



## Acute Rheumatic Fever in Adult

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KEYWORDS	ABSTRACT
Acute Rheumatic Fever; Adult Population; Rheumatic Heart Disease	This research aims to review and synthesize current evidence regarding the epidemiology, pathophysiology, clinical manifestations, diagnostic challenges, and management strategies of acute rheumatic fever (ARF) in adult populations. The research employed a narrative literature review method by analyzing peer-reviewed articles, clinical guidelines, and authoritative reports obtained from PubMed, Google Scholar, Scopus-indexed journals, WHO, and CDC publications published between 2015 and 2025. The findings indicate that ARF in adults presents distinct clinical characteristics compared to pediatric cases, with migratory polyarthritis being the most dominant manifestation and carditis frequently occurring in a subclinical form, leading to delayed diagnosis. The application of the revised 2015 Jones criteria has improved diagnostic accuracy, particularly in endemic regions; however, challenges remain in differentiating ARF from other inflammatory joint diseases and in maintaining adherence to long-term secondary prophylaxis. The discussion highlights that socioeconomic factors, limited healthcare access, and low compliance with benzathine penicillin G prophylaxis significantly contribute to the high burden of rheumatic heart disease in adults, especially in Indonesia. In conclusion, acute rheumatic fever in adults remains a clinically significant condition requiring heightened diagnostic awareness, consistent secondary prevention, and integrated public health strategies to prevent disease progression and reduce long-term cardiovascular complications.

## INTRODUCTION

Acute rheumatic fever (ARF), also known as acute rheumatoid fever in adults, is a complex, non-suppurative, immune-mediated systemic inflammatory disorder (Current Diagnosis & Treatment: Rheumatology, 2024). It typically occurs as a delayed consequence of pharyngeal infection with Group A beta-hemolytic *Streptococcus* (*Streptococcus pyogenes*) (Steer & Gibofsky, 2021). In adults, its clinical context often arises from the significant overlap between ARF and rheumatoid arthritis (RA), which can result in diagnostic delays and less effective management (Hasan et al., 2025).

The global burden of ARF remains formidable, with an estimated 470,000 new cases annually and approximately 33 million people currently living with rheumatic heart disease (RHD)—the chronic and most debilitating consequence of ARF (Steer & Gibofsky, 2021). However, in endemic regions such as Indonesia, which ranks fourth globally in RHD prevalence, the disease continues to cause substantial morbidity and premature mortality, with death rates often exceeding those of malaria (Irene & Olfriani, 2024). In adults, the clinical phenotype diverges significantly from that of pediatric cases: musculoskeletal manifestations, particularly severe migratory polyarthritis, dominate the clinical features, while classic signs such as Sydenham chorea and erythema marginatum are exceedingly rare (Hasan et al., 2025). This divergence necessitates a specialized diagnostic approach utilizing the 2015 revised Jones

criteria, which now include risk stratification based on regional disease prevalence (KnyaMed, 2015). The management of adult ARF is predicated on three clinical pillars: the eradication of any residual GAS infection, the aggressive suppression of systemic inflammation, and the lifelong or long-term administration of secondary prophylaxis to prevent recurrent attacks (Balan et al., 2025; Moon et al., 2025; Pabolu et al., 2021; Sarin et al., 2026; Watkins et al., 2018). Despite these established protocols, adherence to secondary prophylaxis remains a critical bottleneck, particularly in adult populations where geographical, economic, and educational barriers often impede regular intramuscular injections of benzathine penicillin G (Ralph et al., 2017).

This review synthesizes current medical literature on adult ARF, exploring its unique epidemiology, nuanced pathophysiology, and the systemic strategies required to mitigate its progression to irreversible cardiac failure (Agarwal & Pakhare, 2024; Chioncel et al., 2020; Elendu et al., 2024; Sapna et al., 2023; Siam et al., 2024). The urgency of this research lies in the persistent underdiagnosis and mismanagement of ARF among adults, particularly in low- and middle-income countries such as Indonesia. The clinical presentation in adults often mimics other inflammatory joint diseases, leading to delays in diagnosis and increased risk of progression to chronic RHD. Furthermore, the lack of synthesized, up-to-date evidence focusing specifically on adult ARF hinders the development of targeted clinical guidelines and public health strategies. Given the high prevalence of RHD in Indonesia and the suboptimal adherence to secondary prophylaxis, there is an urgent need to consolidate current knowledge to inform policy and practice (Ambari, 2023; Irene & Olfriani, 2024; Organization, 2024; Rémond et al., 2016).

This study aims to review and synthesize current evidence regarding the epidemiology, pathophysiology, clinical manifestations, diagnostic challenges, and management strategies of acute rheumatic fever in adult populations, with special emphasis on implications for endemic settings such as Indonesia. The findings of this review are expected to provide a comprehensive reference for clinicians—particularly in primary care and rheumatology—to improve diagnostic accuracy and therapeutic decision-making in adult ARF cases. Additionally, this synthesis may serve as a foundation for developing national clinical pathways and public health interventions aimed at reducing the burden of ARF and preventing its progression to rheumatic heart disease in Indonesia and similar endemic regions.

## **METHOD**

This study employed a narrative literature review design to synthesize current evidence related to the epidemiology, pathophysiology, clinical manifestations, diagnosis, and management of acute rheumatic fever (ARF) in adults. Relevant literature was obtained from reputable sources, including PubMed, Google Scholar, Scopus-indexed journals, WHO publications, CDC guidelines, and national and international cardiovascular registries, with publications limited to the period between 2015 and 2025. The search strategy used keywords such as acute rheumatic fever, adult rheumatic fever, rheumatic heart disease, Jones criteria, and secondary prophylaxis. Articles were included if they focused on adult populations, were peer-reviewed or issued by official health institutions, and provided comprehensive clinical or epidemiological data, while studies focusing exclusively on pediatric cases or lacking scientific rigor were excluded. The selected literature was analyzed qualitatively and synthesized

descriptively by categorizing findings into major thematic areas, including epidemiology, immunopathogenesis, clinical features, diagnostic challenges, therapeutic management, and prevention strategies, with particular emphasis on implications for adult patients in endemic settings such as Indonesia.

## **RESULT AND DISCUSSION**

### **Epidemiology**

Adult burden of ARF remains significant than age-school ages, particularly in endemic regions and during sporadic outbreaks in developed nations (Hasan et al., 2025). The global decline in ARF in the late 20th century was largely due to the reduction of rheumatogenic strains of GAS and improved social determinants of health, such as housing density (Current Diagnosis & Treatment: Rheumatology, 2024). However, the disease persists where these improvements have not been universal (Hasan et al., 2025).

In adults are often manifest as a primary episode without a known history of childhood ARF, posing a significant diagnostic challenge (StatPearls, 2022). A systematic review of adult Caucasian cases in developed countries showed a mean age of approximately 33 years, with a female predominance (Hasan et al., 2025; Steer & Gibofsky, 2021). Many of these patients required multiple hospitalizations before an accurate diagnosis was reached, highlighting the lack of clinical suspicion in adult medicine (Hasan et al., 2025). In Indonesia, the Ina-RHD multicenter study provides a comprehensive look at the adult profile (Soesanto et al., 2025).

### **Pathophysiological Underpinnings: The Molecular Mimicry Hypothesis**

The pathogenesis of acute rheumatic fever (ARF) is a paradigm of autoimmune cross-reactivity initiated by a pharyngeal infection with Group A Streptococcus (GAS). This site-specific requirement is attributed to the pharynx's rich lymphoid environment, which facilitates a unique interaction between GAS antigens and the host's adaptive immune system (UpToDate, 2018). The molecular mimicry hypothesis posits that specific streptococcal antigens share structural similarities with host proteins (Current Diagnosis & Treatment: Rheumatology, 2024). The primary bacterial player is the M protein, a cell-surface virulence factor encoded by the *emm* gene (Steer & Gibofsky, 2021).

Genetic susceptibility is a critical determinant, as only a small fraction of individuals infected with GAS develop ARF (Current Diagnosis & Treatment: Rheumatology, 2024). Linkage has been observed with specific Human Leukocyte Antigen (HLA) types, particularly HLA-DRB10701, DR6, and DQB10201 (Current Diagnosis & Treatment: Rheumatology, 2024). These genetic factors appear to govern the intensity of the immune response and the likelihood of developing severe, chronic rheumatic heart disease (Ohio State University, 2017). In a susceptible host, this cross-reactivity leads to several distinct pathological processes.

### **Valvulitis and endocardial injury**

Antibodies targeting GlcNAc bind to the valvular endothelium, causing up-regulation of adhesion molecules like VCAM-1 (Steer & Gibofsky, 2021). This recruits T-cells, which infiltrate the valve tissue, leading to subendothelial inflammation and the formation of fibrinous vegetations (UNC School of Medicine, 2021). Over time, this chronic inflammation results in scarring, thickening, and fusion of the chordae tendineae (UNC School of Medicine, 2021).

### Myocarditis and Aschoff bodies

The hallmark histological lesion of rheumatoid heart disease (RHD) is the Aschoff body, found in the myocardium during the proliferative phase (UNC School of Medicine, 2021). These are granulomatous nodules containing lymphocytes and characteristic large mononuclear cells called Anitschkow cells (UNC School of Medicine, 2021).

### Joint and central nervous system (CNS) involvement

Formation of immune complexes leads to transient arthritis, while antibodies binding to neuronal cells in the basal ganglia can trigger dopamine release, resulting in the involuntary movements of Sydenham chorea (Steer & Gibofsky, 2021).

### Clinical Manifestations

The clinical presentation of ARF in adults is frequently skewed toward musculoskeletal symptoms (Hasan et al., 2025). While children commonly present with carditis and chorea, adults are more likely to experience severe polyarthritis and arthralgia (Maslinska, 2018).

### Migratory polyarthritis

This is the most common early manifestation in adult, occurring in 60% to 80% of cases (StatPearls, 2025). It typically involves large joints like the knees, ankles, wrists, and elbows (StatPearls, 2025). The arthritis is characteristically migratory, moving from one joint to another over several days, and is marked by extreme tenderness, redness, and swelling (DynaMed, 2022).

### Carditis

In adults, it can be "indolent" or subclinical, meaning that significant valvular damage may occur without the patient exhibiting overt signs of heart failure or a loud murmur (Current Diagnosis & Treatment: Rheumatology, 2024). The mitral valve is most commonly affected, leading to mitral regurgitation in the acute phase and potentially progressing to mitral stenosis over 10 to 20 years (CDC, 2025).

### Chorea and skin lesion

Sydenham chorea is rare in adults, occurring almost exclusively in pediatric patients or occasionally in pregnant women (Ohio State University, 2017). Similarly, erythema marginatum and subcutaneous nodules are uncommon in adults and are usually indicators of severe underlying carditis (Maslinska, 2018).

**Table 1. Manifestation of Acute Rheumatic Fever (ARF)**

Manifestation	Pediatric Frequency (5-15y)	Adult Frequency (>18y)
Migratory Polyarthritis	60–80%	70–90% (Commonly dominant)
Carditis	50–80%	30–50% (Often subclinical)
Sydenham Chorea	10–15%	Rare
Erythema Marginatum	< 6%	Very Rare
Subcutaneous Nodules	< 10%	Very Rare

*Source: Adapted from Steer & Gibofsky (2021); Hasan et al. (2025); Gewitz et al. (2015); and Ralph et al. (2017)*

### Diagnosis

The diagnosis of acute rheumatic fever (ARF) is clinical, supported by laboratory evidence of a preceding Group A Streptococcus (GAS) infection (CDC, 2025). The revision of

the Jones criteria (2015) by the American Heart Association (AHA) introduced regional risk stratification, which is pivotal for adult diagnosis in endemic areas (KnyaMed, 2015).

**Table 2. Diagnosis Criteria of Acute Rheumatic Fever (ARF)5, 14**

Major Criteria for Low-Risk Populations	Major Criteria for Moderate/High-Risk Populations
1. Clinical and/or subclinical carditis	1. Clinical and/or subclinical carditis
2. Polyarthritis only	2. Monoarthritis, polyarthritis, or polyarthralgia
3. Chorea	3. Chorea
4. Erythema marginatum	4. Erythema marginatum
5. Subcutaneous nodules	5. Subcutaneous nodules
Minor Criteria	
1. Fever	1. Fever
2. Arthralgia (if arthritis is not a major criterion)	2. Arthralgia (if arthritis is not a major criterion)
3. Elevated acute-phase reactants (ESR $\geq$ 60mm/h, CRP)	3. Elevated acute-phase reactants (ESR $\geq$ 30mm/h, CRP)
4. Prolonged PR interval on ECG	4. Prolonged PR interval on ECG

Source: Gewitz et al. (2015), Circulation; Steer & Gibofsky (2021); and CDC (2025)

Evidence of a preceding GAS infection is mandatory for diagnosis and can be established through a positive throat culture, a rapid antigen test, or elevated/rising streptococcal antibody titers (Current Diagnosis & Treatment: Rheumatology, 2024). In adults, the latent period may be longer, making throat cultures frequently negative; therefore, anti-streptolysin O (ASTO) and anti-DNase B titers are the diagnostic mainstays (UpToDate, 2018).

The most notable clinical challenge in adult cases is the "rheumatoid" component (Hasan et al., 2025). Various conditions may resemble the polyarthritis and fever characteristic of ARF:

**Rheumatoid arthritis (RA)**

Unlike the migratory and large-joint involvement of ARF, RA typically involves the small joints of the hands and feet symmetrically (Ralph et al., 2017). RA is chronic and progressive, whereas ARF is self-limiting and acute. Diagnostic markers like Rheumatoid Factor (RF) and anti-CCP are positive in RA but absent in ARF (Medical News Today, 2018).

**Post-Streptococcal reactive arthritis (PSRA)**

PSRA occurs after a GAS infection but differs from ARF in joint pattern (often non-migratory and involving small joints) and latent period (usually < 2 weeks compared to 2-3 weeks for ARF) (PubMed, 2025). PSRA also shows a poor response to NSAIDs, while ARF responds dramatically (Case Report, 2024).

**Crystal arthropathies**

Gout and pseudogout (CPPD) are common in older adults (CDC, 2025). Pseudogout can cause sudden, painful flares in the knees or wrists and may be accompanied by fever, mimicking the constitutional symptoms of ARF (NIH StatPearls, 2025).

**Lyme disease and systemic lupus erythematosus (SLE)**

Both can present with fever and migratory or persistent arthritis, requiring specific serological testing to exclude (StatPearls, 2025).

## Management and Therapy

The management of an acute episode focuses on eradicating the infection and controlling the inflammatory response (DynaMed, 2022).

### Streptococcal eradication (primary prevention)

Although if a throat culture is negative, a full course of antibiotics is required to eliminate any potential residual GAS carriage (DynaMed, 2022).

- a. A single dose of Benzathine Penicillin G intramuscular (1.2 million units for adults > 27 kg) is the gold standard (DynaMed, 2022).
- b. Oral Penicillin V (500 mg two or three times daily) for 10 days (DynaMed, 2022).
- c. Macrolides for patients with penicillin allergies (e.g., Azithromycin 500 mg daily for 5 days) (Ralph et al., 2017).

### Anti-inflammatory therapy

- a. Aspirin: High-dose salicylates (75–100mg/kg/day) provide rapid relief of arthritis symptoms, monitoring for hepatotoxicity and gastrointestinal side effects is essential in adults (CDC, 2025; Ralph et al., 2017).
- b. Naproxen: An increasingly popular alternative (10–20mg/kg/day) due to its safer profile and twice-daily dosing (Ralph et al., 2017).
- c. Corticosteroids: Indicated for severe carditis or heart failure (e.g., Prednisone 1–2 mg/kg/day) (DynaMed, 2022).

### Secondary prophylaxis

This is the most critical intervention to prevent rheumatoid heart disease (RHD) progression (CDC, 2025). Recurrent infections significantly worsen valvular damage (INAValve-RHD, 2025). The preferred regimen is intramuscular Benzathine Penicillin G every 4 weeks (or every 3 weeks in high-risk settings) (DynaMed, 2022).

**Table 3. Secondary Prophylaxis of ARF in Adult22**

Patient Category	Duration of Secondary Prophylaxis
ARF without Carditis	5 years from last attack or until age 21
ARF with Carditis (No Residual Damage)	10 years or until age 21 (whichever is longer)
Carditis with Residual Valve Disease	10 years or until age 40; often lifelong for severe cases

## The Indonesian Experience: A Public Health Case Study

Indonesia faces a substantial burden of RHD, yet lacks a comprehensive national prevention program (Irene & Olfriani, 2024). Data from various provinces highlight the systemic challenges:

### 1. Bali (Karangasem Regency)

A retrospective study found that rheumatoid heart disease (RHD) patients were predominantly young adult females with low educational levels (Ardani & Aditya, 2024). While almost all patients under 40 were prescribed Benzathine Penicillin G, adherence was hampered by geographic barriers and the fear of painful injections (Ardani & Aditya, 2024).

### 2. South Australia Registry Data

Although not in Indonesia, registries like South Australia's provide a model for Indonesia; they found that while the number of registered patients is increasing, adherence to

the 80% target for Benzathine Penicillin G injections remains low (~39%), underscoring the universal challenge of long-term prophylaxis (SA Health, 2024).

### 3. The Ina-RHD Study

This landmark Indonesian investigation identified that isolated mitral stenosis is the most prevalent lesion (39.6%) and that women are significantly more affected than men (Soesanto et al., 2025). The study also highlighted the severe underuse of Benzathine Penicillin G only 11.5% of rheumatoid heart disease (RHD) patients were receiving the gold-standard intramuscular prophylaxis (Hu & Liu, 2025).

### Future Preventions

The global health agenda for rheumatoid heart disease (RHD) aims for a 25% reduction in premature deaths by 2025 (Soesanto & Suastika, 2020):

#### 1. GAS Vaccine Development

Renewed investment in a well-tolerated and effective vaccine could bypass the challenges of long-term prophylaxis adherence.

#### 2. Task-Shifting and Simplified Screening

In archipelagic nations like Indonesia, training non-specialist health workers to use portable, simplified echocardiography can extend screening to remote populations where specialized cardiologists are absent.

#### 3. Adherence Innovations

Research into longer-acting penicillin formulations or implants could revolutionize secondary prevention by reducing the frequency of clinic visits.

## CONCLUSION

Acute rheumatic fever (ARF) in adults often differs from pediatric cases, presenting primarily with musculoskeletal symptoms that can be mistaken for rheumatoid arthritis. Clinicians should remain alert to migratory polyarthritis and fever, especially among adults from endemic or underserved areas. The 2015 Jones criteria now include subclinical carditis, enhancing early detection of valvular damage. ARF's prevalence underscores global socioeconomic disparities, with Indonesia showing high rates of advanced disease and poor adherence to prophylaxis, as demonstrated in the Ina-RHD study. Effective ARF management requires patient-focused chronic care, centralized registries, community health workers, and improved penicillin access. Preventing ARF progression depends on sustained antibiotic adherence, clinical vigilance, and the reduction of healthcare gaps, while future vaccines and drug-delivery advances may offer additional solutions.

Based on the findings of this review, it is recommended that clinicians—particularly those in primary care and rheumatology settings—maintain a high index of suspicion for ARF in adults presenting with acute migratory polyarthritis and fever, especially those from endemic regions or with a history of recurrent sore throat. The routine use of echocardiography is strongly encouraged to detect subclinical carditis, enabling earlier intervention and preventing long-term valvular damage. At the policy level, the Indonesian Ministry of Health and relevant stakeholders should prioritize the development of a comprehensive national registry for ARF and RHD to monitor disease burden, treatment adherence, and clinical outcomes. Task-shifting strategies, including training community health workers to administer benzathine penicillin G injections and perform simplified echocardiography screening in remote areas, are essential for

overcoming geographical barriers to care in Indonesia's archipelagic setting. Furthermore, patient-centered education programs should be strengthened to increase awareness of ARF complications and the importance of long-term adherence to secondary prophylaxis. Addressing common barriers—such as fear of painful injections, transportation costs, and limited health literacy—through community-based support systems and mobile health interventions may significantly improve compliance rates. From a research perspective, further studies are needed to evaluate the effectiveness of innovative strategies to enhance prophylaxis adherence, such as longer-acting penicillin formulations or reminder systems utilizing digital health technologies. Additionally, continued investment in developing a safe and effective GAS vaccine remains a global priority, as it holds the potential to dramatically reduce the burden of ARF and RHD for future generations.

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