Acute rheumatic fever
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INTRODUCTION
The term acute rheumatic fever describes the usual presentation of the disease, although it may not be acute, rheumatic, or febrile. Arthritis is common in acute rheumatic fever, but the morbidity and mortality of the disease are usually related to involvement of the heart. These observations were made as early as 1884 by Lasègue, who noted that “rheumatic fever is a disease that licks the joints but bites the heart.” The subject of rheumatic fever and rheumatic heart disease was reported in detail by the World Health Organization (WHO) in 2004 arising from a WHO Expert Consultation held in Geneva during 2001 and also reviewed recently by Carapetis and colleagues.

EPIDEMIOLOGY
Acute rheumatic fever was common in Europe and North America at the beginning of the 20th century. Since then there has been a rapid decline in the incidence of the disease in industrialized countries, and this was further accelerated with the introduction of antibiotics in 1950. At present the average incidence recorded in most affluent or developed countries is less than 5/100,000 population.

A reduction in the incidence of acute rheumatic fever in industrialized countries in Europe and North America and also in Japan suggested that improvement in living conditions with less overcrowding and better hygiene as well as the widespread availability and use of antibiotics were responsible in the United States the incidence of rheumatic fever was as low as 0.23 to 1.88/100,000 per year among children and adolescents in the early 1980s and had risen nearly 10-fold in some areas by the mid 1980s. A large outbreak in Utah was followed by smaller outbreaks in Pennsylvania and Ohio and in military bases in San Diego and Missouri. During the Utah outbreak most of the affected children were from upper middle-class homes with access to medical care, emphasizing the importance of factors other than poverty and overcrowding in the pathogenesis of this disease.

Studies from developing countries have reported incidence rates varying from 1.0/100,000 schoolchildren in Costa Rica, 72.2/100,000 in French Polynesia, 100/100,000 in Sudan to 150/100,000 in China. A systematic review of population-based incidence studies shows an overall mean incidence of first attack of acute rheumatic fever of 5 to 51/100,000 people. The low incidence rate of less than or equal to 10/100,000 is confirmed in Western Europe and North America, whereas a persistently high incidence (>10/100,000) exists in Eastern Europe, the Middle East, Asia, and Australasia [Fig. 108.1]. There are no population-based studies of first attack of acute rheumatic fever in Africa.

The prevalence rate of rheumatic heart disease in developed communities is usually 0.2 to 0.5/100,000. By contrast, there is still an unacceptably high prevalence of rheumatic fever and rheumatic heart diseases in developing countries. The prevalence of rheumatic heart diseases among schoolchildren in developing countries around the world has been recently reviewed. The prevalence has ranged from 0.2/1000 schoolchildren in Havana, Cuba, to 77.8/1000 schoolchildren in Samoa. In India, the prevalence of rheumatic heart disease is between 1.5 and 5.6 cases/1000. In Africa the prevalence rate from recent studies has ranged from 2.7/1000 schoolchildren in Nairobi (Kenya) to 14.8/1000 in Kinshasa (Democratic Republic of the Congo) and 31/1000 according to echocardiographic studies in Maputo (Mozambique).

At the time of the resurgence of acute rheumatic fever in the United States, cases of invasive, life-threatening streptococcal infections were reported in the United States, United Kingdom, Scandinavia, and other parts of Europe. This toxic streptococcal syndrome was characterized by localized or generalized rash, hypotension, and multiorgan failure. It occurred mainly in adults and resulted from cutaneous or soft tissue infections with streptococci of type I and strains producing pyrogenic toxin A. It has been proposed that changes in streptococcal epidemiology are related to changes in the virulence of the Streptococcus strains.

GROUP A STREPTOCOECCUS
Structure
Streptococci are a group of gram-positive bacteria that are morphologically characterized as coccis and are arranged in chains. Streptococcus pyogenes, also referred to as the group A streptococcus, belongs to the group of hemolytic streptococci that have in common their ability to produce toxins that are capable of lysing red blood cells. The cell wall of the group A streptococcus shows the characteristics of gram-positive bacteria. The cytoplasmic membrane is surrounded by a thick peptidoglycan layer that acts as an outer skeleton. This layer is covered by the surface layer [S-layer] containing carbohydrates, proteins, and glycoproteins. These include the group-specific carbohydrate, which is a rhamnose-N-acetyl-glucosamine dimer that may cross react with the glycosides of the heart valves. The S-layer also contains the M proteins, which have a considerable variation in their molecular structure. These allow group A streptococci to be differentiated into more than 130 M-serotypes.

M protein plays a role in the pathogenesis of streptococcal infections with different M-types associated with different disease manifestations. Several of these M-types are associated with acute rheumatic fever. M protein also offers escape from immunity by inhibiting complement activation and phagocytosis. M-like proteins bind to the Fc portion of IgG and IgA molecules irrespective of their antigen specificity. This results in a layer of human immunoglobulins around the bacteria with the Fab portion facing outward. This prevents phagocytosis and immune recognition. The cell wall is surrounded by a hyaluronic acid capsule. Because the molecular structure is very similar to that of human hyaluronic acid, this provides additional protection against the innate immune forces. Some of the rheumatogenic M-types are characterized by a thick capsule, resulting in the mucoid appearance of the colonies when grown on a blood agar.

The cytoplasmic membrane is made up of antigenic lipoproteins that cross react with the glomerular basement membrane and sarcolemmal antigen.

Acute rheumatic fever is a systemic inflammatory disease that occurs 2 to 3 weeks after infection with group A β-hemolytic streptococci.

The disease is mediated by an autoimmune response to antigenic components of the organism that cross react with similar epitopes in human tissues such as the heart, joints, brain, and skin.

The acute form of the illness is characterized by the following:
- Fever
- Arthritis, which is usually migratory and affects predominantly the large joints
- Cardiac manifestations due to involvement of the pericardium, myocardium, endocardium, and heart valves
- Neurologic involvement, which manifests as Sydenham chorea
- Cutaneous involvement, consisting of erythema marginatum and subcutaneous nodules, which are less common
ANNUAL SPECIFIC INCIDENCE RATE (TEMPORAL TREND) OF FIRST ATTACK OF ACUTE RHEUMATIC FEVER

![Graph showing annual specific incidence rate of first attack of acute rheumatic fever](image)

**Fig. 108.1** Serial changes in the incidence of first attack of acute rheumatic fever in population-based studies. (From Tibazawana KB, Volfmink JA, Mayosi BM. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. Heart 2008;94:1534-1540.)

### Streptococcal toxins
The streptococcus produces many extracellular products, which include the erythrogenic toxin, streptolysin O, streptolysin S, streptokinase, diphosphoryridine nucleotidase, and deoxyribonucleases. Streptolysin O elicits an antibody response, antistreptolysin [ASO], which is the basis of the antibody assay. The antigenicity of streptolysin O is inhibited by lipid in the skin, and this may account for the lack of association between streptococcal skin infections and rheumatic fever. The streptococcus has many antigens that are similar to mammalian tissue and may cross-react with the joint, heart (myocardium, valvular tissue), skin, kidney, and brain.

### Rheumatic fever and the streptococcus
Epidemiologic studies have shown a causal relationship between group A streptococcal pharyngitis and acute rheumatic fever. However, not all group A streptococcal infections cause rheumatic fever even if the site of the antecedent infection is pharyngeal. A survey among untreated military recruits with pharyngitis reported acute rheumatic fever in 3%. Acute glomerulonephritis may be associated with streptococcal pyoderma owing to certain strains of group A streptococci that show primary tropism for the skin. Acute rheumatic fever and acute post-streptococcal glomerulonephritis rarely occur together.

There is little evidence for the direct invasion of the affected tissues by group A streptococci in patients with acute rheumatic fever. The role of group A streptococcal infection in acute rheumatic fever is supported by the following observations:

- Outbreaks of rheumatic fever follow epidemics of either streptococcal sore throat or scarlet fever.
- Treatment of documented streptococcal pharyngitis markedly reduces the incidence of subsequent rheumatic fever.
- Antimicrobial prophylaxis prevents recurrence in known patients with acute rheumatic fever.
- Most patients will have elevated titers of antistreptococcal antibodies [streptolysin O, hyaluronidase, and streptokinase] regardless of whether they recall an antecedent streptococcal sore throat.

### PATHOGENESIS
The pathogenesis of acute rheumatic fever has been reviewed in detail. Carapetis and colleagues suggested, in 1996, that the pathogenesis could be considered on the basis of factors related to the host [genetic susceptibility], the organism [rheumatogenicity], and the immune response.

The current concept of the pathogenesis of acute rheumatic fever is that it is due to group A streptococcal infection occurring in a susceptible host, which leads to an autoimmune response to epitopes in the organism that cross react with similar epitopes in human tissues [e.g., in the joints, heart, brain, and skin]. Thus, the characteristics of the organism [organism factors or rheumatogenicity], host factors [genetic susceptibility], and the immune response are identified as the major factors leading to the development of acute rheumatic fever.

### Organism factors
The observation that infections with only some of the strains of group A streptococci leads to the development of acute rheumatic fever has led to the recognition of the concept of “rheumatogenicity.” Rheumatogenic strains are primarily tropic for the throat and not the skin.

A large amount of M protein can be extracted from the rheumatogenic strains, which helps in their identification. The role of the surface M protein in the pathogenesis of acute rheumatic fever is supported by the observation that rheumatogenic strains tend to be rich in M protein, express certain epitopes associated with acute rheumatic fever, induce an intense M-type specific immune response, and also share M-epitopes with human tissue. They cannot produce lipoprotein lipase and the opacity factor, the latter being characteristic of strains associated with skin infection. Rheumatogenic strains are also highly contagious and are rapidly transmitted by close person-to-person contact. Many authors have reported associations of rheumatic fever with certain M-types of group A streptococci, such as types I, V, 6, 14, 18, 19, 24, 27, and 29. Bessen and associates reported that there were two classes of M protein. The rheumatogenic strains have M protein with distinct epitopes that they called class I M protein, and the M protein of non-rheumatogenic strains is called class II M protein.

The emphasis on the M protein in the pathogenesis of acute rheumatic fever has recently been questioned. Some strains of group A streptococci associated with acute rheumatic fever in an endemic area were not M-typeable or were from M-types that are usually associated with skin disease. The rheumatogenicity of group A streptococci is now considered to be associated with the strain per se rather than the M-type and it is thought that any group A streptococcus can acquire the ability to cause disease. Group A streptococci have the ability to
horizontally transfer genetic material so that the epitopes that cross react with human tissue may be transferred between strains. These observations may explain why, in endemic areas, rheumatic fever–associated strains come from M-types that are not usually associated with rheumatic fever or are not M-typeable.

Other potential mechanisms that have been implicated in the pathogenesis of acute rheumatic fever are the abilities of components and products of group A streptococci to act as superantigens and stimulate the T cells without requiring antigen presentation.

However, this view has been questioned, because these properties may be due to contamination. The role of co-pathogens has also been suggested, and coxsackievirus has been postulated as a possible co-pathogen. In Australian aborigines, serotyping of group A streptococci isolates suggested that skin lesions were the main source of all strains of group A streptococcus isolates regardless of the site of isolation. In Thailand, emm sequence typing did not differentiate between skin or throat strains associated with acute rheumatic fever or post-streptococcal glomerulonephritis. This is thought to be the result of genetic recombination between different strains. Thus, it appears that in developing countries and in populations with high rates of superficial infections, the distinction between rheumatogenic and non-rheumatogenic strains is blurred. McDonald and coworkers have noted that control measures have been ineffective in aboriginal communities who have a high incidence of persons with rheumatic fever and rheumatic heart disease. In these communities, group A streptococcal throat colonization is uncommon, group A streptococcal pharyngitis is rare, pyoderma is a major manifestation of group A streptococcus infection, and typical rheumatogenic strains do not occur. They suggest that group A streptococcal pyoderma and/or non-group A streptococcal infections are responsible for acute rheumatic fever in these communities.

**Host factors**

There is a high prevalence of streptococcal pharyngitis in many populations but only a small percentage develops acute rheumatic fever. Acute rheumatic fever occurs in 3% to 6% of people during outbreaks of pharyngitis, and the incidence is lower with sporadic pharyngitis. The disease is familial, but the transmission of the disease has been variously suggested as being autosomal recessive or autosomal dominant with limited penetrance. An inherited susceptibility to acute rheumatic fever and rheumatic heart disease is supported by twin studies that show an increased concordance in monozygotic twins compared with dizygotic twins, although the lower than expected concordance indicates it is a simple mendelian single-gene inheritance.

Because autoimmune responses have been postulated in the pathogenesis of acute rheumatic fever, an immunogenetic predisposition has been sought. An earlier study using serologic methods showed an association with human leukocyte antigen (HLA)-DR4 in whites and HLA-DR2 in African Americans. The association of patients with acute rheumatic fever and rheumatic heart disease with HLA antigens, B- and T-cell alloantigens, and immune gene polymorphisms in different ethnic populations and different regions has been recently reviewed.

Subsequent associations with HLA-DR4 have been reported in whites, with HLA-DR2 in African Americans, HLA-DR3 in Indians, and HLA-DR1 and HLA-DR6 in South African blacks. Studies using molecular HLA typing techniques have led to a re-evaluation of the major histocompatibility complex (MHC) class II associations with rheumatic fever and rheumatic heart disease. It is now suggested that DRB1*0701, DR6 and DQB1*0201 confer susceptibility to rheumatic fever; such observations are in agreement with those reported in Turkey, Mexico, South Africa, and Japan. An association of rheumatic fever with HLA-DR7 was recently reported in a Brazilian study.

Recent studies have identified a non-HLA B cell marker that is present in patients with acute rheumatic fever. A monoclonal antibody (D8/17) was prepared by immunizing mice with B cells from a patient with rheumatic fever. The B-cell antigen was expressed on an increased number of B cells in 100% of patients from different ethnic groups and only in 10% of normals. This marker was, however, absent in one third of north Indian patients. A new monoclonal antibody developed against the B cells of the north Indian patients with rheumatic fever, PGI/MNII, was positive in 86% and 94% of patients with rheumatic fever and rheumatic heart disease, respectively.

Family studies have shown marked elevations of the B-cell antigens defined by the D8/17 monoclonal antibody in unaffected family members. The B-cell alloantigen D8/17 has been shown to be of value in differentiating Sydenham’s chorea from lupus chorea.

In summary, it is likely that the susceptibility to acute rheumatic fever is polygenic, with the reported HLA class antigens being close to or in linkage disequilibrium with the putative rheumatic fever susceptibility gene, and the D8/17 antigen may be associated with one of the genes.

**Immune response**

Rheumatic fever is recognized as one of the diseases in which there is molecular mimicry between a foreign agent (group A streptococci) and host tissue (e.g., heart, brain). Many antigens or components of group A streptococci have been shown to cross react directly with various human tissues. It was postulated that components of streptococci such as streptococcal membrane, group-specific glycoprotein, or carbohydrate components induce both a humoral and a cell-mediated immune response that cross reacts with the host tissues. The detection of antibodies to streptococcal antigens that are similar to human tissues suggested that humoral immunity played a major role in the pathogenesis of acute rheumatic fever. Evidence, however, suggests that the primary damage may be mediated by cellular immunity and that the antibodies are produced in response to antigens released from damaged tissues.

Immunopathologic studies of heart tissue showed that infiltrates of the heart valve consisted mainly of T lymphocytes and the Aschoff body, which is the characteristic cardiac lesion of rheumatic fever and is derived from macrophage lineage. The T cells and macrophages are present in cell-mediated immune responses. B cells, which are associated with humoral immunity, are uncommonly found.

The role of cellular immunity is also supported by the detection of increased levels of several markers of cellular immune activation such as circulating CD4+ lymphocytes, interleukin (IL)-1 and IL-2, IL-2 receptor-positive T cells, tumor necrosis factor (TNF)-α receptors, leukocyte migration inhibition, natural killer (NK) cell cytotoxicity, mono-nuclear cell cytotoxicity, T-cell responsiveness to streptococcal antigens, neopterin and oxygen free radical production by phagocytes. The response by T cells to an epitope on the M protein of group A streptococci and cardiac myosin epitopes was reported by Praksakorn and associates.

A hypothesis on the pathogenesis of rheumatic fever that includes some of the just-mentioned observations has been proposed by Carapetis and colleagues. The cross-reactive antigens of streptococci are presented to helper T cells (Th) by antigen-presenting cells in conjunction with MHC class II antigens. Abnormal presentation or recognition of these antigens leads to uncontrolled Th activation and proliferation, possibly mediated by IL-2. This leads to the release of lymphokines, activation of NK cells and cytoxic T cells and secondary activation of macrophages and neutrophils. As a result, there is eradication of the streptococci and damage to the host tissue due to cross-reactivity. Antigens released from the host tissue induce an antibody response that may further damage the tissue or serve as a marker of damaged tissue.

Measurements of T-cell responsiveness in rheumatic fever have shown increased reactivity during acute episodes. The ability of T cells to amplify and perpetuate the chronic rheumatic process is unknown.

**PATHOLOGY**

Rheumatic fever can cause pathologic changes throughout the body, especially in the connective tissue and around blood vessels.

**Cardiac involvement**

In the heart, the pericardium, myocardium, and endocardium can be affected, resulting in a pancarditis.

**Myocarditis**

In the acute phase there may be diffuse myocardial involvement leading to conduction disturbances and heart failure. Death may result in a
small proportion of patients, and at postmortem examination there is
dilation of the chambers and the myocardium is pale, flabby, and
edematous.

The histologic changes in the myocardium may consist of a non-
specific myocarditis with edema of the muscle fibers and focal collect-
tions of inflammatory cells in the interstitial connective tissue or a
specific granulomatous myocarditis with the presence of the character-
istic Aschoff nodules. The typical acute and subacute inflammatory
foci seen in heart muscle are shown in Figure 108.2. The Aschoff
nodules are composed of a central area of fibrinoid necrosis surrounded
by specialized histiocytes called Aschoff giant cells and Anitschkow
cells, which, in turn, are mixed with lymphocytes. Silver and Stoller-
man defined three phases in the progression of Aschoff nodules:
- The early stage with central fibrinoid necrosis, edema, and an
  infiltrate of lymphocytes and plasma cells (non-specific stage or
  exudative-degenerative phase)
- The specific granulomatous stage with accumulation of charac-
teristic Aschoff giant cells and Anitschkow cells
- The late stage with diminution of the cellular infiltrate and
  replacement by scar tissue

The presence of Aschoff nodules indicates that there has been an
episode of acute rheumatic fever. They can persist for many years
and may be identified at the time of valve replacement surgery even in
patients who do not have any clinical or laboratory evidence of rheu-
matic activity. The persistence of the Aschoff nodules seems to cor-
relate with the tendency of the host to develop progressive stenosis and
fibrosis of the mitral valve.

Endocarditis
In the early stages, endocarditis is associated with thickening of the
valves as a result of edema and a row of vegetations or verrucous lesions
are present along the free borders of the cusps. These tiny vegetations
are platelet-rich microthrombi, which do not become dislodged and
therefore do not produce the embolic phenomena seen with the larger
vegetations of infective endocarditis. The mitral valve is most com-
monly affected followed by the aortic valve, either alone or with the
mitral valve. During healing, vascularization takes place, with an
increase in fibroblastic activity resulting in fibrosis. The degree of
fibrosis is variable, and in most cases it does not affect the function of
the valve. In other patients the scarring is progressive over years and
may affect the subendocardial tissue, as well as the annulus, cusp, and
chordae tendineae. These changes can lead to contraction of the cusp
or thickening and stiffening of the cusp, leading to valvular incompe-
tence or fusion of commissures, resulting in stenosis.

The reason why some patients have progressive scarring while
others do not is not known. Some patients have recurrent episodes of
streptococcal infection resulting in further immunologic injury whereas
others may develop small mural thrombi on the damaged valves, and
the release of growth factors from the platelets and other components
of the thrombi may lead to further fibrosis.

Pathologic analysis of heart valves obtained at the time of valve
replacement shows foci of abundant mononuclear or lymphocytic infl-
itrates within tissues (Figure 108.3). Immunologic study of the inflamma-
tory cell types has shown a predominance of T cells of the OKT4 (CD4)
or Th lineage. The prominence of Th cells suggests that local produc-
tion of potent lymphokines such as IL-2, TNF, or even IL-6 contributes
to the chronic pathologic changes.

Pericarditis
Pericarditis affects both layers of the pericardium, which may be thick-
ened and covered by a fibrin-rich exudate. There may also be serosa-
ginous fluid in the pericardial cavity. The pericarditis resolves
completely with fibrosis and adhesions, but constriction does not
occur.

Articular involvement
Pathologic changes in the joints consist of exudative changes with
edema of the synovial membrane, focal necrosis in the joint capsule,
edema and inflammation in the periarticular tissues, and joint effu-
sion. These changes are completely reversible.

Other changes
The subcutaneous nodules (Figure 108.4) that are seen in the acute phase
resemble Aschoff nodules. The pathologic changes in the brain in
patients with chorea are not well defined, because patients with active
chorea rarely die of this complication and brain tissue is rarely available
for postmortem examination.
CLINICAL MANIFESTATIONS

The clinical manifestations of acute rheumatic fever are variable, and there is no single clinical feature or laboratory test that is diagnostic.

The typical attack of acute rheumatic fever follows an episode of streptococcal pharyngitis after a latent period of 2 to 3 weeks [average of 18.6 days]. During the latent period there is no clinical or laboratory evidence of active inflammation. About one third of patients cannot remember having an upper respiratory tract infection preceding the first attack of acute rheumatic fever.

Acute rheumatic fever occurs most commonly in children between the age of 4 and 9 years. In developing countries such as India, juvenile mitral stenosis may occur at the age of 3 to 4 years. The prevalence of the various major criteria varies in different studies depending on whether the patients are studied prospectively or in retrospect. The illness usually begins with a high fever, but in some patients the fever may be low grade or absent. The most common of the major criteria is polyarthritis, which occurs in between two thirds and three fourths of the patients, followed by carditis and chorea.

Major criteria

Arthritis

Arthritis is the most common presenting manifestation of acute rheumatic fever and occurs in up to 75% of the first attacks. Joint involvement is usually more common (nearly 100%), and more severe, in young adults than in teenagers (82%) and children (66%). The joint pain is typically described as migratory, which refers to the sequential involvement of joints, with inflammation resolving in one joint and then beginning in another joint. Sometimes, the joint involvement may be additive rather than migratory, with simultaneous involvement of several joints. In untreated patients the number of joints involved may vary from 6 to 16.

The affected joints may be painful and swollen, although many patients have joint pain and tenderness with little objective evidence of inflammation. The affected joint may be inflamed for only a few days to a week before the inflammation subsides. In about two thirds of patients, the polyarthritis is severe for about a week and may last another 1 to 2 weeks in the remainder before it resolves completely. If joint swelling persists after 4 weeks, it is then necessary to consider other conditions such as juvenile idiopathic arthritis or systemic lupus erythematosus.

At the onset of the illness the joint involvement is asymmetric and usually affects the lower limbs initially before spreading to the upper limbs. Monarthritis has been reported in 17% to 25% of patients. The large joints such as the knees, ankles, elbows, and wrists are most frequently involved. The hip, shoulder, and the small joints of the hands and feet are less frequently involved.

The clinical pattern of joint involvement in a large series of patients was as follows:

- One or both knees in 76%
- One or both ankles in 50%
- Elbows, wrists, hips, or small joints of the feet in 12% to 15%
- Shoulder or small joints of the hand in 7% to 8%
- Lumbosacral in 2%
- Cervical in 1%
- Sternalclavicular in 0.5%
- Temporomandibular in 0.5%

In clinical practice most patients who develop joint pain will be treated empirically with aspirin or non-steroidal anti-inflammatory drugs (NSAIDs). The progression of the arthralgia or arthritis thus may be prevented, and the typical migratory pattern of acute rheumatic fever may not be seen.

Analysis of the synovial fluid has shown the presence of sterile inflammatory fluid. There may be a reduction in complement components C1q, C3, and C4, suggesting their consumption by immune complexes.

Radiographs may show the presence of effusion, but no other abnormalities are noted.

Jaccoud arthritis or Jaccoud arthropathy [also called chronic post-rheumatic fever arthropathy] is a rare manifestation of acute rheumatic fever that is characterized by deformities of the fingers and toes. There is ulnar deviation of the fingers, especially the fourth and fifth fingers, flexion of the metacarpophalangeal joints, and hyperextension of the proximal interphalangeal joints. The hand is usually painless, and there are no signs of inflammation. The deformities are usually correctible but may become fixed in the later stages. There are no true erosions on radiographs, and the rheumatoid factor is usually negative.

Jaccoud arthropathy may occur after repeated attacks of rheumatic fever and results from recurrent inflammation of the fibrous articular capsule. A similar form of arthropathy is seen in patients with systemic lupus erythematosus.

Carditis

Carditis is the most serious manifestation of acute rheumatic fever because it may lead to chronic rheumatic heart disease and sometimes severe heart failure. However, usually it is less severe and may produce scarring of the heart valve. In some patients the carditis may be asymptomatic and is detected during clinical examination of a patient with arthritis or chorea. The incidence of carditis during the initial attack of acute rheumatic fever varies from 40% to 91%, depending on the selection of patients and whether the diagnosis is made on clinical assessment alone or combined with echocardiography.

The incidence of carditis in rheumatic fever varies with the age of the patient. It is reported in 90% to 92% of children younger than the age of 3 years, in 50% of children aged 3 to 6 years, in 32% of teenagers aged 14 to 17 years, and only in 15% of adults with a first attack of rheumatic fever. In Bland and Jones’ review of 1000 patients in 1951, 65% were diagnosed as having carditis. In the Utah outbreak in the United States, 91% had carditis when clinical examination was combined with echocardiography.

The symptoms and signs of carditis depend on whether there is involvement of the pericardium, myocardium, or a heart valve. The clinical diagnosis of carditis is based on the detection of an organic murmur that was not previously present, presence of a pericardial friction rub, or signs of pericardial effusion, cardiomegaly, or congestive heart failure.

Myocarditis in the absence of valvulitis is unlikely to be rheumatic in origin. It should be accompanied by an apical systolic or basal diastolic murmur. Patients with myocarditis may develop cardiomegaly and congestive heart failure, which may be severe and life threatening. They require aggressive treatment with diuretics and anti-inflammatory drugs, which may include corticosteroids. Myocardial damage may manifest as electrocardiographic changes, which include varying
degrees of the heart block. Patients with first-degree heart block are usually asymptomatic. Patients with second- and third-degree heart block may be symptomatic and require a pacemaker if they develop congestive heart failure.

Pericarditis is associated with anterior chest pain, and a pericardial friction rub may be detected on clinical examination. Pericarditis can be detected clinically in about 10% of patients. The pericardial effusion may sometimes be large, but cardiac tamponade is rare. Constrictive pericarditis does not occur.

Endocarditis or valvulitis is diagnosed by the presence of an apical holosystolic murmur of mitral regurgitation or basal early diastolic murmur in patients who do not have a history of rheumatic heart disease. In patients who have a history of previous rheumatic heart disease, a change in the character of the murmurs or the appearance of a new murmur will indicate the presence of endocarditis. Echocardiography can lead to the early diagnosis of valvular involvement, confirm the presence of suspected valvular regurgitation, and help to exclude non-rheumatic causes of valvular involvement. Echocardiography is not a prerequisite for the diagnosis of carditis and should not be considered a limitation where it is not available.

The mitral valve is involved most often, followed by the aortic valve. Mitral stenosis is a classic finding in acute rheumatic fever. Mitral incompetence may occur alone or with mitral stenosis or other valvular lesions. When the aortic valve is involved, aortic incompetence is more common than aortic stenosis.

Echocardiography is more sensitive than clinical examination alone for the detection of valvular abnormalities. The typical echocardiogram findings in a patient with mixed mitral valve disease are shown in Figure 108.5. The significance of the milder lesions detected on echocardiography is uncertain but it is possible that some of them may heal without any sequelae. In 1992 when the Jones criteria for the diagnosis of acute rheumatic fever were revised, the American Heart Association recommendations noted that “at present there is insufficient information to allow the use of echocardiography, including Doppler, to document valvular regurgitation without accompanying auscultatory findings as the sole criterion for valvulitis in acute rheumatic fever.”

Echocardiography is widely available in most developed countries and is likely to be used for the detection of valvular involvement or the assessment of severity.

Congestive heart failure may be due to myocarditis or severe involvement of one or more heart valves. It occurs in 5% to 10% of the initial episodes and is more frequent during recurrences of rheumatic fever.

If patients do not have a high fever, arthritis, chest pain due to pericarditis, or chorea, they may not seek medical attention and later present with rheumatic heart disease without an antecedent history of rheumatic fever. A survey of 12,000 black schoolchildren in South Africa reported a prevalence of rheumatic heart disease in 6.9/1000, and 82.5% of the affected children were previously undiagnosed.

**Sydenham’s chorea**

Chorea may be the only presenting manifestation of acute rheumatic fever. It is more common in females, and after puberty there is an even greater female predominance. The latent period between the episode of streptococcal pharyngitis and the development of chorea is considerably longer (6 to 8 weeks) than for arthritis and carditis. Chorea is characterized by the presence of involuntary, purposeless, and jerky movements of the hands, arms, shoulders, feet, legs, face, and trunk. The purposeless movements interfere with voluntary activity and disappear during sleep. Initially, chorea may be confined to the face or one arm, and sometimes it may be completely unilateral (hemichorea).

Chorea may last for a week to 2 years but usually lasts 8 to 15 weeks. When chorea occurs alone, the erythrocyte sedimentation rate (ESR), C-reactive protein, and streptococcal antibody titers may be normal, because of the long latent period and resolution of the original infection. Chorea does not occur simultaneously with arthritis but may co-exist with carditis. Some patients with chorea may have a cardiac murmur whereas others may only later manifest involvement of the mitral valve.

**Subcutaneous nodules**

The subcutaneous nodules of acute rheumatic fever resemble the nodules of rheumatoid arthritis and may be detected over the occiput, elbows, knees, ankles, and Achilles tendons. In rheumatic fever, the nodules around the elbow tend to occur over the olecranon while rheumatoid nodules tend to occur more distally along the extensor aspect of the upper forearm. They are usually firm, painless, and freely movable over the subcutaneous tissue. They vary in size from 0.5 to 2.0 cm and tend to occur in crops. They are usually smaller, more discrete, and less persistent than rheumatoid nodules. They were detected in only 1.5% of patients in a series of 786 patients, but a higher prevalence was reported in earlier studies.

Nodules are usually seen in children with prolonged active carditis rather than in the early stages of acute rheumatic fever. They may persist for a few weeks but seldom more than a month. Multiple crops of nodules may be related to the severity of the rheumatic carditis.

**Erythema marginatum**

Erythema marginatum is a less common manifestation of acute rheumatic fever and occurs on the upper arms or trunk but not the face. It has a characteristic appearance and is therefore helpful in the diagnosis of acute rheumatic fever but is not pathognomonic of rheumatic fever. The rash is evanescent, pink, and non-pruritic. It extends centrifugally while the skin at the center returns to normal, hence the name “erythema marginatum.” It has an irregular serpiginous border. The rash may also become more prominent after a hot shower.

Erythema marginatum usually occurs only in patients with carditis and may occur early or later in the course of the disease.

**Other manifestations**

The temperature is usually raised during attacks of acute rheumatic fever and ranges from 38.4° to 40°C (101.1° to 104°F). A survey of patients with acute rheumatic fever noted a low-grade fever of 38°C or less in 29%. The temperature usually decreases in a week, and fever rarely lasts more than 4 weeks.

Abdominal pain may be severe and may mimic acute appendicitis. Epistaxis was reported as a common manifestation in the past but is now uncommon. Rheumatic pneumonia is uncommon and is difficult to distinguish from pulmonary edema and other causes of alveolitis.

A recent survey has shown that patients with Sydenham’s chorea and rheumatic fever have a high risk of developing neuropsychiatric symptoms. Obsessive-compulsive disorder was more common and attention deficit/hyperactivity disorder is a risk factor for Sydenham’s chorea in children with rheumatic fever. The association with obsessive-compulsive disorder is interesting in view of the finding of increased D8/17 B-cell positivity in these patients.
INVESTIGATIONS

The investigation of a patient with suspected acute rheumatic fever includes seeking evidence of streptococcal infection, acute-phase reactants such as ESR and C-reactive protein, electrocardiography, chest radiography, and other supporting tests.

Throat cultures

Throat cultures should be taken at presentation to isolate the organism. They are usually negative by the time patients present with arthritis or carditis. A positive throat culture may be due to convalescent carriage of the original rheumatogenic strain or a new infection with a different strain.

Streptococcal antibody tests

The antibody tests are directed against the extracellular products of streptococci and include ASO, anti-DNase B (ADB), antihyaluronidase, anti-NADase (anti-DPNase), and antistreptokinase. ASO is the most widely used test. Streptococcal antibody tests are useful because they usually reach a peak at the time of clinical presentation of acute rheumatic fever, the presence of a high titer indicates a true infection, and a significant rise in the titer on repeat testing will support the diagnosis of a recent infection.

The antibody levels usually reach a peak at 4 to 5 weeks after the pharyngeal infection. They decrease rapidly over the next few months and then more slowly after 6 months. Because only about 80% of the patients have a rise in the titer of the ASO, it may be necessary to perform other antibody tests such as the ADB.

A recent study from Fiji has shown that the normal ranges for the ASO and ADB were similar to those reported in countries with a temperate climate, and the authors suggest that a uniform upper limit of normal could be applied globally.26

The rapid antigen detection test for streptococcal pharyngitis was shown to have a sensitivity of 89.7% and a specificity of 97.2% in a group of 475 children with a positive throat culture out of a sample of 1248 children with acute upper respiratory tract infections.27

Acute-phase reactants

The ESR and C-reactive protein usually show variable elevation during the acute illness with arthritis or carditis. They may, however, be normal when chorea is the only clinical manifestation. They usually respond to salicylates or NSAIDs. They may also be useful in monitoring recurrences of acute rheumatic fever.

Chest radiography

Moderate or massive cardiomegaly may be present, depending on the severity of the carditis. Heart failure may occur with severe myocarditis or valvular involvement. Pericarditis with an effusion may produce a globular heart.

Electrocardiography

There may be features of pericarditis with diffuse elevation of the ST segments. Myocarditis may be associated with tachycardia and prolongation of the PR interval. Some patients may have second-degree heart block or, rarely, complete heart block. An earlier series of 700 patients reported electrocardiographic abnormalities in 21%, with 60% of them having varying degrees of heart block.

Echocardiography

The role of echocardiography in acute rheumatic fever has not been clearly defined and was not included in the 1992 revised Jones criteria24 and the 2002-2003 WHO criteria.1 However, it is likely to be used widely in clinical practice, especially where cardiac murmurs are not detected on clinical examination. The long-term significance of subclinical abnormalities that are detected on echocardiography is unknown. In the Utah epidemic, carditis was detected on auscultation in 68% of patients.28 Doppler ultrasound examination detected inaudible valvular incompetence in 47% of patients with only polyarthritis at onset and in 57% of patients with chorea alone.29

Other tests

A mild normocytic normochromic anemia may be present. Antibodies to cardiac troponomyosin are elevated in most patients with acute rheumatic fever and can be detected by enzyme-linked immunosorbent assays. Using a monoclonal antibody (D8/17), patients with acute rheumatic fever show increased levels of D8/17-positive cells. They have been detected in 63% to 100% of patients of diverse ethnic origins and only in 4.4% to 14% of normal individuals. The latter tests are not widely available at present.

DIAGNOSIS

The original Jones criteria for rheumatic fever were proposed in 1944 and were modified in 1992, as shown in Table 108.1.28 They served as a guideline for the diagnosis of the initial attack of rheumatic fever and included a combination of clinical and laboratory features. The WHO has adopted the 2002-2003 WHO criteria3 for the diagnosis of rheumatic fever (based on the revised Jones criteria28) as shown in Table 108.2.

The revised WHO criteria facilitate the diagnosis of:

- A primary episode of rheumatic fever
- Recurrent attacks of rheumatic fever in patients without rheumatic heart disease
- Recurrent attacks of rheumatic fever in patients with rheumatic heart disease
- Rheumatic chorea
- Insidious-onset rheumatic carditis
- Chronic rheumatic heart disease

The diagnosis of a primary episode of rheumatic fever and recurrent attack of rheumatic fever in patients with or without rheumatic heart disease requires evidence of preceding group A streptococcal infection and varying combinations of major and minor manifestations. However, it is possible to diagnose rheumatic fever in the absence of evidence of preceding group A streptococcal infection in patients with rheumatic chorea, insidious-onset rheumatic carditis, and chronic valve lesions of rheumatic heart disease.

It is important to establish a diagnosis of acute rheumatic fever so that patients can be treated with penicillin (or erythromycin if the patient is allergic to penicillin) and a decision can be made on the need for long-term prophylaxis to prevent recurrent attacks of rheumatic

<table>
<thead>
<tr>
<th>Major manifestations</th>
<th>Minor manifestations</th>
<th>Supporting evidence of antecedent group A streptococcal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Clinical findings</td>
<td>Positive throat culture or rapid streptococcal infection test</td>
</tr>
<tr>
<td>Poliarthritis</td>
<td>Arthralgia</td>
<td>Elevated or rising streptococcal antibody titer</td>
</tr>
<tr>
<td>Chorea</td>
<td>Fever</td>
<td>Laboratory findings:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated acute-phase reactants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-reactive protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged PR interval</td>
</tr>
</tbody>
</table>

If supported by evidence of preceding group A streptococcal infection, the presence of two major manifestations or of one major and two minor manifestations indicates a high probability of acute rheumatic fever. Jones criteria, updated 1992.
TABLE 108.2 2002-2003 WHO CRITERIA FOR THE DIAGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary episode of rheumatic fever*</td>
<td>Two major* or one major and two minor** manifestations plus evidence of a preceding group A streptococcal infection***</td>
</tr>
<tr>
<td>Recurrent attack of rheumatic fever in a patient without established rheumatic heart disease</td>
<td>Two major or one major and two minor manifestations plus evidence of a preceding group A streptococcal infection</td>
</tr>
<tr>
<td>Recurrent attack of rheumatic fever in a patient with established rheumatic heart disease</td>
<td>Two minor manifestations plus evidence of a preceding group A streptococcal infection</td>
</tr>
<tr>
<td>Rheumatic chorea</td>
<td>Other major manifestations or insidious onset rheumatic evidence of group A streptococcal infection not required</td>
</tr>
<tr>
<td>Chronic valve lesions of rheumatic heart disease (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve)</td>
<td>Do not require any other criteria to be diagnosed as having rheumatic heart disease</td>
</tr>
</tbody>
</table>

*Major manifestations: carditis, polyarthritis, chorea, erythema marginatum, subcutaneous nodules

**Minor manifestations: clinical—fever, polyarthralgia; laboratory findings—elevated acute-phase reactants (ESR or leukocyte count).

***Supporting evidence of: electrocardiogram—prolonged PR interval; preceding streptococcal infection; elevated or rising antistreptolysin-O or streptococcal infection with another streptococcal antibody; infection in the past 45 days; a positive throat culture; rapid antigen test for group A streptococcus; recent scarlet fever.

A period of bed rest is usually advised during an attack of acute rheumatic fever, and patients should be monitored for the onset of carditis. Once the symptoms and signs of acute inflammation have resolved, patients should be gradually mobilized. There are no randomized trials on the effect of prolonged bed rest.

<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>50.4</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>57.6</td>
</tr>
<tr>
<td>Chorea</td>
<td>34.8</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>1.6</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>São Paulo, Brazil</th>
<th>Utah, USA</th>
<th>Boston, USA</th>
<th>Konya, Turkey</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>786</td>
<td>274</td>
<td>1000</td>
<td>274</td>
</tr>
<tr>
<td>Carditis</td>
<td>50.4</td>
<td>68.2</td>
<td>65.3</td>
<td>60.9</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>57.6</td>
<td>36.1</td>
<td>41.0</td>
<td>81.4</td>
</tr>
<tr>
<td>Chorea</td>
<td>34.8</td>
<td>36.4</td>
<td>51.8</td>
<td>17.9</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>1.6</td>
<td>4.0</td>
<td>7.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>1.5</td>
<td>2.6</td>
<td>8.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Antimicrobial therapy

Adequate treatment of the streptococcal pharyngeal infection is essential to avoid prolonged and repetitive exposure to streptococcal antigen. The treatment of choice is penicillin, which is best given as a single intramuscular dose of benzathine benzylpenicillin. If penicillin is given orally, a 10-day course is necessary.

A New Zealand study of 353 children with positive throat swabs showed that a 10-day course of once-daily oral amoxicillin was not inferior to a standard 10-day course of twice-daily penicillin V. A recent Cochrane review noted that in countries with low rates of rheumatic fever, 3 to 6 days of oral antibiotics (azithromycin, clarithromycin, and cefuroxime) had comparable efficacy to standard 10-day oral penicillin therapy in treating children with streptococcal pharyngitis.

Analgesics and NSAIDs

Patients with mild symptoms of fever and joint pain without carditis may respond to analgesics alone. If there is moderate or severe arthritis with or without carditis, they should be treated with salicylates in a dose of 80 to 100 mg/kg/day to maintain a blood level of 20 to 30 mg/dL. Salicylate doses of 4 g or more may be required in adults. Patients on high-dose salicylates will require monitoring for adverse effects, including nausea, vomiting, abdominal pain, and gastrointestinal bleeding. Treatment should be continued until the symptoms and signs of inflammation have resolved. The higher dose of salicylates should be continued for 2 weeks and then reduced. Use of other NSAIDs is also of value and naproxen has been reported to be effective and well tolerated.

Corticosteroid therapy

A meta-analysis of the long-term outcome of carditis with the use of corticosteroids and salicylates failed to show any benefit for either agent. The role of anti-inflammatory treatment for carditis has been reviewed and failed to show any benefit of using corticosteroids, intravenous immunoglobulin, and aspirin in preventing cardiac disease in patients with acute rheumatic fever. Corticosteroids have a potent anti-inflammatory effect and have been used in patients with severe carditis or carditis associated with heart failure even though there is insufficient evidence for their efficacy. These agents are not helpful if the heart failure is due to severe valvular damage.

Treatment of heart failure

Heart failure is treated with bed rest, and corticosteroids are used if there is active carditis. Conventional management may also include the use of diuretics, digoxin, or vasodilators depending on the nature of the underlying abnormalities. When carditis complicated by marked valvular regurgitation causes severe hemodynamic compromise, valve surgery is lifesaving and should not be delayed by trials of anti-inflammatory medication.
Sydenham’s chorea
Chorea is usually a self-limiting and benign manifestation that does not require specific therapy. It may be protracted and disabling in some patients and responds to haloperidol.

PREVENTION
Primary prevention
Primary prevention refers to the prevention of the first attack of rheumatic fever by early treatment of the streptococcal pharyngeal infection. In 1950, Denny and colleagues showed that rheumatic fever can be prevented if the preceding pharyngeal infection due to group A streptococci is adequately treated with penicillin. Penicillin is the treatment of choice because it is bactericidal. Ideally the streptococcal infection should be confirmed by throat culture, which requires overnight incubation, or by using a rapid diagnostic antigen detection kit. A positive throat culture does not differentiate between active streptococcal pharyngeal infection and an asymptomatic carrier with viral pharyngitis. Many of the kit tests are specific; and if the test is positive, the patient should be treated. The kit tests are less sensitive than culture, and the American Heart Association has recommended that a negative antigen test is confirmed with a throat culture.

A different strategy may be needed in developing countries where throat cultures and serologic tests are not readily available in community clinics. The use of a syndromic approach to the management of throat infections has been shown to reduce the incidence of rheumatic fever. In Costa Rica, the treatment of throat infections (without the need for throat cultures) with intramuscular benzathine benzylpenicillin (instead of oral agents, which are associated with poor compliance) resulted in a significant reduction in the incidence of rheumatic fever. A meta-analysis of the use and effectiveness of antibiotics for the prevention of acute rheumatic fever showed an 80% reduction in the risk of acute rheumatic fever with penicillin treatment for suspected streptococcal sore throat infection. This meta-analysis also showed that it was necessary to treat only 60 patients with throat infections with intramuscular penicillin to prevent one case of acute rheumatic fever. Based on this information, the marginal cost of preventing one case of rheumatic fever by a single intramuscular injection of penicillin is $46 (US) in South Africa.

The most effective treatment is a single injection of benzathine benzylpenicillin G intramuscularly. The recommended dose is 600,000 units in children weighing less than 27 kg (60 lb) and 1.2 million units in those who weigh more than 27 kg (60 lb). The alternative is to use oral penicillin V (phenoxymethyl penicillin) for 10 days (250 mg two to three times daily in children and 500 mg two to three times daily in adolescent and adults). The use of intramuscular penicillin obviates the need for oral medication to be taken for 10 days and overcomes the problem of compliance because patients may stop treatment when they feel better after a few days. Patients who are allergic to penicillin should be treated with oral erythromycin for 10 days with a maximum dose of 1 g/day (erythromycin estolate, 20-40 mg/kg/day in two to four divided doses, or erythromycin ethylsuccinate, 40 mg/kg/day in two to four divided doses).

During an epidemic, mass penicillin prophylaxis is of value and intramuscular penicillin has been effective in military camps. Acute rheumatic fever is a notifiable disease in some countries as a key strategy to guide the implementation of prevention programs. In South Africa, acute rheumatic fever has been a notifiable disease since 1977 and National Guidelines for the Prevention and Prophylaxis of Rheumatic Fever and Rheumatic Heart Disease for Health Professionals at Primary Level were published in 1997. A recent survey in Cape Town, South Africa, revealed a failure by health professionals to adhere to the guidelines and also to notify rheumatic fever despite this being a legal requirement.

Secondary prevention
Secondary prevention refers to the prevention of recurrences of rheumatic fever with the use of continuous prophylaxis against streptococcal infection. A systematic review of the trials comparing oral and intramuscular penicillin regimens reported that intramuscular penicillin is more effective than oral penicillin in preventing the recurrence of rheumatic fever. The authors also noted that 2-weekly or 3-weekly injections appeared to be more effective than 4-weekly injections. They also reported that the evidence was based on poor-quality trials and that outdated formulations of oral penicillin were used in the earlier trials. Earlier trials used oral penicillin G, which is more susceptible to gastric hydrolysis than penicillin V, which is now widely available.

The most effective regimen is the use of benzathine benzylpenicillin G 1.2 million units by intramuscular injection for children and adults weighing more than 27 Kg (60 lb) and 600,000 units for those weighing less than 27 Kg (60 lb). In developing countries where there is a high incidence of acute rheumatic fever and an increased risk of recurrence, intramuscular penicillin G should be given at least once every 3 weeks because the levels of penicillin are low in the fourth week. The alternative treatment is penicillin V, 250 mg twice daily orally, or sulfadiazine, 0.5 g once a day if weighing less than 27 kg (60 lb), or 1 g/day if weighing more than 27 kg. Patients who are allergic to penicillin and sulfadiazine should be treated with erythromycin 250 mg twice a day. A large survey of 1790 patients who received 32,000 injections of benzathine benzylpenicillin G showed a prevalence of rheumatic fever of 0.45% in patients on intramuscular benzathine benzylpenicillin G compared with 11.5% in patients who were not compliant.

Patients who have significant rheumatic heart disease, a history of a recent attack, or a history of recurrence should receive prophylactic treatment. The risk of an attack of acute rheumatic fever after a group A streptococcal infection increases from 1% to 3% with the first attack of streptococcal pharyngitis to 25% to 75% in subsequent attacks. The risk of recurrence depends on many factors, such as the presence of carditis, the severity of cardiac involvement, the time interval since most recent attack, and the risk of streptococcal throat infections depending on living conditions and occupation. Patients with previous carditis have an increased risk of carditis during recurrence of rheumatic fever. The recent WHO guidelines recommend prophylaxis for 5 years after the last attack or until the age of 18 years (whichever is longer) for patients without proven carditis and for 10 years after the last attack or at least until 25 years of age (whichever is longer) for patients with carditis (mild mitral regurgitation or healed carditis). Patients with more severe carditis or who had valve surgery should receive lifelong therapy.

Patients with rheumatic heart disease should receive prophylactic antibiotics to prevent infective endocarditis when they undergo surgical procedures of the mouth (dental extractions), eyes, ears, nose, throat, and gastrointestinal and genitourinary tracts.

Vaccines
Rheumatic fever and rheumatic heart disease are the most common causes of cardiac-associated deaths in young adults in developing countries. The high prevalence of rheumatic fever in developing countries and the resurgence of rheumatic fever in the United States and the occurrence of a severe illness such as the toxic streptococcal syndrome have further emphasized the need to develop an effective vaccine.

The strategies for the development of vaccines have been reviewed. Most of them have focused on either the N-terminal region or the C-terminal region of the M protein. The characterization of the M-protein molecule has already been completed.

Some of the important considerations in the development of the vaccine are as follows:

- The vaccine should not exacerbate the rheumatic disease it is designed to prevent. M-protein sites that are associated with tissue cross-reactivity or infiltrates should be avoided and therefore thorough testing in animals is necessary.
- There are more than 80 different M-protein serotypes which cause infection, and only a few of the serotypes can be used for a type-specific vaccine. M-protein serotypes are also cyclic, and different serotypes produce rheumatic fever in different parts of the world.
- The immune response should produce lasting protection.
Efforts to produce the ideal vaccine have been going on for more than 3 decades since the use of a partially purified M3 vaccine. Research on M-protein vaccines has taken place since the 1970s, and although there has been considerable experience and improvement in our knowledge of vaccines, there has been little success. Other potential targets for vaccines are C5a peptidase, streptococcal proteinase (pyrogenic exotoxin B) and carbohydrate-protein conjugates. Current research is promising, and it is hoped that vaccines will be available for clinical trials in the future.

REFERENCES