

REVIEW FOR THE PRIMARY CARE PHYSICIAN RHEUMATIC FEVER

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INTRODUCTION

In spite of the dramatic decline of acute rheumatic fever (RF) and rheumatic heart disease (RHD) in developed nations, there is still a significant morbidity and mortality in developing countries. Although accurate data on the incidence of RF are lacking in developing countries, estimates range from 100 to 200 per 100,000 school aged children per year while in developed nations the mean annual incidence is 0.5/100,000 in children of the same age (1). Over 12 million people are affected by rheumatic fever worldwide and approximately 40,000 deaths result from rheumatic heart disease annually, mainly among children and young adults. It is estimated that two million patients now require heart surgery due to RF and one million more will require heart surgery in the next 5 to 20 years (2).

EPIDEMIOLOGY

Risk factors pertaining to the 3 components of classical epidemiologic triad – agent, host and environment – have been identified as important determinants of disease distribution in the population.

The etiologic agent – To initiate acute RF, the site of infection caused by a strain of group A beta hemolytic streptococcus (GABHS) must be pharyngeal. Yet, not all strains that infect the pharynx cause acute RF. All age groups can be infected by streptococcus, but RF usually occurs among school-age children, where the prevalence of group A streptococci isolated from sporadic pharyngitis varies from 20 to 35%. The infection is asymptomatic in half of the patients and the diagnosis can be documented only retrospectively by a rise of antistreptococcal antibodies. It is important to differentiate the carrier state from actual infection. Detection of GABHS from the throat does not necessarily indicate a recent active infection and a rise of an immune response to the bacteria is an additional prerequisite (3).

Attack rates of RF are related to the virulence of the infecting strains and possibly by the capacity of the immune response of the host. In the 1950's, it was reported that 3% of untreated epidemic streptococcal pharyngitis in military recruits in the US resulted in RF (4, 5). In civilians and in children the rates were about 0 and 3%, respectively (6-10). The risk of recurrences of RF is still high in patients following repeated episodes of GABHS pharyngitis and in the pre-antibiotic era, 50% or more of patients had one or more recurrent attacks of RF during their lifetime (11, 12).

Epidemiologic observations during epidemics of streptococcal infections associated with RF outbreaks suggest that the “rheumatogenic” potential could be closely linked to the streptococcal virulence. The virulence appears to be linked to the protein M present in the streptococcal cell wall. The protein M has the ability to resist phagocytosis by neutrophils (13, 14) and may also be an attachment factor providing the bacterium with an adherence advantage (15). Although there are approximately one hundred different serotypes of streptococcus based on the protein M, only a limited number of streptococcal M-types have been isolated or have been associated with one or more outbreaks of RF.

Other extracellular and cell-associated products of streptococcus could play a role in the virulence. These products include the presence of hyaluronate capsules that may make

strains more resistant to phagocytosis and lipoteichoic acid on the streptococcal surface that is responsible for the ability to adhere to pharyngeal mucosa.

The host - RF affects mainly children between 6 and 15 years, is uncommon in children under 5 years, and rare in children younger than 3 years. The frequency of the disease declines after puberty and is rare in adulthood. Both sexes are equally affected although there is a slight predominance of chorea in females. RF is reported in all ethnic groups although living conditions, socioeconomic status, and access to health care may be more important and represent potential confounders.

The first evidences of genetic predisposition for the disease were based on a higher predisposition to RF in certain families (16,17) as well as the higher incidence of concordance of RHD among monozygotic twins (18.7% of 56 twin pairs) compared to dizygotic twins (2.5% of 40 pairs) (18). More recently a variety of genetic markers such as class II HLA haplotypes and a specific B-cell alloantigen (D8/17) were noted to be associated with a higher incidence of RF in certain populations. In fact, significant associations were encountered for the class II HLA-DR alleles, but these differences were related to the ethnicity of the populations studied. The diversity of these associations raised a number of questions regarding the absence of a clear association between susceptibility to RF and a specific HLA-DR (19-22). The specific B-cell alloantigen (D8/17) has been identified in a high percentage of B cells in most RF patients, but a commercial test for this alloantigen is not yet available to the clinician. Furthermore, the costs of these tests and the low specificity and sensitivity do not allow their use as a preventive strategy directed towards individuals predisposed to RF (23).

The environment – Overcrowding and poor access to health care, both linked to socioeconomic development, seem to be the most important determinants of disease distribution. Seasonal variations in RF are not pronounced in the tropics (24), although in temperate climates, streptococcal infections have a peak in late winter and early spring.

PATHOGENESIS

A complete understanding of the pathogenesis of RF remains elusive. The etiologic agent is the GABHS and the site infected is the throat. However, how and why a small percentage of patients develop RF is still under investigation. The latent period between the

streptococcal infection and the clinical manifestation of rheumatic fever associated with the evidence of molecular mimicry between streptococcus structures and human tissues favor the hypothesis of a cross reaction between the streptococcus and the host (25,26). In fact, it is believed that the pathogenicity is related to development of autoimmunity as several humoral and cellular immune responses can be observed in patients with RF (27).

Some streptococcal antigens, such as protein M, can cross-react with human tissues and this could induce a specific immunological response in some genetically predisposed patients. Besides the well studied humoral immunity related to the presence of cross-reaction antibodies in patients with rheumatic fever (myocardium, valves, cartilage, nervous system), attention has recently been drawn to the involvement of cellular immunity in RF. The contribution of cellular immunity has been suggested by changes in the number and function of lymphocytes in the peripheral blood in different phases of the disease (28). The presence of several markers of cellular immunity activation, including a higher production of cytokines, has been observed in some RF patients (29). However, the most direct evidence linking cell mediated immune response against streptococcal proteins to the pathogenesis of RHD came from the studies of Guilherme et al (30). They generated T cells clones from rheumatic valvular tissues and demonstrated that these clones recognized specific epitopes of the M5 type protein. More recently, the role of superantigens in the pathogenesis of RF has been suggested. In fact, some structures of GABHS, including protein M, have superantigen properties (31-33).

CLINICAL MANIFESTATIONS

RF is a multisystemic disease affecting multiple organs: heart, joints, central nervous system and skin (1). The beginning of the symptoms usually occurs after a latent period from 1 to 3 weeks (mean 18 days) after a streptococcal pharyngitis caused by GABHS and does not become shorter in repeated attacks. Onset may be acute or insidious. Usually acute attacks are associated with arthritis or carditis with pericardial effusion. Insidious onset of RF is seen in some cases of carditis and chorea, in which early behaviour changes may be misinterpreted.

Arthritis- Arthritis is the commonest mode of onset and tends to occur early in the disease. In the first attack of RF, approximately 60 to 75% of children have arthritis as the major sign.

The classic pattern is migratory polyarthritis with overlap of joint involvement. Pain is more marked than swelling and frequently leads to functional impairment. In general, arthritis starts in large joints but it can also affect the small ones. The most common sites of involvement are knees (75%) and ankles (50%), followed by elbows, wrists, hips and small joints of feet (12-15%). Shoulders and small joints of the hands are the least involved (7-8%). Rarely, spine and temporomandibular joints are involved. Arthritis is usually self-limited: each joint swelling lasts from few days to one week and the total episode rarely lasts more than one month. The therapeutic response to anti-inflammatory doses of aspirin or other NSAID's is considered an important clue to the diagnosis as it stops pain in 24 hours and the other inflammatory signs in 2 or 3 days.

Some patients can exhibit a different pattern of arthritis adding some difficulty to the diagnosis, mainly when there is no other major sign of RF. They can show an additive and more prolonged duration of arthritis and a weak response to NSAID's, in the same way as it has been described in poststreptococcal reactive arthritis (34-35). Monoarthritis can occur but it is usually related to the early use of nonsteroidal anti-inflammatory drugs before the disease is fully expressed in its migratory pattern.

Carditis - Heart involvement occurs in 40-50% cases of initial attack. It is the most serious manifestation as it can cause a permanent damage - rheumatic heart disease (RHD) - or can be fatal.

All cardiac structures such as endocardium, myocardium and pericardium may be involved but the lesion that defines carditis is mitral regurgitation in 98% (being the only involved valve in 70 to 75% of the patients) or isolated aortic regurgitation in 2%.

Carditis onset is quite variable. Its severity may range from asymptomatic to severe. It can be diagnosed as an isolated manifestation or together with other major signs. Asymptomatic carditis often is detected in patients who present with arthritis or develop chorea. In general, older patients present more with carditis associated with arthritis. The articular pain often brings the patient to the doctor who then makes the diagnosis of carditis

as well. In these cases, usually carditis appears in the first 2 weeks of arthritis onset. After the first two weeks, the chance of developing carditis is reduced. However, younger patients often have an insidious onset of isolated carditis, and 50% of all patients diagnosed with RHD don't recall any past history of joint pain.

Auscultatory findings are the most indicative findings of carditis. Tachycardia and murmur are the commonest clinical manifestations of carditis. Tachycardia is not related to fever and basal pulse rate is high. Mitral regurgitation is manifested by an apical, high pitched, blowing, holosystolic murmur. It may be accompanied by a low-pitched, short, mid-diastolic murmur (Carey-Coomb's murmur) which does not have a presystolic accentuation typical of mitral stenosis and disappears on follow-up. The severity of mitral regurgitation is of prognostic significance, as in the majority of patients with mild or moderate mitral regurgitation, the lesion disappears on follow-up (36). Aortic regurgitation is present in 20 to 25% of the patients and is manifested by a high-pitched, soft, decrescendo murmur. Tricuspid valve and pulmonary valve lesions are rarely clinically significant (37). If the valvular insufficiency persists or later on evolves to stenosis, rheumatic heart disease (RHD) is the accepted terminology.

Pericarditis is associated with small to moderate effusions but never produces cardiac tamponade. Clinically it is present in 6 to 15% of the patients and is usually suspected in the presence of precordial discomfort or pain or a pericardial rub (scratchy, leathery sound altered by varying pressure of stethoscope) heard in both phases of cardiac cycle. Myocarditis is confined to the interstitium and does not usually result in significant myocyte damage, consistent with the preserved left ventricular ejection phase indices seen in patients with active rheumatic activity.

Severe carditis comes with cardiac failure and may be fatal in the acute stage. In cases of severe carditis, cardiomegaly, a third heart sound and symptoms of cardiac failure may be present. It is now believed that rheumatic myocarditis is not the primary cause congestive heart failure in patients with acute carditis. It is important to note that pathologic data show little damage in the myocardium in patients dying from RF (38) and cardiac failure does not occur in the absence of significant valvular lesions (39).

The diagnosis of a new flare of carditis in a patient with an established RHD may be difficult. Cardiac manifestation such as pericardial friction rub, a new murmur or worsening

of a pre-existent one, increasing heart size, unexplained congestive cardiac failure in the presence of evidence of recent streptococcal infection should be considered highly suspicious for the diagnosis of recurrence of active rheumatic carditis.

Silent carditis is a term used to define patients with subclinical carditis, without murmur but in whom valve regurgitation is detected by Doppler echocardiography. However, according to the last revision of Jones' criteria in 1992, this exam by itself can not be considered as evidence of carditis. The use of echocardiography to document carditis without auscultatory findings remains controversial.

Chorea - Chorea occurs in approximately one-third of the patients with RF. It is characterized by an array of neuropsychiatric symptoms that vary in severity, timing and character (40). The latent period can be long, as much as 9 months, so that no evidence of previous streptococcal infection can be found. The onset can be associated to other RF manifestations, mainly carditis, during an acute episode or as an isolated form characterizing the "pure" chorea in 35%. Follow up of patients with pure rheumatic chorea has shown RHD in 23 % in a 20-year period (41). Thus, chorea may be a good marker for future occurrence of valvar heart disease.

Clinically, the main features are involuntary movements, diffuse hypotonia, dysarthria, emotional disorders and less frequently by other neuropsychiatric manifestations (42). Emotional lability precedes the onset of chorea movements. Most reported are impatience, irritability and inattention to school-work. However, in the last decade, more severe neuropsychiatric abnormalities, such as obsessive compulsive and tics disorders, have been associated with chorea. Incoordination and involuntary movements are initially perceived as clumsiness and as a tendency to drop objects. Then, purposeless, unilateral (hemichorea) or bilateral movements become evident. All voluntary muscles may be involved although they can be suppressed voluntarily for short time. During the physical examination, the physician should observe involuntary movements in face, tongue, hands, where they are more evident. Some tests to detect them include: quality of handwriting, slurred speech when counting from 1 to ten, milking sign when gripping the examiner hand, spooning or dishing of hands (flexion of wrist and hyperextension of MCP) when extending hands and pronator sign (pronation of hand) when raising hands above the head. The

difficulties can become more evident when asking to perform 2 or more motor functions, one after another.

Subcutaneous Nodules - They are infrequent as they occur in less than 10% of the patients and their presence usually suggests an underlying carditis. They are rare in adults. Usually they appear after some weeks after the first few weeks of cardiac findings. Subcutaneous nodules are small (few mm to 1-2 cm in size), round, firm, painless, multiple on bony prominences or extensor tendons without signs of skin inflammation. They are better felt than seen.

Erythema Marginatum - This is an infrequent manifestation of RF (less than 5%) and due to its evanescent nature and lack of associated symptoms, it can often be missed in patients with dark skin. It is nearly always indicative of underlying carditis. It is an early manifestation of RF but may reappear at later stages. It is seen on the trunk and proximal limbs, but the face is spared. It is a non-pruritic, transient rash, 1-3 cm in size with a slightly raised periphery and clear central skin.

Other manifestations:

Arthralgia and fever are not rare but are not specific of RF, being considered minor signs according to Jones' criteria. Arthralgia can be present for days or weeks and should be considered as a minor sign only in patients without arthritis. Fever usually occurs in all patients with arthritis, can be low in carditis and never occurs in isolated chorea. There is no characteristic pattern and often lasts only 1 week.

LABORATORY INVESTIGATIONS

There is no specific diagnostic laboratory test for RF. Lab exams can only demonstrate a recent streptococcal infection, the presence of inflammation, and the presence and severity of heart disease. Other tests can be performed initially to exclude other diseases in the differential diagnosis.

Evidence of a recent streptococcal infection

Throat cultures – Only 20% of throat cultures are positive for GABHS in patients with RF. This low rate occurs because of the latent period between the infection and symptoms onset and sometimes due to previous use of antibiotics.

Rapid antigen detection – The specificity of this test is high (over 95%) but not the sensitivity (43). Its positivity is equivalent to a positive culture throat.

Streptococcal antibody tests – GABHS have many antigens and antibodies directed towards some of them have been utilized to identify a previous streptococcal infection even in asymptomatic cases. The most utilized is anti-streptolysin O (ASO). When the first symptoms of RF present, titers generally are high due to the latency period. ASO antibodies start to appear 7 to 10 days after onset of the infection, reach the maximum between the second and third weeks, and maintain this plateau for 3 to 6 months and then decline (44). As chorea has a long latency period, many times there is no evidence of streptococcal infection at the time of diagnosis. If a test is positive in a patient with arthritis, it does not mean that the diagnosis is RF but only that the patient had a previous streptococcus infection.

Unfortunately, in approximately 20% of patients with RF, the ASO titer may be normal. In these cases, this test should be repeated after 2 or 4 weeks to check if the titer increases. If it continues to be negative, other antibodies, such as anti-DNaseB and anti-hyaluronidase, should be performed in order to improve the capacity to confirm a previous infection. All three tests together establish the diagnosis of previous streptococcal infection in 95% of the patients (45). However, in most of developing countries, where the incidence of RF is high and resources are limited, the only test available is ASO and sometimes it seems better to treat a suspected case of RF despite a normal ASO titer result.

Tests for systemic inflammation

Acute phase reactants are non-specific and only indicate the presence of an inflammatory process. They help to confirm and monitor the acute phase of the inflammation. Erythrocyte sedimentation rate (ESR) and C-reactive protein are the main tests used in RF as both are often abnormal during the period of carditis and arthritis. Neither is specific but both are very sensitive and reflect the magnitude of the inflammatory

process (rheumatic activity). C-reactive protein is better than ESR because it should be negative in healthy subjects whereas false positive elevations of ESR may occur.

Tests for recent carditis:

Electrocardiographic abnormalities can occur during an episode of acute rheumatic carditis. The most important finding, although non-specific, is the increased PR interval, present in 28-40% cases with carditis.

Currently, chest radiographs are not important in the diagnosis of rheumatic fever as Doppler echocardiography is the best non-invasive method to evaluate and follow cardiac changes. It can evaluate chamber size, systolic ventricular function, detect presence of pericardial effusion and demonstrate absence or presence of valve lesions and abnormal regurgitation. Doppler echocardiography is able to identify subclinical carditis in patients with RF who do not have audible murmurs.

PATHOLOGY

Arthritis - Histologically, there is swelling of the articular and periarticular surfaces, but there is no erosion of the articular surface. Synovial fluid may be turbid but non-purulent. Initially there is a predominance of neutrophils but later on, mononuclear cells predominate. Fibrin may be enmeshed with the exudative cells. Swelling and fibrinoid degeneration of the connective tissue occurs.

Carditis - The morphologic hallmark of cardiac involvement in RF is the Aschoff body which is not described in any other cardiovascular disorder. Typically it is a granulomatous lesion, round to oval, usually less than 1 mm in size and found almost always in the endocardium, subendocardium or perivascular regions of myocardial interstitium. Aschoff bodies may be seen years after the initial illness and do not correlate with the activity of the disease.

Usually pericarditis with myocardial damage predominates in severe cases. Pericarditis is accompanied by a serofibrinous effusion, but does not cause constriction at any time. Myocardium is flabby, edematous or pale. Chambers are enlarged. Heart enlarges due to dilatation of chambers or hypertrophy of the heart musculature. Within the

muscle there is an exudative inflammatory response with lymphocytosis and plasma cells in the interstitium. Aschoff bodies are much less frequent in the myocardium (5% of cases) compared to the endocardium (72%) (39).

Endocarditis is always present. Acute inflammation of valves is characterized by tiny translucent vegetations of 1 to 2 mm in diameter on the atrial surface at sites of the valve closure and on chordae tendinae. The valves have inflammatory infiltrate, edema and vascularization. Repeated fibrin deposits on the valve cusp results in fibrosis of the valvular ring causing stenosis (e.g. mitral stenosis). Later, commissures may be fused and chordae tendinae may be retracted and fused. Valve lesions are often responsible for cardiac failure. Calcification of valve leaflets occurs over a time. The most frequent valves involved are mitral and aortic valves, while right sided valves are rarely involved. The endocardium and subendocardium regions away from the valves are often inflamed and Aschoff bodies are frequently present.

Chorea - The main histological features were described in the cortex, cerebellum and basal ganglia. They consist mainly in perivascular infiltration, petechial hemorrhages, and hyalinisation of small blood vessels.

Subcutaneous Nodules - Histologically, a nodule consists of fibrinoid material in strands with clear space in between. There is much edema with very few cells- fibroblasts or histocytes and occasional lymphocytes. There is no palisading characteristically seen in rheumatoid nodules.

DIAGNOSIS

In spite of significant advances, there is no single laboratory test to establish a diagnosis of RF. It is still based on Jones' criteria, proposed initially in 1944 and reviewed and modified four times, in order to avoid missed diagnosis or overdiagnosis. The most important items are the identification of at least one major sign (polyarthritits, carditis, chorea, erythema marginatum and subcutaneous nodules) and the detection of a previous streptococcal infection.

In the last revision of Jones' criteria (1992) (46) (Table. 1), the basic rule for the diagnosis - presence of two major or one major and two minor signs together with an evidence of streptococcal infection - was not altered but, for the first time, this formula was to apply only to the initial attack of RF. They also recognized and accepted three exceptions where diagnosis could be done without strict adherence to the criteria: recurrent attacks in which signs and symptoms could be less apparent, insidious or late onset carditis or chorea as the only manifestation of RF (pure chorea). In these patients, the diagnosis should be presumptive until other causes have been excluded.

Table I: Modified Jones' Criteria for diagnosis of RF:

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS
Carditis	Fever
Polyarthrititis	Arthralgia
Chorea	Elevated acute phase reactants: erythrocyte sedimentation rate, C- reactive protein
Erythema marginatum	Prolonged PR interval on ECG
Subcutaneous nodules	
SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION: Positive throat culture or rapid streptococcal antigen test or an elevated or rising streptococcal antibody titer	

TREATMENT

Treatment of RF should be directed toward suppressing the ongoing inflammatory process in its different presentations, eradicating GABHS still present in the throat, and preventing new recurrences that could cause more damage in the future.

Treatment of the clinical manifestations

Arthritis

Acetylsalicylic acid was the first anti-inflammatory drug to be used in the treatment of RF. In arthritis, anti-inflammatory doses usually are used as a diagnostic test as the response is often dramatic. Pain ceases in one day and the other inflammatory signs in two days, a pattern that is not observed in several other causes of polyarthritis. An initial dose of 80 mg per kilogram per day, in 4 or 5 divided doses is usually well tolerated and does not cause important hepatotoxicity. It is recommended to give this dose during the first two weeks and then taper it over the next 3 or 4 weeks. Nowadays, other nonsteroidal antiinflammatory drugs have been used with the same efficacy. Rest is only necessary during the acute phase.

Carditis

Bed rest is advisable for all patients and should be proportional to the severity of the disease and continue as long as necessary. Steroids are more potent antiinflammatory drugs than salicylates as they can cause a more rapid improvement of acute manifestations of carditis, although they do not alter the course of rheumatic fever and subsequent development of rheumatic heart disease. There is still some controversy as to whether steroids are better than salicylates for mild carditis, but according to the guidelines for treatment of patients with RF (47), the use of corticosteroids should be reserved for patients with severe rheumatic carditis.

Many experts in developing countries prefer to treat all cases of carditis (mild to severe) with steroids and do not feel that it is necessary to add salicylates at the end of the treatment. They suggest starting with an initial high dose (2 mg/kg / day – maximum 60 mg/day) during the first 3 weeks and then decreasing the dose by 20% every week. This treatment will be completed, on average, in 6 to 8 weeks and it will be not necessary to add acetylsalicylic acid. Some authors recommend the use of intravenous methylprednisolone in severe cases of heart failure (48), but occasionally, surgical intervention will be indicated in patients with refractory congestive heart failure (39).

Immunological mechanisms appear to be involved in the pathogenesis of acute rheumatic fever but intravenous immunoglobulin did not alter the natural history of acute

RF. There was no evidence of reduction in the extent and severity of carditis, more rapid resolution of inflammatory activity, or decreased chronic morbidity (49). In established rheumatic heart disease, recurrence of carditis may present as congestive heart failure. Both the carditis as well as congestive failure need to be treated.

Chorea

Bed rest is required only for severe attacks to prevent injury. Several drugs have been used to treat chorea with varying success. Since choreiform movements are known to be influenced by emotional stress, there has been some success with sedative drugs especially phenobarbital, diazepam, and chlorpromazine. Other drugs used successfully are haloperidol and valproic acid. (49-51). Recently, in a double blind study using prednisone and placebo in 37 children with chorea, the authors could demonstrate a significant reduction of symptoms in the first week of treatment, and this response was maintained until the end of the study ($p < 0.001$) (52). Medication should be given until chorea is controlled and then gradually tapered.

Erythema marginatum and subcutaneous nodules

These manifestations do not require specific medication.

Treatment of streptococcal pharyngitis and prophylaxis

It is difficult to be sure if there is still streptococcal infection in the throat of a patient with RF at the diagnosis. Therefore, all patients should receive antistreptococcal antibiotics. In developing countries, benzathine penicillin is the preferred drug, followed by oral penicillin or erythromycin for penicillin allergic patients (**Table 2**).

Table 2: Streptococcal eradication

Benzathine Penicillin

- Patients > 27 Kg: 600.000 U, IM
- Patients < 27 Kg: 1.200.000 U, IM

Oral penicillin for 10 days

Erythromycin

- 20 mg to 40 mg/kg in 2 to 4 divided doses for 10 days

To prevent recurrent RF, it is essential to start a secondary prophylaxis as soon as the diagnosis is established. Preferentially it should be done with benzathine penicillin in the same doses used to eradicate streptococci given every 3 weeks. Other options are oral penicillin or sulfadiazine (1 g once a day) or erythromycin for allergic patients.

There is no agreement about the duration of secondary prophylaxis. In some developing countries, for patients without carditis, it can be withdrawn at the age of 18 since the patient has received the prophylaxis for a minimum of 5 years. In patients with carditis, it is advisable to continue prophylaxis until at least the age of 35. There is even less evidence-based medicine and agreement in prophylaxis of children with rheumatic fever without carditis or for post-streptococcal arthritis (**Table 3**).

Table 3: Secondary prophylaxis
Benzathine Penicillin each 21 days
• Patients < 27 Kg: 600,000 U , IM
• Patients > 27 Kg: 1,200,000 U, IM
Benoxymethylpenicillin
• 250 mg twice a day
Sulfadiazine
• Patients < 27 Kg: 0,5 g/day
• Patients > 27 Kg: 1g /day
Duration:
• No carditis: until 18 years old (and minimum of 5 years)
• With carditis: until at least 35 years old (or life long)

OUTCOME

Recurrences of RF often have the same clinical pattern as the previous attack. Patients with chorea or arthritis have the best prognosis. The prognosis is usually good

with a full recovery. Patients with chorea generally have good prognosis with a full recovery. However, rheumatic heart disease can be diagnosed years after the initial attack of chorea and this possibility should be considered carefully in respect to maintaining secondary prophylaxis. Chorea can rarely recur after an intercurrent illness, drug exposure or pregnancy.

The outcome of carditis has a wide range of possibilities - from total recovery (with risk of recurrences) to death due to cardiac failure. Between these two ends of the spectrum are various kinds of chronic RHD. Approximately 58-74% lose evidence of cardiac involvement. This occurs mainly in patients with a single valve (mostly mitral) involvement without cardiomegaly. However, it rarely occurs in patients who present with multiple valve involvement, cardiomegaly and cardiac failure. Mitral stenosis develops later but it is more precocious in developing countries. Chances of recurrence are higher (50%) within the first 6 months of the initial attack and lessen to only 10% after 5 years.

Death is rare during the first attack but the chances increase during recurrences, especially in patients with pre-existing heart involvement. If the heart is spared in the first attack, it is likely to be spared in subsequent occurrences. Patients with valvular disease should be educated on how to avoid infective endocarditis. Specific prophylaxis should be given before any minor or major surgical procedure, including minor suturing and removal of tartar from teeth. **(Table 4)** (53).

Table 4: Infective Endocarditis Prophylaxis
For almost all patients, the drug is given one hour before the procedure unless mentioned otherwise.
1. Oral Amoxicillin 50mg/kg, it may be given IM or IV. Adults: 2 gms.
2. For patients with Amoxicillin/ Ampicillin allergy:
• Oral Clindamycin 20 mg/kg. Adults: 600mg.
OR
• Oral Cephalexin or Cefadroxil 50mg/kg. Adults: 2.0gm
OR

<ul style="list-style-type: none"> • Oral Azithromycin or Clarithromycin 15 mg/kg. Adults: 500 mg
OR
<ul style="list-style-type: none"> • IV Clindamycin 20mg/kg. Adults: 600 mg
OR
<ul style="list-style-type: none"> • IV Cefazolin 2.5 mg/kg. Adults: 1.0 gm
3. If gastrointestinal or genitourinary surgery is contemplated, then the following drugs can be given:
High risk procedure:
<ul style="list-style-type: none"> • IV Ampicillin/ Amoxicillin 50 mg/ kg + Gentamycin 1.5 mg/kg 30 minutes • before the procedure and 6 hours after the procedure.
High risk procedure in patients with Amoxicillin allergy:
<ul style="list-style-type: none"> • IV Vancomycin 20 mg/kg (Adults 1gm) over 1-2 hours + IV Gentamycin 1.5 mg/kg 30 minutes before the procedure.
Moderate risk surgery:
<ul style="list-style-type: none"> • Only IV or IM Amoxicillin 50 mg/kg (Adults: 1gm)
Moderate risk surgery in patients with Amoxicillin allergy:
<ul style="list-style-type: none"> • Vancomycin 20 mg/kg (Adults: 1gm) over 1-2 hours.

In summary, rheumatic fever is still a major health problem in many developing countries and still occurs in developed countries. It is a systemic illness whose effects, particularly cardiac, can be devastating. Its cause is well-known but the immune mechanisms remain poorly understood. Prevention awaits a better understanding of who is susceptible and how to prevent the triggering streptococcal infections in a practical and cost-effective manner.

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