Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia

An evidence-based review

Heart Foundation

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Endorsing organisations

As well as the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, these guidelines are endorsed by the following organisations.

Australian Society for Infectious Diseases

Australian Indigenous Doctors' Association

CRANA

National Aboriginal Community Controlled Health Organisation

THE ROYAL AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS

The Royal Australasian College of Physicians

ROYAL COLLEGE OF NURSING Australia

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SUMMARY

Acute rheumatic fever (ARF) is an illness caused by a reaction to a bacterial infection, which often results in lasting damage to heart valves. This is known as rheumatic heart disease (RHD) and it is an important cause of premature mortality. 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 and better availability of medical care. 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. RHD is the most frequent form of heart disease in children worldwide.

There is also considerable regional variation within countries. In Australia, ARF and RHD are highly prevalent among Aboriginal and Torres Strait Islander communities, mostly affecting young people. Aboriginal and Torres Strait Islander people are up to eight times more likely than non-Aboriginal and Torres Strait Islander people to be hospitalised for ARF and RHD, and nearly 20 times as likely to die.

The National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) jointly developed this evidence-based review to address factors contributing to inadequate diagnosis and management of ARF and RHD in Australia. The review covers diagnosis and management of ARF, secondary prevention and RHD control programs, and diagnosis and management of chronic RHD.

DIAGNOSIS AND MANAGEMENT OF ACUTE RHEUMATIC FEVER

ARF is an auto-immune response to bacterial infection with group A streptococcus (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.

While it is widely thought that only upper respiratory tract infection with GAS can cause ARF, there is evidence that GAS skin infections may play a role in certain populations, including Aboriginal and Torres Strait Islander Australians.

ARF is predominantly a disease of children aged 5–14 years, although people can have recurrent episodes well into their forties. The prevalence of RHD peaks in the third and fourth decades. Therefore, although ARF is a disease with its roots in childhood, its effects are felt throughout adulthood, especially in the young adult years when people might otherwise be at their most productive.

Diagnosis of ARF

Accurate diagnosis of ARF is important. Over-diagnosis results in unnecessary treatment over a long time, while under-diagnosis 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. In this guideline, the Jones and WHO criteria have been further modified to form the 2006 Australian criteria for the diagnosis of acute rheumatic fever.

> **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 incidence of ARF, a person with fever and arthritis is more likely to have ARF. Some post-streptococcal syndromes may be confused with ARF 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 ARF

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 to patients with ARF has been proven to alter the outcome of the acute episode, or the amount of damage to heart valves. Thus, there is no urgency to begin definitive treatment. 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.

Ideally, all patients with suspected ARF (first episode or recurrence) should be hospitalised as soon as possible after onset of symptoms. This ensures that all investigations are performed and, if necessary, the patient 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 effective and cost-effective at both community and population levels. Randomised controlled trials 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 3-weekly administration is recommended. The benefits of 3-weekly BPG injections are offset by the difficulties of achieving good adherence, even to the standard 4-weekly regimen. Prospective data from New Zealand showed that few, if any, recurrences occurred among people who fully adhered to a 4-weekly BPG regimen.

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. For patients taking oral penicillin, the consequences of missed 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 (eg 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. Intramuscular bleeding is rare when BPG injections are used in conjunction with anti-coagulation therapy.

The appropriate duration of secondary prophylaxis is determined by age, time since the last episode of ARF, 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 Islander Australians. People with established RHD or prosthetic valves should receive antibiotic prophylaxis prior to procedures expected to produce bacteraemia (eg dental procedures, surgical procedures where infection is present).

Adherence to secondary prophylaxis

Persistent high rates of recurrent ARF in Australia highlight the continued failure of 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, while 45% of all episodes of ARF were recurrences.

A variety of factors, mainly sociological, combine to limit the effectiveness of secondary prophylaxis. The major reasons for poor adherence in remote Australian Aboriginal and Torres Strait Islander communities are the availability and acceptability of health services, rather than personal factors such as injection refusal, pain of injections, or a lack of knowledge or understanding of ARF and RHD. Adherence is improved when patients feel a sense of personalised care and "belonging" to the clinic, and when recall systems extend beyond the boundaries of the community.

Hospitalisation for ARF provides an ideal opportunity to begin secondary prophylaxis, and to educate patients and families on how important it is to prevent future episodes of ARF. Continuing education and support by primary care staff, using culturally appropriate educational materials, should follow 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:

- routine review and care planning;

- recall and reminder systems;

- having local staff members dedicated to secondary prophylaxis and coordinating routine care;

- supporting and utilising the expertise, experience, community knowledge and language skills of Aboriginal health workers;

- improving staff awareness of diagnosis and management of ARF and RHD;

- taking measures to minimise staff turnover; and

- implementing measures to reduce the pain of injections (eg use a 23-gauge needle, warm syringe to room temperature, apply pressure with thumb before inserting needle, deliver injection very slowly).

RHD 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.

Recommended elements of RHD control programs include the following:

- a single, centralised (preferably computerised) ARF/RHD register for each program;

- a dedicated coordinator (this is critical to the success of the program); and

- integration of activities into the established health system to ensure the control program continues to function well despite staffing changes.

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

<div style="background:red;color:white;font-weight:bold">DIAGNOSIS AND MANAGEMENT OF CHRONIC RHEUMATIC HEART DISEASE</div>

It is difficult and expensive for Aboriginal and Torres Strait Islander people to travel to major centres for cardiac services which are often hospital based. Although specialist outreach services are improving in many regions, access to specialist care is suboptimal in rural and remote areas.

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

- access to a specialist physician and/or cardiologist (preferably the same specialist over a long time);

- access to echocardiography — portable echocardiography may be required so that all RHD patients in Australia have access to echocardiography, regardless of location;

- adequate monitoring of anticoagulation therapy in patients with atrial fibrillation and/or mechanical prosthetic valves; and

- secondary prevention with penicillin prophylaxis.

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 surgical intervention.

> **The fundamental goal in long-term management of chronic RHD is to avoid, or at least delay, valve surgery. Therefore, prophylaxis with BPG to prevent recurrent ARF is a crucial strategy in managing patients with chronic RHD. Where adherence to secondary prevention is poor, there is greater need for surgical intervention, and long-term surgical outcomes are not as good.**

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Valvular lesions in RHD

Mitral regurgitation

Mitral regurgitation is the most common valvular lesion in RHD, particularly in young patients. In chronic mitral regurgitation, 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 mitral regurgitation 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 atrial fibrillation.

There is wide individual variation in the rate of progression of mitral regurgitation, although many cases tend to progress over 5–10 years, especially if there is a recurrence of ARF.

Key points in diagnosis and management of mitral regurgitation include the following.

- Echocardiography 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 mitral regurgitation, echocardiography should be performed at least every 6–12 months.

- Clinical heart failure requires diuretic therapy and ACE inhibitors.

- Patients with severe mitral regurgitation should be referred for surgery if they become symptomatic or if they have echocardiographic indicators of reduced LV systolic function or an end systolic diameter by echo of ≥40mm. Patients who are asymptomatic or mildly symptomatic and have severe mitral regurgitation and normal LV systolic function should consult cardiac surgeons early, so that appropriate care plans can be developed.

- Mitral valve repair rather than replacement is the operation of choice for symptomatic dominant or pure mitral regurgitation. If the mitral valve is not suitable for repair, the options are valve replacement, either with a mechanical valve prosthesis or a bioprosthetic valve.

Mitral stenosis

In mitral stenosis, progressive obstruction to LV inflow develops due to fibrosis and partial fusion of the mitral valve leaflets. Approximately 30% of Aboriginal RHD patients in the Northern Territory aged 10–19 years have mitral stenosis, and the mean age of those with mitral stenosis is 33 years. In the Aboriginal and Torres Strait Islander population, mitral stenosis progresses more rapidly than in the non-Aboriginal and Torres Strait Islander population 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 $1.0–1.5cm^2$.

Key points in diagnosis and management of mitral stenosis include the following.

- Doppler and two-dimensional echocardio-graphy is used to quantitate the severity of mitral stenosis; assess associated valve lesions, LV function, left atrial size; and estimate pulmonary artery systolic pressure.

- The treatment of symptomatic moderate to severe mitral stenosis is interventional therapy. Patients who develop congestive heart failure respond to diuretic therapy.

- Atrial fibrillation is the most common complication of mitral stenosis, requiring long-term prophylactic anticoagulation with warfarin. When new-onset atrial fibrillation is associated with symptoms, consideration should be given to direct-current cardioversion to restore sinus rhythm.

- Percutaneous balloon mitral valvuloplasty is the treatment of choice for dominant or pure mitral stenosis. The indication is a mitral valve area <1.5cm^2 with progressive symptoms, or if asymptomatic, a history of thromboembolism or significant pulmonary hypertension.

- The short-term and medium-term results are comparable to surgical valvuloplasty, with 65% of patients being free of restenosis after 10 years.

- Surgical intervention has largely been replaced by percutaneous balloon mitral valvuloplasty. 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, there is volume and pressure overload of the left ventricle, eventually leading to contractile dysfunction in the 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 diagnosis and management of aortic regurgitation include the following.

- Echocardiography is used to assess LV size and function. The severity of aortic regurgitation 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 can reduce LV dilatation and the regurgitant fraction, slow progression of LV dilatation and possibly 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 aortic regurgitation.

- Patients with moderate to severe aortic regurgitation who become symptomatic should be referred for surgery. In asymptomatic or mildly symptomatic patients, surgery is indicated if LV function is reduced (LV ejection fraction <55%) or LV end systolic diameter is approaching 55mm.

- Options for aortic valve surgery are replacement with 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).

- Patients who demonstrate good adherence to medications are suitable for replacement with the newer bileaflet mechanical valve prosthesis, which has the best long-term durability and freedom from re-operation. 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 foetus posed by anticoagulation during pregnancy.

Aortic stenosis

Aortic stenosis results from fibrosis and partial fusion of aortic valve cusps, causing progressive obstruction to LV outflow. RHD is an uncommon cause of aortic stenosis 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 diagnosis and management of aortic stenosis include the following.

- Two-dimensional echocardiography 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.

- Patients usually do not develop symptoms of exertional dyspnoea and fatigue until a moderate or severe systolic gradient develops (>40–50mmHg). 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 aortic stenosis. 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 foetal risk are reduced LV systolic function, significant aortic or mitral stenosis, 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 occurs. If they are already symptomatic due to significant RHD, serious consideration should be given to intervention prior to pregnancy. In patients with moderate or severe mitral stenosis, percutaneous balloon mitral valvuloplasty should be considered, because of the high risk of maternal and foetal complications during pregnancy. Patients with mechanical valves who are on warfarin should be given appropriate contraceptive advice and should be counselled about the risks to mother and foetus with pregnancy.

Warfarin crosses the placenta but heparin does not. However, there is an increased risk of prosthetic thrombosis with heparin and a risk of embryopathy with warfarin, especially in the first trimester. The choices for antithrombotic therapy during pregnancy are low molecular weight heparin throughout, warfarin throughout, or low molecular weight heparin for the first trimester and then warfarin.

Warfarin throughout pregnancy is the favoured regimen if the dose can be kept to ≤5mg.

INTRODUCTION

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

By 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 USA[1] highlight the need to remain aware of this disease in all populations.

The National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) have identified several factors contributing to inadequate and management of ARF and RHD in Australia:

- although strategies for preventing RHD are proven, simple, cheap and cost-effective, they are not adequately implemented — in fact sometimes not implemented at all — 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 lack of up-to-date training and experience in the management of ARF and RHD occasionally resulting in inappropriate management; and

- access to health care services by population groups experiencing the highest rates of ARF and RHD is limited.

The NHFA and CSANZ have jointly developed this review with the following aims:

- **identifying the standard of care, including preventive care, that should be available to all people**

- **identifying areas where current management strategies may not be in line with available evidence**

- **in the interests of equity, ensuring that high-risk populations receive the same standard of care as that available to other Australians.**

This review was developed by a writing group comprising experts in the area, with the involvement of selected individuals with experience in ARF and RHD as well as relevant stakeholders — a wide range of general and specialist clinicians, allied health professionals, and Aboriginal and Torres Strait Islander representative groups. The development process is described in the Appendix.

The development process was informed by National Health and Medical Research Council (NHMRC) principles for guideline development.[2] The review includes levels of evidence and grades of diagnosis recommendation (Table 1.1). The NHMRC levels[3] and grades have been adapted from those produced by the US National Institutes of Health.

This review has been produced for Australia, and is endorsed by Australian organisations. Our New Zealand colleagues have considerable experience with ARF and RHD in the Maori and Pacific Islander populations. In recognition of this, two members of the writing group and many of the reviewers who provided comments are from New Zealand. We thank them for their contributions.

TABLE 1.1   LEVELS OF EVIDENCE FOR CLINICAL INTERVENTIONS AND GRADES OF RECOMMENDATION

LEVEL OF EVIDENCE	STUDY DESIGN
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-I	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
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
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 pre-test and post-test

GRADE OF RECOMMENDATION	
A	Rich body of high-quality randomised controlled trial (RCT) data
B	Limited body of RCT data or high-quality non-RCT data
C	Limited evidence
D	No evidence available — panel consensus judgement

Note: 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).

Scope of the review

This review focuses on:

- diagnosis and management of ARF;

- secondary prevention and RHD control programs; and

- diagnosis and management of chronic RHD.

Some important recent developments and controversies addressed by the review include:

- the need for different criteria for the diagnosis of ARF in high-risk compared to low-risk populations;

- use of corticosteroids in treatment of ARF;

- use of echocardiography in diagnosis and monitoring of patients with ARF and RHD;

- timing of referral for valve surgery in RHD;

- valve replacement versus valve repair for mitral and aortic valve disease; and

- the importance of ARF/RHD registers and coordinated control programs.

The review does not address primary prevention of ARF — this area is controversial and the literature is extensive.[4–7] The authors consider that such discussion would detract from the focus on best practice in the diagnosis and management of ARF and RHD. Moreover, while there is good evidence for the efficacy and cost-effectiveness of secondary prevention of ARF, there is no clear evidence that systematic, population-wide, sore-throat treatment programs are cost-effective.[8]

Target audience

This review 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 over-ride good clinical judgement).

A guide for health professionals — medical, nursing, allied health and Aboriginal health workers — has been developed based on this review, 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.

For the purposes of this review, the terms 'Aboriginal and Torres Strait Islanders' and 'Aboriginal' have been used interchangeably in accordance with the references utilised.

1   OVERVIEW

Acute rheumatic fever (ARF) is an auto-immune consequence of infection with the bacterium group A streptococcus (GAS). It causes an acute generalised inflammatory response and 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 rheumatic heart disease (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. The reader is referred to two recent overviews of acute rheumatic fever for a perspective on some of the issues not covered in this review.[9,10]

1.1   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.[11]

It is clear that only some strains of GAS are "rheumatogenic", although the basis of rheumatogenicity is also unknown.[12,13] 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 (eg Aboriginal Australians), GAS skin infections may play a role in ARF pathogenesis.[5]

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.

1.2   EPIDEMIOLOGY

The burden of ARF in industrialised countries declined dramatically during the 20th century, mainly due to improvements in living standards (and hence reduced transmission of GAS) and better availability of medical care.[14,15] In most affluent populations, ARF is now rare. RHD is also rare in younger people in industrialised countries, although it is still seen in some elderly patients, a legacy of ARF half a century earlier.

By contrast, ARF and RHD remain common in many developing countries. A recent 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.[16] Almost all cases and deaths occur in developing countries. These figures are all likely to be underestimates of the true burden of the disease.

There is substantial regional variation in the burden of ARF and RHD. The highest documented rates in the world are found in Aboriginal Australians, and Maori and Pacific Islander people 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.[16]

A recent summary of the available data on ARF and RHD burden in Australia concluded that these diseases are almost exclusively restricted to Aboriginal and Torres Strait Islander people living in regional and remote areas of central and northern Australia.[17] The annual incidence of ARF in Aboriginal children aged 5–14 years in the Northern Territory ranged from 250 to 350 per 100,000. In the same region, the prevalence of RHD was 13 to 17 per 1,000 Aboriginal people of all ages, compared to under 2 per 1,000 non-Aboriginal and Torres Strait Islander people living in the Northern Territory. Some data suggested similarly high rates in the Kimberley region of Western Australia and in Far North Queensland. Aboriginal and Torres Strait Islander people were up to eight times more likely than non-Aboriginal and Torres Strait

Islander people to be hospitalised for ARF and RHD, and nearly 20 times as likely to die. While 45% of Aboriginal and Torres Strait Islander people receiving heart valve surgery for RHD were aged less than 25 years, only 4% of heart valve procedures were performed on other Australians aged less than 25 years.

ARF is predominantly a disease of 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.[11] Therefore, although ARF is a disease with its roots in childhood, its effects are felt throughout adulthood, especially in the young adult years when patients might otherwise be at their most productive. For example, between 1966 and 1979 there were 171 deaths due to ARF and RHD in Aboriginal people in the Northern Territory, which resulted in 5,037 years of potential life lost to age 65 years.[18]

Key points

- **Acute rheumatic fever, an auto-immune response to group A streptococcus 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 rheumatic heart disease. Recurrences are likely in the absence of preventive measures, and may cause further cardiac valve damage.**

- **Although acute rheumatic fever is rare in industrialised countries, it is a significant cause of disease among Aboriginal and Torres Strait Islander children. Prevalence of rheumatic heart disease is also high among these populations, with significant rates of procedures and death among young adults.**

2 DIAGNOSIS AND MANAGEMENT OF ACUTE RHEUMATIC FEVER

2.1 IMPORTANCE OF ACCURATE DIAGNOSIS

It is important that an accurate diagnosis of acute rheumatic fever (ARF) is made:

- over-diagnosis will result in the individual receiving benzathine penicillin G (BPG) injections unnecessarily every 3–4 weeks for a minimum of 10 years; and

- under-diagnosis 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 pre-test probability for diagnosis of ARF varies according to location and ethnicity. For example, in a region with high compared with low incidence of ARF, a person with fever and arthritis is more likely to have ARF. Similarly, in a region with high incidence, Aboriginal and Torres Strait Islander patients are more likely than non-Aboriginal and Torres Strait Islander patients to have ARF.

2.2 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 prevalence of ARF are often the most isolated. 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 rheumatic heart disease (RHD) in northern Australia have not been previously diagnosed with ARF.[19] It is very important that health staff receive appropriate education about ARF before remote postings.

2.3 CURRENT APPROACHES TO DIAGNOSIS — JONES CRITERIA AND WHO CRITERIA

The Jones criteria for the diagnosis of ARF were introduced in 1944.[20] 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 to be 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.[21] 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, which suggests that the consequences of under-diagnosis are likely to be greater than those of over-diagnosis. All cases of suspected ARF should be judged against the most recent version of the Jones criteria, but the criteria need not be rigidly adhered to when ARF is the most likely diagnosis.

An expert group convened by the World Health Organization (WHO) has recently provided additional guidelines as to how the Jones criteria should be applied in primary and recurrent episodes.[6] Because the Jones and WHO criteria appear too restrictive, modified criteria for high- and low-risk populations in Australia are presented in Table 2.1.

TABLE 2.1   2005 AUSTRALIAN GUIDELINES FOR THE DIAGNOSIS OF ACUTE RHEUMATIC FEVER

	HIGH-RISK GROUPS*	ALL OTHER GROUPS
Initial episode of ARF	2 major **or** 1 major and 2 minor manifestations **plus** evidence of a preceding GAS infection[†]	
Recurrent attack of ARF in a patient with known past ARF or RHD	2 major **or** 1 major and 2 minor **or** 3 minor manifestations **plus** evidence of a preceding GAS infection[†]	
Major manifestations	Carditis (including subclinical evidence of rheumatic valve disease on echocardiogram) Polyarthritis or aseptic mono-arthritis or polyarthralgia[‡] Chorea[¥] Erythema marginatum[§] Subcutaneous nodules	Carditis (excluding subclinical evidence of rheumatic valve disease on echocardiogram) Polyarthritis[‡] Chorea[¥] Erythema marginatum[§] Subcutaneous nodules
Minor manifestations	Fever[H] ESR ≥30mm/hr or CRP ≥30mg/L Prolonged P-R interval on ECG[Θ]	Fever[H] Polyarthralgia or aseptic mono-arthritis[‡] ESR ≥30mm/hr or CRP ≥30mg/L Prolonged P-R interval on ECG[Θ]

Notes: All categories assume that other more likely diagnoses have been excluded.
Please see text for details about specific manifestations.
CRP=C-reactive protein; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; GAS=group A streptococcus

[*]   High-risk groups are those living in communities with high rates of ARF (incidence >30 per 100,000 per year in 5–14-year-olds) or RHD (all-age prevalence >2 per 1,000). Aboriginal and Torres Strait Islander Australians living in rural or remote settings are known to be at high risk. Data are not available for other populations, but Aboriginal and Torres Strait Islander Australians living in urban settings, Maori and Pacific Islander people, and potentially immigrants from developing countries may also be at high risk.

[†]   Elevated or rising anti-streptolysin 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. Other causes of arthritis/arthralgia should be carefully excluded, particularly in the case of mono-arthritis (eg septic arthritis, including disseminated gonococcal infection), infective or reactive arthritis (eg Ross River virus, Barmah Forest virus, influenza, rubella, *Mycoplasma*, cytomegalovirus, Epstein–Barr virus, parvovirus, hepatitis and *Yersinia*), and auto-immune arthropathy (eg juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis, sarcoidosis). 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.

[¥]   Rheumatic (Sydenham's) chorea does not require other manifestations or evidence of preceding GAS infection, provided other causes of chorea are excluded.

[§]   Erythema marginatum is a distinctive rash (see text). Care should be taken not to label other rashes, particularly non-specific viral exanthemas, as erythema marginatum.

[H]   Oral, tympanic or rectal temperature ≥38°C on admission or documented during the current illness.

[Θ]   Note that, if carditis is present as a major manifestation, prolonged P-R interval cannot be considered an additional minor manifestation in the same person.

Patients who do not fulfil these criteria, but in whom the clinician remains suspicious that the diagnosis may be ARF, should be offered a single dose of benzathine penicillin G at secondary prophylaxis doses (see Section 3.1) and reviewed in 1 month with a repeat echocardiogram to detect the appearance of new lesions. If there is evidence of rheumatic valve disease clinically or on echocardiogram, the diagnosis is confirmed, and long-term secondary prophylaxis can be continued.

Arthritis

Arthritis 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). Indeed, 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-arthralgia 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 Section 2.11).

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 high ARF/RHD prevalence.

In high-risk populations in Australia, mono-arthritis or polyarthralgia is a common manifestation of ARF, and is often associated with overt or subclinical carditis.[22] 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 2.6) should be carefully excluded. 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 affects females predominantly, particularly in adolescence.[23,24] It is very common in Aboriginal Australians (28% of ARF presentations in this population).[24] 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); and

- inability to maintain protrusion of the tongue.

Because chorea may occur after a prolonged latent period following group A streptococcus (GAS) infection,[25–27] 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 mildly elevated erythrocyte sedimentation rate (ESR, approx 40mm/hr), but have a normal serum C-reactive protein (CRP) level and white cell count.[24,28,29] Chorea is the ARF manifestation most likely to recur, and is often 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.

During recent outbreaks of ARF in the USA, up to 71% of patients with chorea had carditis.[30] However, only 25% of Aboriginal Australians with rheumatic chorea have evidence of overt carditis.[24] Even though clinically evident carditis increases the risk of later development of RHD, approximately 25% of patients with "pure" chorea also eventually develop RHD.[31,32] This is explained by the finding that over 50% of patients with chorea, but without cardiac murmurs, have echocardiographic evidence of mitral regurgitation.[1]

Therefore, echocardiography is essential for 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 subsequent development of RHD.

Carditis

Although pericarditis and myocarditis may occur, cardiac inflammation in ARF almost always affects the valves, especially the mitral and aortic valves.[33,34] Early disease usually leads to valvular regurgitation. With prolonged or recurrent disease, scarring may lead to stenotic lesions.[33] Acute carditis usually presents clinically as an apical holosystolic murmur with or without a mid-diastolic flow murmur (Carey Coombs murmur), or an early diastolic murmur at the base of the heart (aortic regurgitation). The rheumatic aetiology can

usually be confirmed by a typical appearance on echocardiography (see Section 2.9). Congestive heart failure in ARF results from valvular dysfunction secondary to valvulitis, and is not due to primary myocarditis.[35] If pericarditis is present, the friction rub may obscure valvular murmurs.

Subcutaneous nodules

These are very rare (less than 2% of cases) but highly specific manifestations of ARF in Aboriginal Australians.[22] They are 0.5–2.0cm 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 Australians and populations of developing countries.[22,36] 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 2.2   KEY POINTS IN IDENTIFYING MAJOR MANIFESTATIONS OF ACUTE RHEUMATIC FEVER

MANIFESTATION	POINTS FOR DIAGNOSIS
Arthritis	• Most common presenting symptom of ARF • Extremely painful • Polyarthritis is usually asymmetrical and migratory, but can be additive • Mono-arthritis may be a recurrent presenting feature in high-risk populations • Large joints are usually affected, especially knees and ankles • Usually responds within 3 days of starting NSAID therapy
Sydenham's chorea	• Present in around one-quarter of ARF presentations among Aboriginal Australians, particularly females and predominantly in adolescence • Consists of jerky, uncoordinated movements, especially affecting the hands, feet, tongue and face • Echocardiography is essential for all patients with chorea
Carditis	• 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
Subcutaneous nodules	• Rare but highly specific manifestastions of ARF in Aboriginal Australians and strongly associated with carditis • Present as crops of small, round, painless nodules over the elbows, wrists, knees, ankles, Achilles tendon, occiput and posterior spinal processes of the vertebrae
Erythema marginatum	• Extremely rare as well as difficult to detect in Aboriginal Australians but highly specific for ARF • Occurs as circular patterns of bright pink macules or papules on the trunk and proximal extremities

2.5   CLINICAL FEATURES OF ACUTE RHEUMATIC FEVER — MINOR MANIFESTATIONS

Arthralgia

Arthralgia 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 2.6) should be considered in a patient with arthralgia that is not typical of ARF.

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,[21,37] but lower-grade temperatures have been described more recently.[22]

In Aboriginal Australians, defining fever as a temperature greater than 38°C results in improved sensitivity for diagnosis of ARF.[22] In New Zealand, fever greater than 39°C is now rare at presentation, and many patients report a history of fever that has resolved prior to hospitalisation.

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 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 count is $<15 \times 10^9$/L in 75% of patients, so an elevated white cell count is an insensitive marker of inflammation in ARF.[22] Further analysis of these data demonstrated that less than 4% of patients with confirmed ARF, excluding chorea, had both a serum CRP level of <30mg/L and an ESR of <30mm/hr [unpublished data, J. Carapetis].

Therefore, it is recommended that a serum CRP level of ≥30mg/L or ESR of ≥30mm/hr 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 electrocardiogram (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 1–2 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 2.3).[38]

TABLE 2.3   UPPER LIMITS OF NORMAL OF P-R INTERVAL

AGE GROUP (YEARS)	UPPER LIMIT OF NORMAL P-R INTERVAL (SECONDS)
3–12	0.16
12–16	0.18
17+	0.20

Source: Adapted from Park, M.K., *Pediatric Cardiology for Practitioners*, 2nd ed. 1988. Year Book Medical Publishers: Chicago. p.42.

Other less common clinical features

These include abdominal pain, epistaxis, rheumatic pneumonia (pulmonary infiltrates in patients with acute carditis), mild elevations of plasma transaminase levels, microscopic haematuria, pyuria or proteinuria. None is specific for ARF.

TABLE 2.4   KEY POINTS IN IDENTIFYING MINOR MANIFESTATIONS OF ACUTE RHEUMATIC FEVER

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 during the current illness, should be considered as fever
Elevated acute-phase reactants	Serum CRP level of ≥30mg/L or ESR of ≥30mm/hr meets this diagnostic criterion
Electrocardiogram	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

Group A streptococci (GAS) are isolated from throat swabs in less than 10% of ARF cases in New Zealand[39] and less than 5% of cases in Aboriginal Australians.[22] Streptococcal antibody titres are therefore crucial in confirming the diagnosis. The most commonly used tests are the plasma anti-streptolysin O (ASO) and the anti-deoxyribonuclease B (anti-DNase B) titres. The serum ASO titre 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.[40]

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.[41] In the absence of reinfection, the ASO titre usually approaches pre-infection levels after 6–12 months, whereas the anti-DNase B titre tends to remain elevated for longer.[42] The reference range for these antibody titres varies with age and geographical location.

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 in non-Aboriginal and Torres Strait Islander children in Melbourne with no history of recent GAS infection suggests the following upper limits of normal (ULN) (Table 2.5).[43]

TABLE 2.5   UPPER LIMITS OF NORMAL FOR SERUM STREPTOCOCCAL ANTIBODY TITRES IN NON-ABORIGINAL AND TORRES STRAIT ISLANDER CHILDREN IN MELBOURNE

AGE GROUP	UPPER LIMIT OF NORMAL (IU/ML)	
Years	ASO titre	Anti-DNase B titre
4–5	120	100
6–9	480	400
10–14	320	380

Source: Danchin, M.H. et al, New normal ranges of antistreptolysin O and anti-deoxyribonuclease B titres for Australian children. *J Paediatr Child Health*, (in press).

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.[44,45] In one study, the median titres of ASO and anti-DNase B in children of three remote Aboriginal communities were 256 and 3,172 IU/mL, respectively.[45] Therefore, single measurements of streptococcal antibody serology are difficult to interpret in this population. Relying on rising titres in paired sera may not always be helpful for two reasons. Firstly, ARF occurs after a latent period, so the titres may already be at or near their peak when measured, and secondly, it is difficult to demonstrate a 4-fold rise in titre when the baseline is very high.

It is recommended that ULN for serum streptococcal antibody titres be determined in a subset of individuals without recent streptococcal infection in each population if possible.[6,46] This is not possible in most populations of Aboriginal children, in whom background titres are elevated because most of them have had a recent GAS infection. In the absence of other local data, it is recommended that the ULN values presented in Table 2.5 be used for children (**Level IV, Grade C**). All cases of suspected ARF should have elevated serum streptococcal serology demonstrated. If the initial titre is above 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.

Many of the clinical features of ARF are non-specific, so a wide range of differential diagnoses should be considered (Table 2.6).[10] The most likely alternative possibilities will vary according to location (eg arboviral arthritis is less likely in temperate than tropical climates) and ethnicity (eg some auto-immune conditions may be more or less common in particular ethnic groups).

TABLE 2.6   DIFFERENTIAL DIAGNOSES OF COMMON MAJOR PRESENTATIONS OF ACUTE RHEUMATIC FEVER

	PRESENTATION		
	POLYARTHRITIS AND FEVER	CARDITIS	CHOREA
Differential diagnoses	• Septic arthritis (including gonococcal) • Connective tissue and other auto-immune disease* • Viral arthropathy† • Reactive arthropathy† • Lyme disease¥ • Sickle-cell anaemia • Infective endocarditis • Leukaemia or lymphoma • Gout and pseudogout	• Innocent murmur • Mitral valve prolapse • Congenital heart disease • Infective endocarditis • Hypertrophic cardio-myopathy • Myocarditis — viral or idiopathic • Pericarditis — viral or idiopathic	• Systemic lupus erythematosus • Drug intoxication • Wilson's disease • Tic disorder‡ • Choreoathetoid cerebral palsy • Encephalitis • Familial chorea (including Huntington's) • Intracranial tumour • Lyme disease¥ • Hormonal§

Notes:

*   Includes rheumatoid arthritis, juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis and sarcoidosis, among others.

†   *Mycoplasma*, cytomegalovirus, Epstein–Barr virus, parvovirus, hepatitis, rubella vaccination, *Yersinia* spp and other gastrointestinal pathogens.

‡   Possibly including PANDAS (paediatric auto-immune neuropsychiatric disorders associated with streptococcal infection).

¥   Lyme disease has not been confirmed in Australia or New Zealand.

§   Includes oral contraceptives, pregnancy (chorea gravidarum), hyperthyroidism, hypoparathyroidism.

Source: Reprinted with permission from Carapetis, J. et al, Seminar: Acute rheumatic fever. *Lancet*, 2005. 366: 155–68.

2.8   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, and is less responsive to anti-inflammatory treatment. These patients are said not to be at risk of carditis, and therefore not to 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**).[47,48]

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**). Patients so diagnosed 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 auto-immune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

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. The term "paediatric auto-immune 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.[49]

However, the evidence supporting PANDAS as a distinct disease entity has been questioned.[50] Hence, in high-risk populations, clinicians should rarely, if ever, make a diagnosis of PANDAS, and should rather err on the side of over-diagnosis of ARF and secondary prophylaxis (**Grade D**). They should make this diagnosis only if they have excluded echocardiographic evidence of valvular damage (ie ARF). 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.

2.9 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. Today, all patients with suspected or definite ARF should undergo echocardiography, if possible, to identify evidence of carditis, as outlined in Table 2.7

(**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. Operators must be experienced in the use of modern echocardiography in areas with high rates of ARF.[1,51–53]

TABLE 2.7   USES OF ECHOCARDIOGRAPHY IN ACUTE RHEUMATIC FEVER

PERICARDITIS
Confirming the presence of a pericardial effusion
Revealing inaudible or subclinical valvular regurgitation in the presence of a friction rub
MYOCARDITIS AND CONGESTIVE HEART FAILURE
Defining left ventricular function
Confirming the severity of valvulitis (valvulitis is always present in ARF with heart failure)
VALVULITIS
Visualisation of anatomy of the valves, especially in mitral regurgitation. This is paramount in surgical decision-making
Defining the severity of mitral, aortic and/or tricuspid regurgitation
Defining the severity of mixed valve disease
Identifying subclinical evidence of rheumatic valve damage

In patients with suspected ARF and a murmur, reliance on clinical findings alone may result in misclassification of carditis.[6,54] Some patients have been shown on echocardiography to have a physiological or flow murmur, or even congenital heart disease. The likelihood of misclassification has increased in recent years, as physicians' auscultatory skills have become less proficient.[6] The use of echocardiography to diagnose carditis in the absence of a heart murmur is more controversial and is discussed below.

It is currently impossible to distinguish confidently between acute carditis and pre-existing rheumatic valve disease by echocardiography. In a patient with known prior RHD, the diagnosis of acute carditis during a recurrence of ARF relies on accurate documentation of the cardiac findings before the recurrence, so that new clinical or echocardiographic features can be confirmed. But, in a patient with no prior history of ARF or RHD, diagnostic echocardiographic changes imply an ongoing ARF episode or a previous subclinical episode if there are not other acute clinical features.

The anatomy and physiology of ARF as shown by echocardiography M-mode and two-dimensional echocardiography (2DE) are used in evaluating chamber size and ventricular function. More complex formulae based on 2DE can also be used to calculate left ventricular function (eg single-plane ellipse and Simpson's methods of discs).[35] 2DE allows visualisation of the functional anatomy of acute mitral regurgitation. The degree of annular dilatation is easily shown; annular size is normally related to body surface area. Mitral valve prolapse is a frequent finding with greater degrees of mitral regurgitation. Chordal elongation and sometimes chordal rupture may occur in the presence of significant valve prolapse.[55–58]

Valvular regurgitation can be accurately graded with pulsed and colour Doppler echocardiography as nil, physiological, mild, moderate and severe for both rheumatic[59] and non-rheumatic valve disease.[60–63] Colour Doppler echocardiography shows the direction of the regurgitant jet, which is directed posteriorly with anterior mitral valve leaflet prolapse, and anteriorly with the less common posterior leaflet prolapse.

If valvulitis is not found at presentation, it may appear within 2 weeks,[59] or occasionally within 1 month,[64] but no longer. Valvular regurgitation is usually relatively mild in the absence of pre-existing disease; in first episodes of ARF, severe mitral and aortic regurgitation occurred in less than 10% of patients in New Zealand.[65] Evolution to mitral stenosis has been rarely observed in children in Australia, but is more commonly seen in adolescence or adulthood (see Chapter 4).

Echocardiography and physiological valvular regurgitation

Trivial valvular regurgitation is commonly detected on echocardiography as a normal finding. It can now be readily distinguished from pathological regurgitation. First, valve closure is associated with physiological displacement of a small amount of blood, the closing volume, which is detectable by colour flow Doppler imaging. Second, true regurgitant jets, albeit trivial in nature, may be observed in normal individuals of all ages.[66–68] These leaks extend beyond the valve coaptation point, but usually by only 1cm or less.[66,68] They may have a high-velocity component, generally for only part of systole or diastole.

Trivial right-sided regurgitation is very common,[69] but trivial aortic regurgitation is uncommon, occurring in 0–1% of normal subjects, except in one study[66] where closing volumes were included. The characteristic Doppler echocardiographic feature of trivial mitral regurgitation in normal subjects is an aliasing flow pattern in early systole, with a velocity usually <1m/sec.[66,67,70] One study reported holosystolic flow signals, but these were recorded only at the valve leaflets, and had a poorly defined spectral envelope.[68] Sometimes a brief high-velocity component may be detected.[68]

Echocardiography and pathological valvular regurgitation

The minimal criteria for a diagnosis of abnormal regurgitation are summarised in Table 2.8 (Level IV). To be classified as pathological, both the colour and Doppler signals must be holodiastolic for aortic regurgitation, or holosystolic for mitral regurgitation. The Doppler signal must be of high velocity, either from a pulsed or continuous wave. These criteria can readily distinguish a small colour jet of physiological regurgitation in a normal child from pathological regurgitation in a child with RHD.

TABLE 2.8   MINIMAL ECHOCARDIOGRAPHIC CRITERIA TO ALLOW A DIAGNOSIS OF PATHOLOGICAL VALVULAR REGURGITATION

AORTIC REGURGITATION
- Colour: - substantial colour jet seen in 2 planes extending well beyond* the valve leaflets   - Continuous wave or pulsed Doppler: - holodiastolic with well-defined, high-velocity spectral envelope
MITRAL REGURGITATION
- Colour: - substantial colour jet seen in 2 planes extending well beyond* the valve leaflets   - Continuous wave or pulsed Doppler: - holosystolic with well-defined, high-velocity spectral envelope
If the aetiology of aortic or mitral regurgitation on Doppler echocardiography is not clear, the following features support a diagnosis of rheumatic valve damage: - both mitral and aortic valves have pathological regurgitation   - the mitral regurgitant jet is directed posteriorly, as anterior mitral valve prolapse is more common than posterior valve prolapse   - the presence of morphological or anatomical changes consistent with RHD (see text), but excluding slight thickening of valve leaflets

Note: *   Some authors have suggested that a minimal jet length of 1cm supports pathological regurgitation.[6]

Source: Adapted with permission from Wilson, N.J. & Neutze, J.M., Echocardiographic diagnosis of subclinical carditis in acute rheumatic fever. *Int J Cardiol*, 1995. 50: 1–6.

Tricuspid and pulmonary regurgitation graded mild or greater may be seen in people with normal hearts who have fever, volume overload or pulmonary hypertension. For this reason a diagnosis of carditis should not be based on right-side regurgitation alone. Although pulmonary and tricuspid regurgitation are 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.

Echocardiography and abnormal valve morphology

Echocardiography also allows the operator to comment on the appearance of valves that are affected by rheumatic inflammation. The degree of thickening gives some insight into the duration of valvulitis, with no significant thickening being seen in the first weeks of acute rheumatic carditis (**Level IV**). Only after several months is immobility of the subchordal apparatus and posterior leaflet observed. Several other findings have also been reported, including acute nodules, seen as a beaded appearance of the mitral valve leaflets,[71] and an "elbow" or "dog-leg" appearance of the anterior

mitral valve leaflet, indicative of chronic RHD. Although none of these morphological features are unique to ARF, the experienced echocardiographic operator can use their presence as supportive evidence of a rheumatic aetiology of valvulitis.

Subclinical evidence of rheumatic valve damage

There is convincing evidence that subclinical or silent rheumatic valve damage detected by echocardiography is part of the spectrum of rheumatic carditis and should not be ignored. This has been confirmed by investigators in many regions around the world with high rates of rheumatic fever, including New Zealand,[53,59,64] Australia, USA,[1,72,73] Qatar,[51,52] Brazil,[74] Turkey, Chile,[75] Tahiti,[76] Nepal,[77] Portugal,[78] Egypt and India.[79] A single report from India describing 28 patients with polyarthritis or chorea failed to detect any subclinical carditis.[71] In experienced hands, subclinical rheumatic valve damage can usually be differentiated on echocardiography from physiological regurgitation.[59,63,75] However, some authors advocate against the concept of subclinical rheumatic valve damage.[80]

A World Health Organization expert committee concurred that subclinical rheumatic valve damage exists.[6] However, because the clinical significance of this finding is not yet known, they decided against recommending its inclusion in the Jones criteria.

In the opinion of the authors of this review, echocardiographic diagnosis of subclinical valve damage can help experienced clinicians in making the diagnosis of ARF, or in confirming the presence of carditis in cases of ARF without an obviously pathological heart murmur. Therefore, it is recommended that echocardiographically suggested valve damage (subclinical or otherwise), diagnosed by a clinician with experience in echocardiography of patients with ARF/RHD, be included as a major manifestation (Table 2.1) (**Level IV, Grade C**).

Subclinical valve damage influences the diagnosis of ARF in relatively few individuals. Most patients have either migratory poly-arthritis, or clinically overt carditis that can be confirmed by echocardiography. However, there are some cases in which the finding may help to confirm the diagnosis, and to reinforce in the minds of patients and their families the importance of adherence to a secondary prophylactic regimen (Table 2.9).

TABLE 2.9   DIAGNOSTIC AND CLINICAL UTILITY OF SUBCLINICAL RHEUMATIC VALVE DAMAGE IN ACUTE RHEUMATIC FEVER

| MAIN CLINICAL FEATURES OF ARF | IMPLICATIONS OF A FINDING OF SUBCLINICAL VALVE DAMAGE | |
	DIAGNOSTICALLY	CLINICALLY
Polyarthritis	Usually none, as Jones criteria fulfilled, but can increase confidence in diagnosis of ARF	Helps to reinforce the importance of secondary prophylaxis
Mono-arthritis or arthralgia	May confirm the diagnosis as ARF, as long as other causes of joint disease are excluded	
Chorea	Confirms the diagnosis as ARF. Avoids the need to exclude other causes of chorea	
Erythema marginatum	Nil, because clinical carditis or polyarthritis usually present	
Subcutaneous nodules	Nil, because clinical carditis or polyarthritis usually present	
Clinical carditis	Nil	Defines involvement of second valve if only 1 valve has clinical carditis

2.10   INVESTIGATIONS

The recommended investigations in ARF are listed in Table 2.10.

TABLE 2.10   INVESTIGATIONS IN SUSPECTED ACUTE RHEUMATIC FEVER

RECOMMENDED FOR ALL CASES
• White blood cell count • Erythrocyte sedimentation rate • C-reactive protein • Blood cultures if febrile • Electrocardiogram (repeat in 2 weeks and 2 months if prolonged P-R interval or other rhythm abnormality) • 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 • Anti-streptococcal serology: both anti-streptolysin O 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, anti-nuclear antibody, drug screen for choreiform movements • Serology and auto-immune markers for arboviral, auto-immune or reactive arthritis

2.11   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 has been proven to alter the outcome of the acute episode or the amount of damage to heart valves.[81,82] Thus, there is no urgency to begin definitive treatment. The priorities in managing ARF are outlined in Table 2.11.

TABLE 2.11   PRIORITIES IN MANAGING ACUTE RHEUMATIC FEVER

ADMISSION TO HOSPITAL
CONFIRMATION OF THE DIAGNOSIS
Observation prior to anti-inflammatory treatment — paracetamol (first line) or codeine for fever or joint pain Investigations (as per Table 2.10)
TREATMENT
All cases Single-dose intramuscular benzathine penicillin G (preferable) or 10 days oral penicillin V (intravenous not needed; oral erythromycin if allergic to penicillin)
Arthritis and fever Aspirin (first line) or naproxen once diagnosis confirmed, if arthritis or severe arthralgia present Paracetamol (first line) or codeine until diagnosis confirmed 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

continued

Carditis/heart failure

Bed rest

Urgent echocardiogram

Anti-failure medication

- diuretics/fluid restriction for mild or moderate failure
- ACE inhibitors for more severe failure, particularly if aortic regurgitation present
- glucocorticoids optional for severe carditis (consider treating for possible opportunistic infections — see page 21)
- digoxin if atrial fibrillation 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 health staff to ensure follow-up

Provide culturally appropriate education to patient and family

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

Hospitalisation

Ideally, all patients with suspected ARF (first episode or recurrence) should be hospitalised as soon as possible after onset of symptoms (**Grade D**).[6] This ensures that all investigations are performed and, if necessary, the patient observed for a period prior to commencing treatment to confirm the diagnosis (see Section 2.12).

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.

Occasionally, when the diagnosis has already been confirmed and the patient is not unwell (eg 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 2.12 (**Grade D**).

The arthritis, arthralgia and fever of ARF respond to NSAIDs.[83–85] 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**).[6] 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 2.1). Thus, the opportunity to make a diagnosis of ARF will rarely be adversely affected.

TABLE 2.12   GUIDELINES FOR GENERAL IN-HOSPITAL CARE

NURSING RECORDINGS
Temperature, pulse, RR, BP 4 times daily
Sleeping pulse (eg 0200 hrs)
If pulse >100, apical HR

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
See general guidelines for bed rest (page 22)
Plan care to provide rest periods
Provide age-appropriate activities
Notify school teacher
Involve family in care

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 (see page 21)
Anticoagulation if atrial fibrillation present
Cardiology opinion

Note: BP=blood pressure; HR=heart rate; RR=respiratory rate

Source: Adapted from New Zealand guidelines with permission (courtesy D. Lennon).

2.12   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.[86,87] 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 10-day course of oral penicillin V (250mg twice daily in children, 500mg twice daily in adolescents and adults), or a single injection of intramuscular BPG (1,200,000 U or 600,000 U if less than 20kg).

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 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.[88]

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 stated penicillin allergy be investigated carefully, preferably with the help of an allergist, before being accepted as truly allergic (**Grade D**).

Arthritis/arthralgia

The arthritis of ARF has been shown in controlled trials to respond dramatically to salicylate or other NSAID therapy,[83–85] 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.

Salicylates are recommended as first-line treatment because of the extensive experience with their use in ARF.[6,89,90] They should be commenced in patients with arthritis or severe arthralgia as soon as the diagnosis of ARF has been confirmed (**Grade B**), but they should be withheld if the diagnosis is not certain. In such cases, paracetamol or codeine should be used instead for pain relief (see Table 2.11).

Aspirin should be started at a dose of 80–100mg/kg/day (4–8g/day in adults) in four to five divided doses. If there is an incomplete response within 2 weeks, the dose may be increased to 125mg/kg/day, but at higher doses the patient should be carefully observed for features of salicylate toxicity. If facilities are available, blood levels may be monitored every few days, and the dose increased until serum levels of 20–30mg/100dL are reached. However, most patients can be managed without blood level monitoring.

Toxic effects (tinnitus, headache, hyperpnoea) are likely above 20mg/100dL, 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 influenza vaccine (**Grade D**).

The duration of treatment is dictated by the clinical response and improvement in inflammatory markers (ESR, CRP). Many patients need aspirin for only 1–2 weeks, although some patients need it for up to 6 weeks. In such cases, the dose can often be reduced to 60–70mg/kg/day after the initial 1–2 weeks.[27,29,30] As the dose is reduced, or

within 3 weeks of discontinuing aspirin, joint symptoms may recur. This does not indicate recurrence, and can be treated with another brief course of high-dose aspirin. Most ARF episodes subside within 6 weeks, and 90% resolve within 12 weeks. Approximately 5% of patients require 6 months or more of salicylate therapy.[91]

In tropical regions where strongyloides infestation is endemic, patients should be treated with ivermectin if the steroid course is likely to exceed 0.5mg/kg/day for more than 2 weeks. Obtain advice from a local infectious diseases specialist about ivermectin dose, adverse events, contraindications and other possible opportunistic infections before treatment begins.[89,92]

Naproxen (10–20mg/kg/day) 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**).[93,94] It has the advantage of only twice-daily dosing. In many countries it is also available in an elixir for young children, but this is currently not the case in Australia. The experience with this medication is limited, so the recommendation currently is to restrict it to patients intolerant to aspirin, or to use it as a step-down treatment once patients are discharged from hospital (**Grade D**).

Chorea

Sydenham's chorea is self-limiting. Most cases will resolve within weeks, and almost all cases within 6 months,[95] although rare cases may last as long as 2–3 years.[24,96] Mild or moderate chorea does not require any specific treatment, aside from rest and a calm environment. Over-stimulation 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. Aspirin and glucocorticoid therapy do not have a significant effect on rheumatic chorea.[97]

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.[64,98] 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.[99,100] A small, prospective comparison of these three agents recently concluded that valproic acid was the most effective.[101]

Other anti-chorea 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 withdrawn. Recurrences of chorea are usually mild and can be managed conservatively but, in severe recurrences, the medication can be recommended 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.[81,82] All of these studies of glucocorticoids were performed more than 40 years ago, and did not use drugs 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**).[83–85] 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 more rapid resolution of cardiac compromise, and even be life-saving in severe acute carditis.[82,102] 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 (1–2mg/kg/day, to a maximum of 80mg once daily or in divided doses). Intravenous methyl prednisolone may be given in very severe cases. If a week or less of treatment is required, the medication can be ceased when heart failure is controlled and inflammatory markers are improving. 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 anti-failure treatments outlined below. 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 recommended after glucocorticoids are discontinued to avoid rebound joint symptoms or fever.

An urgent echocardiogram and 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 above), and ACE inhibitors may be used, particularly if aortic regurgitation is present.[89] Digoxin is usually reserved for patients with atrial fibrillation. 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 a separate NHFA clinical guideline.[103]

Role of acute surgery

Surgery is usually deferred until active inflammation has subsided. Rarely, valve leaflet or chordae tendinae rupture leads to severe regurgitation, and 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.[104]

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 pre-penicillin era, prolonged bed rest in patients with rheumatic carditis was associated with shorter duration of carditis, fewer relapses and less cardiomegaly.[105] 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" on page 19 and also Chapter 3.

Notify case to ARF/RHD register
There should be an easy means to do this, 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 patient and family
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 (eg pamphlets and video) and interactive discussion.

Organise dental check 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.

TABLE 2.13   MEDICATIONS USED IN ACUTE RHEUMATIC FEVER

MEDICATION	INDICATION	REGIMEN	DURATION
Benzathine penicillin G IM or	Treat streptococcal infection	900mg (1,200,000 U) ≥20kg 450mg (600,000 U) <20kg	Single dose
Penicillin V po or	Initial treatment of streptococcal infection	250mg bd children 500mg bd adolescents and adults	10 days
Erythromycin ethyl succinate po (only if allergic to penicillin)	Initial treatment of streptococcal infection	20mg/kg (max 500mg) bd	10 days
Paracetamol po	Arthritis or arthralgia — mild or until diagnosis confirmed	60mg/kg/day (max 4g) given in 4–6 doses/day; may increase to 90mg/kg/day if needed, under medical supervision	Until symptoms relieved or NSAID started
Codeine po	Arthritis or arthralgia until diagnosis confirmed	0.5–1.0mg/kg/dose (adults 15–60mg/ dose) 4–6hrly	Until symptoms relieved or NSAID started
Aspirin po	Arthritis or severe arthralgia (when ARF diagnosis confirmed)	80–100mg/kg/day (4–8 g/day in adults) given in 4–5 doses/day Reduce to 60–70mg/kg/day when symptoms improve 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 (if aspirin intolerant)	10–20mg/kg/day (max 1,250mg) given bd	As for aspirin
Prednisone or prednisolone po	Severe carditis, heart failure, pericarditis with effusion	1–2mg/kg/day (max 80mg); if used >1 week, taper by 20–25% per week	Usually 1 to 3 weeks
Frusemide po/IV (can also be given IM)	Heart failure	Children: 1–2mg/kg stat, then 0.5–1mg/kg/dose 6–24 hrly (max 6mg/kg/dose) Adults: 20–40mg/dose 12–24 hrly, up to 250–500mg/day	Until failure controlled and carditis improved
Spironolactone po	Heart failure	1–3mg/kg/day (max 100–200mg/day) in 1–3 doses; round dose to multiple of 6.25mg (quarter of a tab)	As for frusemide
Enalapril po	Heart failure	Children: 0.1mg/kg/day in 1–2 doses, increased gradually over 2 weeks to max of 1mg/kg/day in 1–2 doses Adults initial: 2.5mg daily; maintenance: 10–20mg daily (max 40mg)	As for frusemide
Lisinopril po	Heart failure	Children: 0.1–0.2mg/kg once daily, up to 1mg/kg/dose Adults: 2.5–20mg once daily (max 40mg/day)	As for frusemide

MEDICATION	INDICATION	REGIMEN	DURATION
Digoxin po/IV	Heart failure/atrial fibrillation	Children: 15mcg/kg stat and then 5mcg/kg after 6 hrs, then 3–5 mcg/kg/dose (max 125mcg) 12-hrly Adults: 125–250mcg daily Check serum levels	Seek advice from specialist
Carbamazepine	Severe chorea	7–20mg/kg/day (7–10mg/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 15–20mg/kg/day (can increase to 30mg/kg/day) given tds	As for carbamazepine

Monitoring

Expected progress and timing of discharge

Most cases 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. Most cases of ARF without severe carditis can be discharged from hospital after approximately 2 weeks. The length of admission will partly depend on 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 health care team. In some cases, it may be advisable to prolong the hospital stay until recovery is well advanced.

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. 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, electrocardiograms and chest x-rays according to their clinical course.

2.13 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.

3 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 2001[6]

This chapter deals with long-term management of individuals who have been diagnosed with acute rheumatic fever (ARF) or rheumatic heart disease (RHD), excluding management of heart failure (see Chapter 4). 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). Secondary prophylaxis is the only RHD control strategy shown to be cost-effective at both community and population levels.[16]

However, the effectiveness of secondary prophylaxis is impaired by factors affecting adherence to antibiotic regimens and by incidence rates of ARF. These factors relate to overcrowded housing, poor access to health services, limited educational opportunities and poor environmental conditions, all of which are a consequence of poverty. Communities with the highest rates of ARF and RHD are often the least equipped to deal with the problem.

Secondary prevention 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.

TABLE 3.1   SUMMARY OF MAJOR ELEMENTS OF SECONDARY PREVENTION OF ACUTE RHEUMATIC FEVER/ RHEUMATIC HEART DISEASE

INDIVIDUAL LEVEL
Accurate and timely diagnosis of ARF
Secondary prophylaxis
Prevention of infective endocarditis
Routine review and structured care planning
Health education for individuals, families and community
Screening for undiagnosed RHD

ORGANISATIONAL LEVEL
RHD control programs

Accurate and timely diagnosis of ARF

ARF is often difficult to diagnose. If 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 2.

Secondary prophylaxis

The regular administration of antibiotics to prevent infection with group A streptococcal (GAS) and recurrent ARF is recommended for all people with a history of ARF or RHD.[106,107] This strategy has been proven in randomised controlled trials 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**).[91]

A recent Cochrane meta-analysis[108] concluded that the use of penicillin (compared to no therapy) is beneficial in the prevention of recurrent ARF, and that intramuscular benzathine penicillin G (BPG) is superior to oral penicillin in the reduction of both recurrent ARF (87–96% reduction) and streptococcal pharyng-itis (71–91% reduction) (**Level I**). Secondary prophylaxis also reduces the severity of RHD,[16] is associated with regression of heart disease in approximately 50–70% of those with adequate adherence over a decade (**Level III-2**),[32,54,109] and reduces mortality (**Level III-2**).[110]

Antibiotic regimens for secondary prophylaxis
The internationally accepted standard dose of BPG for the secondary prevention of ARF in adults is 900mg (1,200,000 U).[6,111,112] The dose for children is less clear. The American Heart Association and the Australian Antibiotic Guidelines recommend 900mg (1,200,000 U) regardless of weight or age.[111,113,114] Some authorities recommend that the dose be reduced for children; for example, WHO recommends a

dose of 450mg (600,000 U) for children weighing less than 30kg.[6]

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 27kg.[115,116] In New Zealand, the 600,000 U dose is used only for children weighing less than 20kg. The ARF recurrence rate in this group is only 0.6 per 100 patient-years.[117]

Therefore, it is recommended that 1,200,000 U of BPG should be used for secondary prophylaxis for all persons weighing 20kg or more, and 600,000 U for those weighing less than 20kg (**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.[6]

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.[118] Fewer streptococcal infections and ARF recurrences occurred among patients receiving 3-weekly BPG (**Level I**).[108,119,120] Moreover, the 3-weekly regimen resulted in greater resolution of mitral regurgitation in a long-term randomised study in Taiwan (66% vs 46%) (**Level II**).[121] An alternative strategy is the administration of larger doses of BPG, leading to a higher proportion of people with detectable serum penicillin levels 4 weeks after injection.[122] However, until more data are available, this strategy cannot be recommended.

Although Australian Aboriginal and Torres Strait Islander peoples are at higher risk of developing ARF than other ethnic groups in Australia, the benefits of 3-weekly BPG injections are offset by the difficulties of achieving good adherence even to the standard regimen.[16,123,124] Furthermore, prospective data from New Zealand[125] showed that few, if any, recurrences occurred among people who were fully adherent to a 4-weekly BPG regimen.

Therefore the use of 4-weekly BPG is currently the treatment of choice, except in patients considered to be at "high risk", for whom 3-weekly administration is recommended.[6,126,127] The latter include the following patient groups:

- those with moderate or severe carditis, or a history of valve surgery, who demonstrate good adherence to less frequent injections; and

- those who have confirmed breakthrough ARF, despite full adherence to 4-weekly BPG (Table 3.3) (**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 regimens, but the pharmacokinetic data suggest that prolonging the dosing interval beyond 4 weeks may increase the risk of breakthrough ARF. Therefore, monthly rather than 4-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 BPG

Oral penicillin is less efficacious than BPG in preventing GAS infections and subsequent recurrences of ARF.[6,128,129] Twice-daily oral regimens are also likely to result in poorer rates of adherence over long periods of time[130] and less predictable serum penicillin concentrations, when compared to intramuscular BPG.[131] Oral penicillin should be reserved for patients 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 also been affected by inconsistent supply of benzathine penicillin over recent years. This poses potential risks to patients requiring 4-weekly prophylaxis. Organisational approaches to secondary prevention should seek to ensure consistent supply at the national, regional and local levels. However, when benzathine penicillin is unavailable, patients can be given oral penicillin or erythromycin (as per Table 3.2).

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.[118,126,130,131] The rates of allergic and anaphylactic reactions to monthly BPG are 3.2% and 0.2%, respectively, and fatal reactions are exceptionally rare.[132,133]

There is no increased risk with prolonged BPG use. A prospective study of 1,790 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**).[133]

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 (eg erythromycin) should be used instead (**Grade D**).[6,127]

When patients state they are allergic to penicillin but there is no unequivocal evidence, they should be investigated for penicillin allergy, preferably in consultation with an allergist. The options include skin testing[133] or a supervised challenge test. Most such 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.[114,134]

TABLE 3.2   RECOMMENDED ANTIBIOTIC REGIMENS FOR SECONDARY PREVENTION

ANTIBIOTIC	DOSE	ROUTE	FREQUENCY
First line			
Benzathine penicillin G	1,200,000 U ≥20kg 600,000 U <20kg	Deep intramuscular injection	4-weekly, or 3-weekly for selected groups*
Second line (if intramuscular routine is not possible or refused)**			
Phenoxymethylpenicillin (Penicillin V)	250mg	Oral	Twice daily
Following documented penicillin allergy			
Erythromycin	250mg	Oral	Twice daily

Notes: * 3-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. Monthly BPG is an acceptable alternative only if it is considered that the practicalities of monthly dosing will substantially improve adherence.

  ** If oral regimens are prescribed, adherence should be carefully monitored.

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**).[6] Erythromycin is also considered safe in pregnancy, although controlled trials have not been conducted.

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 anti-coagulated 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, time since the last episode of ARF and potential harm from recurrent ARF. Critical factors are outlined in Table 3.3. Based on these factors, the recommended duration of secondary prophylaxis is outlined in Table 3.4 (**Grade D**).

TABLE 3.3   FACTORS THAT AFFECT THE DURATION OF SECONDARY PROPHYLAXIS

FACTOR	IMPLICATION
Age	ARF recurrence is less common in people aged 25–40 yrs and rare >40 yrs
Presence and severity of RHD	ARF recurrence could be life-threatening in people with moderate or severe RHD, or a history of valve surgery
Presence of carditis during initial attack	Increases the likelihood of further cardiac damage should a recurrence occur
Time elapsed since last episode of ARF	ARF recurrences are less common >5 yrs since last episode
Socio-economic circumstances	ARF recurrences are more common in lower socio-economic groups (particularly related to overcrowded housing)
The 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 attack 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

Note: * 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, hostels or overcrowded housing with large numbers of children.

Source: Adapted from *Report of a WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease 29 October–1 November 2001.* 2001. World Health Organization: Geneva.

TABLE 3.4   DURATION OF SECONDARY PROPHYLAXIS

CATEGORY	DEFINITION OF CATEGORY	DURATION
All persons with ARF or RHD*		Minimum 10 yrs after most recent episode of ARF or until age 21 yrs (whichever is longer)
Status after initial period elapsed:		
No RHD		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	Any of: • any valve lesion of moderate severity clinically (eg mild or moderate cardiomegaly and/or mild or 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 coexisting with a left-sided valve lesion	Continue until age 35 yrs
Severe RHD	Any of: • any severe valve lesion clinically (eg moderate to severe cardiomegaly or heart failure) or on echocardiography • any impending or previous cardiac valve surgery for RHD	Continue until age 40 yrs, or longer†

Notes: *   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.

   †   The risk of a 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.

Ceasing secondary prophylaxis

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

Data from Northern Territory Aboriginal patients show that less than 1% of 555 ARF episodes occurred after 40 years of age.[135] A 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.[136] Therefore, it is reasonable to cease secondary prophylaxis at that age, except when individual circumstances warrant continuing (eg 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 (eg 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 Section 3.4). 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**).

Secondary prevention and rheumatic heart disease control programs   29

Improving adherence to secondary prophylaxis

The persistence of high rates of recurrent ARF in Australia highlights the continued failure of 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,[137] while 45% of all episodes of ARF were recurrences.[19]

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 of the efficacy of parenteral BPG compared to oral regimens, inadequate adherence, unreliable data collection and the lack of long-term continuity of care.[138] Poor adherence was rarely due to injection refusal, pain of injections, or a lack of knowledge or understanding of ARF/RHD in remote Australian Aboriginal and Torres Strait Islander communities. Instead, the major factors were the availability and acceptability of health services. 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.[139] 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 [unpublished data, A. Brown]. Studies from Egypt[140] and north Western Australia[141] reached similar conclusions.

A local ARF register can assist with routine assessment and surveillance, recording of prophylaxis delivery and recall of patients who miss doses of BPG, recall of those with ARF, and improved health education and health promotion programs.[7] Centralised registers can support the provision of prophylaxis for those who move between communities.[142]

Health education is critical at all levels.[6,7,143] In the Northern Territory, 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.[142] Health education is also recommended for patients and families during hospitalisation and outpatient visits, but its efficacy has not been evaluated.[142,144]

Lack of parental awareness of the causes and consequences of ARF/RHD was a key contributor to poor adherence among children on long-term prophylaxis in Egypt.[140] In a number of regions in India, comprehensive health education has improved community awareness of sore throat, ARF and RHD[145] and assisted case identification.[146] Comprehensive health education and promotion was also a key component in the successful control of RHD in the French Caribbean.[147]

These and other potential strategies to improve the delivery of secondary prophylaxis are listed in Table 3.5.[7,143]

TABLE 3.5   POTENTIAL STRATEGIES TO IMPROVE THE DELIVERY OF SECONDARY PROPHYLAXIS

Employ 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
- identify local, dedicated staff members to deliver secondary prophylaxis and coordinate routine care
- support and utilise the expertise, experience, community knowledge and language skills of Aboriginal health workers
- minimise staff turnover in remote and rural primary health care centres and regional hospitals
- improve staff awareness of diagnosis and management of ARF and RHD
- improve quality and delivery of health education
- focus on improving communication between health staff and patients/families
- implement measures to reduce pain of injections
- base routine care on standardised evidence-based guidelines.

Reducing the pain of BPG injections

The pain of BPG injections is usually not a critical factor in determining adherence to secondary prophylaxis. Nonetheless, techniques that safely reduce injection pain should be promoted. A smaller-gauge needle and increasing the volume of injection to 3.5mL improved acceptability in Taiwan.[121] 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.[148]

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.[149,150] The manufacturers of pre-packaged 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 intra-muscular injections.[151] Other techniques that are easy to implement include warming of the syringe 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 lack of evidence (Table 3.6) (**Grade D**).

TABLE 3.6   MEASURES THAT MAY REDUCE THE PAIN OF BENZATHINE PENICILLIN G INJECTIONS

• Use a 23-gauge needle   • Warm syringe to room temperature before using   • Allow alcohol from swab to dry before inserting needle   • Apply pressure with thumb for 10 secs before inserting needle
• Deliver injection very slowly (preferably over at least 2–3 mins)   • Distract patient during injection (eg with conversation)   • (The addition of 0.5–1.0mL of 1% lignocaine is used elsewhere, but is not recommended with pre-loaded syringes currently available in Australia)

3.2   PREVENTION OF INFECTIVE ENDOCARDITIS

Infective endocarditis is a dangerous complication of RHD,[6] and a common adverse event following prosthetic valve replacement in Aboriginal Australians. Although the effectiveness of additional antibiotic prophylaxis prior to dental or surgical procedures has not been proven, its use is supported by animal models of endocarditis and empirical observations, such as the reduction of bacteraemia.[6,114]

Therefore, persons with established RHD or prosthetic valves 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 are outlined in Tables 3.7 and 3.8 (**Grade D**).

TABLE 3.7   PROCEDURES REQUIRING ENDOCARDITIS PROPHYLAXIS

DENTAL PROCEDURES	OTHER PROCEDURES
Dental extractions	Tonsillectomy/adenoidectomy
Periodontal procedures	Rigid bronchoscopy
Dental implant placement	Surgery involving the bronchial mucosa
Gingival surgery	Sclerotherapy of oesophageal varices
Initial placement of orthodontic appliances	Dilatation of oesophageal stricture
Surgical drainage of dental abscess	Surgery of the intestinal mucosa or biliary tract (except for endoscopy, biopsy and percutaneous endoscopic gastrostomy)
Maxillary or mandibular osteotomies	Endoscopic retrograde cholangiography
Surgical repair or fixation of a fractured jaw	Prostate surgery
Endodontic surgery and instrumentation	Cystoscopy and urethral dilatation
Placement of orthodontic bands	Vaginal delivery in the presence of infection, prolonged labour or prolonged rupture of membranes
Intraligamentary local anaesthetic injections	Surgical procedures of the genitourinary tract in the presence of infection (eg urethral catheterisation, uterine dilatation and curettage, abortion, sterilisation, placement or removal of intrauterine contraceptive devices)

Source: Adapted from Anonymous, *Therapeutic Guidelines: Antibiotic.* 2003. Therapeutic Guidelines Limited: Melbourne.

TABLE 3.8   ANTIBIOTICS FOR ENDOCARDITIS PROPHYLAXIS DURING PROCEDURES

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: 15mg/kg up to) 600mg orally as single dose 1 hour prior to procedure
If unable to take orally	
Clindamycin	(Child: 15mg/kg up to) 600mg IV, over at least 20 mins just prior to procedure
or	
Vancomycin	(Child: 20mg/kg up to) 1g IV, over at least 1 hour just prior to 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: 50mg/kg up to) 2g orally as 1 dose 1 hour prior to the procedure
Amoxycillin/Ampicillin	(Child: 50mg/kg up to) 2g IV just prior to procedure or IM (30 mins prior)
Genitourinary and gastrointestinal procedures	
Gentamicin	(Child: 2.5mg/kg) 2mg/kg IV just prior to procedure or IM (30 mins prior)
plus	
Vancomycin	(Child: 20mg/kg up to) 1g IV over at least 1 hour just prior to procedure
or	
Teicoplanin	(Child: 10mg/kg up to) 400mg IV just prior to procedure

Source: Adapted from Anonymous, *Therapeutic Guidelines: Antibiotic.* 2003. Therapeutic Guidelines Limited: Melbourne.

3.3 ROUTINE REVIEW AND STRUCTURED CARE PLANNING

A structured care plan should be developed and recorded in the primary health care record of all persons with a history of ARF, or with established RHD. Table 3.9 lists recommended care plan schedules, which may be tailored to the needs of the individual (**Grade D**).

TABLE 3.9   RECOMMENDED ROUTINE REVIEW AND MANAGEMENT PLAN

CLASSIFICATION	CRITERIA*	REVIEW AND MANAGEMENT PLAN	FREQUENCY†
Low risk	ARF with no evidence of RHD **or** Trivial to mild valvular disease	Secondary prophylaxis (BPG) Doctor review Echocardiography	4-weekly Yearly Children 2-yearly† Adults 2–3 yearly†
Medium risk	Any moderate valve lesion in the absence of symptoms and with normal left ventricular function **or** Mechanical prosthetic valves	Secondary prophylaxis (BPG) Doctor review Influenza vaccination ECG (optional) Cardiologist/physician/paediatrician review Echocardiography Dental review Polysaccharide pneumococcal vaccination (Pneumovax 23) Endocarditis prophylaxis	4-weekly 6-monthly Yearly Yearly Yearly Yearly Yearly 5-yearly (max 3 doses) As required
High risk¥	Severe valvular disease **or** Moderate/severe valvular lesion with symptoms **or** Tissue prosthetic valves and valve repairs	Secondary prophylaxis (BPG) Doctor review Cardiologist/physician/paediatrician review Influenza vaccination Echocardiography Dental review Polysaccharide pneumococcal vaccination (Pneumovax 23) Endocarditis prophylaxis Warfarin + aspirin	3–4 weekly 3–6 monthly 3–6 monthly Yearly 3–6 monthly Within 3 months and yearly thereafter 5-yearly (max 3 doses) As required As prescribed

CLASSIFICATION	CRITERIA*	REVIEW AND MANAGEMENT PLAN	FREQUENCY†
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	

Notes:

*   Serial echocardiographic assessments are required in the long-term management of RHD. If cultural differences or difficulties with communication hinder standard clinical measures of heart failure (eg New York Heart Association criteria), serial echocardiography becomes 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, review should become more frequent in the event of symptom onset, symptomatic deterioration or a change in clinical findings.

‡   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.

¥   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 (**Grade D**).

Sources: Adapted from:

Couzos, S. & Carapetis, J. Rheumatic fever. In: *Aboriginal Primary Health Care: An Evidence-based Approach,* 2nd ed. 2003. S. Couzos & R. Murray (Eds) Oxford University Press: South Melbourne.

Bonow, R.O. et al, Guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol*, 1998. 32: 1486–588.

Central Australian Rural Practitioners Association, *CARPA Standard Treatment Manual,* 4th ed. 2003. Central Australian Rural Practitioners Association: Alice Springs.

Northern Territory Rheumatic Fever Registry Guidelines for Assignation of Priority.

Dental care

Routine dental care 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**).

3.4 ORGANISATIONAL APPROACHES TO SECONDARY PREVENTION

RHD control programs

A coordinated control program is the most effective approach to improving BPG adherence and clinical follow-up of people with RHD, including specialist review and echocardiography (**Level III-3**).[7] The major aims of RHD control programs are summarised in Table 3.10.

TABLE 3.10   PRIMARY AIMS OF RHEUMATIC HEART DISEASE CONTROL PROGRAMS

Improve uptake of and adherence to secondary prophylaxis

Improve clinical care and follow-up

Identify and register new cases of ARF and RHD

Provide education and training for health care providers

Provide 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 delivery of secondary prophylaxis, the most cost-effective approach to RHD control.[6,16] 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.[152] Hospitalisations and surgical management of ARF and RHD have been estimated to cost the Northern Territory over $3 million per year in direct medical costs alone.[143] Management of chronic RHD has been estimated to consume up to 70% of the total national ARF/RHD budget for New Zealand.[153] There is little doubt that much of this expenditure could be prevented with targeted and coordinated secondary prevention programs.[6]

Registers of people with RHD or a history of ARF are a key element of RHD control at an individual, community and national level.[154] Register-based programs:

- improve case detection;[142,144,147,155–157]

- increase adherence to secondary prophylaxis;[156,157]

- reduce recurrences of ARF;[117,156–160] and

- decrease hospitalisations from ARF/RHD (**Level III**).[156,157]

Registers also provide a mechanism for monitoring patient movements, orientating staff to ongoing care requirements (eg BPG injections, clinic appointments and echocardiograms), and identifying individuals with poor adherence to long-term therapy for targeted educational activities and other interventions. Registers can also provide data for monitoring the success of programs and changes in disease epidemiology.

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.[161] 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.[117]

Australia's first register-based RHD control program was established in 1997 in the Top End of the Northern Territory.[162] 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.[163] This rate of decline did not continue in subsequent years, showing that further efforts are needed to improve secondary prophylaxis.[144]

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.[142] By mid-2005 these were the only coordinated RHD control programs in Australia.

It is recommended that all regions of Australia with substantial populations with ARF or RHD establish a coordinated control program, including the elements listed in Table 3.11 (**Grade C**).

TABLE 3.11   RECOMMENDED ELEMENTS OF RHEUMATIC HEART DISEASE CONTROL PROGRAMS

RHD control programs should incorporate a single centralised (preferably computerised) ARF/RHD register, established within existing health care networks, and linked to local registers in regions and individual communities. The register may be stand-alone, part of a more comprehensive chronic disease register, or housed within clinical departments or public health units. Registers should: • maintain patient confidentiality • conform to privacy legislation • be established with the relevant institutional and/or individual approval
Commitment from national, regional and local services, particularly to ensure long-term funding
Activities guided by locally relevant, evidence-based guidelines
A dedicated, centrally based coordinator for each control program
A commitment to partnerships between clinicians and public health services in order to support the needs of people with ARF/RHD and the community
An effective advisory committee that includes cardiologists, paediatricians, general practitioners, physicians, epidemiologists, nurses, public health practitioners, and relevant community representatives
Prioritisation of antibiotic prophylaxis delivered within the framework of primary health care
Planning and advocacy for a stable supply of benzathine penicillin, 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
Provision of education for health practitioners, the community, those with disease and their families
Provision of health education within the local community, community health service and for community health workers
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, program reporting and independent evaluation

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 clinical expertise when individual case management issues arise. 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 coordinator 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 3.10.

Case finding: surveillance, legislated notification and screening

Surveillance

Passive surveillance of ARF usually depends on case identification from health care providers. Historically, this has under-estimated the burden of disease due to inaccuracies and incompleteness.[164] In under-resourced settings, the deficiencies of passive surveillance are exacerbated by high turnover of hospital and primary care staff and lack of awareness of ARF/RHD by many health care providers.

Ideally, active surveillance should be used to augment passive surveillance (**Grade D**).[165] This entails establishing mechanisms to identify new cases of ARF/RHD, and to update information about existing cases.

This could include:

- mechanisms allowing access to hospital separation data;

- echocardiography reports;

- specialist review correspondence;

- primary health care clinic information; and

- notifiable disease databases.

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

A diverse range of activities has been utilised for the active surveillance of ARF/RHD in the Northern Territory,[142,144] 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. Staff educational activities have focused on rotating medical staff from metropolitan referral centres, new staff, and primary health care staff within rural and remote communities.

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 (eg 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 health care providers for individual patient and epidemiological information; and

- 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.[142,144,146] 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 ARF/RHD registers

The minimum dataset for ARF/RHD registers is outlined in Table 3.12. Some programs may choose to have all of these data entered into the centralised register, whereas others may choose to have a subset of data (eg 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 (eg developing individualised education strategies for patients, and/or tracking patients if they have moved).

These communities should also provide data to the coordinator every 6 months on the number of BPG doses due to be delivered and the number of doses actually delivered for each patient in the community. These data can be de-identified if the community so desires. 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.

TABLE 3.12   PROPOSED MINIMUM DATASET FOR ACUTE RHEUMATIC FEVER/RHEUMATIC HEART DISEASE REGISTERS

DOMAIN	DATA ELEMENTS
Demographics	Name, date of birth, address or community, alternate address/community, parent/guardian, ethnicity
ARF diagnosis	Onset date of primary episode of ARF, place first diagnosis made, presence (and severity) of carditis, presence of chorea
RHD diagnosis	Onset date/date of diagnosis, documented history of ARF, valvular dysfunction and disease severity at time of diagnosis
ARF recurrences	Onset date, presence of carditis, other symptoms and signs at each recurrence
Secondary prophylaxis	Agent, dose and frequency, date commenced on prophylaxis, expected date of cessation, number of doses received over preceding 12 months
Surgical intervention	Date surgery recommended; date, site, procedure and outcome of surgery
Medications	Anticoagulant prescribed: type, dose, date commenced, frequency of monitoring, therapeutic target (INR range) Type and dose of other cardiac medications
Follow-up/recall	Date and place of last review, and date and place of next scheduled review by each provider (cardiologist, paediatrician, physician, surgeon, local medical officer, echocardiography)
Mortality	Date and cause of death according to agreed criteria (eg due to RHD, not due to RHD)

Legislated notification of ARF/RHD

In New Zealand, following the establishment of ARF/RHD registries, ARF became a notifiable condition under a national surveillance and management framework in 1986.[161] In Australia, ARF became notifiable in the Northern Territory in 1994, and in Queensland in 1999. Rheumatic heart disease is not notifiable anywhere in New Zealand or Australia.

ARF meets most criteria for notification of the Communicable Diseases Network of Australia (CDNA),[166] specifically:

- *feasibility of collection* — ARF cases are usually hospitalised, making collection of notification data more straightforward

than if they remained in the community. The feasibility of data collection has been demonstrated in the Northern Territory and Queensland, but the process sometimes requires enhancement to improve completeness;[142,144,167]

- *priority* — the incidence of ARF among Aboriginal and Torres Strait Islander people, and its effect on premature mortality and long-term morbidity, suggest that it is a high priority in this community;

- *immediacy of intervention possible/required* — there are many examples of children with ARF who have not had rapid

follow-up and registration, and have returned with recurrent ARF (sometimes with disastrous consequences) within months of the original episode;

- *outbreak potential* — although outbreaks have not been a feature of ARF in Australia to date, they have been demonstrated in some settings, particularly in temperate climates;[1]

- *potential for new programs* — formal RHD control programs currently exist in the Northern Territory only, hence there is great potential for the creation of new programs;

- *maintenance/evaluation of existing/future programs* —ARF incidence data are key indicators of the success of RHD control programs;

- *community/political concern* — currently, political concern is focused mainly within the Northern Territory. This does not accord with community concern. Aboriginal and Torres Strait Islander stakeholders frequently identify ARF/RHD as a major health priority; and

- *international concern* — the World Health Organization identifies ARF/RHD as an important health problem for which demonstrated control interventions exist.[6]

Therefore, the case for ARF becoming notifiable Australia wide seems relatively strong.[168] However, policy makers also take other considerations into account, including political and financial issues, increasing complexity of the notification system, and the claims of other potentially notifiable diseases. At present, the CDNA has decided not to include ARF in its list of nationally notifiable conditions.

RHD meets fewer of the CDNA criteria for notification than does ARF, but there are good reasons for considering its candidacy. Almost half of Aboriginal and Torres Strait Islander patients 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 RHD

In the Aboriginal and Torres Strait Islander population, RHD satisfies all except one of the Council of Europe criteria for selecting diseases suitable for screening:[169]

- *the disease should be an obvious burden for the individual and/or community in terms of death, suffering, economic or social costs* — this is implicit in populations with high rates of RHD and has been quantified by economic analysis;[170]

- *the natural course of the disease should be well known and the disease should go through an initial latent stage or be determined by risk factors that can be detected by appropriate tests* — the natural history of RHD is well understood (thanks to classic studies of the 20th century),[102,171] and there is a latent or early symptomatic stage (as described above);

- *adequate treatment or other intervention possibilities are indispensable. Adequacy is determined both by proven medical effect and ethical and legal acceptability* — secondary prophylaxis prevents the development or worsening of RHD and, with good adherence, leads to disease resolution in many cases;[102,172] and

- *screening followed by diagnosis and intervention in an early stage of the disease should provide a better prognosis than intervention after spontaneously sought treatment* — milder valve lesions, which are often asymptomatic and thus the most common lesions that will be detected with screening, are more likely to resolve than more severe lesions in patients who adhere to secondary prophylaxis.[51,109]

Echocardiography satisfies the remaining criterion — an appropriate test is highly sensitive and specific for the disease as well as being acceptable to the person screened — but the exact way in which auscultation and echocardiography should be combined has not yet been agreed. 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.[6] The WHO Global Programme on Rheumatic Heart Disease undertook auscultatory screening of over a million children.[157] 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.

Therefore, it is recommended that RHD control programs should also coordinate screening to detect previously undiagnosed RHD in high-risk populations, wherever this is possible (**Grade D**). Although RHD prevalence is highest in adults,[10] they are difficult to screen. It is recommended that screening focus rather on school-age children (**Grade D**). In the Northern Territory, it is recommended that all children undergo cardiac auscultation at school entry, and again at age 10 years for this purpose.

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 screening.

The ideal method of RHD screening is not known, and the sensitivity of cardiac auscultation is highly dependent on the skill of the operator. One study found that a non-specialist auscultator, trained only to detect cardiac murmurs, can be more sensitive in detecting echocardiographically confirmed RHD than a paediatrician.[173] The author of this study concluded that an ideal screening protocol might use a single-stage auscultation, with any child found to have a cardiac murmur then being assessed echocardiographically.

The availability of portable echocardiography and the ability to perform a limited assessment in 5–10 minutes make such a protocol feasible. In the abovementioned study, the echocardiographic assessment consisted of parasternal long axis and apical four-chamber views, noting valve morphology on cross-sectional imaging and the degree and extent of mitral and aortic regurgitation, using colour flow interrogation. In addition the severity of stenotic valvular flow was examined, by measuring the peak velocity of transvalvular flow with continuous wave Doppler. 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**).

Suggested indicators for evaluating RHD control programs

Control programs for ARF/RHD should be evaluated in relation to criteria for routine care and key epidemiological objectives.[7] 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; and

- support structures and appropriate follow-up processes.

As has been highlighted throughout the developing world, the availability of and support for routine primary health care is essential to 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 health care providers, and should lead to improved clinical results. A list of suggested indicators is provided in Table 3.13 (**Grade D**).

TABLE 3.13   PROPOSED INDICATORS FOR EVALUATING ACUTE RHEUMATIC FEVER/RHEUMATIC HEART DISEASE CONTROL PROGRAMS

Secondary prophylaxis

- The proportion of scheduled BPG injections delivered in the previous 12 months
- Individual, community and regional figures, expressed as:
  - median percentage of doses delivered
  - proportion of patients who receive 80% or less of scheduled doses
  - proportion of patients who receive 50% or less of scheduled doses

Medical review

- Proportion of registered individuals who are more than 3 months overdue for specialist or other medical officer review, as defined by local guidelines
- Proportion of individuals who have echocardiography performed within 3 months of scheduled timing
- Median time elapsed between recommendation and performance of valvular surgery

Epidemiology

- Yearly (or other appropriate time frame) age-specific incidence rates of ARF
- Proportion of ARF episodes in the register classified as recurrences
- Rates of ARF recurrence per 100 patient-years
- Number of deaths and age-standardised rates of mortality due to ARF/RHD in the previous 12 months (or other appropriate time frame)
- Yearly age-specific and overall point prevalence of RHD
- Proportion of ARF cases notified to and recorded by public health authorities (where appropriate) in the previous 12 months (or other appropriate time frame)
- Proportion of newly registered individuals with an initial diagnosis being established of RHD (rather than ARF)

4 DIAGNOSIS AND MANAGEMENT OF CHRONIC RHEUMATIC HEART DISEASE

4.1 BACKGROUND AND MANAGEMENT PRINCIPLES

In Australia the vast majority of people with chronic rheumatic heart disease (RHD) are Aboriginal and Torres Strait Islander people, many of whom live in remote areas of Western Australia, the Northern Territory and Queensland.[15] It is difficult and expensive for Aboriginal and Torres Strait Islander people to travel to major centres for cardiac services, often hospital based. Although specialist outreach services are improving in many regions, the access to specialist care is suboptimal in rural and remote areas.[174]

The implementation of guidelines for chronic RHD has major implications for Aboriginal and Torres Strait Islander health care services, especially in rural and remote regions. In addition to access to appropriate primary care services, best practice for RHD prescribes:

- access to a specialist physician and/or cardiologist (preferably the same specialist over a prolonged time);

- access to echocardiography;

- adequate monitoring of anticoagulation therapy in patients with atrial fibrillation and/or mechanical prosthetic valves; and

- secondary prevention with penicillin prophylaxis.

The increasing availability of specialist outreach services and portable echocardiography should mean that all RHD patients in Australia, regardless of location, have access to the first two of these requirements.[175,176]

Importance of echocardiography

All patients with murmurs suggestive of valve disease, or a past history of acute rheumatic fever (ARF), require echocardiography (**Grade D**). This will detect any valvular lesion, and allow assessment of its severity and also left ventricular (LV) systolic function. Many patients with chronic RHD do not have a past history of ARF, and it may be difficult to judge their symptomatic status by standard clinical criteria (eg 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.

Serial echocardiography plays a critical role in the diagnosis and follow-up of rheumatic valve disease, allowing objective monitoring of the severity of valve lesions, LV chamber size, LV function and any increase in pulmonary artery pressure. These objective echocardiographic data are crucial in helping to determine the timing of any surgical intervention.

Monitoring anticoagulation therapy

The ability to adequately monitor and achieve therapeutic anticoagulation levels may be difficult because of language and cultural differences, mobility of the population and remoteness from pathology services.[177] For these reasons there may be difficulties in achieving good adherence to anticoagulation and other medications in remote communities.[177] Point-of-care international normalised ratio (INR) testing is now available, and its application needs to be systematically tested in remote regions.[178]

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 requiring anticoagulant therapy achieve consistency of INR readings, as required in patients with mechanical prosthetic valves.

Secondary prevention with penicillin prophylaxis

The fundamental goal in long-term management of chronic RHD is to avoid, or at least delay, valve surgery. Therefore, penicillin prophylaxis for prevention of recurrent ARF is a crucial strategy in the management of patients with chronic RHD. Where adherence to secondary prevention is poor, there is greater need for surgical intervention and long-term surgical outcomes are not as good.[179]

The specific valvular lesions in chronic RHD are discussed in subsequent sections. Many patients (eg 47% of RHD patients in the Top End of the Northern Territory)[135] will have involvement of two or more valves, most commonly mitral and aortic, although pathology in one is usually dominant. The assessment of severity of each valvular lesion is made by echocardiography. Management is usually focused on the most severe valve lesion, especially with regard to timing of intervention.

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4.2   MITRAL REGURGITATION

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Natural history

Mitral regurgitation is the most common valvular lesion in RHD, and is particularly frequent in young patients, who have not yet developed scarred and stenotic valves from persistent or recurrent valvulitis. In Aboriginal RHD patients in the Northern Territory, one observer noted that 41% had pure mitral regurgitation, while in children aged under 10 years, over 90% of mitral valve lesions were pure regurgitation. In patients aged between 10 and 39 years, the proportion was 60–70%.[135]

In chronic mitral regurgitation, volume overload of the left ventricle and left atrium occurs.[180] This leads to increased mitral regurgitant flow into the low-pressure left atrium, especially during the earliest phase of systole. LV and left atrial size increases in response to large volumes of regurgitant mitral blood flow. LV systolic function may remain within normal limits for many years, despite the presence of severe mitral regurgitation. Eventually this degree of volume overload results in a progressive decline in systolic contractile function.

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

vascular disease and pulmonary hypertension is much less common in mitral regurgitation than in mitral stenosis.

There is wide individual variation in the rate of progression of mitral regurgitation, although many cases tend to progress over the following 5–10 years, especially if there is a recurrence of ARF.[181–83]

Symptoms

Patients with mild to moderate mitral regurgitation may remain asymptomatic for many years.[181] Patients with moderate to severe mitral regurgitation may also be asymptomatic or mildly symptomatic. Initial symptoms include dyspnoea on exertion, fatigue and weakness,[184] and these may progress slowly over time. Patients often become symptomatic if they develop atrial fibrillation, particularly with a rapid ventricular rate. Worsening symptoms may also result from a recurrence of ARF or chordal rupture, both of which can cause an acute increase in the severity of regurgitation.

Examination

In patients with mild to moderate mitral regurgitation, the LV apex will not be displaced, and there will be a mid- or pansystolic murmur heard best at the apex, which may radiate laterally or medially, depending on the direction of the regurgitant jet.[184] Patients with moderate or more severe mitral regurgitation will have an apex beat displaced to the anterior or

mid-axillary line and a loud pansystolic murmur maximal at the apex. There may be an associated diastolic murmur of mitral stenosis, or a mid-diastolic murmur from increased transmitral flow.

ECG/chest x-ray

ECG and chest x-ray are not usually helpful in diagnosis of this condition. In more severe degrees of mitral regurgitation, especially in older patients, atrial fibrillation may be present. Chest x-ray will show an enlarged left ventricle and radiological signs of pulmonary congestion in more advanced cases.

Echocardiography

Echocardiography allows accurate assessment of LV size and systolic function, as well as left atrial size.[180,184,185] The two-dimensional (2D) 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.

The main feature of pure mitral regurgitation is over-riding or prolapse of the anterior mitral valve leaflet due to elongation of the chordae to the anterior leaflet and, in the more severe cases, dilatation of the posterior mitral annulus. This results in an eccentric posteriorly directed jet of variable severity depending on the degree of prolapse.[186] There may be some thickening and tethering of either or both leaflets, even in mild valvular disease. This results in an "elbow" (or "dog leg") appearance of the anterior leaflet and reduced mobility of the posterior leaflet. This abnormality is especially common if there is associated mitral stenosis. Leaflet and annular calcification tends to be a late development and is unusual in young patients. Accurate measurement of LV end systolic and end diastolic dimensions and systolic function by M mode and 2D echocardiography must be obtained. Patients with moderate or greater mitral regurgitation almost always have LV and left atrial enlargement.

Pulse Doppler and colour flow mapping in the left atrium allows a semi-quantitative 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 pulse Doppler. Milder degrees of regurgitation may be missed, unless "sweeping" scans of the left atrium and mitral valve from parasternal and apical windows are used. An experienced echocardiographer may be required to distinguish physiological (trivial) from pathological mitral regurgitation.

Quantitative grading of mitral regurgitation using Doppler echocardiography to calculate effective regurgitant orifice area has been proposed as a more accurate method to assess mitral regurgitation severity.[187] However, this measurement is time consuming and technically demanding and therefore has not yet been widely used.

Due to higher-quality imaging, transoesophageal echocardiography provides more optimal evaluation of mitral valve morphology and is commonly used pre-operatively to help assess suitability for valve repair and intra-operatively to assess adequacy of surgical repair. It is also useful in patients yielding poor image quality with transthoracic echocardiography, such as obese patients.

Cardiac catheterisation

Cardiac catheterisation is only necessary when there is a need to exclude coronary artery disease. In Aboriginal and Torres Strait Islander people this may need to be considered in patients aged over 30 years because of the premature onset of coronary artery disease in this population. Left ventriculography is another method of assessing the degree of mitral regurgitation, but the radiographic assessment may be affected by catheter-induced ventricular ectopy.

Medical management

Vasodilator drug therapy (eg 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 aortic regurgitation, there are limited data available on the efficacy of chronic vasodilator therapy for patients with mitral regurgitation.

The absence of increased afterload in mitral regurgitation (instead there is a low-resistance leak into the left atrium) suggests that vasodilator therapy would not be beneficial in improving outcome.[188] Therefore, this drug therapy is not recommended in the medical management of mitral regurgitation, 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 Section 4.3. Patients who develop evidence of clinical heart failure with symptoms and signs of fluid retention (eg elevated venous pressure) require diuretic therapy and ACE inhibitors.

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

Surgical management

Choice of operation
The operation of choice for dominant or pure rheumatic mitral regurgitation is mitral valve repair, rather than replacement (**Level II, Grade B**).[189,190] 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. 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, and warfarin is also highly undesirable in women of childbearing 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.

Although there have been no randomised comparative trials, more recent surgical experience has shown that the long-term results of repaired rheumatic mitral valve are superior to those of valve replacement. 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.[190] The superior survival rate was statistically significant, even after correction for baseline differences between patient groups. 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 myxomatous mitral valves and the long-term results are not as good. Nevertheless, very acceptable results have been obtained in centres that perform these operations regularly. In a French series of 951 patients, who had repair for dominant rheumatic mitral regurgitation, the in-hospital mortality was 2% and the actuarial survival was 89% at 10 years and 82% at 20 years.[191] Freedom from re-operation was 82% at 10 years and 55% at 20 years. Whether these good results for mitral valve repair can be extrapolated to Aboriginal and Torres Strait Islander people 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 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 re-operation during that period.[186,192] These authors concluded that active carditis at the time of surgery was the major predictor of late valve failure.

Therefore, strict adherence to a prophylactic antibiotic program post surgery is vital to prevent progression of valvular disease due to recurrence of ARF. Regular echocardiographic studies are required in all patients post repair to monitor the degree of any residual regurgitation and detect any increase in its severity that might suggest valve failure.

The re-operation rate is higher with mitral valve repair than replacement, but in experienced centres re-operation can be carried out at low risk. This may require mitral valve replacement, but initial valve repair should delay the need for long-term anticoagulation for many years.

If the mitral valve is not suitable for repair, the options are valve replacement, either with a mechanical valve prosthesis or a bioprosthetic valve. 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 3.0 (range 2.5–3.5), compared to those in the aortic position (2.5).[193]

The pros and cons of mechanical versus bioprosthetic valves are discussed in Section 4.4. However, the major disadvantage of bioprosthetic valves is their limited durability, and 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.[194] Nevertheless, a woman of childbearing 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.[193]

The need for re-do valve surgery is higher in the Aboriginal and Torres Strait Islander population than in other populations. All patients need a careful pre-operative assessment of the likelihood of adherence to anticoagulation therapy before a decision regarding choice of mitral valve 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, adherence to other medications and social circumstance.

Indications for surgery

Patients with severe mitral regurgitation should be referred for mitral valve surgery if they become symptomatic, or if they have echocardiographic indicators demonstrating reduced LV systolic function (**Level III-2, Grade B**). These include evidence of reduced LV systolic function (ejection fraction <60%), or an LV end systolic diameter ≥40mm determined by echocardiography in the adult.[195] A critical LV end systolic dimension has not been identified in children.

In addition, patients with **severe** mitral regurgitation who are asymptomatic or mildly symptomatic should be referred for **early** surgical consultation.[188] This is because compared to those with normal LV function, patients who develop reduced LV systolic function have increased surgical risk, less likelihood of restoring normal LV function and increased risk of late heart failure and death. Early referral is particularly important in children. Additional indicators favouring early referral for surgical consultation are progressive but rapid LV enlargement, the presence of pulmonary hypertension (pulmonary artery systolic pressure >50mmHg) and chronic or recurrent atrial fibrillation.

Nevertheless, there is controversy about timing of surgery in patients who are asymptomatic or mildly symptomatic and have severe mitral regurgitation and normal LV systolic function (ejection fraction ≥60%).[188,196] The arguments for early valve repair in these patients include:

- borderline systolic function (LVEF 50–60%) may indicate LV dysfunction in severe mitral regurgitation, due to the relatively low impedance to LV outflow;

- in most cases mitral regurgitation slowly worsens, with most of these patients becoming symptomatic during the next 5–10 years;[181] and

- these patients are very likely to be suitable for mitral valve repair since younger patients tend to have preservation of the anterior leaflet and chordae and relatively pliable valve leaflets. The operative risk is very low in patients repaired early compared to valve replacement, and thromboembolic sequelae are rare because there is no need for anticoagulation.

The arguments against early mitral valve surgery are:

- up to 10% of patients develop significant mitral regurgitation after mitral valve repair, requiring re-operation within 2 years;

- in some patients initially thought to be suitable, the mitral valve cannot be repaired, necessitating valve replacement.

As indications for surgery in asymptomatic patients are still evolving, it is important that physicians caring for patients with asymptomatic moderate to severe mitral regurgitation 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 both mitral regurgitation and associated mitral stenosis who have severely fibrotic, calcified valves may require mitral valve replacement. Because of the long-term morbidity accompanying prosthetic valve replacement in many Aboriginal and Torres Strait Islander people, 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 4.1   KEY POINTS IN MANAGING RHEUMATIC MITRAL REGURGITATION

Symptoms	May be asymptomatic for many years Exertional dyspnoea and fatigue
Examination	Pansystolic murmur at left ventricular apex
Echocardiography	Over-riding or prolapse of anterior mitral valve leaflet Thickened "dog leg" anterior mitral valve leaflet, especially if associated mitral stenosis Retrograde colour (mosaic) regurgitant jet into left atrium, often posteriorly directed Severity graded by area of colour regurgitant jet in left atrium Left ventricular chamber dimensions enlarged if moderate or greater mitral regurgitation Assess left ventricular systolic function
Cardiac catheterisation	Only to exclude coronary artery disease
Medical management	No role for vasodilators, eg nifedipine Diuretics and ACE inhibitors if heart failure
Indications for surgery	Moderate/severe mitral regurgitation with symptoms NYHA FC II, III, IV Asymptomatic severe mitral regurgitation in children Asymptomatic severe mitral regurgitation in adults when: • reduced LVEF (<60%) • LVESD ≥40mm • pulmonary hypertension (PAS >50mmHg)
Choice of operation	Mitral valve repair operation of choice Mitral valve replacement only in older patients with very calcified leaflets Avoid mechanical prostheses if concerns about warfarin adherence or future pregnancy

Notes: LVEF=left ventricular ejection fraction; LVESD=left ventricular end systolic diameter (Echo); NYHA FC=New York Heart Association Functional Class; PAS=pulmonary artery systolic pressure

4.3   MITRAL STENOSIS

Natural history

The natural history of mitral stenosis varies according to the population being studied. In the non-Aboriginal and Torres Strait Islander population there is often a latent period of 20–40 years between episodes of ARF and presentation with mitral stenosis.[197,198] However, in the Aboriginal and Torres Strait Islander population, mitral stenosis progresses more rapidly and patients become symptomatic at a younger age. In some developing countries, such as India, this trend is more marked, where mitral stenosis is not uncommon in children aged under 10 years.

Approximately 30% of Aboriginal RHD patients in the Northern Territory aged 10–19 years have mitral stenosis, and the mean age of all those with mitral stenosis is 33 years, which is older than Aboriginal patients with pure mitral regurgitation.[135] At the time of diagnosis, the majority of patients with mitral stenosis do not recall having had ARF.

The progression of mitral stenosis is variable, and best monitored with serial Doppler echocardiography.[199] More rapid progression may be due to undetected recurrences of ARF. Secondary pulmonary hypertension results from the elevated pressures in the pulmonary vascular bed, leading to right ventricular (RV) hypertension, dilatation and tricuspid regurgitation.

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 atrial fibrillation with rapid ventricular rates. Patients usually do not develop symptoms until the mitral valve orifice decreases to $<2cm^2$.

The initial symptom is exertional dyspnoea, which worsens slowly over time, with the 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 $<1.0–1.5cm^2$.[200] Less commonly, patients may present with signs of arterial embolism from the left atrium, such as a stroke or peripheral arterial occlusion. The occurrence of systemic embolism does not correlate with the severity of mitral stenosis[201,202] but is related to the presence of atrial fibrillation.

Physical examination

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

The murmur of mitral stenosis 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 health care 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 mitral stenosis. If the patient is in sinus rhythm, there will be pre-systolic accentuation, but this is lost once atrial fibrillation occurs.

ECG/chest x-ray

Electrocardiograms (ECGs) are not particularly helpful in diagnosing mitral stenosis, although they may show evidence of left atrial enlargement. However, an ECG shows whether the heart is in sinus rhythm or atrial fibrillation.

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 mitral stenosis and associated valve lesions, and assess LV function and left atrial size.[184,200,203] Two-dimensional echocardiography 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 mitral stenosis 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 mitral regurgitation 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, especially if the patient has developed chronic atrial fibrillation with inadequately controlled ventricular rate.

If tricuspid regurgitation is present, the pulmonary artery systolic 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 (gradient = $4 \times$ velocity^2). By adding an estimate of right atrial pressure to the pressure gradient, RV systolic pressure can then be calculated. In the absence of pulmonary valve disease, RV systolic pressure is the same as pulmonary artery systolic pressure.

Cardiac catheterisation

Doppler echocardiography has replaced cardiac catheterisation as the gold standard for determining the severity of mitral stenosis.[200] Cardiac catheterisation is only required to identify associated coronary artery disease. Therefore, younger patients can 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 (eg frusemide). In general, the treatment of symptomatic mitral stenosis is interventional therapy.

Atrial fibrillation

The most common complication of mitral stenosis is atrial fibrillation.[201] Initially, this may be paroxysmal but eventually it becomes chronic, as mitral stenosis and left atrial dilatation progress. Approximately 40% of patients with mitral stenosis will exhibit chronic atrial fibrillation, and the incidence increases with age and left atrial size. Atrial fibrillation may lead to systemic embolism from left atrial thrombi, which form predominantly in the left atrial appendage (the area of lowest velocity).

Patients with mitral stenosis and chronic or paroxysmal atrial fibrillation should receive long-term prophylactic anticoagulation with warfarin (**Level III-3, Grade C**).[193] However, left atrial thrombus can occur in mitral stenosis, 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 mitral stenosis, a large left atrium and sinus rhythm.

Patients who develop atrial fibrillation with a rapid ventricular rate may develop heart failure, including pulmonary oedema, and require intravenous diuretic therapy. The ventricular rate in atrial fibrillation is best slowed with beta-blockers, digoxin, rate-slowing calcium channel blockers (eg diltiazem), or combinations of these medications. Anti-arrhythmics, such as amiodarone or sotalol, should not be used for long-term rate or rhythm control of atrial fibrillation in younger patients, because of long-term adverse effects.

When new-onset atrial fibrillation is symptomatic, consideration should be given to direct-current cardioversion to restore sinus rhythm (**Grade B**). Anticoagulation is indicated prior to this procedure[193,204] and long term. Patients can be anticoagulated initially with intravenous or low molecular weight heparin 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.[205]

If sinus rhythm is achieved, the most effective medications for maintenance are the Class III agents, sotalol or amiodarone. These are not 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 symptomatic dominant or pure mitral stenosis is percutaneous balloon mitral valvuloplasty (PBMV) (**Level III, Grade B**).[206–209] The balloon catheter is inserted via the femoral vein and placed into 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-term and medium-term results are comparable to surgical valvuloplasty.[209,210] However, PBMV usually requires only one or two nights in hospital, is considerably cheaper and has less associated morbidity than mitral valve surgery.[200] Mitral orifice area usually increases to 1.5–2.0cm^2 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.[206–208] 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 mitral regurgitation. Of 528 patients with rheumatic mitral stenosis (mean age 56.1 years) treated with PBMV at the Prince of Wales Hospital in Sydney (R.M. McCredie, personal communication, August 2005) only 4% developed mitral regurgitation requiring semi-urgent mitral valve surgery, usually valve repair. Other rare complications are cardiac tamponade and systemic embolism.

Patient selection

The indication for PBMV is progressive exertional dyspnoea (NYHA FC II, III or IV), associated with documented evidence of moderate or severe mitral stenosis (mitral orifice area <1.5cm^2) (**Grade B**).[200,211] Asymptomatic patients usually do not need intervention, unless there is a history of thromboembolism, paroxysmal atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure >50mmHg).

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 mitral stenosis requiring intervention should be referred for PBMV to a centre with considerable experience in the technique and documented low complication rates, regardless of the anatomy of their mitral valves.[200,209] Early referral is recommended for younger patients as they have the most favourable valve morphology and have the best long-term results.

A large left atrial thrombus is a contraindication to PBMV.[209] However, it can often be performed safely in the presence of a small, stable thrombus in the left atrial appendage. Mild regurgitation is acceptable, but patients with moderate or greater mitral regurgitation are not suitable, and should be referred for surgery if symptoms are significant. Most patients do not develop worsening of mitral regurgitation over time after successful PBMV.

Surgical management

PBMV has largely replaced surgical mitral commissuroplasty and commissurotomy.[209,210] 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**). 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 mitral valve prosthesis has been discussed in Section 4.2. In the presence of paroxysmal or chronic atrial fibrillation, replacement with a mechanical prosthesis is usually recommended, since long-term anticoagulation is already required.

Replacement with a bioprosthesis may be necessary for females in the childbearing years (especially those in sinus rhythm), to avoid anticoagulation during pregnancy (see Section 4.7).

Surgery for atrial fibrillation

Patients with paroxysmal or chronic atrial fibrillation who require mitral valve surgery can have sinus rhythm restored in more than 80% of cases with atrial ablation procedures at the time of surgery, using radiofrequency and other modalities.[212,213] In most cases, the mechanical contractile function of the atria returns. Since it is now believed that most atrial fibrillation 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 minutes. Not all surgical units are performing this procedure as it is a relatively new technique and long-term results are not yet available.

TABLE 4.2   KEY POINTS IN MANAGING RHEUMATIC MITRAL STENOSIS

Symptoms	May be asymptomatic
	Exertional dyspnoea, fatigue, palpitations
Examination	Low-pitched mid-diastolic "rumble" at left ventricular apex
Echocardiography	Thickened restricted "dog leg" anterior mitral valve leaflet
	Restricted posterior leaflet
	Measure mean mitral gradient from continuous wave Doppler signal
	Calculate MVA from slope of Doppler mitral inflow velocity
	Calculate PAS pressure from peak tricuspid regurgitant jet velocity ($4V^2$)
Cardiac catheterisation	Only to exclude coronary artery disease
Atrial fibrillation	Common
	Rate control using beta-blockers or digoxin, or consider cardioversion if recent onset
	Need anticoagulation to prevent thromboembolic complications
Indications for intervention	Symptoms NYHA FC II–IV
	MVA <1.5cm^2 or PAS >50mmHg
	No left atrial thrombus
	Mild or no mitral regurgitation
Procedure of choice	Percutaneous balloon mitral valvuloplasty by high-volume operator/centre
	65% of patients free of restenosis after 10 years
	Mitral valve repair or replacement if valve leaflets heavily calcified

Notes: MVA=mitral valve area; NYHA FC=New York Heart Association Functional Class; PAS=pulmonary artery systolic; V=velocity

4.4   AORTIC REGURGITATION

Natural history

Moderate or more severe aortic regurgitation results in LV overload with an increase in LV end diastolic volume, which helps maintain the increased total stroke volume.[214] As the severity of regurgitation increases, the left ventricle undergoes progressive dilatation and hypertrophy. In chronic aortic regurgitation 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.[188,215]

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.

Patients may also experience episodes of angina, despite having normal coronary arteries, probably due to hypotension in diastole, when most coronary flow occurs. In severe aortic regurgitation, 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. An obvious "waterhammer" pulse at the brachial artery and a collapsing carotid pulse are clinical indications of at least moderate aortic regurgitation.

The typical murmur of aortic regurgitation is a diastolic, blowing decrescendo murmur best heard at the left sternal border, with the patient sitting upright. 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 aortic stenosis, due

to the increased antegrade flow across the aortic valve and, in occasional cases, a mitral diastolic murmur.

ECG/chest x-ray

With severe aortic regurgitation, 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. The degree of LV dilatation is usually greater in severe aortic than in severe mitral regurgitation. The aortic valve is usually thickened and the aortic root is dilated in more severe cases.

The extent of aortic regurgitation is examined with colour flow mapping in the left ventricle.[60,61] The spatial extent of the colour flow jet in the LV outflow tract is an approximate guide to the severity of aortic regurgitation. 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 mitral stenosis.

A useful method for assessing the severity of aortic regurgitation 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 reversal of diastolic flow in the abdominal aorta. A pressure half-time of <400ms usually indicates at least moderate aortic regurgitation. However, additional factors, such as heart rate and LV end diastolic pressure, can affect pressure half-time.[60,61]

Cardiac catheterisation

Cardiac catheterisation is not required for diagnosis or assessment of the severity of aortic regurgitation. It should only be carried out if coronary artery disease must be excluded. Since coronary artery disease presents much earlier in Aboriginal and Torres Strait Islander patients, coronary angiography may be required in those over 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 aortic regurgitation.

Medical management

In asymptomatic patients with significant aortic regurgitation, vasodilator therapy has been demonstrated to reduce LV dilatation and regurgitant fraction.[188] This has the potential for slowing progression of LV dilatation, and hence delaying the need for surgery. These drugs may also be beneficial because these patients usually have systolic hypertension. Most of the publications describe experience with the dihydropyridine, nifedipine,[216] although smaller studies have shown that ACE inhibitors are also effective.[217]

However, there is some 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 aortic regurgitation and normal LV function.[218] 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 aortic regurgitation (**Level III-3, Grade C**), especially when systolic hypertension is present.

Patients with symptoms of pulmonary congestion will benefit from diuretic therapy (eg frusemide) but should be referred for surgery, even if symptoms subside. Atrial fibrillation is uncommon in aortic regurgitation, 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 severity of aortic regurgitation. 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.

Surgical management

Patients with moderate/severe aortic regurgitation, who become symptomatic, should be referred for surgery (**Level III-2, Grade B**).[180,188,219] Without surgery, symptomatic patients have a significantly impaired prognosis, the mortality rate being over 20% per year. Patients with reduced systolic function (LVEF <50%) should be referred as soon as possible for valve surgery, as long-term studies suggest progression of heart failure and death occurs in up to 25% of these patients per year.[220,221]

Asymptomatic and mildly symptomatic patients with severe aortic regurgitation

In patients with normal LV systolic function and few or no symptoms, the aim is to delay surgery as long as possible, but before onset of LV systolic dysfunction.[188] If serial echocardiography shows that the LV end systolic diameter is approaching 55mm, or the systolic ejection fraction is <55%, these patients should be referred for aortic valve surgery (**Grade C**).[215] In addition, an LV end diastolic diameter >70mm 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.[188]

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.[194,222] Other surgical options are either aortic valve repair or the Ross procedure (pulmonary autograft with homograft replacement of pulmonary valve).[194] It is important that the choice of operation be fully discussed with the patient, his or her family and, if possible, the patient's primary health care provider before a final decision is made.

Replacement with a bioprosthesis has the advantage of avoiding long-term anticoagulation. The main disadvantages of bioprostheses are their limited durability[194,223] in younger patients (15–50 years). Structural deterioration of bioprostheses, such as the Hancock valve, has been reported to be 50% at 10 years and 90% at 15 years.[224] Newer stentless bioprosthetic valves appear to have a similar rate of structural degeneration, at least up to 10 years follow-up,[225] but long-term outcome studies are not yet available.

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 re-operation will be required in the majority of younger patients because of valve degeneration and recurrence of symptoms.

Homografts are also subject to structural deterioration, often with associated calcification.[226–228] 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%.[229] Difficulties in obtaining donor homografts, and the significantly increased complexity of re-operation 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 outcome if good warfarin adherence can be achieved. If patients already have chronic atrial fibrillation requiring anticoagulation, the valve of choice is a mechanical valve prosthesis. The main complications of mechanical valves are bleeding and thromboembolic events, usually due to problems with anticoagulation adherence.[179,230] Patients with newer disc/bileaflet mechanical aortic valves can usually be anticoagulated to a lower INR (2.0–3.0) than was needed with the earlier-generation caged ball/disc valves, because these newer prostheses appear to have a lower risk of thromboembolism,[193,231] 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.[232] 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.[179,230,233] 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 repair of rheumatic aortic valves is limited.[234] The Carpentier group in Paris has pioneered this approach, and has recently reported 92% freedom from re-operation at 5 years with cusp augmentation techniques.[235] 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, and its role remains limited in the local environment. Patients at risk of recurrence of ARF, because of poor adherence with antibiotic prophylaxis, are not suitable, as rheumatic activity can lead to valve dysfunction.

Another alternative for aortic valve surgery is the Ross procedure,[236,237] which uses a pulmonary autograft for aortic valve replacement and a homograft for pulmonary valve replacement. The surgery is more complex and consequently has a slightly higher operative risk. It is best suited for aortic valves 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, recurrence of ARF can involve the neo-aortic valve (pulmonary autograft), causing regurgitation. Late follow-up has also shown that patients may develop significant aortic regurgitation, especially after 5 years. The 10-year freedom from re-operation was 75% in a recent surgical series.[238] Also in younger patients, structural degeneration of the pulmonary homograft, manifesting usually as pulmonary stenosis, remains a problem.[239] The need for re-operation is the principal limitation of the Ross procedure.

Recommendations

A careful pre-operative assessment of the likelihood of medication adherence, especially with 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, since these have the best long-term durability and highest freedom from re-operation. However, in young female patients every effort must be made to avoid a mechanical prosthesis, because of the significant risk to mother and foetus posed by anticoagulation during pregnancy.

Aortic homograft replacement is also a possible option, but is currently not favoured because of the technical difficulties of later re-operation. Aortic valve repair or Ross procedure are other options in selected cases where the surgeon is skilled in the technique.

TABLE 4.3   KEY POINTS IN MANAGING RHEUMATIC AORTIC REGURGITATION

Symptoms	May be asymptomatic for many years
	Exertional dyspnoea and fatigue
Signs	Diastolic blowing, decrescendo murmur at left sternal border, usually associated with systolic ejection murmur
Echocardiography	Retrograde diastolic regurgitant colour jet in LVOT and left ventricular chamber
	Area of jet in LVOT correlates with severity
	Left ventricular chamber dimensions enlarged if moderate or greater aortic regurgitation
	May have associated mitral valve disease
	Pan-diastolic reversed diastolic flow in descending thoracic aorta if moderate/severe aortic regurgitation (Doppler)
	Assess left ventricular systolic function
Cardiac catheterisation	Only to exclude coronary artery disease
Medical management	Vasodilator therapy with dihydropyridines (eg nifedipine), especially if systolic hypertension in asymptomatic, moderate or greater aortic regurgitation
	Diuretics and ACE inhibitors if heart failure
Indications for surgery	Moderate/severe aortic regurgitation with symptoms NYHA FC II–IV
	Asymptomatic moderate/severe aortic regurgitation if:
	• LVEF <55%
	• LVESD ≥55mm
	• LVEDD >70mm
Choice of surgery	Valve replacement:
	• bioprosthesis or homograft
	– no warfarin if in sinus rhythm
	– limited durability in younger patients
	• mechanical valve
	– warfarin required
	Aortic valve repair:
	• limited experience
	Ross procedure:
	• aortic autograft (pulmonary valve) and pulmonary homograft replacement
	Ross procedure and aortic valve repair only in selected cases with experienced surgeons

Notes: LVEDD=left ventricular end diastolic diameter; LVEF=left ventricular ejection fraction; LVESD=left ventricular end systolic diameter; LVOT=left ventricular outflow tract; NYHA=New York Heart Association

Natural history

RHD is an uncommon cause of aortic stenosis. Isolated aortic stenosis is a very rare manifestation of RHD.[240,241] It almost always occurs in the presence of associated rheumatic mitral valve disease. As with rheumatic mitral stenosis, aortic stenosis 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 aortic stenosis is variable in the individual patient, but it is generally progressive.

Symptoms

The classic symptoms of aortic stenosis 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 aortic stenosis is a loud, low-pitched mid-systolic ejection murmur best heard in the aortic area, radiating to the neck and the apex.[242] In patients with haemodynamically significant aortic stenosis, useful physical signs are a slowed and reduced carotid pulse upstroke, and the presence of a thrill in the suprasternal notch. The murmur of aortic stenosis is sometimes difficult to distinguish from mitral regurgitation.

ECG/chest x-ray

ECG usually shows sinus rhythm and may demonstrate voltage criteria for LV hypertrophy with or without secondary repolarisation abnormalities. A chest x-ray usually shows normal heart size, unless there is associated mitral regurgitation. Calcification of the aortic valve may be visible in the lateral chest x-ray.

Echocardiography

Two-dimensional echocardiography demonstrates thickened and restricted aortic valve leaflets. LV size and systolic function can be assessed quantitatively. The peak and mean velocity across the aortic valve is measured by continuous wave Doppler and converted to a systolic gradient using the simplified Bernoulli equation of gradient = 4 x velocity^2. 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 gradient less reliable.[214] In these circumstances, an aortic valve orifice area <1.0cm^2 usually indicates severe disease.

Cardiac catheterisation

Cardiac catheterisation is usually not needed to measure the severity of aortic stenosis, but may be required to document coronary artery disease if anginal symptoms are disproportionate to the severity of aortic stenosis. Coronary angiography should also be considered in Aboriginal and Torres Strait Islander patients who are 30 years or older, due to the high incidence of premature coronary artery disease in this population group. 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 >40–50mmHg). Initially, symptoms are exertional dyspnoea and fatigue. However, many patients may remain asymptomatic, despite having evidence of haemodynamically significant aortic stenosis. Once symptoms develop, prognosis is poor without surgery.

Aortic valvuloplasty

Percutaneous aortic valvuloplasty[243] may improve the severe aortic stenosis, but usually leaves a significant residual gradient. The procedure has significant morbidity and occasional mortality, particularly in elderly 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.[243] 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 aortic stenosis.

Surgical management

Aortic valve replacement is a definitive therapy for symptomatic aortic stenosis. (**Level III-2, Grade B**). It should be performed in all patients with significant gradients and a reduced valve orifice (mean gradient >50mm, aortic valve orifice <1cm^2), once they develop exertional symptoms.[244] 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 <50mmHg and symptoms clearly due to aortic stenosis. Aortic valve surgery involves replacement with either a mechanical valve, a bioprosthetic valve or a homograft.[194]

TABLE 4.4   KEY POINTS IN MANAGING 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 (4V^2)
	Assess left ventricular systolic function
Cardiac catheterisation	Only to exclude coronary artery disease
Indications for surgery	Symptoms plus mean systolic gradient >50mmHg or AVA <1.0cm^2

Choice of surgery	Valve replacement:
	
	• bioprosthesis or homograft
	   – limited durability
	   – no warfarin if in sinus rhythm
	• mechanical valve
	   – long-term warfarin required

Note: AVA=aortic valve area; V=velocity

4.6   MULTIVALVULAR DISEASE

In many patients with chronic rheumatic heart disease, both the mitral and aortic valves may be involved (eg aortic regurgitation and mitral stenosis or aortic and mitral regurgitation). The management is usually that of the dominant lesion. However, the proximal valve lesion may modify the effects of the distal lesion — eg severe mitral stenosis may prevent the development of significant LV dilatation secondary to aortic regurgitation.

The progression of the milder valve lesion is variable. However, 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.[245] In younger patients, the degree of adherence to antibiotic prophylaxis would be the major determinant of the progression of the non-operated valve disease.

The combination of significant mitral and aortic regurgitation is a surgical challenge[246] and carries a high risk of ventricular dysfunction. Surgical intervention is indicated at the onset of symptoms, or if LV dysfunction is identified

by echocardiography. The preferred surgery for Aboriginal and Torres Strait Islander patients would depend on the likelihood of maintaining optimal anticoagulation. If significant difficulties are anticipated, the preferred surgery would be mitral valve repair, accompanied by aortic valve repair or bioprosthetic aortic replacement to minimise the likelihood of the need for long-term anticoagulation (see).

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4.7   PREGNANCY IN PATIENTS WITH RHEUMATIC HEART DISEASE

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Normal pregnancy is associated with a 20–100% 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 mitral stenosis, is first diagnosed during pregnancy, through the detection of a heart murmur or the development of heart failure.[247]

Ideally, patients with known rheumatic valvular disease should be properly assessed before pregnancy. This 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 patients with moderate or severe mitral stenosis (orifice area <1.5cm^2), PBMV should be considered, even for the asymptomatic or mildly symptomatic woman, because of the high risk of maternal and foetal complications during pregnancy.

Risk factors

The predictors of increased maternal and foetal risk in the pregnant patient with rheumatic valvular disease are (1) reduced LV systolic function, (2) significant aortic or mitral stenosis, (3) moderate or severe pulmonary hypertension, (4) a history of heart failure, and (5) symptomatic valvular disease before pregnancy.[247] 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 with close collaboration between the cardiologist and the obstetrician is important for care of the pregnant patient with rheumatic valvular disease.

Mitral/aortic regurgitation

In general, pregnancy is well tolerated in patients with moderate or severe valvular regurgitation.[248,249] 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 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 (eg nifedipine), should be used if vasodilator therapy is needed (**Level IV, Grade C**).

Vaginal delivery 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 foetal loss.

Mitral stenosis

Mitral stenosis is the most commonly encountered valvular lesion in pregnancy.[200,249] 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 mitral stenosis (mitral valve orifice <1.5cm^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 heart rate is usually sufficient to provide symptomatic relief. Development of atrial fibrillation with a rapid ventricular rate requires initial rate control with the use of beta-blockers (eg metoprolol) and digoxin. A higher dose of digoxin is usually required in pregnancy (eg 250mcg bd). Diltiazem should be avoided. 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 foetus, and relief of mitral stenosis is usually required. Patients with NYHA Class III or IV symptoms with a mitral valve orifice of <1.0–1.5cm^2, suitable valve characteristics and no atrial thrombus should undergo PBMV[250,251] at the end of the second trimester or the beginning of the third. Radiation exposure should be minimized by using abdominal shielding and avoiding acquiring cardiac images for archiving. The safety of this procedure in pregnancy has been well established in more than 250 patients.[252] Cardiac surgery should be avoided because of the 30% foetal loss that occurs with cardiopulmonary bypass.[250] There

is a small risk of traumatic mitral regurgitation resulting from PBMV, but this can usually be managed medically, without the need for surgery until after pregnancy.

In patients with mitral stenosis, vaginal delivery is the usual approach, with the use of assisted delivery devices during the second stage to avoid the need for pushing and to shorten the second stage. Severe mitral stenosis with severe pulmonary hypertension is associated with increased maternal and foetal 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 aortic stenosis in pregnancy is far less common than mitral stenosis. Suspected aortic stenosis should be accurately assessed by Doppler echocardiography. Most patients with mild or moderate aortic stenosis can usually be safely followed during pregnancy. Rare cases with severe aortic stenosis (gradient over 50mmHg and/or valve orifice <1.0cm^2) are at significant risk of adverse maternal and foetal outcomes. In experienced centres, severely symptomatic patients can have percutaneous balloon aortic valvuloplasty in order to avoid the risks of cardiac surgery.

Prosthetic heart valves in pregnancy

In the childbearing 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 re-operation later in life because of structural valve degeneration. The choice of valve prosthesis in the childbearing age group requires careful judgement of the need for later re-operation, 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. Most patients with normally functioning prosthetic 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. Treatment of symptomatic heart failure requires digoxin, diuretics, hydralazine, nitrates and beta-blockers. ACE inhibitors and angiotensin antagonists are contraindicated in pregnancy.

Mechanical prosthetic valves: management of anticoagulation therapy

Pregnant women with mechanical valves are a very high-risk group in which all anticoagulation options pose maternal and/or foetal risks.[253–257] Therefore, patients with mechanical prosthetic valves should be given appropriate contraceptive advice and counselled about the risks to mother and foetus with pregnancy (**Grade D**).

The high risk is due to the hypercoagulable state that exists throughout pregnancy and the adverse effects of anticoagulation on mother and foetus. Warfarin crosses the placenta, increasing the risk of early abortion, embryopathy and late foetal loss. Both unfractionated and low molecular weight heparin do not cross the placenta, and have been suggested as alternatives to warfarin during pregnancy.[258,259] However, the rate of prosthetic valve thrombosis in patients treated with heparin has been reported to be as high as 20%.[253,260] The risk of maternal thromboembolism and maternal death also more than double in the first trimester with the use of heparin, especially when more aggressive therapeutic anticoagulation must be used with older-generation mechanical valves, such as caged ball or tilting disc in the mitral position.[260] Most of the reported cases of heparin-associated prosthetic valve thrombosis occurred with older-generation prosthetic valves (eg caged ball), often with unmonitored

low molecular weight heparin or inadequate levels of anticoagulation with unfractionated heparin.[256] Therefore if heparin (usually low molecular weight heparin) is used, it is essential that anticoagulation levels be regularly monitored with measurement of anti-factor Xa (anti-Xa) levels. Anti-Xa monitoring may be difficult to obtain outside an urban environment. The addition of low-dose aspirin to heparin may also reduce the risk of valve thrombosis.

The problems with heparin have led to the use of warfarin in pregnancy, especially in patients at higher thrombotic risk with first-generation mechanical valves in the mitral position, atrial fibrillation or a history of thromboembolism. Warfarin use in pregnancy is more efficacious in preventing valve thrombosis, but is associated with a high rate of foetal loss (up to 30%) and warfarin embryopathy (approximately 5–29%).[253] The risk of embryopathy is greatest during the first trimester, especially between 6 and 12 weeks. This has led to a recommendation of using low molecular weight heparin for the first trimester 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 can be ≤5mg, the risk of foetal loss or embryopathy is low.[248] This is usually possible with lower-risk bileaflet prostheses in the aortic position where an INR of 2.0–3.0 is usually adequate, but may not be possible with mitral valve prostheses where an INR between 2.5 and 3.5 is recommended.

It is important that the choice of anticoagulant regimens be fully discussed with the pregnant patient and family, preferably before pregnancy and certainly early in the first trimester. 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 in 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**).[253,256]

Regimen 1

Low molecular weight heparin (LMWH) throughout pregnancy

- Weight-adjusted dose of LMWH throughout pregnancy, administered subcutaneously every 12 hours with anti-Xa monitoring.

- The dose must be adjusted to maintain a trough (pre-dose) level of anti-Xa heparin of 0.6 U/mL in cases at lower risk (aortic valve prosthesis), and at 0.7 U/mL in higher-risk patients (older-generation prosthetic valve in mitral position). Peak levels should not exceed 1.5 U/mL. Anti-Xa levels should be measured every 2 weeks.

- The addition of low-dose aspirin daily (75–100mg) may add additional antithrombotic efficacy.

- LMWH ceased 36 hours before delivery or at onset of labour. Unfractionated heparin (UFH) used until onset of labour, with activated partial thromboplastin time maintained at or above 2.0 to allow for the increased heparin resistance in the third trimester.

Regimen 2

LMWH/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 LMWH or intravenous UFH at 36 weeks of gestation.

- Addition of low-dose aspirin (75–100mg) may add additional antithrombotic efficacy.

- Reversal of warfarin with vitamin K and caesarean section if onset of labour prior to cessation of warfarin.

- LMWH should be ceased 36 hours before elective delivery or at onset of labour, and UFH used until onset of labour.

Regimen 3 (especially older prostheses)

Warfarin throughout pregnancy

- Maintain target INR with the lowest dose of warfarin possible.

- Addition of low-dose aspirin daily (75–100mg) may add additional antithrombotic efficacy.

- Switch to LMWH or UFH at 36 weeks because about 30% of patients have premature labour.

- Reversal of warfarin with vitamin K and caesarean section if onset of labour prior to cessation of warfarin.

- LMWH ceased 36 hours before delivery or at onset of labour.

- UFH used until onset of labour.

Because of the risk of prosthetic thrombosis with heparin and the difficulty in obtaining anti-Xa monitoring, the European Society of Cardiology has recently strongly recommended regimen 3 as the preferred anticoagulation approach in patients with mechanical prosthetic valves — ie warfarin throughout pregnancy until the 36th week.[261]

Management of delivery

Patients on LMWH at the end of pregnancy should be switched to UHF at least 36 hours prior to elective delivery in the 38th week. Patients receiving warfarin should be switched to heparin at 36 weeks, since about 30% experience premature labour.[255] 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. Vaginal delivery is recommended if the patient is not on warfarin at the onset of labour and there is no significant prosthetic dysfunction or other significant cardiac disease. Careful titration of the intravenous heparin over the first 3–4 days postpartum is necessary, particularly following caesarean section, to avoid major bleeding. Warfarin is recommended 24–48 hours after delivery, and the heparin ceased once INR is over 2. Breastfeeding can be encouraged in women taking anticoagulants, as heparin is not secreted in breast milk and the amount of warfarin in breast milk is low (**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.[256] 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 having a vaginal or abdominal delivery.[249] However, antibiotics are certainly recommended if labour is prolonged or if there is premature rupture of the membranes. The recommended regimen is ampicillin 2.0g intravenous plus gentamicin (1.5mg/kg, not to exceed 120mg), given at the start of labour or within 30 minutes of caesarean section. A second dose of intravenous ampicillin or oral amoxycillin should be given 6 hours later.

TABLE 4.5   KEY POINTS IN MANAGING PREGNANCY IN PATIENTS WITH CHRONIC RHEUMATIC HEART DISEASE

	Blood volume increases 20–100%
	Will exacerbate any pre-existing rheumatic valvular heart disease
Factors that put pregnancy and mother at increased risk	Decreased left ventricular systolic function
	Significant aortic and mitral stenosis
	Pulmonary hypertension
	Heart failure
	Symptoms before pregnancy
Cardiac assessment	Early comprehensive assessment with echocardiography to assess valves and left ventricular function
	Plan multidisciplinary management
Mitral/aortic regurgitation	Usually well tolerated
	Treat medically with diuretics, vasodilators (no ACE inhibitors/angiotensin II receptor blockers) for heart failure
Mitral stenosis	Mild to moderate mitral stenosis — manage medically
	Moderate to severe mitral stenosis (MVA <1.5cm^2) — consider percutaneous balloon mitral valvuloplasty during late second trimester if patient remains symptomatic and PAS pressure >50mmHg
	Beta-blockers, digoxin for rate control of atrial fibrillation
Aortic stenosis (rare)	Mild to moderate — well tolerated
	Diuretics for heart failure
	Beta-blockers, digoxin for rate control of atrial fibrillation
	Severe aortic stenosis (AVA >50mmHg mean gradient) — percutaneous aortic valvuloplasty if severely symptomatic
	Avoid cardiac surgery, as high risk of foetal loss
Mechanical/prosthetic valves and anticoagulation in pregnancy	High maternal and foetal risk
	Risk of warfarin embryopathy in first trimester
	Embryopathy may be avoided if warfarin dose ≤5mg
Choice of three antithrombotic regimens	1 LMWH throughout pregnancy, weight-adjusted dose with anti-Xa level monitoring
	2 Warfarin throughout pregnancy if can keep warfarin ≤5mg, eg INR 2.0–3.0 in aortic prosthesis, sinus rhythm; change to LMWH or UFH 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	Haemodynamic monitoring — non-invasive if mild to moderate valve disease
	Antibiotic prophylaxis if prolonged labour and/or ruptured membranes
	Aim for short second stage, multidisciplinary management
	Approach with low threshold for obstetric intervention

Notes: anti-Xa=anti-factor Xa; AVA=aortic valve area; INR=international normalised ratio; LMWH=low molecular weight heparin; MVA=mitral valve area; PAS=pulmonary artery systolic; UFH=unfractionated heparin

APPENDIX

Development process of this review

This review was jointly developed by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. The review is the product of a rigorous and iterative process:

- a writing group comprising experts in the area (see page ii) prepared an initial draft review;

- selected individuals (listed on page ii) with experience in ARF/RHD management then reviewed each chapter, and their suggestions were incorporated into a second draft;

- the revised draft was widely distributed to a range of stakeholders (listed on page ii), who were then invited to a one-day workshop in November 2004;

- the stakeholders reviewed the draft and reached consensus on areas of disagreement;

- a third draft was then prepared and re-distributed for further comment;

- comments were then incorporated into a final draft, which was endorsed by the stakeholders.

This scientifically rigorous development process has been endorsed by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, and informed by National Health and Medical Research Council principles for guideline development.

> **This review provides a general framework and should not over-ride good clinical judgement. Treatment should take into account the patient's comorbidities, 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.**

ACRONYMS AND ABBREVIATIONS

2DE	two-dimensional echocardiography
anti-DNase B	anti-deoxyribonuclease B
anti-Xa	anti-factor Xa
ARF	acute rheumatic fever
ASO	anti-streptolysin O
AVA	aortic valve area
BP	blood pressure
BPG	benzathine penicillin G
CRP	C-reactive protein
CSANZ	Cardiac Society of Australia and New Zealand
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
GAS	group A streptococcus
HR	heart rate
INR	international normalised ratio
IVIG	intravenous immunoglobulin
LMWH	low molecular weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
LVEDD	left ventricular end diastolic diameter
LVESD	left ventricular end systolic diameter
LVOT	left ventricular outflow tract
MVA	mitral valve area
NHFA	National Heart Foundation of Australia
NSAIDs	non-steroidal anti-inflammatory drugs
NYHA FC	New York Heart Association Functional Class
PANDAS	paediatric auto-immune neuropsychiatric disorders associated with streptococcal infections
PAS	pulmonary artery systolic (pressure)
PBMV	percutaneous balloon mitral valvuloplasty
RHD	rheumatic heart disease
RR	respiratory rate
UFH	unfractionated heparin
ULN	upper limit of normal
V	velocity
WHO	World Health Organization

REFERENCES

1. Veasy, L.G. et al, Persistence of acute rheumatic fever in the intermountain area of the United States. *J Pediatr*, 1994. 124: 9–16.

2. National Health and Medical Research Council, *A Guide to the Development, Implementation, and Evaluation of Clinical Practice Guidelines*. 1999. Commonwealth of Australia: Canberra. pp. 1–79.

3. National Health and Medical Research Council, *Clinical Practice Guidelines for the Management of Overweight and Obesity in Children and Adolescents.* 2003. Commonwealth of Australia: Canberra.

4. Anonymous, Strategy for Controlling Rheumatic Fever/Rheumatic Heart Disease, with Emphasis on Primary Prevention: Memorandum from a Joint WHO/ISFC Meeting. *Bull World Health Organ*, 1995. 73: 583–87.

5. McDonald, M. et al, Acute rheumatic fever: a chink in the chain that links the heart to the throat? *Lancet Infect Dis*, 2004. 4: 240–45.

6. Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease, *Report of a WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease 29 October–1 November 2001.* 2001. World Health Organization: Geneva.

7. Couzos, S. & Carapetis, J., Rheumatic fever. In: *Aboriginal Primary Health Care: An Evidence-based Approach,* 2nd ed. 2003. S. Couzos and R. Murray (Eds). Oxford University Press: Melbourne.

8. Carapetis, J.R., *A Review of the Technical Basis for the Control of Conditions Associated with GAS Infections.* 2004. WHO/FCH/CAH/05.08. World Health Organization: Geneva.

9. Lennon, D., Acute rheumatic fever in children: recognition and treatment. *Pediatr Drugs*, 2004. 6: 363–73

10. Carapetis, J. et al, Seminar: acute rheumatic fever. *Lancet,* 2005. 366: 155–68.

11. Carapetis, J.R. et al, Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? *Epidemiol Infect*, 2000. 124: 239–44.

12. Cunningham, M.W., Autoimmunity and molecular mimicry in the pathogenesis of post-streptococcal heart disease. *Front Biosci*, 2003. 8: s533–43.

13. Cunningham, M.W., Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev*, 2000. 13: 470–511.

14. Gordis, L., The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. *Circulation*, 1985. 72: 1155–62.

15. Quinn, R., Comprehensive review of morbidity and mortality trends for rheumatic fever, streptococcal disease, and scarlet fever: the decline of rheumatic fever. *Rev Infect Dis,* 1989. 11: 928–53.

16. Carapetis J.R. et al, The global burden of group A streptococcal diseases. *Lancet Infect Dis*, 2005. 5: 685–94.

17. AIHW, *Rheumatic Heart Disease: All but Forgotten in Australia except among Aboriginals and Torres Strait Islander Peoples.* 2004. Australian Institute of Health and Welfare: Canberra.

18. Carapetis, J.F. & Currie, B.J., Mortality due to acute rheumatic fever and rheumatic heart disease in the Northern Territory: a preventable cause of death in Aboriginal people. *Aust N Z J Public Health*, 1999. 23: 159–63.

19. Carapetis, J.R. et al, Acute rheumatic fever and rheumatic heart disease in the Top End of Australia's Northern Territory. *Med J Aust*, 1996. 164: 146–49.

20. Jones, T.D., Diagnosis of rheumatic fever. *JAMA*, 1944. 126: 481–84.

21. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association, Guidelines for the Diagnosis of Rheumatic Fever. Jones criteria 1992 update. *JAMA*, 1992. 268: 2069–73.

22. Carapetis, J.R. & Currie, B.J., Rheumatic fever in a high incidence population: the importance of monoarthritis and low grade fever. *Arch Dis Child*, 2001. 85: 223–27.

23. Lessof, M., Sydenham's chorea. *Guys Hosp Rep,* 1958. 107: 185–206.

24. Carapetis, J.R. & Currie, B.J., Rheumatic chorea in northern Australia: a clinical and epidemiological study. *Arch Dis Child*, 1999. 80: 353–58.

25. Taranta, A. & Stollerman, G.H., The relationship of Sydenham's chorea to infection with group A streptococci. *Am J Med*, 1956. 20: 170–75.

26. Taranta, A., Relation of isolated recurrences of Sydenham's chorea to preceding streptococcal infections. *N Engl J Med*, 1959. 260: 1204–10.

27. Ayoub, E.M. & Wannamaker, L.W., Streptococcal antibody titers in Sydenham's chorea. *Pediatrics*, 1966. 38: 846–956.

28. Stollerman, G.H. et al, Determination of C-reactive protein in serum as a guide to the treatment and management of rheumatic fever. *Am J Med*, 1953. 15: 645–55.

29. Aron, A.M. et al, The natural history of Sydenham's chorea. Review of the literature and long-term evaluation with emphasis on cardiac sequelae. *Am J Med*, 1965. 38: 83–95.

30. Anonymous, Centers for Disease Control. Acute rheumatic fever — Utah. *MMWR*, 1987. 36: 108.

31. Bland, E.F., Chorea as a manifestation of rheumatic fever: a long-term perspective. *Trans Am Clin Climatol Assoc,* 1943. 73: 209–13.

32. Sanyal, S.K. et al, Sequelae of the initial attack of acute rheumatic fever in children from north India. A prospective 5-year follow-up study. *Circulation*, 1982. 65: 375–79.

33. Edwards, W.D. et al, Active valvulitis associated with chronic rheumatic valvular disease and active myocarditis. *Circulation*, 1978. 57: 181–85.

34. Marcus, R.H. et al, The spectrum of severe rheumatic mitral valve disease in a developing country. Correlations among clinical presentation, surgical pathologic findings, and hemodynamic sequelae. *Ann Intern Med*, 1994. 120: 177–83.

35. Gentles, T.L. et al, Left ventricular mechanics during and after acute rheumatic fever: contractile dysfunction is closely related to valve regurgitation. *J Am Coll Cardiol*, 2001. 1: 201–07.

36. Jamal, M. & Abbas, K.A., Clinical profile of acute rheumatic fever in children. *J Trop Pediatr*, 1989. 35: 10–13.

37.   Committee of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association. Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation*, 1984. 69: 204A–08A.

38.   Park, M.K., *Pediatric Cardiology for Practitioners*, 2nd ed. 1988. Year Book Medical Publishers: Chicago.

39.   Martin, D.R. et al, Acute rheumatic fever in Auckland, New Zealand: spectrum of associated group A streptococci different from expected. *Pediatr Infect Dis J*, 1994. 13: 264–69.

40.   Kaplan, E.L. et al, Comparison of the antibody response to streptococcal cellular and extracellular antigens in acute pharyngitis. *J Pediatr*, 1974. 84: 21–28.

41.   McCarty, M., The antibody response to streptococcal infections. In: *Streptococcal Infections*, 1954. M. McCarty (Ed), Columbia University Press: New York. pp. 130–42.

42.   Stollerman, G.H. et al, Relationship of immune response to group A streptococci to the course of acute, chronic and recurrent rheumatic fever. *Am J Med*, 1956. 20: 163–69.

43.   Danchin, M.H. et al, New normal ranges of antistreptolysin O and anti-deoxyribonuclease B titres for Australian children. *J Paediatr Child Health*, (in press).

44.   Nimmo, G.R. et al, Group A streptococcal infection in an Aboriginal community. *Med J Aust*, 1992. 157: 521–22.

45.   Van Buynder, P.G. et al, Streptococcal infection and renal disease markers in Australian aboriginal children. *Med J Aust*, 1992. 156: 537–40.

46.   Kaplan, E.L. et al, Antistreptolysin O and antideoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. *Pediatrics*, 1998. 101: 86–88.

47.   De Cunto, C.L. et al, Prognosis of children with poststreptococcal reactive arthritis. *Pediatr Infect Dis J*, 1988. 7: 683–86.

48.   Shulman, S.T. & Ayoub, E.M., Poststreptococcal reactive arthritis. *Curr Opin Rheumatol*, 2002. 5: 562–65.

49.   Swedo, S.E. et al, Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. *Am J Psychiatry*, 1997. 154: 110–12.

50.   Kurlan, R. & Kaplan, E.L., The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics*, 2004. 113: 883–86.

51.   Folger, G.M. & Hajar, R., Doppler echocardiographic findings of mitral and aortic valvular rergurgitation in children manifesting only rheumatic arthritis. *Am J Cardiol*, 1989. 63: 1278–80.

52.   Folger, G.M. et al, Occurrence of valvular heart disease in acute rheumatic fever without evident carditis: colour flow Doppler identification. *Brit Heart J*, 1992. 67: 434–38.

53.   Wilson, N.J. & Neutze, J.M., Echocardiographic diagnosis of subclinical carditis in acute rheumatic fever. *Int J Cardiol*, 1995. 50: 1–6.

54.   Feinstein, A.R. et al, The prognosis of acute rheumatic fever. *Am Heart J*, 1964. 68: 817–34.

55.   Marcus, R.H. et al, Functional anatomy of severe mitral regurgitation in active rheumatic carditis. *Am J Cardiol*, 1989. 63: 577–84.

56.   Wu Y.N. et al, Rupture of chordae tendineae in acute rheumatic carditis: report of one case. *Acta Paediatrica Sinica*, 1992. 33: 376–82.

57. Zhou, L.Y. & Lu, K., Inflammatory valvular prolapse produced by acute rheumatic carditis: echocardiographic analysis of 66 cases of acute rheumatic carditis. *Int J Cardiol*, 1997. 58: 175–78.

58. Lembo, N.J. et al, Mitral valve prolapse in patients with prior rheumatic fever. *Circulation*, 1988. 77: 830–36.

59. Abernathy, M., Doppler echocardiography and the early diagnosis of acute rheumatic fever. *A N Z J Med*, 1994. 24: 530–35.

60. Jaffe, W.M. et al, Clinical evaluation versus Doppler echocardiography in the quantitative assessment of valvular heart disease. *Circulation*, 1988. 78: 267–75.

61. Perry, G.L. et al, Evaluation of aortic insufficiency by Doppler colour flow mapping. *J Am Coll Cardiol*, 1987. 9: 952–59.

62. Thomas, L. et al, The mitral regurgitation index: an echocardiographic guide to severity. *J Am Coll Cardiol*, 1999. 33: 16–22.

63. Wilson, N.J. et al, Colour-Doppler demonstration of pathological valve regurgitation should be accepted as evidence of carditis in acute rheumatic fever. *N Z Med J*, 1995. 108: 200.

64. Voss, L.M. et al, Intravenous immunoglobulin in acute rheumatic fever: a randomized control trial. *Circulation*, 2001. 103: 401–06.

65. Kostucki, W. et al, Pulsed Doppler regurgitant flow patterns of normal valves. *J Am Coll Cardiol*, 1986. 58: 309–13.

66. Wilson N.J. et al, The natural history of acute rheumatic fever to one year in the echocardiographic era. In: *Proceedings of the 2nd World Congress of Pediatric Cardiology and Cardiac Surgery*. 1997. Y. Imai & K. Momma (Eds). Futura Publishing Co: New York. pp. 971–72.

67. Yoshida, K. et al, Colour Doppler evaluation of valvular regurgitation in normal subjects. *Circulation*, 1988. 78: 840–47.

68. Berger, M. et al, Pulsed and continuous wave Doppler echocardiographic assessment of valvular regurgitation in normal subjects. *J Am Coll Cardiol*, 1989. 13: 1540–45.

69. Sahn, D.J. & Maciel, B.C., Physiological valvular regurgitation: Doppler echocardiography and the potential for iatrogenic heart disease. *Circulation*, 1988. 78: 1075–77.

70. Choong, C.Y. et al, Prevalence of valvular regurgitation by Doppler echocardiography in patients with structurally normal hearts by two dimensional echocardiography. *Am Heart J*, 1989. 117: 636–42.

71. Vasan, R.S. et al, Echocardiographic evaluation of patients with acute rheumatic fever and rheumatic carditis. *Circulation*, 1996. 94: 73–82.

72. Veasy, L.G. et al, Resurgence of acute rheumatic fever in the intermountain area of the United States. *New Engl J Med*, 1987. 316: 421–27.

73. Minich, L.L. et al, Doppler echocardiography distinguishes between physiologic and pathologic "silent" mitral regurgitation in patients with rheumatic fever. *Clin Cardiol*, 1997. 11: 924–26.

74. Mota, C.C., Doppler echocardiographic assessment of subclinical valvulitis in the diagnosis of acute rheumatic fever. *Cardiol Young*, 2001. 11: 251–54.

75. Figueroa, F.E. et al, Prospective comparison of clinical and echocardiographic diagnosis of rheumatic carditis: long term follow-up of patients with subclinical disease. *Heart*, 2001. 85: 407–10.

76. Lionet, P. et al, Significance and importance of the discovery of a subclinical aortic regurgitation for the diagnosis of rheumatic carditis. *2nd International Cardiology Congress of South Pacific, Tahiti, 2001*. [Abstract].

77. Regmi, P.R. & Pandey, M.R., Prevalence of rheumatic fever and rheumatic heart disease in school children of Kathmandu city. *Indian Heart J*, 1997. 49: 518–20.

78. Cotrim, C. et al, O ecocardiograma no primeiro surto de fibre reumatica no crianca (The echocardiogram in the first attack of rheumatic fever in childhood). *Revista Portuguesa do Cardiologia* (*Portuguese J Cardiol*), 1994. 13: 581–86.

79. Agarwal. P, K. et al, Usefulness of echocardiography in detection of subclinical carditis in acute rheumatic polyarthritis and rheumatic chorea. *J Assoc Physicians India*, 1998. 46: 937–38.

80. Narula, J. & Kaplan, E.L., Echocardiographic diagnosis of rheumatic fever. *Lancet*, 2001. 358: 2000.

81. Albert, D.A. et al, The treatment of rheumatic carditis: a review and meta-analysis. *Medicine* (Baltimore), 1995. 74: 1–12.

82. Cilliers, A.M. et al, Anti-inflammatory treatment for carditis in acute rheumatic fever. *Cochrane Database Syst Rev*, 2003. CD003176.

83. Illingworth, R.S. et al, Acute rheumatic fever in children: a comparison of six forms of treatment in 200 cases. *Lancet*, 1957. 2: 653–59.

84. Dorfman, A. et al, The treatment of acute rheumatic fever. *Pediatrics*, 1961. 27: 692–706.

85. Bywaters, E.G.L. & Thomas, G.T., Bed rest, salicylates and steroid in rheumatic fever. *BMJ*, 1961. 1: 1628–34.

86. Carter, M.E. et al, Rheumatic fever treated with penicillin in bactericidal dosage for six weeks. Report of a small controlled trial. *BMJ*, 1962. 1: 965–67.

87. Mortimer, E.A. et al, The effect of penicillin on acute rheumatic fever and valvular heart disease. *N Engl J Med*, 1959. 260: 101–12.

88. Melcher, G.P. et al, Comparative efficacy and toxicity of roxithromycin and erythromycin ethylsuccinate in the treatment of streptococcal pharyngitis in adults. *J Antimicrob Chemother*, 1988. 22: 549–56.

89. Thatai, D. & Turi, D.G., Current guidelines for the treatment of patients with rheumatic fever. *Drugs*, 1999. 57: 545–55.

90. Silva, N.A. & Pereira, B.A., Acute rheumatic fever: still a challenge. *Rheumatic Disease Clin N Am*, 1997. 23: 545–68.

91. Stollerman, G., *Rheumatic Fever and Streptococcal Infection.* 1975. Grune & Stratton: New York.

92. Davis J.S. et al, Prevention of opportunistic infections in immunosuppressed patients in the tropical top end of the Northern Territory. *Comm Dis Intell,* 2003. 27: 526–32.

93. Hashkes, P.J. et al, Naproxen as an alternative to aspirin for the treatment of arthritis of rheumatic fever: a randomized trial. *J Pediatr*, 2003. 143: 399–401.

94. Uziel, Y. et al, The use of naproxen in the treatment of children with rheumatic fever. *J Pediatr*, 2000. 137: 268–71.

95.   Lessof, M.H. & Bywaters, E.G., The duration of chorea. *BMJ*, 1956: 1520–3.

96.   al-Eissa, A., Sydenham's chorea: a new look at an old disease. *Brit J Clin Practice*, 1993. 47: 14–16.

97.   Markowitz, M. & Gordis, L., *Rheumatic Fever,* 2nd ed. 1972. W.B. Saunders: Philadelphia.

98.   Swedo, S.E., Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders. *JAMA*, 1994: 1788–91.

99.   Daoud, A.D. et al, Effectiveness of sodium valproate in the treatment of Sydenham's chorea. *Neurology*, 1990. 40: 1140–41.

100.   Genel, F. et al, Sydenham's chorea: clinical findings and comparison of the efficacies of sodium valproate and carbamazepine regimens. *Brain Dev*, 2002. 24: 73–76.

101.   Pena, J. et al, Comparison of the efficacy of carbamazepine, haloperidol and valproic acid in the treatment of children with Sydenham's Chorea. *Arq Neuropsiquiatr*, 2002. 60: 374–77.

102.   Party, R.F.W., The natural history of rheumatic fever and rheumatic heart disease: ten-year report of a cooperative clinical trial of ACTH, cortisone and aspirin. *Circulation*, 1965. 32: 457–76.

103.   Krum, H. et al, *Guidelines on the Contemporary Management of the Patient with Chronic Heart Failure in Australia*. 2002. National Heart Foundation of Australian and Cardiac Society of Australia and New Zealand.

104.   al Kasab, S. et al, Valve surgery in rheumatic heart disease. *Chest*, 1988. 94: 830–33.

105.   Taran, L.M., The treatment of acute rheumatic fever and acute rheumatic heart disease. *Am J Med*, 1947. 2: 285–95.

106.   Anonymous, Community control of rheumatic heart disease in developing countries (2): Strategies for prevention and control. *WHO Chronicle*, 1980. 34: 389–95.

107.   Anonymous, *Rheumatic Fever and Rheumatic Heart Disease — Report of a WHO Study Group*. 1988, World Health Organization: Geneva.

108.   Manyemba, J. & Mayosi, B.M., Penicillin for secondary prevention of rheumatic fever. *Cochrane Database Sys Rev*, 2002. 3.

109.   Majeed, H. et al, Acute rheumatic fever and the evolution of rheumatic heart disease: a prospective 12 year follow-up report. *J Clin Epidemiol*, 1992. 8: 871–75.

110.   Lue, H.C. et al, Clinical and epidemiological features of rheumatic fever and rheumatic heart disease in Taiwan and the Far East. *Indian Heart J*, 1983. 35: 139–46.

111.   Dajani, A. et al, Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. *Pediatrics*, 1995. 96: 758–64.

112.   Group, W.S., *Rheumatic Fever and Rheumatic Heart Disease*. 1988. World Health Organization: Geneva.

113.   Anonymous, *Therapeutic Guidelines: Antibiotic Version 2*. 2000. Therapeutic Guidelines Limited: Melbourne.

114.   Anonymous, *Therapeutic Guidelines: Antibiotic*. 2003, Therapeutic Guidelines Limited: Melbourne.

115. Ginsburg, C. et al, Serum penicillin concentrations after intramuscular administration of benzathine penicillin G in children. *Pediatrics*, 1982. 69: 452–54.

116. Meria, Z. et al, Evaluation of secondary prophylactic schemes, based on benzathine penicillin G, for rheumatic fever in children. *J Pediatr*, 1993. 123: 156–58.

117. Lennon, D., Rheumatic fever, a preventable disease? The New Zealand experience. In: *Streptococci and Streptococcal Disease: Entering the New Millenium*, 2000. D.R. Martin & J.R. Tagg (Eds). ESR: Porirua. pp. 503–12.

118. Kaplan, E. et al, Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1,200,000 units. *J Pediatr*, 1989. 115: 146–50.

119. Lue, H.C. et al, Rheumatic fever recurrences: controlled study of 3 week versus 4 week benzathine penicillin prevention programs. *J Pediatr*, 1986. 108: 299–304.

120. Padmavati, S. et al, Penicillin for rheumatic fever prophylaxis 3 weekly or 4 weekly schedule. *J Assoc Physicians India*, 1987. 35: 753–55.

121. Lue, H.-C. et al, Long term outcome of patients with rheumatic fever receiving benzathine penicillin G prophylaxis every three weeks versus every four weeks. *J Pediatr*, 1994. 125: 812–16.

122. Currie, B. et al, Penicillin concentrations after increased doses of benzathine penicillin G for prevention of secondary rheumatic fever. *Antimicrobial Agents Chemother*, 1994. 38: 1203–04.

123. Currie, B., Are the currently recommended doses of benzathine penicillin G adequate for prophylaxis for recurrent rheumatic fever? *Pediatrics*, 1996. 97: 989–91.

124. McDonald, K. & Walker A., Rheumatic heart disease in Aboriginal children in the Northern Territory. *Med J Aust*, 1989. 150: 503–05.

125. Spinetto, H. et al, *The Auckland Rheumatic Fever Register, 1993–1999: An Audit.* 2002. Paediatric Society of New Zealand: Auckland.

126. Division of Drug Management and Policies (World Health Organization), *WHO Model Prescribing Information. Drugs used in the Treatment of Streptococcal Pharyngitis and Prevention of Rheumatic Fever.* 1999. World Health Organization: Geneva.

127. Bonow, R.O. et al, Guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of patients with valvular heart disease). *J Am Coll Cardiol*, 1998. 32: 1486–588.

128. Kassem, A.S. et al, *Guidelines for Management of Children with Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) in Egypt.* The Egyptian Society of Cardiology and the Egyptian Society of Pediatric Cardiologists: Alexandria.

129. Feinstein, A. et al, A controlled study of three methods of prophylaxis against streptococcal infection in a population of rheumatic children. *New Engl J Med*, 1959. 260: 697–702.

130. Dajani, A., Adherence to physicians' instructions as a factor in managing streptococcal pharyngitis. *Pediatrics*, 1996. 97: 976–80.

131. Wood, H.F. et al, Rheumatic fever in children and adolescents. A long term epidemiological study of subsequent prophylaxis, streptococcal infections and clinical sequelae. 111. Comparative effectiveness of three prophylaxis regimes in preventing streptococcal infections and rheumatic recurrences. *Ann Int Med*, 1964. 60: Suppl 5: 31–46.

132. International Rheumatic Fever Study Group, Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet*, 1991. 337: 1308–10.

133. Markowitz, M. & Lue, H.-C., Allergic reactions in rheumatic fever patients on long-term benzathine penicillin G: The role of skin testing for penicillin allergy. *Pediatrics*, 1996. 97: 981–83.

134. Weiss, M.E. & Adkinson, N.F., Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy*, 1988. 18: 515.

135. Carapetis, J.R., *Ending the Heartache: the Epidemiology and Control of Acute Rheumatic Fever and Rheumatic Heart Disease in the Top End of the Northern Territory*. 1998, Unpublished Doctor of Philosophy thesis, University of Sydney: Sydney.

136. Spinetto, H., *Recurrences of Rheumatic Fever in Auckland, 1993–1999*. 2003. Thesis for Master of Health Science, University of Auckland.

137. Carapetis, J. & Currie, B., Clinical epidemiology of rheumatic fever and rheumatic heart disease in tropical Australia. *Adv Experimental Med & Biol*, 1997. 418: 233–36.

138. Frankish, J.D., Rheumatic fever prophylaxis: Gisborne experience. *N Z Med J*, 1984. 97: 674–75.

139. Harrington, Z., *Rheumatic Heart Disease Prevention and Concepts of Care for Yolngu Patients*. Part 2 of Thesis for Master of Science (Health Sciences), Flinders University: Adelaide.

140. Bassili, A. et al, Profile of secondary prophylaxis among children with rheumatic heart disease in Alexandria, Egypt. *Eastern Mediterranean Health J*, 2000. 6: 437–46.

141. Mincham, C. et al, Patient views on the management of rheumatic fever and rheumatic heart disease in the Kimberley: A qualitative study. *Aust J Rural Health*, 2003. 11: 260–65.

142. Brown, A. et al, Central Australian Rheumatic Heart Disease Control Program: A report to the Commonwealth November 2002. *N T Disease Control Bull*, 2003. 10: 1–8.

143. Northern Territory Department of Health and Community Services, *Report on the National Workshop on Rheumatic Heart Disease*. 2004, Northern Territory Department of Health and Community Services/Commonwealth Department of Health and Ageing: Darwin.

144. Kelly, A., Top End Rheumatic Heart Disease Program: A report to the Commonwealth, February–November 2002. *N T Disease Control Bull*, 2003. 10: 9–11.

145. Arya, R., Awareness about sore throat, rheumatic fever and rheumatic heart disease in a rural community. *Indian J Public Health*, 1992. 36: 63–67.

146. Lyengar, S. et al, A rheumatic fever and rheumatic heart disease control programme in a rural community of North India. *Nat Med J India*, 1991. 4: 268–71.

147. Bach, J. et al, 10 year educational programme aimed at rheumatic fever in two French Caribbean Islands. *Lancet*, 1996. 347: 644–48.

148. Amir, J. et al, Lidocaine as a dilutent for administration of benzathine penicillin G. *Pediatr Infect Dis J*, 1998. 17: 890–93.

149. Bass, J., A review of the rationale and advantages of various mixtures of benzathine penicillin G. *J Pediatr*, 1996. 96: 960–63.

150. Bass, J. et al, Streptococcal pharyngitis in children: a comparison of four treatment schedules with intramuscular penicillin G benzathine. *JAMA*, 1976. 235: 1112–16.

151. Barnhill, B.J. et al, Using pressure to decrease the pain of intramuscular injections. *J Pain Symptom Manage*, 1996. 12: 52–58.
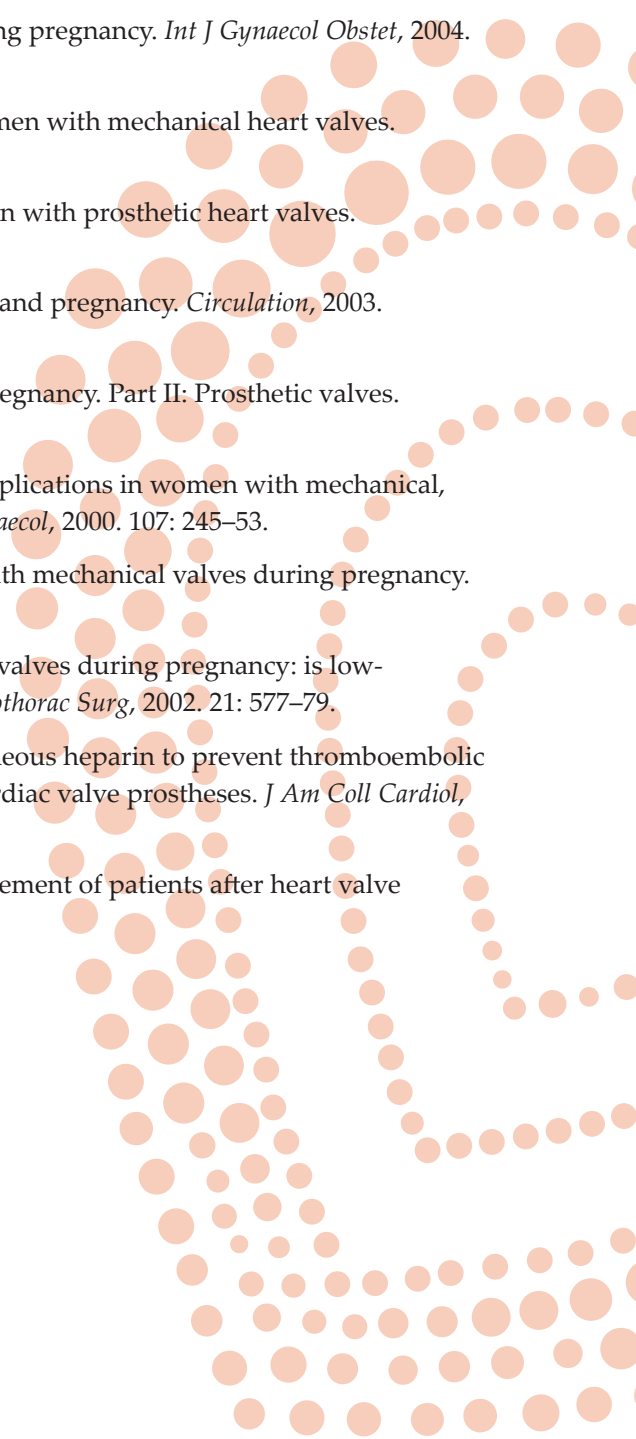
152. Michaud, C. et al, Rheumatic heart disease. In: *Disease Control Priorities in Developing Countries*. 1993. D.T. Jamison, (Ed). Oxford University Press: New York.

153. North, D. et al, Analysis of costs of acute rheumatic fever and rheumatic heart disease in Auckland. *N Z Med J*, 1993. 106: 400–03.

154. Anonymous, WHO program for the prevention of rheumatic fever/rheumatic heart disease in 16 developing countries: report from phase 1 (1986–90). *WHO Bull*, 1992. 70: 213–18.

155. Gordis, L. et al, An evaluation of the Maryland rheumatic fever registry. *Public Health Report*, 1969. 84: 333–39.

156. Strasser, T., Cost-effective control of rheumatic fever in the community. *Health Policy*, 1985. 5: 159–64.

157. WHO, *The WHO Global Programme for the Prevention of Rheumatic Fever and Rheumatic Heart Disease: Report of a Consultation to Review Progress and Develop Future Activities 29 November– 1 December 1999*. 2000. World Health Organization: Geneva.

158. Neutz, J. & Clarkson, P., Rheumatic fever: an unsolved problem in New Zealand. *N Z Med J*, 1984. 97: 591–93.

159. Kumar, R. et al, Compliance of secondary prophylaxis for controlling rheumatic fever and rheumatic heart disease in a rural area of Northern India. *Indian Heart J*, 1997. 49: 283–88.

160. Kumar, R. et al, A community based rheumatic fever/rheumatic heart disease cohort: twelve year experience. *Indian Heart J*, 2002. 54: 54–58.

161. Thornley, C. et al, Rheumatic fever registers in New Zealand. *Public Health Report*, 2001. 8: 41–44.

162. Noonan, S. et al, The Top End rheumatic heart disease control program 1: Report on program objectives. *N T Disease Control Bull*, 2001. 8: 15–18.

163. Edmond, K. et al, The Top End rheumatic heart disease control programme 2: Rates of rheumatic heart disease and acute rheumatic fever. *N T Disease Control Bull*, 2001. 8: 18–22.

164. Rice, M. & Kaplan, E., Rheumatic fever in Minnesota 2: evaluation of hospitalized patients and utilization of a state rheumatic fever registry. *Am J Public Health*, 1979. 69: 767–71.

165. MacQueen, J., State registries and the control of rheumatic fever. *Am J Public Health*, 1979. 69: 761–62.

166. Krause, V., Should Acute Rheumatic Fever and Rheumatic Heart Disease be Notifiable? 2004. Minutes for the Communicable Disease Network of Australia Meeting 2004.

167. Hanna, J. & Heazlewood, R.J, The epidemiology of acute rheumatic fever in Indigenous people in North Queensland. *Aust N Z J Public Health*, 2005. 29: 313–17.

168. Binns, P. & Krause, V., Should acute rheumatic fever and rheumatic heart disease be nationally notifiable? *N T Disease Control Bull*, 2004. 11: 25–29.

169. Council of Europe, *Recommendation No. R(94)11 on Screening as a Tool of Preventative Medicine*. 1994. Council of Europe.

170. Michaud, C. et al, Cost-effectiveness analysis of intervention strategies for reduction of the burden of rheumatic heart disease. In: *Rheumatic Fever*. 1999. American Registry of Pathology: Washington, D.C. pp. 485–97.

171. Bland, E.F. & Jones, T.D., Rheumatic fever and rheumatic heart disease: A twenty-year report on 1,000 patients followed since childhood. *Circulation*, 1951. 4: 836–43.

172. Tompkins, D.G. et al, Long-term prognosis of rheumatic fever and patients receiving regular intramuscular benzathine penicillin. *Circulation*, 1972. 45: 543–51.

173. Hardy, M. et al, High rates of rheumatic heart disease in Tongan children, and a protocol for echo-based screening in developing countries. *16th Lancefield International Symposium on Streptococci and Streptococcal Disease, Cairns, 2005*. [Abstract].

174. AIHW, *The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples.* 2005. Australian Institute of Health and Welfare: Canberra.

175. Gruen, R.L. et al, Improving access to specialist care for remote Aboriginal communities: evaluation of a specialist outreach service. *Med J Aust*, 2001. 174: 507–11.

176. Salustri, A. & Trambaiolo, P., Point of care echocardiography: small, smart and quick. *Eur Heart J*, 2002. 23: 1484–87.

177. Smyth, T. Anticoagulation in patients with metallic valvular prosthesis in the Top End of the Northern Territory. In: *39th CARPA Conference Central Australian Rural Practitioners Association in conjunction with the Royal Australasian College of Physicians NT Annual Scientific Meeting*. 2003. CARPA, Alice Springs.

178. Gill, J.M. & Landis, M.K., Benefits of a mobile, point of care anticoagulation therapy management program. *Joint Commission J Quality Improvement*, 2002. 28: 625–30.

179. Carapetis, J.R. et al, Outcomes of cardiac valve replacement for rheumatic heart disease in Aboriginal Australians. *Asia Pacific Heart J*, 1999. 8: 138–47.

180. Carabello, B.A. & Crawford, F.A., Valvular heart disease. *New Engl J Med*, 1997. 337: 32–41.

181. Enriquez-Sarano, M. et al, Progression of mitral regurgitation — a prospective Doppler echocardiographic study. *J Am Coll Cardiol*, 1999. 34: 1137.

182. Marcus R.H. et al, The spectrum of severe rheumatic mitral valve disease in a developing country: Correlations among clinical presentation, surgical pathologic findings, and hemodynamic sequelae. *Ann Int Med*, 1994. 120: 177–83.

183. Meira Z.M.A. et al, Long term follow up of rheumatic fever and predictors of severe rheumatic valvular disease in Brazilian children and adolescents. *Heart*, 2005. 91: 1019–22.

184. Alpert, J.S. et al, Mitral valve disease. In: *Textbook of Cardiovascular Medicine*. 2003. E.J. Topol, et al (Eds). 2003, Lippincott, Williams & Wilkins.

185. Otto, C.M. Evaluation and management of chronic mitral regurgitation. *N Engl J Med*, 2001. 345: 740–46.

186. Essop, M.R. & Nkomo, V.T. Rheumatic and Nonrheumatic valvular heart disease: epidemiology, management and prevention in Africa. *Circulation*, 2005. 112: 3584–91.

187. Enriquez-Sarano, M. et al, Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*, 2005. 352: 875–83.

188. Borer, J.S. & Bonow, R.O., Contemporary approach to aortic and mitral regurgitation. *Circulation*, 2003. 108: 2432–38.

189. Thourani, V.H. et al, Outcomes and long-term survival for patients undergoing mitral valve repair versus replacement. Effects of age and concomitant coronary artery bypass grafting. *Circulation*, 2003. 108: 298–304.

190. Yau, T. et al, Mitral valve repair and replacement for rheumatic heart disease. *J Thorac Cardiovasc Surg*, 2000. 119: 53–61.

191. Chauvaud, S. et al, Long-term (29 years) results of reconstructive surgery in rheumatic mitral valve insufficiency. *Circulation*, 2001. 104 (suppl 1): 1-12–1-15.

192. Skoularigis, J. et al, Evaluation of the long-term results of mitral valve repair in 254 young patients with rheumatic mitral regurgitation. *Circulation,* 1994. 90: 167–74.

193. Salem, D.N. et al, Antithrombotic therapy in valvular heart disease — Native and prosthetic. *Chest*, 2004. 126: 457S–82S.

194. Rahimtoola, S.H., Choice of prosthetic heart valve for adult patients. *J Am Coll Cardiol,* 2003. 41: 893–904.

195. Wisenbaugh, T. et al, Prediction of outcome after valve replacement for rheumatic mitral regurgitation in the era of chordal preservation. *Circulation,* 1994. 89: 191–97.

196. Otto, C.M. & Salerno, C.T., Timing of surgery in asymptomatic mitral regurgitation. *N Engl J Med*, 2005. 352: 928–29.

197. Rowe, J.C. et al, The course of mitral stenosis without surgery: ten-and twenty-year perspectives. *Ann Intern Med*, 1960. 52: 741.

198. Olesen, K.H., The natural history of 217 patients with mitral stenosis under medical treatment. *Brit Heart J*, 1962. 24: 349.

199. Sagie, A. et al, Doppler echocardiographic assessment of long-term progression of mitral stenosis in 103 patients: valve area and right heart disease. *J Am Coll Cardiol*, 1996. 28: 472–79.

200. Carabello, B.A., Modern management of mitral stenosis. *Circulation*, 2005. 112: 432–37.

201. Keren, G. et al, Atrial fibrillation and atrial enlargement in patients with mitral stenosis. *Am Heart J*, 1987. 114: 1146–55.

202. Chiang, C.W. et al, Predictors of systemic embolism in patients with mitral stenosis — a prospective study. *Ann Intern Med*, 1998. 128: 885–89.

203. Lutas, E.M. et al, Echocardiographic evaluation of mitral stenosis: a critical appraisal of its clinical value in detection of severe stenosis and valvular calcification. *J Cardiovasc Ultrasound*, 1983. 2: 131.

204. Fuster, V. et al, ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation: Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practical Guidelines and the European Society of Cardiology Committee for Practical Guidelines and Policy Conferences (Committee to Developing Guidelines for the Management of Patients With Atrial Fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. *Circulation*, 2001. 104: 2118–50.

205. Klein, A.L. et al, Use of transoesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*, 2001. 344: 1411–20.

206. Turi, Z.G. et al, Percutaneous balloon versus surgical closed commissurotomy for mitral stenosis; a prospective randomised trial. *Circulation,* 1991. 83: 1179–85.

207. Hernandez, R. et al, Long-term clinical and echocardiographic follow-up after percutaneous valvuloplasty with the Inoue balloon. *Circulation,* 1999. 99: 1580–86.

208. Iung, B. et al, Late results of percutaneous mitral commissurotomy in a series of 1024 patients. Analysis of late clinical deterioration: frequency, anatomic findings and predictive factors. *Circulation,* 1999. 99: 3272–78.

209. Vahanian, A. & Palacios, I.F., Percutaneous approaches to valvular disease. *Circulation*, 2004. 109: 1572–79.

210. Reyes, V.P. et al, Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. *N Engl J Med*, 1994. 331: 961–67.

211. Pendergast B.D. et al, Contemporary criteria for the selection of patients for percutaneous balloon mitral valvuloplasty. *Heart J.* 2002. 87: 401–04.

212. Doukas G. et al, Left atrial frequency ablation during mitral valve surgery for continuous atrial fibrillation, a randomized controlled trial. *JAMA*, 2005. 294: 2323–29.

213. Lee, J.W. et al, Surgical outcome of the Maze procedure for atrial fibrillation in mitral valve disease: Rheumatic versus degenerative. *Ann Thorac Surg*, 2003. 75: 57–61.

214. Stewart, W.J. & Carabello, B., Chronic aortic valve disease. In: *Textbook of Cardiovascular Medicine*, 2003. E.J. Topol et al (Eds). Lippincott, Williams & Wilkins: Philadelphia.

215. Enriquez-Sarano, M. & Tajk, A.J., Aortic regurgitation. *N Engl J Med*, 2004. 351: 139–46.

216. Scognamiglio R. et al, Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med*, 1994. 331: 689.

217. Wisenbaugh, T. et al, Six-month pilot study of captopril for mildly symptomatic severe isolated mitral and isolated aortic regurgitation. *J Heart Valve Dis*, 1994. 3: 197–204.

218. Evangelista A. et al. Long term vasodilator therapy in patients with severe aortic regurgitation. *New Engl J Med* 2005. 353: 1342–49.

219. Tarasoutchi, F. et al, Ten-year clinical laboratory follow-up after application of a symptom-based therapeutic strategy to patients with severe chronic aortic regurgitation of predominant rheumatic etiology. *J Am Coll Cardiol*, 2003. 41: 1316–24.

220. Dujardin, K.S. et al, Mortality and morbidity of aortic regurgitation in clinical practice: a long term follow-up study. *Circulation*, 1999. 99: 1851–57.

221. Ishii, D. et al, Natural history and left ventricular response in chronic aortic regurgitation. *Am J Cardiol*, 1996. 78: 357–61.

222. Vongpatanasin, W. et al, Prosthetic heart valves. *New Engl J Med*, 1996. 414: 407–16.

223. Hammermeister, K. et al, Outcomes 15 years after valve replacement with a mechanical versus a bioprosthesis valve: final report of the Veterans Affairs randomised trial. *J Am Coll Cardiol*, 2000. 36: 1152–58.

224. Yun, K.I. et al, Durability of the Hancock MO bioprosthesis compared with the standard aortic valve bioprosthesis. *Ann Thorac Surg*, 1995. 60: 5221–28.

225. David, T.E. et al, Aortic valve replacement with stentless porcine aortic valves: a ten-year experience. *J Heart Valve Dis*, 1998. 7: 250–54.

226. Barratt-Boyes, B.G. et al, Long-term follow-up of patients with antibiotic-sterilized aortic homograft inserted freehand in the aortic position. *Circulation*, 1987. 75: 768–77.

227. Clarke, D.R. et al, Degeneration of aortic valve allografts in young recipients. *J Thorac Cardiovasc Surg*, 1993. 105: 934–41.

228. Yap, C.H. & Yii, M., Allograft aortic valve replacement in the adult: A review. *Heart Lung Circ*, 2004. 13: 41–51.

229. Lund, O. et al, Primary aortic valve replacement with allografts over twenty-five years: valve related and procedure related determinants of outcome. *J Thorac Cardiovasc Surg*, 1999. 17: 77–91.

230. Kejiriwal, N.K. et al, Follow-up of Australian Aboriginal patients following open-heart surgery in Western Australia. *Heart Lung Circ*, 2004. 13: 70–73.

231. Fihn, S.D., Aiming for safe anticoagulation. *New Engl J Med*, 1995. 333: 54–55.

232. Cannegieter, S.C. et al, Optimal oral anticoagulant therapy in patients with mechanical heart valves. *New Engl J Med*, 1995. 333: 11–17.

233. McDonald, M. & Currie, B., Outcomes of cardiac surgery in Aboriginal Australians: What are the problems and what's to be done? *Heart Lung Circ*, 2004. 13: 129–31.

234. Carr, J.F. & Savage, E.B., Aortic valve repair for aortic insufficiency in adults: a contemporary review and comparison with replacement techniques. *Eur J Cardiothorac Surg*, 2004. 25: 6–15.

235. Grinda, J.M. et al, Aortic cusp extension valvuloplasty for rheumatic aortic valve disease: Midterm results. *Ann Thorac Surg*, 2002. 74: 438–43.

236. Gerosa, G. et al, Aortic valve replacement with pulmonary homografts; early experience. *J Thorac Cardiovasc Surg*, 1994. 107: 424–36.

237. Aklog, L. et al, Pulmonary autograft versus aortic homograft for aortic valve replacement: interim results from a prospective randomised trial. *J Heart Valve Dis*, 2000. 9: 176–88.

238. Kouchoukos, N.T. et al, The Ross procedure: long-term clinical and echocardiographic follow-up. *Ann Thoracic Surg*, 2004. 78: 773–81.

239. Feier, H. et al, Risk factors, dynamics and cutoff values for homograft stenosis after the Ross procedure. *Ann Thorac Surg*, 2005. 79: 1669–75.

240. Matsumura, T. et al, Etiology of aortic valve disease and recent changes in Japan: a study of 600 valve replacement cases. *Intern J Cardiol*, 2000. 86: 217–23.

241. Lester, S.J. et al, The natural history and rate of progression of aortic stenosis. *Chest*, 1998. 113: 1109–14.

242. Munt, B. et al, Physical examination in valvular aortic stenosis: Correlation with stenosis severity and prediction of clinical outcome. *Am Heart J*, 1999. 137: 298–306.

243. Lieberman, E.B. et al, Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *J Am Coll Cardiol*, 1995. 26: 1522–28.

244. Carabello, B.A., Timing of valve replacement in aortic stenosis: Moving closer to perfection. *Circulation*, 1997. 95: 2241–43.

245. Mordehay, V. et al, The natural history of aortic valve disease after mitral valve surgery. *J Am Coll Cardiol*, 1999. 33: 2003–08.

246. Skudicky, D. et al, Time-related changes in left ventricular function after double valve replacement for combined aortic and mitral regurgitation in a young rheumatic population. *Circulation*, 1997. 95: 899–904.

247. Reinhold, S.C. & Rutherford, J.D., Valvular heart disease in pregnancy. *New Engl J Med*, 2003. 349: 52–59.

248. Oakley, C. et al, Pregnancy and heart disease: Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J*, 2003. 24: 761–81.

249. Elkayam, U. & Bitar, F., Valvular heart disease and pregnancy. Part I: Native valves. *J Am Coll Cardiol*, 2005. 46: 223–30.

250. De Souza, J.A.M. et al, Percutaneous balloon mitral valvuloplasty in comparison with open mitral valve commissurotomy for mitral stenosis during pregnancy. *J Am Coll Cardiol*, 2001. 37: 900–03.

251. Martinez-Reding, J. et al, Treatment of severe mitral stenosis with percutaneous balloon valvuloplasty in pregnant patients. *J Clin Cardiol*, 1998. 21: 659–63.

252. Routray, S.N. et al, Balloon mitral valvuloplasty during pregnancy. *Int J Gynaecol Obstet*, 2004. 85: 18–23.

253. Grinsberg, J.S. et al, Anticoagulation of pregnant women with mechanical heart valves. *Arch Int Med*, 2003. 163: 694–98.

254. Elkayam, U. et al, Anticoagulation in pregnant women with prosthetic heart valves. *J Cardiovasc Pharmaco Therapeut*, 2004. 9: 107–15.

255. Hung, L. & Rahimtoola, S.H., Prosthetic heart valves and pregnancy. *Circulation*, 2003. 107: 1240–46.

256. Elkayam, U. & Bitar, F., Valvular heart disease and pregnancy. Part II: Prosthetic valves. *J Am Coll Cardiol*, 2005. 46: 403–10.

257. Sadler, L. et al, Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *Brit J Obstet Gynaecol*, 2000. 107: 245–53.

258. Rowan, J.A. et al, Enoxaparin treatment in women with mechanical valves during pregnancy. *Am J Obstet Gynecol*, 2001. 185: 663–7.

259. Leyh, R.G. et al, Anticoagulation for prosthetic heart valves during pregnancy: is low-molecular-weight heparin an alternative? *Eur J Cardiothorac Surg*, 2002. 21: 577–79.

260. Salazar, E. et al, Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prostheses. *J Am Coll Cardiol*, 1996. 27: 698–703.

261. Butchart, E.G. et al, Recommendations for the management of patients after heart valve surgery. *Eur Heart J,* 2005. 26: 2463–71.

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and the Cardiac Society of Australia and New Zealand

Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia

An evidence-based review

Heart Foundation