




## THERAPEUTIC MANAGEMENT OF ACUTE RHEUMATIC FEVER

### MANEJO TERAPÊUTICO DA FEBRE REUMÁTICA AGUDA

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#### ABSTRACT

Acute rheumatic fever (ARF) is a multisystem inflammatory disease resulting from an autoimmune response triggered by infection with *Streptococcus pyogenes* (group A streptococcus), which may progress to chronic rheumatic heart disease, one of the leading causes of acquired heart disease in children and young adults in low- and middle-income countries. The disease remains a significant global public health issue, particularly among socially vulnerable populations, where factors such as limited access to healthcare services, unfavorable socioeconomic conditions, and challenges in early diagnosis contribute to persistently high morbidity and mortality rates. In this context, appropriate therapeutic management of ARF is essential for controlling systemic inflammation, eradicating the infectious agent, and reducing recurrences associated with the progression of valvular heart damage. The present study consists of a narrative bibliographic review, descriptive and qualitative in nature, conducted using the PubMed database and the descriptor "Rheumatic Fever," according to the Medical Subject Headings (MeSH) terminology. Articles published in the last five years and directly related to the therapeutic management of the disease were included. The literature analysis shows that ARF treatment is based on the eradication of streptococci through appropriate antibiotic therapy, control of inflammatory manifestations, and prolonged secondary prophylaxis with benzathine penicillin.

**Keywords:** Acute Rheumatic Fever. Rheumatic Heart Disease. *Streptococcus pyogenes*. Antibiotic Prophylaxis. Therapeutic Management.

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## RESUMO

A febre reumática aguda (FRA) constitui uma doença inflamatória multissistêmica decorrente de resposta autoimune desencadeada por infecção pelo *Streptococcus pyogenes* (estreptococo do grupo A), podendo evoluir para cardiopatia reumática crônica, uma das principais causas de doença cardíaca adquirida em crianças e adultos jovens em países de baixa e média renda. A enfermidade permanece como importante problema de saúde pública global, especialmente em populações socialmente vulneráveis, nas quais fatores como acesso limitado a serviços de saúde, condições socioeconômicas desfavoráveis e dificuldades no diagnóstico precoce contribuem para a manutenção de elevadas taxas de morbidade e mortalidade. Nesse contexto, o manejo terapêutico adequado da FRA torna-se fundamental para o controle da inflamação sistêmica, a erradicação do agente infeccioso e a redução de recorrências associadas à progressão do comprometimento valvar cardíaco. O presente estudo consiste em uma revisão bibliográfica narrativa, de caráter descritivo e qualitativo, realizada na base de dados PubMed, utilizando o descritor “Rheumatic Fever”, conforme a terminologia do Medical Subject Headings (MeSH). Foram incluídos artigos publicados nos últimos cinco anos, diretamente relacionados ao manejo terapêutico da doença. A análise da literatura evidencia que o tratamento da FRA baseia-se na erradicação do estreptococo por meio de antibioticoterapia adequada, no controle das manifestações inflamatórias e na profilaxia secundária prolongada com penicilina benzatina.

**Palavras-chave:** Febre Reumática Aguda. Cardiopatia Reumática. *Streptococcus pyogenes*. Profilaxia Antibiótica. Manejo Terapêutico.

## RESUMEN

La fiebre reumática aguda (FRA) constituye una enfermedad inflamatoria multisistémica derivada de una respuesta autoinmune desencadenada por la infección por *Streptococcus pyogenes* (estreptococo del grupo A), pudiendo evolucionar hacia cardiopatía reumática crónica, una de las principales causas de enfermedad cardíaca adquirida en niños y adultos jóvenes en países de ingresos bajos y medios. La enfermedad sigue siendo un importante problema de salud pública global, especialmente en poblaciones socialmente vulnerables, en las que factores como el acceso limitado a los servicios de salud, condiciones socioeconómicas desfavorables y dificultades en el diagnóstico precoz contribuyen al mantenimiento de altas tasas de morbilidad y mortalidad. En este contexto, el manejo terapéutico adecuado de la FRA se vuelve fundamental para el control de la inflamación sistémica, la erradicación del agente infeccioso y la reducción de recurrencias asociadas a la progresión del compromiso valvular cardíaco. El presente estudio consiste en una revisión bibliográfica narrativa, de carácter descriptivo y cualitativo, realizada en la base de datos PubMed, utilizando el descriptor “Rheumatic Fever”, conforme a la terminología de Medical Subject Headings (MeSH). Se incluyeron artículos publicados en los últimos cinco años, directamente relacionados con el manejo terapéutico de la enfermedad. El análisis de la literatura evidencia que el tratamiento de la FRA se basa en la erradicación del estreptococo mediante antibioticoterapia adecuada, en el control de las manifestaciones inflamatorias y en la profilaxis secundaria prolongada con penicilina benzatina.

**Palabras clave:** Fiebre Reumática Aguda. Cardiopatía Reumática. *Streptococcus pyogenes*. Profilaxis Antibiótica. Manejo Terapéutico.



## 1 INTRODUCTION

Acute rheumatic fever (ARF) is a multisystem complication of an autoimmune nature that arises after an untreated throat or skin infection with *Streptococcus pyogenes* (group A streptococcus - GAS) (Auala et al., 2022; Ali Sulafa et al., 2024). Although preventable, the disease remains a significant public health burden in low- and middle-income countries and marginalized populations in developed countries, being the leading cause of acquired heart disease in children and youth (Dougherty et al., 2023; Tu'akoi et al., 2023). The pathogenesis involves a molecular mimicry reaction, where the immune response against the bacterium ends up attacking the host's own tissues, especially the heart, joints, and central nervous system (Auala et al., 2022).

About acute rheumatic fever, the infection can lead to the development of autoimmune diseases. It affects children and adolescents, aged 5 to 15 years. However, cardiac involvement appears later, in the range of 25 and 45 years of age. This cardiac involvement occurs due to a failure in the body's defenses, which start to attack the heart instead of bacteria (Dougherty et al., 2023).

The clinical management of ARF focuses on three fundamental pillars: the eradication of the infectious agent, the relief of inflammatory manifestations, and, primarily, the prevention of permanent damage to the heart valves, which configure chronic rheumatic heart disease (CRC) (Ralph and Currie, 2022; Dougherty et al., 2023). The effectiveness of treatment depends on the early identification of acute episodes and strict adherence to secondary prophylaxis protocols, which aim to prevent recurrences that aggravate valve lesions (Bray et al., 2024; Ralph and Currie, 2022).

In addition, the persistence of rheumatic fever in several regions of the world is closely related to social determinants of health, such as poor housing conditions, limited access to medical services, and difficulties in implementing prevention and early diagnosis programs. These factors contribute to the maintenance of high incidence rates and the progression of the disease to chronic forms, reinforcing the need for effective therapeutic strategies and public health approaches aimed at controlling the disease (Dougherty et al., 2023; Tu'akoi et al., 2023). The objective of this review is to synthesize current therapeutic strategies, ranging from the acute phase to long-term interventions to mitigate the global impact of this disease (Dougherty et al., 2023; Ali Sulafa et al., 2024).



## 2 METHODOLOGY

The present study is characterized as a narrative literature review, developed with the objective of synthesizing and analyzing the most recent scientific evidence related to the Therapeutic Management of Acute Rheumatic Fever. The search was carried out in the PubMed database, using the descriptor "Rheumatic Fever", in accordance with the terminology of the Medical Subject Headings (MeSH). Articles published in the last five years, available in full and written in Portuguese or English, that directly addressed the topic, were included. Studies that did not have a direct relationship with the central theme, duplicate publications, narrative reviews with low methodological rigor, and articles not indexed in the database used were excluded. The selection of studies was conducted in two stages: screening of titles and abstracts, followed by the evaluation of full texts to confirm relevance. The information extracted was organized in a descriptive way.

## 3 RESULTS AND DISCUSSION

### 3.1 STREPTOCOCCUS ERADICATION AND ACUTE PHASE TREATMENT

Initial treatment of ARF aims to eliminate any remaining focus of GAS infection to stop the antigenic stimulus. The standard regimen consists of the administration of benzathine (V) penicillin or oral penicillin (Ralph and Currie, 2022; Ali Sulafa et al., 2024) and, in this context, penicillin remains the first-line treatment due to the persistent sensitivity of *Streptococcus pyogenes* to this antibiotic, being used both in the eradication of the initial infection and in secondary prophylaxis aimed at preventing recurrences of rheumatic fever. Periodic administration of intramuscular benzathine benzylpenicillin is the most effective strategy to reduce new episodes of ARF and, consequently, limit the progression of rheumatic heart disease (RALPH; CURRIE, 2022; AUALA et al., 2022). There are alternatives to treatment with beta-lactams if necessary, such as the use of macrolide antibiotics, such as erythromycin, azithromycin, and clarithromycin (Ralph and Currie, 2022). For the management of arthritis and systemic discomfort, nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or naproxen, are highly effective in controlling joint symptoms and fever (Ralph and Currie, 2022). In cases of severe carditis, the use of corticosteroids may be indicated to reduce myocardial inflammation, although their role in preventing long-term valve damage is still discussed in the literature (Ralph and Currie, 2022). In the case of Sydenham's chorea, carbamazepine is used as a first-line treatment, accompanied by sodium valproate. Even with treatment, there is a



possibility that treatment will only reduce symptoms, and not eliminate chorea completely. Corticosteroids are often added to treatment when carbamazepine and sodium valproate do not produce a satisfactory result (Ralph and Currie, 2022).

### 3.2 SECONDARY PROPHYLAXIS: THE ROLE OF BENZATHINE PENICILLIN

The most critical therapeutic measure for disease control is secondary prophylaxis. Secondary prophylaxis is recommended for patients with previous cases of rheumatic fever, as well as patients with rheumatic heart disease, as they have a higher risk of infection with group A streptococci (Auala et al.; 2022). Intramuscular administration of benzathine G penicillin (BPG) every four weeks (or every three weeks in high-risk areas) is the gold standard (Ralph and Currie, 2022; Bray et al., 2024). Systematic reviews and meta-analyses confirm that intramuscular BPG is significantly superior to oral penicillin in preventing ARF recurrences and halting progression to severe rheumatic heart disease (Bray et al., 2024). Maintenance of this prophylactic regimen should last at least 10 years after the last episode or until the patient reaches adulthood, depending on the severity of cardiac involvement (Ralph and Currie, 2022; Ali Sulafa et al., 2024). Maintenance of secondary antibiotic prophylaxis remains essential even in adults, since reinfection with group A streptococcus can trigger new inflammatory episodes and aggravate valve involvement. At the same time, clinical management includes treatment of heart failure, control of arrhythmias, prevention of infective endocarditis and, when indicated, percutaneous or surgical interventions to correct valvular heart diseases. These integrated approaches are key to reducing the morbidity and mortality associated with RBD, particularly in populations in low- and middle-income countries, where the burden of disease remains high (AUALA et al., 2022; RALPH; CURRIE, 2022).

### 3.3 MANAGEMENT OF COMPLICATIONS AND INTERVENTIONS IN RHEUMATIC HEART DISEASE

When the acute phase progresses to permanent valve damage (CRC), management focuses on optimizing cardiac function and preventing complications such as heart failure, arrhythmias, and infective endocarditis (Dougherty et al., 2023). The management of rheumatic heart disease depends on some factors and characteristics involved, for example, which valve was affected, the severity of the valve involvement, in



addition to the individual characteristics of each patient, such as the presence of complications in many cases (Auala et al., 2022).

In the case of clinical symptoms resulting from cardiac involvement, it is common to have shortness of breath when performing an activity, at rest, or when lying down. In addition to palpitations and chest pain. In the comprehensive evaluation, there is the presence of electrocardiogram, chest X-ray, in addition to the echocardiogram, which acts fundamentally in confirming clinical findings and severity, contributing to a good evaluation and consequently to a better management of the disease, enabling efficient treatment planning. Thinking about early diagnosis for better treatment, access to the tools mentioned above contribute significantly to the patient's quality of life, since with adequate resources and fluidity in diagnosis, it is possible to improve planning seeking to control the disease and bring greater functionality and quality to the patient during treatment (Auala et al., 2022).

The electrocardiogram can be used as an essential piece in the treatment of rheumatic fever, making it possible to analyze the degree of hemodynamic involvement, complications of valve lesions, and the progression of the disease (Auala et al.; 2022). In advanced stages of valve stenosis or insufficiency, surgical interventions, such as balloon mitral valvuloplasty or valve replacement, become necessary to improve survival and quality of life (Dougherty et al., 2023). In the case of patients with prosthetic valves, it is necessary to use anticoagulants, such as warfarin, on a permanent basis (Ali Sufala et al; Aluara el al). In endemic countries such as Sudan, simplified protocols are proposed to facilitate diagnosis and management in resource-limited settings (Ali Sulafa et al., 2024). In addition to structural interventions, clinical treatment plays a fundamental role in controlling complications associated with chronic rheumatic heart disease. Patients with signs of heart failure may benefit from the use of diuretics to reduce congestion, as well as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, which help improve cardiac function and reduce hemodynamic overload. In cases of arrhythmias, especially atrial fibrillation associated with atrial dilation secondary to valve disease, it may be necessary to use medications to control heart rate and anticoagulation to prevent thromboembolic events (Dougherty et al., 2023; Ralph; Currie, 2022).

Another essential aspect of management is secondary prophylaxis of rheumatic fever, which aims to prevent new episodes of infection by *Streptococcus pyogenes* and, consequently, prevent the progression of valve damage. This prophylaxis is usually



performed through the periodic administration of intramuscular benzathine penicillin, and can be maintained for years or even for life in patients with established rheumatic heart disease, depending on the severity and risk of recurrence (Bray et al., 2024). Adequate adherence to this prophylactic regimen is considered one of the most effective measures to reduce the morbidity and mortality associated with the disease.

In addition to drug prophylaxis, primary prevention strategies are also fundamental in controlling the global burden of rheumatic fever and rheumatic heart disease. These measures include early diagnosis and appropriate treatment of strep throat with appropriate antibiotics, as well as public health actions aimed at improving socioeconomic conditions, access to health services, and health education in the most vulnerable communities (Auala et al., 2022; Tu'Akoi et al., 2023). Community-level interventions, especially in endemic regions, have shown potential to reduce the incidence of the disease and reduce inequalities related to access to care and appropriate treatment.

Thus, the management of rheumatic heart disease involves a multidimensional approach, which integrates clinical treatment of complications, surgical interventions when indicated, and continuous prophylaxis and prevention strategies. This comprehensive approach is essential to reduce disease progression, improve patients' quality of life, and lessen the impact of this condition on the most affected populations (Dougherty et al., 2023; Ali Sulafa et al., 2024).

### 3.4 SOCIAL BARRIERS AND EQUITY IN TREATMENT

The effectiveness of therapeutic management is often limited by social and logistical factors. The erratic availability of quality penicillin and impaired access to health services are significant barriers in underserved regions (Dougherty et al., 2023). In New Zealand, Māori and Pacific populations have been observed to be disproportionately affected, which reinforces the need for community-based preventive interventions that address social determinants, such as housing overcrowding, to reduce the incidence of primary GAS infection (Tu'akoi et al., 2023).

The global distribution of rheumatic fever and rheumatic heart disease shows important inequalities between different regions of the world. High-income countries currently have a significantly lower incidence of the disease, reflecting better socioeconomic conditions, expanded access to health services, and structured strategies for early diagnosis and treatment. In contrast, in several low- and middle-income



countries, especially in regions of Africa and other endemic areas, the disease remains highly prevalent, reflecting limitations in access to the health system and difficulties in implementing effective prevention programs (Auala et al., 2022; Dougherty et al., 2023).

In addition, social determinants of health, such as poverty, overcrowding at home, and limited access to medical care, contribute significantly to the persistence of *Streptococcus pyogenes* transmission and to the higher incidence of the disease in vulnerable populations. In this scenario, although secondary prophylaxis with benzathine penicillin is recognized as the most effective strategy to prevent recurrences of rheumatic fever, challenges related to drug availability, periodic administration logistics, and treatment adherence still represent important barriers. Thus, reducing the burden of disease depends not only on the clinical efficacy of interventions, but also on ensuring equity in access to therapeutic strategies and prevention actions (Bray et al., 2024; Tu'Akoi et al., 2023).

Patients affected by rheumatic heart disease need to follow up with cardiology services on a regular basis. It is of paramount importance that there is an integration between rheumatic heart disease control programs and systems and policies related to primary health care, in such a way as to allow early consultations, resources and tools, or interventions aimed at greater control of the disease and higher quality during treatment. By quickly identifying and treating infections caused by *Streptococcus pyogenes*, a good pillar is established in the scope of primary prevention. Seeking to avoid an evolution to rheumatic heart disease through regular monitoring and administration of penicillin, there is a second pillar, found within secondary prevention (Auala et al., 2022).

#### 4 CONCLUSION

Acute rheumatic fever remains a relevant public health problem, especially in vulnerable socioeconomic contexts, in which structural factors favor the persistence of *Streptococcus pyogenes* infection and the progression to chronic rheumatic heart disease. The literature shows that effective therapeutic management depends on the early eradication of the infectious agent by appropriate antibiotic therapy, the control of inflammatory manifestations, and the strict maintenance of secondary prophylaxis with benzathine penicillin, considered the most effective strategy to prevent recurrences and limit the progression of heart valve damage (RALPH; CURRIE, 2022; BRAY et al., 2024).



At the same time, continuous clinical follow-up and management of cardiovascular complications are essential to reduce the morbidity and mortality associated with the disease, and should be integrated into public policies that expand access to early diagnosis, appropriate therapy, and prevention strategies, especially in endemic regions (AUALA et al., 2022; DOUGHERTY et al., 2023). In this scenario, the strengthening of health policies aimed at epidemiological surveillance and health education actions are equally important to expand access to antibiotic therapy, becoming essential pillars to reduce the occurrence of the disease and prevent its cardiovascular complications over time.

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