

RHEUMATIC FEVER: AN UPDATE

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ABSTRACT

Rheumatic fever (RF) and rheumatic heart disease (RHD) are non-suppurative complications of group A beta haemolytic streptococcal (GABHS) pharyngitis due to a delayed immune response.

When talking about epidemiology it varies from 1.0 to 5.4/1,000 school children (mean 2.1). The incidence of rheumatic fever (RF) varies from 0.2 to 0.75/1,000/year (mean 0.54) in school children 5 - 15 years of age in India¹. Apart from many virulent factors produced by GABHS, the most important ones for the pathogenesis are the M proteins i.e. antigens and the Streptolysin O. Diagnosis of GABHS pharyngitis is best accomplished by combining clinical judgment with diagnostic test results, the criterion standard of which is the throat culture. Penicillin (either oral penicillin V or injectable benzathine penicillin) is the treatment of choice, because it is cost-effective, has a narrow spectrum of activity, and has long-standing proven efficacy, and GAS resistant to penicillin have not been documented. Secondary prophylaxis prevents the development or worsening of RHD. Benzathine penicillin G (BPG) is the only RHD control strategy shown to be effective and cost-effective at both community and population levels but sulfadiazine or a macrolide or azalide are acceptable alternatives in penicillin-allergic individuals. The prevalence of RHD has declined in the West, but continues to be an important cause of cardiac morbidity and mortality in India.

Keywords: Rheumatic fever (RF), RHD.

INTRODUCTION

Acute rheumatic fever is a non-suppurative complication of group A beta haemolytic streptococcal (GABHS) sore throat. It affects joints, skin, subcutaneous tissue, brain and heart². Except heart, all other effects are reversible, needing only symptomatic relief during the episodes. Cardiac complications are significant in absence of secondary prophylaxis and culminate into chronic and life threatening valvular heart disease³. The prevalence rate of rheumatic heart disease in India is around 6-11/1000 in school children⁴. RF is considered as a social disease i.e. alteration in socio-economic state of a community will adversely or favourably affect the incidence of this disease⁴. Globally, India contributes nearly 25%-50% of newly diagnosed cases, deaths, hospitalizations and burden of RHD⁵. The most important sequel of rheumatic fever is the rheumatic heart disease (RHD), which results in significant morbidity and mortality.

PATHOGENESIS

RF is a delayed autoimmune response to Group A streptococcal pharyngitis, and the clinical manifestation of the response and its severity in an individual is determined by host genetic susceptibility, the virulence of the infecting organism, and a conducive environment^{6,7,8}. Although streptococci from serogroups B, C, G and F can cause pharyngitis and trigger a host immune response, they have not been linked to the aetiology of RF or rheumatic heart disease (RHD). Major Histocompatibility antigens, potential tissue-specific antigens, and antibodies developed during and immediately after a streptococcal infection are being investigated as potential risk factors in the pathogenesis of the disease. Recent evidence suggests that T-cell lymphocytes play an important role in the pathogenesis of rheumatic carditis. It has also been postulated that particular M types of group A streptococci have rheumatogenic potential that can resist phagocytosis, traverse and penetrate bacterial cell wall, multiply rapidly in human tissues and ultimately initiate disease. M-protein is one of the best-defined determinants of bacterial virulence. The streptococcal M-protein extends from the surface of the streptococcal cell more than 130 M-protein types identified, M types such as 1, 3, 5, 6, 14, 18, 19 and 24 have been associated with RF⁹. Evidence of an antecedent Group A streptococcal (GAS) infection is required for the confirmation of the initial diagnosis of acute rheumatic fever (RF). At the time of diagnosis of acute RF, only about 11% of patients have throat cultures positive for GAS. The paucity of positive cultures is due, in part to elimination of the organism by host defence mechanisms

during the latent period between the onset of infection and the subsequent development of RF¹⁰. Because the presence of GAS in the throat may not reflect active infection, elevated or rising ASO titres provide more reliable evidence of a recent streptococcal infection than a positive culture or a positive rapid antigen test. The most commonly used antibody tests are the antistreptolysin O (ASO) and antideoxyribonuclease B (Anti-DNAase B). The ASO test is usually done first and if not elevated, the anti-DNAase B test is done. Elevated titres for both tests may persist for weeks or months. ASO titres rise and fall rapidly than anti-DNAase B. Other antibody tests which are occasionally done are anti hyaluronidase H (AH) and antistreptozyme (ASTZ). It must be stressed that elevated ASO titre (>250 Todd units (adults) and >333 Todd units (Children) are considered to be significant for diagnosis. ASO level may rise and fall irrespective of the course of rheumatic fever¹¹. During a Streptococcus infection, mature antigen presenting cells such as B cells present the bacterial antigen to CD4-T cells which differentiate into helper T₂ cells. Helper T₂ cells subsequently activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus. However the antibodies may also react against the myocardium and joints, producing the symptoms of rheumatic fever¹².

DIAGNOSIS

Jones criteria for the diagnosis of rheumatic fever

The Jones criteria were introduced in 1944 as a set of clinical guidelines for the diagnosis of rheumatic fever (RF) and carditis¹³. The clinical features of RF were divided into major and minor categories, it was proposed that the presence of two major, or one major and two minor, manifestations offered reasonable clinical evidence of rheumatic activity.

The Jones criteria were subsequently reviewed by the American Heart Association (AHA) and the World Health Organization (WHO)¹⁴ and were modified to encompass vexing clinical issues and to improve the specificity (Table 1)

Two major or one major and two minor criteria plus evidence of preceding streptococcal infection indicate a high probability of rheumatic fever. In the three special categories listed below, the diagnosis of rheumatic fever is acceptable without two major or one major and two minor criteria. However, only for a and b can the requirement for evidence of a preceding streptococcal infection be ignored.

- a. Chorea, if other causes have been excluded
- b. Insidious or late-onset carditis with no other explanation
- c. Rheumatic recurrence: in patients with documented rheumatic heart disease or, prior rheumatic fever, the presence of one major criterion or of fever, arthralgia or elevated acute phase reactants suggests a presumptive diagnosis of recurrence.

Table 1: 2002-2003 WHO criteria for the diagnosis of rheumatic fever rheumatic heart disease (based on revised Jones criteria)

Major criteria	Minor criteria
Carditis	Fever
Arthritis, migratory	Arthralgia
Erythema marginatum	Elevated acute phase reactants (ESR, CRP)
Sydenham's chorea	Prolonged PR interval in ECG
Subcutaneous nodules	
Plus	
Evidence of preceding group (Electrocardiogram: prolonged P-R interval elevated or rising antistreptolysin-O or other streptococcal antibody, or a positive throat culture, or rapid antigen test for group A Streptococci, or recent scarlet fever.)	

CRP=C reactive protein, ESR=Erythrocyte sedimentation rate, ECG=Electrocardiogram

Source: Ferrieri P. Proceedings of the Jones Criteria Workshop (Reference 14)

Evidence of previous streptococcal infection is needed

1. Major Criteria

Carditis

The carditis of acute rheumatic fever is a pancarditis with involvement of pericardium, epicardium, myocardium and endocardium. Valvular insufficiency is the commonest defect. It most often involves the mitral valve.

Clinical features of Rheumatic Carditis

Pericarditis: Audible friction rub; can be supported by echocardiographic evidence of pericardial effusion. Simultaneous demonstration of valvular involvement generally considered essential. Pericarditis is equally diagnostic in primary episode, or a recurrence of RF.

Myocarditis: Unexplained CHF or cardiomegaly, almost always associated with valvular involvement. Left ventricular function is rarely affected. In presence of RHD, CHF and minor manifestations, and elevated streptococcal antibody titers provide reasonable evidence of rheumatic carditis.

Endocarditis/valvulitis: Presence of apical holosystolic murmur of mitral regurgitation (with or without apical mid-diastolic murmur, Carey Coombs), or basal early diastolic murmur in patients who do not have a history of RHD.

On the other hand, in an individual with previous RHD, a definite change in the character of any of these murmurs or the appearance of a new significant murmur indicates the presence of carditis.

Echocardiography^a can provide early evidence of valvular involvement, can confirm suspected valvular regurgitation, and can exclude non-rheumatic causes of valvular involvement.

^a Echocardiographic demonstration of valvular regurgitation is not a prerequisite for the diagnosis of rheumatic carditis and should not be considered a limitation where the facilities are not available. The strict application of diagnostic criteria is mandatory to demonstrate pathological valvular regurgitation. Currently, data do not allow subclinical valvular regurgitation detected by echocardiography to be included in the Jones criteria, as evidence of a major

manifestation of carditis. Echocardiography can only play a limited role in cases of recurring RF, unless a previous echocardiographic study is available for comparison.

Arthritis

Arthritis is the most frequent occurring in up to 75% of patients in the first attack of RF most often in the larger joints (commonly in the knees and ankles); the wrists, elbows, shoulders and hips are less frequently involved; and the small joints of the hands, feet and neck are rarely affected^{15, 16}. Inflamed joints are characteristically warm, red and swollen, and an aspirated sample of synovial fluid may reveal a high average leukocyte count.¹⁷

Erythema marginatum

A evanescent, erythematous, non-tender, non-pruritic macular¹⁸. Long lasting rash that begins on the trunk or arms as macules and spreads outward to form a snake like ring while clearing in the middle. This rash never starts on the face and it is made worse with heat. Erythema marginatum usually occurs early in the course of a rheumatic attack.

Sydenham's chorea

Chorea occurs primarily in children and females. The prevalence of chorea in RF patients varied from 5–36% in different reports¹⁹. Sydenham's chorea is characterized by emotional lability, uncoordinated movements, and muscular weakness^{20, 21}. The onset may often be difficult to determine, as initially the child may become fretful, irritable, inattentive to schoolwork, fidgety, or even severely disturbed. Physical uncoordination soon becomes apparent, perhaps manifested as clumsiness and a tendency to drop objects, which progresses to spasmodic, uncoordinated movements. Facial movements include grimaces, grins and frowns. When the tongue is protruded it resembles a "bag of worms," and speech is jerky and staccato. Handwriting becomes illegible, when the hands are extended; the dorsum assumes a "spoon" or "dish" configuration due to flexion of the wrist and hyperextension of the metacarpophalangeal joints²².

Subcutaneous nodules

The subcutaneous nodules are round, firm, freely movable, painless lesions varying in size from 0.5–2.0 cm. Because the skin over them is not inflamed, they may easily be missed if not carefully sought on physical examination. They occur in corps over bony prominences or extensor tendons. Common locations are the elbows, wrists, knees, ankles and Achilles tendons. They may also be found over the scalp, especially the occipital, and the spinous processes of the vertebrae. Nodules are found more frequently in patients with severe carditis and may appear in recurrent corps²³.

2. Minor Criteria

Fever

Fever occurs in almost all rheumatic attacks at the onset, usually ranging from 101 °F to 104 °F (38.4–40.0 °C).

Arthralgia

Arthralgia is a non-specific symptom, and usually occurs in the same pattern as rheumatic polyarthritis (migratory, asymmetrical, affecting large joints). It is diagnosed only in the absence of underlying arthritis¹⁸.

Evidence of group

A streptococcal infection: It requires evidence of preceding streptococcal infection as confirmed by a positive throat culture, a history of scarlet fever, or elevated streptococcal antibodies such as antistreptolysin-O (ASO), antideoxyribonuclease-B (anti-DNAase-B) or antihyaluronidase (AH)¹⁸.

3. Current Diagnostic Techniques

To establish the current diagnosis, latest imaging technique and laboratory diagnosis are preferred. Table 2. A brief discussion is done below about these diagnostic techniques.

Table 2: Current diagnostic techniques

Imaging Tech	Laboratory Diagnosis
Echocardiography	Throat culture
Endomyocardial biopsy	Streptococcal antibody test
Radionuclide imaging	Acute phase reactants
	Antigen Detection Tests

Source: Feigenbaum H, Zaky A, Waldhausen JA. Use of ultrasound in the diagnosis of pericardial effusion. (Reference 24)

Echocardiography

Echocardiography is an imaging technique; the technique includes transthoracic, transesophageal and intracardiac echocardiography^{24, 25, 26}. Doppler echocardiography is sufficiently sensitive and provides specific information not previously available. Of these, M-mode echocardiography provides parameters for assessing ventricular function, while 2D echocardiography provides a realistic real-time image of anatomical structure. Two-dimensional echo-Doppler and colour flow Doppler echocardiography are most sensitive for detecting abnormal blood flow and valvular regurgitation. The use of 2D echo-Doppler and colour flow Doppler echocardiography may prevent the over diagnosis of a functional murmur as valvular heart disease²⁷. Similarly, the over interpretation of physiological or trivial valvular regurgitation may result in a misdiagnosis of iatrogenic valvular disease^{28, 29}. Echocardiography is not mandatory to establish the diagnosis of rheumatic fever although it is an important role in detection of subclinical carditis³⁰.

Endomyocardial biopsy

The value of endomyocardial biopsy has been investigated for diagnosing rheumatic carditis³¹. To establish the histological characteristics of carditis, endomyocardial biopsies from patients presenting with a first episode of RF were compared to biopsies from patients with quiescent chronic RHD. These results suggested that an endomyocardial biopsy is not likely to provide additional diagnostic information for patients with clinical carditis in a primary episode of RF.

Radionuclide imaging

Radionuclide techniques are simple, non invasive modalities that have been commonly used to evaluate a variety of cardiovascular disorders. Rheumatic myocarditis is characterized predominantly by the presence of myocardial inflammation, with some damage to myocardial cells^{31, 32}. Gallium-67³³ radiolabelled leukocytes^{34, 35}, and radiolabelled antimyosin antibody³⁶ have all been used to image myocardial inflammation. Although radionuclide imaging has been used successfully to identify rheumatic carditis by non-invasive means, there is not enough experience with such methods to allow them to be used for the routine diagnosis of RF.

Throat Culture

Throat culture is the conventional method for establishing the diagnosis of group A β -haemolytic streptococcal (GAS) pharyngitis and is the criterion standard. In an untreated patient with (GAS) pharyngitis, at the time of acute rheumatic fever, only 11% of the patients have a positive throat culture for group-A beta haemolytic streptococci³⁷. The correct procedure for taking a throat swab is to directly observe the tonsillar-pharyngeal area while vigorously swabbing the tonsils or tonsillar crypts and the posterior pharyngeal wall³⁸, thus throat culture is almost always positive; however, a positive throat culture may reflect chronic colonization by (GAS), and the acute illness may be caused by another agent. Quantitation of (GAS) from the throat swab culture cannot be used to differentiate carriage from infection, because sparse growth may be associated with true infection. A negative throat culture permits the physician to withhold antibiotic therapy from the large majority of patients with sore throats

Streptococcal antibody test

Streptococcal serum antibody tests should be undertaken for all suspected cases of acute RF³⁹, Antistreptococcal antibody titers reflect past and not present immunologic events and therefore

cannot be used to determine whether an individual with pharyngitis and GAS in the pharynx is truly infected or merely a streptococcal carrier. The most commonly used and commercially available antibody assays are antistreptolysin O and antideoxyribonuclease B. The antistreptolysin O test is usually obtained first, and if it is not elevated, an antideoxyribonuclease B test may be performed. Antistreptolysin O titers begin to rise approximately 1 week and peak 3 to 6 weeks after the infection. Antideoxyribonuclease B titers begin to rise 1 to 2 weeks and peak 6 to 8 weeks after the infection. About 60-80 % of the healthy population may show an elevated ASO titre (>300 IU/ml in children) in developing countries like ours⁴⁰. Hence, one must remember that single raised ASO titre does not equate to ARF, so paired sera collected at an interval of 4-8 weeks with 2- fold increase or decrease gives a more meaningful interpretation. Similarly, a negative ASO titre does not exclude the diagnosis of ARF^{41, 42}. Both the traditional antistreptolysin O and antideoxyribonuclease B tests are neutralization assays. Newer tests use latex agglutination or nephelometric assays. Unfortunately, these newer tests have not been well standardized against the traditional neutralization assays⁴³. A commercially available slide agglutination test for the detection of antibodies to several streptococcal antigens is the Streptozyme test (Wampole Laboratories, Stamford, Conn). This test is less well standardized and less reproducible than other antibody tests, and it should not be used as a test for evidence of a preceding GAS infection^{44, 45}.

Acute phase reactants

Erythrocyte sedimentation rate (ESR), C reactive protein (CRP) is raised in almost all patients of carditis and arthritis and, sometimes in patients with chorea. ESR is useful in following the course of disease since the levels decline as rheumatic activity subsides.

Antigen Detection Tests

Many GAS antigen detection tests are available commercially. These tests vary in method. Most of these tests have a high degree of specificity, but their sensitivity in clinical practice can be unacceptably low⁴⁶. Therefore, treatment is indicated for the patient with acute pharyngitis who has a positive rapid antigen detection test (RADT). As with the throat culture, a positive RADT may reflect chronic colonization by GAS, and the acute illness may be caused by another agent. With most RADTs, a negative test does not exclude the presence of GAS, and a throat culture should be performed^{47, 48}. Newer tests have been developed that may be more sensitive than other RADTs and perhaps even as sensitive as blood agar plate cultures^{49, 50}. However, the definitive studies to determine whether some RADTs are significantly more sensitive than others and whether any of the RADTs are sensitive enough to be used routinely in children without throat culture confirmation of negative test results have not been performed.

Though a number of dilemmas in the diagnosis of acute rheumatic fever (ARF) have been discussed. An over diagnosis at the initial phase of the illness and starting appropriate treatment earlier is always better in the prevention of serious cardiac morbidity and mortality, than missing the diagnosis altogether⁵¹.

PROPHYLAXIS OF RHEUMATIC FEVER

1. Suppression of the inflammatory process

Total duration of antiinflammatory therapy after the diagnosis of acute rheumatic fever is established, must be 12 weeks. All anti-inflammatory drugs may cause gastrointestinal bleeds. Steroids may lead to cushingoid facies and flaring up of dormant infections. Aspirin may cause tinnitus. For side effects, monitoring is needed. Aspirin and steroids are primarily used to control inflammation. Naproxen and methylprednisolone can be used alternatively⁵². The Drugs For Control Of Inflammation In Acute Rheumatic Fever Are Summarised In Table 3.

Hospitalization: Hospital admission may be helpful for confirming a diagnosis of rheumatic fever (RF)⁶. All patients with acute RF should be placed on bed-chair rest and monitored closely for the onset of carditis. In patients with carditis, a rest period of at least four weeks is recommended⁵³. For arthritis, rest for two weeks is adequate. Patients with chorea must be placed in a protective environment so they do not injure themselves⁵³.

Table 3: Drugs for Control of Inflammation in Acute Rheumatic Fever

Inflammation	Doses
Arthritis ± mild carditis Aspirin*	Regime I Starting doses: Children: 100 mg/kg/day for 2-3 weeks Adult: 6-8g/day - divide in 4-5 doses Tapering doses: once symptoms resolved, taper to 60-70 mg/kg/day. For older children 50 mg/kg/day (Level of evidence: Class I) Regime II 50 to 60 mg//kg /day for total 12 weeks (Level of evidence-Class Ib) 10-20 mg/kg/day
Naproxen*(If aspirin intolerance detected) No response to aspirin in four days	Switch over to steroid. Rule out other conditions like chronic inflammatory/myelo-proliferative disorders before switching over to steroids.
Moderate to severe carditis Steroids*	Regime I Prednisolone: 2mg/kg/d, maximum 80mg/day till ESR normalizes -usually 2 weeks. Taper over 2-4 weeks, reduce dose by 2.5-5mg every 3rd day. start aspirin 50-75mg/kg/d simultaneously, to complete 12 weeks. (Level of evidence: Class I) Regime II Prednisolone same doses × 3-4 weeks. Taper slowly to cover total period of 10-12 weeks (Level of evidence-Class IIb) If no response to oral steroid therapy then start IV Methyl prednisolone, 30mg/kg/day for 3 days
Non responders Methyl Prednisolone (Intravenous)	

* Consider antacids. Avoid gastric irritants. Allow frequent feeding. Medicines must not be taken on empty stomach

Source: Mishra S. Consensus Guidelines on Pediatric Acute Rheumatic Fever and Rheumatic Heart Disease. (Reference 52)

2. Antimicrobial therapy

Intramuscular benzathine penicillin G and oral penicillin V are the recommended antimicrobial drugs for the treatment of GAS, except in individuals with histories of penicillin allergy. The only currently recommended antimicrobial therapy that has been investigated in controlled studies and demonstrated to prevent initial attacks of acute rheumatic fever is intramuscular repository-penicillin therapy^{54, 55}.

2.1 Oral Penicillins

The oral antibiotics of choice are penicillin V and amoxicillin. Comparative clinical trials used penicillin V dosages of 40 mg/kg (not to exceed 750 mg for those weighing >27 kg) per 24 hours, given in 3 equally divided doses. Generally, 250 mg 2 times daily is recommended for most children. A dose of 500 mg 2 to 3 times daily is recommended for adolescents and adults. All patients should continue to take penicillin regularly for an entire 10-day period, even though they likely will be asymptomatic after the first few days. Penicillin V is preferred to penicillin G because it is more resistant to gastric acid.

2.2 Intramuscular Benzathine Penicillin G

Benzathine penicillin G should be considered particularly for patients who are unlikely to complete a 10-day course of oral

therapy and for patients with personal or family histories of rheumatic fever or rheumatic heart disease or environmental factors (such as crowded living conditions or low socioeconomic status) that place them at enhanced risk for rheumatic fever^{56, 57}. The recommended dosage of benzathine penicillin G is 600 000 U IM for patients who weigh 27 kg (60 lb) or less and 1 200 000 U for patients who weigh more than 27 kg. The combination of 900 000 U of benzathine penicillin G and 300 000 U of procaine penicillin G (Bicillin C-R 900/300) is satisfactory therapy for smaller children⁵⁸. Allergic reactions to penicillin are more common in adults than in children. A careful history regarding allergic reactions to penicillin should be obtained.

2.3 Oral Cephalosporin's

A 10-day course of a narrow-spectrum oral cephalosporin is recommended for most penicillin-allergic individuals. Several reports indicate that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx⁵⁹.

Other reports suggest that a 5-day course with selected oral broad-spectrum cephalosporins is comparable to a 10-day course of oral penicillin in eradicating GAS from the pharynx⁶⁰.

Table 4: Drugs for the Treatment of Streptococcal Pharyngitis and Secondary Prophylaxis

Drugs Prophylaxis	Dose	Sore-Throat Treatment (duration)	Secondary (interval)*
Benzathine Penicillin G (deep IM inj)	1.2 million unit (> 27 Kg) after sensitivity test (AST) 0.6 million unit (<27 Kg) (after sensitivity test)	single dose**	21d
Penicillin-V (oral)	contraindication: penicillin allergy children: 250 mg qid day adult: 500 mg tid 10d	10d	twice a
Azithromycin (oral)	contraindication: penicillin allergy 12.5 mg/kg/day once daily recommended	5d	twice a day
Cephalexin (oral)	15-20 mg/kg/dose bid recommended	10d	not
Erythromycin (oral)	20 mg/kg/dose max 500 mg Contraindication: liver disorder	not recommended	not
			twice a day

* see text for duration of secondary prophylaxis and references. ** only one dose is sufficient for GABHS pharyngitis.

Source: Mishra S. Consensus Guidelines on Pediatric Acute Rheumatic Fever and Rheumatic Heart Disease. (reference 52.)

2.4 Macrolides

The use of an oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin) is reasonable for patients allergic to penicillins. Ten days of therapy is indicated, except for azithromycin, which is given for 5 days. Macrolides can cause prolongation of the QT interval in a dose dependent manner. Because macrolides are metabolized extensively by cytochrome P-450 3A, they should not be taken concurrently with cytochrome P-450 3A inhibitors.^{61, 62} Macrolides are recommended as an alternative therapy for GAS pharyngitis. Macrolide resistance has been associated with certain *emm* types, a sequence-based typing system of the hypervariable region of the GAS M-protein gene, leads to complications including acute rheumatic fever and rheumatic heart disease. The use of macrolides in the management of GAS pharyngitis should be limited to patients with significant penicillin

allergy⁶³. The Drugs for the Treatment of Streptococcal Pharyngitis and Secondary Prophylaxis Are Summarized in Table 4.

POST TREATMENT CONDITION

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS are eradicated from the pharynx⁶⁴. Post treatment throat cultures 2 to 7 days after completion of therapy are indicated only in the relatively few patients who remain symptomatic, whose symptoms recur, or who have had rheumatic fever and are therefore at unusually high risk for recurrence. Failure to eradicate GAS from the throat occurs more frequently after the administration of oral penicillin than after the administration of intramuscular benzathine penicillin G⁶⁵. Many patients in whom treatment fails are chronic carriers who have prolonged periods of GAS colonization⁶⁶.

Table 5: Symptomatic treatment of Rheumatic fever

Medication	Indication	Regimen	Duration
Paracetamol po	Arthritis or arthralgia — mild or until diagnosis confirmed	60mg/kg/day (max 4g) given in 4–6 doses/day; may increase to 90mg/kg/day if needed, under medical supervision	until symptoms relieved or NSAID started
Codeine po	Arthritis or Arthralgia until diagnosis confirmed	0.5–1.0mg/kg/dose (adults 15–60mg/ dose) 4–6hrly	until symptoms relieved or NSAID started
Aspirin po	Arthritis or Severe arthralgia (when ARF diagnosis confirmed)	80–100mg/kg/day (4–8 g/day in adults) given in 4–5 doses/day Reduce to 60–70mg/kg/day when symptoms improve Consider ceasing in the presence of acute viral illness, and consider Influenza vaccine if administered during autumn/winter	until joint symptoms relieved
Naproxen po	Arthritis (if aspirin Intolerant)	10–20mg/kg/day (max 1,250mg) given bd	As for aspirin
Prednisone or Prednisolone po	Severe carditis, heart failure, pericarditis with effusion	1–2mg/kg/day (max 80mg); if used >1 week, taper by 20–25% per week	Usually 1 to 3 weeks bedrest recommended
Frusemide po/IV (can also be given IM)	Heart failure	Children: 1–2mg/kg stat, then 0.5–1mg/kg/dose 6–24 hrly (max 6mg/kg/dose) Adults: 20–40mg/dose 12–24 hrly, up to 250–500mg/day	Until failure controlled and carditis improved.
Spirinolactone po	Heart failure	1–3mg/kg/day (max 100–200mg/day) in 1–3 doses; round dose to multiple of 6.25mg (quarter of a tab)	As for frusemide
Spirinolactone po	Heart failure	1–3mg/kg/day (max 100–200mg/day) in 1–3 doses; round dose to multiple of 6.25mg (quarter of a tab)	As for frusemide
Enalapril po	Heart failure	Children: 0.1mg/kg/day in 1–2 doses, increased gradually over 2 weeks to max of 1mg/kg/day in 1–2 doses Adults initial: 2.5mg daily; maintenance: 10–20mg daily (max 40mg)	As for frusemide
Lisinopril po	Heart failure	Children: 0.1–0.2mg/kg once daily, up to 1mg/kg/dose Adults: 2.5–20mg once daily (max 40mg/day)	As for frusemide
Digoxin po/IV	Heart failure/atrial fibrillation	Children: 15mcg/kg stat and then 5mcg/kg after 6 hrs, then 3–5 mcg/kg/dose (max 125mcg) 12-hrly Adults: 125–250mcg daily	Check serum levels
Carbamazepine	Severe chorea	7–20mg/kg/day (7–10mg/kg/day usually sufficient) given tds	Until chorea controlled for several weeks, then trial off medication
Valproic acid po	Severe chorea (may affect metabolism)	Usually 15–20mg/kg/day salicylate (can increase to 30mg/kg/day) given tds	As for Carbamazepine

Source: Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia (Reference. 78)

SECONDARY PROPHYLAXIS

Secondary prevention of rheumatic fever is defined as the continuous administration of specific antibiotics to patients with a previous attack of rheumatic fever, or documented RHD⁶⁷. The purpose is to prevent colonization or infection of the upper respiratory tract with group A beta-haemolytic streptococci and the development of recurrent attacks of rheumatic fever. Secondary prophylaxis should be started only after establishing the diagnosis of acute rheumatic fever⁶⁸. A recurrent attack can be associated with worsening of the severity of rheumatic

heart disease that developed after a first attack, or less frequently with the new onset of rheumatic heart disease in individuals who did not develop cardiac manifestations during the first attack. So prevention of such recurrent attack is must in order to prevent rheumatic heart disease.

Duration of Secondary Prophylaxis: The appropriate duration of secondary prophylaxis is determined by age, time since the last episode of ARF and potential harm from recurrent ARF. Critical factors are outlined (Table 6). Based on these factors, the recommended duration of secondary prophylaxis is outlined (Table 7).

Table 6: Factors that affect the duration of secondary prophylaxis

Factors	Implication
Age	ARF recurrence is less common in people aged 25–40 yrs and rare >40 yrs.
Presence and severity of RHD	ARF recurrence could be life-threatening in people with moderate or severe RHD, or a history of valve surgery.
Presence of carditis during initial attack	Increases the likelihood of further cardiac damage
last episode of ARF	Time elapsed since ARF recurrences are less common >5 yrs since last episode. Should a recurrence occur.
Socio-economic circumstances	ARF recurrences are more common in lower socio-economic groups (particularly related to overcrowded housing).
The background risk of GAS infection settings* and ARF within the community	ARF recurrences are more common in higher-incidence communities or .
Adherence to	Optimised adherence for a few years after the initial attack treatment may provide greater protection from recurrences than offered by poor adherence for many years.
Assessment at time of cessation of secondary prophylaxis	Evidence of moderate or greater RHD may warrant prolonged prophylaxis.

Note: *Consideration should be given to the higher risk of exposure to GAS and subsequent development of ARF among individuals residing or working in environments or settings such as boarding schools, childcare settings, barracks, hostels or overcrowded housing with large numbers of children.

Source: Adapted from *Report of a WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease 29 October–1 November 2001*. 2001. World Health Organization: Geneva. (Reference. 5)

Table 7: Duration of Secondary Prophylaxis

Category of Patient	Duration of Prophylaxis
Patient without proven carditis.	For 5 years after the last attack, or until 18 years of age (whichever is longer).
Patient with carditis until 25 (mild mitral regurgitation or healed carditis).	For 10 years after the last attack, or at least years of age (whichever is longer).
More severe valvular disease.	Life long.
After valve surgery.	Life long.

* See Text. These are only recommendations and must be modified by individual circumstances as warranted

Source: Adapted from *Report of a WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease 29 October–1 November 2001*. 2001. World Health Organization: Geneva. (Reference. 5)

Antibiotics used in secondary prophylaxis of RF

Intramuscular injection of benzathine benzylpenicillin (BPG) every three weeks (every four weeks in low-risk areas or low risk patients) is the most effective strategy for preventing recurrent attacks of RF⁶⁹. Oral penicillin should be reserved for patients who refuse intramuscular BPG due to severe muscle pain caused by (BPG). For those patients who are known to be, or are suspected of being, allergic to penicillin, oral sulfadiazine or oral sulfasoxazole represent optimal second choices⁷⁰. The incidences of allergic and anaphylactic reactions to monthly benzathine penicillin injections are 3.2% and 0.2% respectively; fatal reactions are rare⁷¹. The overall incidence of hypersensitivity reactions has been estimated to be 2–5% ⁷². The most common allergic reactions are manifest as skin rashes. Anaphylaxis is rare and occurs in only about 0.2% of cases⁷³. Penicillin skin testing is an acceptable and usually

accurate method to determine whether a person is at risk of having an immediate reaction to penicillin. Only 10–20% of patients reporting penicillin allergy are truly allergic when assessed by skin testing⁷⁴. In patients with a confirmed, immediate and severe allergic reaction to penicillin, a nonbeta-lactam antimicrobial (erythromycin) should be used instead of BPG. In pregnant patients, penicillin does not cause teratogenicity during ARF treatment. An emergency kit for treating anaphylaxis should be available in any clinical setting where intramuscular penicillin is administered.

It is nevertheless recommended that all patients who are to receive secondary prophylaxis are carefully questioned as to whether they are allergic to penicillin. If a hypersensitivity reaction of any degree develops during prophylaxis a different antibiotic should be used in the future (Table 8).

Table 8: Antibiotics Used in Secondary Prophylaxis of Rheumatic fever

Antibiotic	Mode of Administration	Dose
Benzathine benzylpenicillin G	Single intramuscular injection every 3–4 weeks.	For adults and children ≥30kg in weight: 1200000 units. For children <30kg in weight: 600000 units.
Penicillin V.	Oral.	250mg twice daily.
Sulfonamide (e.g. sulfadiazine, sulfadoxine, sulfisoxazole).	Oral.	For adults and children ≥30kg in weight: 1 gram daily. For children <30kg in weight: 500mg daily.
Administered in response to penicillin allergy		
Erythromycin.	Oral.	250mg twice daily.

Source: Carapetis JR. Acute rheumatic fever. (Reference 75)

BRIEF MANAGEMENT OF CARDIAC COMPLICATIONS

a) **Mitral regurgitation:** In chronic mitral regurgitation, volume overload of the left ventricle and left atrium occurs, which in more severe cases eventually results in a progressive decline in systolic contractile function. Echocardiography is used to confirm the diagnosis, requires diuretic therapy and ACE inhibitors. Symptoms and/or signs of left ventricular systolic dysfunction (defined by an ejection fraction <0.60, or an end-systolic dimension ≥4.5 cm) are indications for surgery ⁷⁶. Mitral valve repair rather than replacement is the first choice.

b) **Mitral stenosis:** In mitral stenosis, progressive obstruction to LV inflow develops due to fibrosis and partial fusion of the mitral valve leaflets. Mitral valve orifice decreases to less than 1.0-1.5cm². Doppler and two-dimensional echocardiography is used to quantitate the severity of mitral stenosis. Atrial fibrillation is the most common complication of mitral stenosis, requiring long-term prophylactic anticoagulation with warfarin. Percutaneous balloon mitral valvuloplasty is the treatment of choice for dominant or pure mitral stenosis. Surgical intervention has largely been replaced by percutaneous balloon mitral valvuloplasty.

c) **Aortic regurgitation:** This results in LV overload with an increase in LV end diastolic volume, which helps maintain the increased total stroke volume⁷⁷. As the severity of regurgitation increases, the left ventricle undergoes progressive dilatation and hypertrophy. In the chronic situation, many patients remain asymptomatic, despite having moderate or severe regurgitation. Eventually, they become symptomatic with exertional dyspnoea, angina and heart failure. Echocardiography is used to assess LV size and function. Vasodilator therapy can reduce LV dilatation and the regurgitant fraction, slow progression of LV dilatation and possibly delay the need for surgery. Patients with moderate to severe aortic regurgitation who become symptomatic should be referred for surgery only when LV function is reduced (LV ejection fraction <55%) or LV end systolic diameter is approaching 55mm.

d) **Aortic stenosis:** Aortic stenosis results from fibrosis and partial fusion of aortic valve cusps, causing progressive obstruction to LV outflow. Two-dimensional echocardiography shows the thickened and restricted aortic valve leaflets (valve area ≤1.0cm²) and allows assessment of LV size and systolic function. Percutaneous aortic valvuloplasty is reserved only for patients who are not candidates for surgery, aortic valve replacement with a mechanical valve, a bioprosthetic valve or a homograft is the definitive therapy for symptomatic aortic stenosis.

e) **Bacterial Endocarditis Prophylaxis:** Infective endocarditis poses a special threat for individuals with chronic rheumatic valvular disease but who have no evidence of damage to heart valves, *do not* require endocarditis prophylaxis⁶. For the vast majority of patients who develop infective endocarditis (either with bacteria or with fungi), normal laminar blood flow is converted into turbulent flow causing endothelial damage. Early studies also suggested that Gram-positive oral flora, such as viridans group streptococci are responsible for endocarditis. In latter half of century, with an increase in the number of episodes of infective endocarditis associated with *Staphylococcus aureus* and coagulase-negative staphylococci were recovered from infective endocarditis

patients. Prophylaxis use of antibiotic is done to prevent or minimize bacteremia in patients with heart disease, to prevent the development of infective endocarditis. Antibiotics for endocarditis prophylaxis during dental, oral and respiratory tract procedures are Clindamycin, Vancomycin, Amoxycillin or Ampicillin 1 hour prior to procedure. For genitourinary and gastrointestinal procedures gentamicin plus vancomycin is used⁷⁸.

CONCLUSION

The establishment of a national prevention programme is essential in India where considering a median incidence of 0.5/1000, approximately 131 000 children suffer from RF every year in India⁷⁹. At least one-third of them develop chronic valvular heart disease, i.e. nearly 44 000 patients are added every year. In 1966 when prevalence of rheumatic fever was significant, Government of India had included rheumatic fever in the fourth five year plan. However in subsequent five year plans, it was dropped. The ICMR has carried out six, nationwide research projects on rheumatic fever and rheumatic heart disease between 1966 and 1990 but due to lack of enthusiasm of governments (central and state), these programmes have not become popular. Finally, rheumatic fever (RF) vaccine, ICMR is working actively to produce RF vaccine. ICMR has initiated Jal Vigyan Mission Mode Project at Chandigarh and Vellore where the development of RF vaccine is in progress. Vaccine is being prepared using Indian strains of A streptococci. It is now 102 years since the first case of RHD has been reported the question is same that whether RF and RHD in India has declined significantly that we can ignore this problem. The answer is no. Since the coronary artery disease, hypertension have come to India in epidemic proportion, the hospitals (private, public) and cardiologists are concentrating on management of these diseases. Hence RHF and RHD is receiving less publicity and attention. The bottom line is that we should detect RHD early and should carry out secondary prophylaxis. If a safe RF vaccine becomes available, it will be a boon for control of the disease⁸⁰.

REFERENCES

1. Grover A, Vijayvergiya R, Thingam S. Burden of rheumatic and congenital heart disease. Indian Heart J 2002; 54: 104-7.
2. English PC. Rheumatic fever in America and Britain. A biological, epidemiological and medical history. New Jersey: Rutgers University Press; 1999.
3. Sanyal SK, Berry AM, Duggal S, et al. Sequelae of the initial attack of acute rheumatic fever in children from north India. A prospective 5-year follow-up study. Circulation 1982; 65: 375-379.
4. Community control of rheumatic heart disease in developing countries: 1. A major public health problem. WHO Chronicle 1980; 34:336-45.
5. World Health Organization. Rheumatic fever and rheumatic heart disease: Report of a WHO expert consultation. Geneva, 29 Oct-1 Nov 2001. World Health Organ Tech Rep Ser 2004; 923:1-122.
6. Rheumatic fever and rheumatic heart disease. Report of a WHO Study Group. Geneva, World Health Organization, 1988 (Technical Report Series No. 764).

7. Kaplan EL. The group A streptococcal upper respiratory tract carrier state: an enigma. *Journal of Pediatrics* 1980; 97:337-339.
8. Taranta A, Markowitz M. Rheumatic fever. Boston: Kluwer Academic Publishers; 1989.
9. Stevens D, Kaplan E. Streptococcal infections. Clinical aspects, microbiology and molecular pathogenesis. New York: Oxford University Press; 2000.
10. Bisno Alan L. Rheumatic fever. In *Text Book of Rheumatology* edited by Kelly, Harris, Ruddy & Sledge. 4th edition. Philadelphia: WB Saunders Co; 1993.p. 1209-1223
11. Strollerman GH. Rheumatogenic streptococci and autoimmunity. *Clin Immunol Immunopathol* 1991; 61:131-42.
12. Abbas, Abul K, Lichtman, Andrew H, Baker, David L. et al. Basic immunology: functions and disorders of the immune system. 2nd ed. Philadelphia: Elsevier Saunders; 2004.
13. Jones TD. Diagnosis of rheumatic fever. *Journal of the American Medical association* 1944; 126:481-484.
14. Ferrieri P. Proceedings of the Jones Criteria Workshop. *Circulation* 2002; 106: 2521-2529.
15. Feinstein AR et al. Rheumatic fever in children and adolescents. A long-term epidemiologic study of subsequent prophylaxis, streptococcal infections, and clinical sequel. VI. Clinical features of streptococcal infection and rheumatic recurrences. *Annals of Internal Medicine* 1964; 60 Suppl 5:68-86.
16. Sanyal SL et al. Sequelae of the initial attack of acute rheumatic fever in children from North India: a prospective 5-year follow-up study. *Circulation* 1982; 65:375-379.
17. Svartman M et al. Immunoglobulins and complement components in synovial fluid of patients with acute rheumatic fever. *The Journal of Clinical Investigation* 1975; 56:111-117.
18. Sainani GS, Sainana AR, Rheumatic fever - How relevant in India today? *JAPI* 2006; 54:42-47.
19. Bisno A. Noncardiac manifestations of rheumatic fever. *American Registry of Pathology* 1994; 64:245-256.
20. Aron AM, Freeman JM, Carter S. The natural history of Sydenham's chorea: review of the literature and long-term evaluation with emphasis on cardiac sequelae. *American Journal of Medicine* 1965; 38:83-95.
21. Markowitz M, Gordis L. Rheumatic fever. 2nd ed. Philadelphia: WB Saunders Co; 1972.
22. Al-Eissa A. Sydenham's. chorea: a new look at an old disease. *British Journal of Clinical Practice* 1993; 47:14-16.
23. Massell BF, Fyler DC, Roy SB. The clinical picture of rheumatic fever: diagnosis, immediate prognosis, course and therapeutic implications. *American Journal of Cardiology* 1958; 1:436-439.
24. Feigenbaum H, Zaky A, Waldhausen JA. Use of ultrasound in the diagnosis of pericardial effusion. *Annals of Internal Medicine* 1966; 65:443-452.
25. Seward JB et al. Transesophageal echocardiography: technique, anatomic correlations, implementation, and clinical applications. *Mayo Clinic Proceedings* 1988; 63:649-680.
26. Minich LL et al. Role of echocardiography in the diagnosis and follow-up evaluation of rheumatic carditis. *American Registry of Pathology* 1994; 56: 307-318.
27. Pandian NG et al. Three-dimensional and four-dimensional transesophageal echocardiographic imaging of the heart and aorta in humans using a computed tomographic imaging probe. *Echocardiography* 1992; 9:677-687.
28. Regmi PR, Pandey MR. Prevalence of rheumatic fever and rheumatic heart disease in school children of Kathmandu city. *Indian Heart Journal* 1997; 9:518-520.
29. Shah PM. Quantitative assessment of mitral regurgitation. *Journal of the American College of Cardiology* 1989; 13:591-593.
30. Narula J, Kaplan, EL. Echocardiographic diagnosis of rheumatic fever. *Lancet* 2001; 358: 2000-2010.
31. Narula J et al. Endomyocardial biopsies in acute rheumatic fever. *Circulation* 1993; 88:2198-2205.
32. Narula J et al. Acute myocarditis masquerading as myocardial infarction. *New England Journal of Medicine* 1993; 328 suppl 2:100-104.
33. Calegaro JU et al. Galio-67 na febre rheumatica: experiencia preliminar. [Gallium-67 in rheumatic fever: preliminary experience.] *Arquivos Brasileiros de Cardiologia, [Brazilian Archives of Cardiology]* 1991, 56:487-492.
34. Kao CH, Wang SJ, Yeh SH. Detection of myocarditis in dilated cardiomyopathy by Tc-99m HMPAO WBC myocardial imaging in a child. *Clinical Nuclear Medicine* 1992; 17:678-679.
35. Kao CH et al. Comparison of Tc-99m HMPAO labeled white blood scanning for the detection of carditis in the differentiation of rheumatic fever and inactive rheumatic heart disease in children. *Nuclear Medicine Communications* 1992; 1:478-481.
36. Narula J, Chandrashekhar Y, Rahimtoola SH. Echoes of change: diagnosis of active rheumatic carditis. *Circulation* 1999; 100:1576-1581.
37. Dajani AS. Current status of non-supportive complications of group-A streptococci. *Pediatr Infect Dis J* 1991; 10:S25-7.
38. Dajani A et al. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. *Pediatrics* 1995; 96:758-764.
39. Kellogg JA. Suitability of throat culture procedures for detection of group A streptococci and as reference standards for evaluation of streptococcal antigen detection kits. *Journal of Clinical Microbiology* 1990; 28: 165-169.
40. Zaman MM, Hassan MMM, Ahmed J, Zareen S et al. Streptococcal antibodies among rural school children in Bangladesh. *Bang. Med. Res. Coun. Bull* 2002; 28 suppl1:1-6.
41. Rheumatic fever and rheumatic heart disease. Report of a WHO Expert Consultation. Geneva: WHO Technical Report Series. Nov. 2001 No.923.
42. Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2009; 119 suppl 11:1541-1551.
43. Shet A, Kaplan EL. Clinical use and interpretation of group A streptococcal antibody tests: a practical approach for the pediatrician or primary care physician. *Pediatr Infect Dis J* 2002; 21:420-426.
44. Kaplan EL, Huew BB. The sensitivity and specificity of an agglutination test for antibodies to streptococcal extracellular antigens: a quantitative analysis and comparison of the Streptozyne test with anti-streptolysin O and anti-deoxyribonuclease B tests. *J Pediatr* 1980; 96:367-373.
45. Gerber MA, Wright LL, Randolph MF. Streptozyne test for antibodies to group A streptococcal antigens. *Pediatr Infect Dis J* 1987; 6:36-40.
46. Humair JP, Revaz A, Bovier P. et al. Management of acute pharyngitis in adults; reliability of rapid antigen streptococcal tests and clinical findings. *Arch. Intern Med* 2006; 166: 640-644.
47. Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis* 2002; 35:113-125.
48. American Academy of Pediatrics, Committee on Infectious Diseases. *Red Book: Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2006.
49. Webb KH. Does culture confirmation of high-sensitivity rapid streptococcal tests make sense? A medical decision analysis. *Pediatrics* 1998; 101:E2.
50. Gerber MA, Tanz RR, Kabat W, Dennis E, Bell GL, Kaplan EL, Shulman ST. Optical immunoassay test for group A beta-hemolytic streptococcal pharyngitis: an office-based, multicenter investigation. *JAMA* 1997; 277:899-903.
51. Padmavati S. Rheumatic heart disease: prevalence and preventive measures in the Indian subcontinent. *Heart* 2001; 86:127.

52. Mishra S. Consensus Guidelines on Pediatric Acute Rheumatic Fever and Rheumatic Heart Disease. *INDIAN PEDIATRICS* 2007; 45: 565-573.
53. Silva NA, Pereira BA. Acute rheumatic fever: still a challenge. *Rheumatic Disease Clinic of North America* 1997, 23 suppl 3:545-568.
54. Denny FW, Wannamaker LW, Brink WR, Rammelkamp CH Jr, Custer EA. Prevention of rheumatic fever: treatment of the preceding streptococcal infection. *J Am Med Assoc* 1950; 143:151-153.
55. Wannamaker LW, Rammelkamp CH Jr, Denny FW, Brink WR, Houser HB, Hahn EO, Dingle JH. Prophylaxis of acute rheumatic fever by treatment of preceding streptococcal infection with various amounts of depot penicillin. *Am J Med* 1951; 10:673- 695.
56. Griffiths SP, Gersony WM. Acute rheumatic fever in New York City (1969 to1988): a comparative study of two decades. *J Paediatric* 1990; 116:882-887.
57. Gordis L, Lilienfeld A, Rodriguez R. Studies in the epidemiology and preventability of rheumatic fever, II: socio-economic factors and the incidence of acute attacks. *J Chronic Dis* 1969; 21:655- 666.
58. Bass JW, Crast FW, Knowles CR, Onufer CN. Streptococcal pharyngitis in children: a comparison of four treatment schedules with intramuscular penicillin G benzathine. *JAMA* 1976; 235:1112-1116.
59. Pichichero ME, Margolis PA. A comparison of cephalosporins and penicillin in the treatment of group A beta-hemolytic streptococcal pharyngitis: a meta-analysis supporting the concept of microbial copathogenicity. *Pediatr Infect Dis J* 1991; 10:275-281.
60. Pichichero ME, Gooch WM, Rodriguez W, Blumer JL, Aronoff SC, Jacobs RF, Musser JM. Effective short-course treatment of acute group A beta-hemolytic streptococcal tonsillopharyngitis: ten days of penicillin V vs 5 days or 10 days of cefpodoxime therapy in children. *Arch Pediatr Adolesc Med* 1994; 148:1053-1060.
61. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; 351:1089 -1096.
62. Huang BH, Wu CH, Hsia CP, Yin Chen C. Azithromycin-induced torsade de pointes. *Pacing Clin Electrophysiol* 2007; 30:1579 - 1582.
63. Logan LK, McAuley JB, Shulman ST. Macrolide Treatment Failure in Streptococcal Pharyngitis Resulting in Acute Rheumatic Fever. *Pediatrics* 2012; 129 suppl 3: e798 -e802.
64. Gerber MA. Treatment failures and carriers: perception or problems? *Pediatr Infect Dis J* 1994; 13:576 -579.
65. Feinstein AR, Wood HF, Epstein JA, et al. A controlled study of three methods of prophylaxis against streptococcal infection in a population of rheumatic children, II: results of the first three years of the study, including methods for evaluating the maintenance of oral prophylaxis. *N Engl J Med* 1959; 260:697-702.
66. Markowitz M, Gerber MA, Kaplan EL. Treatment of streptococcal pharyngotonsillitis: reports of penicillin's demise are premature. *J Pediatr* 1993; 123:679-685.
67. Report of expert consultation on rheumatic fever and rheumatic heart disease 29 October-1 November 2001. World Health Organization. Available from: URL: http://www.who.int/cardiovascular_diseases/resources/en/cvd_trs_923.pdf. Accessed February 21, 2008.
68. Kumar R, Thakur JS, Aggarwal A, et al. Compliance of secondary prophylaxis for controlling rheumatic fever and rheumatic heart disease in a rural area of Northern India. *Indian Heart J* 1997; 49: 283-288.
69. Lue HC et al. Rheumatic fever recurrences: controlled study of 3-week versus 4-week benzathine penicillin prevention programs. *Journal of Pediatrics* 1986; 108:299-304.
70. WHO model prescribing information. Drugs used in the treatment of streptococcal pharyngitis and prevention of rheumatic fever. Geneva, World Health Organization, 1999 (WHO/EDM/PAR/99.1)
71. International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet* 1991; 337:1308-1310.
72. Markowitz M, Lue HC. Allergic reactions in rheumatic fever patients on long term benzathine penicillin G: the role of skin testing for penicillin allergy. *Pediatrics* 1996; 97 suppl S: 981-983.
73. Idsoe O et al. Nature and extent of penicillin reactions, with particular reference to fatalities from anaphylactic shock. *Bulletin of the World Health Organization* 1968; 38:159-188.
74. Redelmeier DA, Sox HC. The role of skin testing for penicillin allergy. *Archives of Internal Medicine* 1990; 150 suppl 9:1939-1945.
75. Carapetis JR. Acute rheumatic fever. Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, Loscalzo. Eds. *Harrison's Principles of Internal Medicine*. United States of America. The McGraw-Hill Companies, Inc, 2008; vol II: 2092-6.
76. Bonow RO et al. ACC/AHA guidelines for the management of patients with valvular heart disease. *Journal of the American College of Cardiologists*. 1998; 32:1486-1588.
77. Stewart WJ, Carabello B. Chronic aortic valve disease. In: *Textbook of Cardiovascular Medicine*. Lippincott, Williams & Wilkins: Philadelphia; 2003.
78. Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia An evidence-based review. National heart foundation of Australia and the cardiac society of Australia and New Zealand, June 2006.
79. Shrivastava S. Rheumatic heart disease: Is it declining in India? *Indian Heart J* 2007; 59:9-10.
80. Padmavati S. Rheumatic fever and Rheumatic heart disease in India at the turn of the country. *Indian Heart Journal* 2001; 53:35-37.