FEATURE

Acute rheumatic fever

When to still 'think ARF'

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Acute rheumatic fever is still common in at-risk populations within Australia. GPs have a vital role to play in prevention, diagnosis and management of this often neglected disease. This is important to prevent the serious complication of rheumatic heart disease.

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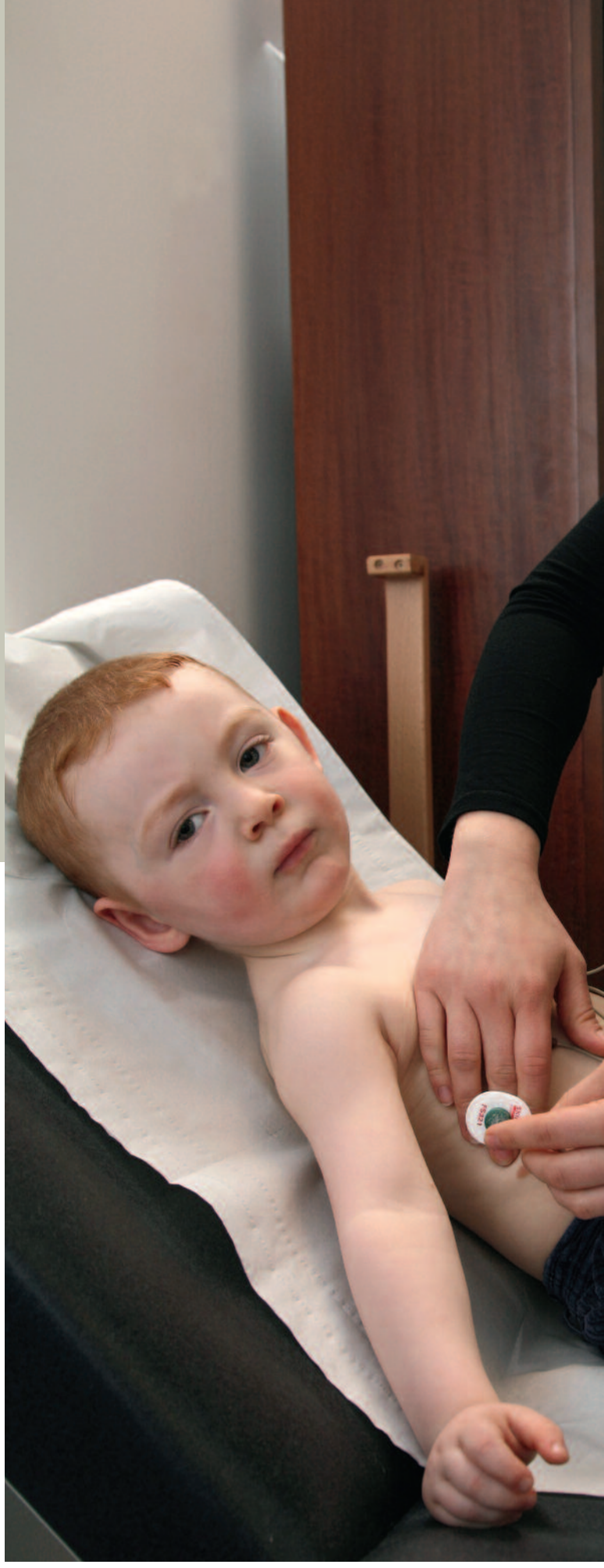

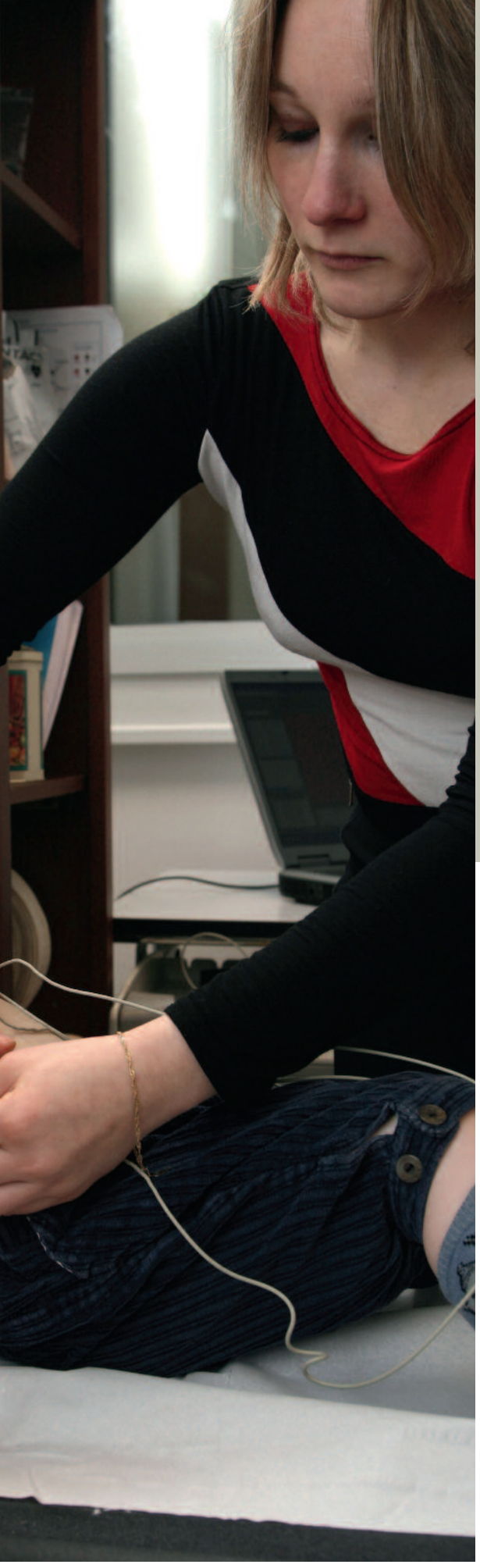

Key points

- **Acute rheumatic fever is common in school-aged Indigenous children in Northern Australia.**
- **GPs should 'think ARF' in any school-aged child presenting with painful joints and fever, especially in those of Aboriginal or Torres Strait Island background or recent immigrants from high-risk areas, including Maori and Pacific Islanders.**
- **All possible cases should be admitted to the patient's local paediatric hospital for confirmation of diagnosis.**
- **Acute rheumatic fever and rheumatic heart disease are classic diseases of poverty, and socioeconomic improvements in overcrowding, hygiene and access to health care are the most important means of decreasing rates of disease.**
- **Secondary prophylaxis effectively reduces the risk of subsequent acute rheumatic fever and progression to rheumatic heart disease.**
- **The GP has an important role to play in promoting adherence to secondary prevention programs.**

Figure 1. RHD Australia Queensland poster encouraging health workers to 'think ARF.' Reproduced with permission.[1]

Acute rheumatic fever is a common disease in the Indigenous population of northern Australia, where the incidence of the disease is among the highest in the world. It is also common in neighbouring Pacific Island countries. Many doctors in Australia will never have seen a case of acute rheumatic fever during their career because the disease is now rare in most urban areas of Australia; however, isolated cases still occur in urban populations, so GPs should still 'think ARF' (Figure 1).[1]

Acute rheumatic fever is an autoimmune disease that causes inflammation in several tissues leading to characteristic clinical manifestations including arthritis and carditis. Acute rheumatic fever is triggered by infection with the bacterium *Streptococcus pyogenes* (group A β-haemolytic streptococcus [GAS]) in a genetically susceptible host. The natural history of acute rheumatic fever is for the inflammatory response to subside over a period of weeks; however, residual damage to cardiac tissue, specifically the left-sided cardiac valves, leads to the development of chronic rheumatic heart disease. In this way, it was said as long ago as 1884 by French physician Ernest-Charles Lasègue that acute rheumatic fever 'licks the joints and bites the heart.'

Epidemiology

The worldwide prevalence of rheumatic heart disease has been estimated to be more than 15 million cases, with 280,000 new cases and 230,000 deaths due to rheumatic heart disease occurring annually.[2] These figures are likely to be underestimates, with new screening methods using echocardiography suggesting true figures may be much higher. School-aged children (peak 5 to 14 years) are most commonly affected by acute rheumatic fever, whereas the prevalence of rheumatic heart disease

2012 Australian guidelines for the diagnosis of acute rheumatic fever[10]

Diagnosis of an initial episode of acute rheumatic fever requires:

- two major manifestations (Table 1) OR
- one major and two minor manifestations (Table 1)

PLUS evidence of preceding group A β-haemolytic streptococcus infection.

Table 1. Manifestations of acute rheumatic fever

	Manifestations	
Populations	**Major**	**Minor**
High risk*	Polyarthritis† or aseptic monoarthritis or polyarthralgia Carditis (including subclinical carditis on echocardiogram) Chorea‡ Erythema marginatum§ Subcutaneous nodules	Monoarthralgia Fever‖ ESR ≥30 mm/hour or CRP ≥30 mg/L Prolonged PR interval on ECG¶
All other	Polyarthritis† Carditis Chorea‡ Erythema marginatum§ Subcutaneous nodules	Aseptic monoarthritis or polyarthralgia Fever‖ ESR ≥30 mm/hour or CRP ≥30 mg/L Prolonged PR interval on ECG¶

* High-risk groups are those living in communities with high rates of ARF (incidence >30/100,000 per year in 5 to 14-year-olds) or RHD (all-age prevalence >2/1000 per year). Aboriginal people and Torres Strait Islanders living in rural or remote settings are known to be at high risk. Data are not available for other populations, but Aboriginal people and Torres Strait Islanders living in urban settings, Maoris and Pacific Islanders, and potentially immigrants from developing countries may also be at high risk. Those with elevated or rising antistreptolysin O or other streptococcal antibodies, or a positive throat culture or rapid antigen test for GAS infection are also at high risk.

† A definite history of arthritis is sufficient to satisfy this manifestation. Note that if polyarthritis is present as a major manifestation, polyarthralgia or aseptic monoarthritis cannot be considered an additional minor manifestation in the same person.

‡ Chorea does not require other manifestations or evidence of preceding GAS infection, provided other causes of chorea are excluded.

§ Care should be taken not to label other rashes, particularly nonspecific viral exanthemas, as erythema marginatum.

‖ An oral, tympanic or rectal temperature of ≥38°C on admission or a reliably reported fever documented during the current illness satisfies this manifestation.

¶ If carditis is present as a major manifestation, a prolonged PR interval cannot be considered an additional minor manifestation.

ABBREVIATIONS: ARF = acute rheumatic fever; CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; GAS = group A β-haemolytic streptococcus; RHD = rheumatic heart disease.

peaks in early adulthood, affecting adults in their prime years of productivity.[3]

Indigenous populations in northern Australia have among the highest burden of acute rheumatic fever and rheumatic heart disease in the world, with one in 300 children developing acute rheumatic fever each year and up to 2% of people of all ages having rheumatic heart disease.[4-6] Similar rates are seen throughout the Western Pacific region, including in Maori and Pacific Islander populations in New Zealand where some of the most reliable data are available.[7]

Acute rheumatic fever is a disease of poverty and overcrowding. High-risk populations are exposed to frequent GAS infections that lead to repeated or prolonged episodes of acute rheumatic fever, thereby leading to an increased risk of developing rheumatic heart disease. Limited access to medical care for diagnosis, treatment and follow up is an important risk factor in many populations, particularly in resource-poor areas. There appears to be an inherent susceptibility to developing acute rheumatic fever after GAS infection, affecting 3 to 5% of the population.[8]

Clinical presentation

The diagnosis of acute rheumatic fever is based on the Jones criteria, a set of clinical criteria initially developed in 1944. The criteria are divided into major and minor manifestations, which reflect the effect of inflammation in a variety of tissues: synovium, cardiac tissue, brain tissue, skin and soft tissue. As the incidence of acute rheumatic fever has fallen in the USA, the American Heart Association and American Academy of Pediatrics have revised and updated the Jones criteria to avoid false-positive diagnoses.[9] However, in high-risk populations, high sensitivity is required to avoid underdiagnosis. As a result, national authorities in a variety of countries have adapted the guidelines to suit the local context. This is true of Australia, where national guidelines published in 2006 and 2012 are more sensitive than the 1992 version of the Jones criteria. The 2012 Australian guidelines for the diagnosis of acute rheumatic fever differ from the Jones criteria by assigning more importance to joint symptoms of monoarthritis and arthralgia, and incorporating the diagnosis of subclinical carditis on echocardiogram (see the box on this page and Table 1).[10] The new

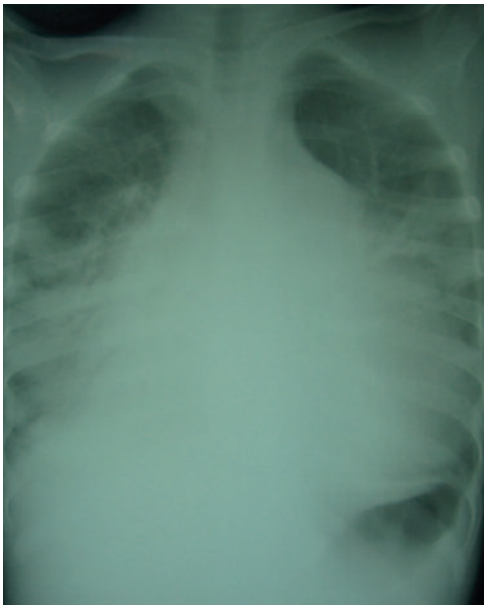

Figure 2. Chest x-ray demonstrating heart failure due to rheumatic heart disease.

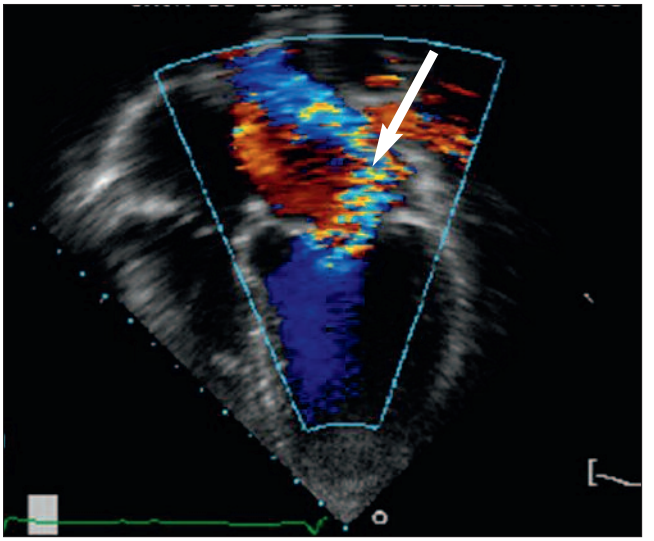

Figure 3. Echocardiogram demonstrating mitral regurgitation due to rheumatic valvulitis (arrow).

guidelines also include definitions and suggested management for patients with probable acute rheumatic fever (either highly suspected or uncertain).[10]

Joint manifestations are the most common manifestation of acute rheumatic fever. The classic description of the arthritis of acute rheumatic fever is a migratory polyarthritis of large joints (especially knees and ankles), which is extremely painful and highly responsive to anti-inflammatory treatment. However, in high-risk groups, patients may present with aseptic monoarthritis or arthralgia of one or more joints; it is these patients in whom it is important to 'think ARF'.[1]

Carditis occurs in about 50% of initial cases of acute rheumatic fever. The left-sided heart valves (mainly mitral and sometimes aortic) are almost invariably involved. Valves become diffusely inflamed and thickened. Clinical findings include the apical pansystolic murmur of mitral regurgitation or the early diastolic murmur of aortic regurgitation. Clinical heart failure can result from valvular dysfunction (Figure 2), and pericardial effusion may cause chest pain and a friction rub. However, many patients with mild valvular dysfunction may have no clinical signs. Echocardiography may demonstrate typical features of rheumatic carditis in these patients; therefore, it is important that all patients with suspected acute rheumatic fever undergo echocardiography performed by a cardiologist experienced in treating patients with acute rheumatic fever (Figure 3). ECG abnormalities include a prolonged PR interval for age, and second-degree and complete heart block.

Sydenham's chorea often presents later, up to six months after infection, and is characterised by involuntary, irregular movements of the face and limbs, often with emotional lability (see http://www.rhdaustralia.org.au/resources/sydenhams-chorea for a video example of the condition).

Skin manifestations are rare (less than 5% of cases) and can be difficult to diagnose in dark-skinned patients, but are highly specific for acute rheumatic fever. Subcutaneous nodules are small, 0.5 to 2 cm in diameter, painless, round nodules that develop over bony prominences or extensor tendons. They are highly associated with carditis. Erythema marginatum occurs as bright pink, blanching macules or papules that spread outwards in a circular pattern, usually on the trunk and proximal limbs. They may recur for months. Care must be taken not to overdiagnose viral exanthemas or urticaria as erythema marginatum.

Fever (above 38°C) is present in almost all cases, with the notable exception of isolated chorea. Acute phase reactants (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) are commonly elevated, whereas the peripheral white blood cell count is often normal. Preceding streptococcal infection is usually demonstrated by elevated or rising streptococcal antibodies (antistreptolysin O, anti-deoxyribonuclease B). A positive throat culture for GAS may also be used as evidence of preceding infection, but is frequently negative.

In high-risk patients presenting with joint symptoms, GPs are encouraged to 'think ARF.' All patients suspected of having acute rheumatic fever should be referred to a local paediatric service, and be admitted for formal diagnostic evaluation. Investigations should include ECG, chest x-ray, echocardiography, throat swab, blood cultures, streptococcal serology, and measurement of CRP levels, ESR and white blood cell count.

The differential diagnoses of acute rheumatic fever are numerous, particularly for patients presenting with fever and joint symptoms. Septic arthritis should be considered and assessed in patients presenting with monoarthritis.[11] Other differential diagnoses of arthritis and fever include connective tissue disorders, viral reactive arthritis and haematological malignancy. In low-risk populations

for acute rheumatic fever, patients with fever, arthritis and elevated streptococcal serology, but no other features of acute rheumatic fever, may meet the criteria for poststreptococcal reactive arthritis. However, due to the overlap with acute rheumatic fever, this diagnosis should rarely be made in high-risk populations.[12]

Management

No treatment has been shown to alter the progression of acute rheumatic fever to rheumatic heart disease, which occurs in more than 60% of cases.[8] Symptomatic management of inflammation is important, along with management of heart failure if present, and commencement of secondary prophylaxis with appropriate patient and family education. The goals of management are outlined in the box on this page.

In patients presenting with monoarthritis and possible acute rheumatic fever, it may be necessary to withhold anti-inflammatory medication and monitor the patient until diagnostic criteria are satisfied. Paracetamol or codeine can be used in this situation. Once the diagnosis is confirmed, anti-inflammatory medication can be commenced. High-dose aspirin (up to 80 to 100 mg/kg/day in four to five divided doses) has traditionally been used and there is an established evidence base for its use.[13] Influenza vaccine is recommended to reduce the risk of Reye's syndrome. Ibuprofen and naproxen have also been used with success.[14] The arthritis of acute rheumatic fever is highly sensitive to anti-inflammatory treatment and if symptoms persist after two to three days of treatment the diagnosis should be reconsidered.

Heart failure is managed with bed rest and medications including diuretics and ACE inhibitors. Acute surgery is rarely required. Most cases of chorea do not require treatment; rarely severe chorea can be treated with carbamazepine or valproic acid. All patients should receive treatment to eradicate GAS infection, with intramuscular benzathine penicillin or 10 days oral penicillin. Benzathine penicillin is often practical because it also serves as the start of secondary prophylaxis.

Confirmation of the diagnosis of acute rheumatic fever should prompt commencement of long-term preventive measures, including notification to the local acute rheumatic fever/rheumatic heart disease register (currently established in Queensland, Western Australia and Northern Territory), culturally appropriate education, dental care and commencement of secondary prophylaxis. Secondary prophylaxis is the key component of long-term management.

Aims of the management of patients with acute rheumatic fever

- Confirm the diagnosis of acute rheumatic fever
- Provide symptomatic treatment and treatment to shorten the acute inflammatory phase, particularly for joint involvement, which can be very painful
- Determine the presence and severity of carditis and manage cardiac failure if present
- Manage chorea if present
- Commence secondary prophylaxis in all patients
- Monitor the patient in hospital
- Provide education for the patient and his or her family about rheumatic fever and rheumatic heart disease, and emphasise the importance of compliance to secondary prophylaxis
- Ensure that follow-up care is arranged

Prevention

Prevention of acute rheumatic fever and rheumatic heart disease can be considered at three levels (Table 2):[4]

- primordial prevention, which refers to modification of social and environmental risk factors such as poverty, overcrowding, hygiene and access to housing and medical care[15]
- primary prevention, which refers to timely diagnosis and treatment of streptococcal tonsillopharyngitis
- secondary prevention, which refers to the continuous administration of antibiotics to prevent colonisation or infection with GAS and development of recurrent attacks of acute rheumatic fever in patients with a past history of acute rheumatic fever or established rheumatic heart disease.[16]

Table 2. Prevention of rheumatic fever and rheumatic heart disease[4]

Type of prevention	Measures taken
Primordial	Address housing issues such as overcrowding Ensure good hygiene
Primary (performed after GAS infection)	Treat streptococcal sore throat adequately Control streptococcal skin infections
Secondary (performed after acute rheumatic fever)	Provide secondary prophylaxis
Tertiary (performed after rheumatic heart disease)	Provide heart failure medication and anticoagulation as needed Perform valve surgery as needed

ABBREVIATION: GAS = group A β-haemolytic streptococcus.

Table 3. Antibiotics for secondary prophylaxis

Antibiotic	Dose	Frequency, route
First line		
Benzathine penicillin G	900 mg (1.2 million units) 450 mg (600,000 units) if <20 kg	Every three to four weeks, intramuscular injection
Second line – only if intramuscular route is impossible or refused		
Penicillin V	250 mg	Twice daily, oral
If documented penicillin allergy		
Erythromycin	250 mg	Twice daily, oral

Primary prevention

The GP has an important role to play in the detection and treatment of patients with a sore throat due to GAS infection. Appropriate antibiotics (usually penicillin) commenced within nine days of onset can prevent most cases of acute rheumatic fever.[3] In high-risk populations, patients presenting with a sore throat should be investigated by throat swab, and be treated if the swab is positive for GAS infection.

Secondary prevention

There is clear evidence that secondary prophylaxis reduces the risk of developing rheumatic heart disease in patients with a history of acute rheumatic fever.[16] In addition, secondary prophylaxis is effective in reducing the severity of rheumatic heart disease in patients with established rheumatic heart disease; adequate adherence over a decade is associated with regression of heart disease in 50 to 70% of cases.[17] Intramuscular benzathine penicillin is the most effective treatment (Table 3). Oral penicillin is less effective and should be reserved for patients who refuse intramuscular treatment. Erythromycin should be used in patients with a documented, immediate allergic reaction to penicillin. Most patients who report a reaction may not be truly allergic and should be referred for assessment of penicillin allergy.

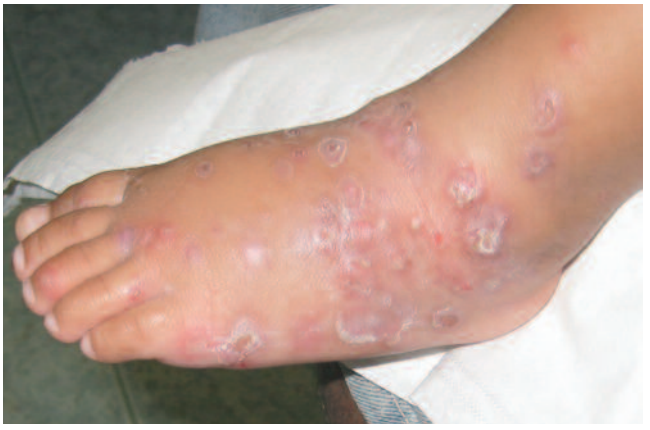

Figure 4. Scabies and secondary skin infection due to *Streptococcus pyogenes*.

The frequency of injections and duration of secondary prophylaxis depend on the risk of recurrence and potential harm from recurrent acute rheumatic fever. In Australia, all patients should continue prophylaxis for 10 years after an acute attack or until the age of 21 years, whichever is longer. Patients with clinical evidence of rheumatic heart disease should continue prophylaxis into adulthood. Prophylaxis should only be ceased after specialist evaluation and recommendation.

Secondary prophylaxis is best delivered as part of a comprehensive control program including a centralised registry, and a program of health promotion and education for health workers, patients and their families. The GP has a key role in promoting adherence to prophylaxis.

Future developments

There is increasing global interest and advocacy efforts in the control of rheumatic heart disease at an international level. A number of vaccines against GAS are approaching clinical trials. The development of a successful vaccine continues to face a number of challenges, including protection against a wide range of GAS strains and avoiding cross-reactivity with human tissue.[18]

New research initiatives into the pathogenesis of acute rheumatic fever have commenced, including in Australia. An important avenue of research is unraveling the role of GAS skin infection in the pathogenesis of acute rheumatic fever. The traditional view that acute rheumatic fever can only result from pharyngitis has been challenged following the observation of low rates of pharyngitis due to GAS infection, high rates of acute rheumatic fever and high rates of GAS infection of the skin in Aboriginal populations in the Northern Territory of Australia.[19,20] If streptococcal skin infection, frequently occurring secondary to scabies infestation (Figure 4), is shown to be an important cause of acute rheumatic fever, primary prevention through treatment of skin conditions may be important.[21]

Conclusion

GPs require a high index of suspicion of acute rheumatic fever in children presenting with fever and joint symptoms, especially those from high-risk populations. Inpatient diagnostic assessment and ongoing specialist care is required. Antibiotic prophylaxis is vital for the prevention of progression to valvular heart disease. **CT**

Further reading

RHD Australia. http://www.rhdaustralia.org.au/resources

Includes quick reference guides for the prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease.

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