Rheumatic Fever

ETIOLOGY

As many as ⅔ of the patients with an acute episode of rheumatic fever have a history of an upper respiratory tract infection several weeks before, and the peak age and seasonal incidence of acute rheumatic fever closely parallel those of GAS infections. Patients with acute rheumatic fever almost always have serologic evidence of a recent GAS infection. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by outbreaks of acute rheumatic fever. Antimicrobial therapy that eliminates GAS from the pharynx also prevents initial episodes of acute rheumatic fever, and long-term, continuous prophylaxis that prevents GAS pharyngitis also prevents recurrences of acute rheumatic fever.

EPIDEMIOLOGY

Worldwide, rheumatic heart disease the most common form of acquired heart disease in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions. The incidence of both initial attacks and recurrences of acute rheumatic fever peaks in children 5–15 yr of age, the age of greatest risk for GAS pharyngitis. In addition, there appears to be a genetic predisposition to acute rheumatic fever. Studies in twins have shown a higher concordance rate of acute rheumatic fever in monozygotic than in dizygotic twin pairs.

PATHOGENESIS

GAS produces several enzymes that are cytotoxic for mammalian cardiac cells, such as streptolysin O, which has a direct cytotoxic effect on mammalian cells in tissue culture. Additionally, the involvement of GAS superantigens such as pyrogenic exotoxins in the pathogenesis of acute rheumatic fever has been proposed.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The **Jones criteria** are intended only for the diagnosis of the initial attack of acute rheumatic fever and not for recurrences. There are **5 major** and **4 minor criteria** and an absolute requirement for evidence (microbiologic or serologic) of recent GAS infection. The diagnosis of acute rheumatic fever can be established by the Jones criteria when a patient fulfills 2 major criteria or 1 major and 2 minor criteria and meets the absolute requirement. There are 3 circumstances in which the diagnosis of acute rheumatic fever can be made without strict adherence to the Jones criteria. Chorea may occur as the only manifestation of acute rheumatic fever. Similarly, indolent carditis may be the only manifestation in patients who 1st come to medical attention months after the onset of acute rheumatic fever.

Guidelines for the Diagnosis of Initial Attack of Rheumatic Fever

MAJOR MANIFESTATIONS[1]	MINOR MANIFESTATIONS	PPORTING EVIDENCE OF ANTECEDEI ROUP A STREPTOCOCCAL INFECTIO
Carditis	**Clinical features:**	sitive throat culture or rapid streptococcal antig test
Polyarthritis	Arthralgia	
	Fever	evated or increasing streptococcal antibody tit
Erythema marginatum	**Laboratory features:**	
Subcutaneous nodules	Elevated acute phase reactants:	
	Erythrocyte sedimentation rate	

MAJOR MANIFESTATIONS[1]	MINOR MANIFESTATIONS	SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION
	C-reactive protein	
	Prolonged PR interval	
Chorea		

* The presence of 2 major or of 1 major and 2 minor manifestations indicates a high probability of acute rheumatic fever if supported by evidence of preceding group A streptococcal infection

Major Manifestations

There are 5 major criteria. The presence of 2 major criteria with evidence (microbiologic or serologic) of recent GAS infection fulfills the Jones criteria.

MIGRATORY POLYARTHRITIS

Arthritis occurs in about 75% of patients with acute rheumatic fever and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. The joint involvement is characteristically migratory in nature; a severely inflamed joint can become normal within 1–3 days without treatment, as 1 or more other large joints become involved. A dramatic response to even small doses of salicylates is another characteristic feature of the arthritis, and the absence of such a response should suggest an alternative diagnosis. Rheumatic arthritis is typically not deforming.

CARDITIS

Carditis and resultant chronic rheumatic heart disease are the most serious manifestations of acute rheumatic fever and account for essentially all of the associated morbidity and mortality. Endocarditis (valvulitis), which manifests by 1 or more cardiac murmurs, is a universal finding in rheumatic carditis, whereas the presence of pericarditis or myocarditis is variable.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial involvement. Mitral regurgitation is characterized by a high-pitched apical holosystolic murmur radiating to the axilla. Carditis occurs in about 50–60% of all cases of acute rheumatic fever. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease.

CHOREA

Sydenham chorea occurs in about 10–15% of patients with acute rheumatic fever and usually presents as an isolated, frequently subtle, neurologic behavior disorder. Clinical maneuvers to elicit features of chorea include (1) demonstration of **milkmaid's grip** (irregular contractions of the muscles of the hands while squeezing the examiner's fingers), (2) spooning and pronation of the hands when the patient's arms are extended, (3) wormian darting movements of the tongue upon protrusion, and (4) examination of handwriting to evaluate fine motor movements.

ERYTHEMA MARGINATUM

Erythema marginatum is a rare (<3% of patients with acute rheumatic fever) but characteristic rash of acute rheumatic fever. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic. It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

SUBCUTANEOUS NODULES

Subcutaneous nodules are a rare (≤1% of patients with acute rheumatic fever) and consist of firm nodules approximately 1 cm in diameter along the extensor surfaces of tendons near bony

prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Manifestations

The 2 clinical minor manifestations are arthralgia (in the absence of polyarthritis as a major criterion) and fever (typically temperature ≥102°F and occurring early in the course of illness). The 2 laboratory minor manifestations are elevated acute-phase reactants (e.g., C-reactive protein, erythrocyte sedimentation rate) and prolonged PR interval on electrocardiogram (1st degree heart block).

Acute rheumatic fever typically develops 2–4 wk after an acute episode of GAS pharyngitis .One third of patients have no history of an antecedent pharyngitis. If only a single antibody is measured (usually antistreptolysin O), only 80–85% of patients with acute rheumatic fever have an elevated titer; however, 95–100% have an elevation if 3 different antibodies (antistreptolysin O, anti-DNase B, antihyaluronidase) are measured.

Differential Diagnosis.

Rheumatoid arthritis in particular must be distinguished from acute rheumatic fever. Spiking fevers, lymphadenopathy, and splenomegaly are more suggestive of rheumatoid arthritis than acute rheumatic fever. The response to salicylate therapy is also much less dramatic with rheumatoid arthritis than with acute rheumatic fever. Systemic lupus erythematosus can usually be distinguished from acute rheumatic fever on the basis of the presence of antinuclear antibodies with systemic lupus erythematosus.

When carditis is the sole major manifestation of suspected acute rheumatic fever, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should also be considered. These patients can usually be distinguished from patients with acute rheumatic fever by blood cultures and the presence of associated findings (e.g., hematuria, splenomegaly, splinter hemorrhages). When chorea is the sole major manifestation of suspected acute rheumatic fever, Huntington chorea, Wilson disease, systemic lupus erythematosus, and various encephalitides should also be considered. These other diseases are usually identified by the history, laboratory studies, and clinical findings.

TREATMENT

Antibiotic Therapy

Once the diagnosis of acute rheumatic fever has been established and regardless of the throat culture results, the patient should receive 10 days of orally administered penicillin or erythromycin, or a single intramuscular injection of benzathine penicillin to eradicate GAS from the upper respiratory tract.

Anti-Inflammatory Therapy

Anti-inflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute rheumatic fever. Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 100 mg/kg/day in 4 divided doses PO for 3–5 days, followed by 75 mg/kg/day in 4 divided doses PO for 4 wk. Patients with carditis and cardiomegaly or congestive heart failure should receive corticosteroids. The usual dose of prednisone is 2 mg/kg/day in 4 divided doses for 2–3 wk followed by a tapering of the dose that reduces the dose by 5 mg/24 hr every 2–3 days. At the beginning of the

tapering of the prednisone dose, aspirin should be started at 75 mg/kg/day in 4 divided doses for 6 wk. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen.

Sydenham Chorea

Sedatives may be helpful early in the course of chorea; phenobarbital (16–32 mg every 6–8 hr PO) is the drug of choice. If phenobarbital is ineffective, then haloperidol (0.01–0.03 mg/kg/24 hr divided bid PO) or chlorpromazine (0.5 mg/kg every 4–6 hr PO) should be initiated.

COMPLICATIONS

The the long-term sequelae of rheumatic fever are usually limited to the heart. Patients with residual rheumatic valvular disease do not always require endocarditis prophylaxis. Patients who have had rheumatic fever but have no evidence of residual valvular disease do not require endocarditis prophylaxis.

PROGNOSIS

Approximately 70% of the patients with carditis during the initial episode of acute rheumatic fever recover with no residual heart disease; the more severe the initial cardiac involvement, the greater the risk for residual heart disease. Patients who have had acute rheumatic fever are susceptible to recurrent attacks following reinfection of the upper respiratory tract with GAS. Therefore, these patients require long-term continuous chemoprophylaxis.

The risk of recurrence is highest immediately after the initial episode and decreases with time. Approximately 20% of patients who present with “pure” chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 yr. Therefore, patients with chorea, even in the absence of other manifestations of rheumatic fever, require long-term antibiotic prophylaxis.

PREVENTION

Prevention of both initial and recurrent episodes of acute rheumatic fever depends on controlling GAS infections of the upper respiratory tract. Prevention of initial attacks (primary prevention) depends on identification and eradication of the GAS that produces episodes of acute pharyngitis. Individuals who have already suffered an attack of acute rheumatic fever are particularly susceptible to recurrences of rheumatic fever with any subsequent GAS upper respiratory tract infection, whether or not they are symptomatic. Therefore, these patients should receive continuous antibiotic prophylaxis to prevent recurrences (**secondary prevention**).

Primary Prevention

Appropriate antibiotic therapy instituted before the 9th day of symptoms of acute GAS pharyngitis is highly effective in preventing 1st attacks of acute rheumatic fever from that episode. However, about ⅓ of patients with acute rheumatic fever do not recall a preceding episode of pharyngitis.

Secondary Prevention

Because patients who have had carditis with their initial episode of acute rheumatic fever are at a relatively high risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive antibiotic prophylaxis well into adulthood and perhaps for life.

Patients who did not have carditis antibiotic prophylaxis may be discontinued when they reach their early 20s and after at least 5 yr have elapsed since their last episode of acute rheumatic fever.The regimen of choice for secondary prevention is a single intramuscular injection of

benzathine penicillin G (1.2 million IU) every 4 wk . In certain high-risk patients of the world use of benzathine penicillin G every 3 wk. Penicillin V given twice daily and sulfadiazine given once daily are equally effective when used in such patients. For the exceptional patient who is allergic to both penicillin and sulfonamides, erythromycin given twice daily may be used .