ARTICLE

Prescribing for people with acute rheumatic fever

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SUMMARY

Acute rheumatic fever and its consequence, rheumatic heart disease, remain important problems in remote indigenous Australian communities.

Aboriginal and Torres Strait Islander people living in urban settings, Maori and Pacific Islanders, and immigrants from developing countries are also likely to be at elevated risk.

Guidelines and resources are available for healthcare professionals working with at-risk populations, and for patients with acute rheumatic fever or rheumatic heart disease and their families.

There have been some recent changes in Australian recommendations for antibiotic use, dose of aspirin, first-line choice for management of severe Sydenham's chorea, and prevention of endocarditis.

For individuals diagnosed with acute rheumatic fever, the recommended treatment to prevent recurrences and development of rheumatic heart disease is benzathine penicillin G administered as an intramuscular injection every four weeks.

Introduction

Acute rheumatic fever is an autoimmune disease occurring in response to infection with group A streptococci. Repeated or severe acute rheumatic fever episodes lead to rheumatic heart disease, a form of valvular heart disease with high morbidity and mortality.[1]

Many healthcare providers have little experience with acute rheumatic fever and rheumatic heart disease and may be unaware of the many resources to guide diagnosis and management (see Box 1).

Much of the information available on acute rheumatic fever treatment derives from old data,[2] observational studies[3] and small open-label comparative studies.[4-6] It is important to be aware of the current evidence base, principles of prescribing for people with acute rheumatic fever and rheumatic heart disease, recent changes in guidelines, and available resources.

High-risk populations

Group A streptococcal infection is associated with socioeconomic factors such as household crowding.[7,8] Acute rheumatic fever and rheumatic heart disease are now rare in affluent societies. High rates persist among Aboriginal and Torres Strait Islander populations, especially those living in rural or remote settings. The most recent Australian Institute of Health and Welfare report highlighted rheumatic heart disease as one of the conditions accounting for the greatest rate of discrepancy between indigenous versus non-indigenous

Box 1 **RHDAustralia contacts and educational resources**

Control program contacts

Northern Territory (Top End)	08 8922 8454
Northern Territory (Central)	08 8951 6909
Queensland	1300 135 854 or 07 4226 5544
Western Australia	1300 622 745
South Australia	08 7425 7146
New South Wales	1300 066 055 or 02 9391 9195

Videos and other resources
https://www.rhdaustralia.org.au/resources

Online training modules for patients
www.rhdaustralia.org.au/health-worker-modules

Online training modules for staff
www.rhdaustralia.org.au/clinician-modules

Diagnosis calculator
www.rhdaustralia.org.au/apps

Australians.[9] Current estimates for definite and borderline rheumatic heart disease in Australian children range from less than 1 per 1000 population in low-risk children, to 33 per 1000 in parts of the Northern Territory.[10] Maori and Pacific Islanders and immigrants from developing countries are also likely to be at elevated risk.[1]

Diagnosis

The diagnosis of acute rheumatic fever is made using the modified Jones criteria (Table 1).[11] These were updated in 2015 by the American Heart Association and endorsed by the World Heart Federation to incorporate Australian recommendations for improved diagnostic sensitivity in high-risk populations. These criteria have been built into a freely available diagnosis calculator available as a smart device application (see Box 1).[12]

The most challenging aspect of diagnosis is recognition, since cases can present subtly, for example as a single painful joint. There is no diagnostic test, although work towards this is an active field of research.

Acute rheumatic fever is notifiable to public health units in Australian states and territories which

Table 1 **Australian guidelines for the diagnosis of acute rheumatic fever**

Diagnosis	Modified Jones criteria	
Definite initial episode of acute rheumatic fever	2 major **or** 1 major and 2 minor manifestations **plus** evidence of a preceding group A streptococcal infection*	
Definite recurrent episode of acute rheumatic fever in a patient with known past acute rheumatic fever or rheumatic heart disease	2 major **or** 1 major and 1 minor **or** 3 minor manifestations, **plus** evidence of a preceding group A streptococcal infection*	
Probable acute rheumatic fever (first episode or recurrence)	A clinical presentation that falls short by either 1 major or 1 minor manifestation, or the absence of streptococcal serology results, but one in which acute rheumatic fever is considered the most likely diagnosis. Such cases should be further categorised according to the level of confidence with which the diagnosis is made: • highly suspected acute rheumatic fever • uncertain acute rheumatic fever	
	High-risk groups †	**All other groups**
Major manifestations	• Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram) • Polyarthritis ‡ or aseptic monoarthritis or polyarthralgia • Chorea • Erythema marginatum • Subcutaneous nodules	• Carditis (excluding subclinical evidence of rheumatic valvulitis on echocardiogram) • Polyarthritis ‡ • Chorea • Erythema marginatum • Subcutaneous nodules
Minor manifestations	• Monoarthralgia • Fever § • ESR ≥30 mm/h or CRP ≥30 mg/L • Prolonged P-R interval on ECG #	• Polyarthralgia or aseptic monoarthritis • Fever § • ESR ≥30 mm/h or CRP ≥30 mg/L • Prolonged P-R interval on ECG #

* Evidence includes elevated or rising antistreptolysin O or other streptococcal antibody, or a positive throat culture or rapid antigen test for group A streptococci.

† High-risk groups are those living in communities with high rates of acute rheumatic fever (incidence >30/100 000 per year in 5–14 year olds) or rheumatic heart disease (all-age prevalence >2/1000). Aboriginal and Torres Strait Islander people living in rural or remote settings are known to be at high risk. Data are not available for other populations, but Aboriginal and Torres Strait Islander people living in urban settings, Maoris and Pacific Islanders, and potentially immigrants from developing countries, may also be 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 infection with group A streptococci, provided other causes of chorea are excluded. Care should be taken not to label other rashes, particularly non-specific viral exanthemas, as erythema marginatum.

§ Fever is defined as oral, tympanic or rectal temperature ≥38 °C on admission, or a reliably reported fever documented during the current illness.

If carditis is present as a major manifestation, a prolonged P-R interval cannot be considered an additional minor manifestation.

ESR erythrocyte sedimentation rate

CRP C-reactive protein

Source: Adapted from Table 3.2 of the Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition) with permission from RHDAustralia[1]

have rheumatic heart disease control programs – Western Australia, Northern Territory, Queensland, South Australia and New South Wales.[13]

Management

The management of acute rheumatic fever involves treatment of the infection, management of the inflammatory process and complications, and secondary prevention.

Eradication of streptococcal infection

The clinical onset of acute rheumatic fever is typically 1–4 weeks after group A streptococcal infection (longer for Sydenham's chorea).[1] Given this time frame, it is often not possible to isolate streptococci from cultures, but antibiotic eradication therapy is recommended nonetheless (Table 2).[1,14-16] Acute rheumatic fever is well documented to occur following group A streptococcal pharyngitis (throat infection).[17] In Australian indigenous communities, there is much circumstantial evidence that high rates of acute rheumatic fever can also occur after skin infection with group A streptococci.[18,19] A recent case report from New Zealand implicates antecedent skin streptococcal infection or non-group A streptococci in acute rheumatic fever.[20]

In most instances, penicillin can be used to clear group A streptococcal infection. It should be given as a single intramuscular dose of benzathine penicillin G (also known as benzylpenicillin). The injection forms the first of the 21- or 28-day dosing schedule required for continuing secondary prophylaxis.

It is estimated that only 10–20% of patients reporting penicillin allergy are truly allergic when assessed by skin testing.[21] However, in rare instances of true allergy, azithromycin is now recommended by Therapeutic Guidelines: Antibiotic,[14] Therapeutic Guidelines: Rheumatology[15] and US guidelines[22] for clearance of the antecedent streptococcal infection due to drawbacks with other macrolides. For example, roxithromycin appears poorly effective in achieving group A streptococci microbiological cure,[23] and erythromycin is poorly tolerated.

Group A streptococci are consistently penicillin-susceptible, probably due to a lack of capacity to express beta-lactamase or to develop low-affinity penicillin-binding proteins under antibiotic pressure.[24] However, macrolide resistance was present in 3.4% of invasive group A streptococcus isolates in Darwin in 2005–2009,[25] and in at least 30% of isolates in international studies.[26,27] This is a further reason to ensure that penicillin is the treatment used whenever possible. It is important to note that penicillin or other antibiotic therapy does not influence the course or outcome of the acute rheumatic fever episode itself.

Symptomatic management of joint symptoms

Once a diagnosis of acute rheumatic fever is made, aspirin is commenced for symptomatic management. Non-steroidal anti-inflammatory drugs (NSAIDs) also appear effective. However, a major Jones criterion is migratory arthritis. If this is masked, the opportunity to make a definite diagnosis can be missed. Since joint symptoms of acute rheumatic fever often respond promptly to salicylates or NSAIDs, these should be withheld pending diagnostic certainty, with other analgesics used in the interim (Table 2).

Aspirin

Previously the recommended dose of aspirin was 80–100 mg/kg/day in divided doses. However, due to toxicity (gastrointestinal, tinnitus), the revised starting dose is 50–60 mg/kg/day although up-titration may be needed (Table 2).[1,15] This is then tapered as symptoms improve and continued for 1–2 weeks after they resolve. Rebound of symptoms can occur with a rapid taper or early cessation, hence acute rheumatic fever symptoms within approximately three months of an initial episode are counted as the same episode rather than a recurrence.[28]

NSAIDs

The effectiveness of naproxen has been reported in a retrospective chart review of 19 patients,[4] and in an open-label comparative study of naproxen and aspirin in 33 children.[3] In the open-label trial, efficacy was similar to aspirin, but gastrointestinal adverse effects were fewer with naproxen. Hence although published data are scanty, NSAIDs are endorsed as an alternative to aspirin.[1]

Symptomatic management of chorea

Sydenham's chorea is usually self-limiting and treatment is only considered in severe cases. Carbamazepine and sodium valproate appear to have similar efficacy,[5,6] with carbamazepine being recommended as first line due to a better safety profile.[1] This replaces older recommendations to use haloperidol.[5] A recent case report from South America describes successful use of leviteracitam for Sydenham's chorea.[29] This may warrant further investigation.

Management of cardiac failure

Acute rheumatic fever with severe carditis may require pharmacological management of cardiac failure, in addition to bed rest and fluid restriction. Drugs typically include furosemide (frusemide), spironolactone, enalapril and digoxin.

Table 2 **Drugs used in acute rheumatic fever**

DURING ACUTE RHEUMATIC FEVER EPISODE

Indication	Drug (choice)	Comment
Eradication of inciting streptococcal infection	1. Benzathine penicillin G 900 mg (child 3–6 kg: 225 mg, 6–10 kg: 337.5 mg, 10–15 kg: 450 mg, 15–20 kg: 675 mg) given intramuscularly as a single dose* OR 2. Penicillin hypersensitivity: cephalexin 1 g (child: 25 mg/kg up to 1 g) orally, 12-hourly for 10 days 3. Immediate penicillin hypersensitivity: azithromycin 500 mg (child: 12 mg/kg up to 500 mg) orally daily for 5 days	Streptococcal infection may not be evident by the time acute rheumatic fever manifests (e.g. cultures often negative), but eradication therapy for possible persisting streptococci is still recommended. Intramuscular penicillin is preferred due to better adherence.
Initial analgesia while awaiting diagnostic confirmation	1. Paracetamol 15 mg/kg orally, 4-hourly up to a maximum of 60 mg/kg/day (not more than 4 g daily)	Preferred initial analgesia during diagnostic uncertainty, to avoid the masking effect anti-inflammatory use can have on migratory joint symptoms.
Symptomatic management of arthritis or arthralgia	1. Aspirin 50–60 mg/kg/day up to a maximum of 80–100 mg/kg/day in four or five divided doses 2. Naproxen (10–20 mg/kg/day) orally, twice-daily[3,4]	Due to the rare possibility of Reye's syndrome in children, aspirin may need to be ceased during an intercurrent acute viral illness, and an influenza vaccination provided if aspirin is used during influenza season. Naproxen may be safer than aspirin, and convenient due to twice-daily dosing and the availability of an oral suspension. However, there is less experience with naproxen in acute rheumatic fever.

SECONDARY PROPHYLAXIS

Indication	Drug	Comment
Prevention of subsequent streptococcal infections[16]	1. Benzathine penicillin G 900 mg (child <20 kg: 450 mg)* intramuscularly as a single dose once every 21 or 28 days 2. Immediate penicillin hypersensitivity: erythromycin 250 mg (child: 10 mg/kg up to 250 mg) orally 12-hourly	Rare breakthrough acute rheumatic fever cases occur despite regular dosing, due to waning penicillin concentrations towards the end of the 28-day period. Therefore an injection every 3 weeks is prescribed for some individuals (generally <2% of people with acute rheumatic fever). Oral penicillin is less effective and is not recommended except in exceptional circumstances (e.g. temporary inability to access injection while travelling).

ENDOCARDITIS PROPHYLAXIS IN ESTABLISHED RHEUMATIC HEART DISEASE

Indication	Drug	Comment
Individuals having high-risk dental or respiratory procedures †	1. Ampicillin 2 g (child: 50 mg/kg up to 2 g) intravenously within 60 min (ideally 15–30 min) before the procedure 2. Penicillin hypersensitivity: cefazolin 2 g (child: 50 mg/kg up to 2 g) intravenously within 60 min before the procedure 3. Immediate penicillin hypersensitivity: clindamycin 600 mg (child: 20 mg/kg) intravenously within 60 min before the procedure	Note intravenous ampicillin and clindamycin can be substituted with appropriately timed oral dosing of amoxycillin or clindamycin respectively.
Individuals having high-risk genitourinary, gastrointestinal or infected skin or soft tissue procedures	1. Ampicillin 2 g (child: 50 mg/kg up to 2 g) intravenously within 60 min (ideally 15–30 min) before the procedure 2. Penicillin hypersensitivity or immediate hypersensitivity: teicoplanin 400 mg (child: 10 mg/kg up to 400 mg) intravenously within 60 min (ideally 15–30 min) before the procedure	Note the drugs listed here which provide Gram positive cover are given in addition to any standard prophylactic recommendation required for that procedure (e.g. in combination with metronidazole plus cephazolin or gentamicin for colorectal surgery). Note vancomycin can be used instead of teicoplanin if the timing of administration can be appropriately arranged.

* Note that the child dose of benzathine penicillin G is higher for secondary prophylaxis than for primary treatment.
† High-risk procedures are defined in Therapeutic Guidelines: Antibiotic[14]
Source: References 1, 14 and 15

Disease-modifying treatments

There are currently no drugs for acute rheumatic fever that effectively target the immune perturbation, or reduce the progression to, or severity of, rheumatic heart disease. Trials of corticosteroids or related compounds (adrenocorticotrophic hormone) have been unconvincing, including a comparative study of methylprednisolone and oral prednisolone in 18 patients.[30] Meta-analyses have also failed to show benefit.[31] Despite this, the national guideline observes that 'corticosteroids are sometimes used for severe carditis, although there is no evidence that they alter the longer-term outcome'.[1] Internationally, steroids are used as a treatment of last resort. A randomised trial of intravenous immunoglobulin, with outcomes being time to resolution of inflammation and severity of cardiac disease, also identified no benefit in the intervention arm.[32]

Secondary prevention

To avoid recurrences of acute rheumatic fever and the development of rheumatic heart disease, future group A streptococcal infections need to be avoided using antibiotic prophylaxis with benzathine penicillin G (Table 2). Oral penicillin is strongly discouraged and is known to be associated with higher rates of acute rheumatic fever recurrence.[16] This should be accompanied by advice to families about the need for prompt treatment when a suspected group A streptococcal infection occurs. They should also be advised of ways to reduce exposure at home, for example by avoiding sharing of beds when possible and culturally appropriate.

The required duration of secondary prevention for those with mild or no rheumatic heart disease is for a minimum of 10 years or until age 21 (whichever comes later), until age 35 for those with moderate heart disease, and until age 40 or longer for those with severe heart disease.

Children embarking on the daunting prospect of at least 10 years of benzathine penicillin G injections require sensitive, culturally appropriate engagement with healthcare systems, use of strategies to minimise the pain of injections (Box 2), and provision of tools to support adherence. Adherence resources including smartphone applications, calendars, reminder cards and incentive programs are offered at some clinics.[33] Rheumatic heart disease control programs[13] are a vital resource in managing people with acute rheumatic fever or rheumatic heart disease (see Box 1) by providing education and support to clinicians and patients as well as coordinating the jurisdictional registers.

Shortages or unavailability of benzathine penicillin G occur regularly in Australia and neighbouring countries with heavy burdens of acute rheumatic fever and rheumatic heart disease (e.g. Timor Leste).[34] This adds a further challenge to the prevention of this serious and potentially fatal condition.

Changes in penicillin formulation over the years have required changes to the dose volumes stated in the manual provided for Aboriginal health workers and nurses working in remote areas. There have also been changes in recommendations regarding the safety of adding lignocaine to the syringe. Although adding lignocaine reduces the pain of injections,[35] the manufacturer of the pre-filled syringe recommends against its use for infection control reasons.

In the setting of true penicillin allergy, the recommended alternative drug is oral erythromycin (Table 2). This is in contrast to the recommendation for azithromycin treatment of acute group A streptococcal infection.

Conclusion

Healthcare providers working with people who have an elevated risk of acute rheumatic fever and rheumatic heart disease, such as in Australian indigenous communities, refugee health clinics or an area with high migrant populations, must be familiar with this important, preventable condition. Resources to aid diagnosis and management can assist clinicians working in these settings. Research is underway to generate improved knowledge and inform evidence-based guidelines. This will be incorporated in the third edition of the Australian guideline, anticipated for release in 2018. <

Conflict of interest: none declared

Box 2 Measures that may reduce the pain of benzathine penicillin G injections

Use a 21-gauge needle.

Warm syringe to room temperature immediately before use.

Allow alcohol from swab to dry before inserting needle.

Apply pressure with thumb for 10 seconds before inserting needle, or vibration before and/or during injection (e.g. see http://buzzy4shots.com.au).

Deliver injection very slowly (preferably over at least 2–3 minutes).

Distract patient during injection (e.g. with conversation).

The addition of 0.5–1 mL of 1% lignocaine is used elsewhere, but is not recommended with preloaded syringes currently available in Australia.

Source: Reference 1

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