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Acute rheumatic fever

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Acute rheumatic fever is an inflammatory response to group A streptococcal infection which typically occurs two to three weeks after a throat infection. Acute rheumatic fever is characterised by a clinical syndrome, and the most common manifestations are painful joints and carditis. Carditis occurs in about 80% of people with rheumatic fever[3] and commonly affects the mitral and aortic valves, resulting in regurgitation.[4]

The inflammatory process slowly resolves over weeks to months, but about half of individuals are left with chronic rheumatic heart disease.[5-7] The aim of this review is to discuss acute rheumatic fever, in particular its diagnosis and management for the non-specialist.

SOURCES AND SELECTION CRITERIA

We searched Medline and the Cochrane Database of Systematic Reviews using the thesaurus terms "rheumatic fever" AND "rheumatic heart disease". We also used personally archived references. Preference was given to systematic reviews, randomised trials, and evidence based clinical guidelines.

What causes acute rheumatic fever?

Streptococcal pharyngitis is a common infection in childhood. Pharyngitis caused by rheumatogenic strains of group A streptococcus in a susceptible host triggers an abnormal immune inflammatory response. The exact nature of this response is incompletely understood. It is thought to involve cross reactivity of streptococcal antibodies against myocardium, synovial tissue, and, in chorea, the basal ganglia.[10] Molecular mimicry directs the immune response, and the cross reacting antibodies activate the inflammatory process in body tissues.[11] In carditis, activated monoclonal autoantibodies produce T cell infiltration in the valve endothelium.[11]

Who gets it?

Most cases of acute rheumatic fever occur in children aged 5 to 15 years,[12 13] but it may occasionally occur in young adults.

The highest reported incidence globally is among Pacific people, New Zealand Maori,[12] and indigenous Australians.[1 14] The incidence in these population groups has increased in recent years, in contrast to the dramatic decline in the developed world during the latter half of the 21st century.[15] A resurgence of acute rheumatic fever in the intermountain areas of the United States, occurred in the 1980s.[16 17]

Although high rates of acute rheumatic fever and rheumatic heart disease have been observed within particular families and ethnic groups,[27] susceptibility is incompletely understood.[28] Risk is strongly associated with household crowding[30] and socioeconomic deprivation.[31] Currently a large African genome-wide association study aims to determine whether there is a genetic susceptibility to rheumatic heart disease.[32]

How is it diagnosed?

There is no single confirmatory clinical sign or laboratory test. Diagnosis is based on the Jones criteria, which have recently been updated for the first time since 1992. Either two major criteria or one major and two minor criteria, plus laboratory evidence of a recent Group A streptococcal throat infection, are required to confirm the diagnosis of a first episode of rheumatic fever.[33-35]

The updated American Heart Association Jones criteria, together with diagnostic criteria developed in New Zealand and Australia (two high incidence countries), acknowledge the role of echocardiography in the diagnosis of carditis, along with epidemiological considerations. The three sets of diagnostic criteria are risk stratified and aim to improve sensitivity and avoid underdiagnosis in high incidence populations (table 1).[34 36 37]

Major criteria

Carditis (valvulitis)

Globally, about 50-65% of people with rheumatic fever have clinically detectable carditis (inflammation of the heart valve leaflets leading to valvular regurgitation).[3 7] The mitral valve is most often affected, followed by the aortic valve. Pericarditis and myocarditis also occasionally occur.[38] Severe carditis occurs in approximately 20% and can lead to congestive cardiac failure.[4] Milder rheumatic carditis may be subclinical in around 30%—that is, detected by echocardiography but not audible by stethoscope.[3 39-43]

Rheumatic carditis can evolve over weeks to months, underscoring the importance of repeating echocardiography in 2-4 weeks if the first echocardiogram is normal.

Arthritis

Classically, a migratory asymmetrical polyarthritis affecting the large joints occurs. This causes pain, swelling, limitation of movement, and local heat. In practice, the joint

THE BOTTOM LINE

- Acute rheumatic fever and its sequel, chronic rheumatic heart disease, are important global health problems: about 500 000 new cases occur annually and 34 million people worldwide have rheumatic heart disease
- There is no diagnostic laboratory test for rheumatic fever
- Diagnosis requires demonstration of the presence of major and minor criteria and laboratory evidence of a recent streptococcal throat infection
- The recent Australian and New Zealand Diagnostic Criteria extend the 1992 Jones criteria for acute rheumatic fever by including echocardiographic evidence of carditis and a wider spectrum of joint manifestations as major criteria
- Intramuscular benzathine penicillin (benzathine benzylpenicillin) every 3-4 weeks, for 10 years after the most recent episode of rheumatic fever, remains the most effective method for preventing rheumatic fever recurrences and progressive rheumatic heart disease

Table 1 | Major and minor diagnostic criteria for acute rheumatic fever according to the Jones criteria (updated by the American Heart Association (AHA) 2015)[34] and the New Zealand and Australian guidelines[36 37]

Manifestation	Jones criteria[34]		New Zealand guidelines[37]	Australian guidelines[36]
	Low risk population*	Moderate and high risk population		
Clinical carditis	Major	Major	Major	Major
Subclinical (echo) carditis	Major	Major	Major	Major
Polyarthritis	Major	Major	Major	Major
Monoarthritis (aseptic)	—	Major	Major	Major
Polyarthralgia†	Minor	Major	Minor	Major
Monoarthralgia	—	Minor	—	Minor
Chorea	Major	Major	Major	Major
Erythema marginatum	Major	Major	Major	Major
Subcutaneous nodules	Major	Major	Major	Major
Prolonged PR interval in ECG	Minor	Minor	Minor	Minor
Elevated acute phase reactants‡	Minor	Minor	Minor	Minor
Fever	Minor	Minor	Minor	Minor

ECG=electrocardiography.
*AHA defines a low risk population as having rheumatic fever incidence of ≤2/100 000/year.
†Polyarthralgia should be considered as a major manifestation only in moderate to high risk populations after other causes have been excluded.
‡Erythrocyte sedimentation rates: ≥60 mm in first hour in low risk populations and ≥30 mm in high risk populations (AHA); ≥50 mm (New Zealand); ≥30 mm in high risk populations (Australia).

manifestations can be difficult to assess because of good response to non-steroidal anti-inflammatory drugs (NSAIDs), which can mask the symptoms. Monoarthritis, particularly involving the hip, has also been described as a presenting feature in populations with a high incidence of rheumatic fever,[44 45] and all three diagnostic guidelines now accept monoarthritis as a major manifestation (table 1).

Chorea

Chorea affects up to 15% of people with rheumatic fever and is more common in females and adolescents.[46] Chorea typically occurs after a longer latent period (up to six months) after a streptococcal infection, by which time the other inflammatory features of rheumatic fever have resolved. It can follow a fluctuating course over many months, occasionally years, before eventually resolving. Chorea consists of involuntary jerky movements which may be asymmetrical (hemichorea), facial grimacing, fidgeting, clumsiness, and emotional lability. Patients may experience deterioration in handwriting, inability to feed themselves, and unsteady gait leading to falls. Choreiform movements improve during sleep. Up to 60% of patients with chorea will have residual rheumatic heart disease.[47 48] Long term neuropsychiatric problems have also been described in up to 20%.[49]

Subcutaneous nodules

These are rare, described in <5% of cases.[46 50 51] They are small (<2 cm diameter), firm, painless, mobile nodules that occur over the extensor surfaces of elbows, wrists, knees, ankles, and, occasionally, Achilles tendon and spine. They last for up to a fortnight and usually appear during the first weeks of the inflammatory phase. Nodules are often found in association with carditis.[34]

Erythema marginatum

This is also rare, occurring in <5% of cases.[50 51] It is an annular erythema occurring on the torso, upper arms, and legs. Macules and papules spread outwards, with the edges becoming raised. Erythema marginatum can fluctuate over many weeks. It is not itchy or painful. It can be difficult to identify in people with darker skin.

Minor criteria

Arthralgia

If polyarthritis is present, then arthralgia cannot also be used as a minor feature of acute rheumatic fever. There may be no overt signs of arthritis, particularly when NSAIDs have been used. Joint manifestations can take a fluctuating course over days to several weeks, and it can be difficult to differentiate arthritis from arthralgia based on history alone.

First degree heart block

In the absence of carditis, first degree heart block can be included as one of the minor criteria to support the diagnosis of rheumatic fever. The electrocardiographic PR interval should be interpreted according to age and heart rate. In children the upper limit of a normal PR interval is 0.16 seconds if age <12 years and 0.18 seconds if ≥12 years old.[37]

Fever

Varying fever patterns can occur. The fever response is very sensitive to anti-inflammatory medication, and widespread use of paracetamol and NSAIDs can mean fever is short lived. Conversely, when rheumatic fever patients have a marked inflammatory response with evolving arthritis and carditis then persisting high fevers may be observed. In high risk populations, a single temperature measurement ≥38.0°C is nowadays accepted as adequate evidence of fever and a minor criterion for rheumatic fever.[34 36 37]

Elevated acute phase reactants

The erythrocyte sedimentation rate (ESR) is elevated, usually above 50 mm in first hour, and the diagnostic guidelines use varying thresholds ≥30 mm.[34 36 37] The ESR remains elevated for several weeks, often after symptoms have resolved, and can take several months to normalise. C reactive protein concentrations are also elevated, but typically rise and fall more quickly than the ESR. Elevated inflammatory markers are non-specific and may occur with infection and other inflammatory conditions.

Evidence of prior infection with group A streptococcus

A positive pharyngeal culture, or elevated streptococcal blood antibody titre to confirm an immune response to group A streptococcal pharyngitis, is required within the Jones criteria, but these laboratory investigations may not be available in many of the resource limited countries where rheumatic fever is common. Streptococcal antibodies include deoxyribonucleic (anti-DNAase B) and anti-streptolysin titre (ASOT). Antibody titres can rise over several weeks and decline over several months. A fourfold rise or fall in titres is diagnostic of a recent streptococcal infection. Reference ranges have been developed to help interpretation of streptococcal antibody titres in high risk populations.[36 37]

Table 2 | Differential diagnosis of acute rheumatic fever

Differential diagnoses to consider	Discriminating features, investigations
Carditis	
Congenital heart disease	Diagnosis confirmed on echocardiogram
Infective endocarditis	Positive blood culturesEchocardiogram: evidence of vegetations, new regurgitationEmbolic and immune phenomena
Viral mycoarditis	Evidence of prior viral infectionElevated cardiac enzymesECG: impaired ventricular function
Other causes of pericarditis (viral, bacterial, connective tissue disorders)	ECG: diffuse saddle ST elevation Echocardiogram: pericardial effusion Evidence of viral or bacterial infection
Innocent cardiac murmur	Normal echocardiogram
Arthritis	
Septic arthritis	Purulent joint fluid, bacterial growth on culture of joint fluid or blood
Reactive arthritis (hepatitis B, rubella, parvovirus, cytomegalovirus, Epstein-Barr virus, yersiniosis, mycoplasma, Lyme disease)	Serology indicative of recent infection
Juvenile idiopathic arthritisOther connective tissue disorders including SLE, sarcoidosis, psoriatic arthritis, systemic vasculitis	May involve small joints, rash, nephritis, other organ systemsBlood tests: rheumatoid factor, antinuclear antibodies, extractable nuclear antibodies, double stranded DNA, anti-CCP antibodiesOphthalmoscopy: uveitisRadiology: erosive changes
Sickle cell disease	Haemoglobin electrophoresis
Leukaemia	Blood film demonstrating blasts
Gout	Elevated uric acid
Chorea	
Wilson's disease	Abnormal copper and ceruloplasmin levelsKayser-Fleischer rings
Familial (Huntington's chorea)	Genetic testing
Drugs and toxins	Careful historyUrine toxicology
Intracranial tumour	Neuroimaging
Metabolic ataxia telangiectasia, Lesch-Nyhan Syndrome	Characteristic features on neuroimagingGenetic testing
Choreo-athetoid cerebral palsy	History, clinical features of cerebral palsy
Tic disorder, Tourette syndrome	
Autoimmune disorders including SLE, anti-phospholipid antibody syndrome, NMDA receptor antibody encephalitis	Antinuclear antibodies screen, NMDA receptor antibodies, double stranded DNA
Hormonal (pregnancy, oral contraceptive, hyperthyroidism)	

ECG=electrocardiogram. SLE=systemic lupus erythematosus.

What alternative diagnoses should be considered?

Rheumatic fever remains a clinical diagnosis. A range of alternatives should be considered when a person presents with some features but does not fulfil all the diagnostic criteria (table 2).

How is acute rheumatic fever treated?

Initial management when the diagnosis is suspected

Most individuals with suspected rheumatic fever are hospitalised for diagnostic work-up and to initiate treatment. Treatment of the acute inflammatory phase is supportive and focuses on providing symptomatic relief of arthritis, supportive care for carditis, and education for the patient and family. After obtaining a throat swab, penicillin is commenced to eradicate group A streptococcus from the pharynx. Either oral phenoxymethylpenicillin (penicillin VK) for 10 days, or a single dose of intramuscular benzathine penicillin (benzathine benzylpenicillin) can be given until the patient is established on long term secondary antibiotic prophylaxis. For patients with penicillin allergy, erythromycin is the recommended alternative antibiotic.

Antibiotic prophylaxis

Secondary antibiotic prophylaxis is recommended for individuals following an episode of acute rheumatic fever to prevent group A streptococcal infection and rheumatic fever recurrences.[36 37] A 2006 Cochrane systematic review, based on data from cohort studies, showed that intramuscular benzathine penicillin is superior to either no prophylaxis or oral penicillin in reducing rheumatic fever recurrences.[52-56] Benzathine penicillin also improves long term cardiac outcomes in rheumatic heart disease.[5 57] Intramuscular benzathine penicillin is the method of prophylaxis recommended by the World Health Organization[58] and is given every three to four weeks. A three weekly dose interval has been reported to result in fewer recurrences,[59] but the recurrence rate is low with good adherence to a four weekly regimen.[60] For patients with penicillin allergy, erythromycin is the recommended alternative antibiotic.

Recommendations regarding duration of secondary prophylaxis are based on expert opinion, and observations that recurrences are extremely uncommon after the age of 21 years or more than 10 years after the first acute rheumatic fever episode.[58] Practice varies, but in most regions benzathine prophylaxis is continued for a minimum of 10 years after diagnosis for patients with carditis,[36 37] and this is also recommended by the WHO.[58] Prophylaxis should be continued for longer in individuals with severe rheumatic heart disease, particularly those who have had cardiac surgery or recurrences. New Zealand and Australian guidelines recommend prophylaxis until ≥40 years old in this situation.[36 37] A recent clinical trial showed that injection related pain can be reduced by using lignocaine as a diluent with benzathine penicillin without affecting penicillin concentration in body fluids.[61]

Management of specific symptoms in rheumatic fever

Carditis

A 2006 Cochrane systematic review of clinical trials found that neither aspirin nor corticosteroids improved cardiac outcomes at one year after diagnosis.[62] However,

some clinicians believe that corticosteroids have a role in the acute inflammatory phase of severe carditis, particularly for patients with pericardial effusions or severe pancarditis. Bed rest for several weeks, followed by gentle ambulation, is still recommended for patients with moderate to severe carditis,[37] but this practice has not been scientifically evaluated in recent years.[63] Diuretics and vasodilators are used in severe carditis. Typically furosemide is used in mild to moderate congestive heart failure. Angiotensin converting-enzyme inhibitors have a particular role in severe aortic regurgitation as they reduce cardiac afterload. Serial echocardiography to measure cardiac dimensions and function can help cardiologists determine whether valve surgery is indicated. In many patients, the severity of the carditis stabilises or improves over weeks to months, as the inflammatory phase resolves. Wherever possible, surgery is delayed until the active inflammation has settled, as surgery during the acute inflammatory phase is associated with higher failure rates.[64] Mitral valve repair is favoured over mechanical replacement when technically feasible. Excellent outcomes have been reported with repair surgery (90% survival and 75% freedom from reoperation at 10 years),[65] and this avoids need for long term anticoagulant treatment.

Chorea

Chorea is a clinical diagnosis, made after a careful assessment to exclude other causes. It is important to consider whether a child presenting with chorea could have Wilson's disease, an autoimmune disorder, or another neuro-metabolic condition. Laboratory investigations and neuro-imaging may be indicated, particularly if there are no other features to support a diagnosis of rheumatic fever, if the child comes from a population where rheumatic fever is rare, or there are atypical features (table 2).

Treatment of chorea is supportive. Patients and caregivers must be informed of the potential for chorea to continue for several months and to fluctuate during times of intercurrent illness and stress.

Small case series have shown that sodium valproate and carbamazepine are similarly effective and well tolerated for reducing involuntary movements.[67-69] Haloperidol and other neuroleptics should be avoided because of the potential for extrapyramidal side effects. A small randomised study compared intravenous immunoglobulin with plasma exchange and short course corticosteroids in chorea and found that all three agents resulted in an improvement one month after treatment. Greater improvements were noted with intravenous immunoglobulin and plasma exchange compared with oral steroids.[70]

Benzathine penicillin is recommended for all cases of chorea because of the strong association with carditis and eventual rheumatic heart disease.

Arthritis and arthralgia

The joint manifestations of acute rheumatic fever can be extremely painful. NSAIDs may mask signs of acute rheumatic fever, and paracetamol is the preferred symptomatic treatment until the diagnosis is established (based on clinical opinion). Once the diagnosis is certain the treatment of choice is naproxen twice daily, at a dose of 10-20 mg/kg/day.[37] A small randomised controlled study showed that naproxen is equivalent to aspirin for treatment of arthritis, and is less likely to cause liver enzyme derangement.[71] In our experience, a response to NSAIDs generally occurs within several days of initiation. Most cases require one to two weeks of regular NSAID treatment, and it is uncommon to require more than several weeks.

What are the long term complications?

For many people with mild to moderate carditis the degree of valvular regurgitation stabilises or improves within 12 months after diagnosis.[6 7 72] Individuals who experience severe carditis during the initial episode, or recurrences of rheumatic fever, are at greatest risk of severe chronic rheumatic heart disease,[4] which is associated with an increased risk of heart failure, infective endocarditis, pregnancy complications, stroke, arrhythmias, and premature death.[8 9 73-75]

Antibiotic prophylaxis for endocarditis before dental procedures is recommended for all individuals with rheumatic heart disease in Australasia,[76 77] in contrast with the American Heart Association guidelines, which restrict antibiotics to a small group at highest risk of adverse outcomes from endocarditis,[78] and the UK, where the National Institute for Health and Care Excellence (NICE) advocates that prophylactic antibiotics are not given in any circumstances.[79]

What are the population health implications?

Globally, up to 40% of children and adults with rheumatic heart disease do not have a history of a recognised rheumatic fever episode.[1] Active case finding is recommended by the WHO, and when children or adults from high incidence populations or demographic backgrounds are found to have cardiac murmurs or complications as described above, echocardiography should be performed wherever possible to look for rheumatic heart disease.[58] The World Heart Federation Consensus Diagnostic Criteria for now allow a consistent global approach to echocardiographic diagnosis.[80] In recent years population based echocardiographic screening for rheumatic heart disease has been conducted in regions with a high incidence of rheumatic fever.[19 21 25 26 81]

The past decade has seen growing awareness of the need for comprehensive and coordinated global efforts to control rheumatic fever and rheumatic heart disease. Various primary prevention strategies are being considered, including development of an effective vaccine for group A streptococcus[83 84] and improving population awareness and treatment of group A streptococcal pharyngitis. Global registries are collating morbidity and mortality data from regions such as Africa where there has previously been limited epidemiological information.[8 88]

There is a recognised association between household crowding and rheumatic fever,[30 89] and well designed studies to assess the role of specific environmental risk factors and effectiveness of targeted interventions are urgently needed to inform future primary prevention strategies.