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# Rheumatic fever—is it still a problem?

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**The incidence of rheumatic fever has declined in industrialized countries since the 1950s and now has an annual incidence of around 0.5 cases per 100,000 children of school age. In developing countries it remains an endemic disease with annual incidences ranging from 100 to 200 per 100,000 school-aged children and is a major cause of cardiovascular mortality. Interest in the pathogenesis of rheumatic fever was rekindled by outbreaks in the USA (1985–1987) and the rare cases still seen in industrialized countries. The current concept is that the disease results from the host's poorly adapted autoimmune response to group A β-haemolytic streptococci. The risk of developing rheumatic fever following untreated tonsillopharyngitis is 1% in the civilian population. Knowledge of virulence factors has been greatly enriched by progress in molecular biology. One of the key elements is protein M, a surface protein on the bacterial wall which carries specific epitopes. Several serotypes which lead to rheumatic fever have been recognized among more than 80 identified serotypes. However, the reason why specific strains within a given serotype have increased rheumatogenic virulence remains unknown. The causal strain adheres to the oral and pharyngeal cells and then releases its degradation products. These products present antigenic determinants which cross-react with certain human tissues, particularly in cardiac valve tissue and myocardium. Diagnosis is now difficult owing to the low incidence. Late diagnosis can have serious consequences and acute rheumatic fever is a therapeutic emergency requiring immediate antibiotic and anti-inflammatory treatment. In most of Europe there is tacit agreement that all cases of pharyngitis and tonsillitis should be treated with antibiotics without identification of the causal agent despite the fact that only about 20% of the cases are caused by group A β-haemolytic streptococci, and could lead to rheumatic fever.**

## Epidemiology

Rheumatic fever still poses many questions.[1–6] Does the disease still exist and what is its epidemiology? How can we understand its pathogenesis? Have its clinical expression and evolution changed and how should we manage the treatment of sore throat in the future? There are radical differences in the epidemiology of rheumatic fever between countries. In developing countries, rheumatic fever is endemic and remains one of the major causes of cardiovascular disease; 25–45% of cases are due to rheumatic fever. It is a major cause of mortality among subjects under 50 years of age and has been identified as one of the major problems in large cities of the Third World by the World Health Organization. The annual incidence of rheumatic fever is 100–200 times greater than that observed in developed countries and fluctuates between 100 and 200 per 100,000 children of school age (from 5 years to 17 or 18 years depending on the study). In the French West Indies, the incidence of rheumatic fever in 1980 was 50/100,000 children under 20 years of age. By 1993, this had fallen to 20/100,000, a reduction of 78%, in Martinique and to 17/100,000, a 74% reduction, in Guadeloupe following a 10 year programme of medical and social education.[7] The prevalence of rheumatic heart disease per 1000 children has been reported as follows: Egypt, 10; Thailand, 1.2–2.1; India, 6–12; Pakistan, 1.8–11; Sri Lanka, 100–150; with a very high prevalence in China, Taiwan, French and American Polynesia, South Africa, and among the Maori population in New Zealand.[8]

In developed countries,[9–12] rheumatic fever has become a rare disease with a mean annual incidence since the 1980s of 0.5/100,000 children of school age. Incidences fluctuate between 0.23 and 1.88/100,000 in the USA, Japan, Den-

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mark,[13] Great Britain and Australia. During the last 25 years the number of cases has fallen by up to 99% in the USA and rheumatic fever is no longer a notifiable disease. This disappearance of the disease, which has been observed in all developed countries, is one of the most striking features of the evolution of rheumatic fever. In the USA, epidemic outbreaks[14–18] have been observed in a dozen or so geographically separate states since 1985 which has increased the annual incidence to 18/100,000 (Salt Lake City, UT, USA) without affecting the general incidence. Since that time, 90–157 cases have been reported annually, distributed across 40 states.

In France, a similar incidence of 0.08–0.15/100,000 among children of 5–14 years was found in a survey[19] conducted over 3 years (1995–97): nine regions had not had any cases in 3 years. The regional incidence was highest in Limousin (1.3) and Alsace (1) and lowest (0.13) in Ile de France and Rhône-Alpes. A general paediatric department in the Paris suburbs[20] has reported eight cases in 15 years (1980–1995). Four of these were imported cases, in which the bout of rheumatic fever had started within 6 weeks of the child's return from his country of origin. The other four children had not left France, or had been back there for 7–9 months, before the onset of the rheumatic fever which may therefore be considered indigenous.

The spectacular evolution of rheumatic fever over the years is surprising. The frequency of the disease was very high at the beginning of the twentieth century (100–200 cases per 100,000 head of population in the USA in 1900, and 50/100,000 in 1940). Rheumatic fever was a major cause of mortality among children and adolescents and of heart disease among young adults, with pockets of the disease found in closed military communities such as those of Wyoming where the incidence was 50/1000 recruits. However, the incidence has fallen progressively since the late 1920s with a marked reduction after the 1940s.[12] The Danish frequency curve (Figure 1) illustrates this decline which has also been observed in Japan, Great Britain and Australia. The diminishing mortality curve and the influence of key factors over the years is illustrated in Figure 1. In developing countries, rheumatic fever was rarely described until after the 1940s, possibly because it resulted mainly from imported strains.[8]

## Pathogenesis

The close link between *Streptococcus pyogenes* and rheumatic fever is well established but the precise pathogenesis of rheumatic fever and of rheumatic heart disease is not fully understood despite the considerable advances in understanding of the molecular biology of *S. pyogenes* and the interrelations of the autoimmune response between the microorganism and the host. It has become possible to establish a closer correlation between the cardiac manifestations and the autoimmune response.[8,21]

Denny[1] has provided a schematic illustration (Figure 2) of the relative roles of environment, individual predisposition, and the pathogen (group A $\beta$-haemolytic streptococcus, GABHS) responsible for sore throat.

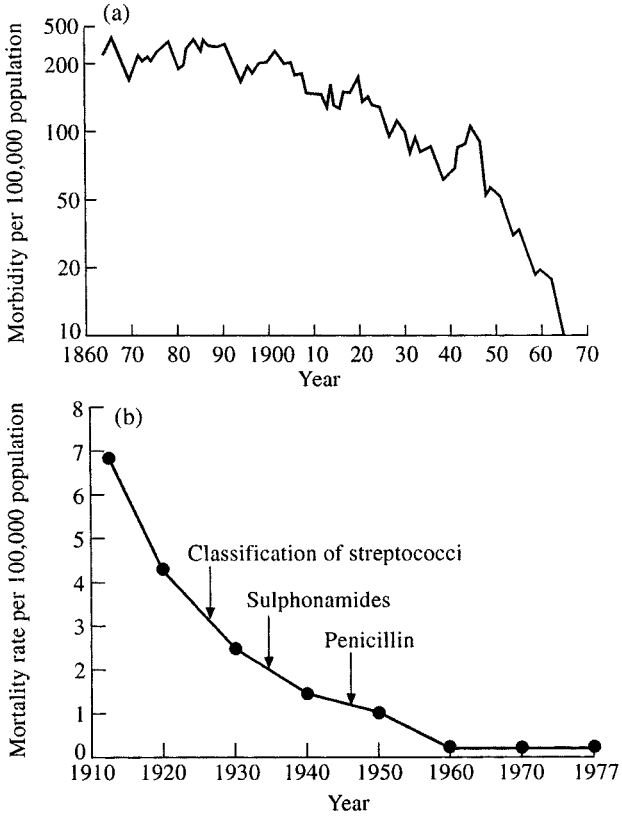


**Figure 1.** (a) Incidence of rheumatic fever in Copenhagen and (b) mortality rate owing to rheumatic fever in the USA, 1910–1977.

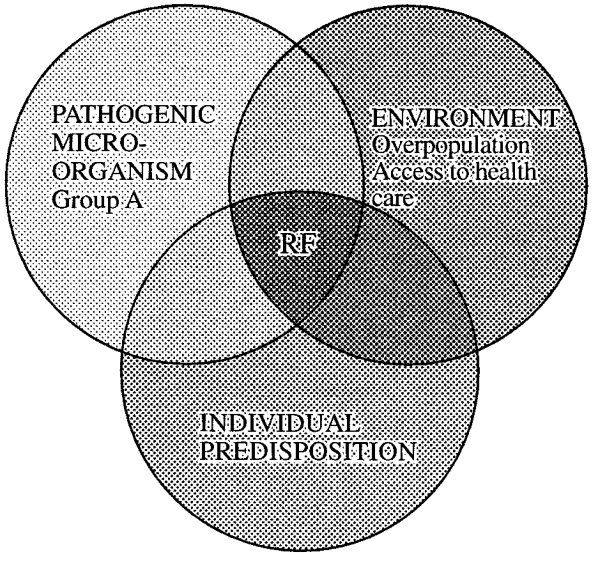


**Figure 2.** Factors involved in the pathogenesis of acute rheumatic fever according to Denny.[1]

## Environment

The classical socio-economic factors of an unfavourable environment (promiscuity and overpopulation leading to overcrowding; poor or non-existent financial resources; restricted access to health care; and the ensuing malnutrition) remain important in developing countries, although their true role needs to be reassessed. The programme implemented in the French West Indies showed that the incidence of rheumatic fever declined over a period of 10 years[7] even though socio-economic conditions remained unfavourable (low income; 15% of the population without running water/electricity/toilets; predominantly poor rural setting) with the number of children per family appreciably greater than in the general population of the two islands.

The rise in the standard of living resulting from industrialization has contributed to the fall in the incidence of rheumatic fever but it has not completely abolished the disease. Published reports of its resurgence between 1985 and 1987 in the USA emphasize the current change in its socio-economic context: the affected populations are no longer migrant but indigenous, and white in the majority of cases, usually with a rural lifestyle and middle class income. The rapid decline in the incidence of rheumatic fever began before the introduction of antibiotics and cannot be completely explained by improvement in standards of living which take a number of years to have any influence.

## Individual predisposition

It has been suspected for more than a century that individual host factors may be important in rheumatic fever.[22] The first authors to describe the disease noted that there was frequently a family predisposition but it has never been possible to demonstrate a specific genetic profile or Mendelian transmission of the disease. The discovery of specific HLA antigens within the context of various autoimmune diseases led to an intensive search for such antigens in rheumatic fever. Ayoub *et al.*[23] were the first to demonstrate an increased frequency of HLA-DR4 in white subjects and HLA-DR2 in black subjects. However, although this remains true in Utah and in Turkey, other HLA types have been found in combination in other countries in subjects with rheumatic heart disease. Examples include DRA and DRw6 in black African subjects in South Africa; DR7 and Dw53 in Brazil; DQw2 in India; HLA-B17, HLA-B21 and HLA-Cw4 in Russia (Uzbeks). The marked variability of dominant HLA antigens in different populations renders their close association with the disease unlikely.

Alloantigens, brought to the surface of lymphocytes and recognized by monoclonal antibodies, appear to be markers of host susceptibility, especially when there is cardiac involvement (found in 75–90% of cases). These appear to be expressed only after stimulation by a GABHS antigen.[22]

## Streptococcal pharyngitis

As a result of the many findings accumulated over the last 100 years, the relationship between GABHS pharyngitis and the development of rheumatic fever is now universally recognized. Effective treatment of GABHS tonsillopharyngitis reduces the risk of rheumatic fever by about 90% but various clinical studies have demonstrated that GABHS remains present in the throat even after adequate treatment in about 10% of cases. Only the sore throat, when untreated, is capable of inducing rheumatic fever, and all its major consequences. The risk among the civilian population is 1%. The tonsils and the pharyngeal region are rich in lymphoid tissue which is essential for initiation of the immune response (GABHS skin infections can only cause glomerulonephritis). The currently accepted theory is that, after apparent recovery, the host has an inappropriate autoimmune response since a number of streptococcal degradation products exhibit molecular mimicry with human tissues recognized by the immune system. The three organs concerned are the heart, the joints and the central nervous system, and these account for almost all the clinical manifestations. The skin disorders (erythema marginatum and subcutaneous nodules) usually occur in the presence of carditis and/or polyarthritis.

## The microorganism

Cheadle reported the association between a throat infection and rheumatic fever in 1889.[24] As early as 1900, several authors pointed to the role of the streptococcus and the proliferative and non-suppurative character of rheumatic fever; clinicians had known for a long time that epidemics of scarlet fever were followed by rheumatic fever. Rebecca Lancefield's work[25] in the 1930s led to the identification of the streptococcal subgroups. From this starting point, epidemiological studies conducted in England[26] and the USA[27] in the 1930s demonstrated the close relationship between streptococcal pharyngitis and onset of rheumatic fever. The introduction of antibiotics (sulphonamides and then penicillin in the 1940s) and the trials conducted during the 1940s and in the USA, demonstrated that penicillin treatment for streptococcal pharyngitis has a preventive effect against rheumatic fever.[5,28] Programmes of primary and secondary prevention were subsequently developed which speeded up the disappearance of the disease in the USA and in practically all developed countries but, as may be seen from Figure 1, the disease was already declining from the beginning of the twentieth century.

The microorganism exerts its action through its virulence factors.[6,8,12,29] The appearance of 'toxic shock syndrome' and the stability of the levels of glomerulonephritis and of sore throat in industrialized countries, suggests that the evolution of these factors in specific strains accounts for the epidemic outbreaks of rheumatic fever in the USA, and its persistence in France as a sporadic infection.

## Rheumatogenic strains

More than 80 specific serotypes can be distinguished and some types can cause pharyngitis just as easily as skin infection. The consequence of infection at these sites varies since a skin infection can give rise to acute glomerulonephritis whereas rheumatic fever can only occur after pharyngitis. Johnson *et al.*[30] showed that certain serotypes are common to uncomplicated pharyngitis, systemic infections and rheumatic fever.

Rheumatogenic strains have been described.[8] A serotype can acquire a rheumatogenic potential at a given time; the subject, who does not possess opsonic circulating antibodies for more than one or two serotypes, is not protected on pharyngeal acquisition of this serotype. The onset of rheumatic fever may be related to an increase in the virulence of a specific strain within the same serotype although the reasons for this are not clearly understood. There is no clear distribution between serotypes responsible for skin and throat infections but there is a relationship between certain serotypes and the resulting disease.[30,31] The specific types most frequently encountered in rheumatic fever (epidemic outbreaks) in the USA[32] are M types 1, 3, 5, 6, 18, 19 and 24. The glomerulonephritis strains are most frequently M types 1, 4, 12 (after throat infection) and 49, 55, 57, 60 (after skin infection). The strains of a given serotype are not all equally rheumatogenic or nephritogenic and a serotype does not in itself allow definition of a rheumatogenic strain whose potential for pathogenicity is variable. There are also clear geographic variations by country: type M 18 has been found in the USA but is rare in Great Britain.[33] There are many temporal variations: certain serotypes appear for a few years and then subsequently disappear.[34]

Other studies conducted in New Zealand, Kuwait and Australia have demonstrated the predominance of other types in rheumatic fever and it is possible that this disease may arise with any type of GABHS. An opacity factor can be demonstrated by culture; its presence or absence allows the strains to be classified as class I (absence of the factor) or class II (presence of the factor). Class I strains are most frequently found after pharyngeal infections and are thus of importance in the context of rheumatic fever. Molecular variation in the carboxyl-terminal end of the M protein allows class I and class II microorganisms to be identified and distinguished. Strains rich in hyaluronic acid are highly encapsulated and appear mucoid in culture. These isolates are often associated with virulence and rheumatogenic risk.

Group A streptococcal pharyngitis is a necessary precondition for the triggering of the autoimmune phenomenon. Rheumatic strains adhere to the oral and pharyngeal cells in patients with rheumatic fever. This process of adhesion is most frequently associated with strains that have a large quantity of M protein and the principal factor would seem to be the lipoteichoic acid incorporated in the fimbriae of the M protein and stretching out from the cell wall. The lipoteichoic acid attaches itself to the fibronectin in the buccal or pharyngeal cells. Another protein that has the same property has recently been identified on the surface of the GABHS. Although this process of adhesion is essential and differs between normal subjects and subjects with rheumatic fever, its precise role in the pathogenesis of rheumatic fever is not clearly understood.

## An inappropriate immune response

The following cascade of events occurs after a symptom-free interval of 2–3 weeks which is a further point in favour of the idea of an autoimmune process. Rheumatic fever is linked to the pathological result of interference of the host with GABHS with an inappropriate immune response.[35]

Streptococcal somatic constituents (known as virulence factors) can be disseminated and diffuse through the human body. The precise mechanisms of interaction are not known. The phase of virulence for a given strain of group A streptococcus may be the initial determinant of rheumatogenicity.[21,36] M proteins of the streptococcal serotypes associated with acute rheumatic fever share an epitope with human heart tissue including cardiac myosin and sarcolemmal membrane proteins. These give rise to cross-reactions and inflammatory responses inducing heart valve damage.[21] The cross-reactions were first identified in extracts of cell wall and two sets of studies demonstrated this effect, one with human cardiac sarcolemma and the other with human muscle. Kaplan *et al.*[29,37] showed that injection of a cell-wall extract into rabbits immunized the animals and allowed them to develop antibodies that bound to myocardial tissue from patients who had died from acute rheumatic carditis. Zabriske & Freimer[38] used indirect immunofluorescence studies to show that antibodies could establish a cross-reaction between the streptococcal cell wall and human muscle. The same type of reaction was demonstrated for patients with Sydenham's chorea.

## The body's immune responses

Humoral and cellular immune reactions are triggered in this way and probably take place concomitantly. The humoral phase predominates during an acute episode of rheumatic fever whereas the cellular phase is initiated during the acute phase and leaves traces in the chronic phase.

The humoral response to various components of the streptococcal wall is marked during the first weeks and then slowly returns to normal over a period of a few months or even years. A non-HLA antigen can be detected in subjects with rheumatic fever; a D8/17 antibody has been detected by monoclonal antibodies in a murine model and its incidence is far greater in rheumatic subjects than in the

normal population. During the acute episode, all three cardiac layers are involved in the autoimmune inflammatory reaction[39] and pancarditis occurs. Acute pericarditis, when present, does not evolve towards constrictive pericarditis. The degree of myocarditis varies. The valvular disorder is characterized in childhood by mitral regurgitation. Involvement of the aortic valve, when present, is always associated with involvement of the mitral valve. The mitral regurgitation is linked to incompetence of the anterior valve with annular dilatation and caudal elongation (prolapse).

The cellular response is observed early and is expressed in the Ashoff bodies found in myocardial tissue. More detailed analysis reveals the existence of inflammatory cells: mononuclear cells, macrophages and fibroblasts in the rheumatic valvular tissue. T cells[40] are present from the acute stage of carditis: CD4 cells predominate and the CD4/CD8 ratio is increased. This ratio takes several weeks to return to normal as in the peripheral blood. The presence of HLA-DR antigen on the fibroblasts suggests that these cells present the antigen to the CD4 lymphocytes thus promoting the valvular inflammatory response. CD4 cell clones have strong cross-reactivity with sequences of M protein, especially in valvular tissue (mainly mitral tissue, but aortic tissue also to a lesser degree) and this is much more marked in the valves than in the remainder of the myocardium. This cellular response, which is present from the acute phase, has long-term consequences resulting in persistence of chronic valvular lesions especially at the mitral level. It may be involved in the subsequent development of mitral stenosis. All these factors, although favouring autoimmunity, are not in themselves proof of their role in the pathogenesis of rheumatic fever.

## Clinical expression

The clinical aspects of acute rheumatic fever are described in terms of Jones' criteria (Table I) first established in the 1940s and brought up to date in 1965 with the introduction of evidence of streptococcal infection.[41–45] They are applicable at the acute stage of the disease; patients satisfying these criteria very probably (but not definitely) have rheumatic fever: the diagnosis is clinical in the absence of any pathognomonic laboratory test. These criteria do not exclude other causes of febrile polyarthritis, which need to be tested for. In the absence of any other explanation, the diagnosis of rheumatic fever may be maintained even if the symptoms are incomplete. It is very rare to diagnose rheumatic fever in patients under 3 years of age and older than 23 years; 92% of cases occur under 18 years of age; the frequency of the disease is the same among both sexes.

The clinical appearance of an attack of rheumatic fever has not changed over time. Polyarthritis with fever is still the initial warning sign. Arthritis is only present in 75% of patients. The main joints affected are knees, ankles, elbows, wrists (and, far more rarely, the hips and spine). The migratory character of the arthritis and the intensity of the pain are suggestive of rheumatic fever and are not consistently bilateral and symmetrical.

Carditis occurs early (within 3 weeks of onset) and inconsistently: it is seen in 50% of cases on clinical examination and 70% of cases by cardiac sonography. This investigation is essential and should always be carried out promptly when a diagnosis of rheumatic fever is suspected. Polyarthritis with fever is frequent in children but has many causes. Therefore, demonstration of concurrent carditis supports the diagnosis of rheumatic fever. The carditis may appear during each bout of the disease. It is an inflammatory pancarditis affecting all three tunics. Endocarditis is always present; and is the most serious sequela to GABHS infection leading frequently to rheumatic heart disease. Extended murmurs are detected on auscultation that express isolated mitral, or mixed mitral and aortic, regurgitation. These findings should be confirmed by Doppler sonography. Myocardial disease is inconsistent and may range from congestive heart failure, which is rarely life-

**Table I.** Jones' criteria for diagnosis of rheumatic fever[a]

| Criterion | Major | Minor |
|---|---|---|
| Clinical | carditis | fever |
| | periarthritis | arthralgia |
| | chorea | previous bouts of rheumatic or cardiac disease |
| | erythema marginatum | |
| | subcutaneous nodules | |
| Laboratory | | inflammation proteins |
| | | lengthening of PR segment (ECG) |
| | | evidence of streptococcal infection: antistreptodornase, positive culture for GABHS, recent scarlet fever |

[a]Rheumatic fever is very likely if two major criteria or one major and two minor criteria are satisfied in a subject with previous streptococcal infection.

threatening, to more frequent disorders of atrioventricular conduction. The classic lengthening of the PR interval is a good diagnostic feature in febrile children with polyarthritis. Electrocardiography, a simple baseline investigation, should always be carried out in all patients. Pericarditis is rare (<5%). Myocarditis and pericarditis, once cured, do not leave sequelae.

The quasi-pathognomonic skin signs (erythema marginatum and subcutaneous nodules) are rare and more frequently observed when there is cardiac involvement. These features occur late. A rash like that seen in scarlet fever is possible, reflecting recent streptococcal infection. Finally, the diagnosis can be confounded if there is fever and abdominal pain initially.[46]

## Laboratory criteria

When investigating a febrile patient with polyarthritis, the erythrocyte sedimentation rate (ESR) should be obtained as an emergency measure. This is usually >80; an initial ESR of <60 renders a diagnosis of rheumatic fever less likely and is more compatible with a post-streptococcal syndrome.[47] The other laboratory tests contribute to the diagnosis retrospectively: positive culture of GABHS is inconsistent and the absence of a positive culture does not exclude the diagnosis. It is better to take throat swabs from the immediate family and, if GABHS is found, to carry out serotyping. Tests for various antibodies—antistreptolysin O antibody (ASLO) and anti-DNase B (ASDB)—where necessary, are of limited diagnostic value: obtaining results is slow: two samples are required at an interval of 15 days or 3 weeks and 20% of cases of rheumatic fever are not accompanied by raised antibody levels.

## Evolution

Given the current rarity of the disease and the absence of formal laboratory criteria, the diagnosis of rheumatic fever is based on clinical criteria and is difficult to make. Late diagnosis is prejudicial since a bout of rheumatic fever is a therapeutic emergency.

The therapeutic management of the disease[48–53] is summarized in Table II which describes the anti-infective and anti-inflammatory measures needed and the curative and preventive phases of the treatment. Steroid dependence prolongs the treatment. Intramuscular penicillin is the most reliable route provided that the injections are given sufficiently frequently (every 3 weeks).

For an initial bout of rheumatic fever the prognosis is good, except for the rare deaths owing to heart failure. Correct prophylaxis prevents any risk of recurrence, stressing the importance of satisfactory compliance with the

**Table II.** Principles of therapeutic management

**A.** Antibiotic regimens

| Antibiotic | Eradication regimen | Secondary prophylaxis |
|---|---|---|
| Benzathine penicillin, im | | |
| bodyweight < 27 kg | 600,000 IU × 1 | 1.2 MIU every 3–4 weeks |
| bodyweight > 27 kg | 1.2 MIU × 1 | |
| Penicillin V, oral | 100,000 IU/kg/day for 10 days in 3 doses/day | 20,000–30,000 IU/kg/day in 2 doses/day |
| Erythromycin | 50 mg/kg/day in 3 doses/day | 10–20 mg/kg/day in 2 doses/day |

**B.** Anti-inflammatory treatment

| | Anti-inflammatory agent | |
|---|---|---|
| Duration of carditis | corticosteroids | aspirin |
| Life-long treatment (carditis positive) | prednisolone 2 mg/kg/day<br>1 dose/day for 3–4 weeks decreasing over 6–8 weeks | –<br>(⩽80 mg) |
| Five years treatment (carditis negative) | not essential | 70–100 mg/kg/day<br>4 doses/day for 3–4 weeks decreasing over 6–8 weeks |

preventive anti-infective treatment. Relapses are more frequent in the first 3–5 years following the first episode. Each bout carries the risk of cardiac involvement and the existence of cardiac disorders in the initial phase increases this risk.

The seriousness of rheumatic fever resides entirely in the cardiac sequelae: they are mainly mitral and sometimes aortic. Cardiac sonography must be carried out on these subjects every 6 months; usually there is attenuation of the lesions during the first 2 years. It is important to remember the strict instructions for prevention of the risk of bacterial endocarditis in all children who have suffered cardiac disorders.

## Conclusions

It is important to understand the significance of infection sequelae when about 238 million cases of pharyngitis are diagnosed annually judging by prescriptions for antibiotics in children and adults. GABHS plays a limited role in the aetiology of sore throat, being present in only about 20% of cases, but the current strategy in much of Europe and North America is to give antibiotic therapy for all cases of pharyngitis and tonsillitis without prior investigation to confirm GABHS. It has been demonstrated in many countries that this approach has contributed to the decline in the incidence of rheumatic fever. Until now the micro-organism has remained susceptible to penicillin *in vitro*. A number of surveys have shown that oral penicillin accounts for 10–40% of the antibiotics now prescribed for tonsillopharyngitis. The introduction of simple tests for the rapid diagnosis of GABHS could allow a more rational approach to the treatment of pharyngitis with improved targeting of antibiotic therapy. An additional strategy may be to use antibiotics other than penicillin, possibly for a shorter period of 5 days to increase compliance with treatment. The combined strategies, rapid tests for GABHS and short-duration treatments, have proved as efficacious as penicillin without evidence of a rise in the incidence of rheumatic fever (see D. Adam *et al.*, this supplement).

Rheumatic fever is now a rare disease in much of Europe and North America and this renders its diagnosis more difficult. Initial treatment is well defined but poor compliance with preventive treatment carries the risk of cardiac disease which can sometimes be severe.

It is very difficult to predict how rheumatic fever may evolve in the coming years. It is not clear whether the epidemic outbreaks or the observed rare cases are aberrations in the generally declining profile currently observed in developed countries or if there is a true risk of resurgence of the disease. Consequently, accurate identification of GABHS sore throats and follow-up of rheumatogenic strains together with their appropriate treatment is still important.

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