistakenly attacking heart tissue	Initiates inflammation	Damage to heart valves, myocardium	Antibodies against heart proteins
Immune cell infiltration	Infiltration of T lymphocytes and macrophages	Releases pro-inflammatory cytokines	Chronic inflammation and valve damage	-
Matrix Metalloproteinases (MMPs)	Enzymes aiding in degradation and remodeling of ECM	Contributes to valve remodeling	Thickening and scarring of heart valves	Elevated MMP-9 levels
Genetic susceptibility	Polymorphisms in HLA and cytokine-related genes	Predisposes individuals to RHD risk	Increases likelihood of severe disease	Specific HLA alleles, cytokine levels

Inflammation

The development of RHD begins with an infection caused by GAS, which usually presents with pharyngitis or scarlet fever. GAS bacteria produce various surface proteins, among which the M protein is of particular importance [37-39]. The initial inflammatory stage of RHD is characterized by an acute immune response. Upon recognition of *streptococcal* antigens, the immune system activates T and B lymphocytes, which then produce antibodies to these antigens [40,41]. However, due to molecular mimicry, these antibodies and T cells inadvertently bind to cardiac myosin and other cardiac tissue proteins, triggering inflammation in the heart. The M protein is highly immunogenic and shares structural features with several human cardiac tissue proteins, including cardiac myosin, tropomyosin, and laminin [42-45]. This mimicry prepares the body for an autoimmune response. When the immune system encounters the M protein, it produces antibodies and activates T cells targeting GAS antigens, but these immune

responses can also mistakenly attack the body's own heart tissue [46-48].

As the immune response develops, B cells produce antibodies to the M protein, and $CD4^+$ T helper cells are activated. These T helper cells secrete cytokines such as Interleukin-2 (IL-2), which stimulates T cell proliferation, and Interferon-gamma (IFN-γ), which activates macrophages [49-51]. Activated macrophages then produce proinflammatory cytokines, including Tumor Necrosis Factor alpha (TNF-α) and interleukin-1 (IL-1), which further enhance the inflammatory response by recruiting more immune cells to the site of infection and activating additional pathways that promote tissue damage [52].

A critical component of this biochemical process is the activity of Matrix Metalloproteinases (MMPs), enzymes secreted by activated macrophages and other cells in the inflamed cardiac tissue [53]. MMPs degrade the Extracellular Matrix (ECM)-a protein network that provides structural support to tissues [54-56]. In RHD, excessive MMP activity results in the breakdown of the ECM in the heart valves, contributing to valve deformities. MMP-9, in particular, has been implicated in the remodeling of heart valve tissue, which leads to thickening, fibrosis, and calcification [57,58].

As inflammation persists, it progresses to a subacute stage, characterized by more extensive damage to heart tissue. At this stage, the inflammation begins to penetrate deeper into the valvular structures, involving the endocardium (the inner lining of the heart) and, in some cases, the myocardium (heart muscle) [59]. This stage is characterized by the formation of Aschoff bodies-nodules of inflammatory cells, including T cells, B cells, macrophages, and plasma cells, surrounded by necrotic tissue. These lesions are characterized by central fibrinoid necrosis surrounded by immune cells [60,61]. The formation of Aschoff bodies is a result of the ongoing immune response and the cytokines released during this process, such as IL-1 and TNF-α, which perpetuate the inflammation and contribute to the chronic nature of the disease. Cells within Aschoff bodies, particularly activated macrophages known as Anichkov cells, produce additional inflammatory mediators that exacerbate tissue damage [62]. The presence of Aschoff bodies is a hallmark of rheumatic fever and indicates an ongoing inflammatory process. The damage results in swelling, thickening, and deformation of the valve leaflets. In some cases, the inflammation may also involve the pericardium (the outer lining of the heart), leading to pericarditis, which further aggravates the condition [63].

The chronic phase of inflammation in RHD is characterized by healing and scarring following the acute and subacute stages. As the inflammation subsides, the body attempts to repair damaged heart tissue, typically resulting in fibrosis, in which normal tissue is replaced by fibrous scar tissue. This fibrosis leads to thickening and stiffening of the heart valves, causing either stenosis (narrowing) of the valve or regurgitation (leaking). Over time, this fibrous tissue may also calcify, further impairing valve function [64,65]. The interplay between chronic inflammation and ongoing tissue repair generates a cycle of injury and healing that worsens the condition and can ultimately lead to heart failure, arrhythmias, and other complications. Transforming Growth Factor beta (TGF-β) plays a critical role in this step by stimulating the differentiation of fibroblasts into myofibroblasts, which produce collagen and other ECM components [66-68]. Although TGF-β is vital for wound healing, its over-activation in RHD leads to excess collagen deposition, resulting in fibrosis, which replaces the normal elastic valve tissue with rigid and thickened structures. This fibrotic process is often associated with calcification, in which calcium deposits accumulate within the valve tissue, further impairing its function [69-72]. Chronic inflammation and fibrosis also lead to increased levels of adhesion molecules, such as Vascular Cell Adhesion Molecule-1 (VCAM-1) and Intercellular Adhesion Molecule-1 (ICAM-1), on endothelial cells. These molecules promote the adhesion and migration of additional immune cells into cardiac tissue, perpetuating the inflammatory cycle [73-75]. Over time, this persistent inflammation and tissue remodeling cause significant structural changes in the heart valves, leading to stenosis or regurgitation, which can lead to heart failure, arrhythmia, and various complications [76,77].

C-Reactive Protein (CRP) serves as a significant biomarker in RHD, reflecting the inflammation characterizing both the acute phase of rheumatic fever and the chronic progression of RHD. Produced primarily by the liver in response to inflammation, CRP synthesis is stimulated by pro-inflammatory cytokines, particularly Interleukin-6 (IL-6), released by macrophages and T cells during an immune response. Elevated CRP levels are closely associated with the body's response to the GAS infection that initiates the disease process [78-80].

During an ARF episode, which precedes RHD, CRP levels increase markedly as the immune system reacts to *streptococcal* antigens, leading to widespread inflammation. CRP plays a role in the immune response by binding to phosphocholine on the surfaces of dead or dying cells and certain bacteria, including those responsible for the initial *streptococcal* infection [81]. By binding to these elements, CRP facilitates their recognition and clearance by the immune system, particularly through complement system activation and enhanced phagocytosis by macrophages. This process is crucial for the body's defense against infection but also contributes to the inflammation observed in ARF and subsequently in RHD [82-84].

During rheumatic fever, CRP levels can rise dramatically, often reaching values significantly above normal, reflecting the severity of the inflammatory response. Increased CRP is not just an indicator of systemic inflammation; it also signifies the autoimmune reaction where the immune system, due to molecular mimicry, begins attacking heart

tissues [85-87]. Elevated CRP levels during ARF are clinically useful for diagnosing the condition, especially when assessed alongside other inflammation markers, such as the Erythrocyte Sedimentation Rate (ESR). As the acute phase subsides, CRP levels typically decrease; however, in cases where RHD develops, CRP may remain elevated or rise again during subsequent disease flare-ups or recurrent *streptococcal* infections [88].

In chronic RHD, persistent low-grade inflammation can maintain slightly elevated CRP levels, reflecting ongoing inflammatory activity in the heart valves. This chronic inflammation leads to progressive valve damage characterized by fibrosis and calcification, which are the hallmarks of RHD [89]. Monitoring CRP levels in patients with established rheumatic heart disease is useful for assessing disease activity and identifying periods of increased inflammation that may indicate a relapse of rheumatic heart disease or worsening valvular disease [90]. Although CRP itself does not directly cause tissue damage, its level serves as a reliable indicator of the inflammatory environment in the body, providing insight into the severity and progression of the disease [91,92].

Furthermore, elevated CRP levels in patients with RHD are associated with worse clinical outcomes, including a higher likelihood of requiring valve surgery and an increased risk of complications such as heart failure and atrial fibrillation. Long-term inflammation, as evidenced by persistently elevated CRP levels, promotes continuous remodeling and deterioration of the heart valves, exacerbating the hemodynamic load on the heart [93,94].

The chronic inflammatory response in RHD is maintained biochemically through persistent activation of immune pathways and continuous production of cytokines and MMPs. Long-term inflammation and fibrosis can lead to irreversible structural changes in the heart, including valve deformation and the development of heart murmurs, which often serve as the initial clinical signs of RHD. In severe cases, chronic inflammation can also lead to thrombus formation on damaged valves, increasing the risk of embolic complications such as stroke [95].

Genetic susceptibility

RHD is understood as the result of a complex interplay between environmental factors-particularly recurrent infections with Group A *Streptococcus* (GAS) and host genetic factors that increase susceptibility to an exaggerated autoimmune response. The genetic predisposition to RHD is believed to be polygenic, involving multiple genes rather than a single mutation [96,97]. A significant genetic factor associated with RHD susceptibility is the Human Leukocyte Antigen (HLA) system, which plays a crucial role in the immune response by presenting antigens to T cells. Certain HLA class II alleles, particularly those from the HLA-DR and HLA-DQ loci, are linked to a heightened risk of developing rheumatic fever and RHD [98,99]. For instance, research indicates that individuals with the HLA-DRB107 and HLA-DRB104 alleles are at greater risk for RHD. These HLA molecules may present *streptococcal* antigens in a manner that elicits a more robust or prolonged autoimmune response, leading to the cross-reactivity observed in RHD, where the immune system attacks cardiac tissue [100,101].

In addition to HLA genes, other immune-related genes have been implicated in susceptibility to RHD. Variants in genes that encode cytokines and their receptors, such as TNF-α, IL-10 and IL-6, have been examined for their roles in modulating the inflammatory response [102,103]. For example, specific polymorphisms in the TNF-α promoter are associated with increased TNF-α production, potentially leading to a heightened and prolonged inflammatory response in individuals with RHD. Similarly, variations in the IL-10 gene, which encodes an anti-inflammatory cytokine, may affect the balance between pro-inflammatory and anti-inflammatory responses, influencing the severity of RHD development [104-106].

Research into RHD genetics also includes the investigation of genes involved in immune response regulation, particularly those related to T-cell activation and the complement system. Variants in genes encoding proteins associated with T-Cell Receptor (TCR) components or complement factors have been studied for their potential role in increasing susceptibility to autoimmune diseases like RHD. For example, polymorphisms in the CTLA4 gene, which encodes a protein that downregulates T-cell activation, have been linked to various autoimmune conditions, including RHD [107].

Moreover, Genome-Wide Association Studies (GWAS) have been employed to uncover additional genetic loci associated with RHD. These studies focus on identifying common genetic variants that are more prevalent in individuals with RHD compared to those without the condition. Some have discovered novel loci that might contribute to disease susceptibility, although research is ongoing to elucidate the specific mechanisms by which these loci affect RHD risk [108,109].

It is essential to recognize that genetic susceptibility to RHD likely interacts with environmental factors such as socioeconomic status, healthcare accessibility, and repeated GAS infections. This gene-environment interaction indicates that individuals who are genetically predisposed to RHD are more likely to develop the disease if they experience frequent *streptococcal* infections, particularly in contexts with limited access to timely medical treatment.

Management & prevention

The key to managing RHD lies in preventing ARF, the precursor to RHD, by promptly treating GAS infections. Primary prevention focuses on the early and effective administration of antibiotics for *streptococcal pharyngitis*, with penicillin being the most commonly used option. A single intramuscular injection of benzathine penicillin

G is highly effective at eliminating the *streptococcal* bacteria, thus preventing the immune response that can lead to ARF. For individuals with penicillin allergies, alternative antibiotics such as erythromycin or cephalexin are available. In regions where GAS infections and ARF are prevalent, public health strategies to improve healthcare access, promote hygiene, and ensure proper nutrition are critical components of primary prevention efforts [110].

Once ARF has developed, secondary prevention becomes essential to avert recurrences, which significantly increase the risk of chronic RHD. This approach involves the long-term use of prophylactic antibiotics, typically benzathine penicillin G administered intramuscularly every three to four weeks [111,112]. This regimen markedly reduces the likelihood of recurrent ARF and, consequently, the progression to RHD. The duration of secondary prophylaxis is influenced by factors such as the patient's age, the severity of the initial ARF episode, and the presence of carditis or valve damage. Generally, prophylaxis is recommended for at least 10 years or until the patient reaches their early twenties; however, in cases of severe valve damage, lifelong prophylaxis may be necessary [113].

Management of established RHD focuses on addressing complications arising from heart valve damage. Patients with significant valvular heart disease may require medical therapies to manage symptoms such as heart failure, atrial fibrillation, or thromboembolism. Commonly prescribed medications in these situations include diuretics, beta-blockers, ACE inhibitors, and anticoagulants [114]. Diuretics help manage fluid overload associated with heart failure, while beta-blockers and ACE inhibitors enhance cardiac function and alleviate the heart's workload. Anticoagulation therapy is particularly crucial for patients with atrial fibrillation or prosthetic heart valves, as they are at increased risk of thromboembolic events, including stroke [115,116].

In instances of severe valvular disease that do not adequately respond to medical therapy, surgical interventions may be necessary. Valve repair or replacement surgery is often indicated in cases of severe stenosis or regurgitation leading to symptomatic heart failure or other complications. When possible, valve repair is the preferred option because it preserves the patient's own valve tissue and eliminates the need for long-term anticoagulation therapy, which is typically required with mechanical valve prostheses [117,118]. If repair is not possible, valve replacement with a mechanical or bioprosthetic valve may be performed. The choice between a mechanical or bioprosthetic valve depends on various factors, including the patient's age, lifestyle, and adherence to anticoagulation therapy [119,120].

In addition to medical and surgical treatment, regular follow-up and monitoring are essential for patients with RPS. Echocardiography is the primary tool used to assess valve function and monitor disease progression. Regular echocardiographic examinations are vital for treatment decisions, particularly regarding the timing of surgical interventions [121-123]. In settings with limited access to advanced medical care, echocardiographic screening programs can help identify RHD early, before symptoms develop, allowing for early intervention and potentially improving outcomes [124,125] (Table 2).

Table 2: Prevention and management strategies for rheumatic heart disease.

Strategy	Type	Description	Target Group	Outcome Goal
Antibiotic treatment	Primary Prevention	Prompt treatment of GAS infections with antibiotics	Individuals with strep throat	Prevent ARF and RHD development
Long-term antibiotic prophylaxis	Secondary Prevention	Regular antibiotic administration to prevent recurrent ARF	Individuals with history of ARF	Reduce recurrence of RHD and complications
Medical therapy	Management	Treatment of complications (e.g., heart failure)	Patients with established RHD	Improve symptoms and quality of life
Surgical interventions	Management	Valve repair or replacement as needed	Severe RHD patients	Address significant valvular dysfunction
Public health initiatives	Prevention	Education and access to healthcare	Communities in high-risk areas	Raise awareness and reduce incidence of RHD

Public health initiatives are critical for the prevention and control of RHD, particularly in low- and middle-income countries where the disease burden is highest. These initiatives include expanding access to primary care, ensuring availability of antibiotics, and educating the public about the importance of seeking treatment for a sore throat, which is often the first sign of *streptococcal* infection. School-based screening and treatment programs for *streptococcal* infections can effectively reduce the incidence of ARF and RHD. Furthermore, efforts to improve socioeconomic conditions, such as reducing school overcrowding and improving sanitation, can help reduce the transmission of *streptococcal* infections.

Conclusion

RHD continues to pose a significant challenge, particularly in resource-limited regions where GAS infections are prevalent. This review emphasizes the complex interactions among infectious agents, autoimmune responses, genetic predispositions, and the resulting pathophysiological changes that define RHD. The persistent inflammation and tissue damage associated with the condition highlight the critical need for timely interventions and preventive strategies to break the cycle of ARF that can lead to chronic heart disease.

Effective primary prevention hinges on the prompt treatment of *streptococcal* infections, which is essential for reducing the risk of developing ARF and subsequent RHD. Secondary prevention strategies, including long-term antibiotic prophylaxis, play a pivotal role in minimizing recurrence rates and related complications. Additionally, advancements in both medical and surgical interventions offer promising pathways for improving outcomes for patients already affected by RHD.

Public health initiatives focused on raising awareness, increasing healthcare access, and educating communities about the significance of early treatment are vital for decreasing the global incidence of RHD. Collaborative efforts among healthcare providers, policymakers, and community members are essential to address the multifaceted nature of RHD and work toward its eventual elimination. Ongoing research into the genetic and biochemical mechanisms underlying RHD will further enhance our understanding and management of this preventable yet devastating condition.

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