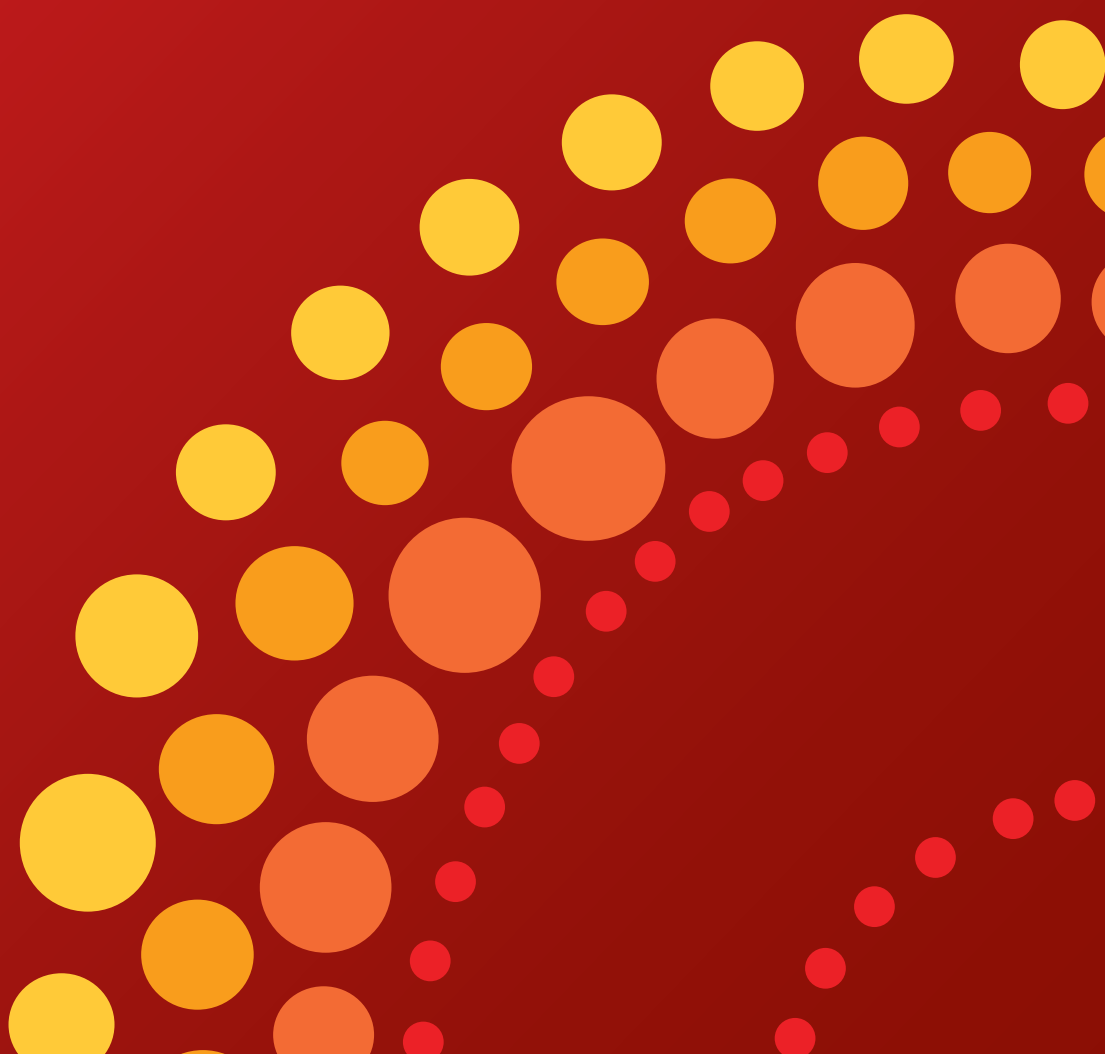




The Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition)



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Introduction

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) occur at very high rates among Aboriginal and Torres Strait Islander people. These diseases predominantly affect children, adolescents, and young adults, and are important causes of premature mortality. Almost all cases of RHD and associated deaths are preventable.

In contrast, ARF is now rare in other population groups in Australia, and RHD in these groups occurs predominantly in the elderly. ARF still occurs from time to time in affluent populations, and the persistently high rates of ARF in some middle-class regions of the USA¹ highlight the need to remain aware of this disease in all populations.

To support this in Australia, an evidence-based review for the diagnosis and management of ARF and RHD was published by the Heart Foundation and the Cardiac Society of Australia and New Zealand (CSANZ) in 2006.²

This second edition of the original evidence-based review has again considered the latest research, guidelines from other jurisdictions and expert opinion, and all of this evidence is combined in a single source. This document should be considered the main source of information to guide all aspects of RHD management, prevention and control across Australia. The overarching purpose for developing these guidelines is to improve health outcomes for people with (or at risk of developing) ARF and RHD, and to encourage the use of appropriate resources.

The key aims of this document are to:

- identify the standard of care, including preventive care, which should be available to all people
- identify areas where current management strategies may not be in line with available evidence
- in the interests of equity, ensure that high-risk populations receive the same standard of care as that available to other Australians.

There are several factors contributing to the inability to ensure adequate diagnosis and management of ARF and RHD in Australia, for example:

- strategies for preventing RHD have been proven to be simple, cheap and cost-effective, however, they must be adequately implemented in the populations at highest risk of the disease
- because ARF is rare in most metropolitan centres where health staff train and practice, the majority of clinicians will have seen very few, if any, cases of ARF
- there is variability in the management of these diseases, with minimal training and experience in the management of ARF and RHD, occasionally resulting in inappropriate management
- access to healthcare services by population groups experiencing the highest rates of ARF and RHD is often limited.

This document includes levels of evidence and grades of recommendation (Table 1.1).

Table 1.1 Levels of evidence for clinical interventions, and grades of recommendation

Level of evidence	Study design	Grade of recommendation	
I	Evidence obtained from a systematic review of all relevant RCT	A	Rich body of high quality RCT data
II	Evidence obtained from at least one properly-designed RCT	B	Limited body of RCT data or high-quality non-RCT data
III-1	Evidence obtained from well-designed pseudo RCT (alternate allocation or some other method)	C	Limited evidence
III-2	Evidence obtained from comparative studies, with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group	D	No evidence available; panel consensus judgement
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group		
IV	Evidence obtained from case series, either post-test or pretest and post-test		

The levels of evidence and grades of recommendations are adapted from the National Health and Medical Research Council levels of evidence for clinical interventions and the US National Institutes of Health clinical guidelines (details can be found at www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm).

RCT, randomised, controlled trial.

Summary of changes to revised national ARF/RHD Guidelines

Introduction

- Original Summary and Introduction combined into *Introduction*
- *Revision process* section added
- Literature review process for this version included (as an Appendix 1)

Chapter 1 - Overview

- Text updated to reflect new content and revisions in the main document

Chapter 2 - Primordial and primary prevention of ARF and RHD

- New section

Chapter 3 - Diagnosis and management of ARF

Diagnosis of ARF

- Addition of *Evolution of the diagnostic criteria for ARF since 1992* (Table 3.1)
- New definition for *Probable ARF* (defined as 'highly-suspected ARF' and 'uncertain ARF')

- Definition change of recurrent episode of ARF in a patient with known past ARF or RHD to 2 major or 1 major and 1 minor or 3 minor manifestations plus evidence of a preceding GAS infection
- *Fever* definition changed to *Oral, tympanic or rectal temperature greater than 38°C on admission, or documented with a reliable history during the current illness, should be considered as fever*
- Inclusion of *monoarthralgia* as a minor manifestation for high risk groups (in Table 3.2)
- Expanded discussion around *Carditis* (in ARF) based on four clinical findings including:
 - significant murmur
 - cardiac enlargement
 - cardiac decompensation
 - pericardial friction rub or effusion
- Expanded discussion on cognitive dysfunction with chorea
- Upper limits of normal (ULN) for serum streptococcal antibody titres expanded to include children and adults based on Fiji data (Table 3.6)

- Expanded discussion on *PANDAS*
- Expanded section on *Echocardiography and ARF* based on the 2012 World Heart Federation echocardiographic criteria for rheumatic heart disease
- Expanded section on *subclinical carditis*

Management of ARF

- New recommended management for *Probable ARF*
- New algorithm for *Management of Probable ARF* (Figure 3.1)
- Expanded discussion around short-course antibiotics for treatment of ARF
- Regimens added for Erythromycin in addition to Erythromycin ethyl succinate for people who are allergic to penicillin:
 - Erythromycin ethyl succinate: Child: 20 mg/kg up to 800 mg, bd Adult: 800 mg, bd for 10 days
 - Erythromycin: Child: 12.5 mg/kg up to 500 mg, bd Adult: 500 mg, bd, for 10 days
- Recommended Frusemide dosage for adults changed to 6–24 hourly
- Further discussion added around the expected progress and timing of discharge
- Addition of ibuprofen as an alternative to aspirin for treatment of ARF
- Recommended aspirin dose changed from 80–100 mg/kg/day to *Begin with 50–60 mg/kg/day, increasing, if needed, up to 80–100 mg/kg/day*

Chapter 4 - Secondary prevention and RHD control programs

Individual approaches to secondary prevention

- New recommendations for duration of secondary prophylaxis for *Probable ARF*
- Revised discussion of Australian/regional studies/evidence
- Recommended 23 g needle changed to 21 g needle (to reduce injection pain) (Table 4.6)

Prevention of infective endocarditis

- Antibiotics for endocarditis prevention updated according to Therapeutic guidelines (Table 4.8)

Routine review and structured care planning

- New algorithm for *recommended routine review and structured care planning* (Figure 4.1)
- New discussion around dental hygiene and use of antiseptic mouth rinse by people with RHD prior to dental procedures
- Restructured routine review and management plan:
 - Reclassification using priority system (mild/moderate/severe. Priority 1–3)
 - New definition and category care plan for *inactive* patients (Priority 4)
- Mechanical prosthetic valves, tissue prosthetic valves and valve repairs including balloon valvuloplasty moved from moderate (Priority 2) classification to severe (Priority 1) classification
- Inclusion of *dental review* for all categories
- Revised discussion around RHD programs in Australia and program principles
- Introduction of National Coordination Unit - *RHDAustralia*
- Expanded discussion around *Surveillance*
- *Proposed minimum dataset* (Table 3.12 in 2006 version) replaced with *Recommended dataset for ARF /RHD Registers* (presented as an Appendix 2)
- Removal of criteria for Communicable Disease Network of Australia (CDNA) national notification (of a condition)
- Revised section on *Screening for RHD*
- *Proposed indicators for evaluating ARF/RHD programs* (Table 3.13 in 2006 version) replaced with *Key Performance Indicators for ARF/RHD* (presented in Appendix 3)

Chapter 5 - Diagnosis and management of RHD

- Revised *Background and management principles* and expanded discussion around access to various services for remote Australians including:
 - secondary prevention with penicillin prophylaxis
 - adequate monitoring of anticoagulation therapy in patients with AF and/or mechanical prosthetic valves
 - access to oral healthcare
 - access to echocardiography
 - access to a specialist physician, paediatrician and/or cardiologist, preferably the same specialist, for regular follow up visits
 - access to cardiothoracic and interventional cardiology services
- New section on *Echocardiographic criteria for* (diagnosis of) *RHD* in the absence of a documented history of ARF, based on the 2012 World Heart Federation evidence-based guideline
- Updated content around echocardiography for each valve lesion
- New algorithms for timing of surgery with mitral regurgitation (MR), mitral stenosis (MS), aortic regurgitation (AR) and aortic stenosis (AS) (Figures 5.1-5.4)
- Revised *indications for surgery* for mitral valve disease
- New section on *tricuspid valve disease*
- Expanded section on *multi-valve disease*

Pregnancy and RHD

- Expanded discussion around the need and strategies for a well-planned pregnancy and delivery
- Further clarification around anticoagulation during pregnancy:
 - Use of low molecular weight heparin (LMWH): *Peak levels 4–6 hours post dose should be 0.8–1.2 U/mL and not exceed 1.5 U/mL. Antifactor Xa (anti-Xa) levels should be measured weekly and LMWH dose increased or decreased by 10 mg twice daily if levels are low or high respectively*
 - Use of unfractionated heparin: *used to maintain therapeutic anticoagulation until the onset of labour or until 4–6 hours prior to elective caesarean delivery*

- Recommendation that to prevent endocarditis pregnant patient to receive *prophylactic antibiotics prior to delivery and for 24–48 hours thereafter*

Quick reference guides (QRGs)

Existing QRGs updated to reflect revised content:

- Diagnosis of ARF
- Management of ARF
- Secondary prevention of ARF
- Management of RHD
- RHD control programs

New QRGs developed based on new and revised content:

- Primary prevention of ARF
- RHD and pregnancy

Target audience

This document provides a detailed discussion of the evidence in regard to ARF and RHD. It is envisaged that this will be of assistance to health professionals with a specific interest in the area (although the framework it provides should not override good clinical judgement).

Quick reference guides for health professionals — medical, nursing, allied health and Aboriginal health workers — have been developed, with the aim of providing an easy form of reference for health professionals who practise in settings where ARF and RHD are encountered, or who plan to work in such regions. In addition, new modes of dissemination of these guidelines, including applications for smart phones and tablet computers, will be made available.

For the purposes of this document, the terms ‘Aboriginal and Torres Strait Islander people’ and ‘Aboriginal’ have been used interchangeably, in accordance with the references used.

Revision process

This document was developed by Rheumatic Heart Disease Australia (RHDAustralia), in collaboration with the Heart Foundation of Australia and the CSANZ. A revision of the original evidence-based review was undertaken by a core multidisciplinary writing group (listed on p. 2). The following systematic, rigorous and iterative process was used:

- a comprehensive and systematic literature review of all publications in ARF and RHD since 2004 was undertaken (Appendix 1). The titles and abstracts of these articles were scanned to select those that might offer new information around the four sections in these guidelines (primordial and primary prevention, ARF diagnosis and management, secondary prevention and control programs and management of RHD), and the full text of relevant articles was reviewed by members of the writing group for the relevant section
- the core writing group prepared an updated version of the existing content, including the new evidence, and an additional, new section on primordial and primary prevention was developed
- selected reviewers with clinical and public health experience in ARF and RHD then reviewed each chapter, and their suggestions were incorporated into a second draft
- a number of additional amendments were made following ongoing discussion, and the final draft was endorsed by the main authors and reviewers at an editorial meeting in October 2011
- the document was then distributed to a range of stakeholders for endorsement (listed on p. 2).

This process has been endorsed by the Heart Foundation and the CSANZ, and informed by National Health and Medical Research Council principles for guideline development.

This revised national guideline provides a general framework, and should not override good clinical judgement. Treatment should take into account the patient's co-morbidities, drug tolerance, lifestyle, living circumstances, cultural sensibilities and wishes. When prescribing medication, clinicians should observe usual contraindications, be mindful of potential adverse drug interactions and allergies and monitor responses and review patients regularly.



1. Overview

ARF is an illness caused by an immunological reaction to infection with the bacterium group A streptococcus (GAS). It causes an acute, generalised inflammatory response, and is an illness that affects only certain parts of the body, mainly the heart, joints, brain and skin. Individuals with ARF are often severely unwell, in great pain and require hospitalisation. Despite the dramatic nature of the acute episode, ARF leaves no lasting damage to the brain, joints or skin.

However, the damage to the heart, or more specifically, the mitral and/or aortic valves, may remain once the acute episode has resolved. This is known as RHD.

People who have had ARF previously are much more likely than the wider community to have subsequent episodes. These recurrences of ARF may cause further cardiac valve damage. Hence, RHD steadily worsens in people who have multiple episodes of ARF.

Because of its high prevalence in developing countries, RHD is the most common form of paediatric heart disease in the world. In many countries, it is the most common cause of cardiac mortality in children and adults aged less than 40 years.

Almost all cases of RHD and associated deaths are preventable.

The burden of ARF in industrialised countries declined dramatically during the 20th century, due mainly to reduced transmission of GAS related to improved living conditions and increased hygiene standards, along with better access to appropriate health services and increased access to penicillin-based medications. In most affluent populations, including much of Australia, ARF is now rare, and RHD occurs predominantly in the elderly. However, ARF and RHD remain common in many developing countries.

There is also considerable regional variation within countries. In Australia, ARF and RHD are highly prevalent among Aboriginal and Torres Strait Islander communities, with the highest rates of ARF found amongst children aged 5-14 years and the highest rates of RHD found in adults aged 35-39.⁹ Aboriginal and Torres Strait Islander people are up to eight times more likely than other groups to be hospitalised for ARF and RHD, and nearly 20 times as likely to die.

Key points:

- ARF, an autoimmune response to GAS infection of the upper respiratory tract (or skin, as has been hypothesised in some Aboriginal populations), may result in damage to the mitral and/or aortic valves. This is known as RHD. Recurrences are likely in the absence of preventive measures, and may cause further cardiac valve damage
- although ARF is rare in industrialised countries, it is a significant cause of disease among Aboriginal and Torres Strait Islander children. The prevalence of RHD is also high among these populations, with significant rates of procedures and death among young adults.

Pathogenesis

Not everyone is susceptible to ARF, and not all GAS strains are capable of causing ARF in a susceptible host. It is likely that 3–5% of people in any population have an inherent susceptibility to ARF, although the basis of this susceptibility is unknown.³

It is clear that only some strains of GAS are 'rheumatogenic', although the basis of rheumatogenicity is also unknown.^{4, 5} Classic teaching states that only upper respiratory tract infection with GAS has the potential to cause ARF. However, there is circumstantial evidence that in certain populations (e.g. Aboriginal people), GAS skin infections may play a role in ARF pathogenesis.⁶

When a susceptible host is infected with a rheumatogenic GAS strain, there is a latent period averaging 3 weeks before the symptoms of ARF begin. By the time the symptoms develop, the infecting strain of GAS has usually been eradicated by the host immune response.

Epidemiology

A review of the global burden of GAS-related disease estimated that there is a minimum of 15.6 million people with RHD; another 1.9 million with a history of ARF, but no carditis (still requiring preventive treatment); 470,000 new cases of ARF each year; and over 230,000 deaths due to RHD annually.⁷ Almost all cases and deaths occur in developing countries. These figures are all likely to be underestimates of the true burden of the disease.

Some of the highest documented rates of ARF and RHD in the world are found in Aboriginal Australians, Maoris, Pacific Islanders in New Zealand and Pacific Island nations. The prevalence of RHD is also high in sub-Saharan Africa, Latin America, the Indian subcontinent, the Middle East and Northern Africa.⁷

Data on ARF and RHD burden in Australia vary between jurisdictions, because surveillance is at various levels of establishment. Data from the Northern Territory suggest that ARF and RHD are common among Aboriginal and Torres Strait Islander people living in regional and remote areas of central and northern Australia.⁸ The incidence of ARF is highest in 5–14 year olds, ranging from 150 to 380 per 100,000. Prevalence rates of RHD since 2000 have steadily increased to almost 2% of the Aboriginal population in the Northern Territory; 3.2% of Aboriginal people aged 35–44 years.⁹ This may be due to improved ascertainment of existing cases. Studies in far North Queensland and the Kimberley region of Western Australia have found slightly lower prevalences of 1.14% and 1%, respectively, but these are early data, and are comparable to the rates found in the Northern Territory in the late 1990s, when the control program was just beginning; these rates are expected to increase over time as case detection improves.^{10, 11}

The incidence of ARF in children from North Queensland between 2004 and 2009 ranged from 156 to 319 per 100,000,¹² and a report on Kimberley children in Western Australia found 375 cases per 100,000,¹³ suggesting that the high burden of disease is found in populations across northern and central Australia.

RHD is much more prevalent among Aboriginal people in the Northern Territory than other Australians (0.2%), and the prevalence rate among Aboriginal people is 25 times as high as for other Australians. Aboriginal and Torres Strait Islanders are up to eight times more likely than non-Aboriginal and Torres Strait Islanders to be hospitalised for ARF and RHD. Between 2005 and 2007, the age-adjusted death rate was four times as high in Aboriginal people as the non-Indigenous rate.⁸ Recent unpublished data from the Northern Territory are encouraging, with adherence rates improving and recurrence rates decreasing.

Recent developments in the control of acute rheumatic fever and rheumatic heart disease in Australia

In 2009, the Australian Government started the Rheumatic Fever Strategy as part of its *New directions: an equal start in life for Indigenous children* policy. The strategy provided funding for register-based RHD control programs in the Northern Territory, Queensland and Western Australia, as well as establishing a national coordination unit (NCU). The NCU is known as RHD Australia, and its major tasks are to establish a national data collection and reporting system; update and disseminate evidence-based, best practice guidelines; developing education, training and health professional resources; provide support to jurisdictional RHD control programs; and increase community awareness of ARF/RHD and its prevention.

Approaches to disease prevention

The prevention of disease may be undertaken at a number of different levels. Primordial and primary prevention aims to stop a disease occurring in the first place, while secondary and tertiary prevention aim to limit the progression and reduce the consequences of established disease. Most of the research, knowledge and health initiatives associated with ARF and RHD prevention relate to secondary prevention, which focuses on limiting the more serious consequences through early diagnosis and treatment, and tertiary prevention targeted at reducing the impact and complications of established RHD.

Prevention in the context of ARF/RHD:

- **primordial prevention:** broad social, economic and environmental initiatives undertaken to prevent or limit the impact of GAS infection in a population
- **primary prevention:** reducing GAS transmission, acquisition, colonisation and carriage, or treating GAS infection effectively to prevent the development of ARF in individuals
- **secondary prevention:** administering regular prophylactic antibiotics to individuals who have already had an episode of ARF to prevent the development of RHD, or who have established RHD in order to prevent progression of disease
- **tertiary prevention:** intervention in individuals with RHD to reduce symptoms and disability, and prevent premature death.

Primordial and primary prevention of acute rheumatic fever

Primordial prevention aims to stop the development of risk factors for a disease in a population. In the case of ARF and RHD, primordial prevention means preventing GAS infections through implementing actions and measures that target environmental, economic, social and behavioural conditions, and cultural patterns of living that are known to increase the risk of such infections. Socioeconomic and environmental disadvantage, in association with household overcrowding and limited access to infrastructure to maintain hygiene, are frequently posited as the predominant drivers of ARF and RHD. Therefore, the incidence of ARF may be reduced by measures that alleviate poverty and crowding.

Primary prevention assumes that the risk factor for ARF and RHD, namely the presence of GAS infection (particularly in the pharynx), is present in a given population. Primary prevention treatment should target populations at elevated risk. In Australia, such populations include Aboriginal and Torres Strait Islanders, Maori, Pacific Islanders and perhaps immigrants from other countries with high rates of ARF and RHD.

In some settings, particularly Australia, it has been suggested that GAS-associated skin infection (impetigo) may play a similar role. There is currently insufficient evidence regarding the impact of skin health interventions on ARF and RHD to warrant

recommending such programs for the primary prevention for ARF/RHD. However, improved skin health is likely to have broader health impacts, and studies documenting the association of reduced rates of GAS skin infections with changes in ARF incidence will provide important information for future primary prevention programs.

Diagnosis and management of acute rheumatic fever

ARF is an autoimmune response to bacterial infection with GAS. People with ARF are often in great pain and require hospitalisation. Despite the dramatic nature of the acute episode, ARF leaves no lasting damage to the brain, joints or skin; however, RHD may persist. People who have had ARF previously are much more likely than the wider community to have subsequent episodes. Recurrences of ARF may cause further valve damage, leading to steady worsening of RHD.

Although the exact causal pathway is unknown, it seems that some strains of GAS are ‘rheumatogenic’, and that a small proportion of people in any population (3–5%) have an inherent susceptibility to ARF.³

ARF is a condition seen predominantly in children aged 5–14 years, although recurrent episodes may continue well into the fourth decade of life. Because RHD represents the cumulative heart damage of previous ARF episodes, the prevalence of RHD peaks in the third and fourth decades of life.³ Therefore, although ARF is a disease with roots in childhood, its effects are felt throughout adulthood, especially in the young adult years when people might otherwise be at their most productive. In 2007, 255 people in Australia died from ARF and RHD, representing 0.2% of all deaths, and 0.5% of cardiovascular disease deaths.⁸

Diagnosis of acute rheumatic fever

An accurate diagnosis of ARF is important. Overdiagnosis results in unnecessary treatment over a long time, while underdiagnosis leads to further attacks of ARF, cardiac damage and premature death. Diagnosis remains a clinical decision, as there is no specific laboratory test.

The diagnosis of ARF is usually guided by the Jones criteria and the more recent World Health Organization (WHO) criteria. To increase sensitivity for ARF diagnosis in Australia’s unique, high-risk population, the Jones and WHO criteria have been further modified to form the 2012 Australian criteria for the diagnosis.

Many medical practitioners in Australia have never seen a case of ARF, because the disease has largely disappeared from the populations among which they train and work. It is very important that health staff receive appropriate education about ARF before postings to remote areas.

Many of the clinical features of ARF are non-specific, so a wide range of differential diagnoses should be considered. In a region with high, compared to low, incidences of ARF, a person with fever and arthritis is more likely to have ARF. Some post-streptococcal syndromes may be confused with ARF such as PANDAS and post streptococcal reactive arthritis, but these diagnoses should rarely, if ever, be made in high-risk populations.

All patients with suspected or confirmed ARF should undergo echocardiography, if available, to confirm or refute the diagnosis of rheumatic carditis. Echocardiographic evidence of valve damage (subclinical or otherwise), diagnosed by a clinician with experience in ARF and RHD, may be included as a major manifestation in the diagnosis of ARF.

Management of acute rheumatic fever

In the first few days after presentation, the major priority is confirming the diagnosis. With the exception of heart failure management, none of the treatments offered for ARF have been proven to alter the outcome of the acute episode, or the amount of damage to heart valves. Non-steroidal anti-inflammatory drugs reduce the pain of arthritis, arthralgia and fever of ARF, but can confuse the diagnosis. Paracetamol and codeine are recommended for pain relief until the diagnosis is confirmed. Corticosteroids are sometimes used for severe carditis, although there is no evidence that they alter the longer-term outcome.

All patients with suspected ARF (first episode or recurrence) should be hospitalised as soon as possible after the onset of symptoms. This ensures that all investigations are performed, and if necessary, the patient should be observed to confirm the diagnosis before commencing treatment.

Secondary prevention and rheumatic heart disease control

Secondary prevention refers to the early detection of disease and implementation of measures to prevent recurrent and worsening disease.

Secondary prophylaxis with benzathine penicillin G (BPG) is the only RHD control strategy shown to be clinically effective and cost-effective at both community and population levels. Randomised, controlled trials (RCT) have shown that regular administration is required to prevent recurrent ARF.

Secondary prophylaxis

Secondary prophylaxis with BPG is recommended for all people with a history of ARF or RHD. Four-weekly BPG is currently the treatment of choice, except in patients considered to be at high risk, for whom three-weekly administration is recommended. The benefits of three-weekly BPG injections are offset by the difficulties of achieving good adherence, even to the standard four-weekly regimen. Data from the Northern Territory show that few, if any, recurrences occurred among people who fully adhered to a four-weekly BPG regimen.⁹

Alternatives to BPG are available, although they are less effective and require careful monitoring. In patients who refuse intramuscular BPG, oral penicillin can be offered, although it is less effective than BPG in preventing GAS infections and subsequent recurrences of ARF. The consequences of missed oral doses must be emphasised, and adherence monitored. In patients who may be allergic to penicillin, an allergist should be consulted. The rates of allergic and anaphylactic reactions to monthly BPG are low, and fatal reactions are exceptionally rare. There is no increased risk with prolonged BPG use. In patients with a confirmed, immediate and severe allergic reaction to penicillin, a non-beta-lactam antimicrobial (e.g. erythromycin) should be used instead of BPG. In pregnant patients, penicillin prophylaxis should continue for the duration of pregnancy to prevent recurrent ARF. There is no evidence of teratogenicity. Erythromycin is also considered safe in pregnancy, although controlled trials have not been conducted. In anticoagulated patients, BPG injections should be continued unless there is evidence of uncontrolled bleeding, or the international normalised ratio is outside the defined therapeutic window.

The appropriate duration of secondary prophylaxis is determined by a number of factors, including age, time since the last episode of ARF, ongoing risk of streptococcal infections and potential harm from recurrent ARF.

All people with ARF or RHD should continue secondary prophylaxis for a minimum of 10 years after the last episode of ARF, or until the age of 21 years (whichever is longer). Those with moderate or severe RHD should continue secondary prophylaxis up to the age of 35–40 years.

Infective endocarditis is a dangerous complication of RHD, and a common adverse event following prosthetic valve replacement in Aboriginal and Torres Strait Islanders. People with established RHD or prosthetic valves should receive antibiotic prophylaxis prior to procedures expected to produce bacteraemia (e.g. dental or surgical procedures where infection is present).

Adherence to secondary prophylaxis

Persistent high rates of recurrent ARF in Australia highlight the ongoing need to improve adherence to secondary prophylaxis. Although patients from the Northern Territory with recurrent ARF receive on average less than 50% of their scheduled injections, and few patients receive the recommended benchmark of 80% of their scheduled injections.⁹ Recent unpublished data from the Northern Territory are encouraging, with adherence rates improving and recurrence rates decreasing. The challenge is to accelerate these improvements and to ensure that other jurisdictions are also able to improve their delivery of secondary prophylaxis.

A variety of factors combine to limit the uptake of long-term secondary prophylaxis. Primary care facilities should be aware of any local barriers to receiving secondary prophylaxis, and work within the system and with patients and families to reduce these barriers. For example, adherence has been seen to improve when patients feel a sense of personalised care and 'belonging' to the clinic, and when recall systems extend beyond the boundaries of the community.¹⁴

Hospitalisation at diagnosis provides an ideal opportunity to begin or re-establish secondary prophylaxis, and to educate patients and families on how important it is to prevent future episodes of ARF. Appropriate continuing education and support by primary care staff should continue once the patient has returned home.

Secondary prevention of further episodes of ARF is a priority. It should include strategies aimed at improving the delivery of secondary prophylaxis and patient care, the provision of education, coordinating available health services and advocacy for necessary and appropriate resources.

Strategies to promote continuing adherence include:

- identifying local, dedicated staff members to deliver secondary prophylaxis and coordinate routine care
- focusing on improving relationships between health staff and patients/families
- supporting and using the expertise, experience, community knowledge and language skills of Aboriginal health workers
- developing and implementing recall and reminder systems (based on a local ARF/RHD register where established) to accommodate the high mobility of individuals and groups
- ensuring that recall systems extend beyond community boundaries
- establishing networks for timely communication between health clinics
- using a centralised coordinator and register to assist in monitoring movement
- minimising staff turnover in remote and rural primary healthcare centres and regional hospitals, or minimising the impact of staff turnover where possible
- promoting the importance of secondary prophylaxis in preventing recurrent ARF and the development or worsening of RHD
- improving the quality and delivery of ongoing health education and support for staff, patients and families
- implementing measures to reduce pain of injections where indicated
- basing routine care on standardised evidence-based guidelines.

Rheumatic heart disease control programs

A coordinated control program, including specialist review and echocardiography, is the most effective approach to improving BPG adherence and clinical follow up of people with RHD. Control programs should aim to support clinical and public health practice indirectly by increasing expertise among health service providers and supporting them to provide services to patients.

Recommended elements of RHD control programs include:

- secondary prevention activities aimed at preventing the recurrence of ARF and severe RHD
- community health education activities
- training of healthcare providers
- epidemiological surveillance.

Control programs for ARF and RHD should be evaluated using criteria for routine care and key epidemiological objectives.

Diagnosis and management of rheumatic heart disease

Implementing guidelines on the diagnosis and management of RHD has major implications for Aboriginal and Torres Strait Islander healthcare services, especially in rural and remote regions. In addition to access to culturally-appropriate primary care services, best practice for RHD requires:

- secondary prevention with penicillin prophylaxis
- adequate monitoring of anticoagulation therapy in patients with atrial fibrillation (AF) and/or mechanical prosthetic valves
- access to oral healthcare
- access to echocardiography
- access to a specialist physician, paediatrician and/or cardiologist
- access to cardiothoracic and interventional cardiology services.

All patients with murmurs suggestive of valve disease, or a past history of rheumatic fever, require echocardiography. This will detect any valvular lesion, and allow assessment of its severity and of left ventricular (LV) size and systolic function. Serial echocardiographic data play a critical role in helping to determine the timing of any intervention.

The fundamental goal in the long-term management of RHD is to prevent ARF recurrences, and therefore, prevent the progression of valve disease. In some cases, this may allow for resolution of their heart disease. This can be achieved by regular delivery of secondary prophylaxis with long-acting, intramuscular penicillin. Where adherence to secondary prevention is poor, there is greater need for surgical intervention, and long-term surgical outcomes are not as good.

Valvular lesions in rheumatic heart disease

Mitral regurgitation

Mitral regurgitation (MR) is the most common valvular lesion in RHD, particularly in young patients. In chronic MR, volume overload of the left ventricle and left atrium occurs, which in more severe cases eventually results in a progressive decline in systolic contractile function. Patients with mild or moderate MR may remain asymptomatic for many years. Initial symptoms include dyspnoea on exertion, fatigue and weakness, and these may progress slowly over time or worsen after a recurrence of rheumatic fever, chordal rupture or onset of AF.

There is wide individual variation in the rate of progression of MR, although many cases tend to progress over 5–10 years, especially if there is a recurrence of ARF. MR may also resolve over time, especially if there are no recurrences of ARF.

Key points in the diagnosis and management of MR include:

- echocardiography, which is used to confirm the diagnosis, quantify the severity of regurgitation and assess LV size and function. In asymptomatic and mildly-symptomatic patients with moderate or more severe MR, echocardiography should be performed at least every 6–12 months
- clinical heart failure, which requires diuretic therapy and angiotensin-converting enzyme (ACE) inhibitors
- patients with severe MR being referred for surgery if they become symptomatic. If they have echocardiographic indicators of reduced LV systolic function or an end-systolic diameter by echocardiogram approaching 40 mm in adults. Patients who are asymptomatic or mildly-symptomatic with severe MR and normal LV systolic function should consult cardiac surgeons early, as some of these patients may need to be considered for surgery, especially if valve repair is likely
- mitral valve repair, rather than replacement, which is the operation of choice for symptomatic dominant or pure MR, because of superior long-term results. If the mitral valve is not suitable for repair, the option is valve replacement with either a mechanical valve prosthesis or a bioprosthetic valve.

Mitral stenosis

In mitral stenosis (MS), progressive obstruction to LV inflow develops due to fibrosis and partial fusion of the mitral valve leaflets. Approximately 30% of Aboriginal people with RHD in the Northern Territory

aged 10–19 years have MS, often in association with MR. However, the mean age of those with MS is 33 years. In the Aboriginal and Torres Strait Islander populations, MS progresses more rapidly than in the non-Aboriginal and Torres Strait Islander populations, and patients become symptomatic at a younger age. More rapid progression may be due to undetected recurrences of rheumatic fever.

The initial symptom is exertional dyspnoea, which worsens slowly over time. Symptoms of heart failure (orthopnoea, paroxysmal dyspnoea and occasionally haemoptysis) develop as the mitral valve orifice decreases to less than 1–1.5 cm².

Key points in the diagnosis and management of MS include:

- Doppler and two-dimensional echocardiography (2DE), which are used to quantitate the severity of MS; assess associated valve lesions, LV function and left atrial size; and estimate pulmonary artery systolic (PAS) pressure
- consideration given to direct current cardioversion to restore sinus rhythm, when new-onset AF is associated with symptoms. AF is the most common complication of MS, requiring long-term prophylactic anticoagulation with warfarin to avoid thromboembolic complications
- percutaneous balloon mitral valvuloplasty (PBMV), which is the treatment of choice for dominant or pure MS. The indication is a mitral valve area (MVA) <1.5 cm² with progressive symptoms, or if asymptomatic, a history of thromboembolism or significant pulmonary hypertension
- the short-term and medium-term results being comparable to surgical valvuloplasty, with 65% of patients being free of restenosis after 10 years
- PBMV, which was largely replace surgical intervention. In the relatively few patients who are not suitable, every effort should be made to repair the mitral valve, rather than replace it.

Aortic regurgitation

In aortic regurgitation (AR), there is volume and pressure overload of the left ventricle, eventually leading to contractile dysfunction in more severe cases. In the chronic situation, many patients remain asymptomatic, despite having moderate or severe regurgitation. Eventually, they become symptomatic with exertional dyspnoea, angina and heart failure.

Key points in the diagnosis and management of AR include:

- echocardiography, which is used to assess LV size and function. The severity of AR is assessed by colour flow mapping of the spatial extent of the regurgitant jet in the left ventricle outflow tract. Patients with mild regurgitation require echocardiographic evaluation every 2 years, whereas those with more severe regurgitation should be studied every 6–12 months
- vasodilator therapy, which can reduce LV dilatation and the regurgitant fraction, slow progression of LV dilatation, and may delay the need for surgery. Therapy with nifedipine or ACE inhibitors is recommended for asymptomatic or mildly-symptomatic patients with preserved systolic function and moderate or greater degrees of AR
- patients with moderate to severe AR, who become symptomatic, being referred for surgery. In asymptomatic or mildly-symptomatic patients, surgery is indicated if LV function is reduced (LV ejection fraction (EF) <55%) or the LV end-systolic diameter is approaching 55 mm
- options for aortic valve surgery, such as replacement with either a mechanical prosthesis, a bioprosthesis or an aortic homograft. Other options are aortic valve repair and the Ross procedure (pulmonary autograft with homograft replacement of the pulmonary valve)
- replacement with the anticoagulant, requiring newer bileaflet mechanical valve prostheses, which have the best long-term durability and freedom from reoperation for patients who demonstrate good adherence to medications. If stable anticoagulation is unlikely to be achieved, an aortic bioprosthesis should be considered. In young female patients, a mechanical prosthesis should be avoided, because of the significant risk to mother and fetus posed by anticoagulation during pregnancy.

Aortic stenosis

Aortic stenosis (AS) results from fibrosis and partial fusion of aortic valve cusps, causing progressive obstruction to LV outflow. RHD is an uncommon cause of AS, and almost always occurs in the presence of associated rheumatic mitral valve disease. The classic symptoms are dyspnoea on exertion, angina and syncope. Symptoms are gradual in onset, but are usually slowly progressive over time, especially if there is associated mitral valve disease.

Key points in the diagnosis and management of AS include:

- 2DE, which shows the thickened and restricted aortic valve leaflets and allows assessment of LV size and systolic function. Continuous-wave Doppler echocardiography is used to calculate the gradient across the aortic valve and the aortic valve area (AVA). Patients usually do not develop symptoms of exertional dyspnoea and fatigue until a moderate or severe systolic gradient develops (>40–50 mmHg). Once symptoms develop, prognosis is poor without surgery
- percutaneous aortic valvuloplasty is reserved only for patients who are not candidates for surgery, as it has a high recurrence rate
- aortic valve replacement with a mechanical valve, a bioprosthetic valve or a homograft is the definitive therapy for symptomatic AS. It should be performed in all patients with significant gradients and a reduced valve area once they develop exertional symptoms.

Pregnancy and rheumatic heart disease

Normal pregnancy will worsen the effects of any pre-existing valvular disease. Predictors of increased maternal and fetal risk are reduced LV systolic function, significant AS or MS, moderate or severe pulmonary hypertension, a history of heart failure and symptomatic valvular disease before pregnancy.

Ideally, patients with known rheumatic valvular disease should be properly assessed before pregnancy. If they are already symptomatic due to significant RHD, serious consideration should be given to intervention prior to pregnancy.

In general, MR or AR is well tolerated during pregnancy, although some patients may require heart failure therapy with diuretics. In pregnant, symptomatic patients with moderate or severe MS, PBMV should be considered, because of the high risk of maternal and fetal complications. Pregnant women with mechanical valves are at a very high risk, as all anticoagulant options carry maternal and/or fetal risks.

Warfarin crosses the placenta, but heparin does not. However, there is an increased risk of prosthetic thromboembolic complications with heparin, and a risk of embryopathy and fetal loss with warfarin, especially in the first trimester. The choices for antithrombotic therapy during pregnancy are low-molecular weight heparin (LMWH) throughout, warfarin throughout or LMWH for the first trimester and then warfarin. The pros and cons of each option need to be discussed fully with the patient and family before any decision is made.

2. Primordial and primary prevention of acute rheumatic fever and rheumatic heart disease

The prevention of disease may be undertaken at a number of different levels (Table 2.1). Primordial and primary prevention aims to stop a disease occurring in the first place, while secondary and tertiary prevention aims to limit the progression and reduce the consequences of established disease. Most of the research, knowledge and health initiatives associated with ARF/RHD prevention relate to the latter: secondary prevention focusing on limiting the more serious consequences of ARF/RHD through early diagnosis and treatment, and tertiary prevention targeted at reducing the impact and complications of established disease.

Introduction

Because of the challenges and costs involved in implementing effective secondary and tertiary prevention programs, the ultimate goal in ARF/RHD prevention must remain the elimination of disease. Changing disease patterns in many high-income populations, where ARF and RHD are now rarely seen, show that the near elimination of ARF and RHD outside rare and isolated outbreaks is possible.¹⁵ The question is therefore not whether ARF/RHD elimination can be achieved, but rather:

- what aspects of environment predispose individuals and populations to an increased risk of ARF and RHD
- what evidence is there that specific interventions can make a difference
- whether such interventions are an appropriate use of finite health and community resources.

This chapter will review the evidence supporting initiatives that aim to stop ARF occurring, and hence, prevent the subsequent development of RHD. The major concept that underlies such initiatives is primary prevention. The purpose of primary prevention is to limit the incidence of disease by controlling causes and risk factors. Primary prevention can either focus on an entire population (e.g. in the case of Australia, this may be all Aboriginal people and Torres Strait Islanders, Maori, Pacific Islanders and perhaps immigrants from other regions with high rates of ARF/RHD), or can focus on individuals within that population who are at elevated risk (e.g. people with GAS infection).

An extension of the concept of primary prevention, termed 'primordial prevention', will also be examined here. This term was first proposed by Strasser, who argued that the prevention of disease should go

Table 2.1 Prevention in the context of ARF and RHD

Primordial prevention	Broad social, economic and environmental initiatives undertaken to prevent or limit the impact of GAS infection in a population
Primary prevention	Reducing GAS transmission, acquisition, colonisation and carriage or treating GAS infection effectively to prevent the development of ARF in individuals
Secondary prevention	Administering regular prophylactic antibiotics to individuals who have had an episode of ARF to prevent the development of RHD or to individuals who have established RHD to prevent the progression of disease
Tertiary prevention	Intervention in individuals with RHD to reduce symptoms and disability, and prevent premature death

beyond primary prevention to include activities that prevent the penetration of risk factors into a population.¹⁶

In the context of ARF (a non-suppurative complication of GAS infection), primordial and primary prevention would involve:¹⁵⁻¹⁹

- eliminating the risk factors associated with GAS infection: primordial prevention
- preventing infection, and perhaps colonisation, with GAS, and the subsequent development of ARF: primary prevention.

This chapter will examine both these concepts, and conclude by providing suggested strategies for how available evidence may be used to conceptualise, advocate and implement primordial and primary prevention initiatives for ARF/RHD in our region.

Primordial prevention

Primordial prevention aims to stop the development of risk factors for a disease in a population. In the case of ARF/RHD, primordial prevention means preventing the acquisition of GAS infection through implementing 'actions and measures that target environmental, economic, social and behavioural conditions, cultural patterns of living...that are known to increase the risk of (GAS infection)'.²⁰

While socioeconomic and environmental disadvantage, in association with household overcrowding and limited access to infrastructure, are frequently posited as the predominant drivers of ARF/RHD, the evidence supporting this supposition remains limited.^{21, 22} Nonetheless, studies from the 1940s onwards in the USA, UK and New Zealand have shown that ARF is associated with household income and overcrowding.²³⁻²⁶ Further, there is evidence that dramatic falls in the rates of ARF/RHD have occurred in populations undergoing improvements in socioeconomic and environmental conditions.^{15, 27, 28}

This has been seen in Australia, New Zealand and other high-income countries over the past 50–150 years.²⁹⁻³¹ This reduction in disease burden now means that in most developed countries, ARF is no longer endemic, and is restricted to rare, sporadic cases and defined outbreaks.³² Such developments make a persuasive case that demographic, socioeconomic and environmental factors are important drivers of ARF/RHD.

Exactly which component of increasing affluence (housing quantity and quality, healthcare access and

quality, education, economic advantage) has played a role in the reduction of rates of ARF/RHD is unknown. However, Holmes and Rubbo, in a review of ARF in Melbourne between 1938 and 1948, did find that the incidence of rheumatic fever was three times greater in low, rather than in high, rental districts.²⁹ Furthermore, in a systematic review identifying potential risk factors for ARF and possible interventions for its prevention, Kerdelidis *et al* found that the incidence of ARF may be reduced by measures that alleviate poverty and crowding.³³ Alleviating household overcrowding has biological plausibility, given the potential for increased risk of GAS transmission when living in close living conditions, such as has been described in studies of outbreaks of GAS infection and ARF in the US military.³⁴ The association between crowding and transmission of GAS is variable, with Danchin *et al*'s prospective Australian study reporting no association between risk of GAS-positive sore throat and socioeconomic disadvantage or household crowding.³⁵ Nonetheless, this study did demonstrate high levels of GAS transmission, even in uncrowded households. Kerdelidis *et al* further argue that health knowledge, health literacy and access to healthcare are important aspects of primordial prevention for ARF.³³ Logically, as the authors state, 'if people do not consider sore throats important or have the knowledge that they can lead to permanent heart damage, they will not seek medical help, creating a barrier in rheumatic fever prevention'. The issue of access to healthcare was explored by Gordis in Baltimore, USA, in the 1960s, when comprehensive primary care programs were implemented in some parts of the city.³⁶ While not an RCT, the results did show a 60% reduction in ARF from 1960 to 1970 in those parts of the city where comprehensive primary care programs were introduced compared with no improvement at other sites.³⁶

Given the uncertainties regarding specific causes, the available evidence does not support advocating for the primordial prevention of ARF/RHD, based on one or another specific environmental or social strategy. Nonetheless, consistent data demonstrating an association between overcrowding and ARF risk across multiple countries would indicate that this particular factor is worthy of further study. The broader context of alleviation of poverty and social and environmental disadvantage, along with improved housing, education, healthcare access and appropriate standards and quality of care, are likely to be key in addressing ARF/RHD, as well as many other health issues in our region.

Despite the lack of evidence to support specific environmental or social interventions to address the acquisition of risk factors for ARF/RHD, this

uncertainty should not dissuade action. The broader context of equity, poverty alleviation and justice, in association with the empirical link observed between improved socioeconomic and environmental factors and reduced ARF incidence, should be sufficient to drive advocacy and change. Such change, as Ursoniu notes, ‘rests mainly on public education, the media, legislation and government policy, and is very dependent on the commitment and determination of individual governments’.²⁰

Primary prevention

Primary prevention assumes that the risk factor for ARF/RHD, namely the presence of GAS (particularly in the pharynx), is present in a given population. In reality, this assumption is borne out, as GAS is present in all populations, both rich and poor, and those with and without high rates of ARF/RHD. Furthermore, GAS has been shown to be associated with up to 37% of throat infections³⁷ and 82% of skin infections.^{38, 39} Whether other streptococci, such as group C (GCS) and group G (GGS), play a similar role in the pathogenesis of ARF/RHD is unclear.

Before further discussing the primary prevention of ARF/RHD, it is necessary to have a clear and consistent definition of a number of terms:⁴⁰

- **colonisation:** organisms are present, but cause no host response. This implies associated transmission and acquisition
- **carriage:** organisms remain in an individual after a clinical infection, but cause no symptoms; an immunological response may remain
- **infection:** the deposition and multiplication of organisms in tissue or on body surfaces, which usually cause adverse effects; this is typically associated with an immunological response
- **pharyngitis:** a clinical syndrome associated with infection/irritation of the pharynx and/or tonsils.

The primary prevention of ARF/RHD through addressing GAS should prioritise identifiable populations at elevated risk of ARF/RHD. In Australia, such populations include Aboriginal and Torres Strait Islanders, Maori, Pacific Islanders and perhaps immigrants from other countries with high rates of ARF/RHD.⁴¹⁻⁴³ However, this may also extend to other groups in the setting of a temporally-defined outbreak of ARF in a specific population that has previously had a low risk of ARF (e.g. as has been described in military recruits³²).

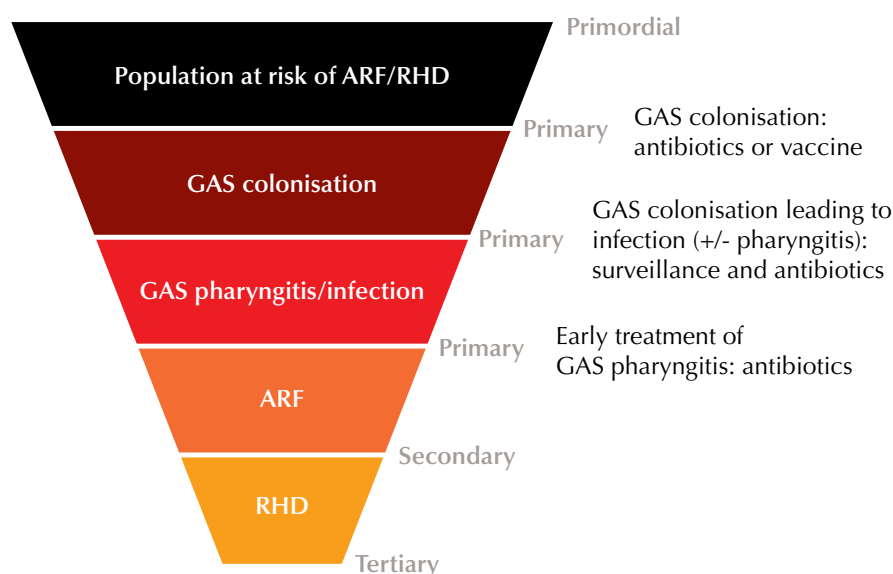
The existing understanding of the pathophysiology of ARF/RHD highlights the importance of GAS-associated pharyngitis 2–3 weeks before the development of ARF.⁴⁴ However, it is apparent that GAS infection without co-existent pharyngitis can precipitate ARF. In a well-described outbreak of ARF in the intermountain area of the USA, centred around Salt Lake City, Utah, a recent history of pharyngitis was frequently absent.^{1, 45} One study reported that only one-third of patients had a clear-cut history of sore throat in the 3 months preceding the onset of ARF.⁴⁵ A follow-up study reported that over an 8-year period, only 28% of children with confirmed ARF reported a history of a sore throat that parents considered serious enough to seek medical care. Only 17% sought medical attention and received antibiotic prescriptions.¹

In some settings, particularly the Australian setting, it has been suggested GAS-associated skin infection (impetigo) may play a similar role.⁶ While the evidence supporting such a link remains limited and contentious, it has provided an additional focus for primary prevention, particularly in Australia, and will be addressed here.

Primary prevention of group A streptococcus in the throat

There is a clear understanding regarding the primacy of pharyngeal GAS in the pathophysiology of ARF.⁴⁵ When an individual is exposed to GAS, the organism attaches to and colonises the pharyngeal mucosa. A process of infection incorporating an immune response is initiated, and as part of this immune response, an episode of ARF occurs. This process is not inevitable. Exposure may not lead to colonisation, colonisation may not lead to infection and the host immune response may not lead to ARF. While it is not within the scope of this chapter to review the factors that may alter this process, such factors are likely to include the burden, type and diversity of GAS in a given population (see ‘Primordial prevention’, above), the inoculating dose, specific organism factors (e.g. the concept of rheumatogenic/ARF-causing strains of GAS),⁴⁶ host factors that may encourage colonisation and infection and host factors that may predispose to ARF once GAS infection is established. Figure 2.1 outlines potential targets for the primary prevention of ARF due to GAS, and their relationship to primordial, secondary and tertiary prevention.

Figure 2.1 Outline of structure for preventive strategies for GAS pharyngeal colonisation and pharyngitis



Preventing group A streptococcus colonisation

There are at least two possible approaches to potentially pre-empt the acquisition of GAS in the pharynx: prophylactic antibiotics and vaccination. A third possibility – the use of probiotics in the primary prevention of GAS – has been raised, but research in this area remains at the exploratory phase.^{47, 48}

Prophylactic antibiotics to prevent the acquisition of GAS employ the same rationale that is used in the secondary prevention of ARF/RHD.^{49, 50} The most compelling evidence for the effectiveness of this approach comes from the US military, where recruit camps have historically seen high rates of GAS and ARF infection.⁵¹ After a significant rise in GAS infections and ARF during World War II, GAS-prevention programs, based on intramuscular BPG prophylaxis, were implemented within US navy and marine corps recruit camps.^{51, 52} Large-scale, mass prophylaxis campaigns in military training centres^{53, 54} saw the incidence of ARF in the US military fall dramatically in the 1960s and 1970s.⁵¹ However, in the 1980s, when routine prophylaxis in some military centres was replaced by prevention programs designed on the basis of local surveillance for GAS infection, further ARF outbreaks were reported.⁵⁵ To combat this ‘re-emergence’ of ARF, prophylaxis with BPG, given as a single dose at the beginning of each training cycle, was re-implemented in 1987 at naval recruit training centres, and was in turn associated with a reduction in ARF.⁵⁰ In one study, navy recruits were studied to determine the prevalence of GAS pharyngeal colonisation cultures before, and 2, 4

and 7 weeks after, receiving BPG prophylaxis.⁵⁰ The prevalence of GAS carriage fell by 75% at 4 weeks, but by 7 weeks, had returned to preprophylaxis levels.

While the evidence is restricted to cohort studies, antibiotic prophylaxis does appear to be effective in reducing GAS pharyngeal colonisation and associated ARF. Nonetheless, the benefits of a single dose of BPG are not sustained beyond 4 weeks. The use of regular prophylactic antibiotics to prevent GAS colonisation in otherwise healthy individuals is unlikely to be sustainable or cost-effective, except in small, defined, static populations that are temporarily at elevated risk of ARF/RHD. Such a strategy would also entail risks for the individual receiving prophylaxis and the potential for antibiotic resistance.

Vaccination against GAS presents an ideal solution for the primary prevention of ARF/RHD. An effective vaccine would provide ongoing protection against GAS colonisation and infection, as opposed to the 4-week protection afforded by a single dose of BPG. Vaccines have been in development since early last century,⁵⁶ but a number of scientific and regulatory obstacles have prevented a GAS vaccine being readily available, including concerns regarding potentially cross-reactive epitopes.⁵⁷⁻⁵⁹ Only one vaccine has entered clinical trials in the past 30 years. However, there has been increasing international interest in the development of GAS vaccines in the past decade,⁶⁰ including from the WHO.⁶¹

Modern vaccines can be categorised into two groups: those that focus on the M protein (the major GAS virulence determinant), and those that focus on

non-M-protein antigens. Although non-M-protein vaccines, such as streptococcal C5a peptidase, GAS carbohydrate and fibronectin-binding proteins, have progressed well in preclinical studies, none have progressed to clinical trials.

The most advanced vaccine candidate is a multivalent vaccine, based on the aminoterminal region of the M protein. It has undergone phase I and II clinical trials in adults, with good evidence of safety and immunogenicity.^{62, 63} It is estimated that this 26-valent vaccine would provide protection against 80–90% of invasive GAS and pharyngitis isolates in North America.⁶⁴ However, there are many circulating types of GAS in developing countries and in northern Australia that would not be covered by this vaccine.⁶⁵ Reformulation of this vaccine into a 30-valent vaccine may circumvent these problems.⁶⁶ A second M-protein vaccine (the 'J8' vaccine), based on the conserved region of the M protein, and developed in Queensland, Australia, may potentially provide protection against all GAS strains.^{67, 68} Clinical trials of this candidate are currently in preparation.

While the development of a safe and effective GAS vaccine to prevent ARF/RHD is yet to be realised, it should remain a priority in ARF/RHD prevention.

Eradication of group A streptococcal colonisation

A number of health programs have sought to identify and eradicate pharyngeal GAS colonisation in high-risk populations to prevent ARF/RHD.⁶⁹ In the 1950s, as a prelude to mass antibiotic prophylaxis programs in the US military, BPG injections were administered to 624 asymptomatic recruits with positive throat cultures for GAS.⁷⁰ This single dose resulted in negative cultures for at least 1 month in 96% of these recruits. While there was no control group, ARF did not occur in any recruit who had received antibiotics. In Australia, one primary prevention program in a remote Aboriginal community in far North Queensland involved tri-annual throat swabbing of 4–16 year olds, and treatment for those with GAS.⁷¹ While ARF surveillance suggested that this program coincided with a reduction in the incidence of ARF, the lack of a control group made it difficult to determine the true efficacy of the intervention.

Another study investigated the impact of a 3-year streptococcal disease control program among the Navajo Indians in North America.⁷² In this program, throat specimens for culture were taken from school children at the beginning of the school

year. Asymptomatic children were then swabbed periodically (usually monthly), while any child who presented to the school clinic with a sore throat was swabbed immediately. If GAS was identified, the child was treated with penicillin or erythromycin. A quasi-control group was included, as schools in only five of the eight Indian Health Service Units that made up the Navajo reservation took part in the program. In 'covered' areas that participated in the surveillance program, the rate of ARF was 39% lower during the program (falling from 13.5 to 8.2 cases per 100,000 per year), while the rates in 'uncovered' areas that did not participate in the program showed little change. Nonetheless, 'covered' areas initially had substantially higher ARF rates compared with 'uncovered' ones, and the program was adopted at different times, with many sites participating only intermittently.

A recent prospective, school-based study into the control of GAS upper respiratory tract infections in southern China has shown that asymptomatic children with positive throat cultures, who were treated with penicillin/erythromycin therapy at school, had a significantly lower prevalence and incidence of GAS pharyngitis than children at the same school who sought medical care from their regular health providers.⁷³ While the incidence of ARF was not reported, this study does provide evidence that controlling GAS colonisation can reduce the incidence of GAS pharyngitis.

While the presence of GAS in the nasopharynx indicates GAS load, there is debate over whether the presence of GAS without symptoms is associated with an elevated risk of ARF. The American Academy of Pediatrics' *Red book: report of the committee on infectious disease* argues that carriage is not a risk to an individual or to spread in the population.⁷⁴ However, as Kaplan notes, the significance of the immunological difference between acute streptococcal upper respiratory tract infection and the relatively harmless streptococcal carrier state is not understood.⁷⁵

Given the limited evidence, it is difficult to advocate for the identification and eradication of GAS colonisation as a mechanism for reducing ARF incidence. Even if such an approach were effective in reducing ARF rates, the use of regular antibiotics to eradicate GAS colonisation in otherwise healthy individuals with no history of ARF/RHD poses issues associated with cost, client inconvenience and risk, and the development of antibiotic resistance.

Early treatment of group A streptococcal pharyngitis

Given the limited evidence, and the level of resources that would be required for preventing or eradicating GAS colonisation through the use of prophylactic antibiotics, and the current lack of an effective vaccine, the next possible focus in ARF primary prevention is the early identification and treatment of symptomatic GAS pharyngitis. In this case, the aim is to identify symptomatic GAS pharyngitis in those individuals most at risk of ARF (typically children aged 5–14 years), and to eradicate the bacterium through the use of effective antibiotic treatment before it can precipitate the cascade of immune-mediated events that lead to the development of ARF. Studies have reported that GAS can be eliminated from the upper respiratory tract.^{76–78} This in turn may prevent ARF if treatment is commenced within 9 days of symptoms appearing.^{25, 76, 79–81} Nevertheless, the question remains whether focused ‘sore throat’ programs result in a reduction in the risk of ARF in high-risk populations.

There are three possible approaches to the early treatment of GAS pharyngitis: standardised antibiotic

treatment of sore throats, antibiotic treatment of those with clinical features suggestive of GAS infection and antibiotic treatment of those in whom testing confirms the presence of GAS.

Standardised antibiotic treatment of sore throats

The management of pharyngitis as a mechanism for preventing ARF/RHD is complicated by the fact that only a minority of sore throats are caused by GAS. While it is possible to treat all cases of pharyngitis with antibiotics, this would expose a significant proportion of patients to unnecessary treatment, as only 20–40% of pharyngitis episodes are associated with GAS infection;⁷⁹ the remainder are caused by viruses or by bacteria for which antibiotic treatment is not recommended. Moreover, such an approach would require substantial resources and expose clients to unwarranted inconvenience and risk, while increasing the possibility of antibiotic resistance. However, some treatment guidelines do suggest that people identified as being from populations at high risk of ARF, or who have established RHD, but are not currently receiving secondary antibiotic prophylaxis, should be

Table 2.2 Recommended antibiotic treatment for streptococcal pharyngitis

All cases				
BPG	Child:	Deep im injection	Once	
	<i>Weight (kg)</i>			<i>Dose (mg)</i>
	≥20			900
	15 to <20			675
	10 to <15			450
	6 to <10			337.5
	3 to <6			225
Adult: 900 mg				
If im injection not possible				
Phenoxymethylpenicillin	Child: 15 mg/kg up to 500 mg, bd Adult: 500 mg, bd	Oral	For 10 days	
For patients hypersensitive to penicillin				
Erythromycin ethyl succinate	Child: 20 mg/kg up to 800 mg, bd Adult: 800 mg, bd	Oral	For 10 days	

In cases of severe sore throat, procaine penicillin may be required. Refer to CARPA Manual for further information.

bd, *bis die* (twice daily); BPG, benzathine penicillin G; im, intramuscular injection.

Source: CARPA standard treatment manual, 5th ed. Rural and Remote Health 2011.

treated with antibiotics if they develop pharyngitis, irrespective of other clinical features, and before confirmatory testing for GAS is available (Table 2.2).⁸² While empirically attractive, there is no clear evidence that such an approach is a safe or cost-effective way to reduce the incidence of ARF.

Antibiotic treatment of those with clinical features suggestive of group A streptococcal infection

Research from the 1950s involving the US armed services indicated that antibiotic treatment of those with clinical features suggestive of GAS infection may be effective in preventing ARF in isolated, at-risk groups. In one seminal study, Denny *et al* conducted a clinical trial of the effectiveness of crystalline procaine penicillin G in preventing ARF following GAS infection.⁷⁶ This trial involved 1602 servicemen admitted to hospital for respiratory tract disease, who exhibited exudates on the tonsils or the pharyngeal wall. Penicillin treatment was provided to 798 patients, while a control group of 804 patients received no treatment. Blinded follow up was undertaken 3–4 weeks after the initial infection. In the treated group, only two patients developed definite ARF, and two patients developed probable ARF. In contrast, in the control group, 17 patients (relative risk (RR) 8.4 times higher than the treated group) developed definite ARF, and six (RR 3) developed probable ARF. This represented a significant reduction in the attack rate of ARF in the treated group. The effect of penicillin treatment on the presence of GAS in throat cultures was also examined. In the treated group, the number of patients with a positive throat swab for GAS fell from 78.3% on admission to 18.1% at the time of follow up. The untreated group saw a reduction from 81.7% to 52.7%. Finally, the results indicated that the development of antistreptolysin O (ASO) in the two groups was different, with 51% of the treated group showing a rise in titre of two or more times, while 73% of the untreated group exhibited such a rise. In summary, this study showed that penicillin treatment of previous GAS pharyngitis significantly reduced the attack rate of ARF, eradicated GAS from most patients and decreased the antibody response to GAS.

In a later study, it was shown that even when penicillin treatment was delayed until 9 days after the onset of illness, at a time when acute symptoms had subsided and when near maximal antibody response had occurred, it was still effective in preventing ARF.⁷⁷ In this study, rates of ARF were comparable in the control and treatment groups before treatment, but then dropped significantly in the treatment group over the 5 weeks following delayed antibiotic treatment.

It should be noted that all these US armed services studies involved very specific conditions and populations. The servicemen were housed in cramped living conditions, and the GAS strains circulating appeared to have been highly virulent and rheumatogenic. Whether the results seen in these studies can be generalised to broader populations is questionable. Nonetheless, the success of these interventions and the inclusion of control groups in each study provide strong evidence that such approaches may be successful in the primary prevention of ARF.

It has been argued that enhanced pharyngitis surveillance and treatment programs may be effective in a broader context than the military situations described previously. For example, Karthikeyan and Mayosi point to the reduced incidence and prevalence of ARF and RHD in Costa Rica⁸³ and Cuba⁸⁴ as evidence that primary prevention strategies are effective.⁸⁵ In Costa Rica, a program was introduced in the 1970s in which all people with clinical signs of GAS pharyngitis were treated with BPG, without the need for throat culture.⁸³ This was associated with a sharp decline in the incidence of ARF (70/100,000 in the early 1970s, down to 1/100,000 in 1990). However, this dramatic fall in ARF incidence preceded an increased uptake in the use of BPG injections, suggesting that other factors were responsible for this decline in ARF incidence. A substantial decline in the occurrence and severity of ARF and RHD was also reported in Cuba, after a 10-year prevention strategy was introduced in the province of Pinar del Rio.⁸⁴ A similar multidimensional strategy in the French Caribbean islands of Martinique and Guadeloupe focused on the development of a registry and recall system for patients with ARF/RHD, and enhanced the education, detection and treatment of GAS-associated pharyngitis.⁸⁶ This was associated with a decline in ARF incidence of 74–78% over a 10-year period. While these findings are encouraging, they share a number of methodological limitations that should caution interpretation. These include the fact that these programs involved elements, in addition to primary prevention (e.g. secondary prevention of ARF/RHD, training of personnel, health education, dissemination of information, community involvement, epidemiological surveillance and the implementation of a national healthcare plan), and the lack of a comparable control group, with outcomes being assessed using historic and surveillance data.⁸³

Antibiotic treatment of those in whom testing confirms the presence of group A streptococcal

Targeting only those people with confirmed GAS pharyngitis would be an effective means of limiting antibiotic use in primary prevention. Such an approach would require the rapid identification of GAS in people presenting with pharyngitis to allow initiation of therapy within 9 days of symptom onset. Such detection may rely on clinical features, antigen detection or the gold standard of bacterial culture.

A number of clinical scoring methods for predicting the presence of GAS, and thus the requirement for antibiotics, have been suggested. Typically, these methods stratify patients according to an algorithm, whereby points are allocated based on factors, such as patient demographics, season and a number of specific signs and symptoms (e.g. elevated temperature, absence of cough, tender anterior cervical adenopathy, tonsillar swelling or exudate, absence of upper respiratory symptoms).⁸⁷⁻⁸⁹ Patients with higher scores are classified as being at greater risk of GAS infection, and are therefore recommended to have a throat swab culture and/or antibiotic treatment. Validation studies of such scoring systems have demonstrated relatively low positive and negative predictive values for the subsequent isolation of GAS on throat swab.^{89, 90} For example, in McIssac *et al*'s study of the validation of the modified Centor score (which incorporates temperature, absence of cough, swollen/tender anterior cervical lymph nodes, tonsillar swelling or exudate and age), the pretest probability of GAS isolation in patients aged 3–17 years with a sore throat was 34%.⁹¹ In this setting, a positive clinical score prompted unnecessary treatment for GAS in one-third of children, and a negative clinical score left one-quarter of children with GAS without treatment. Hence, the utility of such clinical scoring systems in differentiating GAS and non-GAS pharyngitis in populations at higher risk of ARF, where the potential consequences of missed GAS infection are higher, would appear limited.

Given the difficulty in differentiating GAS from non-GAS pharyngitis based on clinical features alone, microbiological laboratory testing to confirm the presence of GAS is recommended, if feasible.⁷⁹ Bacterial culture from a throat swab is often viewed as the gold standard for the diagnosis of GAS pharyngitis.⁹² Unfortunately, this necessitates a time delay of 2–3 days. More rapid diagnostic tools, including rapid antigen detection tests (RADT), for GAS have shown promise, but while most have a high specificity, their sensitivity can be variable.⁹² The American Heart Association (AHA) argues that there have been no definitive studies to determine the

relative sensitivities of different RADT, and whether they are suitable for routine use in the diagnosis of children without confirming negative tests via throat culture.⁹² Nonetheless, the evaluation of RADT in low-resource settings, which may be more analogous to remote Aboriginal communities, has shown promise. In Rimoin *et al*'s study of the utility of RADT in detecting GAS pharyngitis in children aged 2–12 years presenting with a sore throat in a low-resource setting (Brazil, Egypt, Croatia and Latvia), they found a pretest probability of GAS culture-positive pharyngitis of 29%.⁹³ In this setting, a positive RADT (STREP A OIA MAX; Thermo Biostar/Inverness Medical Professional Diagnostics, Princeton, NJ, USA) prompted unnecessary treatment for GAS in one-fifth of children, and a negative RADT missed only 8% of children with GAS pharyngitis.

A further complicating factor in the use of throat cultures and RADT is that a positive result does not indicate whether an individual is truly infected with GAS (with an immunological response to GAS), or is merely a carrier of GAS in the pharynx with a concomitant viral infection.⁹² While an elevated or rising antistreptococcal antibody titre (e.g. ASO and antideoxyribonuclease B) can provide evidence of recent GAS infection, such antibody responses are delayed, require the pain and inconvenience of venepuncture and provide little assistance in the immediate identification and treatment of GAS pharyngitis.⁹²

It would appear, therefore, that in high-risk populations, and particularly for Aboriginal and Torres Strait Islander people, the utility of either clinical scoring systems or RADT to rapidly identify GAS as a cause of pharyngitis is uncertain. While a combination of a clinical scoring system, RADT and bacterial culture may be both sensitive and specific,⁹¹ it is unclear whether this provides any additional benefits to undertaking bacterial culture in all children with symptomatic pharyngitis. The validity and utility of clinical scoring systems, RADT and other rapid diagnostic techniques in facilitating the rapid detection and treatment of GAS pharyngitis in Aboriginal and Torres Strait Islanders as a mechanism for the primary prevention of ARF/RHD should be a priority for further study.

If pharyngitis is to be targeted in populations at high risk of ARF, then only treating those with confirmed GAS on throat swab may be advocated. Two recent systematic reviews have suggested that a benefit may be gained from such interventions.^{94, 95} However, the studies included in these reviews were acknowledged by the authors to be variable and generally of poor quality. Furthermore, a recent large, high-quality study in New Zealand, investigating

the effectiveness of targeted school-based sore throat programs involving oral antibiotic treatment of those with culture-confirmed GAS, showed no significant benefit in reducing the attack rate of ARF.⁹⁶ However, the authors argued that this lack of effect on ARF may have in part been related to a lack of household contact tracing and treatment. In this context, it is worth considering the work of Gordis, whose analyses of the impact of providing increased access to healthcare through publicly-funded primary care clinics over a decade in Baltimore showed an associated reduction of 60% in cases of ARF in a high-risk US civilian community.³⁶ However, this was not a targeted sore throat program, and was not an RCT. While the treatment of GAS pharyngitis may confer a small reduction in the duration of pharyngitis symptoms,⁹² there remains no convincing evidence that specific 'sore throat' programs for GAS pharyngitis treatment outside of comprehensive primary healthcare can provide additional benefit in reducing ARF incidence, even in high-risk populations.

Overall, there is currently no convincing argument or consistent evidence to suggest that structured programs focusing on the early treatment of GAS pharyngitis are likely to be effective in the primary prevention of ARF in high-risk populations. Nonetheless, the lack of good evidence should not dissuade action in providing appropriate, accessible and high-quality early management of pharyngitis as part of comprehensive primary healthcare. The impact of improved clinical scoring and rapid diagnostic tests in facilitating programs for the early treatment of GAS pharyngitis requires further study. As the Cuban, Costa Rican and French Caribbean experiences suggest, prioritising ARF/RHD as part of broader, multidimensional health service capacity building is likely to translate to improved outcomes. Nonetheless, even if primary antibiotic prophylaxis for the prevention of ARF and RHD is found to be effective in some settings, the expense and logistical difficulties in undertaking such initiatives must still be considered.⁸⁵

In high-risk populations where clinical follow up may be difficult, the empirical management of pharyngitis with antibiotics in those at greatest risk of ARF (e.g. 5–14 years of age or with pre-existing RHD) may be warranted. Where possible, confirmatory testing with throat swab culture should be undertaken, and if feasible, any decision to use antibiotic treatment should be based on culture results. The utility of clinical scoring systems, RADT and other rapid diagnostic tests in predicting the presence of GAS versus non-GAS pharyngitis should be evaluated in Australia, particularly in Aboriginal and Torres Strait

Islander communities. Focused programs of early GAS pharyngitis diagnosis and management in populations at high risk of ARF have not yet been shown to translate to a significant reduction in ARF incidence.

Primary prevention of acute rheumatic fever through addressing group A streptococcal-associated skin infection

Whether GAS-associated skin infection plays a role in the development of ARF is unclear.^{6, 97} It has been suggested that the low prevalence of GAS pharyngeal carriage and infection, high rates of pyoderma and rarity of rheumatogenic GAS M serotypes seen in some Aboriginal communities with high documented rates of ARF/RHD indicates that GAS-associated skin disease may be an important cause of ARF.³⁸ Similar patterns of disease, GAS carriage, M serotyping and ARF/RHD have been reported in Ethiopia, Jamaica and Fiji.^{22, 98} It has also been noted that in some Aboriginal populations, there is a greater association between confirmed ARF and elevated antideoxyribonuclease B (anti-DNase B) titres (which correlate with both throat and skin infection⁹⁹), rather than elevated ASO titres, which are strongly associated with throat infection, and less so with skin infection.¹⁰⁰

In the largest prospective study of skin and throat infections and carriage in three remote Aboriginal communities in the north of Australia where ARF rates are high, McDonald *et al* noted high rates of pyoderma and low rates of symptomatic pharyngitis.³⁸ In this study, 4.5% of all throat swabs isolated GAS, 19.5% of children had GAS isolated from their throats at least once during the 2-year study and two of the nine people (22%) who complained of a sore throat during the study had GAS isolated. It is not clear if this amount of exposure to GAS in the throat may be sufficient to explain the extremely high rates of ARF in this population, regardless of the much higher levels of exposure to GAS skin infection. While 37.7% of children had pyoderma at least once during the study, only 29.2% of pyoderma swabs were positive for GAS, although it should be acknowledged that the methodology used in this study may have underestimated the association between GAS and pyoderma, given that other studies in the north of Australia have found GAS in 70–90% of skin swabs.^{101, 102} The authors' conclusion that skin disease, rather than pharyngitis, is associated with ARF differed from their findings in a later, smaller study involving Aboriginal people living in the arid central region of the Northern Territory.^{102, 103} One other study demonstrated high rates of nasopharyngeal carriage in an Aboriginal and Torres Strait Islander community.^{103, 104}

Although rheumatogenic GAS M-protein serotypes appear to be rare in some Aboriginal populations with high rates of ARF, M-non-typable (MNT) GAS serotypes with genetic similarities (emm-patterns) and with classic rheumatogenic strains are often found.¹⁰⁵ This suggests that M-protein serotyping may not identify all potentially rheumatogenic strains, and that MNT GAS may play a significant role in ARF. Moreover there remains debate regarding the exact role of M-protein subtypes of GAS in the pathogenesis of ARF (i.e. whether the concept of rheumatogenicity is sound).¹⁰⁶

Despite the theoretical underpinnings of the possibility of a link between skin infection and ARF, there has only ever been one clearly-documented case of this occurrence, and that case was reported over 30 years ago.¹⁰⁷ Given the high prevalence of skin disease in many Aboriginal and Torres Strait Islander communities,¹⁰⁸ it would be difficult to demonstrate such a causative link. Further research is needed to clarify the association between GAS pyoderma and ARF/RHD.

Whether the early treatment of skin disease may more generally be an effective mechanism for preventing ARF remains to be seen. One study of a multidimensional, community-based intervention to improve skin health in northern Australia was successful in reducing the prevalence of both pyoderma and scabies infections in Aboriginal children.¹⁰⁹ However, the impact of reducing skin disease on ARF and post-streptococcal glomerulonephritis could not be investigated. Another study provides limited evidence to suggest that the installation of swimming pools in remote Aboriginal communities may reduce the prevalence of both skin and throat infections.¹¹⁰ Further work is required to validate these findings and monitor any association with ARF/RHD.

There is currently insufficient evidence regarding the impact of skin health interventions on ARF and RHD to warrant recommending such programs for the primary prevention for ARF/RHD.^{33, 92} However, improved skin health is likely to have broader health impacts, and studies documenting the association of reduced rates of GAS skin infections with changes in ARF incidence will provide important information for future primary prevention programs.

The role of non- group A streptococcus

Although GAS is the major factor associated with the pathogenesis of ARF, there is debate about whether other strains of streptococcus can cause ARF. In particular, GCS and GGS have been discussed in this context.⁶ These strains, such as GAS, may be associated with pharyngitis, polyarthritis, invasive disease, and in the case of GCS, acute post-streptococcal glomerulonephritis.¹¹¹⁻¹¹⁴ Haidan *et al* have also shown that antibodies raised against GCS and GGS, isolated from throat swabs, can react with human cardiac myosin.¹¹⁵ McDonald *et al*⁶ point out that carriage of GCS and GGS can be up to 20% higher than GAS in Aboriginal populations in the Northern Territory,¹¹⁵ and that similar results have been found in Trinidad, Saudi Arabia and Egypt.^{114, 116, 117} Whether this association extends to a role for GCS and GGS in the pathogenesis of ARF remains unclear. However, given that infections with these organisms can be associated with raised ASO and anti-DNase B titres,^{118, 119} their potential role in the pathogenesis of ARF in patients where GAS is not isolated is worthy of further investigation.

Recommendations regarding the primordial and primary prevention of acute rheumatic fever and rheumatic heart disease

Primordial prevention

While there is only limited evidence to support the effectiveness of specific initiatives in the primordial prevention of ARF/RHD, ecological data would suggest that the risk of ARF/RHD is linked to poverty and disadvantage. Housing and overcrowding would appear to be one important factor. However, given the uncertainties regarding specific causes, advocating for the primordial prevention of ARF/RHD, based on one or another specific environmental or social strategy, cannot be supported. The broader context of equity, poverty alleviation and justice, in association with the empirical link observed between improved socioeconomic and environmental factors and reduced ARF incidence, as well as many other health conditions, should be sufficient to drive advocacy and change.

Primary prevention

Primary prevention measures aimed at preventing ARF/RHD through the prevention or eradication of pharyngeal GAS colonisation, or the early identification and treatment of GAS pharyngitis, are of uncertain effectiveness. While programs aimed at preventing GAS colonisation through antibiotic use may be effective in the short term, any long-term implementation is likely to be unsustainable, due to prohibitive costs, client inconvenience and the risk of antibiotic resistance. A GAS vaccine offers the possibility of a longer-term solution. While significant hurdles remain in the development of a safe, effective and affordable vaccine that can be provided to populations at highest risk of ARF/RHD, this should remain a priority.

Although some programs aimed at the identification and treatment of GAS colonisation have shown promise, the evidence supporting such an approach remains poor. In line with preventing GAS colonisation, such initiatives are also likely to be unsustainable, due to cost, client inconvenience and the risk of antibiotic resistance. Although the cost of managing established RHD is high, the number needed to treat to prevent RHD through such primary prevention programs would be high.

While the early treatment of GAS pharyngitis in highly-controlled environments (e.g. military camps) can prevent the subsequent development of ARF, there is no evidence that community-based programs that focus on the early treatment of GAS pharyngitis are effective in reducing the risk of ARF. The treatment of pharyngitis, as part of comprehensive and accessible primary healthcare, remains important. In this context, the education of patients, carers, schools and communities is crucial to ensure that the detection of symptomatic pharyngitis prompts primary healthcare attendance.

The utility of clinical scoring systems or RADT is variable in differentiating GAS and non-GAS pharyngitis. The development and validation of these and newer rapid diagnostic tests in Aboriginal and Torres Strait Islander populations at risk of ARF/RHD should be a priority. Empirical treatment of all cases of pharyngitis or throat swab-directed treatment should remain the priority in populations at high risk of ARF. The lack of a clear episode of symptomatic pharyngitis in all people presenting with ARF will mean there is an inherent failure rate in even the most comprehensive GAS pharyngitis treatment programs.

The link between skin-related GAS infection and the pathogenesis of ARF/RHD remains contentious. The role of GAS skin infection treatment in the primary prevention of ARF/RHD remains unproven, and is likely to be unsustainable without addressing the underlying causes of skin disease (see ‘Primordial prevention’, above). Nonetheless, as with pharyngitis, the management of skin disease should remain a component of high-quality, comprehensive and accessible primary healthcare for all populations, irrespective of ARF/RHD risk.

Conclusion

The primordial and primary prevention of ARF/RHD through vaccination or the eradication or treatment of GAS remains elusive. Despite sound theoretical underpinnings for the effectiveness of such prevention measures, high-quality evidence is lacking, and successful health programs are limited in number. To date, the most effective measures in the control of ARF/RHD appear to be secondary prophylaxis to prevent recurrent episodes of ARF in persons previously affected by ARF or who have already developed RHD.

Nonetheless, given the decreasing incidence and prevalence of ARF and RHD in most developed countries, it is apparent that ARF/RHD can be prevented.

The primordial prevention of ARF/RHD is likely to remain key. Despite uncertainties around which specific primordial factors influence the incidence of ARF/RHD, ecological data suggest that overall improvements in social and environmental conditions will reduce disease prevalence

Ongoing research towards the development of a GAS vaccine should be a priority. Despite the technical and practical issues associated with vaccine development and delivery, it is likely to be the most sustainable primary prevention strategy in the control of ARF/RHD

Evidence supporting primary prevention through the use of antibiotics to prevent or eradicate GAS colonisation or pharyngitis is limited, and such initiatives are likely to be unsustainable. The development and validation of clinical scores and rapid diagnostic tests to rapidly identify those with GAS may enhance the efficacy and sustainability of such programs in Aboriginal and Torres Strait Islander communities.



3. Diagnosis and management of acute rheumatic fever

The importance of accurate diagnosis

It is important that an accurate diagnosis of ARF is made, as:

- overdiagnosis will result in the individual receiving BPG injections unnecessarily every 3–4 weeks for a minimum of 10 years
- underdiagnosis of ARF may lead to the individual suffering a further attack of ARF, cardiac damage and premature death.

Currently, there is no diagnostic laboratory test for ARF, so diagnosis remains a clinical decision. The pretest probability for the diagnosis of ARF varies according to location and ethnicity. For example, in a region with a high incidence of ARF, a person with fever and arthritis is more likely to have ARF. Similarly, in a region with a high incidence, Aboriginal and Torres Strait Islander patients are more likely than non-Aboriginal and Torres Strait Islander patients to have ARF.

Difficulties with diagnosis

The diagnosis of ARF relies on health professionals being aware of the diagnostic features, particularly when presentation is delayed or atypical. Populations with the highest incidence of ARF are often the most isolated. A prospective study of ARF in Australian children found that there were delays in both the presentation and referral of patients. (Noonan S. *unpublished data*) There was little difference in the proportion of delayed presentations and delayed referrals between urban/rural areas and remote areas (range: 16–20%). There was also little difference in the median time of delayed presentation and referral between the two geographical locations (14–17 days for all groups). This highlights the importance of:

- increasing awareness of the symptoms of ARF among the broader community
- training health staff to recognise potential ARF when it does present, and ensuring rapid referral for specialist review and confirmation of the diagnosis.

Many medical practitioners in Australia have never seen a case of ARF, because the disease has largely disappeared from the affluent and non-Aboriginal and Torres Strait Islander populations among whom they trained and work. This may partly explain why 40% of newly-diagnosed cases of RHD in northern Australia have not been previously diagnosed with ARF.¹²⁰ It is very important that health staff receive appropriate education about ARF before remote postings. Moreover, it is strongly recommended that all patients with suspected ARF be admitted to a hospital for specialist paediatric review and echocardiography, in order to maximise the likelihood of an accurate diagnosis (see ‘Management’, p. 43), and to ensure prompt and optimal treatment.

Current approaches to diagnosis: Jones criteria, WHO criteria and Australian guidelines

The Jones criteria for the diagnosis of ARF were introduced in 1944.¹²¹ The criteria divide the clinical features of ARF into major and minor manifestations, based on their prevalence and specificity. Major manifestations are those that make the diagnosis more likely, whereas minor manifestations are considered suggestive, but insufficient on their own, for a diagnosis of ARF. The exception to this is in the diagnosis of recurrent ARF.

The Jones criteria have been periodically modified and updated; the 1992 update is currently the most widely-used and quoted version (Table 3.1).¹²² Each change was made to improve the specificity of the criteria at the expense of sensitivity, largely in response to the falling incidence of ARF in the USA. As a result, the criteria may not be sensitive enough to pick up disease in high-incidence populations, where the consequences of underdiagnosis may be greater than those of overdiagnosis. Clinicians caring for Aboriginal and Torres Strait Islander patients are increasingly recognising cases of ARF that do not fulfil the most recent version of the Jones criteria, suggesting that ARF diagnostic guidelines may need to be adapted to local circumstances.^{123, 124}

An expert group convened by the WHO provided additional guidelines as to how the Jones criteria should be applied in primary and recurrent episodes.¹²⁵ This was taken further in the first version of these Australian guidelines, which proposed additional criteria for high-risk groups, particularly Aboriginal and Torres Strait Islanders (p. 6). Specifically, subclinical

carditis, aseptic mono-arthritis and polyarthralgia were included as major manifestations in the 2006 edition, and monoarthralgia has been included as a minor manifestation in this version.

Definite acute rheumatic fever

The updated Australian guidelines for the diagnosis of ARF are presented in Table 3.2. The major changes from the previous guidelines are:

- the ability to diagnose a recurrence of ARF in a patient from a high-risk group who has only one major plus one minor manifestation, provided that other, more likely diagnoses are excluded
- the inclusion of mono-arthritis as a minor manifestation in patients from high-risk groups
- fever can be considered a minor manifestation based on a reliable history (in the absence of documented temperature) if anti-inflammatory medication has already been administered.

Table 3.1. Evolution of diagnostic criteria for ARF since 1992

Manifestation	AHA 1992	WHO 2003	Australia 2006		Australia 2012	
			High risk	Low risk	High risk	Low risk
Carditis	Major	Major	Major		Major	
Subclinical carditis	n/a	n/a	Major		Major	n/a
Prolonged P-R interval	Minor	Minor	Minor		Minor	
Polyarthrititis	Major	Major	Major		Major	
Polyarthralgia	Minor	Minor	Major	Minor	Major	Minor
Aseptic mono-arthritis			Major	Minor	Major	Minor
Monoarthralgia			n/a	n/a	Minor	n/a
Subcutaneous nodules	Major	Major	Major		Major	
Sydenham's chorea	Major	Major	Major		Major	
Erythema marginatum	Major	Major	Major		Major	
Fever	Minor	Minor	Minor		Minor	
Inflammatory markers	Minor	Minor	Minor		Minor	
Evidence of recent streptococcal infection	Required	Required	Required		Required	

Probable acute rheumatic fever

The 2006 guidelines suggested that, for patients who did not fulfil the criteria, but in whom the clinician suspected ARF, it would be reasonable to administer a single dose of BPG and perform an echocardiogram within 1 month, looking for evidence of rheumatic valvular damage. Since then, evidence has emerged that there are many patients with likely ARF who do not fulfil the criteria, and that the suggested approach is insufficient. For example, a Northern Territory

study found that 31% of patients with suspected ARF had a range of presentations that did not fit the Jones criteria. The authors suggested the creation of categories of 'probable' and 'possible' ARF.¹²⁴ The reasons patients do not fulfil the criteria may include atypical presentations, but also the high incidence of delayed presentation (more than 20% of cases in one study) and incomplete investigation, commonly resulting in the absence of results for the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP),

Table 3.2 2012 Updated Australian guidelines for the diagnosis of ARF

	High-risk groups [†]	All other groups
Definite initial episode of ARF	2 major or 1 major and 2 minor manifestations plus evidence of a preceding GAS infection [‡]	
Definite recurrent episode of ARF in a patient with known past ARF or RHD	2 major or 1 major and 1 minor or 3 minor manifestations plus evidence of a preceding GAS infection [‡]	
Probable ARF (first episode or recurrence)	A clinical presentation that falls short by either one major or one minor manifestation, or the absence of streptococcal serology results, but one in which ARF is considered the most likely diagnosis. Such cases should be further categorised according to the level of confidence with which the diagnosis is made: <ul style="list-style-type: none"> • highly-suspected ARF • uncertain ARF 	
Major manifestations	Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram) Polyarthritis ^{††} or aseptic mono-arthritis 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 ^{§§}	Fever ^{††} Polyarthralgia or aseptic mono-arthritis ESR ≥ 30 mm/h or CRP ≥ 30 mg/L Prolonged P-R interval on ECG ^{§§}

[†]High-risk groups are those living in communities with high rates of ARF (incidence $>30/100,000$ per year in 5–14 year olds) or RHD (all-age prevalence $>2/1000$). 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. [‡]Elevated or rising antistreptolysin O or other streptococcal antibody, or a positive throat culture or rapid antigen test for GAS. ^{††}A definite history of arthritis is sufficient to satisfy this manifestation. Note that if polyarthritis is present as a major manifestation, polyarthralgia or aseptic mono-arthritis 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 non-specific viral exanthemas, as erythema marginatum. ^{§§}Oral, tympanic or rectal temperature $\geq 38^{\circ}\text{C}$ 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.

CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate.

electrocardiogram (ECG) or streptococcal serology. ESR and CRP testing was absent for 19% of 151 ARF cases identified during a national study of ARF in children. Diagnosis was unable to be confirmed for another eight children in whom timely streptococcal serology was not done. (Noonan S. *unpublished data*) The latter problem should be at least partially addressed by adherence to the recommendation of admitting all cases of suspected ARF to hospital for complete diagnostic work-up (see 'Management', p. 43).

This second edition (Table 3.2) includes an additional category of probable ARF (level C), to include patients who do not satisfy the criteria for definite ARF, but in whom the clinician feels that ARF is the most likely diagnosis. Probable ARF is defined as a clinical presentation that falls short by either one major or one minor manifestation, or the absence of streptococcal serology results, but one in which ARF is considered the most likely diagnosis. In order to guide further management (see p. 45), such cases should be further categorised according to the level of confidence with which the diagnosis is made:

- highly-suspected ARF
- uncertain ARF.

Individuals with probable ARF should be referred to a paediatric or medical specialist with specific skills in the diagnosis of ARF, including cardiology, to confirm that ARF is the most likely diagnosis.

Important points about diagnosis in difficult cases:

- patients presenting with mono-arthritis should be considered to have septic arthritis until proven otherwise
- patients presenting with polyarthritis or polyarthralgia should be thoroughly investigated for alternative diagnoses, including arboviral infections in regions where these diseases are prevalent, as outlined in the notes to Table 3.2
- the management implications of making a diagnosis of probable ARF are discussed below, under 'Management' (p. 45).

Clinical features of acute rheumatic fever: major manifestations

Arthritis

Arthritis is defined as a swollen and hot joint with pain on movement. It is the most common presenting

symptom of ARF, yet diagnostically, it can be the most difficult. It is usually asymmetrical and migratory (one joint becoming inflamed as another subsides), but may be additive (multiple joints progressively becoming inflamed without waning). Large joints are usually affected, especially the knees and ankles. Arthritis of the hip is often difficult to diagnose, because objective signs may be limited to a decreased range of movement.

The arthritis is extremely painful, often out of proportion to the clinical signs. It is exquisitely responsive to treatment with non-steroidal anti-inflammatory drugs (NSAIDs). This can be a useful diagnostic feature, as arthritis continuing unabated more than 3 days after starting NSAID therapy is unlikely to be due to ARF. Equally, withholding NSAIDs in patients with mono-arthritis or mono-arthritis, to observe the development of polyarthritis, can also help in confirming the diagnosis of ARF. In these patients, paracetamol or codeine may be used for pain relief (see 'Treatment' section).

Because of the migratory and evanescent nature of the arthritis, a definite history of arthritis, rather than documentation by the clinician, is sufficient to satisfy this criterion (Grade D).

ARF should always be considered in the differential diagnosis of patients presenting with arthritis in high-risk populations. In the hospital setting, physicians and surgeons should collaborate when the diagnosis of arthritis is unclear. Patients with sterile joint aspirates should never be treated speculatively for septic arthritis without further investigation, particularly in areas with a high ARF/RHD prevalence.¹²⁶

In high-risk populations in Australia, mono-arthritis or polyarthralgia are a common manifestation of ARF, and are often associated with overt or subclinical carditis.¹⁰⁰ While ARF can present as mono-arthritis, septic arthritis should initially be ruled out. Mono-arthritis was present in 19% of high-risk children with ARF, and accounted for 24% of all joint manifestations of ARF in a 2-year prospective, national study of ARF in children. (Noonan S, *unpublished data*) Mono-arthritis was included as a major manifestation of ARF for high-risk groups in the 2006 Australian guidelines^{127, 216} to increase sensitivity in populations at high risk of developing RHD.

In these populations, aseptic mono-arthritis or polyarthralgia may be considered as a major manifestation, in place of polyarthritis (level IV, Grade C). However, alternative diagnoses (as suggested in Table 3.7) should be carefully excluded. In particular, patients presenting with mono-arthritis should be thoroughly investigated for septic arthritis, as well as

rheumatic fever and any other relevant differential diagnoses. Once initial investigations have been sent, including joint aspirate for microscopy and culture, it may be appropriate to treat presumptively with antibiotics until an alternative diagnosis, such as rheumatic fever, is confirmed. However, in high-risk populations, such as Aboriginal and Torres Strait Islander communities, ARF should always be considered in the differential diagnosis. Mono-arthritis may also be the presenting feature if anti-inflammatory medication is commenced early in the illness prior to other joints becoming inflamed.

Sydenham's chorea

This manifestation predominantly affects females, particularly in adolescence.^{128, 129} It is very common in Aboriginal people (28% of ARF presentations in this population).¹²⁹ Chorea consists of jerky, uncoordinated movements, especially affecting the hands, feet, tongue and face. The movements disappear during sleep. They may affect one side only (hemichorea).

Useful signs include:

- the 'milkmaid's grip' (rhythmic squeezing when the patient grasps the examiner's fingers)
- 'spooning' (flexion of the wrists and extension of the fingers when the hands are extended)
- the 'pronator sign' (turning outwards of the arms and palms when held above the head)
- inability to maintain protrusion of the tongue.

Because chorea may occur after a prolonged latent period following GAS infection,¹³⁰⁻¹³² the diagnosis of ARF under these conditions does not require the presence of other manifestations or elevated plasma streptococcal antibody titres. Patients with pure chorea may have a mildly-elevated ESR (approximately 40 mm/h), but have a normal serum CRP level and white cell count.^{129, 133, 134} Chorea is the ARF manifestation most likely to recur, and may be associated with pregnancy or oral contraceptive use. The vast majority of cases resolve within 6 months (usually within 6 weeks), although rare cases lasting as long as 3 years have been documented. Chorea patients have a higher-than-expected prevalence of attention-deficit hyperactivity disorder, anxiety, depression and cognitive dysfunction after they have recovered from the movement disorder, although there is some evidence that attention-deficit hyperactivity disorder and anxiety features are often present before the onset of chorea, suggesting that they may be risk factors, rather than long-term complications.¹³⁵⁻¹³⁸

During recent outbreaks of ARF in the USA, up to 71% of patients with chorea were found to have carditis.¹³⁹ However, only 25% of Aboriginal people with rheumatic chorea have evidence of overt carditis.¹²⁹ Even though clinically evident carditis increases the risk of later development of RHD, approximately 25% of patients with 'pure' chorea also eventually develop RHD.^{140, 141} This is explained by the finding that over 50% of patients with chorea, but without cardiac murmurs, have echocardiographic evidence of mitral regurgitation (MR).¹

Therefore, echocardiography is essential for the assessment of all patients with chorea, regardless of the presence of cardiac murmurs (level IV, Grade C). A finding of subclinical carditis is sufficient to confirm the diagnosis of ARF in high-risk populations (Grade D). Even in the absence of echocardiographic evidence of carditis, patients with chorea should be considered at risk of subsequent cardiac damage. Therefore, they should all receive secondary prophylaxis, and be carefully followed up for the subsequent development of RHD, usually confirmed by a typical appearance on echocardiography. Congestive heart failure in ARF results from valvular dysfunction secondary to valvulitis, and is not due to primary myocarditis.¹⁴² If pericarditis is present, the friction rub may obscure valvular murmurs.

Carditis

Rheumatic carditis refers to the active inflammation of the myocardium, endocardium and pericardium that occurs in ARF. While myocarditis¹⁴³ and pericarditis^{1, 127} may occur in ARF, the predominant manifestation of carditis is the involvement of the endocardium presenting as a valvulitis, especially of the mitral and aortic valves.^{1, 127} The incidence of carditis in initial attacks of ARF varies between 30% and 82%.^{1, 125, 128-150}

The clinical picture of carditis in ARF and the timing of the appearance of cardiac findings are variable. In many patients with ARF, evidence of carditis can be found at presentation, along with fever and arthritis, but in some patients, signs of carditis appear after presentation, usually within the first 2–6 weeks,¹⁵⁰⁻¹⁵² and repeated examination during admission is therefore important.¹⁵³ A less common presentation of rheumatic carditis is the so-called 'insidious onset' or 'indolent' carditis. This mode of presentation was described in the USA in the first half of the past century, and is characterised by a subacute illness of several weeks in children aged less than 6 years with mild or no fever, few joint symptoms and relatively severe cardiac involvement. This type of presentation has not been well described recently, and none of

the recent studies in Australia have identified any cases. However, insidious onset carditis may be underrecognised in Aboriginal children, in which case, it could potentially explain some cases of RHD presenting without a clear past history of ARF. However, such presentations in themselves do not constitute evidence of insidious onset carditis.

There are four clinical findings of carditis that are commensurate to the nature and degree of cardiac involvement. They are, in decreasing frequency: (1) significant murmur; (2) cardiac enlargement; (3) cardiac decompensation; and (4) pericardial friction rub or effusion. In addition, evidence of valvulitis on echocardiogram is considered a manifestation of carditis in Australia.

A significant organic murmur as a sign of valvulitis is the most common clinical manifestation of ARF. Valvulitis most commonly affects the mitral valve, leading to MR, although with prolonged or recurrent disease scarring, may lead to stenotic lesions.¹⁵⁴ The clinical features of MR are described in 'Mitral regurgitation' (p. 77). Briefly, MR presents clinically as an apical blowing, holosystolic murmur. The presence of an associated mid-diastolic flow murmur (Carey Coombs murmur) implies significant mitral valve regurgitation; however, it must be differentiated from the diastolic murmur of MS, which is often preceded by an opening snap. Aortic valvulitis manifests as AR, and is characterised by an early diastolic murmur heard at the base of the heart, accentuated by the patient sitting forward in held expiration. During the first episode of ARF, carditis is often mild,^{145, 146} and echocardiographic findings may precede clinical evolution of a murmur^{148, 153, 155}. Given that even moderate valvular lesions can go undetected by auscultation,¹⁵³ echocardiographic evidence alone is sufficient to confirm valvulitis in the setting of ARF.

Cardiac enlargement can be detected clinically by the displacement of the apical impulse, and confirmed on echocardiography or chest X-ray. Cardiac failure in ARF results from valvular dysfunction, secondary to severe valvulitis, and is not due to primary myocarditis.^{142, 150, 152} Cardiac decompensation occurs in less than 10% of patients during their first episode,^{146, 147, 154, 156, 157} and is more common in patients with recurrent attacks of ARF.^{146, 147, 149, 154} The physical findings of heart failure are variable, and depend on the severity of disease and age of the patient. Findings of heart failure in younger children can be subtle, and may include hepatomegaly, facial puffiness and tachypnoea. In older patients, the more

classical findings of pulmonary oedema, raised jugular venous pressure and bipedal oedema may be elicited.

Pericarditis is uncommon in ARF, and is rarely, if ever, an isolated finding.^{158, 159} Pericarditis should be suspected in patients with ARF who have chest pain. The main clinical finding of pericarditis is a friction rub, which is characterised by a superficial scratching or grating sound on auscultation of the praecordium. A pericardial effusion may also be present, and is suspected if there is muffling of the heart sounds. If pericarditis is present, the friction rub may obscure valvular murmurs.

Sinus tachycardia is a non-specific manifestation of ARF. In the absence of a fever and pain, the presence of sleeping tachycardia should raise the suspicion of carditis.

Subcutaneous nodules

These are very rare (less than 2% of cases), but highly-specific manifestations of ARF in Aboriginal people.¹⁰⁰ They are 0.5–2 cm in diameter, round, firm, freely-mobile and painless nodules that occur in crops of up to 12 over the elbows, wrists, knees, ankles, Achilles tendon, occiput and posterior spinal processes of the vertebrae. They tend to appear 1–2 weeks after the onset of other symptoms, last only 1–2 weeks (rarely more than 1 month) and are strongly associated with carditis.

Erythema marginatum

Erythema marginatum is also rare, being reported in less than 2% of cases in Aboriginal people and populations of developing countries. As with subcutaneous nodules, erythema marginatum is highly specific for ARF.

It occurs as bright pink macules or papules that blanch under pressure and spread outwards in a circular or serpiginous pattern. The rash can be difficult to detect in dark-skinned people, so close inspection is required. The lesions are not itchy or painful, and occur on the trunk and proximal extremities, but almost never on the face. The rash is not affected by anti-inflammatory medication, and may recur for weeks or months, despite resolution of the other features of ARF. The rash may be more apparent after showering. Table 3.3 outlines the key points in identifying major manifestations of ARF.

Table 3.3 Key points in identifying major manifestations of ARF

Manifestation	Points for diagnosis
Arthritis	<p>Most common presenting symptom of ARF</p> <p>Extremely painful</p> <p>Polyarthritis is usually asymmetrical and migratory, but can be additive</p> <p>Mono-arthritis may be a presenting feature in high-risk populations</p> <p>Large joints are usually affected, especially knees and ankles</p> <p>Usually responds within 3 days of starting NSAID therapy</p>
or Sydenham's chorea	<p>Present in around one-quarter of ARF presentations among Aboriginal people, particularly females, and predominantly in adolescence</p> <p>Consists of jerky, uncoordinated movements, especially affecting the hands, feet, tongue and face, disappears during sleep</p> <p>Echocardiography is essential for all patients with chorea</p>
Carditis	<p>Usually presents clinically as an apical holosystolic murmur, with or without a mid diastolic flow murmur, or an early diastolic murmur at the base of the heart or left sternal edge</p>
Subcutaneous nodules	<p>Rare, but highly-specific, manifestations of ARF in Aboriginal people, and strongly associated with carditis</p> <p>Present as crops of small, round, painless nodules over the elbows, wrists, knees, ankles, Achilles tendon, occiput and posterior spinal processes of the vertebrae</p>
Erythema marginatum	<p>Extremely rare, as well as difficult to detect in Aboriginal people, but highly specific for ARF</p> <p>Occurs as circular patterns of bright pink macules or papules on the trunk and proximal extremities</p>

NSAID, non-steroidal anti-inflammatory drug.

Clinical features of acute rheumatic fever: minor manifestations

Arthralgia

Arthralgia differs from arthritis in that there is pain on joint movement without evidence of swelling or heat. It is a non-specific symptom, and usually occurs in the same pattern as rheumatic polyarthritis (migratory, asymmetrical, affecting large joints). Alternative diagnoses (as suggested in Table 3.7) should be considered in a patient with arthralgia that is not typical of ARF. Mono-arthralgia can be considered a minor manifestation in high-risk groups.

Fever

With the exception of chorea, most manifestations of ARF are accompanied by fever. Earlier reports of fever described peak temperatures commonly greater than 39°C,^{122, 160} but lower peak temperatures have been described more recently.

In Aboriginal people, defining fever as a temperature greater than 38°C results in improved sensitivity for the diagnosis of ARF.¹⁰⁰

As there are no recent data relating to fever in low-risk populations, it is recommended that an oral, tympanic or rectal temperature greater than 38°C on admission, or documented with a reliable history during the current illness, should be considered as fever (level IV, Grade C). Fever, like arthritis and arthralgia, is usually quickly responsive to salicylate therapy.

Elevated acute-phase reactants

Typically, ARF patients have a raised serum CRP level and ESR. The peripheral white blood cell (WBC) count is $<15 \times 10^9/L$ in 75% of patients, so an elevated WBC is an insensitive marker of inflammation in ARF.¹⁰⁰ Further analysis of these data demonstrated that less than 4% of patients with confirmed ARF, excluding chorea, had both a serum CRP level of <30 mg/L and an ESR of <30 mm/h (J Carapetis, unpublished data).

Therefore, it is recommended that a serum CRP level of ≥ 30 mg/L or ESR of ≥ 30 mm/h is needed to satisfy the minor criterion of elevated acute-phase reactants (level IV, Grade C). The serum CRP concentration rises more rapidly than the ESR, and also falls more rapidly with resolution of the attack. The ESR may remain elevated for 3–6 months, despite a much shorter duration of symptoms.

Prolonged P-R interval and other rhythm abnormalities

Some healthy people show this phenomenon, but a prolonged P-R interval that resolves over the ensuing days to weeks may be a useful diagnostic feature in cases where the clinical features are not definitive. Extreme first-degree block sometimes leads to a junctional rhythm, usually with a heart rate similar to the sinus rate.

Second-degree, and even complete heart block, can occur, and if associated with a slow ventricular rate, may give the false impression that carditis is not significant. In a recent resurgence of ARF in the USA, 32% of patients had abnormal atrioventricular conduction, usually a prolonged P-R interval. A small proportion had more severe conduction abnormalities, which were sometimes found by auscultation or echocardiography in the absence of evidence of valvulitis.¹

Therefore, an ECG should be performed in all cases of suspected ARF (level IV, Grade C). If a prolonged P-R interval is detected, the ECG should be repeated after 2 weeks, and if still abnormal, it should be repeated again at 2 months to document a return to normal. If it has returned to normal, ARF becomes a more likely diagnosis. The P-R interval increases normally with age (Table 3.4)¹⁶¹ Upper limits of normal (ULN) for P-R interval are provided in Table 3.4.

Table 3.4 Upper limits of normal of P-R interval

Age group (years)	Sec
3–12	0.16
12–16	0.18
17+	0.20

Source: Adapted from Park MK, *Pediatric cardiology for practitioners*, 2nd edn. Chicago: Year Book Medical; 1998.

Other less common clinical features

Other less common clinical features include abdominal pain, epistaxis, mild elevations of plasma transaminase levels, and microscopic haematuria, pyuria or proteinuria. Some patients with acute carditis also present with pulmonary infiltrates on chest radiography, and have been labelled as having ‘rheumatic pneumonia’. This is probably a misnomer, as it likely represents unilateral pulmonary oedema in patients with fulminant carditis with ruptured chordae tendinae.^{162, 163} Table 3.5 outlines the key points in identifying minor manifestations of ARF.

Table 3.5 Key points in identifying minor manifestations of ARF

Manifestation	Points for identification
Arthralgia	May suggest ARF if the arthralgia occurs in the same pattern as rheumatic polyarthritis (migratory, asymmetrical, affecting large joints)
Fever	Most manifestations of ARF are accompanied by fever Oral, tympanic or rectal temperature greater than 38°C on admission, or documented with a reliable history during the current illness, should be considered as fever
Elevated acute-phase reactants	Serum CRP level of ≥ 30 mg/L or ESR of ≥ 30 mm/h meets this diagnostic criterion
ECG	If a prolonged P-R interval is detected, the ECG should be repeated after 1–2 months If the P-R interval has returned to normal, ARF becomes a more likely diagnosis

ECG, electrocardiogram; ESR, erythrocyte sedimentation rate.

Evidence of group A streptococcal infection

GAS is isolated from throat swabs in less than 10% of ARF cases in New Zealand,¹⁰⁶ and less than 5% of cases in Aboriginal people.¹⁰⁰ Streptococcal antibody titres are therefore crucial in confirming the diagnosis. The most commonly-used tests are the plasma ASO and the anti-DNase B titres. Previous data suggest that a rise in the ASO titre occurs in 75–80% of untreated GAS pharyngeal infections, and that the addition of anti-DNase B titre increases the sensitivity of testing.¹⁶⁴

The serum ASO titre usually rises within 1–2 weeks, and reaches a maximum at about 3–6 weeks after infection, while the serum anti-DNase B titre can take up to 6–8 weeks to reach a maximum.¹⁶⁵ The rate of decline of these antibodies varies enormously, with the ASO titre starting to fall 6–8 weeks, and the anti-DNase B titre 3 months after infection.¹⁶⁶ In the absence of re-infection, the ASO titre usually approaches pre-infection levels after 6–12 months, whereas the anti-DNase B titre tends to remain elevated for longer.¹⁶⁷

Ideally, it is recommended that the titre be determined in the acute phase, and then in the convalescent phase 14–28 days later, with a positive result defined as a rise in titre of twofold or more.¹⁶⁸ However, relying on rising titres in paired sera may not always be helpful for two reasons. First, ARF occurs after a latent period, so the titres may already be at or near their peak when measured, and second, it is sometimes impractical to draw a second blood sample if the patient has been discharged.

Therefore, it is generally accepted that if only a single specimen is available, a titre greater than the ULN at initial testing be considered presumptive evidence of a preceding GAS infection. The ULN for GAS serology has been defined by separating the upper 20% from the lower 80% of the group distribution in a dichotomous fashion.^{168–170} The choice of the 80th centile cut-off for the ULN is based on the observation that more than 80–90% of patients with ARF have GAS titres that are above the 80th centile of healthy controls, with no clinical evidence of recent streptococcal infection.^{168, 169}

Streptococcal titres vary according to a number of factors, including age. The ranges cited by many laboratories in Australia are taken from adult studies, and are often inappropriately low for use in children.

A recent study of 424 adults and children in Fiji, a population with a similar epidemiology of GAS infection to Aboriginal people and Torres Strait Islanders, including a high prevalence of GAS skin infections, provides ULN for GAS serology applicable to the Australian context across all ages (Table 3.6).¹⁷¹

Table 3.6 Suggested ULN for serum streptococcal antibody titres in children and adults¹⁷¹

Age group (years)	ULN (U/mL)	
	ASO titre	Anti-DNase B titre
1–4	170	366
5–14	276	499
15–24	238	473
25–34	177	390
≥35	127	265

Anti-DNase, antideoxyribonuclease B; ASO, antistreptolysin O; ULN, upper limit of normal.

Streptococcal serology in high-incidence populations

The high prevalence of GAS infections (mainly pyoderma) in Aboriginal communities of northern and central Australia causes very high background titres of serum streptococcal antibodies.^{104, 172} In one study, the median titres of ASO and anti-DNase B in children of three remote Aboriginal communities were 256 and 3172 IU/mL, respectively.¹⁷² Therefore, single measurements of streptococcal antibody serology may be difficult to interpret in this population. However, data from the study in Fiji, which carefully excluded participants with a recent history of GAS infection, and also excluded extreme outlier values, found median and ULN values of ASO and anti-DNase B to be similar to those found in non-Aboriginal and Torres Strait Islander populations in Australia, and to populations in the USA.^{173, 174} Therefore, the values outlined in Table 3.6 should be considered as normal values for both Aboriginal and non-Aboriginal populations (level IV, Grade C).

All cases of suspected ARF should have elevated serum streptococcal serology demonstrated. If the initial titre is above the ULN, there is no need to repeat serology. If the initial titre is below the ULN for age, testing should be repeated 10–14 days later.

Table 3.7 Differential diagnoses of common major presentations of ARF

Presentation		
Polyarthrititis and fever	Carditis	Chorea
Septic arthritis (including disseminated gonococcal infection) [†]	Innocent murmur	Systemic lupus erythematosus
Connective tissue and other autoimmune disease ^{††}	Mitral valve prolapse	Drug intoxication
Viral arthropathy [‡]	Congenital heart disease	Wilson's disease
Reactive arthropathy [‡]	Infective endocarditis	Tic disorder [‡]
Lyme disease [‡]	Hypertrophic cardiomyopathy	Choreoathetoid cerebral palsy
Sickle cell anaemia	Myocarditis: viral or idiopathic	Encephalitis
Infective endocarditis	Pericarditis: viral or idiopathic	Familial chorea (including Huntington's)
Leukaemia or lymphoma		Intracranial tumour
Gout and pseudogout		Lyme disease [‡]
		Hormonal [§]

[†]Gonorrhoea should be actively sought in all sexually-active cases. Tests for gonorrhoea include polymerase chain reaction (PCR) of joint aspirate, endocervical PCR (gonococcal and chlamydia) and microscopy, culture and sensitivity, or urine/self-collected vaginal swabs in cases where endocervical PCR is not possible. ^{††}Includes rheumatoid arthritis, juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis and sarcoidosis. [‡]Mycoplasma, cytomegalovirus, Epstein–Barr virus, parvovirus, hepatitis, rubella vaccination, and *Yersinia* spp and other gastrointestinal pathogens. [‡]Lyme disease has not been confirmed in Australia or New Zealand. [‡]Possibly including PANDAS (paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection). [§]Includes oral contraceptives, pregnancy (chorea gravidarum), hyperthyroidism and hypoparathyroidism.

Differential diagnosis

Many of the clinical features of ARF are non-specific, so a wide range of differential diagnoses should be considered (Table 3.7).¹⁷⁵ The most likely alternative possibilities will vary according to location (e.g. arboviral arthritis is less likely in temperate than tropical climates) and ethnicity (e.g. some autoimmune conditions may be more or less common in particular ethnic groups).

Syndromes that may be confused with acute rheumatic fever

Post-streptococcal reactive arthritis

Some patients present with arthritis not typical of ARF, but with evidence of recent streptococcal infection, and are said to have post-streptococcal reactive arthritis. In these cases, the arthritis may

affect joints that are not commonly affected in ARF, such as the small joints of the hand, is less responsive to anti-inflammatory treatment and may be more prone to relapse after cessation of anti-inflammatory treatment.¹⁷⁶ These patients are said not to be at risk of carditis,¹⁷⁷ and therefore, do not require secondary prophylaxis. However, some patients diagnosed with post-streptococcal reactive arthritis have developed later episodes of ARF, indicating that the initial diagnosis should have been atypical ARF (level IV).^{178, 179}

It is recommended that the diagnosis of post-streptococcal reactive arthritis should rarely, if ever, be made in high-risk populations, and with caution in low-risk populations (Grade C). Diagnosed patients should receive secondary prophylaxis for at least 5 years (high-risk populations), or at least 1 year (low-risk populations) (Grade D). Echocardiography should be used to confirm the absence of valvular damage in all of these patients from both high- and low-risk populations before discontinuing secondary prophylaxis (Grade D).

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

Some cases of chorea are mild or atypical, and may be confused with motor tics, or the involuntary jerks of Tourette's syndrome. There may be overlap between Sydenham's chorea and these conditions. Indeed, obsessive–compulsive features have been found at increased frequency in long-term follow-up studies of patients with ARF and RHD.^{180, 181} The term 'paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections' (PANDAS) refers to a subgroup of children with tic or obsessive–compulsive disorders, whose symptoms may develop or worsen following GAS infection, and who are said to be at no risk of cardiac valvular damage.^{182, 183}

However, the evidence supporting PANDAS as a distinct disease entity has been questioned,^{184, 185} with a recent follow-up study in PANDAS and non-PANDAS patients with tic and obsessive–compulsive disorders failing to find any exacerbations of symptoms associated with streptococcal infections in PANDAS patients.¹⁸⁵ Hence, in high-risk populations, clinicians should rarely, if ever, make a diagnosis of PANDAS, and should rather err on the side of diagnosis of ARF and secondary prophylaxis (Grade D). They should make this diagnosis only if they have excluded echocardiographic evidence of valvular damage (i.e. ARF) and other features of ARF, and have documented

exacerbations of neuropsychiatric symptoms with clear evidence of recurrent GAS infections.¹⁸¹ If ARF is excluded, secondary prophylaxis is not needed, but such patients should be carefully followed up to ensure that they do not develop carditis in the long term.

Echocardiography and acute rheumatic fever

Prior to the introduction of echocardiography, the diagnosis of rheumatic carditis relied on clinical evidence of valvulitis or pericarditis, supported by radiographic evidence of cardiomegaly. Echocardiography is more sensitive and specific for acute rheumatic carditis^{127, 153, 155} (level III-2) than auscultation, and today it is recommended that all patients with suspected or definite ARF should undergo echocardiography (Grade C). With the advent of portable machines and specialist outreach services, echocardiography should be available to all Australians, even those living in remote settings.

In patients with definite ARF, echocardiography can confirm the presence, severity and aetiology of valvular regurgitation. It can identify additional valve involvement (without an associated detectable murmur), pericardial effusion, and assess cardiac size and function, as outlined in Table 3.8.

Table 3.8 Uses of echocardiography in ARF

Valvulitis

Define the severity of mitral, aortic and/or tricuspid regurgitation

Define the severity of mixed valve disease (mixed stenotic and regurgitant)

Identify subclinical evidence of rheumatic valve damage

Visualise valvular anatomy and define mechanism of regurgitation (prolapse, flail leaflet, annular dilatation etc)

Myocarditis and congestive heart failure

Assess LV size and function

Pericarditis

Confirm the presence of a pericardial effusion

Reveal inaudible or subclinical valvular regurgitation in the presence of a friction rub

Exclude other forms of cardiac murmur

Identify congenital heart disease, such as bicuspid aortic valve and congenital mitral valve anomalies, as the cause for a pathological murmur

Confirm normal valvular function and morphology in the presence of flow or innocent murmurs

LV, left ventricle

In patients with suspected ARF, reliance on the clinical finding of a murmur may result in misclassification of congenital heart disease, or even of innocent murmurs, such as rheumatic carditis. The likelihood of misclassification has increased in recent years, as physicians' auscultatory skills have become less proficient.¹²⁵ In patients with suspected ARF without a clinically-significant murmur, echocardiography can identify subclinical valvular damage that is likely to be rheumatic, thus increasing the likelihood that the presentation is due to ARF. Such subclinical carditis is acceptable as a major manifestation of ARF in high-risk groups in the Australian diagnostic criteria (Table 3.2).

In 2011, under the auspices of the World Heart Federation (WHF), an international consortium agreed on minimal criteria for a diagnosis of RHD on echocardiography, which can be found in the RHD section of these guidelines.¹⁹⁸ Those criteria did not specifically address the differentiation between acute carditis and chronic RHD. We recommend the same criteria for defining pathological regurgitation in the acute phase, as in the chronic phase. Morphological changes, however, are often minimal in acute carditis, as these take time to develop and may be somewhat different than those found in chronic RHD (level III-2) (see below).^{145, 156, 186, 187} Many cases of ARF occur on the background of chronic RHD, and acute and chronic changes can co-exist. We currently recommend the following:

- In high-risk patients, pathological regurgitation of the mitral or aortic valve (in the absence of an alternative diagnosis, such as bicuspid aortic or mitral valve prolapse) is sufficient to fulfil the minimal echocardiographic criteria of acute carditis in the setting of suspected or proven ARF (Grade C).
- The presence of additional morphological changes to the mitral or aortic valve increases the confidence with which the diagnosis can be made (Grade C).
- Morphological changes of the mitral or aortic valve, in the absence of pathological valvular regurgitation, are not sufficient to diagnose acute rheumatic carditis. Such cases should be followed with repeat echocardiography after 4–6 weeks to detect evolving acute carditis (Grade D).

Valvulitis: minimal echocardiographic criteria for pathological regurgitation

ARF most commonly affects the left-sided cardiac valves, and regurgitation is frequently mild during the first episode.^{145, 146} Severe aortic or MR, however, does occur in approximately 10% of patients at first presentation.¹⁵⁵ If valvulitis is not found at presentation, it may appear within 2 weeks,¹⁵³ or occasionally within 1 month.¹⁵⁵ Valvular regurgitation can be accurately graded with continuous-wave and colour Doppler echocardiography as nil, physiological, mild, moderate and severe for both rheumatic¹⁵³ and non-rheumatic valve disease.¹⁸⁸⁻¹⁹¹

The minimal criteria for a diagnosis of abnormal regurgitation for the aortic and mitral valve are summarised in Table 3.9.¹⁹⁸ To be classified as pathological on colour-Doppler, the regurgitant jet must extend substantially beyond the valvular closure-line (by 2 cm for MR, and by 1 cm for AR), and be visualised from two views, although it only has to meet the required jet length in one view. On continuous-wave Doppler, the regurgitant jet must be high velocity and pan-diastolic (for AR) or pan-systolic (for MR). These criteria can distinguish a small colour jet of physiological regurgitation in a normal child from pathological regurgitation (level III-2).¹⁸⁹⁻¹⁹⁶

Regurgitation of the right-sided cardiac valves (tricuspid and pulmonary valve) is extremely rare without aortic or mitral valve involvement (level III-3).¹⁹⁷ For this reason, a diagnosis of carditis should not be based on right-sided regurgitation alone (Grade C). Although pulmonary and tricuspid regurgitation is often seen in association with left-sided lesions in ARF, pressure and volume overload must be excluded before attributing even moderate tricuspid regurgitation to valvulitis.¹⁸⁹

Table 3.9 Minimal echocardiographic criteria to allow a diagnosis of pathological valvular regurgitation (from WHF guidelines¹⁹⁸)

Pathological MR (all four Doppler criteria must be met)	Pathological AR (all four Doppler criteria must be met)
1. Seen in 2 views	1. Seen in 2 views
2. In at least one view jet length 2 cm*	2. In at least one view jet length ≥ 1 cm*
3. Peak velocity ≥ 3 m/sec	3. Peak velocity ≥ 3 m/sec
4. Pan-systolic jet in at least one envelope	4. Pan-diastolic jet in at least one envelope

*A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant colour (blue or red) on non-magnified (non-zoomed) images.

AR, aortic regurgitation; MR, mitral regurgitation.

Morphological changes associated with rheumatic carditis

Acute rheumatic carditis is characterised by annular dilation and chordal elongation leading to anterior, and less commonly, posterior mitral valve prolapse.¹⁸⁷ Chordal rupture can also occur and result in a flail leaflet and significant MR.^{127, 187, 199-201} Beading or nodularity of the leaflet tips can also be noted during an episode of ARF.^{127, 145} More chronic anatomic or morphological changes include leaflet and chordal thickening, restricted leaflet motion and later calcification.²⁰¹ Evolution to MS is rarely observed in children in Australia,¹²⁰ but is more commonly seen in adolescents and adults (see Chapter 4). The experienced echocardiographic operator can use these morphological features as supportive evidence of a rheumatic aetiology of valvulitis.

Acute rheumatic fever recurrence

In a patient with known, prior RHD, the diagnosis of acute carditis during a recurrence of ARF relies on the accurate documentation of the cardiac findings before the recurrence, so that new clinical or echocardiographic features can be confirmed.

Left ventricular size and function

M mode and 2DE are used in evaluating chamber size and ventricular function. More complex formulae based on 2DE can also be used to calculate LV function (e.g. single-plane ellipse and Simpson's methods of discs).¹⁴²

Three-dimensional echocardiography

Many cardiac surgical centres now routinely use three-dimensional echocardiography (3DE) to further evaluate RHD, both in its acute and chronic phases.²⁰² It facilitates more detailed assessment of the mechanism of regurgitation, and hence, aids surgical decision-making.

Subclinical evidence of rheumatic valve damage

Subclinical rheumatic carditis that is silent on auscultation, but detectable by echocardiography, has been recognised worldwide as a manifestation of ARF.^{1, 45, 153, 155, 203-215}

This echocardiographic finding has been incorporated as a major diagnostic criterion for ARF in the Australian²¹⁶ and the New Zealand guidelines²¹⁷ for high-risk ARF population since 2006 (Table 3.2). The WHO expert committee acknowledged the existence of subclinical rheumatic valve damage in their last technical report in 2001.¹²⁵ However, it is not incorporated into the revised Jones diagnostic criteria of the AHA.¹²²

A systematic review in 2007 estimated the prevalence of subclinical carditis as 17% among those with ARF.²¹⁴ Echocardiographic findings persisted or progressed in 45% of cases.²¹⁴ A recent study from North Queensland reported that 71% of their patients with subclinical carditis had a long-term valvular consequence.²¹⁸ This likely reflects the low level of compliance with secondary prophylaxis. Complete echocardiographic resolution of mild clinical carditis can be expected within 5 years in two-thirds of patients with high levels of compliance on secondary prophylaxis.¹⁵⁴

The clinical course of subclinical carditis^{214, 215} appears to be similar to that of mild carditis, with an audible murmur^{154, 215} 5L (level III-2), and therefore, it is recommended that echocardiographically-detected valve damage (subclinical or otherwise) is included as a major manifestation of ARF in high-risk populations (Grade C).

Investigations

The recommended investigations in ARF are listed in Table 3.10.

Table 3.10 Investigations in suspected ARF recommended for all cases

Recommended for all cases
White blood cell count
Erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
Blood cultures, if febrile
Electrocardiogram (if prolonged P-R interval or other rhythm abnormality, repeat in 2 weeks and again at 2 months, if still abnormal)
Chest X-ray, if clinical or echocardiographic evidence of carditis
Echocardiogram (consider repeating after 1 month, if negative)
Throat swab (preferably before giving antibiotics): culture for group A streptococcus
Antistreptococcal serology: both ASO and anti-DNase B titres, if available (repeat 10–14 days later if first test not confirmatory)
Tests for alternative diagnoses, depending on clinical features
Repeated blood cultures, if possible endocarditis
Joint aspirate (microscopy and culture) for possible septic arthritis
Copper, ceruloplasmin, antinuclear antibody, drug screen for choreiform movements
Serology and autoimmune markers for arboviral, autoimmune or reactive arthritis

Management

The major priority in the first few days after presentation in ARF is confirmation of the diagnosis. Except in the case of heart failure management, none of the treatments offered to patients with ARF have been proven to alter the outcome of the acute episode or the amount of damage to heart valves.^{219, 220} The priorities in managing ARF are outlined in Table 3.11.

Medical practitioners and nurses who have trained and worked in settings where ARF is rare, and who then move to areas of high ARF incidence, sometimes underestimate the importance and urgency of accurate diagnosis and prompt treatment, which includes admission to hospital. This highlights the need for new medical and nursing staff in hospitals and primary care settings in these regions to undergo education about ARF and RHD management as part of their orientation, and of ensuring that all staff receive

regular updates and follow management guidelines (examples include these and the Central Australian Rural Practitioners Association guidelines).

Hospitalisation

All patients with suspected ARF (first episode or recurrence) should be hospitalised as soon as possible after the onset of symptoms (Grade D).¹²⁵ This ensures that all investigations are performed, and if necessary, the patient observed for a period prior to commencing treatment to confirm the diagnosis.

While in hospital, the patient should be registered in centralised and local ARF/RHD registers, and secondary prophylaxis commenced (for first episodes) or updated (for recurrences). Hospitalisation also provides an ideal opportunity to educate patients and families. Further education by primary care staff, using culturally-appropriate educational materials, should follow once the patient has returned home.

Table 3.11 Priorities in managing ARF

Admission to hospital

Admit all patients suspected to have ARF

Confirmation of the diagnosis

Observation prior to anti-inflammatory treatment: paracetamol (first line) or codeine for fever or joint pain

Investigations (as per Table 3.10)

Treatment

All cases

Single-dose im BPG (preferable) or 10 days' oral penicillin V (iv not needed; oral erythromycin if allergic to penicillin)

Arthritis and fever

Paracetamol (first line) or codeine until diagnosis confirmed

Aspirin, naproxen or ibuprofen once diagnosis confirmed, if arthritis or severe arthralgia present

Mild arthralgia and fever may respond to paracetamol alone

Influenza vaccine for children receiving aspirin during the influenza season (autumn/winter)

Chorea

No treatment for most cases

Carbamazepine or valproic acid if treatment necessary

Carditis/heart failure

Bed rest, with mobilisation as symptoms permit

Urgent echocardiogram

Antifailure medication

- diuretics/fluid restriction for mild or moderate failure
- ACE inhibitors for more severe failure, particularly if AR present glucocorticoids optional for severe carditis (consider treating for possible opportunistic infections, see p. 50)
- digoxin, if AF present

Valve surgery for life-threatening acute carditis (rare)

Long-term preventive measures

First dose of secondary prophylaxis

Notify case to ARF/RHD register, if available

Contact local primary care staff to ensure follow up

Referral to a medical specialist

Provide culturally-appropriate education to patient and family

Arrange dental review and ongoing dental care to reduce risk of endocarditis

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AR, aortic regurgitation; BPG, benzathine penicillin G; im, intramuscular; iv, intravenous.

Occasionally, when the diagnosis has already been confirmed and the patient is not unwell (e.g. mild recurrent chorea in a child with no other symptoms or signs), outpatient management may be appropriate. In such cases, health staff must ensure that investigations, treatment, health education and patient registration are all completed.

Observation and general hospital care

The patient's vital signs should be recorded four times daily, and the pattern and extent of fever noted. The patient should be examined daily for the pattern of arthritis, and the presence of heart murmur, choreiform movements, skin rash and subcutaneous nodules. Guidelines for general in-hospital care are provided in Table 3.12 (Grade D).

The arthritis, arthralgia and fever of ARF respond to NSAIDs.²²¹⁻²²³ Early administration of NSAIDs may mask the development of migratory polyarthritis or the development of fever. Until the diagnosis is confirmed, it is recommended that joint pain be treated with paracetamol or codeine (Grade D).¹²⁵ Paracetamol is more effective than codeine in this situation. While it may mask a fever, the clinician may use the fact of a documented fever prior to admission as a minor manifestation (Table 3.2). Thus, the opportunity to make a diagnosis of ARF will rarely be adversely affected.

Management of probable acute rheumatic fever

Patients with probable ARF may be managed in two ways (Figure 3.1), according to the level of confidence with which the diagnosis is made (Level D):

- **Highly-suspected ARF:** manage as for definite ARF
- **Uncertain ARF:** in patients from high-risk groups, administer 12 months of secondary prophylaxis initially, and reassess (including echocardiography) at that time. If there is no evidence of recurrent ARF, and no evidence of cardiac valvular damage on echocardiography, consider ceasing secondary prophylaxis. In such cases, the residual uncertainty should be discussed with the patient, and they should be encouraged to be particularly vigilant about treatment of sore throats, prevention and treatment of skin sores and early presentation with any symptoms of potentially recurrent ARF.

These guidelines refer to individuals who have presentations with features suggestive of ARF, and are not intended to be applied to patients with incidental findings of possible chronic rheumatic valvular disease on echocardiogram in non-acute (e.g. screening) situations.

Table 3.12 Guidelines for general in-hospital care

Nursing recordings

Temperature, pulse, respiratory rate, blood pressure 4 times daily

Sleeping pulse (e.g. 0200 hours)

If pulse >100, apical heart rate

Diet

Free fluids (if no heart failure)

Normal diet (limit extras)

Early dietary advice if overweight and in heart failure, to avoid further weight gain

Weekly weight

Bed rest and general care

Plan care to provide rest periods

Provide age-appropriate activities

Notify school teacher

Involve family in care

Prepare for discharge to primary care facility and follow up

If clinical carditis present (heart murmur, heart failure, pericardial effusion, valvular damage)

Document cardiac symptoms and signs

Daily weight and fluid balance chart

Diuretics, ACE inhibitors, digoxin if indicated; consider glucocorticoids

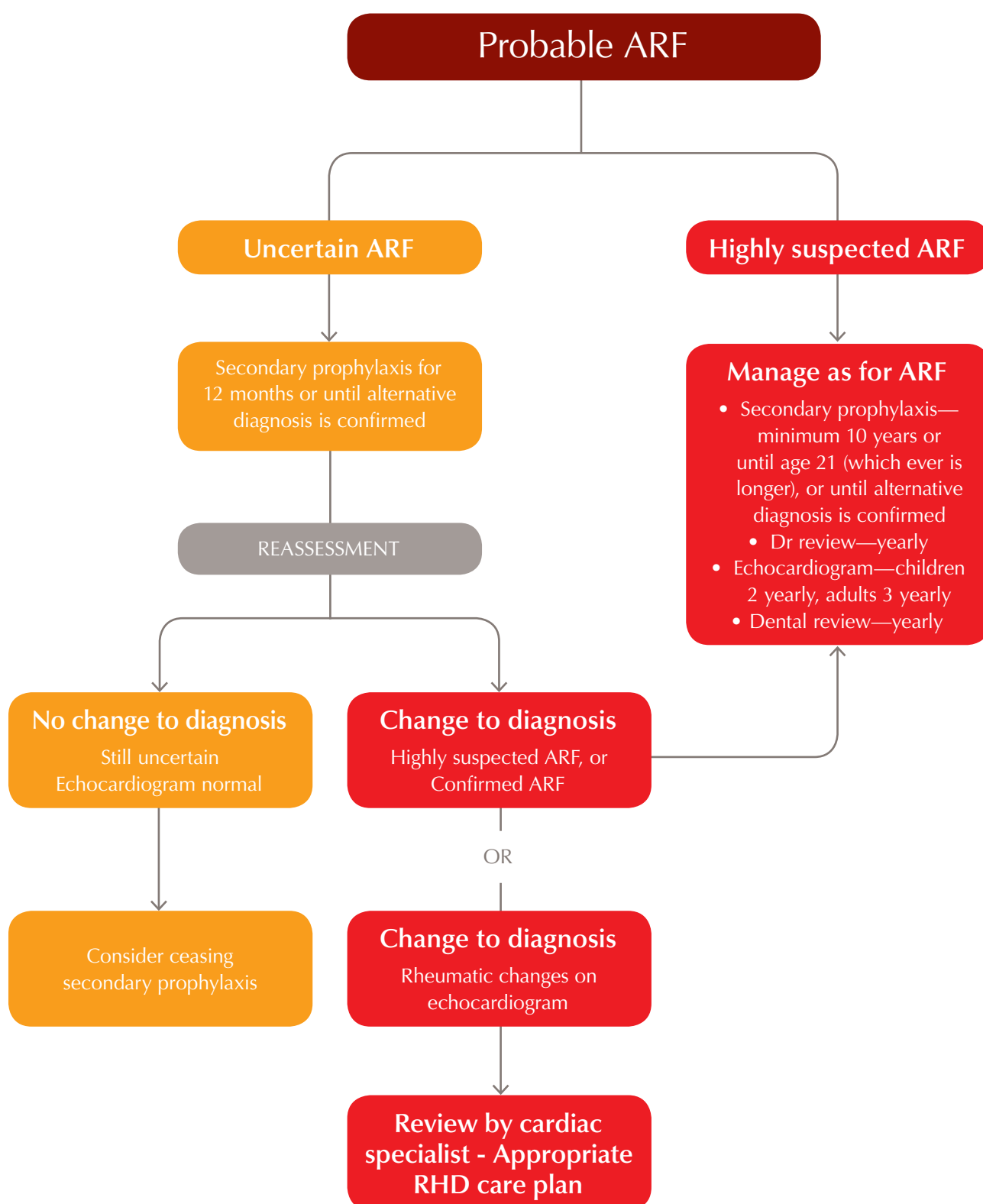
Anticoagulation if atrial fibrillation present

Cardiology opinion

Source: Adapted from National Heart Foundation of New Zealand, Cardiac Society of Australia and New Zealand. *New Zealand Guidelines for Rheumatic Fever 1. Diagnosis, Management and Secondary Prevention*. Wellington, New Zealand: National Heart Foundation of New Zealand and Cardiac Society of Australia and New Zealand; 2006. with permission (courtesy D. Lennon).

ACE, angiotensin-converting enzyme.

Figure 3.1 Management of probable ARF



Treatment

Antibiotics

Controlled studies have failed to show that treating ARF with large doses of penicillin affects the outcome of rheumatic valvular lesions 1 year later.^{224, 225}

Despite this, most authorities recommend a course of penicillin, even if throat cultures are negative, to ensure eradication of streptococci that may persist in the upper respiratory tract (Grade D). This should be either a single injection of intramuscular BPG (1,200,000 U or 600,000 U, if less than 20 kg) or a 10-day course of oral penicillin V (250 mg twice daily in children, 500 mg twice daily in adolescents and adults). Although a systematic review concluded that shorter-duration courses (3–6 days) of oral antibiotics may be an acceptable treatment of streptococcal pharyngitis in children in populations with low-risk ARF (level I, Grade A), the lack of studies in populations with high-risk ARF, a possible increased risk of late bacteriological recurrence in those receiving short courses and the absence of information about whether short course treatment can prevent ARF, suggest that this approach should not be recommended in populations at high risk of ARF (level I, Grade B).¹³⁶ Similarly, it is not recommended as eradication treatment during an episode of ARF (Grade D).

Because this could be considered the commencement of secondary prophylaxis, it may be advisable to use BPG, and to begin education about the importance of secondary prophylaxis at the same time. Some clinicians prefer to use oral penicillin while patients are hospitalised, and to defer the intramuscular injection until they have improved dramatically, and they and their families have been properly counselled. Intravenous penicillin is not indicated.

Patients with a reliably-documented penicillin allergy may be treated with oral erythromycin. Roxithromycin is not recommended, because of the limited available evidence that it is not as effective as erythromycin in eradicating GAS from the upper respiratory tract.²²⁶

However, most patients labelled as being allergic to penicillin are not. Because penicillin is the best antibiotic choice for secondary prophylaxis (see Chapter 3), it is recommended that patients with a stated penicillin allergy be investigated carefully, preferably with the help of an allergist, before being accepted as truly allergic (Grade D).

Arthritis/arthralgia

Salicylates (aspirin) are recommended as first-line treatment, because of the extensive experience

with their use in ARF and an established evidence base.^{125, 227, 228} However, there is increasing experience and anecdotal success with other NSAID therapy, particularly naproxen, and also ibuprofen.

Anti-inflammatory therapy should be commenced in patients with arthritis or severe arthralgia as soon as the diagnosis of ARF has been confirmed (Grade B), but should be withheld if the diagnosis is not certain. In such cases, paracetamol or codeine should be used instead for pain relief (see Table 3.11).

The arthritis of ARF has been shown in controlled trials to respond dramatically to salicylate or other NSAID therapy,^{221–223} often within hours, and almost always within 3 days (level II). If the symptoms and signs do not remit substantially within 3 days of commencing anti-inflammatory medications, a diagnosis other than ARF should be considered.

The duration of treatment is dictated by the clinical response and improvement in inflammatory markers (ESR, CRP). Many patients need anti-inflammatory therapy for only 1–2 weeks (i.e. anti-inflammatory therapy can be stopped at 2 weeks if the patient is pain free with improved inflammatory markers). In some patients, joint symptoms may recur following the cessation of treatment (so-called ‘rebound phenomenon’); this does not indicate recurrence, and can be treated with another course of anti-inflammatory therapy.²²⁹ Some patients who still have symptoms or elevated inflammatory markers at 2 weeks may require anti-inflammatory therapy for up to 6 weeks. In such cases, the anti-inflammatory dose can often be reduced after the initial 1–2 weeks.^{131, 133, 138} As the dose is reduced, rebound symptoms may occur, as described earlier, and can be treated with a brief course of higher-dose anti-inflammatory therapy. Most ARF episodes subside within 6 weeks, and 90% resolve within 12 weeks. Approximately 5% of patients require 6 months or more of anti-inflammatory therapy.¹⁵⁸

Aspirin

Aspirin should be started at a dose of 50–60 mg/kg/day, up to a maximum of 80–100 mg/kg/day (4–8 g/day in adults) in four to five divided doses. If there is an incomplete response within 2 weeks, the dose may be increased to 125 mg/kg/day, but at higher doses, the patient should be carefully observed for features of salicylate toxicity. In such cases, the dose can often be reduced to 60–70 mg/kg/day once symptoms are controlled for the remainder of a 6-week course.^{132, 133, 139} If facilities are available, blood levels may be monitored every few days, and the dose increased until serum levels of 20–30 mg/100 dL are reached. However, most patients can be managed without

blood level monitoring. Toxic effects (tinnitus, headache, hyperpnoea) are likely above 20 mg/100 dL, but often resolve after a few days. There is also the risk of Reye's syndrome developing in children receiving salicylates, who develop certain viral infections, particularly influenza. It is recommended that children receiving aspirin during the influenza season (autumn/winter) also receive the influenza vaccine (Grade D).

Naproxen and ibuprofen

Naproxen (10–20 mg/kg/day) can be used as alternative to aspirin. It has been used successfully in patients with ARF, including one small, randomised trial, and has been advocated as a safer alternative to aspirin (level III-I).^{230, 231} It has the advantage of only twice-daily dosing, and is available in Australia as a suspension. Ibuprofen has also been used successfully at a dose of 30 mg/kg/day divided into three doses, although there are no data to support its use in ARF.

Chorea

Although other causes should be excluded, in populations with endemic ARF, the vast majority of chorea presentations will be due to ARF, and neuroimaging is not needed routinely (level C).²³² Sydenham's chorea is self-limiting. Most cases will resolve within weeks, and almost all cases within 6 months,²³³ although rare cases may last as long as 2–3 years.^{129, 234} Mild or moderate chorea does not require any specific treatment, aside from rest and a calm environment. Overstimulation or stress can exacerbate the symptoms. Sometimes hospitalisation is useful to reduce the stress that families face in dealing with abnormal movements and emotional lability.

Because chorea is benign and self-limiting, and anti-chorea medications are potentially toxic, treatment should only be considered if the movements interfere substantially with normal activities, place the person at risk of injury or are extremely distressing to the patient, family and friends. Valproic acid, in particular, should be avoided in women who are or who may be pregnant, because of the potential for damage to the fetus.

Aspirin does not have a significant effect on rheumatic chorea.^{164, 235} Small studies of intravenous immunoglobulin (IVIG) have suggested more rapid recovery from chorea, but have not demonstrated reduced incidence of long-term valve disease in non-chorea ARF.^{155, 236} Until more evidence is available, IVIG is not recommended, except for severe chorea refractory to other treatments (level II/IV, Grade C).

Carbamazepine and valproic acid are now preferred to haloperidol, which was previously considered the first-line medical treatment for chorea.^{237, 238} A small, prospective comparison of these three agents concluded that valproic acid was the most effective.²³⁹

Other antichorea medications should be avoided because of potential toxicity. Due to the small potential for liver toxicity with valproic acid, it is recommended that carbamazepine be used initially for severe chorea requiring treatment, and that valproic acid be considered for refractory cases (level III-2, Grade B). A response may not be seen for 1–2 weeks, and successful medication may only reduce, but not eliminate, the symptoms.

Medication should be continued for 2–4 weeks after chorea has subsided, and then be withdrawn. Recurrences of chorea are usually mild and can be managed conservatively, but in severe recurrences, the medication can be recommenced, if necessary.

Fever

Low-grade fever does not require specific treatment. Fever will usually respond dramatically to salicylate therapy. Fever alone, or fever with mild arthralgia or arthritis, may not require salicylates, but can instead be treated with paracetamol.

Carditis/heart failure

The use of glucocorticoids and other anti-inflammatory medications in rheumatic carditis has been studied in two meta-analyses.^{219, 220} All of these studies of glucocorticoids were performed more than 40 years ago, and did not use drugs that are in common use today. These meta-analyses failed to suggest any benefit of glucocorticoids or IVIG over placebo, or of glucocorticoids over salicylates, in reducing the risk of long-term heart disease (level I). The available evidence suggests that salicylates do not decrease the incidence of residual RHD (level IV).^{221–223} Therefore, salicylates are not recommended to treat carditis (Grade C).

Glucocorticoids may be considered for patients with heart failure in whom acute cardiac surgery is not indicated (Grade D). This recommendation is not supported by evidence, but is made because many clinicians believe that glucocorticoids may lead to a more rapid resolution of cardiac compromise, and even be lifesaving in severe acute carditis.^{220, 240}

The potential major adverse effects of short courses of glucocorticoids, including gastrointestinal bleeding and worsening of heart failure as a result of fluid retention, should be considered before they are used.

If glucocorticoids are used, the drug of choice is oral prednisone or prednisolone (1–2 mg/kg/day, to a maximum of 80 mg once daily or in divided doses). Intravenous methyl prednisolone may be given in very severe cases. If 1 week or less of treatment is required, the medication can be ceased when heart failure is controlled and inflammatory markers improve. For longer courses (usually no more than 3 weeks is required), the dose may be decreased by 20–25% each week. Treatment should be given in addition to the other antifailure treatments outlined later. Mild to moderate carditis does not warrant any specific treatment.

As glucocorticoids will control joint pain and fever, salicylates can usually be discontinued, or the dose reduced, during glucocorticoid administration. Salicylates may need to be recommenced after glucocorticoids are discontinued to avoid rebound joint symptoms or fever.

In tropical regions, where *Strongyloides* infestation is endemic, patients should be treated with ivermectin if the glucocorticoid course is likely to exceed 0.5 mg/kg/day of prednisolone or equivalent for more than 2 weeks. Obtain advice from a local infectious diseases specialist about the ivermectin dose, adverse events, contraindications and other possible opportunistic infections before starting treatment.^{227, 241}

An urgent echocardiogram and a cardiology assessment are recommended for all patients with heart failure. The mainstays of initial treatment are rest (see below for specific comments regarding bed rest) and diuretics. This results in improvement in most cases. In patients with more severe failure, glucocorticoids can be considered (as discussed above), and ACE inhibitors may be used, particularly if AR is present.²²⁷ Digoxin is usually reserved for patients with AF. There is little experience with beta blockers in heart failure, due to acute carditis, and their use is not recommended (Grade D). Detailed recommendations for the management of heart failure can be found in separate National Heart Foundation of Australia clinical guidelines.²⁴²

Role of acute surgery

Surgery is usually deferred until active inflammation has subsided. Valve leaflet or chordae tendineae rupture rarely leads to severe regurgitation, where emergency surgery is needed. This can be safely performed by experienced surgeons, although the risk appears to be slightly higher than when surgery is performed after active inflammation has resolved.²⁴³

Valve replacement, rather than repair, is usually performed during the acute episode, because of the technical difficulties of repairing friable, inflamed

tissue. Nevertheless, very experienced surgeons may achieve good results with repair in this situation.

Bed rest

In the prepenicillin era, prolonged bed rest in patients with rheumatic carditis was associated with a shorter duration of carditis, fewer relapses and less cardiomegaly.²⁴⁴ Strict bed rest is no longer recommended for most patients with rheumatic carditis. Ambulation should be gradual, and as tolerated in patients with heart failure or severe acute valve disease, especially during the first 4 weeks or until the serum CRP level has normalised and the ESR has normalised or dramatically reduced. Patients with milder or no carditis should remain in bed only as long as necessary to manage other symptoms, such as joint pain (Grade D).

Commencement of long-term preventive measures

Secondary prophylaxis

See 'Antibiotics' (p. 48).

Notify case to ARF/RHD register

There should be an easy means of notifying a case to an ARF/RHD register via a standard notification form, telephone call or otherwise. Depending on local laws, it may be necessary to obtain consent for the patient's details to be recorded in the register. Not all states or territories have registers.

Contact local health staff for follow up

Although the register coordinator should notify community health staff about ARF/RHD patients in their area, the notifying medical practitioner should make direct contact with the community medical staff so that they are aware of the diagnosis, the need for secondary prophylaxis and any other specific follow-up requirements.

Provide culturally-appropriate education to patients and families

At the time of diagnosis, it is essential that the disease process is explained to the patient and family in a culturally-appropriate way, using available educational materials (e.g. pamphlets and video) and interactive discussion.

Organise dental checks and ongoing dental care

This is critical in the prevention of endocarditis. As patients without rheumatic valve damage may still be at long-term risk of developing RHD, particularly in the event of recurrent episodes of ARF, dental care is essential, regardless of the presence or absence of carditis.

Medications for the treatment of ARF

Medications used in the treatment of ARF are outlined in Table 3.13.

Table 3.13 Medications used in ARF

Medication	Indication	Regimen	Duration
BPG, im	Treat streptococcal infection	900 mg (1,200,000 U) ≥ 20 kg 450 mg (600,000 U) < 20 kg	Single dose
or Phenoxymethylpenicillin, po (Penicillin V)	Initial treatment of streptococcal infection	Child: 250 mg, bd Adolescents and Adults: 500 mg, bd	10 days
or Erythromycin ethyl succinate, po (only if allergic to penicillin)	Initial treatment of streptococcal infection	Child: 20 mg/kg up to 800 mg, bd Adult: 800 mg, bd	10 days
or Erythromycin, po (only if allergic to penicillin)	Initial treatment of streptococcal infection	Child: 12.5 mg/kg up to 500 mg, bd Adult: 500 mg, bd	10 days
Paracetamol, po	Arthritis or arthralgia: mild or until diagnosis confirmed	60 mg/kg/day (max 4 g) given in 4–6 doses/day; may increase to 90 mg/kg/day, if needed, under medical supervision	Until symptoms relieved or NSAID started
Codeine, po	Arthritis or until diagnosis Confirmed arthralgia	0.5–1 mg/kg/dose (adults 15–60 mg/dose) 4–6 hourly	Until symptoms relieved or NSAID started
Aspirin, po	Arthritis or severe arthralgia (when ARF diagnosis confirmed)	Begin with 50–60 mg/kg/day, increasing, if needed, up to 80–100 mg/kg/day (4–8 g/day in adults) given in 4–5 doses/day If higher doses required, reduce to 50–60 mg/kg/day when symptoms improve, and cease when symptom free for 1–2 weeks Consider ceasing in the presence of acute viral illness, and consider influenza vaccine if administered during autumn/winter	Until joint symptoms relieved
Naproxen, po	Arthritis or severe arthralgia (when ARF diagnosis confirmed)	10–20 mg/kg/day (max 1250 mg) given, bd	As for aspirin
Ibuprofen, po	Arthritis or severe arthralgia (when ARF diagnosis confirmed)	30 mg/kg/day (max 1600 mg) given tds	As for aspirin

Medication	Indication	Regimen	Duration
Prednisone or prednisolone, po.	Severe carditis, heart failure, pericarditis with effusion	1–2 mg/kg/day (max 80 mg); if used >1 week, taper by 20–25% per week	Usually 1–3 weeks
Frusemide, po/iv (can also be given im)	Heart failure	Child: 1–2 mg/kg stat, then 0.5–1 mg/kg/dose 6–24 hourly (max 6 mg/kg/day) Adult: 20–40 mg/dose, 6–24 hourly, up to 250–500 mg/day	Until failure controlled and carditis improved
Spironolactone, po	Heart failure	1–3 mg/kg/day (max 100–200 mg/day) in 1–3 doses; round dose to multiple of 6.25 mg (1/4 of a tablet)	As for frusemide
Enalapril, po	Heart failure	Child: 0.1 mg/kg/day in 1–2 doses, increased gradually over 2 weeks to a max of 1 mg/kg/day in 1–2 doses Adult: initial dose 2.5 mg daily; maintenance dose 10–20 mg daily (max 40 mg)	As for frusemide
Captopril, po	Heart failure	Child: initial dose 0.1 mg/kg/dose. Beware of hypotension. Increase gradually over 2 weeks to 0.5–1 mg/kg/doses 8 hourly (max 2 mg/kg/dose 8 hourly). Adult: initial dose 2.5–5 mg. Maintenance dose 25–50 mg 8 hourly	As for frusemide
Lisinopril, po	Heart failure	Child: 0.1–0.2 mg/kg once daily, up to 1 mg/kg/dose Adult: 2.5–20 mg once daily (max 40 mg/day)	As for frusemide
Digoxin, po/iv	Heart failure/atrial fibrillation	Child: 15 mcg/kg start, and then 5 mcg/kg after 6 hours, then 3–5 mcg/kg/dose (max 125 mcg) 12 hourly Adult: 125–250 mcg daily Check serum levels	Seek advice from specialist
Carbamazepine	Severe chorea	7–20 mg/kg/day (7–10 mg/kg/day usually sufficient) given tds	Until chorea controlled for several weeks, then trial off medication
Valproic acid, po	Severe chorea (may affect salicylate metabolism)	Usually 15–20 mg/kg/day (can increase to 30 mg/kg/day) given tds	As for carbamazepine

bd, *bis die* (twice daily); BPG, benzathine penicillin G; im, intramuscular; iv, intravenous; NSAID, non-steroidal anti-inflammatory drug; po, per oral; tds, *ter die sumendum* (three times daily).

Monitoring

Expected progress and timing of discharge

Most patients with arthritis respond well to aspirin therapy, and this is usually stopped within 6 weeks. Bed rest should continue until heart failure has largely resolved. Planning for discharge and follow up should take into account the presence and severity of cardiac valve damage and the potential for ongoing valvulitis due to continuing rheumatic inflammation, which sometimes leads to cardiac failure appearing, or worsening, in the weeks after discharge. Normally, discharge should only be considered for patients who are asymptomatic or only mildly symptomatic, in whom the manifestations of ARF have stabilised, and in whom inflammatory markers (particularly CRP) are clearly improving. In patients being discharged to settings where follow up may be unreliable, particularly those with significant carditis, it may be prudent to wait until inflammatory markers are near-normal. Most ARF patients with no, or only mild, carditis can be discharged from hospital within 2 weeks. Those with moderate or severe carditis may require longer admission. The length of admission will also be affected by the social and home circumstances. If patients come from remote communities or other settings with limited access to high-quality medical care, it is advisable to discuss discharge timing with the patient and the local primary healthcare team. In some cases, it may be advisable to prolong the hospital stay until recovery is well advanced. Regardless of the timing of discharge, follow up by the local medical practitioner or community clinic should be organised for within a week of discharge, at which time clinical evaluation and repeat CRP should be undertaken to exclude evidence of recrudescence. Planning the long term follow up of the patient before discharge is critical to optimise long term outcomes. This involves coordination between the community clinic and specialist services. Most fatalities from ARF and RHD in young Indigenous Australians occur in circumstances where such coordination has been difficult or inadequate.

Frequency of laboratory tests

Once the diagnosis has been confirmed and treatment commenced, inflammatory markers (ESR, CRP) should be measured twice weekly initially, then every 1–2 weeks, including after discharge, until they have been normal for one month. Salicylate levels may also be monitored, if the facilities are available, but most cases can be managed without this information.

Echocardiography should be repeated after 1 month if the initial diagnosis was not clear, if the carditis was severe or whenever a new murmur is detected. Cases of severe carditis with heart failure may need frequent echocardiographic assessments, ECG and chest X-rays, according to their clinical course.

Advice on discharge

All patients should have a good understanding of the cause of rheumatic fever and the need to have sore throats treated early. Family members should be informed that they are at increased risk of ARF compared to the wider community.

Patients and families should understand the reason for secondary prophylaxis and the consequences of missing a BPG injection. They should be given clear information about where to go for secondary prophylaxis, and written information on appointments for follow up with their local medical practitioner, physician/paediatrician and cardiologist (if needed). They should be given contact details for the RHD register coordinator (if there is one), and encouraged to telephone if they have any questions concerning their follow up or secondary prophylaxis. They should also be reminded of the importance of antibiotic prophylaxis for dental and other procedures to protect against endocarditis.

Patients receiving penicillin secondary prophylaxis, who develop streptococcal pharyngitis, should be treated with a non-beta-lactam antibiotic, usually clindamycin.

4. Secondary prevention and rheumatic heart disease control programs

‘Secondary prevention of rheumatic fever is defined as the continuous administration of specific antibiotics to patients with a previous attack of rheumatic fever, or well-documented rheumatic heart disease. The purpose is to prevent colonization or infection of the upper respiratory tract with group A beta-hemolytic streptococci and the development of recurrent attacks of rheumatic fever’. World Health Organization 2001¹²⁵

This chapter deals with the long-term management of individuals who have been diagnosed with ARF or RHD, excluding management of heart failure (see Chapter 5). It also discusses issues relating to population-based ARF/RHD control strategies.

Secondary prevention refers to the early detection of disease and implementation of measures to prevent the development of recurrent and worsening disease. In the case of ARF/RHD, this has become synonymous with secondary prophylaxis (see WHO definition above). However, the secondary prevention of RHD also requires attention to a number of patient level factors to improve the quality and outcomes of care, organisational level factors that improve the capacity of health systems to respond to the needs of patients with ARF/RHD and socio-political action and advocacy to ensure adequate resourcing and awareness of the problem (Table 4.1). Secondary prophylaxis remains the most cost-effective RHD control strategy at both community and population levels.^{7, 245}

The effectiveness of secondary prophylaxis is impaired by factors affecting adherence to antibiotic regimens and by the broad determinants that drive the ongoing incidence of ARF. These factors relate to overcrowded housing, poor access to health services, limited educational opportunities and poor environmental conditions, all of which are strongly related to poverty. As a consequence, communities with the highest rates of ARF and RHD are often profoundly disadvantaged, and have suboptimal access to social, environmental and medical resources essential to mitigating the problem.

From the available evidence, secondary prevention should include:

- strategies aimed at improving the delivery of secondary prophylaxis and patient care
- the provision of patient (and family) education
- support for patients to improve self-management
- coordination of available health services
- structured and sustained routine care and follow up
- the establishment of local, regional and/or national control programs
- a commitment to advocacy for necessary and appropriate resources for all people at risk of or with ARF/RHD.

Table 4.1 Major elements of secondary prevention of ARF/RHD

Individual level
Accurate and timely diagnosis of ARF
Appropriate delivery of secondary prophylaxis
Prevention of infective endocarditis
Routine review, structured care planning and coordinated multidisciplinary care
Health education for individuals, families and the community
Screening for undiagnosed RHD
Organisational level
RHD control programs
Societal level
Advocacy for improvements in social, economic, environmental and health service determinants of ARF/RHD incidence and adverse outcomes

Individual approaches to secondary prevention

Accurate and timely diagnosis of acute rheumatic fever

ARF is often difficult to diagnose. If a diagnosis is not made when symptoms are apparent, preventive measures cannot be instituted, and patients will be placed at increased risk of developing recurrent ARF and worsening RHD. Recommendations regarding ARF diagnosis are given in Chapter 3.

Secondary prophylaxis

The regular administration of antibiotics to prevent infection with GAS and recurrent ARF remains the mainstay of secondary prevention of RHD in all people with a history of ARF or RHD.^{246, 247}

This strategy has been proven in RCT to prevent streptococcal pharyngitis and recurrent ARF. In early studies using sulphonamides, 1.5% of treated patients developed ARF recurrences, compared to 20% of untreated patients. Subsequently, penicillin was found to be more efficacious than sulphonamides (level I).²²⁹

A Cochrane meta-analysis⁴⁹ concluded that the use of penicillin (compared to no therapy) is beneficial in the prevention of recurrent ARF, and that intramuscular BPG is superior to oral penicillin in the reduction of both recurrent ARF (87–96% reduction) and streptococcal pharyngitis (71–91% reduction) (level I). Secondary prophylaxis also reduces the severity of RHD,⁷ is associated with the regression of heart

disease in approximately 50–70% of those with adequate adherence over a decade (level III-2),^{141, 248, 249} and reduces mortality (level III-2).²⁵⁰

Antibiotic regimens for secondary prophylaxis

Despite international acceptance of antibiotic prophylaxis as the principal target for the secondary prevention of RHD, significant heterogeneity exists in the recommended dosages, intervals and duration of secondary prophylaxis.²⁴⁵ The internationally-accepted standard dose of BPG for the secondary prevention of ARF in adults is 900 mg (1,200,000 U).^{125, 126} The dose for children is less clear, with significant variations across international guidelines.^{92, 125} Until recently, the AHA and the Australian Antibiotic Guidelines have recommended 900 mg (1,200,000 U), regardless of weight or age.^{251–253} Some authorities recommend that the dose be reduced for children; for example, WHO recommends a dose of 450 mg (600,000 U) for children weighing less than 30 kg.¹²⁵ More recently, the AHA has recommended a lower dose of 450 mg (600,000 U) in children less than or equal to 27 kg.⁹²

Studies of BPG pharmacokinetics in children suggest that higher per kg doses are required to achieve sustained penicillin concentrations in serum and urine, and that 600,000 U is insufficient for most children weighing less than 27 kg.^{254, 255} In New Zealand, the 600,000 U dose is used only for children weighing less than 20 kg. The ARF recurrence rate in this group is only 0.6 per 100 patient-years.²⁵⁶

Therefore, it is recommended that 1,200,000 U of BPG should be used for secondary prophylaxis for all persons weighing 20 kg or more, and 600,000 U for those weighing less than 20 kg (level III-2, Grade B).

BPG is most effectively given as a deep intramuscular injection, into the upper outer quadrant of the buttock or the anterolateral thigh.¹²⁵

While BPG is usually administered every 4 weeks, serum penicillin levels may be low or undetectable 28 days following a dose of 1,200,000 U.²⁵⁷ Fewer streptococcal infections and ARF recurrences have been documented among patients receiving three-weekly BPG, compared to four-weekly BPG (level I).^{49, 258, 259} Moreover, the three-weekly regimen resulted in a greater resolution of MR in a long-term, randomised study in Taiwan (66% vs 46%) (level II).²⁶⁰ An alternative strategy of administration of larger doses of BPG has been suggested, due to the fact that it is associated with a higher proportion of people with detectable serum penicillin levels 4 weeks after injection.²⁷³ However, until more data are available, this strategy cannot be recommended.

Although Australian Aboriginal and Torres Strait Islander people are at higher risk of developing ARF than other ethnic groups in Australia, the benefits of three-weekly BPG injections are offset by the difficulties of achieving good adherence, even to the standard four-weekly regimen.^{7, 262, 263} Prospective data from New Zealand²⁷³ have shown that few, if any, recurrences occur among people who are fully adherent to a four-weekly BPG regimen. Furthermore, in the years between 2002 and 2009, no patients in the Northern Territory who received 100% of their four-weekly injections had a recurrent episode of ARF.⁹

The use of four-weekly BPG is currently the treatment of choice, except in patients considered to be at 'high risk', for whom three-weekly administration is recommended.^{125, 264, 265} High-risk patient groups include:

- those with moderate or severe carditis, or a history of valve surgery, who demonstrate good adherence to less frequent injections
- those who have confirmed breakthrough ARF, despite full adherence to four-weekly BPG (Table 4.2) (Grade D).

Some health services prefer to administer BPG on the same day every month, rather than every 4 weeks. There are no data on the relative efficacies of these approaches, but the pharmacokinetic data suggest that prolonging the dosing interval beyond 4 weeks may increase the risk of breakthrough ARF. Therefore, monthly, rather than four-weekly administration of BPG, is an acceptable alternative, only if it is considered that the practicalities of monthly dosing will substantially improve adherence (Grade D).

Alternatives to intramuscular benzathine penicillin G

Oral penicillin is less efficacious than BPG in preventing GAS infections and subsequent recurrences of ARF.^{125, 266, 267} Twice-daily oral regimens are also likely to result in poorer rates of adherence over long periods of time²⁶⁸ and less predictable serum penicillin concentrations, when compared to intramuscular BPG.²⁶⁹ Oral penicillin should be reserved for patients who experience bleeding problems following injection, and for those who refuse intramuscular BPG (level II, Grade B). If a patient is offered oral penicillin, the consequences of missed doses must be emphasised, and adherence carefully monitored (Grade D).

Australia has been affected by inconsistent supply of BPG over recent years. This poses potential risks to patients requiring four-weekly prophylaxis. Using an alternative injectable penicillin during a shortage in 2007 resulted in an increase in the number of reported cases of ARF in the Northern Territory, almost doubling the previous 3-year average. Organisational approaches to secondary prevention should therefore ensure consistent supply at the national, regional and local levels.

Penicillin allergy

The benefits of long-term BPG administration outweigh the rare risk of serious allergic reactions to penicillin and fatality as a result of anaphylaxis.^{257, 264, 268, 269} The rates of allergic and anaphylactic reactions to monthly BPG are 3.2% and 0.2%, respectively, and fatal reactions are exceptionally rare.^{270, 271}

There is no increased risk with prolonged BPG use. A prospective study of 1790 ARF/RHD patients found similar rates of allergic reactions in those receiving long-term penicillin therapy and those receiving short-term therapy for sexually-transmitted diseases (level III-2).²⁷²

Before commencing penicillin treatment, patients should be carefully questioned about known allergies to penicillin and other beta-lactam antibiotics. If a confirmed, immediate and severe allergic reaction to penicillin is revealed, a non-beta-lactam antimicrobial (e.g. erythromycin) should be used instead (Grade D).^{125, 265}

When patients state they are allergic to penicillin, but there is no unequivocal evidence, they should be investigated for a penicillin allergy, preferably in consultation with an allergist. The options include skin testing²⁷² or a supervised challenge test. Most of these patients are not truly allergic. Penicillin desensitisation is not applicable to these patients, as it would have to be repeated before each dose of BPG.^{253, 272}

Secondary prophylaxis in pregnancy

As there is no evidence of teratogenicity, penicillin prophylaxis should continue for the duration of pregnancy for the prevention of recurrent ARF (Grade D).¹²⁵ Erythromycin is also considered safe in pregnancy, although controlled trials have not been conducted.

Table 4.2 Recommended antibiotic regimens for secondary prevention

Antibiotic	Dose	Route	Frequency
First line			
BPG	900 mg (1,200,000 U) ≥20 kg 450 mg (600,000 U) < 20 kg	Deep im injection	4 weekly, or 3 weekly for selected groups*
Second line (If im route is not possible or refused, adherence should be carefully monitored)			
Phenoxymethylpenicillin (Penicillin V)	250 mg	Oral	Twice daily
Following documented penicillin allergy			
Erythromycin	250 mg	Oral	Twice daily

* Three-weekly BPG may be considered for patients with moderate or severe carditis or a history of valve surgery, who demonstrate good adherence to less frequent injections, and for those who have confirmed breakthrough ARF, despite full adherence to 4-weekly BPG.

BPG, benzathine penicillin G; im, intramuscular.

Table 4.3 Factors that affect the duration of secondary prophylaxis

Factor	Implication
Age	ARF recurrence is less common between 25–40 years of age, and rare >40 years
Presence and severity of RHD	ARF recurrence could be life-threatening in people with moderate or severe RHD, or in those with a history of valve surgery
Presence of carditis during initial episode	Increases the likelihood of further cardiac damage, should a recurrence occur
Time elapsed since last episode of ARF	ARF recurrences are less common >5 years since last episode
Socioeconomic circumstances	ARF recurrences are more common in lower socioeconomic groups (particularly related to overcrowded housing)
Background risk of GAS infection and ARF within the community[†]	ARF recurrences are more common in higher-incidence communities or settings
Adherence to treatment	Optimised adherence for a few years after the initial episode may provide greater protection from recurrences than offered by poor adherence for many years
Assessment at time of cessation of secondary prophylaxis	Evidence of moderate or greater RHD may warrant prolonged prophylaxis

[†] Consideration should be given to the higher risk of exposure to GAS and subsequent development of ARF among individuals residing or working in environments or settings such as boarding schools, childcare settings, barracks and hostels or overcrowded housing with large numbers of children.

Source: Adapted from WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease (2001 : Geneva, Switzerland) *Rheumatic fever and rheumatic heart disease : report of a WHO Expert Consultation*, Geneva, 29 October — 1 November 2001.

Table 4.4 Duration of secondary prophylaxis

Category	Definition of category	Duration
All persons with ARF or RHD[†]		Minimum 10 years after most recent episode of ARF or until age 21 years (whichever is longer).
Status after initial period elapsed:		
No RHD	No pathological mitral or aortic regurgitation, but may have minor morphological changes to mitral or aortic valves on echocardiography	Discontinue at that time [‡]
Mild RHD	Mild mitral or aortic regurgitation clinically and on echocardiography, with no clinical evidence of heart failure, and no evidence of cardiac chamber enlargement on echocardiography	Discontinue at that time
Moderate RHD	<ul style="list-style-type: none"> Any valve lesion of moderate severity clinically (e.g. mild–moderate cardiomegaly and/or mild–moderate heart failure) or on echocardiography Mild mitral regurgitation, together with mild aortic regurgitation clinically or on echocardiography Mild or moderate mitral or aortic stenosis Any pulmonary or tricuspid valve lesion co-existing with a left-sided valve lesion 	Continue until 35 years of age
Severe RHD	<ul style="list-style-type: none"> Any severe valve lesion clinically (e.g. moderate to severe cardiomegaly or heart failure) or on echocardiography Any impending or previous cardiac valve surgery for RHD 	Continue until age 40 years, or longer*

[†] Patients >25 years of age who are diagnosed with RHD, without any documented history of prior ARF, should receive prophylaxis until the age of 35 years. At this time, they should be reassessed to determine whether prophylaxis should be continued. [‡]Decisions to cease secondary prophylaxis should be based on clinical and echocardiographic assessment. ^{*}Risk of recurrence is extremely low in people aged >40 years. In some cases, for example, when the patient decides that they want to reduce even a minimal risk of recurrence, prophylaxis may be continued beyond the age of 40 years, or even for life.

Secondary prophylaxis in anticoagulated patients

Intramuscular bleeding from BPG injections, used in conjunction with anticoagulation therapy in Australia, is rare. Thus, BPG injections should be continued for anticoagulated patients, unless there is evidence of uncontrolled bleeding, or the international normalised ratio (INR) is outside the defined therapeutic window (Grade D). Patients discharged from hospital on oral penicillin following valve surgery should recommence BPG as soon as is practical.

Duration of secondary prophylaxis

The appropriate duration of secondary prophylaxis is determined by age, persistence of environmental risk factors, time since the last episode of ARF and potential harm from recurrent ARF. Critical factors are outlined in Table 4.3. Based on these factors, the recommended duration of secondary prophylaxis is outlined in Table 4.4 (Grade D).

Ceasing secondary prophylaxis

The duration of secondary prophylaxis should be based on individual needs, clinical features, social circumstances and the likelihood of ongoing exposure to GAS and further episodes of ARF.

Data on Northern Territory Aboriginal patients show that approximately 1% of 259 ARF episodes recorded between 2005 and 2009 occurred after 40 years of age.⁸ An earlier review of prospective data from the Auckland Acute Rheumatic Fever Register in New Zealand found that there were no episodes of recurrence among patients over the age of 40 years between 1993 and 1999.²⁷³ It is reasonable to cease secondary prophylaxis at the age of 40, except when individual circumstances warrant continuation (e.g. when patients are keen to reduce even a small chance of a recurrence) (level IV, Grade C). Before stopping prophylaxis, recipients should be evaluated for symptomatic deterioration and the stability and severity of valve lesions. This should include echocardiographic assessment (Grade D).

Where limited echocardiography is available, preference should be given to patients with a history of moderate or greater carditis, a history of one or more ARF recurrences or clinical evidence of carditis (e.g. a murmur) (Grade D). The anticipated and actual dates of cessation should be documented in medical records and on the RHD register (see below and 'Rheumatic heart disease control programs', p. 67). The date of cessation may be reviewed if there is a change in clinical or echocardiographic severity, a specialist recommendation or a recurrence of ARF (Grade D).

Improving adherence to secondary prophylaxis

The persistence of high rates of recurrent ARF in Australia highlights the continued barriers to secondary prevention. In the Top End of the Northern Territory in the 1990s, 28% of patients on secondary prophylaxis missed half or more of their scheduled BPG injections over a 12-month period,²⁷⁴ while 45% of all episodes of ARF were recurrences.¹²⁰ In 2008, 31% of patients missed half or more of their injections, and 12% of all episodes were recurrences.

In the Gisborne area of New Zealand, failure to prevent recurrent ARF was thought to be due to a range of factors, including lack of recognition among health practitioners of the efficacy of parenteral BPG compared to oral regimens, inadequate adherence, unreliable data collection and poor continuity of care.²⁷⁵ Poor adherence in remote Aboriginal and Torres Strait Islander communities has been considered only rarely due to injection refusal, pain

of injections, or a lack of knowledge or understanding of ARF/RHD. Instead, major factors relate to the availability and acceptability of health services. In a detailed study in the Northern Territory, adherence was improved when patients felt a greater sense of personalised care and 'belonging' to the clinic, and when recall systems extended beyond the boundaries of the community.²⁷⁶ A study of patients in the Northern Territory's Katherine region²⁷⁷ found that people were more likely to receive >50% of their prescribed injections if they were aged under 18 years, or if they attended the clinic at least four times within the preceding 12 months for reasons other than their penicillin prophylaxis. Unfortunately, the same study found that patients with more severe disease were less likely to receive their monthly penicillin injections. A wider survey in the Northern Territory found that adherence was substantially better in health centres where active follow up was carried out when BPG doses were missed, and where a dedicated staff member administered the BPG (A Brown, unpublished data). Studies from Egypt²⁷⁸ and north Western Australia³²² reached similar conclusions.

A continuous quality-improvement approach to the prevention and management of ARF and RHD was trialled at six community health clinics in the Northern Territory over a 3-year period to help improve the delivery of secondary prophylaxis. This trial identified a number of factors impacting on injection delivery, including high staff turnover, the lack of supportive infrastructure for chronic disease at health centres, the size and complexity of the health service and community and the mobility of large numbers of patients. (Bailie R. *unpublished data*)

A local ARF register can assist with routine assessment and surveillance, the recording of prophylaxis delivery, the recall of patients who miss doses of BPG or those with ARF, and improve health education and health-promotion programs.²⁷⁹ Centralised registers can support the provision of prophylaxis for those who move between communities.²⁸⁰

Health education is critical at all levels.^{125 280, 281} Across northern Australia, ARF/RHD awareness is incorporated into health staff orientation programs, because staff turnover is high and many new staff are not familiar with ARF/RHD.²⁸⁰ Health education is also recommended for patients and families during hospitalisation and outpatient visits, but its efficacy has not been formally evaluated.^{280 282}

The lack of parental awareness of the causes and consequences of ARF/RHD were key contributors to poor adherence among children on long-term prophylaxis in Egypt.²⁷⁸ In a number of regions

in India, comprehensive health education has improved community awareness of sore throats, ARF and RHD,²⁸³ and assisted in case identification.²⁸⁴ Comprehensive health education and promotion were also key components in the successful control of RHD in the French Caribbean.⁸⁶

These and other potential strategies to improve the delivery of secondary prophylaxis are listed in Table 4.5.^{279, 281}

Table 4.5 Potential strategies to improve the delivery of secondary prophylaxis

<p>Evaluate the local health service environment to identify specific barriers to injection delivery.</p> <p>Based on the outcome of the evaluation the following strategies may be useful:</p> <ul style="list-style-type: none"> • identify local, dedicated staff members to deliver secondary prophylaxis and coordinate routine care • focus on improving relationships between health staff and patients/families • support and use the expertise, experience, community knowledge and language skills of Aboriginal health workers • develop and implement recall and reminder systems (based on a local ARF/RHD register where established) to accommodate the high mobility of individuals and groups: • ensure that recall systems extend beyond community boundaries • establish networks for timely communication between health clinics • use a centralised coordinator and register to assist in monitoring movement • minimise staff turnover in remote and rural primary healthcare centres and regional hospitals, or minimise the impact of staff turnover where possible • promote the importance of secondary prophylaxis in preventing recurrent ARF and the development or worsening of RHD • improve quality and delivery of ongoing health education and support for staff, patients and families • implement measures to reduce pain of injections where indicated • base routine care on standardised, evidence-based guidelines.

Reducing the pain of benzathine penicillin G injections

The pain of BPG injections is not usually a critical factor in determining adherence to secondary prophylaxis; however, it can cause distress in some patients (particularly children), and as a consequence, can be difficult for some health practitioners to deliver. Techniques that safely reduce injection pain should be promoted. A smaller-gauge needle and increasing the volume of injection to 3.5 mL improved acceptability in Taiwan.²⁶⁰ The addition of 1% lignocaine to BPG significantly reduces pain immediately and in the first 24 hours after injection, while not significantly affecting serum penicillin concentrations.²⁸⁵

Procaine penicillin added to BPG reduces pain and local reactions. The combination is effective for the treatment of streptococcal pharyngitis, but the formulations tested to date have not sustained adequate serum penicillin levels for long enough for secondary prophylaxis.^{285, 286} The manufacturers of prepackaged syringes of BPG currently used in Australia for secondary prophylaxis do not recommend the addition of lignocaine or procaine penicillin (Grade D).

Direct application of pressure to the injection site has been shown to decrease pain of intramuscular injections.²⁸⁷ Other techniques that are easy to implement include warming refrigerated syringes to room temperature, ensuring that skin swabbed with alcohol is dry before injection and delivering the injection very slowly.

As these measures are logical and benign, they are recommended, despite the lack of evidence (Table 4.6) (Grade D).

Table 4.6 Measures that may reduce the pain of BPG injections

Use a 21-gauge needle

Warm syringe to room temperature immediately before using

Allow alcohol from swab to dry before inserting needle

Apply pressure with thumb for 10 sec before inserting needle

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

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)

Prevention of infective endocarditis

Infective endocarditis is a dangerous complication of RHD,¹²⁵ and an important adverse event following prosthetic valve replacement in Aboriginal and Torres Strait Islander people. Although the effectiveness of additional antibiotic prophylaxis prior to dental or surgical procedures has not been proven, it remains entrenched in established practice and endorsed by expert consensus.^{288, 289} Despite the lack of level I-II evidence, the rationale for its use includes animal models of endocarditis and empirical observations of the reduction of bacteraemia.^{125, 253}

Recent years have seen tighter eligibility criteria guiding antibiotic recommendations. In Australia and the USA,^{288, 289} criteria are framed around three interconnected considerations: the background risk of infective endocarditis as a consequence of the patient's cardiac condition, the risk of bacteraemia associated with the procedure in question and the risk of adverse events as a consequence of the antibiotics themselves.

In terms of existing Australian guidelines,²⁹⁰ people with prosthetic valves, and all patients with established RHD, should receive antibiotic prophylaxis prior to procedures expected to produce bacteraemia. Individuals with a history of ARF, but no valvular damage, do not require antibiotic prophylaxis. Those already receiving penicillin for secondary prophylaxis

should be offered a different antibiotic for prophylaxis of endocarditis. Recommendations for procedures that require antibiotic prophylaxis are outlined in Tables 4.7 and 4.8 (Grade D).

Further, some authorities recommend the use of an antiseptic mouth rinse (such as chlorhexidine or povidone–iodine) immediately before dental procedures to help reduce the incidence and magnitude of bacteraemia.²⁹¹ Rinsing with 7.5% povidone–iodine can reduce the incidence and magnitude of bacteraemia, and influences the incidence of streptococcal bacteraemia.²⁹²

Therefore, in those without a history of iodine allergy, preprocedure use of antiseptic mouthwash is recommended (Grade C).

Irrespective of procedures, however, good oral health and dental hygiene are essential to reduce the likelihood of recurrent bacteraemia associated with day-to-day activities, and are likely to be important determinants of the degree and duration of bacteraemia associated with oral procedures. Patients should be supported in routine oral care, and regular dental reviews should be encouraged (level D).

Table 4.7 Procedures requiring endocarditis prophylaxis in patients with RHD[§]

Dental

- dental extractions
- periodontal procedures including surgery, subgingival scaling and root planning
- replanting avulsed teeth
- other surgical procedures (e.g. implant placement, apioectomy)

Prophylaxis should be considered for the following if multiple procedures are being conducted, if prolonged or periodontal disease is evident:

- periodontal probing; intraligamentary and intraosseous injections; supragingival cleaning, rubber dam placement with clamps; restorative matrix band/strip placement; endodontics beyond the apical foramen; orthodontic bands; interdental wedges; subgingival placement of retraction cords, antibiotic fibres or strips

Respiratory tract

Any procedure involving incision or biopsy of mucosa, such as:

- tonsillectomy/adenoidectomy
- flexible or rigid bronchoscopy (with incision or biopsy)
- surgery of the bronchial, sinus, nasal or middle ear mucosa (including tympanoplasty)

Genitourinary and gastrointestinal tract

Any procedure where antibiotic prophylaxis is indicated for surgical reasons:

- lithotripsy
- vaginal delivery with prolonged labour
- any genitourinary procedure in the presence of genitourinary infection
- any gastrointestinal procedure in the presence of intra-abdominal infection

Other

- incision and drainage of local abscess
- surgical procedure through infected skin

[§] For more detailed discussion, refer to Infective Endocarditis Prophylaxis Expert Group. *Prevention of endocarditis. 2008 update from Therapeutic guidelines: antibiotic version 14, and Therapeutic guidelines: oral and dental version 1*. Melbourne: Therapeutic Guidelines Limited; 2010.²⁸⁸

Table 4.8 Antibiotics for endocarditis prophylaxis

Antibiotic	Dose
Dental, oral and respiratory tract procedures	
For patients on long-term penicillin therapy, hypersensitive to penicillin or who have taken penicillin or related beta-lactam antibiotic more than once in the last month:	
Clindamycin	(Child: 15 mg/kg up to 600 mg) 600 mg orally as single dose 1 hour prior to procedure
If unable to take orally	
Clindamycin	(Child: 15 mg/kg up to 600 mg) 600 mg iv, over at least 20 min just prior to procedure
Or	
Vancomycin	(Child less than 12 years: 30 mg/kg up to 1.5 g) 1.5 g iv by slow infusion, over at least 1 hour just prior to procedure
Or	
Lincomycin	(Child: 15 mg/kg up to 600 mg) 600 mg iv over 1 hour just prior to procedure
Or	
Teicoplanin	(Child: 10 mg/kg up to 400 mg) 400 mg iv just before the procedure or im 30 min before procedure
For patients not on long-term penicillin therapy, not hypersensitive to penicillin and who have not taken penicillin or related beta-lactam antibiotic more than once in the last month:	
Amoxycillin	(Child: 50 mg/kg up to 2 g) 2 g orally as 1 dose 1 hour prior to procedure
Or	
Amoxycillin/ampicillin	(Child: 50 mg/kg up to 2 g) 2 g iv just prior to procedure or im 30 min prior to procedure
Genitourinary and gastrointestinal procedures	
For patients on long-term penicillin therapy, hypersensitive to penicillin or who have taken penicillin or related beta-lactam antibiotic more than once in the last month:	
Vancomycin	(Child less than 12 years: 30 mg/kg up to 1.5 g) 1.5 g iv by slow infusion, over at least 1 hour just prior to procedure
Or	
Teicoplanin	(Child: 10 mg/kg up to 400 mg) 400 mg iv just prior to procedure

Source: Adapted from Anonymous, *Therapeutic guidelines: antibiotic 14*. Melbourne: Therapeutic Guidelines Limited, 2010.

im, intramuscular; iv, intravenous.

Routine review and structured care planning

A structured care plan should be developed and recorded in the primary healthcare record of all persons with a history of ARF, or with established RHD (Figure 4.1). Table 4.9 lists recommended care plan schedules, which may be tailored to the needs of the individual (Grade D).

Table 4.9 Recommended routine review and management plan

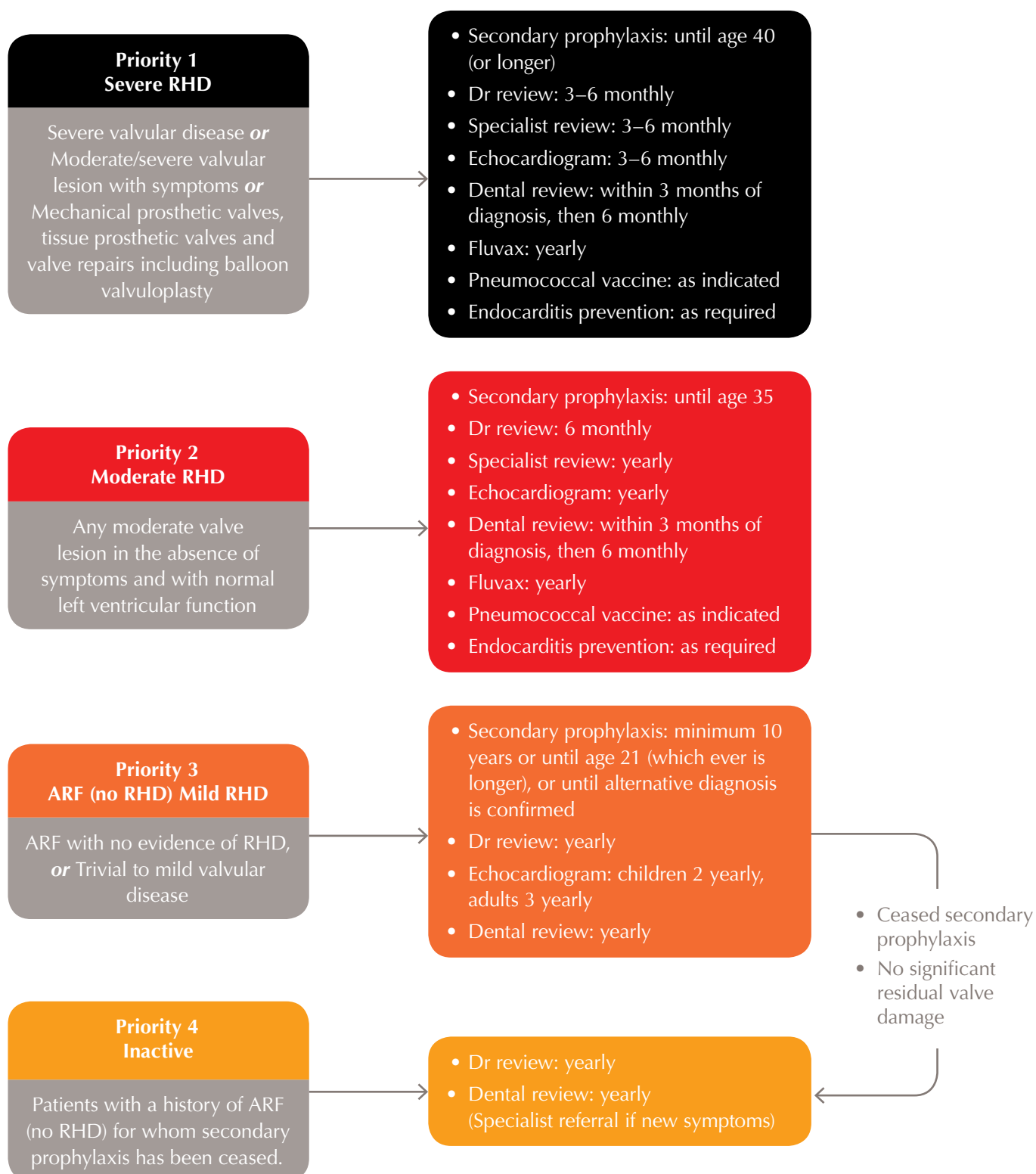
Classification	Criteria*	Review and management plan	Frequency†
Priority 1 (severe)‡	Severe valvular disease	Secondary prophylaxis (BPG)	3–4 weekly
		Doctor review	3–6 monthly
	or moderate/severe valvular lesion with symptoms	Cardiologist/physician/paediatrician review	3–6 monthly
		Influenza vaccination	Yearly
	or mechanical prosthetic valves, tissue prosthetic valves and valve repairs, including balloon valvuloplasty	Echocardiography	3–6 monthly
		Dental review	Within 3 months of diagnosis, then 6 monthly thereafter
		Pneumococcal vaccination	Refer to <i>Immunisation handbook</i>
		Endocarditis prophylaxis	As required Refer to <i>Therapeutic Guidelines: Antibiotics 2010</i>
Priority 2 (moderate)	Any moderate valve lesion in the absence of symptoms, and with normal left ventricular function	Secondary prophylaxis (BPG)	4-weekly
		Doctor review	6-monthly
		Influenza vaccination	Yearly
		ECG (optional)	Yearly
		Cardiologist/physician/paediatrician review	Yearly
		Echocardiography	Yearly
		Dental review	Within 3 months of diagnosis, then 6 monthly
		Pneumococcal vaccination	Refer to <i>Immunisation handbook</i>
		Endocarditis prophylaxis	As required Refer to <i>Therapeutic Guidelines: Antibiotics 2010</i>
Priority 3 (mild)	ARF with no evidence of RHD	Secondary prophylaxis (BPG)	4 weekly
		Doctor review	Yearly
	or trivial to mild valvular disease	Echocardiography	Children: 2 yearly‡ Adults: 2–3 yearly‡
		Dental review	Yearly

Classification	Criteria*	Review and management plan	Frequency†
Priority 4 (inactive)	Patients with a history of ARF (no RHD) for whom secondary prophylaxis has been ceased	Medical review	Yearly
		Dental review	Yearly
		Cardiologist/physician/paediatrician review	As referred with new symptoms
Additional considerations	Following valve surgery	Medical assessment ECG Chest radiograph Echocardiography Full blood count Urea, creatinine, electrolytes INR, if indicated	3–4 weeks' post-discharge
	Missed doses of BPG	Patient should be contacted if they have not presented within 3 days of due injection	
	Patient travelling to another community when injection due	Consideration should be given to bringing forward the date of injection to 2–3 weeks, or arrangements made with other service providers in advance	

* Serial echocardiographic assessments are required in the long-term management of RHD as an essential tool in determining the progress of cardiac damage and the optimal timing of surgery. Therefore, risk stratification should be based on clinical and echocardiographic findings (Grade D). †Review frequency should be determined according to individual needs and local capacity. Most critically, the frequency of review should become more frequent in the event of symptom onset, symptomatic deterioration or a change in clinical findings. ‡Any patient with severe valvular disease or moderate to severe valvular disease with symptoms should be referred for cardiological and surgical assessment as soon as possible. §In patients with no evidence of valvular disease on echocardiography, who have no documented ARF recurrences, good adherence to secondary prophylaxis and no cardiac murmurs on examination at follow up appointments, echocardiography may not be needed as frequently.

BPG, benzathine penicillin G; ECG, electrocardiogram; INR, international normalised ratio.

Figure 4.1 Recommended routine review and structured care planning



Dental care

Routine dental care and appropriate oral hygiene is critically important in patients with a history of ARF and/or RHD. All patients should receive education about oral hygiene, and should be referred promptly for dental assessment and treatment when required. This is especially important prior to valvular surgery, when all oral/dental pathology should be investigated and treated accordingly (Grade D).

Organisational approaches to secondary prevention

Rheumatic heart disease control programs

A coordinated control program is the most effective approach to mitigating the burden of RHD, largely as a result of improved BPG adherence, clinical follow up of people with RHD, including specialist review and echocardiography, and coordinating care across the continuum (level III-3).²⁷⁹ The primary aims of RHD control programs are summarised in Table 4.10.

Table 4.10 Primary aims of RHD control programs

- Identify and register known cases of ARF and RHD
- Improve uptake of and adherence to secondary prophylaxis
- Increase awareness of diagnosis and management among healthcare providers
- Improve clinical care and follow up in line with best practice
- Support education and health promotion for individuals, families and the community
- Promote primary prevention aimed at preventing initial episodes of ARF
- Use data to monitor patient outcomes and improve program strategies

RHD control programs aim to improve the delivery of secondary prophylaxis, the most cost-effective approach to RHD control.^{7, 125} This approach has been estimated to cost less than half that of tertiary services (including cardiac surgery), and less than one-seventh that of primary prophylaxis.²⁹³ The management of chronic RHD has been estimated to consume up to 70% of the total national ARF/RHD budget for New Zealand.²⁹⁴ In a recent review on RHD in the Pacific region, *Colquhoun et al*²⁹⁵ found that the cost of

tertiary-level surgical intervention for one patient is equivalent to the annual running costs for a national RHD control program in Pacific countries with small populations. There is little doubt that much of this expenditure could be prevented with targeted and coordinated secondary prevention programs.¹²⁵

Registers of people with RHD or a history of ARF are a key element of RHD control at an individual, community and national level.²⁹⁶

Register-based programs:

- improve case detection^{86, 280, 282, 297-299}
- increase adherence to secondary prophylaxis^{298, 299}
- reduce recurrences of ARF^{256, 298-302}
- decrease hospitalisations from ARF/RHD (level III).^{298, 299}

Register-based RHD control programs have been successful in New Zealand since the 1980s. By 1998, half of New Zealand's 24 health districts had ARF/RHD registers, covering over 94% of notified ARF cases.³⁰³ These programs were considered largely responsible for reducing ARF recurrence from 22% (of all ARF episodes) between 1972 and 1981 to only 6% between 1982 and 1992.²⁵⁶

Australia's first register-based RHD control program was established in 1997 in the Top End of the Northern Territory.³⁰⁴ In the first 2 years, there was a decline in the recurrence rate from 40% (of all ARF episodes) prior to commencement, to 28% in the first year, and 16% in the second year.³⁰⁵ Since 2002, recurrent episodes made up 12–40% of all notifications in the Northern Territory, with no reduction in trends over that period of time.⁹

The Central Australian ARF/RHD Control Program was established in 2000, and was immediately successful, with 96% of all ARF episodes notified to the program (compared to 24% previously), improvement of secondary prophylaxis adherence from 55% in 2000 to 68% in 2002, and a fall in the recurrence rate from 40% (of all ARF episodes) in 1995–2000 to 26% in 2001–2002.²⁸⁰ The Northern Territory programs have since amalgamated to form a state-wide program.

A number of locally-appropriate strategies have been employed to help improve the uptake of secondary prophylaxis in the Northern Territory, including the 'full moon strategy' in central Australia. Promoting BPG injection delivery to coincide with the full moon cycle led to a 10% increase in uptake around the full moon cycle over a 4-year period; however, the increased uptake was still well below therapeutic levels (57%).³⁰⁶

An RHD control program was established in Far North Queensland in 2006. The program's capacity to increase awareness of ARF, particularly among medical practitioners, resulted in fewer missed cases of ARF, increased notification of ARF and a significant decline in ARF recurrence.¹²

The Western Australia RHD program was established in 2009, and is currently based in Broome in the Kimberley region. Earlier patient audits undertaken in 2007 in the Kimberley, Pilbara and Goldfields regions identified almost 600 people known to have ARF or RHD. ARF notifications have increased; however, it is too early to comment on changes in secondary prophylaxis delivery or the quality of patient management.

It is recommended by the WHO that a coordinated approach be taken where there are substantial populations with ARF or RHD. The main components of a local and jurisdictional coordinated approach include:¹²⁵

- secondary prevention activities aimed at preventing the recurrence of ARF and severe RHD
- community health education activities
- training of healthcare providers
- epidemiological surveillance.

Primary prevention activities, aimed at preventing the first episode of ARF, should also be supported by the program. Specific elements are listed in Table 4.11 (Grade C).

Program implementation should be stepwise,³⁰⁷ starting in one or more defined areas to test whether the structure and processes are appropriate within the local context can be an important first step, with gradual extension of the program to regional and state-wide coverage. The program should aim to support existing healthcare services, and be integrated into the existing healthcare systems, particularly primary healthcare.

Table 4.11 Recommended elements of RHD control programs

- Commitment from national, regional and local services, particularly to ensure long-term funding and governance support
- An effective advisory committee that includes medical specialists, general practitioners, epidemiologists, nurses, public health practitioners, Aboriginal health service organisations and relevant community representatives
- A dedicated coordinating team
- An electronic patient register that contains data elements that support quality patient management, as well as any internal and external reporting requirements
- Prioritisation of primary and secondary antibiotic prophylaxis delivered within the framework of primary healthcare
- Planning and advocacy for a stable supply of BPG, and establish plans for sustainable secondary prophylaxis in the event of supply reductions
- Development of the ability to find new cases of ARF and RHD and to assess and monitor the burden of disease
- A commitment to partnerships between clinicians and public health services in order to support the needs of people with ARF/RHD and the community;
- Provision of education for health practitioners and health workers, and supported health education for the community, those with disease and their families
- Activities guided by locally relevant, evidence-based guidelines
- Legislation and/or regulations warranting the notification of ARF/RHD which is supported by public health surveillance activities at the state or territory level
- A priority system that ensures services are delivered to those at highest risk
- A mechanism for monitoring delivery of secondary prophylaxis and ongoing care
- Evaluation of patient management and program activities

Further, the targets for collation of epidemiological data can also be developed in a staged manner, first focusing on registry data, then prospective incidence data, through to cross-sectional RHD prevalence surveys on the local, regional and then jurisdictional level.

Ideally, the ARF/RHD register is linked to local registers and to a national reporting system. It may be a centralised dedicated database or part of a more comprehensive chronic disease register maintained by program staff, or a primary care patient management system that is overseen by program staff. Registers should maintain patient confidentiality, conform to privacy legislation and be established with the relevant institutional and/or individual approval.

A dedicated coordinator is critical to the success of the program. This person should have skills in data management, basic epidemiology and clinical medicine, or ready access to relevant expertise. To ensure that the program continues to function well despite staffing changes, activities must be integrated into the established health system.

In addition to reporting on ARF/RHD epidemiology and providing other information necessary to monitor the program, the program should be able to provide individual and community reports and recall lists for visiting specialists and new staff. Where possible, reports should include recommendations based on the program aims in Table 4.10.

National coordination unit for rheumatic heart disease

RHDAustralia was established as the national coordination unit in 2009 to support the control of RHD in Australia. The unit was established under the Australian Government's Rheumatic Fever Strategy.

RHDAustralia, as part of the Rheumatic Fever Strategy, supports efforts to address ARF and RHD by providing:

- national education, training and self-management resources for primary health care to assist with the detection and treatment of ARF and RHD
- a performance management system for current activities in the detection and management of acute rheumatic fever and rheumatic heart disease.

Public health approaches to acute rheumatic fever and rheumatic heart disease control

Surveillance

Passive surveillance of ARF usually depends on case identification from healthcare providers. Historically, this has underestimated the burden of disease, due to inaccuracies and incompleteness.³⁰⁸ For example, a 3-year study of ARF in Australian children was conducted by the Menzies School of Health Research in conjunction with the Australian Paediatric Surveillance Unit (APSU) from October 2007 to December 2010. The APSU notification mechanism relies on voluntary reporting from clinicians working in paediatrics and child health who are registered with the APSU. The voluntary nature of reporting, together with the lack of core data for some reported cases, resulted in an underestimate of the true incidence of ARF. (Noonan S. *unpublished data*)

In under resourced settings, the deficiencies of passive surveillance are exacerbated by the high turnover of hospital and primary care staff and lack of awareness of ARF/RHD by many healthcare providers.

Ideally, active surveillance should be used to augment passive surveillance (Grade D).³⁰⁹ This entails establishing mechanisms to identify new cases of ARF/RHD, and to update information about existing cases.

Where possible, these processes should be automated (e.g. with regular downloads of information regarding patients admitted to hospital with a diagnosis of ARF or RHD).

A diverse range of activities has been used for the active surveillance of ARF/RHD in the Northern Territory^{280, 282} and other jurisdictions, including hospital separation data, specialist and radiological reports; automated alerting of registered patients on presentation to hospital; review of patients with presenting complaints, possibly due to ARF; and community and staff education aimed at improving case identification.

When establishing surveillance systems for ARF/RHD control, a range of issues should be considered. These include:

- defining the target population and high-risk groups requiring surveillance
- establishing a process for information flow from a range of potential data sources (case reporting, data collection instruments, data transmission and handling)
- formulating the essential data elements to be collected
- ethical and privacy legislation requirements, including consent
- data management (e.g. the most appropriate format for storing the data)
- proposed process and timeliness of data analysis
- dissemination and targets for the feedback of results
- needs of healthcare providers for individual patient and epidemiological information
- continuing refinement and evaluation of the surveillance system.

When active surveillance is established, an initial apparent increase in the prevalence of RHD is expected, primarily due to the detection and recording of existing cases, rather than the appearance of new cases.^{280, 282, 284} Similarly, improved access to specialist care may also result in greater rates of valvular surgery in the initial years after commencing a program.

Key data elements of acute rheumatic fever and rheumatic heart disease registers

A proposed dataset for ARF and RHD registers in Australia has been developed by RHD Australia and is outlined in Appendix 2. Some RHD control programs may choose to have all of these data collected and reported from a centralised register, whereas others may choose to have a subset of data (e.g. recording of individual doses for secondary prophylaxis) entered only into the local community register.

Where communities do not enter each BPG dose into the central register, local health staff should have clear guidelines as to how to identify and manage patients overdue for secondary prophylaxis, and when to

notify the coordinator of these patients. It is suggested that coordinators be notified when patients are more than 2 months overdue for BPG, so that they and local health staff can institute strategies to improve adherence (e.g. developing individualised education strategies for patients and/or tracking patients if they have moved).

These communities should also provide regular updates to the central register on the number of BPG doses due to be delivered, and the number of doses actually delivered for each patient in the community. They are important in identifying communities with low overall adherence levels, so that their approach to delivery of secondary prophylaxis can be reviewed, if necessary.

Legislated notification of acute rheumatic fever and rheumatic heart disease

In New Zealand, following the establishment of ARF/RHD registries, ARF became a notifiable condition under a national surveillance and management framework in 1986.³⁰³ In Australia, ARF became notifiable in the Northern Territory in 1994, in Queensland in 1999 and in Western Australia in 2007. RHD is not notifiable anywhere in New Zealand or Australia.

ARF meets most criteria for notification of the Communicable Diseases Network of Australia (CDNA),³¹¹ and in 2010, the CDNA proposed to include ARF in the list of nationally-notifiable conditions; however, this has not yet been implemented. To implement this nationally, policy makers are faced with a number of considerations, including political and financial issues, increasing complexity of the notification system and the claims of other potentially-notifiable diseases.

RHD meets fewer of the CDNA criteria for notification than ARF, but there are good reasons for considering its candidacy. Almost half of Aboriginal and Torres Strait Islander people with RHD would not be identified by relying only on ARF notification. Furthermore, there is great potential for RHD notification to improve outcomes for people with RHD, because unlike for most notifiable diseases, there is a simple, cheap and proven intervention: secondary prophylaxis. However, it is unlikely that RHD will be included in the list of notifiable diseases in Australia in the near future.

Screening for rheumatic heart disease

The WHO recommends school-based screening for RHD as a tool for estimating the disease burden, and also for identifying patients in areas with a high prevalence of RHD.¹²⁵ The WHO Global Program on RHD undertook auscultatory screening of over one million children.²⁹⁹ In some regions, this was augmented by echocardiography to confirm the diagnosis of RHD, but there are not yet clear guidelines as to how the screening should be conducted.

Currently, it is recommended that RHD control programs should coordinate screening to detect previously-undiagnosed RHD in high-risk populations, wherever this is practical (Grade D). Although RHD prevalence is highest in adults,¹⁷⁵ they are difficult to screen. It is recommended that screening rather focuses on school-aged children (Grade D).

Recent studies suggest that auscultation is poorly sensitive and specific, and that echocardiographic screening may be the best method.^{312, 313} The availability of portable echocardiography, and the ability to perform a limited assessment of the mitral and aortic valve in only 5–10 min, make echocardiographic screening feasible. Where echocardiography is not available to review all children with murmurs, a highly-experienced auscultator could select all children with non-innocent murmurs for echocardiography (Grade D). Low school attendance rates for children of high-risk groups are an important barrier to the effectiveness of school-based screening programs. However, comprehensive community-based screening activities require substantial resources and high levels of health service and community involvement. If time and other resources allow, consideration should be given to conducting more intensive screening programs, in which children of all ages are reviewed, and attempts are also made to examine children who miss school-based screenings.

The more widespread use of echocardiography in RHD for screening purposes, but also for diagnosing RHD in individual patients, has led to uncertainty about the criteria on which a diagnosis of RHD should be made. As a result, the WHF has established evidence-based criteria for the diagnosis of RHD (see 'Echocardiographic criteria for RHD', p. 74).

Evaluating rheumatic heart disease control programs

Control programs for ARF/RHD should be evaluated in relation to criteria for routine care and key epidemiological objectives.²⁷⁹ These include measurement of individual and community adherence to secondary prophylaxis, indicators of satisfactory care specified in best-practice guidelines and rates of disease occurrence, recurrence and mortality.

Further consideration should be given to:

- assessing the delivery of specialist cardiology services
- availability and accessibility of echocardiography
- referral practices and structures
- transportation for patients
- support structures and appropriate follow up processes.

As has been highlighted throughout the developing world, the availability of and support for routine primary healthcare is essential in controlling ARF/RHD.

Indicators used to evaluate ARF/RHD control programs should be relevant, structured, measurable, routinely available and affordable. In particular, they should not overburden primary healthcare providers, and should lead to improved clinical results. A list of suggested indicators is provided in Appendix 3 (Grade D).



5. Diagnosis and management of rheumatic heart disease

Introduction

Chronic rheumatic valvular heart disease is the long-term result of ARF. It is a disease of poverty and disadvantage. In Australia, the burden of RHD is confined almost exclusively to Aboriginal and Torres Strait Islanders, many of whom live in remote areas of Western Australia, the Northern Territory, Queensland, South Australia and New South Wales.⁴² This continuing high burden of RHD contrasts with its virtual elimination among the non-Indigenous population.³¹⁴

Background and management principles

The implementation of guidelines for chronic RHD has major implications for the healthcare services of Aboriginal people and Torres Strait Islanders, especially in rural and remote regions. In addition to access to culturally-appropriate primary care services, best practice for RHD requires:

- secondary prevention with penicillin prophylaxis
- adequate monitoring of anticoagulation therapy in patients with AF and/or mechanical prosthetic valves
- access to oral healthcare
- access to echocardiography
- access to a specialist physician, paediatrician and/or cardiologist, preferably the same specialist, for regular follow up visits
- access to cardiothoracic and interventional cardiology services.

Secondary prevention with penicillin prophylaxis

The fundamental goal in long-term management of RHD is to prevent ARF recurrences, and therefore prevent progression, and in many cases, to allow for the resolution of heart disease. This can be achieved by the register-based delivery of secondary prophylaxis with long-acting intramuscular penicillin administered every 28 days.¹²⁵ Carditis following the first episode of ARF is often mild,^{145, 146} and on secondary prophylaxis, the majority with mild disease at diagnosis have no detectable disease within 5–10 years.^{146, 154, 157, 315} Those with moderate to severe disease at presentation, and those who suffer from recurrent attacks of ARF, have poorer long-term outcomes, with a greater need for cardiac surgical intervention,^{146, 147, 154} although many with severe heart disease at presentation can avoid cardiac surgery, providing there is a high level of compliance with secondary prophylaxis.¹⁵⁶

Monitoring anticoagulation therapy

At the time these guidelines were written, warfarin (a vitamin K antagonist) was the only oral anticoagulant approved for the management of patients with RHD (mechanical valve replacements or valvular AF). Currently, a new class of oral anticoagulants, which are direct thrombin or factor Xa inhibitors, are being evaluated in clinical trials.⁴⁴⁹ These drugs have the advantage of not requiring regular blood test monitoring. The first agent available is dabigatran, which is a thrombin inhibitor. It is currently restricted to use in non-valvular AF. In the near future, alternatives to warfarin may become available for patients with RHD.

The major limitation of warfarin is the requirement for monitoring of its therapeutic effect (INR) in the form of regular blood tests. Both underanticoagulation and overanticoagulation can lead to a life-threatening event. Dosing requirements are variable, as warfarin interacts with many commonly-used medications and food items. In addition, difficulties may arise because of language and cultural barriers, mobility of the population and remoteness from pathology services. For these reasons, achieving satisfactory anticoagulation is often a challenge.³¹⁷

Point-of-care INR testing is now available for patients remote from regular pathology services, and this should improve anticoagulation management.³¹⁸ Local RHD registers may also be useful in identifying patients requiring recall for INR monitoring. Despite the difficulties, many Aboriginal and Torres Strait Islander patients with mechanical valves or AF are successfully therapeutically anticoagulated.

Access to oral healthcare

It is important for all patients with RHD to have meticulous dental and oral hygiene to minimise the risk of infective endocarditis. While access to dentists has improved during the past decade, oral health remains suboptimal in many Aboriginal communities.³²¹ Mincham highlighted that in the Kimberley region, one of the greatest barriers to dental check-ups was failure of referral by physicians.^{320, 321} Oral health assessment is part of routine management of RHD. It is recommended that all patients with RHD (regardless of severity) undergo annual oral health review (Grade D). Current recommendations for antibiotics prophylaxis in endocarditis are detailed in Chapter 4.

Access to echocardiography

The current availability of portable echocardiography should mean that all RHD patients in Australia, regardless of location, have access to this diagnostic imaging tool.^{312, 323}

Many patients with RHD do not have a documented history of ARF, and it may be difficult to judge their symptomatic status by standard clinical criteria (e.g. New York Heart Association Functional Class (NYHA FC)) because of communication difficulties and cultural barriers. For example, many Aboriginal and Torres Strait Islander patients, especially those from remote communities, report few symptoms, even in the presence of advanced valvular disease (Grade D).

Therefore, obtaining objective evidence of rheumatic valvular disease becomes very important. All patients with murmurs suggestive of possible valve disease, or a history of ARF, require echocardiography (Grade

D). This will detect any valvular lesion and allow assessment of its severity and of LV systolic function. Serial echocardiography plays a crucial role in the diagnosis and follow up of rheumatic valve disease, allowing objective monitoring of any change in the severity of valve lesions, LV chamber size, LV function and any increase in pulmonary artery pressure. These objective echocardiographic data are essential in helping to determine the timing of any possible intervention.

Access to specialist physician, paediatrician and/or cardiologist

It is often difficult and expensive for Aboriginal and Torres Strait Islanders to travel to major centres, usually hospitals, for cardiac services. Although there has been an expansion in specialist outreach services, especially in rural and remote communities with programs, such as Medical Specialist Outreach Assistance and Indigenous Outreach Assistance programs,³²⁴ access to adult and paediatric specialist care is often inadequate in many rural and remote areas.

Access to cardiothoracic and interventional cardiology services

The surgical and interventional cardiology (e.g. balloon valvuloplasty) management of rheumatic valvular heart disease in Australia is challenging. Because the number of patients undergoing rheumatic valvular procedures is low, few cardiothoracic and cardiology services have the opportunity to obtain extensive experience in this field. Problems with medication adherence, especially long-term anticoagulation with warfarin, mean that mechanical valve replacement is not always the preferred surgical option. Long-term follow-up studies in Australia have shown a significantly poorer outcome for Aboriginal patients who have undergone valve surgery compared to non-Aboriginal patients.³²⁵⁻³²⁷ This is partly due to problems with medication adherence, difficulties in providing follow up specialist care to patients who may come from rural or remote communities, inadequate health literacy and cultural and language barriers.

Early engagement with cardiac surgery and interventional cardiology is essential in determining the appropriate timing of valve surgery and balloon valvuloplasty for patients with moderate or moderate to severe rheumatic valvular disease. In younger patients, especially children, it is highly desirable that the mitral and even the aortic valve be repaired, rather than these patients receiving prosthetic valves. Biological valves are a less desirable alternative if the valve cannot be repaired, as this increases the

likelihood of redo surgery later in life because of bioprosthetic degeneration. In general, mechanical valves should be reserved only for adult patients who are likely to be compliant with warfarin. This knowledge is best obtained by direct contact with healthcare providers who work in the patient's community.

Because the field of rheumatic valve surgery and balloon valvuloplasty is highly specialised, they should be carried out only in selected centres, so that the surgeons or interventional cardiologists can have the necessary volume of cases to develop and maintain technical expertise. Repairing rheumatic valves is technically more difficult than non-rheumatic valves, particularly MR and AR. There is increasing interest in conservative surgery for aortic valve disease, but this is an evolving field compared to the established mitral valve repair operation.

The overrepresentation of Aboriginal and Torres Strait Islanders requiring rheumatic valve surgery also emphasises the need to provide a surgical and interventional cardiology service that incorporates appropriate resources to accommodate families and Aboriginal liaison staff. Such resources are required to ensure discussions regarding the risks and implications of surgery and balloon valvuloplasty. This helps ensure that the patient, their family and the surgical service understand the affect of the agreed treatment on future child bearing, activity and the need for anticoagulation. Thus, a close partnership between the primary healthcare team, physician/cardiologist and cardiac surgeon is the prerequisite for the optimal care of patients with RHD.

The specific valvular lesions in RHD are discussed in subsequent sections. Many patients (e.g. 47% of RHD patients from the Top End of the Northern Territory)^{319, 328} will have involvement of two or more valves, most commonly mitral and aortic, although pathology in one is usually dominant. Mixed lesions (both stenotic and regurgitant) of the same valve are also common.³¹⁹ Currently, there are insufficient published data available to make any specific recommendation with regards to the management of multivalvular or mixed valve disease. Clinical symptoms and the nature of the predominant lesion should dictate the medical management and timing of cardiac intervention (Grade D).

Echocardiographic criteria for rheumatic heart disease

In 2011, under the auspice of the WHF, a standardised and evidence-based set of criteria for the echocardiographic diagnosis of RHD was developed (Tables 5.1–5.4).¹⁹⁸ This process was led by Australian and New Zealand investigators. The aims of the guidelines were:

- to make echocardiography reporting simple, reproducible and consistent worldwide, and hence, to facilitate echocardiographic screening for RHD, specifically in school-aged children
- to aid physicians with the diagnosis of RHD in those patients who do not have a history of ARF. The criteria were modified so that they are also applicable to adults (>20 years of age) patients (Table 5.1).

The WHF guidelines specify that echocardiograms should be interpreted in conjunction with the individual's clinical findings and risk or pretest probability of RHD. In individuals without a history of ARF, the diagnosis of RHD on echocardiography is a diagnosis of exclusion. Therefore, other aetiologies (congenital, acquired or degenerative) for valvular pathology must first be excluded by echocardiography and by the clinical context.

The WHF recommends two echocardiographic categories of RHD in individuals ≤20 years of age: 'definite RHD' and 'borderline RHD', based on evidence derived from numerous studies (level III-2–IV, Grade C).¹⁹⁸ The borderline RHD category was established to improve the sensitivity of the test for individuals from regions with a high prevalence of RHD (i.e. high-risk populations), and who, due to their young age, may not have had sufficient time to develop the full echocardiographic manifestations of RHD.^{145, 186} The borderline category is not applicable to patients who are considered to be at low risk of RHD, and therefore, those with a low pretest probability (Grade D). In individuals who are aged over 20 years, minor age-related or degenerative changes^{336–338} may overlap with what is defined as borderline RHD on echocardiography. Hence, the use of the borderline RHD category is not advised in adults beyond 20 years of age (level 4, Grade C).

Criteria for pathological regurgitation and morphological features of RHD are detailed in Tables 5.2 and 5.3. Trivial regurgitation of the mitral valve, and even of the aortic (that does not meet all four criteria for pathological regurgitation), is common,^{192, 195, 203, 339} and should be considered normal or physiological (level III-2, Grade C) (Tables 5.1 and 5.2). The same can be said for isolated morphological changes, such as valvular thickening, that occurs without pathological stenosis or regurgitation (level III-3, Grade C).³⁴⁰ Echocardiographic findings that are considered to be part of normal variation are listed in Table 5.1. Echocardiography machine settings that will allow objective measurements are detailed in Table 5.4.

Table 5.1 WHF criteria for echocardiographic diagnosis of RHD

1. Echocardiographic criteria for individuals ≤20 years of age
Definite RHD (either A, B, C or D):
(A) Pathological MR and at least two morphological features of RHD of the mitral valve
(B) MS mean gradient ≥4 mmHg (note: congenital mitral valve anomalies must be excluded)
(C) Pathological AR and at least two morphological features of RHD of the aortic valve (note: bicuspid aortic valve and dilated aortic root must be excluded)
(D) Borderline disease of both the aortic and mitral valve [†]
Borderline RHD (either A, B or C):
(A) At least two morphological features of RHD of the mitral valve without pathological MR or MS
(B) Pathological MR
(C) Pathological AR
Normal echocardiographic findings (all of A, B, C and D):
(A) MR that does not meet all four Doppler criteria (physiological MR)
(B) AR that does not meet all four Doppler criteria (physiological AR)
(C) An isolated morphological feature of RHD of the mitral valve (e.g. valvular thickening), without any associated pathological stenosis or regurgitation
(D) Morphological feature of RHD of the aortic valve (e.g. valvular thickening), without any associated pathological stenosis or regurgitation
2. Echocardiographic criteria for individuals >20 years of age
Definite RHD (either A, B, C or D):
(A) Pathological MR and at least two morphological features of RHD of the mitral valve
(B) MS mean gradient ≥4 mmHg (note: congenital mitral valve anomalies must be excluded)
(C) Pathological AR and at least two morphological features of RHD of the aortic valve in individuals <35 years of age only (note: hypertension, bicuspid aortic valve and dilated aortic root must be excluded)
(D) Pathological AR and at least two morphological features of RHD of the mitral valve

[†] Combined AR and MR in high-prevalence regions and in the absence of congenital heart disease is regarded as rheumatic.

AR, aortic regurgitation; MR, mitral regurgitation; MS, mitral stenosis.

Table 5.2 Criteria for pathological regurgitation

Pathological mitral regurgitation
(All four Doppler criteria must be met)
<ul style="list-style-type: none"> • Seen in two views • In at least one view, jet length 2 cm[†] • Peak velocity ≥3 m/s • Pan-systolic jet in at least one envelope
Pathological aortic regurgitation
(All four Doppler criteria must be met)
<ul style="list-style-type: none"> • Seen in two views • In at least one view, jet length ≥1 cm[†] • Peak velocity ≥3 m/s • Pan-diastolic jet in at least one envelope

[†] A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant colour (blue or red) on unmagnified images.

Table 5.3 Morphological features of RHD

Mitral valve
AMVL thickening ≥3 mm (age specific) [†]
Chordal thickening
Restricted leaflet motion [‡]
Excessive leaflet tip motion during systole [§]
Aortic valve
Irregular or focal thickening [¶]
Coaptation defect
Restricted leaflet motion
Prolapse

[†] Anterior mitral valve leaflet (AMVL) thickness should be measured during diastole at full excursion. Measurement should be taken at the thickest portion of the leaflet, including focal thickening, beading, and nodularity. Measurement should be performed on a frame with maximal separation of chordae from the leaflet tissue. Valve thickness can only be assessed if the images were acquired at optimal gain settings, without harmonics and with a frequency ≥2 MHz. Abnormal thickening of the AMVL is age specific and defined as follows: ≥3 mm for individuals ≤20 years of age; ≥4 mm for individuals 21–40 years of age; ≥5 mm for individuals >40 years of age.

[‡] Restricted leaflet motion of either the anterior or the posterior mitral valve leaflet is usually the result of chordal shortening or fusion, commissural fusion or leaflet thickening.

[§] Excessive leaflet tip motion is the result of elongation of the primary chords, and is defined as displacement of an involved leaflet's tip or edge towards the left atrium resulting in abnormal coaptation and regurgitation. Excessive leaflet tip motion does not need to meet the standard echocardiographic definition of mitral valve prolapse disease, as that refers to a different disease process. This feature applies to only those <35 years of age. In the presence of a flail mitral valve leaflet in young patients (<20 years of age), this single morphological feature is sufficient to meet the morphological criteria for RHD (i.e. where the criteria state 'at least two morphological features of RHD of the mitral valve', a flail leaflet in a person <20 years of age is sufficient).

[¶] In the parasternal short axis view, the right and non-coronary aortic cusp closure line often appears echogenic (thickened) in healthy individuals, and this phenotype should be considered as normal.

Table 5.4 Echocardiography machine settings

- Nyquist limits for colour Doppler should be set on maximum to avoid overestimation of jet length
- Images for the assessment of valvular and chordal thickness should be acquired, with harmonics turned off and probes with variable frequency set on ≥ 2 MHz. Low-frequency settings and harmonics exaggerate valve and chordal thickness
- The room should be as dark as possible for echocardiography, as it impacts on gain settings. Gain settings should be adjusted to achieve optimal resolution. Images acquired with an overgained setting will not be suitable for objective valve thickness measurements
- All other settings (including depth, sector size and focus) should also be optimized to achieve maximal frame rate and resolution

Mitral regurgitation

MR is the most common valvular lesion in RHD,^{335, 346} and is particularly frequent in young patients who have not yet developed scarred and stenotic valves from persistent or recurrent valvulitis.¹⁵¹ In Aboriginal patients with RHD in the Northern Territory, 40% of the overall patient cohort, and 90% of children aged under 10 years, had pure MR.³²⁸

Natural history

The natural history of isolated rheumatic MR was documented in the prepenicillin and pre-echocardiography era by Bland and Duckett Jones.³⁴⁷ They observed 87 ARF patients with clinical signs of isolated MR for 20 years. They found that in one-third of their patients, MR resolved; in one-third, it persisted; and in one-third, it progressed to severe disease, MS or resulted in death. In the penicillin era, Tompkins *et al* reported that 70% of their patients with MR had no clinical evidence of heart disease at 9 years after initial diagnosis³¹⁵. This clinical resolution of MR in two-thirds of patients on secondary prophylaxis within 5–10 years of diagnosis is also supported by the findings of Kassem and Lue (level IV).^{154, 260} The progression of MR or RHD and the need for subsequent intervention is related to the severity of disease at diagnosis and the presence of ARF recurrences (level III-2).^{147, 151, 154, 348}

In chronic MR, volume overload of the left ventricle and left atrium occurs. Left ventricle and left atrial chamber size increases in response to significant volumes of regurgitant mitral blood flow. LV systolic function may remain within normal limits for many years, despite the presence of severe MR. Eventually, this degree of volume overload results in a progressive decline in systolic contractile function.³⁴⁹

In MR, LV outflow resistance (afterload) is decreased by the ejection into the low-pressure left atrium, so that the LV function may even appear to be normal or low normal when myocardial contractility is actually impaired. Therefore, LV dysfunction is less likely to be reversible following mitral valve surgery than it is with aortic valve surgery for AR. The development of significant pulmonary vascular disease and pulmonary hypertension is much less common in MR than in MS.

Symptoms

Patients with mild to moderate MR may remain asymptomatic for many years. Patients with moderate to severe MR may also be asymptomatic or only mildly symptomatic. Initial symptoms include dyspnoea on exertion, fatigue and weakness,³⁵⁰ and these may progress slowly over time. Patients may become symptomatic if they develop AF, particularly with a rapid ventricular rate. Worsening symptoms may also result from a recurrence of ARF infective endocarditis or chordal rupture, all of which can cause an acute worsening in the severity of regurgitation.

Examination

In patients with mild to moderate MR, the LV apex will not be displaced, and there will be a mid- or pan-systolic murmur heard best at the apex, which may radiate laterally or medially, depending on the direction of the regurgitant jet.³⁵⁰ Patients with moderate or more severe MR will have an apex beat displaced to the anterior or mid-axillary line, and a loud pan-systolic murmur maximal at the apex. There may be an associated diastolic murmur of MS, or a mid-diastolic murmur from increased transmitral flow.

Electrocardiography/chest X-ray

ECG findings are not specific for RHD, but may demonstrate left atrial or LV enlargement and ventricular strain. In more severe degrees of MR, especially in older patients, AF may be present. Chest X-ray may show an enlarged left ventricle and radiological signs of pulmonary congestion in more advanced cases.

Echocardiography

The 2DE images of the rheumatic mitral valve are quite characteristic, and can help confirm a diagnosis of RHD, even without previous documentation of ARF in patients from high-risk populations. Under the auspice of the WHF, international consensus was reached on what constitutes the minimal echocardiographic criteria for RHD in those without a documented history of ARF, and this is detailed in 'Echocardiographic criteria for RHD'.¹⁹⁸

The main echocardiographic feature of pure MR in young people is overriding or prolapse of the anterior (less commonly of the posterior) mitral valve leaflet, due to elongation of chordae leading to a typically posteriorly-directed jet.^{156, 186, 187} In more severe cases, chordal rupture can lead to flail leaflet.¹⁸⁷ Experienced echocardiographers can differentiate degenerative mitral valve prolapse from that of rheumatic process.^{187, 341, 393} Dilation of the posterior mitral annulus, although not specific to RHD, is also a common finding.^{156, 187}

Valvular thickening, chordal thickening and tethering of either or both leaflets can be present, even in mild disease, and is the predominant mechanism of MR in the adult population.³²⁹ The combination of valvular thickening and the restricted leaflet motion gives rise to the characteristic 'elbow' (or 'dog leg') appearance of the anterior mitral leaflet. This abnormality is especially common if there is a degree of associated MS. Leaflet and annular calcification tends to be a late development, and is unusual in young patients.

Continuous-wave and colour flow mapping in the left atrium allows a semiquantitative estimate of the severity of the mitral regurgitant jet. This is done by grading the area of the regurgitant jet in relation to the area of the left atrium, and by examining the spectral intensity of the jet by continuous Doppler.³⁵² Milder degrees of regurgitation may be missed, unless 'sweeping' scans of the left atrium and mitral valve from parasternal and apical windows are used. Physiological (trivial) regurgitation can easily be distinguished from pathological MR.

Quantitative grading of MR using Doppler echocardiography to calculate effective regurgitant orifice area and regurgitant fraction has been proposed as a more accurate method to assess MR severity.³⁵¹ However, this measurement is time consuming, and technically demanding for busy outpatient settings.

An accurate measurement of LV end-systolic dimension (LVESD), end-diastolic dimensions (LVEDD) and systolic function by M mode must be obtained, as current guidelines for timing of surgery are based on M-mode measurements.²⁶⁵ However, the assessment of both cardiac size and cardiac function is more accurate using 2DE (Simpson's or area-length methods). Generally, enlargement of the left ventricle or left atrium indicates at least moderate MR. In children, cardiac measurements should be indexed and expressed as Z-scores (or standard deviations). Normal cardiac structures are considered to be between -2 and +2. Z-score calculators can be found at <http://parameterz.blogspot.com/2008/09/z-scores-of-cardiac-structures.html>.

Due to higher-quality imaging, 2D and 3D transoesophageal echocardiography (TOE) provides more optimal evaluation of mitral valve morphology, and is commonly used preoperatively in adults to help assess suitability for valve repair, and intra-operatively in children and adults to assess the adequacy of surgical repair. It is also useful in patients with poor image quality with transthoracic echocardiography, such as obese patients. However, TOE is usually only available in urban or large regional centres.³⁵³

If secondary tricuspid regurgitation is present, the PAS pressure can be estimated by measuring the peak velocity across the tricuspid valve. This can be converted into a pressure gradient using the Bernoulli equation ($\text{gradient} = 4 \times \text{velocity}^2$). By adding an estimate of right atrial pressure to the pressure gradient, right ventricle systolic pressure can then be calculated. In the absence of pulmonary valve disease, right ventricle (RV) systolic pressure is the same as PAS pressure.

Cardiac catheterisation

Cardiac catheterisation is only necessary when there is a need to exclude coronary artery disease. In Aboriginal and Torres Strait Islanders, this may need to be considered in patients aged more than 25–30 years, because of the premature onset of coronary artery disease in this population.

Medical management

Vasodilator drug therapy (e.g. dihydropyridines, ACE inhibitors) has been suggested as potentially beneficial for volume-overloaded ventricles by decreasing the work of the overloaded left ventricle, potentially minimising myocardial damage and deferring the need for surgery. In contrast to AR, there are limited data available on the efficacy of chronic vasodilator therapy for patients with MR.³⁴⁶

The absence of increased afterload in MR (instead, there is a low resistance leak into the left atrium) suggests that vasodilator therapy is unlikely to be beneficial in improving outcome.³⁵⁴ Therefore, this drug therapy is not recommended in the medical management of MR, unless there is associated heart failure, LV dysfunction or hypertension (level IV, Grade C).

Medical therapy for complications, such as atrial fibrillation, is described in the 'Mitral stenosis' section.

In asymptomatic or mildly-symptomatic patients with moderate or more severe MR, echocardiography should be performed at least every 6–12 months (Grade D). The measurement of LV dimensions, assessment of systolic function, Doppler assessment of the degree of regurgitation and estimation of PAS pressure are essential with every study. Comparison with previous studies is an important part of the process.

Surgical management

Indications for surgery

Patients who are symptomatic, with moderate to severe MR, should be automatically referred for surgical management (level III-2, Grade C) (Figure 5.1).^{265, 346} Patients who develop very enlarged hearts (adults LVESD ≥ 40 mm; a critical LV end-systolic dimension has not been identified in children) or impaired systolic function (EF $< 60\%$) have an increased surgical risk, less likelihood of restoring normal systolic

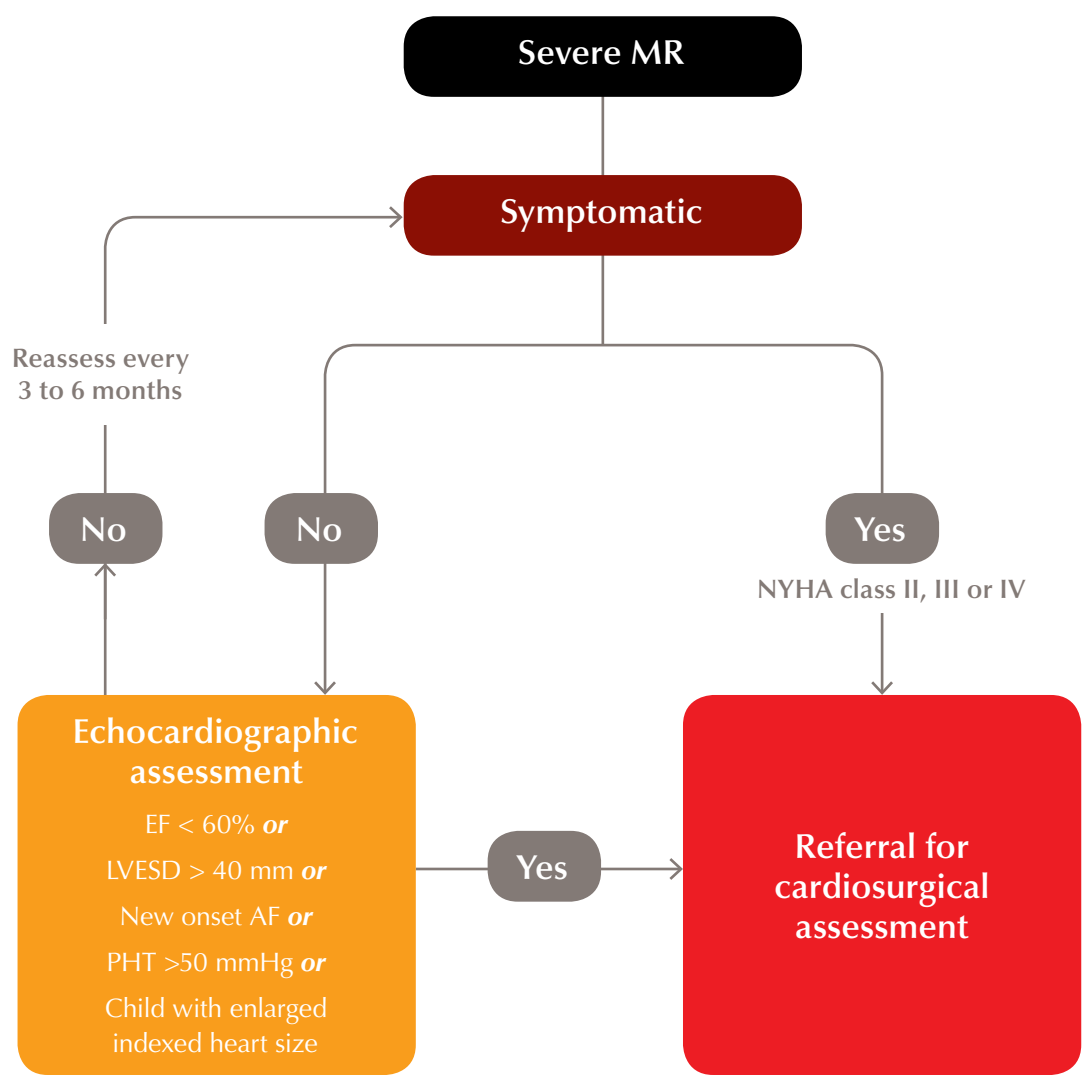
function and increased risk of late heart failure and death (level III-2).³⁵⁵⁻³⁵⁷ This also applies to those with significant pulmonary hypertension (> 50 mmHg)³⁵⁶ and preoperative AF (level III-2).³⁵⁸⁻³⁶⁰ In addition, the presence of AF for more than 1 year is a predictor of persistence of AF after successful valve surgery.²⁶⁵ Therefore, it is recommended that in the setting of severe chronic MR, patients should be recommended for surgery once those parameters are approached, rather than reached, regardless of symptomatic status (level III-2, Grade C) (Table 5.5), especially in children and young people.

The recommended guidelines in Table 5.5 should be applied with a degree of flexibility. For example, patients with severe MR and a favourable anatomy, who do not meet the above criteria, should be considered for early surgery in centres with low perioperative mortality and a policy of mitral valve repair. However, in patients in whom repair is unlikely to be successful, and compliance with anticoagulation is likely to be problematic, it may be appropriate to delay surgery until a definitive indication is met.

As indications for surgery in asymptomatic patients may not be always clear, it is important that physicians caring for patients with asymptomatic moderate/severe MR consult cardiac surgeons early, so that appropriate care plans can be organised, taking into consideration the clinical and echocardiographic findings and the patient's individual circumstance.

Patients with MR and associated MS, who have severely fibrotic, calcified valves, usually require mitral valve replacement. Because of the long-term morbidity accompanying prosthetic valve replacement in many Aboriginal people and Torres Strait Islanders, and the frequent requirement for anticoagulation, it is often preferable to wait until the patient is more symptomatic, despite medical therapy (NYHA FC II–III), provided that LV systolic function is preserved (Table 5.5).

Figure 5.1 Timing of surgery for severe mitral regurgitation



AR, atrial fibrillation; EF, ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; NYHA, New York Heart Association; PHT, pulmonary hypertension.

Choice of operation

All patients need a careful preoperative assessment of the likelihood of adherence to anticoagulation therapy and monitoring before a decision regarding the type of operation is made. Poor adherence with anticoagulation is associated with less favourable long-term outcomes, especially after mechanical valve replacement. Other important factors influencing choice of operation are age, gender, presence or absence of AF, adherence to other medications and social circumstance.

The operation of choice for dominant or pure rheumatic MR is mitral valve repair, rather than replacement (level II, Grade B).³⁶¹⁻³⁶³ mitral valve repair has a lower operative risk, and provides better preservation of LV systolic function, and a better late clinical outcome than mitral valve replacement.^{354, 364} In patients who are in sinus rhythm, it avoids the need for long-term anticoagulation with warfarin. Stable, reliable anticoagulation requires a high level of engagement with the health service. It is often difficult to achieve this in Aboriginal and Torres Strait Islander patients.^{316, 320} Furthermore, warfarin is not desirable in women of child-bearing age, and young, physically-active men. Valve repair avoids the risk of many of the complications of prosthetic valves, including thromboembolic and bleeding events, infection and structural deterioration of bioprosthetic valves in younger patients.³⁶⁵

Although there have been no randomised, comparative trials, more recent surgical experience has shown that the long-term results of mitral valve repair are superior to those of mitral valve replacement in RHD.³⁶³ In a report from Toronto, the 10-year survival rate for mitral valve repair was 88%, compared with 70% for bioprostheses and 73% for mechanical prostheses.³⁶⁶ Freedom from cardiac death was statistically significant, even after correction for baseline differences between patient groups, although they did not correct for baseline cardiac function and dimensions (established risk factors for late mortality). The 10-year freedom from thromboembolic events was 93% for valve repair, 93% for bioprostheses and 72% for mechanical valve replacement.

Valve repair for rheumatic mitral valve regurgitation is more technically demanding than repair of degenerative mitral valve, and the long-term results are not as good.^{367, 368} Nevertheless, very acceptable results have been obtained in surgical centres that perform these operations regularly.^{329, 369} In a French series of 951 patients, who had repair for dominant rheumatic MR, the in-hospital mortality was 2%, and the actuarial survival was 89% at 10 years, and 82% at 20 years. Freedom from reoperation was 82% at 10

years, and 55% at 20 years.³²⁹ Whether these good results for mitral valve repair can be extrapolated to Aboriginal and Torres Strait Islanders is uncertain. Long-term results depend on the population studied, and therefore, will be affected by the public health and general social and geographical environments in which people live.

For example, in a mitral valve surgical series from Baragwanath Hospital in Soweto, South Africa, of predominantly young rheumatic patients, one-third of whom had active carditis, the long-term results of repair were less satisfactory. The freedom-from-valve failure was 66% after 5 years, and 27% of patients required reoperation during that period.^{330, 393} These authors concluded that active carditis at the time of surgery was the major predictor of late valve failure, and could not be recommended unless delay was clinically not possible.

The published experience with mitral valve repair in Australia is quite limited.^{325, 326} In a recent report of an Aboriginal cohort of 91 patients undergoing mitral valve surgery for RHD, 45 underwent mitral valve repair. The mean age of this group was 23 years. There was no operative mortality, but six patients (13.3%) required reoperation (usually mitral valve replacement) during the follow up period. Freedom from reoperation was 100% at 3 years, and 86% at 8 years after repair.

Strict adherence to penicillin prophylaxis post-repair is vital to prevent valve failure, due to the recurrence of ARF. Regular echocardiographic studies are required in all patients post-repair to monitor the degree of any residual regurgitation, and to detect any increase in its severity that might suggest valve failure.

The late reoperation rate is higher with mitral valve repair than replacement, but in experienced centres, reoperation can be carried out at low risk.³⁶⁸ It is also higher in the Aboriginal and Torres Strait Islander populations than in other populations.^{325, 326}

Reoperation may require mitral valve replacement, but initial valve repair may delay the need for long-term anticoagulation for many years. If the mitral valve is not suitable for repair, the option is valve replacement with either mechanical valve prosthesis or a bioprosthetic valve.³⁵⁵ The advantage of mechanical valve prostheses is their long-term durability with extremely low rates of failure. The major disadvantage is the need for long-term anticoagulation with warfarin. Patients with tilting disc or bileaflet valves in the mitral position require a slightly higher target INR of 3 (range: 2.5–3.5), compared to those in the aortic position (2.5).⁴⁵⁰

The pros and cons of mechanical versus bioprosthetic valves are discussed under the 'Choice of operation' section.^{371, 451} However, the major disadvantage of bioprosthetic valves is their limited durability, especially in younger patients. It has been clearly documented that structural valve degeneration occurs earlier, and is more common with mitral bioprosthetic valves than aortic bioprosthetic valves in younger

patients.³⁷¹ Nevertheless, a woman of child-bearing years, who is in sinus rhythm, but is not suitable for repair, may need to be considered for bioprosthetic valve replacement in order to avoid the hazards of anticoagulation during pregnancy. After bioprosthetic valve replacement, most patients in sinus rhythm can be managed without long-term anticoagulation.⁴⁵⁰

Table 5.5 Key points in the management of rheumatic mitral regurgitation

Symptoms	May be asymptomatic for many years Exertional dyspnoea and fatigue
Examination	Pan-systolic murmur at LV apex
Echocardiography	Overriding or prolapse of AMVL Thickened 'dog leg' AMVL, especially if associated with mitral stenosis Retrograde colour (mosaic) regurgitant jet into left atrium, often posteriorly directed Severity graded by area of colour regurgitant jet in left atrium LV chamber dimensions enlarged if moderate or greater MR Assess LV systolic function
Cardiac catheterisation	Only to exclude coronary artery disease
Medical management	In chronic, stable MR (regardless of severity), there is no role for vasodilators, diuretics or ACE inhibitors unless clinical heart failure is present
Indications for surgery	Moderate / severe MR: 1. NYHA FC II-IV symptoms OR 2. Impaired LV systolic function EF <60% OR 3. LVESD \geq 40 mm in adults or enlarged LVSED Z-score in children OR 4. PAS hypertension >50 mmHg OR 5. New onset atrial fibrillation
Choice of operation	Mitral valve repair operation of choice Mitral valve replacement with biological or mechanical prosthesis Avoid mechanical prostheses, if concerns about warfarin adherence or future pregnancy

ACE, angiotensin-converting enzyme; AMVL, anterior mitral valve leaflet; EF, ejection fraction; LV, left ventricle; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NYHA FC, New York Heart Association Functional Class; PAS, pulmonary artery systolic.

Mitral stenosis

Natural history

The natural history of MS is variable. In some populations, there is often a latent period of 20–40 years between episodes of ARF and presentation with MS.^{370, 452} In the Aboriginal and Torres Strait Islander populations, MS progresses more rapidly, and patients become symptomatic at a younger age, although this is rare below 10 years of age. Previously-clinically silent MS can become symptomatic when cardiac output and blood volume increase, as occurs in pregnancy. Approximately 30% of Aboriginal RHD patients in the Northern Territory aged 10–19 years have MS, and the mean age of all those with MS is 33 years.³²⁸ The majority do not recall having ARF. In India, this trend is more marked, where MS is not uncommon in children aged less than 10 years. This rapid progression may be due to undetected recurrences of ARF. With progression of MS, secondary pulmonary hypertension results from the elevated pressures in the pulmonary vascular bed, leading to RV hypertension, hypertrophy and dilatation and tricuspid regurgitation.

Once symptomatic MS develops, the long-term prognosis without cardiac intervention is poor, with 10-year survival ranging from 34% to 61%.^{370, 372, 373, 452} Those with AF, pulmonary oedema or right heart failure have an even worse prognosis.³⁷⁰

Symptoms

Progressive obstruction to LV inflow develops, leading to a diastolic gradient between the left atrium and ventricle. This gradient is accentuated by faster heart rates, for example, during exercise or in the presence of AF with rapid ventricular rates. Patients usually do not develop symptoms until the mitral valve orifice decreases to $<2 \text{ cm}^2$.

The initial symptom is exertional dyspnoea, which worsens slowly over time, with progressive fibrosis and narrowing of the mitral valve orifice. Symptoms of heart failure (orthopnoea, paroxysmal dyspnoea and occasionally haemoptysis) develop as the mitral valve orifice decreases to $<1\text{--}1.5 \text{ cm}^2$.³⁷⁴ Less commonly, patients may present with signs of systemic embolism from the left atrium, such as a stroke or peripheral arterial occlusion. The occurrence of embolism does not correlate with the severity of MS,^{375, 376} but is related to the presence of AF.

Physical examination

It may be possible to palpate an RV heave in the left parasternal region due to RV systolic hypertension.

The murmur of MS is a low-pitched, diastolic rumble heard best at the apex, with the patient in the left lateral position. It may be difficult to hear, especially if the ventricular rate is rapid. An inexperienced healthcare provider may miss this murmur in the resting patient. It can be accentuated by increasing the heart rate through mild exercise. The duration of the murmur correlates with the severity of MS. If the patient is in sinus rhythm, there will be presystolic accentuation, but this is lost once AF occurs.

Electrocardiography/chest X-ray

ECG is not particularly helpful in diagnosing MS, although they may show evidence of left atrial enlargement. However, an ECG shows whether the heart is in sinus rhythm or AF.

A chest X-ray may show left atrial enlargement and redistribution of pulmonary vascular flow to the upper lung fields. Calcification of the mitral valve apparatus may be visible in lateral projections. If the patient has developed heart failure, pulmonary congestion will be visible on the chest X-ray.

Echocardiography

Doppler echocardiography is used to accurately characterise the severity of MS and associated valve lesions, and assess LV function and left atrial size.³⁷⁴ 2DE can demonstrate the thickened, restricted anterior and posterior mitral valve leaflets, the doming motion of the anterior leaflet (elbow or dog leg deformity), involvement of subvalvular apparatus and any associated valvular calcification.

Estimation of the severity of MS requires a continuous-wave Doppler study. When the flow is sampled across the stenotic mitral valve, the mean velocity can be measured, and mean gradient calculated. The mitral orifice area can be calculated using either the pressure half-time method based on the slope of the mitral inflow velocity, or by direct planimetry of the stenotic orifice in the short axis, if the image quality is good. The extent of any associated MR can be assessed by examining the area of regurgitant colour flow within the left atrium during systole. LV systolic function is usually preserved, although in some cases, it may be reduced, particularly if the patient has developed chronic AF with an inadequately-controlled ventricular rate. As mentioned in the section on MR, 3DE is being increasingly used to better evaluate the severity of the MS and its suitability for balloon valvuloplasty.⁴⁵⁹

Cardiac catheterisation

Doppler echocardiography has replaced cardiac catheterisation as the gold standard for determining the severity of MS.³⁷⁴ Cardiac catheterisation is only required to identify associated coronary artery disease. Therefore, younger patients may be referred for interventional therapy without diagnostic cardiac catheterisation.

Medical management

Patients who develop congestive heart failure, with elevated venous pressure and/or pulmonary congestion, respond to oral or intravenous diuretic therapy (e.g. frusemide). In general, the treatment of symptomatic MS is interventional therapy (Table 5.6).

Atrial fibrillation

The most common complication of MS is AF.³⁷⁵ Initially, this may be paroxysmal, but eventually it becomes chronic, as MS and left atrial dilatation progress. Approximately 40% of patients with MS will exhibit chronic AF, and the incidence increases with age and left atrial size. AF may lead to systemic embolism from left atrial thrombi, which form predominantly in the left atrial appendage (the area of lowest velocity). Patients with MS and chronic or paroxysmal AF should receive long-term prophylactic anticoagulation with warfarin (level III-3, Grade C).^{375, 376} However, left atrial thrombus can occur in MS, even when sinus rhythm is present, due to left atrial dilatation, low blood velocity and disorganised blood flow. Therefore, prophylactic anticoagulation should also be considered for patients with MS, a large left atrium and sinus rhythm (Grade D).

Patients who develop AF with a rapid ventricular rate may develop heart failure, including pulmonary oedema, and require intravenous diuretic therapy. The ventricular rate in AF is best slowed with beta-blockers, digoxin, rate-slowing calcium channel blockers (e.g. diltiazem) or combinations of these medications. The long-term use of anti-arrhythmics, such as amiodarone or sotalol, should be avoided for rate or rhythm control of AF in younger patients, because of long-term adverse effects, including pulmonary, thyroid (amiodarone) and pro-arrhythmia (sotalol).³⁷⁷

When new-onset AF is symptomatic, consideration should be given to direct current cardioversion to restore sinus rhythm (Grade B). Anticoagulation is indicated prior to this procedure, and long term in those with valvular AF.^{377, 450} Patients can be anticoagulated initially with intravenous or LMWH to minimise the time required before performing cardioversion. The exclusion of atrial thrombus

by transoesophageal echocardiography allows cardioversion to be performed within a few days, rather than after the previously-recommended 3 weeks of therapeutic anticoagulation.³⁷⁸

If sinus rhythm is achieved, the most effective medications for maintenance are the class III agents, sotalol or amiodarone. However, these agents are not usually recommended in younger patients, as mentioned above. Anti-arrhythmic class I agents, such as quinidine, procainamide or disopyramide, are also not recommended due to their pro-arrhythmic potential.

Percutaneous balloon mitral valvuloplasty

The treatment of choice for dominant or pure MS is percutaneous balloon mitral valvuloplasty (PBMV) (level III, Grade B).³⁷⁹⁻³⁸¹ The balloon catheter is inserted via the femoral vein and placed in the left atrium, using the transeptal technique. The balloon is positioned across the stenotic mitral valve and inflated, thereby separating the stenotic leaflets along the commissures.

The short- and medium-term results are comparable to surgical valvuloplasty.^{382, 383} However, PBMV usually requires only one night in hospital, is considerably cheaper and has less associated morbidity than mitral valve surgery.³⁷⁴ Mitral orifice area usually increases to 1.5–2 cm² or more following balloon valvuloplasty, with corresponding reduction in left atrial pressure and increase in cardiac output. Symptoms of pulmonary congestion are relieved. Long-term results have been good, with 65% of patients being free of restenosis 10 years after the procedure.^{380, 381, 384, 385} Repeat valvuloplasty can be performed, if restenosis leads to recurrence of symptoms, especially if the predominant mechanism of restenosis is commissural fusion.

The most serious complication of the procedure is tearing of the mitral valve leaflets and/or subvalvular apparatus, causing severe MR. Of 528 patients with rheumatic MS (mean age: 56.1 years) treated at the Prince of Wales Hospital in Sydney, Australia, (RM McCredie, pers. comm., 2005), only 4% developed MR, requiring semi-urgent mitral valve surgery, usually valve repair. Other rare complications are cardiac tamponade and systemic embolism.

Indications for balloon valvuloplasty

The indication for PBMV is progressive exertional dyspnoea (NYHA FC II, III or IV), associated with documented evidence of moderate or severe MS (mitral orifice area <1.5 cm²) (Grade B).^{379, 386} There should

be no or only mild associated MR. Asymptomatic patients usually do not need intervention, unless there is a history of thromboembolism, paroxysmal AF or significant pulmonary hypertension (PAS pressure >50 mmHg). Patients with pliable, mobile, relatively thin valves, with no or minimal calcification, and without significant thickening and fusion of the subvalvular apparatus, are the best candidates. This comprises the majority of symptomatic younger patients. However, experienced operators can obtain acceptable results in older patients with less favourable anatomy.

Patients with pure or dominant MS requiring intervention should be referred for PBMV to a high-volume centre with documented low complication rates, regardless of the anatomy of their mitral valve.³⁷⁹ Early referral is recommended for younger patients, as they have the most favourable valve morphology and the best long-term results.

A large left atrial thrombus is a contraindication to PBMV. However, it can often be performed safely in the presence of a small, stable thrombus in the left atrial appendage.³⁸⁷ PBMV is ideally suited to managing MS in pregnancy, where the risk of surgery and associated fetal loss is high.

Surgical management

PBMV has largely replaced surgical mitral commissuroplasty and commissurotomy.^{374, 384} In the relatively few patients who are not suitable for PBMV, every effort should be made to repair the mitral valve, rather than replace it, if patients are in sinus rhythm (Grade D) (Figure 5.2). The goal of surgical repair is to restore the pliability of the mitral valve leaflets by excising fibrous tissue, secondary chordae and areas of calcification, and to increase the orifice area by

performing two commissurotomies extended deep into the respective fused papillary muscles.

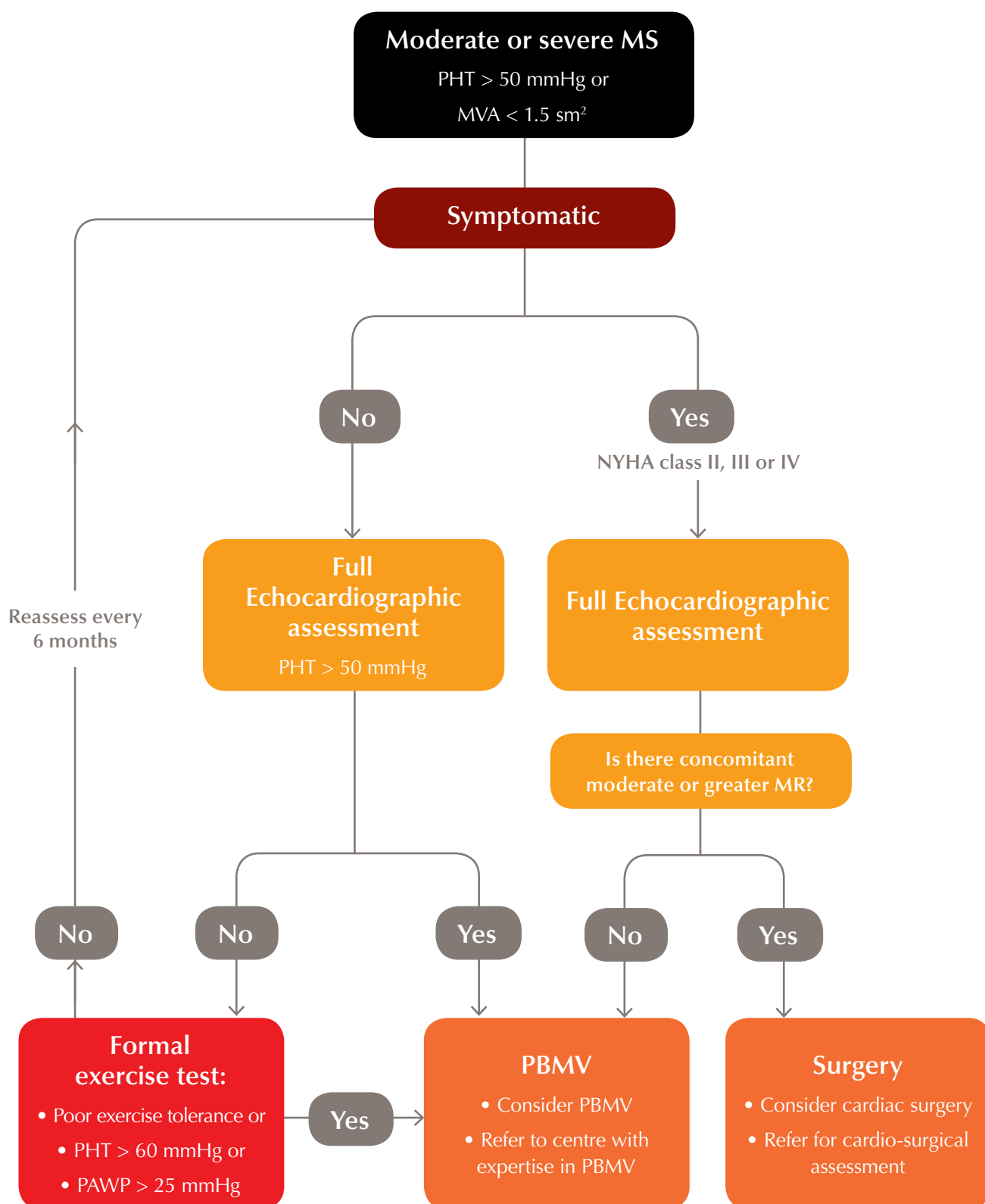
Mitral valve replacement may be necessary in heavily-calcified valves, especially with subvalvular involvement. The choice of valve prosthesis has been discussed in the 'Mitral regurgitation' section. In the presence of paroxysmal or chronic AF, replacement with a mechanical prosthesis is usually recommended, as long-term anticoagulation is already required.

Replacement with a bioprosthesis may be considered for females in the child-bearing years (especially those in sinus rhythm), to avoid anticoagulation during pregnancy. Young patients with bioprosthetic valves in the mitral position require very close follow up, as they have a high rate of valve failure and valve related mortality.³⁶⁵ A more recent report from a series of 823 patients who underwent bioprosthetic valve replacement showed a 15-year freedom from reoperation of 36% in patients less than 40 year of age.³⁸⁸

Surgery for atrial fibrillation

Patients with paroxysmal or chronic AF, who require mitral valve surgery, can have sinus rhythm restored in more than 60–80% of cases with atrial ablation procedures at the time of surgery using radiofrequency and other modalities.^{389, 390} In most cases, the mechanical contractile function of the atria returns. As it is now believed that most AF focal circuits originate around the origin of the pulmonary veins, this site is the main target of ablation. The addition of an ablation procedure usually prolongs the cross-clamp time of the operation by 10–15 min.

Figure 5.2 Timing of surgery for mitral stenosis



AR, atrial fibrillation; EF, ejection fraction; LVESD, left ventricular end-systolic dimension; MS, mitral stenosis; NYHA, New York Heart Association; PBMV, percutaneous balloon mitral valvuloplasty; PHT, pulmonary hypertension.

Table 5.6 Key points in the management of rheumatic mitral stenosis

Symptoms	May be asymptomatic Exertional dyspnoea, fatigue, palpitations
Examination	Low-pitched mid diastolic 'rumble' at LV apex
Echocardiography	Thickened restricted 'dog leg' AMVL Restricted posterior leaflet Measure mean mitral diastolic gradient from continuous-wave Doppler signal Calculate MVA from slope of Doppler mitral inflow velocity Calculate PAS pressure
Cardiac catheterisation	Only to exclude coronary artery disease
Atrial fibrillation	Common Rate control using beta-blockers or digoxin Consider cardioversion, if recent onset Need anticoagulation to prevent thromboembolic complications
Medical management	Diuretics (e.g. frusemide, spironolactone) are only indicated in patients with symptomatic pulmonary venous congestion or pulmonary oedema All symptomatic patients should be referred for cardio-surgical assessment
Indications for intervention	Symptoms NYHA FC II–IV MVA <1.5 cm ² OR PAS pressure >50 mmHg
Procedure of choice	PBMV by high-volume operator/centre Mitral valve repair or replacement if morphology is not suitable for PBMV (e.g. valve is heavily calcified) or if moderate or greater MR is present

AMVL, anterior mitral valve leaflet; LV, left ventricle; MR, mitral regurgitation; MVA, mitral valve area; NYHA FC, New York Heart Association Functional Class; PAS, pulmonary artery systolic; PBMV, percutaneous balloon mitral valvuloplasty.

Aortic regurgitation

Isolated aortic valve regurgitation is a rare but recognised manifestation of RHD, and occurs in 2.8% of adults and 4.5% of children with RHD.³³⁵ More commonly, there is concomitant mitral valve and/or tricuspid valve disease.

Natural history

Moderate or more severe AR results in LV overload, with an increase in LV end-diastolic volume, which helps maintain the increased total stroke volume.³⁵⁴

As the severity of regurgitation increases, the left ventricle undergoes progressive dilatation and hypertrophy. In chronic AR, there is often a long compensated phase with preserved systolic function, despite the pressure and volume overload. However, over time, LV contractile dysfunction occurs in the more severe cases. The rate of progression to symptoms and/or systolic dysfunction is approximately 6% per year.^{391, 392, 394, 395} Aortic valve disease may be due to other conditions in addition to RHD, and the probability of these conditions (including connective tissue disease, aortitis and hypertension) increases with age.¹⁹⁸

Symptoms and examination findings

In the chronic situation, many patients remain asymptomatic, despite having moderate or severe regurgitation. Eventually, dyspnoea on exertion occurs, sometimes accompanied by orthopnoea, and in advanced cases, symptoms of frank congestive heart failure, such as paroxysmal nocturnal dyspnoea and oedema.³⁹⁶

Patients may also experience episodes of angina, despite having normal coronary arteries, probably due to hypotension in diastole, when most coronary flow occurs, as well as subendocardial ischaemia in the presence of LVH. In severe AR, the pulse pressure is widened, and the Korotkoff sounds are heard almost down to the pressure of zero. Examination usually reveals a forceful LV apical impulse, which may be displaced laterally and downwards. A water-hammer pulse at the brachial artery and a collapsing carotid pulse are clinical indications of at least moderate AR.

The typical murmur of AR is a diastolic, blowing decrescendo (pistol shot) murmur best heard at the left sternal border, with the patient sitting upright at the end of expiration. In general, the length of the murmur correlates with severity, with more severe cases producing a pan-diastolic murmur. There is usually an associated systolic murmur, even in the absence of AS, due to the increased antegrade flow across the aortic valve, and in occasional cases, a mitral diastolic (Austin Flint) murmur.

Electrocardiography/chest X-ray

With severe AR, the ECG often shows non-specific ST-T wave changes, with or without increased LV voltages. Chest X-ray may show an enlarged left ventricle and a dilated ascending aorta.

Echocardiography

LV function is assessed quantitatively by measuring LV end-systolic and end-diastolic diameters, as the timing of surgery is traditionally based on these M-mode measurements. 2DE allows for the quantitative assessment of LV volume and EF, which can be calculated using the Simpson's or area-length methods. In children, cardiac Z-scores (heart size indexed to body surface area and expressed as the standard deviation) need to be tracked with time, as they correct for the growth that has taken place between clinic visits. The degree of LV dilatation is usually greater in severe aortic than in severe MR.

Anatomical or morphological rheumatic changes of the aortic valve consist initially of leaflet prolapse. With time, the leaflets thicken the leaflet edges roll,

resulting in a coaptation defect, and the aortic root is dilated in more severe cases.

The extent of AR is examined with colour flow mapping in the left ventricle.^{188, 190} The spatial extent of the colour flow jet in the LV outflow tract is an approximate guide to the severity of AR. If the area is at least two-thirds or more of the LV outflow tract, the regurgitation is in the moderate to severe range. The depth of the jet in the left ventricle is also of some value, although it may be obscured by turbulent mitral valve inflow, particularly in cases of associated MS.

Another useful method for assessing the severity of AR is to sample diastolic flow in the descending thoracic aorta from the suprasternal notch position. The length and velocity of the reversed flow is proportional to the severity of regurgitation. Pan-diastolic-reversed flow, particularly with increased velocity, is indicative of moderate or severe regurgitation, while in more severe cases, there is a reversal of diastolic flow in the abdominal aorta. A pressure half-time of the AR Doppler velocity envelope of <400 ms usually indicates at least moderate AR. However, additional factors, such as heart rate and LV end-diastolic pressure, can affect pressure half-time.^{188, 190}

Transoesophageal 2DE and 3DE are also useful in the assessment of symptomatic AR in adults. The high-quality images allow more precise evaluation of the severity of the AR, the morphology of the leaflets and measurement of the aortic root and sinus dimensions. It is recommended for all adult patients being assessed for aortic valve surgery.³⁹⁷

Cardiac catheterisation

Cardiac catheterisation is not required for the diagnosis or assessment of the severity of AR. It should only be carried out if coronary artery disease must be excluded. As coronary artery disease presents much earlier in Aboriginal and Torres Strait Islander patients, coronary angiography may be required in those more than 25–30 years of age. Aortography may be carried out at the same procedure, allowing assessment of the degree of regurgitation and the dimensions of the ascending aorta. Increasingly, dense opacity, due to contrast medium in the left ventricle, and slower clearance of contrast correlate with greater degrees of AR.

Medical management

In asymptomatic patients with significant AR, vasodilator therapy has been demonstrated to reduce LV dilatation and regurgitant fraction.³⁵⁴ This has the potential for slowing the progression of LV dilatation, hence, delaying the need for surgery. These drugs may also be beneficial, as these patients usually

have systolic hypertension. Most of the publications describe experience with the dihydropyridine, nifedipine,³⁹⁸ although smaller studies have shown that ACE inhibitors are also effective.³⁹⁹ However, there is more recent evidence that prior treatment with nifedipine or an ACE inhibitor does not reduce or delay the need for aortic valve replacement in patients with asymptomatic severe AR and normal LV function.⁴⁰⁰ Nevertheless, until there are more trial data, vasodilator therapy with nifedipine or ACE inhibitors is still recommended for asymptomatic or mildly-symptomatic patients with preserved systolic function and moderate or greater degrees of AR (level III-3, Grade C) especially when systolic hypertension is present.²⁶⁵

Patients with symptoms of pulmonary congestion will benefit from diuretic therapy, but should be referred for surgery, even if symptoms subside. AF is uncommon in AR, but may lead to symptomatic deterioration, due to a rapid ventricular rate. Treatment comprises digoxin and rate-slowing beta-blockers or calcium channel blockers, as described for mitral valve disease. Cardioversion may need to be considered.

Serial echocardiography is essential for monitoring LV size and function, and the severity of AR. Mild regurgitation usually requires evaluation every 2 years, whereas more severe regurgitation should be studied every 6–12 months, depending on the extent and rate of serial change (Table 5.7).

Surgical management

Indication for surgery

Symptomatic patients with moderate/severe AR should be referred for surgery (level III-2, Grade B) (Figure 5.3).^{265, 453} Without surgery, symptomatic patients have a significantly impaired prognosis; the mortality rate being over 20% per year. Patients with reduced systolic function (left ventricular EF (LVEF) <50%) should be referred as soon as possible for valve surgery, as long-term studies suggest that progression of heart failure and death occur in up to 25% of these patients per year.^{394, 395}

Patients with equivocal symptoms may undergo exercise testing, which is useful in assessing functional capacity and symptomatic response (level IV, Grade C).²⁶⁵

For asymptomatic patients with normal LV systolic function, surgery should be delayed for as long as possible.³⁵⁴ If serial echocardiography shows that the LVESD is approaching 55 mm, or the LVEF is <55%, these patients should be referred for aortic valve surgery (Grade C).²⁶⁵ In addition, an LV end-diastolic diameter >70 mm may be a sign of increased cardiovascular risk and the need to consider surgery. More long-term outcome data are required before LV end-diastolic diameter can become a definitive criterion for surgical intervention.³⁵⁴

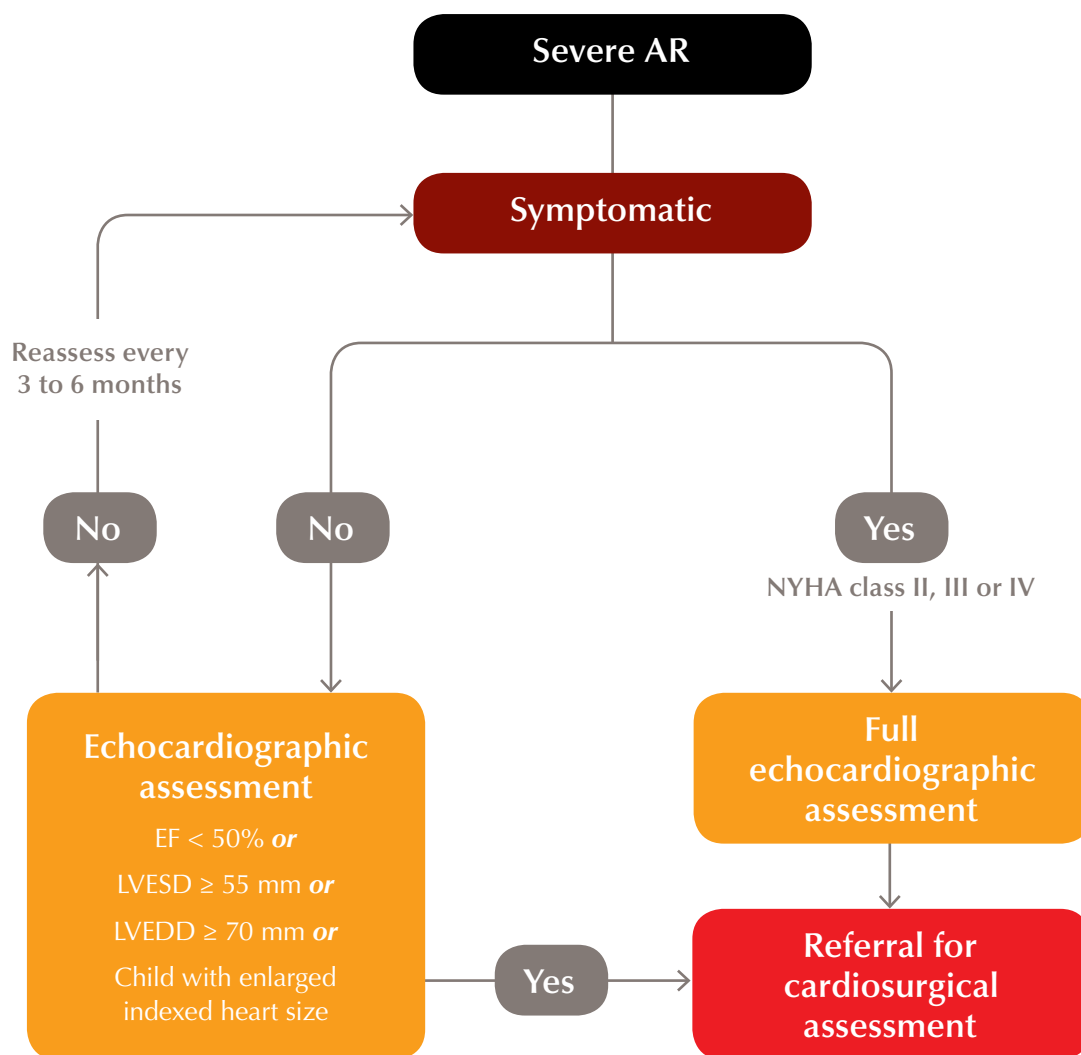
Choice of operation

The options for aortic valve surgery are replacement with either a mechanical valve, a stented or a stentless bioprosthetic valve or an aortic homograft.^{371, 451} Other less common surgical options are either aortic valve repair or the Ross procedure (pulmonary autograft for the valve with homograft replacement of the pulmonary valve). It is important that the choice of operation be fully discussed with the patient and his or her family, and if possible, with the patient's primary healthcare provider before a final decision is made.

Replacement with a bioprosthesis has the advantage of avoiding long-term anticoagulation. The main disadvantage of bioprostheses is their limited durability in younger patients (15–50 years).^{371, 401, 403} Structural deterioration of bioprostheses, such as the Hancock valve, has been reported to be 50% at 10 years, and 90% at 15 years.⁴⁰² Newer, stentless bioprosthetic valves appear to have a similar rate of structural deterioration, at least up to 10 years' follow up,⁴⁰⁴ but long-term outcome studies are not yet available. Bioprosthetic valve degeneration is accelerated in patients with significant chronic kidney disease.

Structural deterioration usually results in prosthetic regurgitation, although some degree of prosthetic stenosis may also occur. It is important that bioprosthetic valves be regularly monitored by echocardiography to detect early manifestations of deterioration with regurgitation and/or stenosis. Late reoperation will be required in the majority of younger patients, because of valve degeneration and recurrence of symptoms.

Figure 5.3 Timing of surgery for aortic regurgitation



AR, aortic regurgitation; EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NYHA – New York Heart Association.

Homografts are also subject to structural deterioration, often with associated calcification.^{405, 407, 408}

Homografts have the advantage of haemodynamics identical to that of a native aortic valve and the avoidance of anticoagulant therapy, if the patient is in sinus rhythm. However, limited donor supply means that valves may not always be available. The largest follow-up study of aortic homografts found a 10- and 20-year freedom from tissue failure (development of significant regurgitation or stenosis) of 62% and 18%, respectively.⁴⁰⁸ Difficulties in obtaining donor homografts, and the significantly increased complexity of reoperation in many of these patients, has led to this procedure becoming much less favoured in recent years, especially in younger rheumatic patients.

Mechanical tilting disc/bileaflet prostheses have excellent long-term durability, with favourable long-term outcomes, if good warfarin adherence can be achieved.⁴⁰⁹ If patients already have chronic AF requiring anticoagulation, the valve of choice is a mechanical valve prosthesis. However, in young patients, it is often not possible to fit an adult-sized prosthesis, and further surgery may be required following a growth spurt. The main complications of mechanical valves are bleeding and thromboembolic events (e.g. prosthetic valve thrombosis), usually due to problems with anticoagulation adherence.⁴¹⁰ Patients with newer disc/bileaflet mechanical aortic valve can usually be anticoagulated to a lower INR (2–3) than was needed with the earlier-generation caged ball/disc valves, because these newer prostheses appear to have a lower risk of thromboembolism,⁴⁵⁰ especially in the aortic position. However, there is still a risk of embolism and bleeding complications occurring, especially in some patients in whom stable anticoagulation is difficult to achieve.

The incidence of major bleeding in non Aboriginal and Torres Strait Islander populations is approximately 1.4 per 100 patient-years, and the risk of stroke is 0.6 per 100 patient-years.^{411, 412} In a series of Aboriginal patients in the Northern Territory, who had aortic or mitral valve replacement with predominantly older-generation mechanical prostheses, the number of major bleeding events was higher at 2.2 per 100 patient-years, and the risk of embolism was also high at 3.9 per 100 patient years, reflecting difficulties with anticoagulation.^{326, 413, 414} In this series, complications were most common in the first 4 years after surgery.

As with all prostheses, other complications, such as endocarditis, prosthetic valve thrombosis, valve dehiscence and haemolysis, may occur.

Experience with the repair of rheumatic aortic valve is limited.^{343-345, 415} The Carpentier group in Paris has pioneered this approach, and has reported 92% freedom from reoperation at 5 years with cusp augmentation techniques.³⁴⁵ Long-term results are not yet available. Repair is best in the early stages of rheumatic valvular disease when the cusps are thin and pliable. Patients do not require warfarin, but most receive antiplatelet therapy. However, there is little experience with aortic valve repair in Australia. Despite concern about the durability of repair, it may be the procedure of choice in some children at high-volume centres, as in this age group, there are limited alternatives. As discussed above, bioprosthetic valves have limited lifespan, and adult-sized mechanical valves often cannot be fitted into the aortic position of smaller children.

Another alternative for aortic valve surgery is the Ross procedure,^{416, 417} which uses a pulmonary autograft for valve replacement, and a homograft for pulmonary valve replacement. The surgery is more complex, and consequently, has a slightly higher surgical risk. It is best suited for the aortic valve in the later stages of rheumatic disease, when leaflets are thickened and retracted. It has the theoretical advantages of the valve 'growing' in younger patients, anticoagulation not being required and pregnancy not resulting in structural valve degeneration.

However, ARF recurrence can involve the neo-aortic valve (pulmonary autograft), causing regurgitation. Late follow up has also shown that some patients may develop significant AR, especially after 5 years, and require reoperation. Also in younger patients, structural degeneration of the pulmonary homograft, usually manifesting as pulmonary stenosis, remains a problem.⁴¹⁸ The need for late reoperation, which is often quite complex, is the principal limitation of the Ross procedure.⁴¹⁹ It is not widely practiced in Australia.

Recommendations

A careful preoperative assessment of the likelihood of medication adherence, especially warfarin, is essential in determining the choice of valve surgery. If stable anticoagulation is unlikely to be achieved, serious consideration should be given to the use of an aortic bioprosthesis. Patients who demonstrate good adherence with medications are suitable for replacement with the newer bileaflet mechanical valve prosthesis, as they have the best long-term durability and highest freedom from reoperation. However, in young female patients, every effort must be made to avoid a mechanical prosthesis, because of the significant risk to mother and fetus posed by anticoagulation during pregnancy.

Table 5.7 Key points in the management of rheumatic aortic regurgitation

Symptoms	<p>May be asymptomatic for many years</p> <p>Exertional dyspnoea and fatigue</p>
Signs	<p>Diastolic blowing and/or decrescendo murmur at left sternal border, usually associated with systolic ejection murmur</p>
Echocardiography	<p>Retrograde diastolic regurgitant colour jet in LVOT and LV chamber</p> <p>Area of jet in LVOT correlates with severity</p> <p>LV chamber dimensions enlarged, if moderate or greater aortic regurgitation</p> <p>Associated mitral valve disease is common</p> <p>Pan-diastolic reversed diastolic flow in descending thoracic aorta, if moderate/severe aortic regurgitation (Doppler)</p> <p>Assess LV systolic function</p>
Cardiac catheterisation	<p>Only to exclude coronary artery disease</p>
Medical management	<p>All symptomatic patients should be commenced on an ACE inhibitor and referred for cardio-surgical evaluation</p> <p>Consider ACE inhibitors or vasodilator therapy with dihydropyridines (e.g. nifedipine) in asymptomatic patients with moderate or greater aortic regurgitation, especially if systolic hypertension is present</p>
Indications for surgery	<p>Moderate/severe aortic regurgitation with symptoms NYHA FC II–IV</p> <p>Asymptomatic moderate/severe aortic regurgitation if:</p> <ul style="list-style-type: none"> • LVEF <55% OR • LVESD ≥55 mm OR • LVEDD >70 mm OR • Enlarged LVESD or LVEDD Z-score (in children only)
Choice of surgery	<ol style="list-style-type: none"> 1. Bioprosthetic or homograft valve replacement: <ul style="list-style-type: none"> • no requirement for anticoagulation if in sinus rhythm • limited durability in younger patients 2. Mechanical valve replacement: <ul style="list-style-type: none"> • anticoagulation is required 3. Aortic valve repair: <ul style="list-style-type: none"> • many centres have limited experience 4. Ross procedure (replacement of the aortic valve with a pulmonary autograft and replacement of the pulmonary valve with a homograft): <ul style="list-style-type: none"> • only in selected cases with experienced surgeons

ACE, angiotensin-converting enzyme; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVOT, left ventricular outflow tract; NYHA FC, New York Heart Association Functional Class.

Aortic stenosis

Natural history

RHD is an uncommon cause of AS.^{420, 421} Isolated AS is a very rare manifestation of RHD.^{331, 332} It almost always occurs in the presence of associated rheumatic mitral valve disease. Like AR, non-rheumatic causes of AS should be considered, including degenerative disease (sometimes accelerated by a co-existent congenital bicuspid aortic valve) and previous infective endocarditis. As with rheumatic MS, AS results from progressive fibrosis and commissural fusion of valve cusps, with eventual calcification. The obstruction to the LV outflow tract results in a significant systolic gradient between the left ventricle and aorta. A 50% reduction in aortic valve orifice results only in a small gradient across the aortic valve, but >50% reduction results in a substantial increase in the gradient, LV pressure overload and the development of concentric ventricular hypertrophy to compensate for the increased systolic wall stress. The natural history of AS is variable in the individual patient, but it is generally progressive.

Symptoms

The classic symptoms of AS are dyspnoea on exertion, angina and syncope. Symptoms are gradual in onset, but are usually slowly progressive over time, especially if there is associated mitral valve disease.

Examination

The characteristic clinical finding in AS is a loud, low-pitched mid-systolic ejection murmur, best heard in the aortic area, radiating to the neck and the apex.⁴²² In patients with haemodynamically-significant AS, useful physical signs are a slowed and reduced carotid pulse upstroke, and the presence of a thrill in the suprasternal notch.

Electrocardiography/chest X-ray

ECG usually shows sinus rhythm, and may demonstrate voltage criteria for LV hypertrophy. Sometimes there are secondary repolarisation abnormalities. Nonetheless, ECG is neither sensitive nor specific for assessing the significance of an ejection systolic murmur in this setting. A chest X-ray usually shows normal heart size, unless there is associated MR. Calcification of the aortic valve may be visible in the lateral chest X-ray.

Echocardiography

2DE demonstrates thickened and restricted aortic valve leaflets, often with visible calcification of the leaflets. LV size and systolic function can be assessed quantitatively. The peak and mean velocity across the valve can be measured. The aortic valve orifice area can also be calculated to help determine severity, and is especially useful when the LV function is reduced, making the aortic velocity gradient less reliable.³⁹⁶ In these circumstances, an aortic valve orifice area <1 cm² usually indicates severe disease.

Cardiac catheterisation

Cardiac catheterisation is usually not needed to measure the severity of AS, but may be required to document coronary artery disease if anginal symptoms are disproportionate to the severity of AS. Coronary angiography should also be considered in Aboriginal and Torres Strait Islander patients 30 years or older, due to the high incidence of premature coronary artery disease in these populations. If there is uncertainty about the Doppler-derived gradients, it is important to measure the transvalvular aortic gradient at the time of cardiac catheterisation, and calculate the aortic orifice area.

Medical management

Patients usually do not become symptomatic until a moderate or severe systolic gradient develops (mean gradient >40–50 mmHg). Initially, symptoms are exertional dyspnoea and fatigue. However, many patients may remain asymptomatic, despite having evidence of haemodynamically-significant AS. Once symptoms develop, prognosis is poor without surgery.

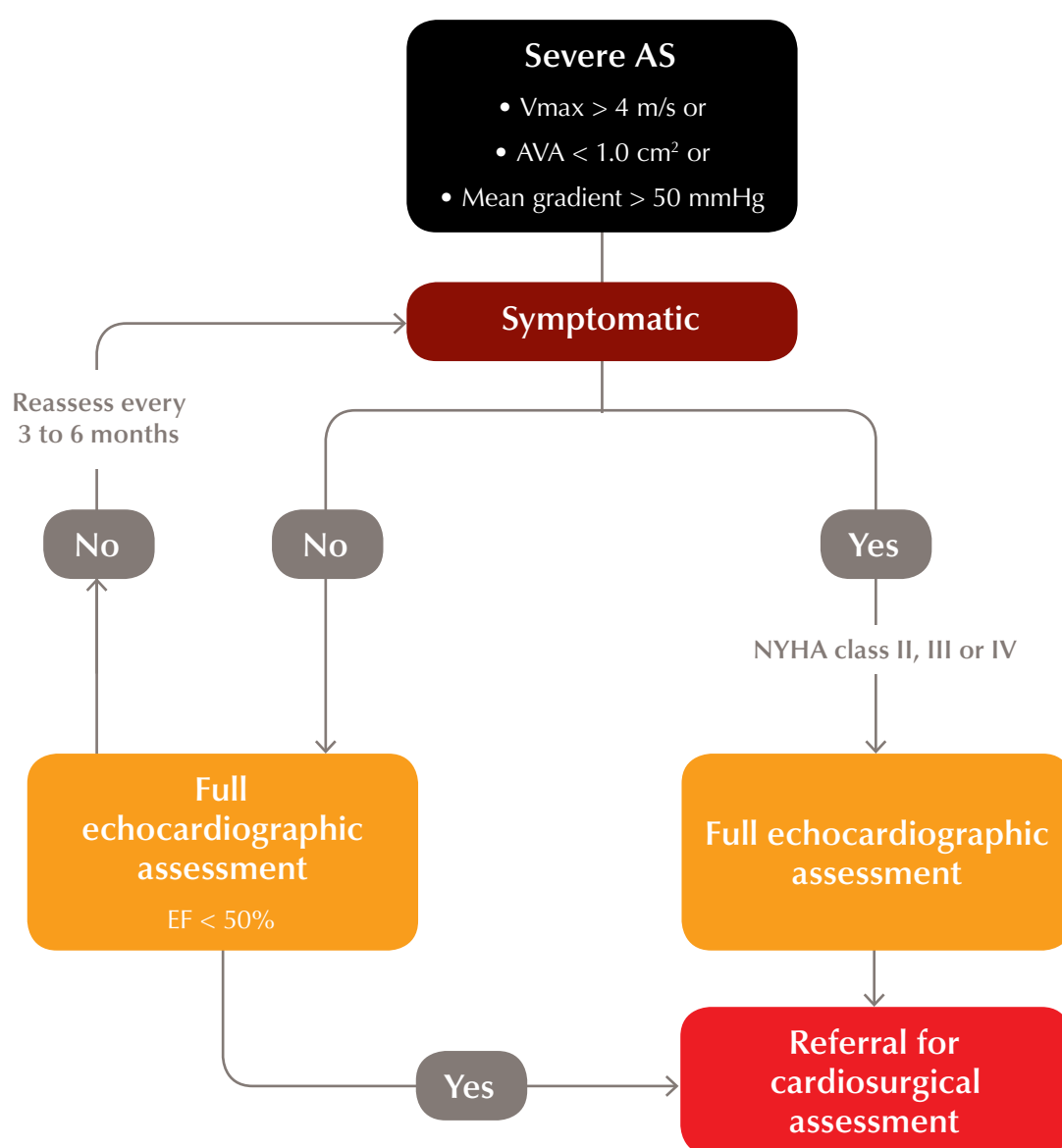
Aortic valvuloplasty

Percutaneous aortic balloon valvuloplasty^{423, 424} may reduce severe AS to moderate stenosis, but usually leaves a significant residual gradient. The procedure may entail substantial morbidity and mortality, particularly in older patients. Follow-up studies have shown that initial improvement is usually not maintained after a few months. There is a high restenosis rate, particularly in very deformed valves.⁴²³ Aortic valvuloplasty is now reserved for patients who are not candidates for surgery, and therefore, it has a very limited application in patients with rheumatic AS. More recently, transcatheter aortic valve implantation has been developed as a percutaneous therapeutic technique for severe AS for patients unsuitable for surgery. Its efficacy and safety are currently being evaluated in clinical trials.⁴⁵⁴

Indications for surgery

Aortic valve replacement is a definitive therapy for symptomatic AS (level III-2, Grade B). It should be performed in all patients with significant gradients and a reduced valve orifice (mean gradient >40 - 50 mm, aortic valve orifice <1 cm²), once they develop exertional symptoms.⁴²⁵ It should also be considered in patients with significant LV dysfunction, but with a lower aortic gradient. Occasionally, some patients with normal LV function have a gradient 40 - 50 mmHg and symptoms clearly due to AS (Figure 5.4). Aortic valve surgery involves replacement with either a mechanical valve, a bioprosthetic valve or a homograft (Table 5.8).^{371, 451}

Figure 5.4 Timing of surgery for aortic stenosis



AS, aortic stenosis; AVA, aortic valve area; EF, ejection fraction; NYHA, New York Heart Association; Vmax, peak velocity.

Table 5.8 Key points in the management of rheumatic aortic stenosis

Symptoms	May be asymptomatic Exertional dyspnoea, angina, syncope
Signs	Low-pitched, systolic ejection murmur in aortic area
Echocardiography	Thickened, restricted aortic valve leaflets Measure peak and mean systolic gradient from Doppler velocity across aortic valve Assess left ventricular systolic function
Cardiac catheterisation	Only to exclude coronary artery disease
Medical management	Medical therapy is not indicated in asymptomatic patients Symptomatic patients require surgery and do not benefit from medical therapy
Indications for surgery	Symptoms plus mean systolic gradient > 40-50 mmHg or AVA <1.0 cm ² OR Impaired cardiac function (EF < 50%) plus mean systolic gradient > 40-50 mmHg or AVA <1.0 cm ²
Choice of surgery	Bioprosthetic or homograft valve replacement: <ul style="list-style-type: none"> • limited durability • no requirement for long-term anticoagulation if in sinus rhythm Mechanical valve replacement: <ul style="list-style-type: none"> • long-term anticoagulation is required

AVA, aortic valve area; EF, ejection fraction.

Rheumatic tricuspid valve disease

Rheumatic tricuspid valve disease is uncommon, and is almost always associated with left-sided rheumatic valve disease, especially mitral.¹⁹⁷ However, there are occasional reports of isolated rheumatic tricuspid valve disease, due to rheumatic inflammation. The most common rheumatic tricuspid valve lesion is tricuspid regurgitation, which may be of variable severity. It is important to distinguish RHD-associated tricuspid regurgitation from the more common functional tricuspid regurgitation secondary to pulmonary hypertension from left-sided valve disease, especially MS.⁴²⁶ Functional tricuspid regurgitation is secondary to RV dilatation and dysfunction, tricuspid annular dilatation and papillary muscle displacement. Tricuspid regurgitation tends to progress, because RV volume overload leads to eventual RV systolic dysfunction and dilation.

Tricuspid regurgitation

Physical examination

The clinical features of tricuspid regurgitation are prominent V waves in the jugular venous pulse, with a steep y descent; a mid- or pan-systolic murmur at the left sternal border, which may increase on inspiration. In severe cases, there may also be a mid diastolic flow murmur and systolic hepatic pulsation with hepatomegaly.

Echocardiography

The severity of tricuspid regurgitation is evaluated with the use of Doppler echocardiography and colour flow mapping of the area of systolic jet in the right atrium. RV chamber size and systolic function can also be assessed qualitatively with 2DE. The echocardiographic diagnosis of rheumatic tricuspid regurgitation may be difficult in the absence of associated tricuspid stenosis. Valve leaflets may appear thickened with evidence of chordal shortening. However, often the diagnosis of rheumatic tricuspid regurgitation can only be made at surgery. At surgery, the most frequent findings are retraction of the leaflet free edge with thickening, calcified foci and some degree of fusion and thickening of the commissures and subvalvular apparatus.

Tricuspid stenosis

Physical examination

The clinical features of tricuspid valve stenosis include a giant 'a' wave, in the jugular venous pulse, a presystolic and a mid-diastolic murmur at the left sternal border, which increases with inspiration. It may be difficult to separate the auscultatory features of rheumatic tricuspid stenosis from that of frequently-associated mitral valve stenosis.

Echocardiography

Rheumatic tricuspid valve stenosis is less common than tricuspid regurgitation, but has more characteristic echocardiographic features similar to that of MS. There

may be thickening and leaflet restriction, with doming of the tricuspid valve leaflets. The diastolic gradient across the tricuspid stenosis can be measured with Doppler echocardiography to assess the severity of the tricuspid valve stenosis, as with MS.

The tricuspid valve is the most complex of the four cardiac valves, and is not visualised as well with echocardiography compared to the left-sided valves. This may make it more difficult to precisely determine if there is rheumatic involvement of the tricuspid valve. The potential role of 3DE is currently being explored in trying to obtain more accurate information about organic tricuspid valve disease than is possible with 2DE.

Table 5.9 Key points in the management of rheumatic tricuspid regurgitation

Symptoms	Exertional dyspnoea and fatigue, usually secondary to left sided rheumatic valve disease
Examination	Elevated jugular venous pressure with prominent v wave in jugular pulse Pansystolic murmur left sternal border Hepatomegaly, may be pulsatile Ascites Peripheral oedema
Echocardiography	Thickened leaflets Retrograde colour jet into right atrium Severity graded by area of colour jet Dilated IVC Retrograde flow in hepatic veins Right ventricular chamber enlargement if moderate or greater TR
Medical Management	Symptoms are generally related to the left sided valve lesions Diuretics (e.g. frusemide, spironolactone) are only indicated in patients with symptomatic right and/or left heart failure Note: Usually impossible to distinguish rheumatic from non-rheumatic tricuspid valve regurgitation clinically or by echocardiogram
Indications for surgery	Moderate/severe TR usually in association with symptomatic MVD Progressive symptomatic right heart failure
Choice of surgery	Tricuspid valvuloplasty Tricuspid valve replacement with mechanical or biological prosthesis if valvuloplasty not possible

IVC, inferior vena cava; MVD, mitral valve disease; TR, tricuspid regurgitation.

Table 5.10 Key points in the management of rheumatic tricuspid stenosis

Symptoms	Usually secondary to left sided rheumatic valve disease
Examination	Elevated jugular venous pressure Prominent a wave in jugular pulse Presystolic and mid diastolic murmur at the left sternal border
Echocardiography	Thickened, restricted tricuspid valve leaflets with doming Diastolic gradient measured across tricuspid valve as per MS
Medical management	Symptoms are generally related to the left sided valve lesions Diuretics (e.g. frusemide, spironolactone) are only indicated in patients with symptomatic right and/or left heart failure
Indications for surgery	Moderate/severe TS in association with symptomatic MVD Progressive right heart failure
Choice of surgery	Percutaneous balloon valvuloplasty or surgical commissurotomy operation of choice Tricuspid valve replacement with mechanical or biological prosthesis if repair or PBTv not possible

MS, mitral stenosis; MVD, mitral valve disease; PBTv, percutaneous balloon tricuspid valvuloplasty; TS, tricuspid stenosis.

Surgical management

Surgical management of rheumatic tricuspid valve disease may be challenging, and is frequently associated with left-sided rheumatic valve disease, especially mitral valve disease.⁴²⁷ In most cases, the tricuspid valve can be repaired without the need for prosthetic valve replacement. This usually involves the placement of a prosthetic ring annuloplasty plus or minus commissurotomy.⁴²⁸ Long-term follow up of surgically-treated patients with tricuspid valve disease has demonstrated relatively poor late outcomes. There is quite a high rate of reoperation, mainly due to left-sided valve problems, rather than tricuspid. Reoperation for patients with tricuspid valve disease has been associated with high mortality in the literature. The relatively poor outcome of patients who have had surgery for rheumatic tricuspid valve disease reflects the recurrent nature of their rheumatic valvular heart disease with multivalvular involvement, RV dysfunction and chronic heart failure.⁴²⁸

The alternative to tricuspid valve repair is valve replacement. This is associated with poorer short- and long-term outcomes than repair, because of the accelerated degeneration of bioprosthetic valves in the tricuspid position, and the increased risk of prosthetic thrombosis with mechanical prostheses in the right-sided, relatively low-pressure situation. Tricuspid valve replacement has a higher surgical risk than repair in most series.

Multivalvular disease

In patients with RHD, both the mitral and aortic valve may be involved (e.g. AR and MS or AR and MR). The management is usually that of the dominant lesion. However, the proximal valve lesion may modify the effects of the distal lesion; for example, severe MS may prevent the development of significant LV dilation secondary to AR. The combination of significant MR and AR is a surgical challenge, and carries a higher risk of ventricular dysfunction.⁴²⁹

In many patients, one valve lesion will be more dominant than the other. Indications for surgery are as for the dominant lesion described in earlier sections. However, the question of what to do with the less severe valve lesion; for example, mild to moderate MR in the presence of significant AR poses a difficult surgical management problem.³⁴² The progression of the milder valve lesion is variable. Double valve surgery carries a higher surgical risk than single valve surgery, particularly in the presence of LV dysfunction. In a recent Japanese study, patients who underwent aortic valve replacement in the presence of untreated mild to moderate MR were followed up long term.⁴³⁰ There was no difference in survival at 1, 5 or 10 years between patients who underwent single valve surgery alone for multivalvular disease, compared with a double-valve surgery group. However, there was a higher incidence of readmission with heart failure in the group who did not undergo mitral valve surgery, indicating that MR may progress, particularly in the presence of LV dysfunction. It is important that the severity of the less severe valve lesion be accurately quantified preoperatively with transoesophageal echocardiography.

Other studies have shown that patients who undergo combined mitral valve repair and mechanical aortic valve replacement, compared with double mechanical valve replacement, have less long-term thromboembolic complications.⁴³¹ This is particularly relevant in the Aboriginal population.³²⁶ However, they do have increased risk of the need for late reoperation on the mitral valve compared to valve replacement.

Conversely, an Israeli follow-up study (mean: 13±7 years) of rheumatic valvular disease patients (mean age: 61 years) with mild aortic valve disease, who

had required mitral valve surgery, showed that in the vast majority of cases, the aortic valve disease remained stable without disease progression.⁴⁵⁵ In younger patients, the degree of adherence to antibiotic prophylaxis would be the major determinant of the progression of the non-operated valve disease.

Pregnancy in patients with rheumatic heart disease

Normal pregnancy is associated with a 30–50% increase in blood volume, reduction in systemic vascular resistance and corresponding increase in cardiac output. These changes begin during the first trimester, peaking at 28–30 weeks of pregnancy and are then sustained until term. The increase in blood volume is associated with an increase in heart rate by 10–15 beats per minute. Because of the hyperdynamic circulation, innocent, soft mid-systolic murmurs are common during pregnancy, particularly along the left sternal border. These circulatory changes of pregnancy will exacerbate any pre-existing valvular disease. Sometimes RHD, especially MS, is first diagnosed during pregnancy or soon after delivery when a woman develops symptoms, usually dyspnoea.⁴³²

Ideally, patients with known rheumatic valvular disease should be properly assessed before pregnancy. Discussion regarding fertility planning should be undertaken with all women with more than mild valvular disease, even if immediate pregnancy is not planned. Assessment should include a full history and examination, with functional assessment and a detailed echocardiographic study. If patients are already symptomatic, due to significant rheumatic valvular disease, serious consideration should be given to interventional therapy or surgery prior to pregnancy, to avoid life-threatening complications, which may occur in these patients. In these patients, the use of contraception with a low failure rate (e.g. etonogestrel implant; Implanon, Organon International, Oss, Netherlands) should be strongly encouraged if there is a risk of pregnancy, while more definitive treatment is being undertaken. In RHD, oestrogen-containing contraceptives may carry a slightly higher risk of thrombosis, but this has not yet been confirmed in published studies.

Asymptomatic moderate–severe MS prior to pregnancy should not reassure the physician that pregnancy is likely to be well tolerated. In patients with moderate or severe MS (orifice area $<1.5\text{ cm}^2$), PBMV should be considered, even for asymptomatic or mildly-symptomatic woman, because of the high risk of maternal and fetal complications during pregnancy. Patients with more than mild rheumatic valvular disease should be identified as being at higher than normal risk of complications in pregnancy, and should receive antenatal care at an appropriate referral centre with an experienced obstetrician, in collaboration with an obstetric physician and/or cardiologist. The most severe cases should be seen at a referral centre, with cardiology and intensive-care facilities. Discussions with the patient regarding timing, nature and site of planned delivery should occur before or early in the pregnancy.

Risk factors

The predictors of increased maternal and fetal risk in the pregnant patient with rheumatic valvular disease are:^{433, 434}

- reduced LV systolic function
- significant AS or MS
- moderate or severe pulmonary hypertension
- a history of heart failure
- symptomatic valvular disease before pregnancy
- AF, especially when anticoagulation is required
- pregnant women with mechanical valves prostheses.

During pregnancy, women with valvular heart disease should have serial cardiac evaluations, the frequency of which is determined by the severity of disease. Women with severe disease may require specialist clinical evaluation every 2–3 weeks after 20 weeks' gestation. Whenever there is a change in symptoms, maternal cardiac status should be reviewed. A multidisciplinary approach to management is an important principle for care of the pregnant patient with rheumatic valvular disease. It is often necessary to advise women with heart disease to cease work earlier in pregnancy for medical reasons, as cardiac demands increase significantly as pregnancy proceeds. Most women with valvular heart disease become more symptomatic in the third trimester, and there is theoretical benefit in reducing the physical and other demands of continuing work.

Mitral/aortic regurgitation

In general, pregnancy is well tolerated in most patients with mild/moderate, and in some with severe valvular regurgitation.^{434, 435} The increase in blood volume and cardiac output in pregnancy increases LV volume overload, but the decrease in systemic vascular resistance partly compensates for this.

Some patients with severe regurgitation may develop congestive heart failure, especially during the third trimester. These patients may need diuretics and vasodilator therapy. Angiotensin receptor antagonists and ACE inhibitors are contraindicated during pregnancy. Therefore, hydralazine and nitrates, or dihydropyridine calcium channel blockers (e.g. nifedipine), hydralazine or nitrates, should be used if vasodilator therapy is needed (level IV, Grade C). These agents require careful observation, as they may cause troublesome tachycardia and need to be ceased or reduced in dosage.

Vaginal delivery, often requiring assistance with vacuum extraction or forceps, is usually possible in most patients with congestive heart failure controlled with medication. Every effort should be made to avoid cardiac valve surgery during pregnancy because of the high risk of fetal loss, which accompanies cardiopulmonary bypass later in pregnancy, although this may be mitigated by adjustments to the bypass process.

Mitral stenosis

Mitral stenosis is the most commonly-encountered valvular lesion in pregnancy.⁴³⁵ The increase in blood volume and cardiac output causes a significant increase in the mitral valve gradient, especially during the second and third trimesters. Pregnancy-associated tachycardia may also shorten diastolic filling and accentuate the gradient. In patients with moderate or severe MS (mitral valve orifice $<1.5\text{ cm}^2$) symptoms of heart failure, including breathlessness due to pulmonary oedema, frequently develop.

In patients with mild or moderate symptoms during pregnancy, medical therapy with diuretics, digoxin and/or beta-blockers to slow the heart rate is usually sufficient to provide symptomatic relief. The development of AF with a rapid ventricular rate requires initial rate control with the use of beta-blockers (e.g. metoprolol) and digoxin. A higher dose of digoxin is usually required in pregnancy (e.g. 250 mcg bd). Diltiazem and ACE inhibitors are contraindicated in pregnancy. Cardioversion should be considered if the patient remains symptomatic, or if rate control is inadequate.

If the patient remains symptomatic despite medical therapy, there is significant risk to both mother and fetus peri-delivery, and relief of MS is usually required. Patients with NYHA FC III or IV symptoms with a mitral valve orifice of $<1\text{--}1.5\text{ cm}^2$, suitable valve characteristics and no atrial thrombus should undergo PBMV^{379, 436, 437} at the end of the second trimester or the beginning of the third. The exact timing of the procedure requires multidisciplinary team consultation. If the fetus is viable, steroids for fetal lung maturation should be given prior to the PBMV. The safety of this procedure in pregnancy has been well established in a number of patient series.^{437, 456} Cardiac surgery should be avoided, because of the fetal loss rate of up to 30% that occurs with cardiopulmonary bypass.⁴³⁶ There is a small risk of traumatic MR resulting from PBMV, but this can usually be managed medically, without the need for surgery until after pregnancy.

In patients with MS, vaginal delivery is favoured if obstetric factors are favourable, with the use of assisted delivery devices during the second stage to avoid the need for pushing and to shorten the second stage. Severe MS with severe pulmonary hypertension is associated with increased maternal and fetal risk during labour. This situation requires multidisciplinary team care and carefully-planned delivery, usually by elective Caesarean section with invasive haemodynamic monitoring.

Aortic stenosis

Severe rheumatic AS in pregnancy is far less common than MS. Suspected AS should be accurately assessed by Doppler echocardiography. Most patients with mild or moderate AS can usually be safely followed during pregnancy. Those women with severe AS (gradient over 50 mmHg and/or valve orifice $<1\text{ cm}^2$), although seen rarely, are at significant risk of adverse maternal and fetal outcomes. Myocardial ischaemia may occur. In experienced centres, severely-symptomatic patients with severe AS should be considered for percutaneous balloon aortic valvuloplasty in order to avoid the risks of cardiac surgery.

Prosthetic heart valves in pregnancy

In the child-bearing age group, tissue valves have the major advantage of not requiring anticoagulation, if the patient is in sinus rhythm. However, the vast majority of patients will require reoperation later in life, because of structural valve degeneration. The choice of valve prosthesis in the child-bearing age group requires careful judgement of the need for

later reoperation weighed against the hazards of anticoagulation in pregnancy required for mechanical prostheses. There are also some reports of accelerated structural valve degeneration of bioprosthetic valves during pregnancy, but this has not been confirmed in other studies.⁴⁵⁷ Most patients with normally-functioning bioprosthetic valves, who are asymptomatic or only mildly symptomatic, tolerate the haemodynamic changes of pregnancy well. However, heart failure may develop, especially if LV function is already impaired. The treatment of symptomatic heart failure requires digoxin, diuretics, hydralazine, nitrates and beta-blockers. The prolonged use of beta blockers, in particular atenolol, is associated with fetal growth retardation, although they are not teratogenic. ACE inhibitors and angiotensin antagonists are contraindicated in pregnancy, and should be ceased before conception.

Mechanical prosthetic valves: management of anticoagulation therapy

Pregnant women with mechanical valves are a very high-risk group, in whom all anticoagulation options carry maternal and/or fetal risks.^{438–443} Therefore, patients with mechanical prosthetic valves should be given appropriate contraceptive advice to avoid unplanned pregnancy, and counselled about the risks to mother and fetus with pregnancy (Grade D).⁴⁴³

The high risk is due to the hypercoagulable state that exists throughout pregnancy, and the adverse effects of anticoagulation on mother and fetus. Warfarin crosses the placenta, increasing the risk of early miscarriage, embryopathy and late fetal loss, and is associated with approximately a 3–5% rate of maternal thromboembolic complications.⁴⁴⁴ Both unfractionated and LMWH do not cross the placenta, and are used as alternatives to warfarin during pregnancy^{445, 446}, but are associated with higher rates of valve thromboembolic events and maternal morbidity and mortality.⁴⁴⁷

The rate of prosthetic valve thrombosis in patients treated with subcutaneous unfractionated heparin is high, in the order of 25%.⁴⁴⁷ The risk of maternal thromboembolism and maternal death is also more than double in the first trimester with the use of heparin.⁴⁴⁷ Given the difficulty achieving effective therapeutic anticoagulation with subcutaneous unfractionated heparin, it is not recommended for pregnant women with mechanical heart valves. Intravenous unfractionated heparin may be used to provide short-term anticoagulation, such as prior to delivery.

Therapeutic subcutaneous LMWH is associated with a 10–20% rate of prosthetic valve thrombus or related thromboembolic events, with lower rates in compliant women on therapeutic-dose LMWH. Most of the reported cases of heparin-associated prosthetic valve thrombosis occur with older-generation prosthetic valves (e.g. caged ball), often with subtherapeutic doses of LMWH or unmonitored LMWH.⁴⁴⁷ However, there are reported cases of maternal deaths while on LMWH with therapeutic anticoagulation. If LMWH is used, it is essential that anticoagulation levels be regularly monitored with the measurement of anti-factor Xa (anti-Xa) activity. Anti-Xa monitoring may be difficult to obtain outside an urban environment. The addition of low-dose aspirin to heparin may reduce the risk of valve thrombosis. LMWH regimens are associated with a lower rate of fetal loss than that seen with warfarin-based regimens, but the risk of prosthetic thromboembolic complication is probably higher.

The potential thromboembolic problems with heparin have led to the use of warfarin in pregnancy, especially in higher thrombotic-risk patients with first-generation mechanical valves in the mitral position, AF or a history of thromboembolism.⁴⁴³ Warfarin use in pregnancy is more efficacious in preventing valve thrombosis, but is associated with a high rate of fetal loss (up to 30% in total, including 10% late fetal losses) and warfarin embryopathy (approximately 5–29%, although the average rate is under 8%). The risk of embryopathy is greatest between 6 and 12 weeks of gestation, therefore it is recommended that patients be switched from warfarin to LMWH before 6 weeks gestation, where possible, to avoid the risk of embryopathy, and then switching to warfarin until the 36th week of pregnancy. However, there is recent evidence that if the warfarin dose is 5 mg or less, the risk of fetal loss or embryopathy may be lower.^{442, 458} This is usually possible with lower-risk bileaflet prostheses in the aortic position, where an INR of 2–3 is usually adequate, but may not be achievable if higher levels of anticoagulation are required, such as for mitral prostheses. Given the high risks to the fetus if a woman labours while taking warfarin, warfarin is usually ceased at 36 weeks, and replaced with either subcutaneous LMWH or intravenous unfractionated heparin to provide therapeutic anticoagulation until delivery.

The use of these aggressive anticoagulation regimens does increase bleeding risk. In one series, serious bleeding complications occurred in 17% of patients antepartum and 19% postpartum.⁴⁴⁵ The decision relating to the most suitable anticoagulant regimen for the individual woman, in particular balancing fetal with maternal risks, is complex and requires a careful

and informed discussion with the woman, her family and the obstetrician, preferably before pregnancy, but otherwise as early as possible in pregnancy. Given the maternal risks, the option of not continuing the pregnancy should be discussed. Some women may choose to increase their own risk for the benefit of their baby, and such decisions need to be respected, provided it is assured that she has a full understanding of the matter. After the patient agrees to the use of an anticoagulant regimen, written consent should be obtained, or the decision fully documented in the patient's health record (Grade D).

Recommendations for anticoagulation in pregnancy for patients with mechanical valves

There are limited published data available on anticoagulant options, and no randomised comparative studies have been or are likely to be performed. There is a choice of three different anticoagulant regimens during pregnancy for patients with mechanical prostheses (level IV, Grade C): LMWH (enoxaparin) throughout pregnancy, LMWH/warfarin, and warfarin throughout pregnancy (especially older prostheses).^{434, 442}

Low molecular weight heparin (enoxaparin) throughout pregnancy

Weight-adjusted dose (1 mg/kg) LMWH throughout pregnancy, administered subcutaneously every 12 hours with anti-Xa monitoring. The dose must be adjusted to maintain a trough (predose) level of anti-Xa heparin activity of at least 0.6 U/mL in cases at lower risk (aortic valve prosthesis), and at least 0.7 U/mL in higher risk patients (older-generation prosthetic valve in mitral position). Peak levels 4–6 hours post-dose should be 0.8–1.2 U/mL, and should not exceed 1.5 U/mL. Anti-Xa levels should be measured weekly and the LMWH dose increased or decreased by 10 mg twice daily, if levels are low or high respectively (level IV). The addition of low-dose aspirin daily (75–100 mg) may add additional antithrombotic efficacy, but there are no data to prove its efficacy or safety in pregnancy.

Delivery should be planned, and LMWH ceased 36 hours before the induction of labour or Caesarean delivery. Intravenous unfractionated heparin is used to maintain therapeutic anticoagulation until the onset of labour, or until 4–6 hours prior to elective Caesarean delivery. Prior to placement of an epidural, the activated partial thromboplastin time (APTT) should be checked to confirm that it is not elevated. If there is spontaneous onset of labour, LMWH should

be ceased at the onset of labour. Obstetric anaesthesia guidelines require cessation of therapeutic dose anticoagulation at least 24 hours before the insertion of an epidural cannula, and 12 hours before any prophylactic-dose anticoagulation. In the setting of spontaneous onset of labour while taking therapeutic subcutaneous LMWH, it is unlikely that an epidural will be possible during labour due to its long half-life.

Low molecular weight heparin/warfarin

LMWH, as above, up to 13 weeks of gestation, with monitoring of anti-Xa levels, as above.

Warfarin for weeks 13–36. Switch to subcutaneous LMWH or intravenous unfractionated heparin at 36 weeks of gestation to maintain therapeutic anticoagulation until a planned delivery. LMWH should be ceased 36 hours before elective delivery, and therapeutic intravenous unfractionated heparin used until onset of labour, or 4–6 hours prior to elective Caesarean section. See 'LMWH (enoxaparin) throughout pregnancy' section for details.

The addition of low-dose aspirin (75–100 mg) may add additional antithrombotic efficacy. If the onset of labour prior to the cessation of warfarin occurs, reverse warfarin with vitamin K/prothrombinex or similar, and deliver by Caesarean section.

Warfarin throughout pregnancy (especially older prostheses)

Maintain target INR with as low a dose of warfarin as possible. The addition of low-dose aspirin daily (75–100 mg) may add additional antithrombotic efficacy. Switch to therapeutic subcutaneous LMWH or intravenous unfractionated heparin at 36 weeks. LMWH should be ceased 36 hours before elective delivery, and therapeutic intravenous unfractionated heparin used until onset of labour, or 4–6 hours prior to elective Caesarean section. See 'LMWH (enoxaparin) throughout pregnancy' for details.

If the onset of labour prior to the cessation of warfarin occurs, reverse warfarin with vitamin K/prothrombinex, and deliver by Caesarean section. Because of the risk of prosthetic thrombosis with heparin and the difficulty in obtaining anti-Xa monitoring, the European Society of Cardiology has recommended this regimen⁴³⁴ as the preferred anticoagulation approach in patients with mechanical prosthetic valves (i.e. warfarin throughout pregnancy until the 36th week); however, this remains controversial.⁴⁴⁸

Management of delivery

Planned delivery is preferred, given the difficulty balancing the need for therapeutic anticoagulation for the prosthetic valve and avoidance of anticoagulation through delivery and the early postpartum period to reduce haemorrhagic risks for the mother, and if on warfarin, the baby. Vaginal delivery is recommended if there is no significant prosthetic dysfunction or other significant cardiac disease. If Caesarean delivery is necessary for fetal or maternal indications, particular care is required with postpartum anticoagulant management.

Patients receiving warfarin should be switched to therapeutic subcutaneous LMWH or intravenous unfractionated heparin at 36 weeks, as approximately 30% of women experience labour sooner than planned.⁴³⁹ Patients on LMWH at the end of pregnancy should be switched to intravenous unfractionated heparin at least 36 hours prior to elective delivery in the 38th week. Labour is induced and intravenous heparin ceased once labour is established, or 4–6 hours before Caesarean section, and resumed 6–12 hours after delivery. Initiate intravenous heparin infusion at 500 u/h, increasing to therapeutic doses over 24–72 hours, depending on the mode of delivery, and if there are any bleeding complications.

The anaesthetist should be consulted concerning these decisions, as there are formal obstetric anaesthesia guidelines that determine the timing of cessation and commencement of anticoagulation when regional anaesthetic techniques are used, especially epidural analgesia. Be aware of the long half-life of therapeutic subcutaneous LMWH, and that normal APTT levels will not exclude an anticoagulant effect.

Careful titration of intravenous heparin over the first 3–4 days postpartum is necessary, particularly following Caesarean section, to avoid major bleeding. Warfarin is recommenced 24–48 hours after delivery, and the heparin ceased once the INR is over 2. Breastfeeding can be encouraged in women taking anticoagulants, as heparin is not secreted in breast milk; the amount of warfarin in breast milk is low and has been shown to have no effect on neonatal prothrombin time (Grade C).

Endocarditis prophylaxis

Patients with prosthetic valves, or with a history of infective endocarditis, are at higher risk, and therefore, should receive prophylactic antibiotics prior to delivery, and for 24–48 hours thereafter.²⁸⁸ The role of prophylactic antibiotics at the time of delivery in patients with valvular heart disease is controversial. Recent reports have suggested a higher rate of bacteraemia than previously thought. This, together with the seriousness of endocarditis in the peripartum period, has led to some major centres recommending prophylactic antibiotics for all patients with valvular heart disease at the time of delivery.⁴⁴² However, antibiotics are certainly recommended if labour is prolonged, or if there is premature rupture of the membranes. The recommended regimen is 2 g intravenous ampicillin plus gentamicin (1.5 mg/kg, not to exceed 120 mg) given at the start of labour, or within 30 min of Caesarean section. A second dose of intravenous ampicillin or oral amoxicillin should be given 6 hours later (Table 5.9). These agents may be unnecessary when routine Caesarean antibiotic prophylaxis is used.

Table 5.11 Key points in the management of pregnancy in women with RHD

Predictors of increased maternal and fetal risk	<p>Decreased LV systolic function</p> <p>Significant aortic and mitral stenosis</p> <p>Moderate or severe pulmonary hypertension</p> <p>Heart failure</p> <p>Symptoms before pregnancy</p> <p>Mechanical valve prostheses</p> <p>Atrial fibrillation requiring warfarin</p>
Cardiac assessment	<p>Early comprehensive assessment with echocardiography to assess valves and LV function</p> <p>Plan multidisciplinary management</p>
Mitral/aortic regurgitation	<p>Usually well tolerated</p> <p>Treat medically with diuretics, vasodilators (no ACE inhibitors/angiotensin II receptor blockers) for clinical heart failure</p>
Mitral stenosis	<p>Mild to moderate mitral stenosis: manage medically moderate to severe mitral stenosis (MVA <1.5 cm²)—consider PBMV during late second trimester, if patient remains symptomatic and PAS pressure >50 mmHg</p> <p>Beta-blockers or digoxin for rate control of atrial fibrillation</p>
Aortic stenosis (rare)	<p>Mild to moderate aortic stenosis: well-tolerated. Diuretics for heart failure</p> <p>Consider PTAV if severe symptoms</p> <p>Beta-blockers or digoxin for rate control of atrial fibrillation. Avoid cardiac surgery, as high risk of fetal loss</p>
Mechanical/prosthetic valves and anticoagulation in pregnancy	<p>High maternal and fetal risk</p> <p>Risk of warfarin embryopathy in first trimester</p> <p>Embryopathy may be avoided if warfarin dose ≤5 mg</p>
Choice of 3 antithrombotic regimens	<ol style="list-style-type: none"> 1. LMWH throughout pregnancy, weight-adjusted dose with anti-Xa level monitoring 2. Warfarin throughout pregnancy, if can keep warfarin ≤5 mg, e.g. INR 2–3 in aortic prosthesis, sinus rhythm; change to LMWH or unfractionated heparin at 36 weeks 3. LMWH until 13 weeks, and then warfarin and aspirin until 36 weeks; change to LMWH or UFH until labour. Monitor anti-Xa levels with LMWH
Labour	<p>Haemodynamic monitoring: non-invasive, if mild to moderate valve disease</p> <p>Antibiotic prophylaxis, if prolonged labour and/or ruptured membranes</p> <p>Aim for short second stage and multidisciplinary management approach, with low threshold for obstetric intervention</p>

ACE, angiotensin-converting enzyme; anti-Xa, antifactor Xa; INR, international normalised ratio; LMWH, low-molecular weight heparin; LV, left ventricle; MVA, mitral valve area; PAS, pulmonary artery systolic; PBMV, percutaneous balloon mitral valvuloplasty; PTAV, percutaneous transluminal aortic valvuloplasty; UFH, unfractionated heparin.

Appendix

Appendix 1

Literature Review Process

Databases searched

The following databases were searched:

- The Cochrane Library of Systematic Reviews and Cochrane Databases
- Ovid Medline
- EMBASE
- PUBMED
- PUBMED Clinical trials
- Scirus Search (deep web)
- Public Library of Science (PLOS - free access database)

Search terms

The following search terms were used:

- Acute rheumatic fever
- Rheumatic heart disease
- Diagnosis
- Management
- Treatment
- Acute rheumatic fever AND diagnosis OR management OR treatment
- Rheumatic heart disease AND diagnosis OR management OR treatment
- Chorea

- Rheumatic chorea
- Sydenham's chorea
- Mitral stenosis
- Mitral regurgitation (rheumatic only)
- Percutaneous mitral valvuloplasty
- Pregnancy and rheumatic heart disease
- Pregnancy and valvular heart disease

Limits

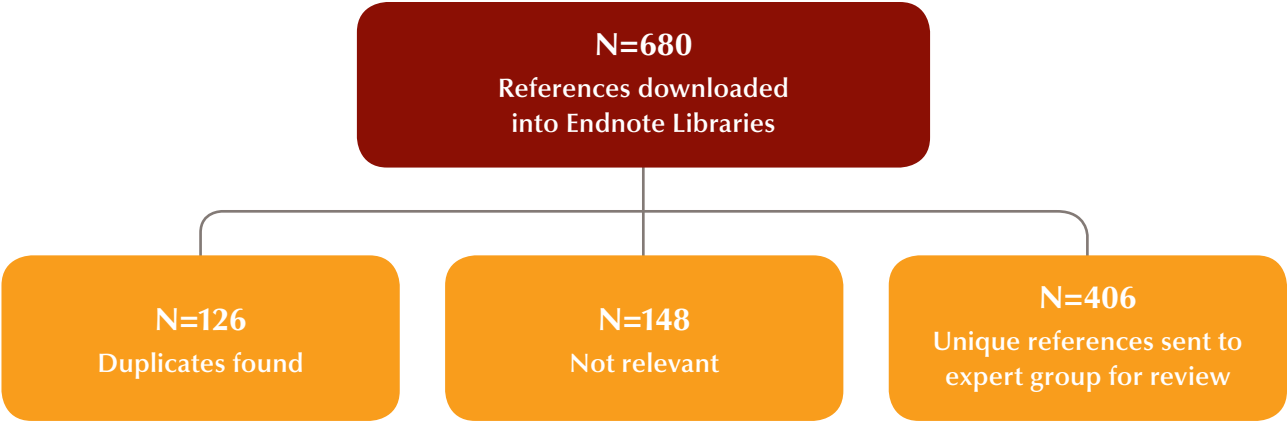
- Date range – 2004 to 'current' (or 31 May 2010)
- Articles in English
- Studies with humans

Other searches were run to ensure that all the terms in the 2006 guidelines document and those specifically identified by the expert group were included. These were:

- Echocardiography
- Serology (new data, new ranges)
- Post-streptococcal sequelae
- Post-streptococcal reactive arthritis
- PANDAS
- Subclinical carditis
- Pregnancy

Results by database

Database	Number retrieved
Scirus	129
Ovid Embase	52
PubMed	105
Ovid Medline	391
Cochrane Library of Systematic Reviews and Cochrane Databases	3
Total retrieved	680



Appendix 2

Recommended dataset for ARF/RHD Registers

ARF/RHD Clinical Dataset

- Individual healthcare identifier
- Identifier (RHD)
- Statistical linkage key
- Family name
- Given name
- Alias
- Date of birth
- Date - accuracy indicator
- Sex
- Indigenous status
- Target group (non-Indigenous)
- Country of birth
- State/territory of birth
- Informal carer existence indicator
- Informal carer relationship to care recipient
- Influenza vaccine administration date
- Pneumococcal vaccine administration date
- Pregnancy indicator
- Expected confinement date
- Anti-coagulant treatment commencement date
- Anti-coagulant treatment cessation date
- Date of death
- Underlying cause of death

Person address

- Address change date
- Address status
- House/property identifier
- Street name
- Street type
- Suburb/town/locality name
- Australian postcode
- Electronic communication address.
- Electronic communication medium
- Indigenous community identifier

Service provider organisation

- Organisation identifier (state/territory)
- Organisation identifier (Australian)
- Organisation name
- Australian postcode

Acute rheumatic fever diagnosis and notification

- Australian state/territory identifier
- Identifier Notification date
- Likely onset date
- Specimen date (streptococcal titres)
- Specimen date (throat swab)
- Notification received date
- Notifiable disease
- Organism
- First or recurrent episode status
- Confirmation status

- Laboratory diagnosis method
- Case found by
- Presence of clinical carditis
- Presence of Sydenham chorea
- Presence of erythema marginatum
- Presence of subcutaneous nodules
- Presence of polyarthralgia
- Presence of aseptic mono-arthritis
- Presence of cardiac lesions on echocardiogram
- Presence of fever (reported 38°C +)
- Presence of erythrocyte sedimentation rate ≥ 30 mm / hour
- c-reactive protein ≥ 30 mg/L
- Prolonged PR interval
- Presence of raised group A streptococcal titres
- Highest anti-deoxyribonuclease B
- Highest antistreptolysin O titre

Rheumatic heart disease diagnosis

- Diagnosis date (RHD)
- Presence of mitral valve regurgitation
- Severity of mitral valve regurgitation
- Presence of mitral valve stenosis
- Severity of mitral valve stenosis
- Presence of aortic valve regurgitation
- Severity of aortic valve regurgitation
- Presence of aortic valve stenosis
- Severity of aortic valve stenosis
- Presence of tricuspid valve lesion
- Presence of pulmonary valve lesion

Acute rheumatic fever and rheumatic heart disease status

- ARF/RHD status assessment date
- ARF/RHD status
- Antibiotics requirement
- INR target range

Health care practitioner review

- Review due date
- Review date
- Health care provider type
- Certified dentally fit

Antibiotic regimen

- ARF prophylaxis commencement date
- ARF prophylaxis expected cessation date
- ARF prophylaxis cessation date
- Antibiotic agent
- Frequency of intramuscular antibiotic (ARF)
- Antibiotic administration date, DDMMYYYY
- Anticoagulant treatment
- Commencement date
- Cessation date
- International normalised ratio measurement date
- International normalised ratio level (measured)
- Dose prescribed, total milligrams per 24 hour
- Rheumatic heart disease surgery
- Date on which RHD surgery was recommended
- Surgical procedure date
- Surgical outcome (patient survival)

Valve procedure

- Heart valve identifier
- Valve procedure type (RHD)
- Heart valve prosthesis identifier

Appendix 3

Key Performance Indicators for ARF/RHD

1 Epidemiology			
	1.1	Yearly age-specific incidence rates of all episodes, and of first episodes of ARF according to sex (refer to 1.1.1) and ethnicity (refer to 1.1.2)	<ul style="list-style-type: none"> • 0-4 • 5-14 • 15-24 • 25-34 • 35-44 • >44yrs
	1.1.1	sex	<ul style="list-style-type: none"> • Male • Female • Indeterminate • Not stated/inadequately described
	1.1.2	ethnicity	<ul style="list-style-type: none"> • Aboriginal but not Torres Strait Islander origin • Torres Strait Islander, but not Aboriginal origin • both Aboriginal and Torres Strait Islander origins • Maori • other Pacific Islanders • other • unknown
	1.2	Proportion of all recorded ARF episodes classified as recurrences	
	1.3	Rates of ARF recurrences per 100 patient-years	
	1.4	Number of deaths and age-standardised rates of mortality due to ARF and RHD in the previous calendar year by ethnicity (refer to 1.1.2)	
	1.5	Yearly age-specific (refer to 1.1) and overall incidence of RHD by ethnicity (refer to 1.1.2) and broken down by method found and presented	<ul style="list-style-type: none"> • all recorded RHD cases • cases classified as mild • cases classified as moderate • cases classified as severe
	1.6	Yearly age-specific (refer to 1.1) prevalence of RHD, by ethnicity (refer to 1.1.2)	<ul style="list-style-type: none"> • all recorded RHD cases • cases classified as mild • cases classified as moderate • cases classified as severe
	1.7	Proportion of newly registered cases of ARF or RHD with an initial recorded diagnosis being established RHD (rather than ARF)	

2 Requirement and uptake of secondary prophylaxis		
	2.1	Proportion of all people indicated for secondary prophylaxis* who are registered to receive benzathine penicillin G (BPG)
	2.2	Median percentage of all scheduled BPG doses actually delivered
	2.3	Proportion of people indicated for BPG secondary prophylaxis who received <50%, 50-79%, and ≥80% of scheduled doses in the previous calendar year
3 Quality of management		
	3.1	Proportion of all registered ARF and RHD cases classified as mild, moderate, severe and inactive
	3.2	Proportion of people classified as moderate or severe RHD who had an echocardiogram within the previous 6 months, 1 year, and 1-2 years
	3.3	Number of cases, and proportion of total cases indicated for cardiac surgery, who have been waiting <6 months, 6-11 months, 12-23 months, or 24+ months
	3.4	<div> <div> Number and type of surgical procedures performed during the previous calendar year by the following: </div> <div> <div>3.4.1 age group</div> <div>3.4.2 ethnicity</div> </div> <div> <div>(refer to 1.1)</div> <div>(refer to 1.1.2)</div> </div> </div>
	3.5	<div> <div> Number (and proportion) of people who died in the previous calendar year within 28 days and 1 year of undergoing rheumatic cardiac surgery by the following: </div> <div> <div>3.5.1 age group</div> <div>3.5.2 ethnicity</div> </div> <div> <div>(refer to 1.1)</div> <div>(refer to 1.1.2)</div> </div> </div>

* If denominator of those indicated for prophylaxis not known, use people with a history of ARF within the last 10 years OR ARF and RHD and aged < 21 years OR aged ≥21 years with moderate or severe RHD

Acronyms and abbreviations

2DE	two-dimensional echocardiography	ECG	electrocardiogram
3DE	three- dimensional echocardiography	EF	ejection fraction
ACE	angiotensin-converting enzyme (inhibitor)	ESR	erythrocyte sedimentation rate
AHA	American Heart Association	GAS	group A streptococcus
anti-DNase B	antideoxyribonuclease B	GCS	group C streptococcus
anti-Xa	antifactor Xa	GGs	group G streptococcus
AF	atrial fibrillation	HR	heart rate
AMVL	anterior mitral valve leaflet	IM	intramuscular (injection)
APSU	Australian Paediatric Surveillance Unit (APSU)	INR	international normalised ratio
APTT	activated partial thromboplastin time	IV	intravenous (injection)
AR	aortic regurgitation	IVC	inferior vena cava
ARF	acute rheumatic fever	IVIG	intravenous immunoglobulin
AS	aortic stenosis	LMWH	low molecular weight heparin
ASO	antistreptolysin O	LV	left ventricular
AV	aortic valve	LVEF	left ventricular ejection fraction
AVA	aortic valve area	LVEDD	left ventricular end-diastolic diameter
bd	<i>bis die</i> (twice daily)	LVESD	left ventricular end-systolic diameter
BP	blood pressure	LVOT	left ventricular outflow tract
BPG	benzathine penicillin G	METeOR	Metadata Online Registry
CDNA	Communicable Disease Network of Australia	MNT	M non-typable
CRP	C-reactive protein	MR	mitral regurgitation
CSANZ	Cardiac Society of Australia and New Zealand	MS	mitral stenosis
		MVA	mitral valve area
		MVD	mitral valve disease

NSAID	non-steroidal anti-inflammatory drug	V	velocity
NYHA FC	New York Heart Association Functional Class	WBC	white blood cell count
PANDAS	paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	WHF	World Heart Federation
		WHO	World Health Organization
PAS	pulmonary artery systolic (pressure)		
PAWP	pulmonary arterial wedge pressure		
PBMV	percutaneous balloon mitral valvuloplasty		
PBTV	percutaneous balloon tricuspid valvuloplasty		
PCR	polymerase chain reaction		
PHT	pulmonary hypertension		
po	<i>per os</i> (by mouth)		
PTAV	Percutaneous transluminal aortic valvuloplasty		
RADT	rapid antigen detection test		
RCT	randomised, controlled trial		
RHD	rheumatic heart disease		
RR	respiratory rate		
RV	right ventricle		
tds	<i>ter die sumendum</i> (three times daily)		
TS	tricuspid stenosis		
TOE	transoesophageal echocardiography		
UFH	unfractionated heparin		
ULN	upper limit of normal		

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