Rheumatic fever

Author: Dr Catherine Weil-Olivier[1]
Creation Date: March 2003
Update: January 2004

Scientific Editor: Dr Frank Dressler

[1]Hôpital Louis Mourier, 178, rue Renouillers, 92700 Colombes, France.
c.weilolivier@lmr.ap-hop-paris.fr

Abstract
Rheumatic fever (RF) is a multisystem inflammatory disease, which occurs as a delayed sequel to group A streptococcal pharyngitis. It may involve connective tissues of the heart, joints, skin and vessels. In developing countries, rheumatic fever is endemic and remains one the major causes of acquired cardiovascular disease. It is a major cause of mortality among subjects under 50 years of age and its annual incidence is 100-200 times greater than that observed in industrialized countries. Migratory polyarthritis with fever is frequently the initial sign. Arthritis is only present in 75% of patients. The most commonly affected joints are the knees, ankles, elbows, wrists and, far more rarely, the hips and small joints of hands and feet. The migratory character of the arthritis and the intensity of the pain are suggestive of RF, and these features 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 in 70% of cases by echocardiography. The carditis may appear during any bout of the disease. Endocarditis is always present and may be the most serious sequela to GABHS (Group A beta haemolytic streptococcal) infection, leading to permanent rheumatic heart disease. Treatment of RF depends on the symptomatology. Fever and joint pain/swelling are usually treated with aspirin. All patients should be treated with a ten-day course of penicillin (or alternative antibiotic in cases of allergy to penicillin). Prophylactic antibiotics to prevent further GABHS infections, which may cause a recurrence of symptoms, should be prescribed. The antibiotic treatment consists of intramuscular injection of penicillin every 3-4 weeks or bi-daily penicillin tablets. Other antibiotics are sometimes required. Antibiotics should be continued at least up to adulthood for children without carditis and for life in patients with carditis

Keywords
Rheumatic fever, GABHS, penicillin, pharyngitis

Disease name and synonyms

Rheumatic fever (RF)
Acute articular rheumatism

Diagnostic Criteria/ Definition

RF is a multisystem inflammatory disease that occurs as a delayed sequel to group A

streptococcal pharyngitis. It may involve connective tissues of the heart, joints, skin and vessels.
The clinical features of acute RF are described under Jones' criteria (table 1), which were first established in the 1940s and updated in 1992 (1-6). These criteria are used at the acute stage of the disease; patients meeting these criteria are highly likely to have RF. The diagnosis is clinical in the absence of any pathognomonic laboratory test. RF criteria do not exclude other causes of febrile polyarthritis, which need to be considered. In the absence of any other explanation, the diagnosis of RF may be maintained, even if the symptoms are incomplete.

Table 1: Jones criteria for the diagnosis of Rheumatic Fever (6)

Criterion	Major	Minor
Clinical	Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules	Fever Arthralgia
Laboratory		Elevated acute-phase reactants (ESR, CRP) Prolonged PR interval (ECG) Evidence of antecedent group A streptococcal infection: positive culture for GABHS*, elevated or rising streptococcal antibody titer

The diagnosis of rheumatic fever is highly suggested when two major criteria or one major and two minor criteria are fulfilled in a patient with previous streptococcal infection
***GABHS: Group A beta haemolytic streptococcus**

Epidemiology

The spectacular evolution of RF over the years is surprising. The frequency of the disease was very high at the beginning of the 20th century (100-200 cases per 100,000 in the US population in 1900 and 50 per100,000 in 1940). RF was a major cause of mortality in children and adolescents and a common cause of heart disease in young adults. Until the early 1980's there was a steep decline to about 0.5 per 100,000 in the USA. Since then, there have been several localized outbreaks of RF. In Europe, there have been similar declines in the overall incidence of RF, and it has become a rare disease. The incidence of RF varies greatly between countries (Table 2). In developing countries, RF is endemic and remains the major cause of acquired cardiovascular disease. It is also a major cause of mortality in subjects under 50 years of age, and the annual incidence of RF is 100-200 times greater than that observed in industrialized countries. RF usually occurs in patients between 5 and 15 years of age. It is rare before the age of 3 years and 92% of cases occur until the age of 18 years.
RF is a complication of GABHS infection in a predisposed human host. Fewer than 2 to 3% of previously healthy persons develop RF following GABHS pharyngitis. RF does not occur after streptococcal pyoderma.

Clinical description

Given the current rarity of the disease and the absence of established laboratory criteria, the diagnosis of RF is based on clinical criteria and may be difficult to establish. However, late diagnosis is prejudicial since a bout of RF is a therapeutic emergency.

Polyarthritis with fever is still the initial warning sign. Arthritis is the most common major manifestation of RF, but only present in 75% of patients. The most commonly affected joints are the knees, ankles, elbows, and wrists and, far more rarely, the hips and the small joints of hands and feet. The migratory character of the arthritis and the intensity of the pain are suggestive of RF, and these features are not consistently bilateral and symmetrical.
Carditis is the most serious manifestation of RF and occurs early (within 3 weeks of onset). It is seen in 50% of cases on clinical examination, and in 70% of cases by echocardiography. Clinically, rheumatic carditis is almost always associated with a murmur of valvulitis, most commonl the apical systolic murmur of mitral regurgitation and/or the basal diastolic murmur of aortic regurgitation. Suspected valvulitis should be evaluated promptly by echocardiography. Carditis may appear during any bout of the disease. It is an inflammatory pancarditis affecting endo-, myo- and pericardium. Endocarditis is almost always present and is the most serious sequela to GABHS (Group A beta haemolytic streptococcal) infection, leading frequently to permanent rheumatic heart disease. Myocardial disease is inconsistent and may range from congestive heart failure, which is rarely life threatening, to more frequent disorders of atrioventricular conduction. The classic lengthening of the PR interval is one of the minor Jones criteria. Electrocardiography should be carried out in all patients. Pericarditis is rare (< 5%). Myocarditis and pericarditis once cured do not leave sequelae.
Sydenham's chorea (SC) is a delayed manifestation (1 to 6 months) of GABHS

infection typically associated with RF. It is characterized by sudden, involuntary, arrhythmic, clonic, and purposeless movements resulting from an autoimmune attack on the CNS. In addition to chorea, the acute attack is almost always characterized by psychiatric symptoms such as irritability, obsessions and compulsions, tics, and psychotic symptoms. Diagnosis of SC is more complicated due to the lower frequency of elevated streptococcal antibodies and acute-phase reactants in patients with SC than that found in patients with acute RF presenting with arthritis or carditis. Motor symptoms observed in patients with SC include ballismus, facial grimacing, gross fasciculations of the tongue, loss of fine motor control, hypotonia, motor impersistence, gait disturbance, and speech abnormalities such as dysarthria and explosive speech. Chorea occurs most commonly between the ages of 7 and 14 years with the peak incidence at 8 years. It is rare after puberty and exceedingly uncommon after the age of 20 years. In the 1950's chorea occurred in approximately 50% of cases of acute RF. The incidence has declined substantially with chorea now being a component of less than 10% of cases of acute RF.

The quasi-pathognomonic skin signs (erythema marginatum and subcutaneous nodules) are rare and more frequently observed when there is cardiac involvement. Compared to arthritis, carditis and erythema marginatum, subcutaneous nodules occur late in the course of RF. A rash similar to that seen in scarlet fever is possible, reflecting recent streptoccocal infection.

Table 2: Differences in the incidence of rheumatic fever between countries (6-12)

Country	Incidence of RF in the children and adolescents
Martinique	20/100,000
Guadeloupe	17/100,000
Egypt	10/100,000
Thailand	1.2-2.1/100,000
India	1.8-11/100,000
USA	0.23-1.88/100,000
Japan	0.23-1.88/100,000
Denmark	0.23-1.88/100,000
Great Britain	0.23-1.88/100,000
Australia	0.23-1.88/100,000
France	0.08-0.15/100,000

Etiology

Pathogenesis

Cheadle reported the association between a throat infection and RF in 1889 (13). As early as 1900, several authors pointed out the role of Streptococcus and the proliferative and non-suppurative character of RF. The introduction of antibiotics, sulphonamides and then penicillin, in the 1940s demonstrated that penicillin treatment for streptococcal pharyngitis had a preventive effect against RF (14,15).

The microorganism action is mediated by its virulence factors (7,11,16,17). The appearance of “toxic shock syndrome” and the stable number of glomerulonephritis and sore throat cases in industrialized countries, suggests that the evolution of these factors in specific strains accounts for the epidemic outbreaks of RF in the USA, and its persistence in France as a sporadic infection.

As a result of the many findings accumulated over the last 100 years, the relationship between GABHS pharyngitis and the development of RF is now universally recognized. Effective treatment of GABHS tonsillopharyngitis prevents RF. However it has been demonstrated that GABHS remains present in the throat even after adequate treatment in about 10% of cases.

The close link between Streptococcus pyogenes and RF is well established, but the precise pathogenesis of RF and rheumatic heart is not fully understood. Correlation between the cardiac manifestations and the autoimmune response has been established (9,18).This autoimmune response is very important and could be detailed (more than predisposition) : refer to the main article for that.

Predisposition

The importance of individual host factors in RF has been suspected for more then a century (19). The first disease reports highlighted a frequent predisposition to RF, but a specific genetic profile or Mendelian transmission of the disease have never been demonstrated. The discovery of specific HLA antigens within the context of various autoimmune diseases led to an intensive search for such antigens in RF. Ayoub *et al* (20) were the first to demonstrate an increased frequency of HLA-DR4 in white RF patients and HLA-DR2 in black RF patients. Although this remains true in Utah and Turkey, associations with other HLA types have been found in other countries in subjects with rheumatic heart disease. Examples include DRA and DRw6 in black African patients in South Africa; DR7 and Dw53 in Brazil; DQw2 in India; HLA-B17, HLA-B21 and HLA-Cw4 in Uzbekistan. The marked variability of dominant HLA antigens in different populations suggests that their close association with the disease is unlikely.

Alloantigens, which are expressed at the surface of lymphocytes and recognized by monoclonal antibodies, appear to be markers of that susceptibility, especially when there is cardiac involvement (found in 75-90% of cases). These alloantigens appear to be expressed only after stimulation by GABHS antigen (19).

Diagnostic Methods

When investigating a febrile patient with polyarthritis, the erythrocyte sedimentation rate (ESR) should be measured in priority. ESR is usually >80; with an initial ESR of <60, the diagnosis of RF is less likely and this rate is more compatible with a post-streptococcal syndrome (21). The other laboratory tests contribute to the diagnosis retrospectively: positive throat culture of GABHS is inconsistent and the absence of a positive culture does not exclude the diagnosis. It is advisable to also take throat swabs from the immediate family and, if GABHS are 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 (20% of cases of RF are not accompanied by raised antibody levels).

Management including treatment and outcome

The therapeutic management of the disease has three main goals: first, the eradication of GABHS, second an anti-inflammatory treatment of the symptoms of RF and third long term prophylaxis of recurrent infection Table 3 describes the antibiotic and anti-inflammatory measures required. The anti-inflammatory treatment is longer in case of steroid dependence. Intramuscular penicillin is the most reliable administration route, provided that the injections are given every 3 weeks. Intramuscular penicillin is the most reliable administration route, provided that the injections are given every 3 weeks.

For an initial bout of RF, the prognosis is good, except for the rare deaths due to heart failure. Correct prophylaxis prevents recurrences, stressing the importance of satisfactory compliance with the preventive anti-infective treatment. Relapses are more frequent in the first 3-5 years following the first episode.

Each bout is associated with a risk of cardiac involvement and the existence of cardiac disorders (*i.e* carditis) in the initial phases increases this risk.

The severity of RF lies entirely in the cardiac sequelae, which are mainly mitral and sometimes aortic valve disease. Echocardiography must be carried out on these patients every 6 months; usually there is attenuation of the lesion during the first 2 years. All children who have suffered cardiac sequelae must be thoroughly instructed on risk prevention of bacterial endocarditis.

Table 3: Principles of therapeutic management

I- Antibiotic regimens

Antibiotic	Eradication regimen	Secondary prophylaxis
Benzathine penicillin im*		
Bodyweight <27kg	600,000 IU x 1	1.2 MIU** every 3-4 weeks
Bodyweight >27kg	1.2 MIU x 1	
Penicillin V, oral	100,000 IU/kg/day for 10 days 750 mg in 3 doses/day	20,00-300,000 IU/kg/day 500 mg in 2 doses/day
Erythromycin	40mg/kg/day in 3 doses/day	500 mg in 2 doses/day

Duration of treatment: if no carditis : five years long, up to adolescence ; if one episode of carditis : life long

II- Anti-inflammatory treatment

	Anti-inflammatory agent	
Carditis	**Corticosteroids**	**Aspirin**
Severe carditis present	Prednisolone 2mg/kg/day< 80 mg /day 1 dose/day for 3-4 weeks decreasing over 6-8 weeks	start aspirin 1 week before termination of steroids
Mild to moderate carditis	Not essential	80-100 mg/kg/day4 doses/day for 4-8 weeks Decreasing over the following 4 weeks

***im: intramuscular**
****MIU: million international units**

Conclusions

Understanding the significance of infection sequelae is crucial when approximately 238 million cases in the world of pharyngitis are diagnosed annually on the basis of the number of antibiotics prescriptions in children and adults. GABHS plays a limited role in the etiology of sore throat, being present in only about 20% of cases. 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 the use of antibiotics other than penicillin, possibly for a shorter period (5 days) in order 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 RF (22).

RF is now a rare disease in most of Europe and North America, making 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 evolution in the coming years. It is not clear whether the epidemic outbreaks or the rare observed 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.

Unresolved questions

RF still poses many questions (23-26).

Does the disease still exist and what is its epidemiology?

How can we understand its pathogenesis?

Have its clinical expression and out come changed and how should we manage the treatment of sore throat in the future?

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, the precise pathogenesis of rheumatic heart disease is not fully understood.

References

1- Ayoub EM. Acute rheumatic fever and poststreptococcal reactive arthritis. In : Cassidy JT, Petty RE (eds.) : Textbook of Pediatric Rheumatology, 4th edition, Saunders, Philadelphia, 2001 ; pp. 690-705.

1- Homer C, Shulman ST. Clinical aspects of acute rheumatic fever. J Rheumatol Suppl. 1991 Apr;29:2-13

2- Pinals RS. Polyarthritis and fever. N Engl J Med. 1994;330:769-74.

3- Gibofsky A, Zabriskie JB. Rheumatic fever and poststreptococcal reactive arthritis. Curr Opin Rheumatol. 1995;7:299-305

4-Schaffer FM, Agarwal R, Helm J, Gingell RL, Roland JM, O'Neil KM. Poststreptococcal reactive arthritis and silent carditis: a case report and review of the literature. Pediatrics. 1994;93:837-9.

5- Stollerman GH. The return of rheumatic fever. Hosp Pract (Off Ed). 1988;23:100-6, 109-13.

6- Dajani AS et al. Guidelinies for the diagnosis of rheumatic fever. Jones criteria, 1992 update. JAMA 1992;268:2069-73.

6- Bach JF, Chalons S, Forier E, Elana G, Jouanelle J, Kayemba S, Delbois D, Mosser A, Saint-Aime C, Berchel C. 10-year educational programme aimed at rheumatic fever in two French Caribbean islands. Lancet. 1996;347(9002):644-8.

7- Stollerman GH. Rheumatogenic group A streptococci and the return of rheumatic fever. Adv Intern Med. 1990;35:1-25.

8- Schwartz B, Facklam RR, Breiman RF. Changing epidemiology of group A streptococcal infection in the USA. Lancet. 1990;336(8724):1167-71.

9- Leiner S. Surveillance for rheumatic fever. N Engl J Med. 1996;334:273-4.

10- Markowitz M. The decline of rheumatic fever: role of medical intervention. Lewis W. Wannamaker Memorial Lecture. J Pediatr. 1985;106:545-50.

11- Markowitz M. Changing epidemiology of group A streptococcal infections. Pediatr Infect Dis J. 1994;13:557-60.

12- Hoffmann S, Henrichsen J, Schmidt K. Incidence and diagnosis of acute rheumatic fever in Denmark, 1980 and 1983. A retrospective analysis of the fulfillment of the revised Jones criteria in hospitalized patients. Acta Med Scand. 1988;224:587-94.

13- Cheadle WB. Harveian lectures on the various manifestations of the rheumatic state as exemplified in childhood and early life. Lancet 1889, 827-7

14- Halperin S, Clogg D, MacDonald NE, Delage G, Jadavjit T, King S, et al. Group A streptococcus: a re-emergent pathogen. Canadian Medical Assocition Journal, 1993; 148: 1909-11

15- Massell BF, Chute CG, Walker AM, Kurland GS. Penicillin and the marked decrease in morbidity and mortality from rheumatic fever in the United States. N Engl J Med. 1988; 318:280-6.

16- Gordis L.The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T. Duckett Jones memorial lecture. Circulation. 1985;72:1155-62.

17- Kaplan MH, Meyeserian M. An immunological cross-reaction between group A streptococcal cells and human heart tissue. Lancet , 1962, 706-10

18- Veasy LG, Hill HR. Immunologic and clinical correlations in rheumatic fever and rheumatic heart disease. Pediatr Infect Dis J. 1997;16:400-7.

19- Kaplan EL. Epidemiological approaches to understanding the pathogenesis of rheumatic fever. Int J Epidemiol. 1985;14:499-501.

20- Ayoub EM, Barrett DJ, Maclaren NK, Krischer JP. Association of class II human histocompatibility leukocyte antigens with rheumatic fever. J Clin Invest. 1986;77:2019-26.

21- Barnert AL, Terry EE, Persellin RH. Acute rheumatic fever in adults. JAMA. 1975;232:925-8.

22- Adam D, Scholz H, Helmerking M. Comparison of short-course (5 day) cefuroxime axetil with a standard 10 day oral penicillin V regimen in the treatment of tonsillopharyngitis. J Antimicrob Chemother. 2000;45 Suppl:23-30.

23- Denny FW Jr. A 45-year perspective on the streptococcus and rheumatic fever: the Edward H. Kass Lecture in infectious disease history. Clin Infect Dis. 1994;19:1110-22.
24- Bisno AL. Acute rheumatic fever: forgotten but not gone. N Engl J Med. 1987;316:476-8.
25- Bisno AL. Group A streptococcal infections and acute rheumatic fever. N Engl J Med. 1991;325:783-93
26- Bisno AL. Nonsuppurative poststreptococcal sequelae: rheumatic fever and glomerulonephritis. In Principles and practice of Infectious diseases, 3rd edn (Mandell GL, Douglas G et Bennet JE Eds) , pp 1528-39