

Acute Rheumatic Fever and Rheumatic Heart Disease: Current Scenario

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Abstract

Rheumatic fever and rheumatic heart disease continue to ravage millions of people around the world. Children and adolescents of the developing countries are especially susceptible to this disease. Overcrowding, poor socioeconomic status and illiteracy contribute to the high prevalence. Specific criteria have been devised to increase sensitivity of the diagnosis. WHO has recently modified certain criteria to help diagnose recurrent rheumatic fever in patients with established rheumatic heart disease. Neither salicylates nor corticosteroids alter the natural history of rheumatic fever definitely. The only proven cost-effective strategy is secondary prevention. Group A streptococcal vaccine is still years away from being commercially available, and even then, its likely exorbitant cost may make it inaccessible to many poor people.

Keywords: Acute rheumatic fever, Rheumatic heart disease, Streptococcal vaccine.

Introduction

Rheumatic fever results from an autoimmune response to infection with group A streptococcus. Although the acute illness causes considerable morbidity, and some mortality, the major clinical and public health effects derive from long-term damage to the heart valves, i.e., rheumatic heart disease (RHD). Over the past century, as living conditions have become more hygienic and less crowded, and nutrition and access to medical care have improved, acute rheumatic fever (ARF) and RHD have become rare in developed countries. But, rheumatic fever/rheumatic heart disease is the commonest cardiac disease in children and young adults and remains a major public health problem in developing countries. The present article revisits the epidemiology, pathogenesis, clinical features, management and recent advances in acute rheumatic fever (ARF).

Epidemiology

The epidemiology of ARF is linked with that of Group A beta-haemolytic streptococcal pharyngitis; both have a maximum incidence in the age group of 5 - 15 years¹. In developed countries, ARF/RHD have become uncommon health problems during the past two decades. In contrast, in third world countries such as India, the middle-east, sub-Saharan Africa, ARF remains the leading cause of heart disease in children and young adults². According to the

WHO, at least 15.6 million people have RHD. Of the 5,00,000 individuals who acquire ARF every year, 3,00,000 go on to develop RHD; and 2,33,000 deaths annually are attributable to ARF or RHD³. However, these estimates are based on conservative assumptions, so the true burden of the disease is likely to be substantially higher.

The prevalence of ARF/RHD in India has been reported to be varying from very infrequent to very high levels depending upon the source of information e.g., Registrar General, population sources, and hospital admissions. Recent data from India suggest that a large number of cases of ARF/RHD are still seen frequently in young children under the age of 10 years. From Delhi, Sharma et al examined 191 children below 12 years of age with definitive clinical features of ARF⁴. As regards the age group, 60% children were between 9 - 12 years, 31.4% were between 5 - 9 years and only 7.9% were below 5 years. We have also reported prevalence of RHD in 378 children below 19 years (mean age 15.1 ± 4.4 years)⁵. The male to female ratio was 4:1. Mild mitral stenosis (MS) was diagnosed in 34.9% and severe MS was diagnosed in 33%. The prevalence of ARF in school children of Kanpur District in Uttar Pradesh was 0.75/1,000 (rural 1.20 and urban 0.42)⁶. In the largest school survey conducted to date at Vellore during 2001 - 2002, a total of 2,29,829 children between 6 - 18 years of age were screened as part of a school health programme⁷. The prevalence of

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RHD was 0.68/1,000 school children, which showed a declining prevalence of RHD in rural children in India.

In contrast, we have reported that there is no significant decline in prevalence of ARF/RHD in India⁸. During the period 1981 – 1990, 9.2% of admitted cases had ARF, whereas during the period 1991 – 2000, 8.9% of admitted cases had ARF. Thus, there was marginal decline in prevalence of ARF which was not statistically significant. During these two periods, the number of RHD patients admitted were 4,458 (37.8%) and 5,340 (36.1%), respectively.

During the epidemic of streptococcal pharyngitis, the primary attack rate was around 3%. Streptococcal pharyngeal infection in patients with history of recent ARF may produce a secondary attack rate of as high as 65%⁹. In the Irvington House Study, rheumatic attack rate per infection (R/I) in children decreased from 23% to 11% between the first and fifth year after the last attack¹⁰.

In India, the average age of presentation of ARF is between 10 to 14 years¹¹. First episodes of ARF are most common just before adolescence, wane by the end of the second decade, and are rare in adults older than 35 years age¹². RHD usually results from cumulative damage of recurrent episodes of ARF, although initial attacks can directly lead to RHD. The prevalence of RHD increased with age, peaking in adults aged 25 – 34 years reflecting ARF activity in previous decades¹².

Pathogenesis

Although the pathogenesis of ARF and RHD remains somewhat elusive, ARF is clearly the result of an exaggerated immune response to specific bacterial epitopes in a susceptible host¹³.

The association between Group A beta-haemolytic streptococci, upper respiratory tract infection and the subsequent development of ARF is fairly well established. The exact pathogenetic mechanisms are unknown largely due to lack of an animal model. Two basic mechanisms are implicated : (1) a toxic effect of the extra-cellular Group A beta-haemolytic streptococci on target organs like myocardium, valves, synovium, and brain; and (2) an abnormal immune response of host to the streptococcal antigen.

Some strains of Group A streptococcus are more likely to cause ARF, i.e., Mtypes 1, 3, 5, 6, 14, 18, 19, and 24. However, some have challenged this theory, arguing instead that rheumatogenicity is not restricted to organisms belonging to only a few serotypes¹³. Classically, rheumatogenic M serotypes are infrequently found in several communities with high burdens of ARF and RHD, where newly identified serotypes have been linked with disease¹⁴.

The autoimmune response that causes ARF is triggered by molecular mimicry between epitopes on pathogen (Group A streptococci) and specific human tissues. The structural and immunological similarities between streptococcal M protein and myosin – both alpha-helical, coiled coil molecules – seem essential to the development of rheumatic carditis¹³. However, valvular disease, rather than acute myocarditis, is responsible for most of the cardiac morbidity and mortality of ARF. There is evidence that antibodies to cardiac valve tissues cross-react with N-acetyl glucosamine in group A carbohydrate¹⁵. An exaggerated antibody response to group A carbohydrate has been detected in patients with ARF, and titres remain raised in individuals with residual mitral valve disease, providing further support to the concept that these antibodies cause valve damage. Fig. 1 sums up the pathogenesis of ARF and RHD.

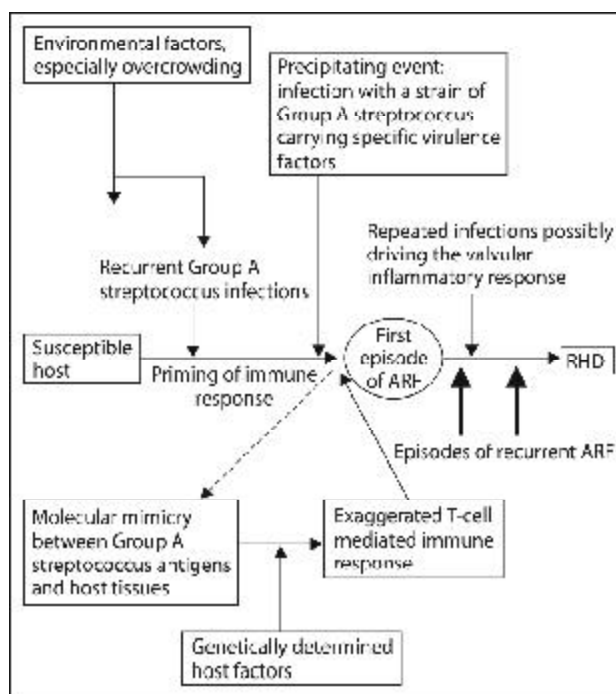


Fig. 1: Pathogenetic pathways for ARF and RHD.

The Host : In spite of knowledge about the inciting agent, it is not well understood why only certain individuals develop ARF subsequent to streptococcal pharyngitis. The immunological system of the host including both cell-mediated and humoral is an important factor for the susceptibility to ARF, but the exact mechanisms are unknown¹. Certain genetic influences also seem to play a role since only about 3% of individuals develop ARF following acute streptococcal pharyngitis. There is also higher concordance among monozygotic twins for development of ARF. A B-lymphocyte alloantigen has been implicated in the determination of susceptibility to ARF in 70 – 90% of rheumatic patients.¹⁶ HLA types, viz., HLA-DR 1, 2, 3, and 4 haplotypes have also been implicated in certain ethnic groups¹⁷.

Pathology

The hallmark of ARF is an exudative and proliferative inflammatory reaction involving the collagen and connective tissue primarily of the heart, joints, brain, and skin¹. The basic change is in the form of fibrinoid degeneration of the collagen characterised by the presence of Aschoff cells, which are modified histiocytic cells. Aschoff nodules are pathognomonic of rheumatic carditis. Valvulitis is the main lesion responsible for principal clinical manifestations. Valvulitis is characterised by oedema, cellular infiltration of the valve and chordae tendinae causing verrucae formation and hyaline degeneration with subsequent regurgitant valves. There is eventual fibrosis and calcification leading to stenotic valves.

Diagnostic criteria

The American Heart Association recommends the revised Jones criteria as a guide for diagnosis of acute ARF (Table I)¹⁸. According to the WHO criteria, requirements are less stringent for the diagnosis of recurrent ARF in patients with established RHD¹⁷. The Jones and WHO criteria are only diagnostic guidelines, however, and should be adopted to increase sensitivity of diagnosis in populations at high risk of ARF¹¹. While the Jones criteria are only for the diagnosis of first episode of ARF, the WHO criteria are applicable for the diagnosis of first episode as well as recurrence.

Table I: Jones criteria (1992).

Major criteria	Minor criteria
Carditis	Fever
Polyarthrititis	Arthralgia
Erythema marginatum	Elevated acute phase reactants (ESR, CRP)
Chorea	Prolonged PR interval in ECG
Subcutaneous nodules	

Plus

Evidence of preceding group A streptococcal infection (culture, rapid antigen, and antibody rise/elevation).

Two major, or one major and two minor criteria, plus evidence of preceding streptococcal infection indicates a high probability of rheumatic fever.

WHO criteria (2002 – 03)¹⁹

- a Chorea and indolent carditis do not require evidence of antecedent Group A streptococcus infection.
- b First episode – as per Jones criteria
- c Recurrent episode –
 - i In a patient without established RHD : as per first episode,
 - i In a patient with established RHD : requires two minor manifestations plus evidence of antecedent Group A streptococcus infection as per Jones criteria, but with addition and recent scarlet fever.

Major clinical manifestations

Carditis

Carditis of acute ARF is a pancarditis involving pericardium, endocardium, and myocardium. Carditis occurs in 40 – 60% of cases of ARF. Valvular insufficiency is the most common defect. It most often involves the mitral valve. The Carey Coombs murmur of acute ARF is a sign of active mitral valvulitis. It is a soft, high pitched, early diastolic murmur. The murmur varies on a day-to-day basis and is higher in pitch than obstructive mitral stenosis murmurs. Isolated aortic valvular involvement is rare, while tricuspid and pulmonary valvular involvement is unusual¹. Pericarditis is manifested by typical chest pain, pericardial rub, and

characteristic ECG changes. Myocarditis manifests itself as disproportionate tachycardia, soft heart sounds, cardiomegaly, and congestive heart failure. RHD is the only residual sequel of ARF. Sometimes 'indolent carditis' can occur as a sole manifestation characterised by cardiomegaly and persistent heart failure.

Use of echocardiography to diagnose ARF is controversial, especially when there is clinically inaudible mitral or aortic regurgitation¹³. The report from the WHO expert committee recognises the usefulness of echocardiography in providing supporting evidence for diagnosis of rheumatic carditis in the presence of an equivocal pathological murmur or in patients with polyarthrititis and equivocal minor manifestations¹⁹. However, the committee did not suggest that echocardiographically diagnosed subclinical carditis be added to the Jones criteria.

In a study carried out by Vasan *et al*, cross-sectional and colour doppler echocardiography examination was performed in 108 consecutive patients with ARF within 24 – 48 hours of diagnosis²⁰. In a quarter of the patients with rheumatic carditis, they observed valve nodules that might represent echocardiographic equivalent of rheumatic verrucae. However, they failed to establish any incremental diagnostic utility of echocardiography and colour doppler flow imaging in ARF without clinical evidence of rheumatic carditis.

Polyarthrititis

It occurs in about 75% of cases. It presents as red, swollen, warm, and tender joints and is typically migratory in nature. Elbows, knees, ankles, and wrist joints are most commonly involved, while fingers, toes, and spine are rarely involved. Patients with arthrititis not typical of ARF, but who have recently had a streptococcal infection, are said to have post-streptococcal reactive arthritis (PSRA). This form of arthritis generally affects the small joints of the hand, is less responsive to anti-inflammatory treatment, and does not carry a risk of accompanying carditis²¹. However, some patients go on to develop ARF, suggesting that they originally had ARF rather than PSRA.

Chorea

It is a late manifestation, occurring as late as 3 months

following throat infection. At times, chorea may be the only manifestation of ARF (pure chorea). Chorea is seen in about 20% of patients, and lasts for weeks to months.

Erythema marginatum

It is a rare finding of ARF. The lesion is evanescent, erythematous, non-tender, and non-pruritic macular rash occurring over the trunk.

Subcutaneous nodules

These are non-tender, firm, and pea-sized nodules present over the extensor surfaces of joints like knees, elbows, and spine and are seen in less than 3% of patients. There is usually associated carditis.

Minor criteria

Fever ranges from 101° – 102° F. Arthralgia is diagnosed only in the absence of underlying arthritis.

Laboratory findings

Acute phase reactants like ESR and C-reactive protein are almost always elevated during acute stages of the disease in patients with carditis or polyarthrititis, but is usually normal in patients with chorea. Prolonged PR interval in ECG is a common finding but is not diagnostic of carditis. Leukocytosis may be observed in acute stages of ARF. Anaemia is usually mild-to-moderate.

Evidence of an antecedent streptococcal infection is necessary for confirmation of the initial diagnosis of acute ARF. Only 11% of patients have throat cultures positive for Group A streptococcus²². Several rapid Group A strep antigen detection tests are commercially available. Most have a high degree of specificity but low sensitivity. Elevated or rising anti-streptococcal antibody titres provide more reliable evidence of a recent streptococcal infection. The most commonly used antibody tests are the anti-streptolysin O (ASO) and anti-deoxyribonuclease B (anti-DNase B) test. Elevated titres for both tests may persist for several weeks or months.

Differential diagnosis

The diagnosis of ARF is based on a constellation of non-

specific symptoms and signs. The disease needs to be differentiated from other causes like septic arthritis, tubercular arthritis, gonococcal arthritis and serum sickness. Recurrent ARF may be confused with infective endocarditis in presence of established RHD.

Treatment

Not all treatments for acute ARF have been tested in randomised clinical trials¹³. Some are based on anecdotal evidence, common sense, and proven safety. Penicillin is considered mandatory for the eradication of possibly persistent Group A streptococcus infection of the upper respiratory tract, though this treatment does not alter the cardiac outcome. Long-term bed rest is no longer advised.

Salicylates lead to prompt resolution of fever, arthritis, and arthralgia. Aspirin at doses of 100 mg/kg/day is given four to five times daily. Salicylates are particularly effective in relieving joint pain. Absence of prompt relief calls for revising the diagnosis of acute ARF. Salicylates do not decrease the incidence of residual RHD. Salicylates may be administered in presence of carditis without congestive heart failure (CHF). However, corticosteroids are given if severe carditis or CHF is present. Prednisolone is given at a dose of 1 – 2 mg/kg/day. Again, steroids do not influence the subsequent development of RHD. However, they may be life-saving in severe cases of acute carditis. However, there is little objective evidence to prove this.

Role of other anti-inflammatory agents in management of ARF is controversial. Naproxen has been used successfully in small cases series²³. Assessment of newer therapies are difficult because of natural improvement of rheumatic carditis. Voss *et al* have reported that in 27% of patients with ARF who had initial carditis and were treated with placebo, carditis resolved without sequelae after 1 year, and that 41% of regurgitant aortic or mitral valves were no longer regurgitant after only 6 months²⁴.

Sydenham's chorea is managed with diazepam and haloperidol. Valproic acid may be more effective.

Prevention of ARF

The overall lack of effective treatment for ARF means that any reduction of the burden of ARF and RHD will most likely come from new initiatives in the prevention. Table II

lists the frequently used regimens for prophylaxis of ARF.

Primary prophylaxis of ARF has focussed on antibiotic treatment of symptomatic pharyngitis caused by Group A streptococcus. A course of antibiotics started within nine days of the onset of sore throat prevents most cases of ARF²⁵. Additional regimens that have been studied include once-daily dosing with amoxicillin, which seems effective²⁶. Cure rates might be higher with high-dose amoxicillin (2 g/day) in adults. Several other antibiotics, e.g., azithromycin and newer cephalosporins given for 3 – 5 days have been studied, but none is presently recommended as first-line treatment. Even in optimum circumstance, the efficacy of primary prophylaxis is limited by the fact that upto two-third of patients with ARF do not get a symptomatic sore throat and do not therefore seek medical attention²⁷.

At present, no practical and affordable strategy for the primary prevention of acute ARF is available in India. The only proven cost-effective intervention is secondary prophylaxis, i.e., the long-term administration of antibiotics to people with a history of acute ARF or RHD, to prevent ARF recurrences and the development or deterioration of RHD¹³. The best drug for this purpose is intramuscular benzathine penicillin G administered once every 3 weeks. Techniques used to reduce the pain of benzathine penicillin injections include use of small gauge needles, increased injection volumes, addition of 1% lignocaine or procaine penicillin and warming the medication to room temperature. Decisions about duration of secondary prophylaxis relate to the balance between the risk of recurrent ARF (reduced with older age, longer duration since last ARF episode, and in low-incidence population) and the risk to the patient, should a recurrence occur (higher with increasingly severe heart disease)¹³.

Streptococcus vaccine

Several potential Group A streptococcus vaccines are in development, including a multi-valent, M-serotype specific construct²⁸. The diversity of M-serotypes limits the efficacy of the vaccines. Various alternative vaccines based on antigens common to all or most strains of Group A streptococcus using either the conserved region of M protein or antigens against non-M protein antigens are in pre-clinical development. An effective vaccine is unlikely to be available before 2015²⁹.

Table II: Recommended antibiotic regimens for primary and secondary prophylaxis of ARF.

	Dose	Frequency	Duration
Primary prophylaxis (treatment of Group A streptococcal pharyngitis)			
Benzathine penicillin G	1-2million units I.M. (6,00,000 units if bodyweight < 27 Kg)	Single Dose	Single Dose
Phenoxymethyl penicillin or amoxicillin	Children: 250 mg orally Adolescents and adults 500 mg orally	2 – 3 times daily	10 days
1st generation cephalosporins or erythromycin (only if allergic to penicillin)	Orally: dose varies with drug and formulation	Varies with agent and formulation	10 days
Secondary prophylaxis (long-term therapy in patients with h/o ARF or RHD)			
Benzathine penicillin G	1-2million units I.M. (6,00,000 units if bodyweight < 27 Kg)	Every 3 – 4 weeks	5 years or until age 21, whichever is longer (for ARF without carditis); 10 years or well into adulthood, whichever is longer (for ARF with carditis but no residual valvular disease); 10 years after last episode and at least until age 40, sometimes lifelong prophylaxis (for ARF with carditis and residual valvular disease)
Phenoxymethyl penicillin	250 mg orally	Twice daily	
Erythromycin	250 mg orally	Twice daily	

Conclusion

ARF and RHD have become rare in developed countries but continue to be major public health problem in developing countries. Considerable number of children and adolescents still suffer from ARF and its long-term sequel such as RHD, causing enormous morbidity and mortality. Group A streptococcal vaccines are still years away from being available and even if the obstacles of serotype coverage and safety can be overcome, high cost could well make them inaccessible to many. A consolidated effort is necessary to improve the socio-economic condition of the poorer strata in society to stem the tide of ARF and RHD epidemic.

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