The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease

(3.2 edition, March 2022)

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VERSION	DATE	CHANGES
3.0	February 2020	New version published
3.1	September 2020	Updated duration of secondary prophylaxis in selected groups (Table 10.2) Minor changes to Priority classifications (Table 7.4 and Table 11.2 and related text)
3.2	March 2022	Updated recommendations for the management of borderline RHD (Table 7.4, Table 10.2, Table 11.2, and related text on pages 153–154 and page 158) Updated indication for treatment of borderline RHD identified through screening (Table 9.2) New Reference 11, page 162

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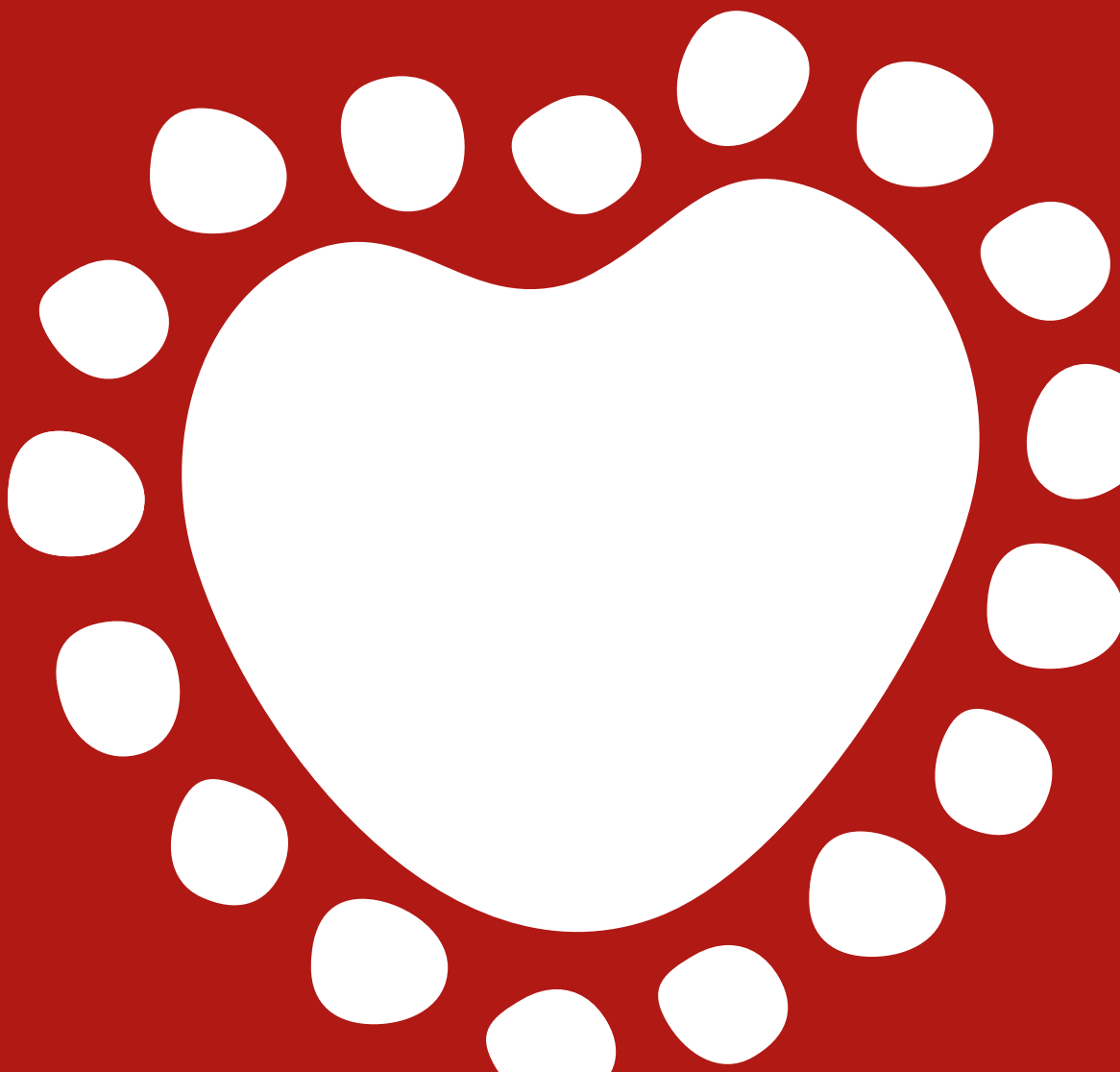

Introduction

FOREWORD

This edition of the Australian guideline for the prevention, diagnosis and management of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) has a new focus which places people with ARF and RHD, and their families and communities, at the centre of care. To achieve a value-based healthcare system that breaks down the complex and hierarchical structures based on Western ideologies, we must look at whose values are represented.

There are many cultural and structural barriers for Aboriginal and Torres Strait Islander peoples requiring evidence-based care. Most, however, are poorly understood. If guidelines are to be successful, we need to move beyond the 'evidence base' – what is known and understood – to what we do not know. We need to understand the complex relationships between the social, cultural, political and economic situations in which people live.

Despite advances in medical treatment and management of ARF and RHD, the associated health benefits at population and community level have not been as evident for Aboriginal and Torres Strait Islander peoples as they have for non-Indigenous Australians. These challenges are more than biomedical and are driven by the social, cultural and environmental determinants of health. The Australian Institute of Health and Welfare reported that between 2013 and 2017, there were 1043 new diagnoses of RHD among Indigenous Australians, and that this group made up 94% of all new RHD cases. The report also indicated that only 15% of Aboriginal and Torres Strait Islander peoples were receiving their prescribed secondary prophylaxis. The healthcare system must respond to these disparities and refocus on people with this disease; acknowledging their unique culture, and the social, economic and environmental circumstances in which they live.

There is a growing interest in ethnomedicine where traditional biomedical healthcare methods are guided by Indigenous cultural beliefs and practices. Within each chapter of this guideline, the medical problems and solutions have been viewed within a socio-cultural context, with the aim of reducing the evidence-practice gap. This guideline identifies the systemic factors that drive disparities in best-practice care delivery, and offers solutions. We have come a long way from the first edition, and this journey has culminated in an important balance between cultural and clinical competence.

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February 2020

SUMMARY OF CHANGES FROM THE SECOND (2012) EDITION

Culture and Workforce

This is a new chapter.

Burden of acute rheumatic fever and rheumatic heart disease

This is a new chapter.

Primordial prevention and social determinants of acute rheumatic fever

This is a new chapter.

The abbreviation used for Group A Streptococcus used in this chapter and throughout the guideline is 'Strep A' (previously 'GAS').

Primary prevention

Updated definition of high-risk groups for ARF.

New recommendations for management of Strep A skin infections to prevent ARF.

The term *benzathine benzylpenicillin G* (BPG) replaces benzathine penicillin G.

BPG dosing has been streamlined to three dose bands for simplicity compared to the previously recommended five dose bands.

Tablet dosing is provided for use of cotrimoxazole for Strep A impetigo if syrup is in short supply.

Diagnosis of acute rheumatic fever

In low-risk populations, subclinical carditis is now a major diagnostic criterion.

In low-risk populations, erythrocyte sedimentation rate (ESR) as a minor criterion is now **≥60 mm/h** rather than ≥30 mm/h.

In low-risk populations, fever as a minor criterion is now **≥38.5°C** rather than ≥38.0°C.

For all populations, a definite recurrent episode of acute rheumatic fever (ARF) in a patient with documented history of ARF or rheumatic heart disease (RHD) now requires 2 major, or 1 major and **2 minor**, or 3 minor criteria, (plus evidence of preceding Strep A infection) rather than 2 major, or 1 major and 1 minor, or 3 minor criteria.

Management of acute rheumatic fever

Probable ARF – 'Highly suspected' has now been renamed **Probable ARF**.

Probable ARF – 'Uncertain' has now been renamed **Possible ARF**.

The Priority definitions in the 'priority classification system' for presence and severity of RHD have changed to align with appropriate timing of follow-up.

Non-steroidal anti-inflammatory drugs are recommended ahead of aspirin in children requiring anti-inflammatory treatment.

Expanded therapeutic approaches for Sydenham chorea are provided.

Diagnosis of rheumatic heart disease

The World Heart Federation guidelines for the diagnosis of RHD, which were developed and validated in multiple populations including high and low prevalence groups, inform this chapter.

The echocardiographic features of severity have been aligned with updated international guidelines for valvular heart disease (European Society of Cardiology 2017 and American Heart Association/American College of Cardiology 2014).

Exercise stress testing is recommended with echocardiography to determine severity of RHD and planning for intervention.

A new section on distinguishing RHD from other valvular pathology is provided.

An update on new echocardiography technology including hand-held and portable echo and their role in RHD diagnosis is provided.

Screening for rheumatic heart disease

This is a new chapter.

Secondary prophylaxis

Doses are provided in units - not milligrams (mg) - for BPG in response to Therapeutic Goods Administration requirements for labelling.

Guidance for the ventrogluteal injection site is provided.

New approaches to managing injection pain, fear and distress are provided, including the option of medically prescribed lidocaine (lignocaine) and procedural sedation.

New recommendations for the duration of secondary prophylaxis are described.

A focus on the responsibility of health services to provide a culturally safe service, and for staff to be culturally competent in the management of secondary prophylaxis, is emphasised.

Calculation of *days at risk* (which is the best predictor of ARF recurrence) as well as *percent delivery* of BPG injections (which is easier to calculate and comprehend) are both recommended for RHD control program reporting.

Management of rheumatic heart disease

The Priority definitions in the 'priority classification system' for presence and severity of RHD have changed to align with appropriate timing of follow-up.

The new option of transcatheter valve replacement may influence choice of valve replacement in younger individuals.

A focus on transition from paediatric to adult services is included.

The role of non-vitamin K antagonist oral anticoagulants in RHD is described.

Definition of non-valvular atrial fibrillation in the setting of RHD and the role of CHA_2DS_2-VA score to determine thromboembolic risk are detailed.

Antibiotic prophylaxis to prevent infective endocarditis following dental procedures now comprises amoxicillin instead of clindamycin, even for people on regular penicillin-based treatment (e.g. regular BPG), in keeping with revisions to the Australian Therapeutic Guidelines: Antibiotic.

Women and girls with rheumatic heart disease

The ***Women and Girls with RHD*** (previously *RHD in Pregnancy*) section has been substantially revised and extended to incorporate a whole-of-life approach.

A new section on transition to adult care, reproductive health, and preconception care is provided.

Discussion around the need and strategies for a well-planned pregnancy and delivery are updated.

Anticoagulation during pregnancy has been revised.

Care pathways for women and girls with RHD are provided.

Care pathways and a referral algorithm for pregnant women with RHD are provided.

Rheumatic heart disease control programs

This chapter has been significantly expanded.

Legislated notification requirements for ARF and RHD in Australian jurisdictions are described.

A recommended dataset for ARF and RHD is not included.

New technologies

This is a new chapter.

CLASSIFICATIONS OF ACUTE RHEUMATIC FEVER (ARF) AND RHEUMATIC HEART DISEASE (RHD) USED IN THIS GUIDELINE

Classification of ARF

(See *Chapter 6. Diagnosis of ARF, ARF categorised as definite, probable or possible*)

Definite ARF: acute presentation which fulfils Jones diagnostic criteria for ARF.

Probable ARF: acute presentation which does not fulfil Jones diagnostic criteria for ARF, missing one major or one minor criterion or lacking evidence of preceding streptococcal infection, but ARF is still considered the most likely diagnosis.

Possible ARF: acute presentation which does not fulfil Jones diagnostic criteria for ARF, missing one major or one minor criterion or lacking evidence of preceding streptococcal infection, and ARF is considered uncertain but cannot be ruled out.

Classification of ARF / RHD severity

(Table 11.2)

Priority 1 (P1): severe RHD.

Priority 2 (P2): moderate RHD.

Priority 3 (P3): mild or no RHD.

Priority 4 (P4): secondary prophylaxis no longer required.

Classification of RHD

(Table 8.5)

Borderline RHD: echocardiographic features in an individual aged ≤20 years which are abnormal but do not fulfil criteria for the diagnosis of RHD.

Definite RHD: echocardiographic features in an individual of any age which are abnormal and fulfil criteria for the diagnosis of RHD.

RHD in pregnancy risk levels

(Figure 12.1)

Level I: low risk of maternal mortality, low to moderate risk of morbidity (e.g. mild RHD with no mitral stenosis).

Level II: elevated risk of maternal mortality or moderately increased risk of morbidity (e.g. bioprosthetic valve or mild mitral stenosis).

Level III: further elevated risk of maternal mortality or severe morbidity (e.g. mechanical heart valve, severe asymptomatic mitral / aortic regurgitation or severe asymptomatic aortic stenosis or moderate mitral stenosis.

Level IV: extremely high risk of maternal mortality or severe morbidity (e.g. severe mitral stenosis or valve disease with pulmonary hypertension).

Types of penicillin used in ARF

(Table 10.1)

Benzathine benzylpenicillin G: long-acting intramuscular formulation of penicillin.

Phenoxymethylpenicillin: short-acting oral formulation of penicillin.

LEVELS OF EVIDENCE FOR GRADING RECOMMENDATIONS

Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1] is used in this document where the level of evidence of a recommendation requires grading. The GRADE approach is an internationally recognised system for grading quality of evidence and strength of recommendations. The GRADE approach rates evidence across studies for specific clinical outcomes to link evidence-quality evaluations to recommendations in clinical guidelines.

Table 1.1. GRADE evidence grade

CODE	QUALITY OF EVIDENCE	DEFINITION
A	High	Further research is very unlikely to change the level of confidence in the estimate of effect. i.e. • Several high-quality studies with consistent results
B	Moderate	Further research is likely to have an impact in current confidence in the estimate of effect and may change the estimate. i.e. • One high quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on the level of confidence in the estimate of effect and would likely change the estimate. i.e. • One or more studies with significant limitations
D	Very low	Estimate of effect is very uncertain. i.e. • No direct research evidence • One or more studies with very significant limitations

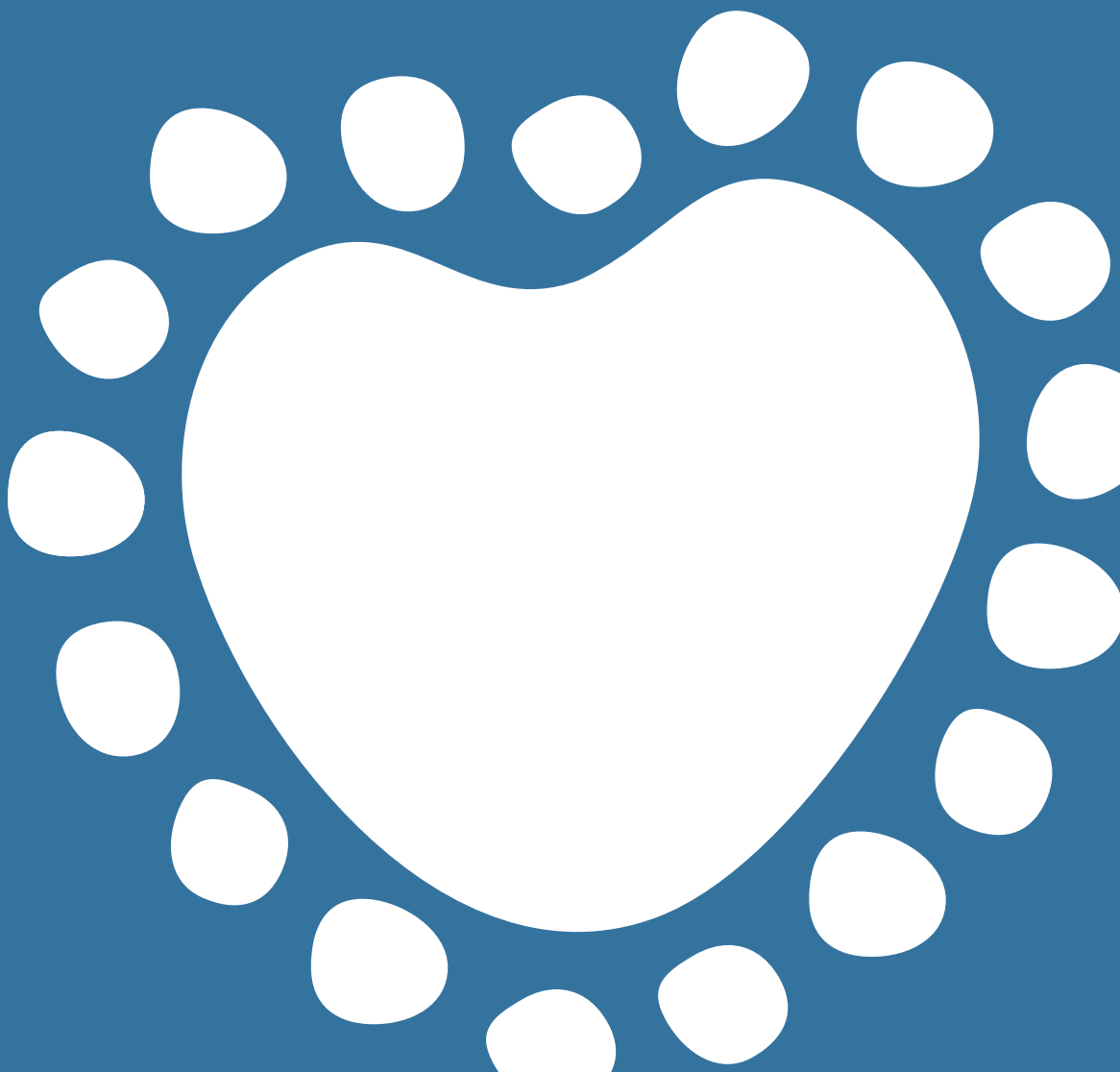
Table 1.2. GRADE strength of recommendations

CODE	STRENGTH OF RECOMMENDATION	IMPLICATIONS WHEN COMBINED WITH EVIDENCE GRADE
1	Strong	1A: Strong recommendation, applies to most patients without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present 1B: Strong recommendation, applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present 1C: Strong recommendation, applies to most patients. Some of the evidence • base supporting the recommendation is, however, of low quality
2	Weak	2A: Weak recommendation. The best action may differ depending on circumstances of patients or societal values 2B: Weak recommendation. Alternative approaches likely to be better for some patients under some circumstances 2C: Very weak recommendation. Other alternatives may be equally reasonable 2D: No evidence available; expert consensus judgement

1 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. British Medical Journal 2008; 336(7650): 924-6 https://doi.org/10.1136/bmj.39489.470347.AD

CHAPTER 2

Culture and Workforce



Culture and Workforce

OVERVIEW

There is often a mismatch between the ethnicity of populations bearing greatest burdens of ARF and RHD, and the healthcare providers tasked with managing these conditions. In Australia, the vast majority of ARF and RHD diagnoses occur in Aboriginal and Torres Strait Islander peoples. This chapter seeks to highlight the importance of cultural competence as the underpinning requirement for the safe and effective delivery of healthcare for Aboriginal and Torres Strait Islander peoples affected by ARF and/or RHD.

Workforce and cultural issues have been identified and highlighted throughout the following chapters. There is a move to go beyond *cultural competence* to *structural competence*, and to explore how systems respond to the needs of people.[1] Moving from cultural competence to structural competence to address the cultural and social determinants of ill-health, and the structures that perpetuate disparities, have been woven throughout this guideline in highlighted boxes or case studies.

KEY INFORMATION

- Centrality of culture is the core component of clinical guidelines.
- Cultural and structural competencies in healthcare are necessary to close the evidence-practice gap.
- An ethnomedical framework (respecting and incorporating traditional Indigenous medical practices) should be used to inform guideline development.
- A socioecological model (understanding the personal and environmental factors - interpersonal, community, organisational and environmental – that determine health behaviours) can highlight the complex relationships that exist for Aboriginal and Torres Strait Islander peoples.
- An adequately trained and supported Aboriginal and Torres Strait Islander workforce is the key driver for successful health programs.
- The current health workforce will contribute to closing the evidence-practice gap.

DISCUSSION

"The systematic neglect of culture in health is the single biggest barrier to advancing the highest attainable standards of health worldwide".[2]

It is well known that patient's perceptions and definitions of health can conflict with the priorities set out in clinical guidelines and standards, and this can significantly affect health outcomes. Everyone receiving healthcare has a right to feel culturally safe, and healthcare providers have an obligation to deliver culturally competent care. Healthcare providers must be prepared to 'translate' care delivery to patients with diverse cultural backgrounds, expectations and needs.

Aboriginal and Torres Strait Islander peoples in Australia belong to the oldest living civilisation in the world, dating back more than 65,000 years. Aboriginal and Torres Strait Islander peoples' cultures are complex and diverse, with more than 500 language and kinship groups. The kinship system puts everybody in a specific relationship to each other, the water, and the land, based on their clan or kin. It is important that Australian healthcare providers acknowledge and understand the unique Aboriginal and Torres Strait Islander cultures, to work effectively with all communities.

It is necessary to acknowledge the ongoing impact and trauma that colonisation has on the health and wellbeing of Aboriginal and Torres Strait Islander peoples.

Many Aboriginal and Torres Strait Islander peoples continue to experience discrimination and social disadvantage today, and this has a significant impact on health.[3]

Aboriginal and Torres Strait Islander peoples have a holistic view of health that is not adequately met by the biomedical model of healthcare; health is not just the physical wellbeing of an individual, but refers to the social, emotional and cultural wellbeing of the whole community.

The Cultural Respect Framework for Aboriginal and Torres Strait Islander Health[4] commits the Commonwealth government and all States and Territories to embed cultural respect principles into their health systems; from developing policy and legislation, to how organisations are structured and managed, through to the planning and delivery of services. The Cultural Respect Framework will guide and underpin the delivery of culturally safe, responsive, and quality healthcare for all Aboriginal and Torres Strait Islander peoples.

In 2015, the Aboriginal and Torres Strait Islander Health Curriculum Framework was completed. Its implementation will provide a benchmark towards national consistency for the minimum level of capability required by graduates to effectively deliver culturally safe and responsive healthcare to Aboriginal and Torres Strait Islander peoples.[5]

We know that policies alone are not enough to bring about change, so these frameworks must be adapted into clinical practice, including into guideline development. Social justice and the right to quality healthcare are basic human rights. Translation of these values to tangible policies and reforms is paramount to closing the gap between Aboriginal and Torres Strait Islander peoples and non-Indigenous peoples; and putting people and their culture at the centre of healthcare.

Centrality of *culture*

Throughout this guideline, there is an emphasis on the person who is receiving care, their family, community and their culture. This includes:

- respect for cultural diversity, rights, views, values and expectations of Aboriginal and Torres Strait Islander peoples;
- Aboriginal and Torres Strait Islander health workforce participation as an essential element within all health workforce initiatives, settings and strategies;
- effective, comprehensive and culturally safe and responsive approaches to service delivery that have the flexibility to reflect the local context and the diversity of Aboriginal and Torres Strait Islander communities.
- Workforce initiatives and processes within the wider health system that embed, acknowledge and respect Aboriginal and Torres Strait Islander holistic views of health that includes attention to physical, spiritual, cultural, emotional and social wellbeing, community capacity and governance
- Cultural knowledge, expertise and skills of Aboriginal and Torres Strait Islander health professionals reflected in health services models and practice

The importance of *workforce*

Aboriginal and Torres Strait Islander peoples have the right to feel confident and safe in accessing the Australian healthcare system, and the system is responsible for the delivery of quality healthcare to Aboriginal and Torres Strait Islander peoples that is culturally appropriate and clinically sound.[6] The health workforce must therefore be adequately resourced and supported, with considerations for the complex needs of Aboriginal and Torres Strait Islander peoples, especially those living in remote areas.[7] It is equally important that we identify the barriers and enablers within the current workforce that prevent uptake of the recommendations in this guideline, so we can identify areas for improvement.

The 2016–2023 National Aboriginal and Torres Strait Islander Health Workforce Strategic Framework[8] calls for an "Australian health system that is free of racism and inequality, and where all Aboriginal and Torres Strait Islander people have access to health services that are effective, high quality, appropriate and affordable; and that the health system is comprised of an increasing Aboriginal and Torres Strait Islander health workforce delivering culturally safe and responsive healthcare".

The principles enshrined in the Framework have been integrated into the guideline's subsequent chapters.

The Aboriginal and Torres Strait Islander health workforce has unique insight into the lived experiences of families and community supported by their knowledge of cultural beliefs, practices and protocols with Aboriginal and Torres Strait Islander peoples. They possess a cultural intellect that cannot be replicated by mainstream.

Aboriginal and Torres Strait Islander health workforce capacity

Workplaces must be free of racism, culturally safe and supportive, and attractive to the Aboriginal and Torres Strait Islander health workforce.

Supporting and expanding the skills and knowledge of Aboriginal and Torres Strait Islander staff who are involved in caring for Aboriginal and Torres Strait Islander peoples with ARF and / or RHD is critical. The presence and integration of Aboriginal and Torres Strait Islander staff across the entire care system is essential for effective care.

This needs to occur predominately at a primary care level, acknowledging that admission to hospital and transfer back into the community is also important. The roles of Aboriginal and Torres Strait Islander staff are often undervalued within the multidisciplinary team. Scope of practice is often poorly understood, resulting in their expertise being underused.

Aboriginal Health Workers and Aboriginal Health Practitioners provide an important service in primary care centres and hospitals, and support members of their local community to navigate the health systems. Appropriate, ongoing professional development and training that is recognised, supported and resourced is essential to achieving this. They must be well supported, with opportunities for mentoring and career advancement to ensure success, best practice and staff retention.

A well-resourced Aboriginal Community Controlled Health Service is well-placed to provide holistic care for Aboriginal and Torres Strait Islander peoples with ARF and or RHD. This care considers the social and economic context of the patient, and involves social and emotional wellbeing, trauma informed care, cultural care, legal and family care, and is provided in a culturally safe way. A strengths-based approach has been applied throughout this Guideline, which provides case studies and evidence that can be turned into action.[9]

Socio-ecological model

The socio-ecological (or Social ecological) model is a framework developed to describe the factors that interact to determine health behaviours of individuals or societies. We have adapted this to depict a socio-ecological model for ARF and RHD *(Figure 2.1)* which reflects the complex and dynamic interrelationships between systems, people and the guidelines areas. In this model, the individual is central, surrounded by culture, family and the wider community. This has a direct influence on how quality evidence-based care is received and adopted. The social-ecological model:

- demonstrates that various factors influence health-seeking behaviour patterns;
- demonstrates the complexities and importance of the relationships and partnerships of the various parts of the health system and community;
- can help health professionals understand how layers of influence intersect to shape the Aboriginal and Torres Strait Islander person, family and communities in choices about relevant elements of care.

Figure 2.1. Socio-ecological model underpinning the guidelines

Adapted from the Centers for Disease Control and Prevention (CDC), The Social Ecological Model: A Framework for Prevention.[10]

The importance of partnerships between the health system and the community to engage with, and implement, the recommendations in this guideline is critical and requires ongoing education and training across multiple levels.

Patient journey mapping

Patient journey mapping has been used to highlight the complexities of navigating the health system for Aboriginal and Torres Strait Islander peoples, especially for those living in remote areas who access centralised health services. It has also allowed gaps in care to be identified from a cultural and clinical perspective.[11] The Managing Two Worlds Together mapping tool[12] was used during development of this guideline to identify existing evidence-practice gaps in relation to culture and workforce. Barriers, enablers and solutions to best practice care for people on a journey with ARF or RHD were also reviewed from a cultural and workforce perspective.

CONCLUSION

Clinical practice guidelines have become an increasingly useful tool for supporting safe and efficient healthcare. It is clear that judgments and decision-making processes during guideline development are central to producing information to support high-quality care.[13] However, guidelines do not always come with high adoptability of recommendations. Only an estimated one-third of the evidence informing guidelines tends to be routinely adhered to,[14] and this is especially true where recommendations are directed to vulnerable groups.

Clinical expertise is important but equally important is the understanding and underpinning of cultural knowledge and workforce issues embedded within guideline development and recommendations.

The cultural and workforce working group provided Aboriginal cultural input, and highlighted workforce issues input and contextual factors that are critical to the successful implementation of this guideline.

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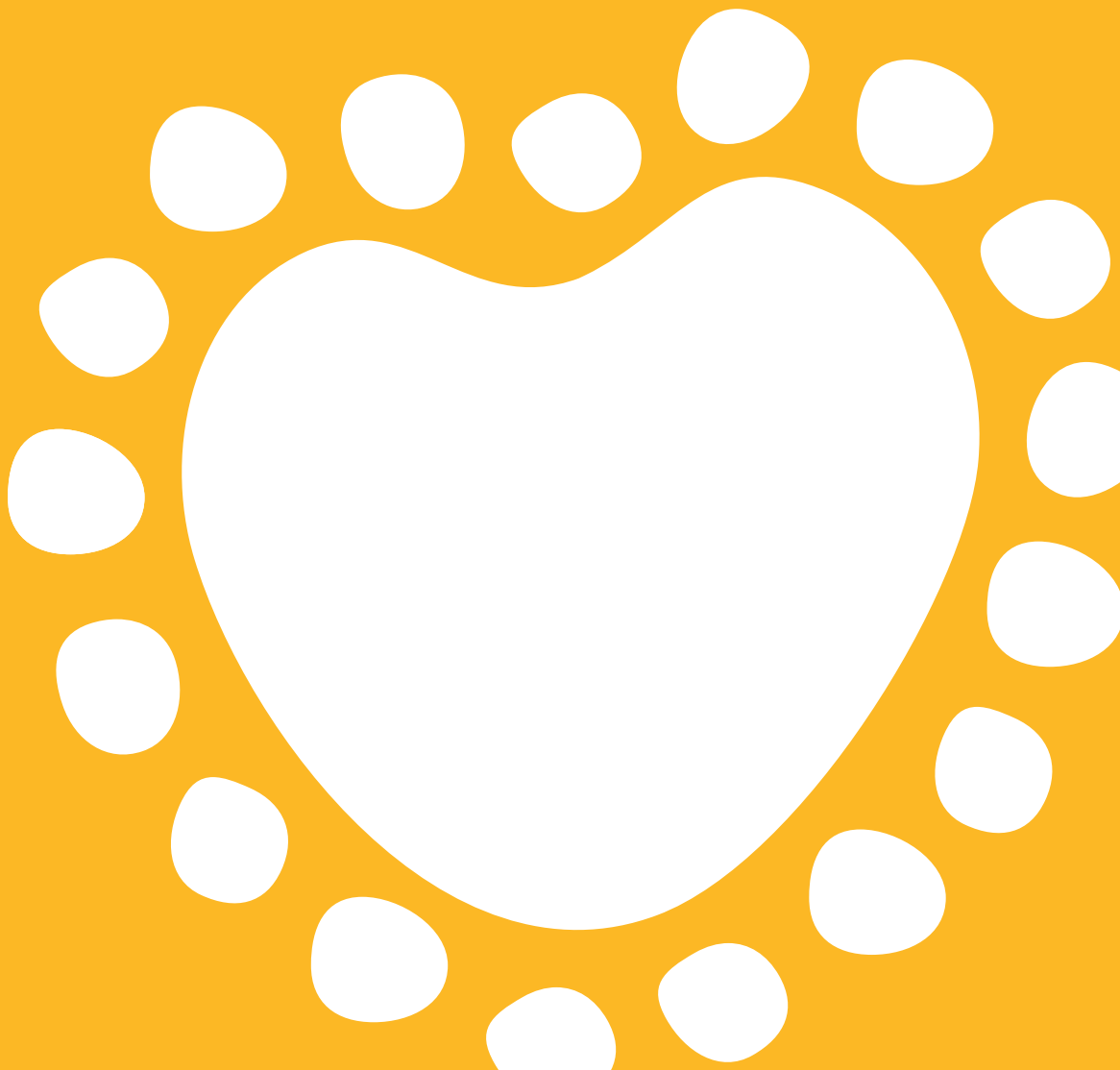
CHAPTER 3

Burden of acute rheumatic fever and rheumatic heart disease



Burden of acute rheumatic fever and rheumatic heart disease

CHANGES FROM THE SECOND (2012) EDITION

This is a new chapter.

KEY INFORMATION

- Since the early 1990s, acute rheumatic fever (ARF) has occurred almost exclusively in young Aboriginal and Torres Strait Islander peoples, particularly in the 5-14-year-old age group.
- During the same period, rheumatic heart disease (RHD) has predominately affected young to middle-aged Aboriginal and Torres Strait Islander peoples as a consequence of the current era of endemic ARF among this population, and it has affected older non-Indigenous people due to a past era of endemic ARF.
- Females are more likely to be diagnosed with ARF than males.
- The number of Aboriginal and Torres Strait Islander peoples affected by ARF and RHD appears to be increasing.
- The burden of disease often spans the majority of a person's lifetime, starting with ARF in childhood, where ongoing active engagement with the healthcare system is needed for many years, and progressing in many cases to RHD and associated heart conditions during adulthood.
- People with ARF are prone to a further episode, with one in five people having a recurrent episode of ARF within 10 years of their first.
- There is a high risk of valvular damage (RHD) from a recurrent or single severe episode of ARF; more than half of those with ARF progress to RHD within 10 years of their initial ARF episode, and more than one-third of these people develop severe RHD.
- More than one in 10 people with RHD are affected by atrial fibrillation or heart failure attributable to RHD.
- Aboriginal and Torres Strait Islander peoples with RHD were more likely to die compared to non-Indigenous Australians with RHD; however, the death rates have decreased for both population groups over the past few decades.

INTRODUCTION

This chapter provides an overview of the changing global burden of ARF and RHD over the past century, the strengths and limitations in the data used to inform current estimates, and a demographic summary of the burden of ARF and RHD in Australia.

The writers acknowledge that this section is written in an epidemiological style, and that figures and other statistics represent the loss of health and human life with profound impact and sadness for people, families, community and culture. The 'numbers story' originating from this project will hopefully supplement the 'lived stories' that reflect the voices of people with RHD and their families, jointly contributing to evidence to erase suffering caused by ARF and RHD in Australia.

The global burden of ARF and RHD

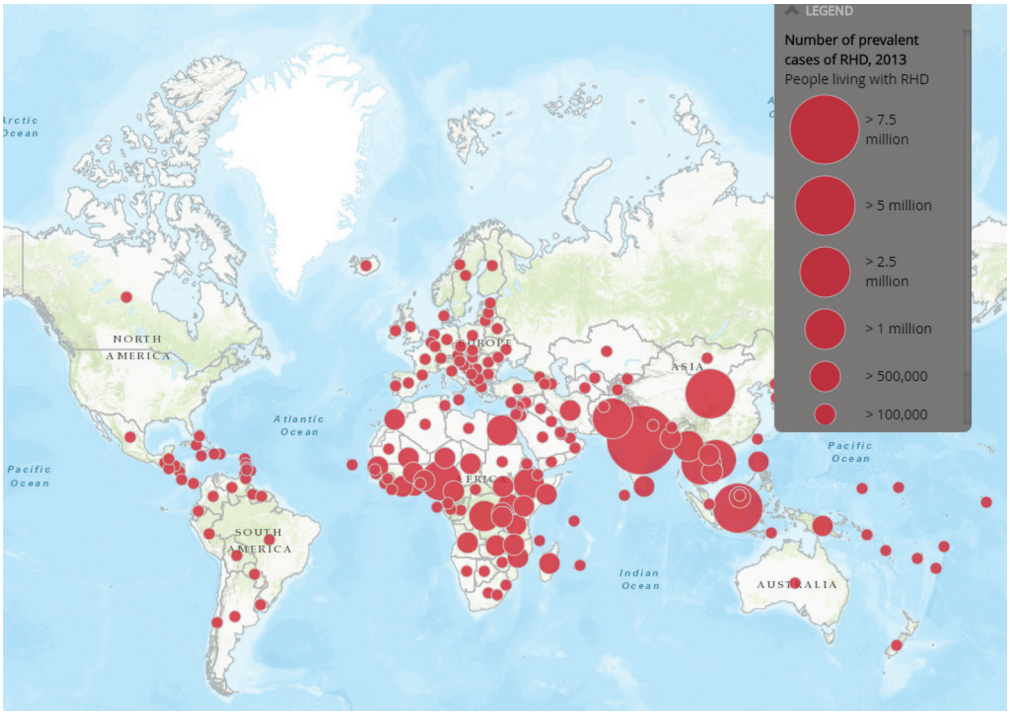
The Global Burden of Disease (GBD) study estimated that in 2015, RHD contributed 10.5 million Disability-Adjusted Life Years (DALY) globally, incorporating 33.4 million cases of RHD and 319,499 deaths.[1] Global age-standardised mortality decreased by 47.8% from 1990 to 2015 but large differences were observed across regions.

The majority of ARF and RHD are in low- and middle-income countries where more than 80% of the world's ARF cases occur.[2] Global estimates indicate that the burden of RHD is highest among people living in poor-quality housing, followed by rural areas, and it is lowest in urban areas.[3] The highest occurrence of disease has been documented in sub-Saharan Africa, where the prevalence of RHD is about 5.7 cases per 1000 children aged 5-14 years old, and in the Pacific at 3.5 cases per 1000 children aged 5-14 years old.[2,4] Aboriginal and Torres Strait Islander Australians, New Zealand Māori and Pacific Islanders are considered to experience the next highest rates of disease. While fewer reliable estimates are available from Asia, a considerable RHD prevalence has been documented, particularly in central and southeast Asian countries.[2,5,6]

Many Aboriginal and Torres Strait Islander peoples live remotely or very remotely. Geographical isolation along with past government policies have impacted negatively on health, and have led to some of the highest rates of ARF and RHD of all First Nations people.

The global burden of RHD includes many premature deaths. RHD-attributable deaths usually result from conditions that develop as complications of RHD, such as infective endocarditis, arrhythmia, heart failure and stroke.[5,6] Consequently, accurate estimates for RHD-related deaths are difficult to produce; however, estimates suggest that about 1.5% of people living with RHD are thought to die each year in low-resource settings, where secondary prophylaxis programs are not delivered and management of RHD is limited.[5,6] Premature death from RHD is pronounced; for example, the average age at death from RHD among Aboriginal and Torres Strait Islander peoples was estimated as 44 years.[7] RHD in pregnancy is an important cause of maternal death in low- and middle-income countries,[8] and is also a cause of maternal morbidity among high-risk populations in high-income countries.[9]

Figure 3.1. Estimated global prevalence of disease in 2013: http://rhdaction.org/atlas/ (Accessed 25 March 2019)



Historical changes in the burden of ARF and RHD

ARF was once common in the general child population across Europe, North America and the Pacific.[9,10] At the start of the 20th century, ARF was the leading cause of death for people aged 5-20 years old in the USA.[10] Specialised hospital wards cared for very sick children in many high-income countries. Rates of ARF declined in most of these countries during the mid-20th century (with rates of <0.1 case per 100,000 population). The decline of ARF was associated with reductions in household crowding, improvements in socioeconomic conditions, better access to healthcare, and increasingly widespread availability of penicillin to treat streptococcal infections.[11,12] By contrast, high rates of ARF and RHD persist among young people (particularly females) across many low- and middle-income countries, where widespread poverty persists and access to quality secondary and tertiary prevention services is poor.[13]

Many high-income countries have a burden of RHD among older surviving adults who developed ARF in their youth prior to improvements in socioeconomic conditions and antibiotic treatment. Simultaneously, some Indigenous minority populations living in high-income countries continue to be affected by ARF and RHD, including children and young people. To date, Aboriginal and Torres Strait Islander peoples and New Zealand Māori and Pacific Islanders have among the highest rates of ARF in the world and experience an inequitable burden of RHD. These groups experience considerable inequities across a wide range of social, educational and health outcomes compared with the general population.[14-17]

Estimating the burden of ARF and RHD

Accurate estimates of the burden of ARF and RHD are difficult to obtain. Such estimates often rely on data available from field studies, predominately echocardiographic screening studies; ARF and RHD disease registers; and general administrative databases of health services. In *Figure 3.2* Zühlke & Steer 2013[6] highlight the sources of ARF and RHD data globally, including how the burden of RHD can be assessed. The GBD study has produced the most recent global and regional estimates using two analytic tools to statistically model cause of death and prevalence estimates based on the best available published data.[1] No single source provides definitive data; each source has its limitations but contributes to understanding the burden of disease.

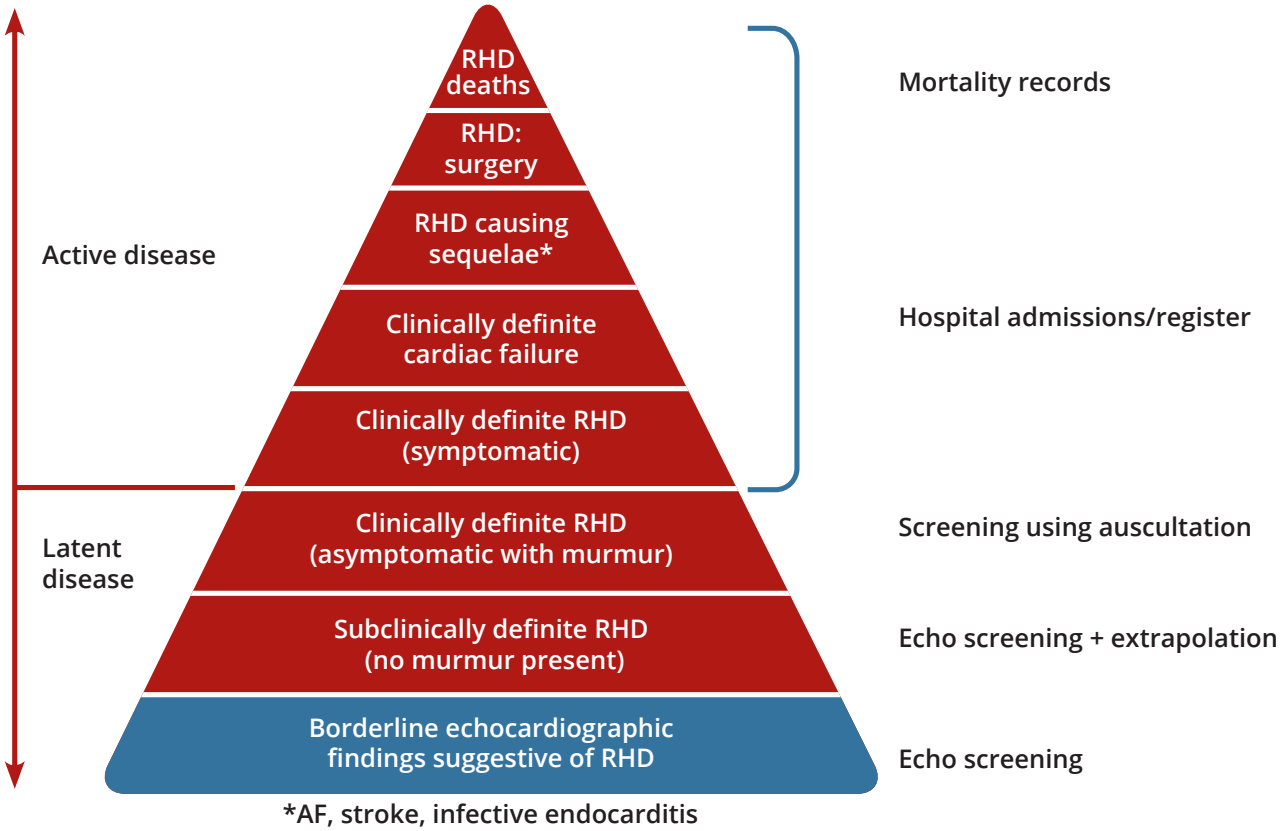
Countries with the poorest health services and public health infrastructure are often the worst affected by ARF and RHD. In such countries, people with disease are less likely to access healthcare, receive a diagnosis, appear on an accessible disease register, and 'be counted' within the health system. ARF is often undiagnosed due to the lack of a diagnostic test, and ARF and RHD can go unnoticed, particularly when not severe.[2] Screening for RHD requires a significant health resource investment, which is not always available.[18,19] Even in countries with well-developed public health infrastructure and record keeping, cases may still be undercounted if diagnoses are missed. The widely used *International Classification of Diseases, 10th revision*, (ICD-10) includes valvular disease of unspecified origin in some of its classifications related to, but not specific for RHD, making such classifications (and medical records coded as such) non-specific to RHD.[20] Consequently, different sources of epidemiological data (both within and between countries) are used to provide indications of the local and global burden of disease – none of which are necessarily complete or accurate.[2]

In Australia, various methods are used to collect and report data on ARF and RHD, including hospital admission and death datasets, disease notification systems, ARF/RHD registers, cardiology clinics and echocardiographic screening studies. Data collection systems usually operate independently and are managed by different custodians; they capture different populations and the type of data collected are based on their differing intended purposes. This has important implications for future policy regarding the nature of national data management in Australia.

Data analysis is usually conducted within each source and jurisdiction separately, and each system has limitations. For example, hospital and death data are not linked within and between sources, and disease registers may not capture all cases. As a result, data analysis provides a partial picture of the true burden of ARF/RHD within a jurisdiction and nationally.

Hospital admission and death data are regularly used in government reports to estimate ARF/RHD admission and death rates.[21,22] However, these reports use data that are not person-linked (i.e. they do not have a mechanism to identify records that belong to the same individual).

Figure 3.2. Model for assessing the burden of RHD *(Adapted from Zühlke and Steer 2013)*



Such hospital data which are not linked within and across the various systems cannot provide accurate information on incidence, prevalence and outcome estimates because longitudinal analyses are not possible.[23] Both linked and unlinked data are affected by miscoding of cases and misdiagnosis.[20]

Disease registers are widely recognised to be an important mechanism to support RHD control. The World Health Organization, the World Heart Federation and RHDAustralia recommend the implementation of ARF/RHD registers in areas where there is a significant burden of disease. Registers can assist with patient management, treatment delivery and collection of surveillance information.[24-26] RHD control programs, with disease registers, exist in five Australian jurisdictions; however, legislated notification of ARF and RHD is inconsistent and under-notification is a known issue *(Table 13.1)*.

Jurisdictional program registers have been established across Australia at different times, with different priorities, and for different populations.[24]

The maps in *Figure 3.3* and *Figure 3.4* show how rates of registered ARF and RHD are distributed in different regions of five jurisdictions with registers. However, producing accurate national burden of disease estimates is difficult due to a lack of standardisation in public health surveillance data. Statistics which draw on Australian ARF and RHD data may not be comparable, either between the jurisdictions, or over time.

Similar issues affect New Zealand data, with national hospital admission data estimated to overcount the true number of ARF cases by 25-33%,[27,28] while regional notification data has an undercount of true cases by 50%.[29] Eleven regional ARF registers have been established across New Zealand, however, there is limited ability to monitor people who move between regions, and information may become out-of-date rapidly.[30] However, the National Health Index allows hospitalisation and mortality data to be linked at a national level, and thus national rates can be estimated. ARF is notifiable in New Zealand, however RHD is not.

Figure 3.3. Rate of ARF diagnoses per 100,000 among Aboriginal and Torres Strait Islander Australians by region of management jurisdiction registers 2013–2017[31]

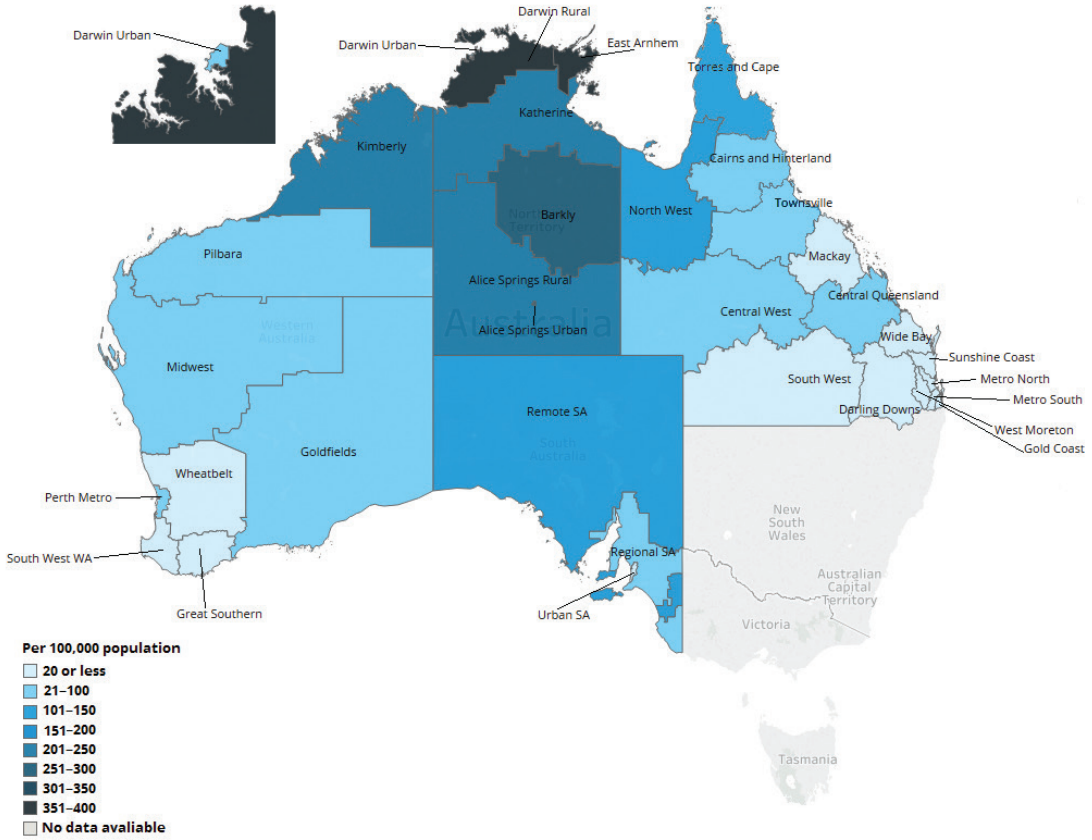
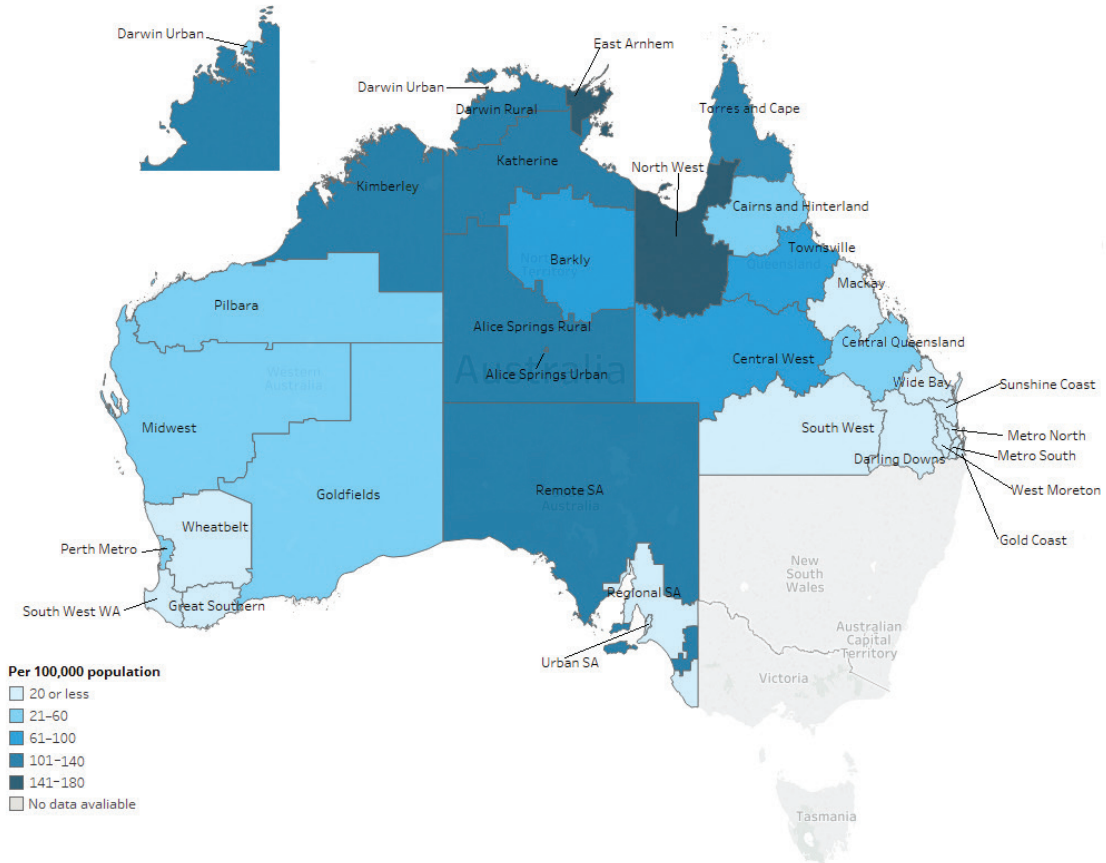


Figure 3.4. Rate of new RHD diagnoses per 100,000 among Aboriginal and Torres Strait Islander Australians by region of management, jurisdiction registers, 2013–2017[31]



BURDEN OF ARF AND RHD IN AUSTRALIA

The following sections include summaries of several Australian data sources to demonstrate the burden of ARF and RHD in the Australian population, with respect to the size of the problem, age distribution, sub-populations most affected, and significant differences at the population level. Each section or subsection is based on a single data source, which is highlighted under the section heading, along with the key points that were described by each source. Additionally, each section may contain one or more key points that relate to a graphic that was derived or taken directly from the data source. These sections provide a snapshot of the burden of ARF and RHD in contemporary Australia. Different data sources provide different types of data that are not always directly comparable. The Northern Territory register contains more data over a longer period and is the only jurisdiction for which there are reasonably complete data over time. Consequently, some data are available for the NT only.

Demographic distribution of ARF and RHD

This section shows the demographic distribution of ARF and RHD in Australia based on two independent data sets: hospital admission records from the Australian Institute of Health and Welfare (AIHW) and patient registrations from the RHD Control Programs. Although from independent sources, the following themes emerge from these data.

- Since the early 1990s, ARF has occured almost exclusively in young Aboriginal and Torres Strait Islander peoples, particularly in the 5-14-year-old age group.
- During the same period, RHD has predominately affected young to middle-aged Aboriginal and Torres Strait Islander peoples as a consequence of the current era of endemic ARF among this population, and it has affected older non-Indigenous people due to a past era of endemic ARF.
- Females are more likely to be diagnosed with ARF than males.
- The NT and Queensland incur the highest numbers of ARF/RHD registrations, while registers in South Australia and New South Wales contain the smallest numbers of registrants.

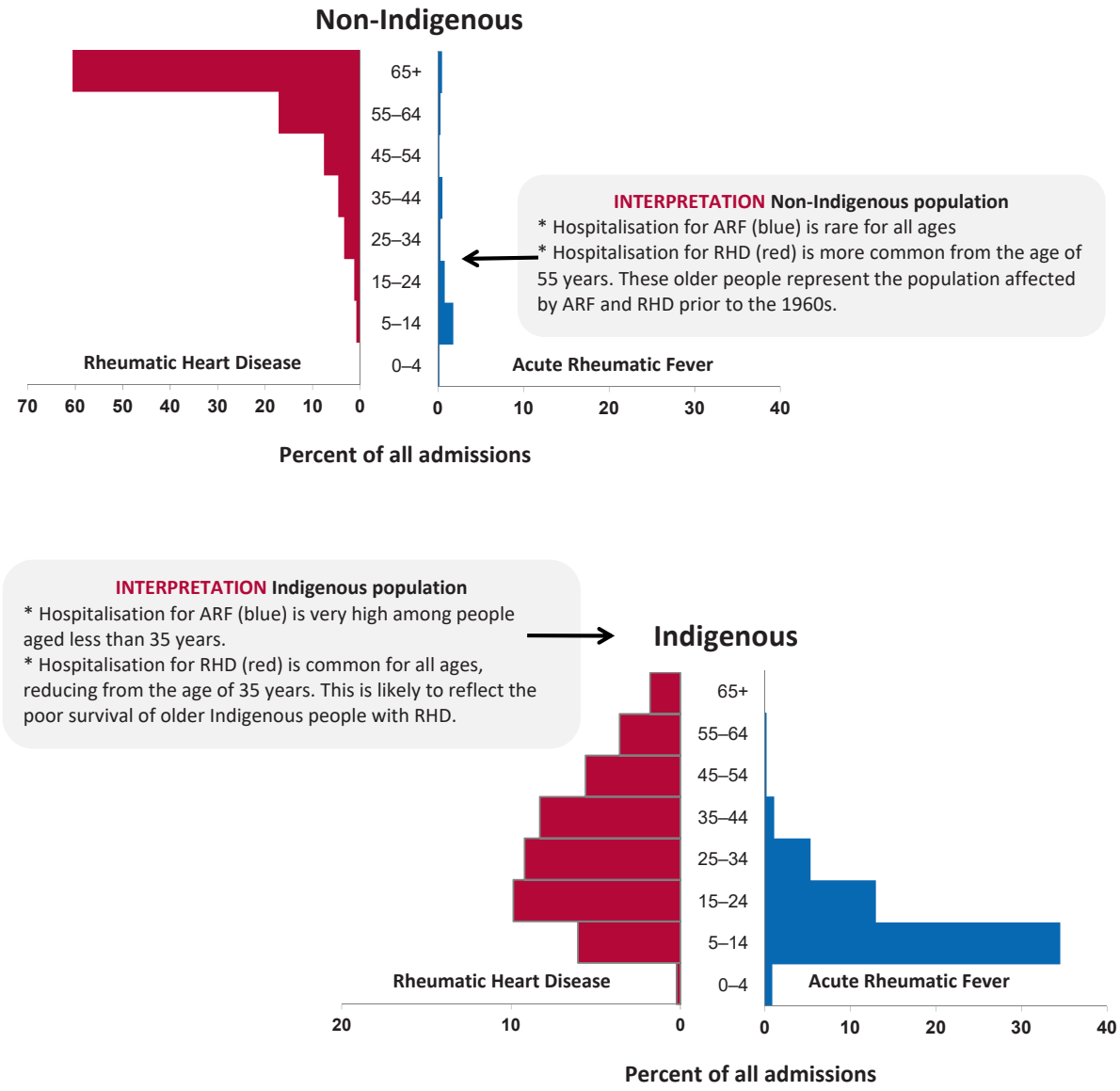
The following section uses Australian hospital admissions data to illustrate demographic details. This includes Australian data where ARF or RHD was the principal diagnosis recorded for admission (i.e. the main reason for hospitalisation). The numbers reflect the number of admissions, not the number of people. Some people could have been admitted more than once in the time period.

The age distributions for ARF and RHD hospital admissions are very different for Aboriginal and Torres Strait Islander and non-Indigenous people. Points to highlight include:

- high rates of hospital admission for ARF and RHD in the younger Aboriginal and Torres Strait Islander population reflects the ongoing epidemic affecting this population group *(Figure 3.5)*;
- in 2011-2012, Aboriginal and Torres Strait Islander peoples represented 3% of the Australian population but accounted for 16.3% of all admissions for ARF or RHD; they contributed 74.1% of all ARF admissions in Australia, and 8.3% of all RHD admissions;
- the majority (79%) of all admissions for Aboriginal and Torres Strait Islander peoples were in people younger than 35 years, compared with only 7% of non-Indigenous admissions in this age group. In contrast, 78% of non-Indigenous admissions were in people aged over 55 years;
- the high concentration of RHD admissions among Aboriginal and Torres Strait Islander peoples aged under 45 years compared to the relatively low concentration in this age group among non-Indigenous people *(Figure 3.5)* indicates that:
    - the Aboriginal and Torres Strait Islander population experiences declining survival with RHD into older age, and/or
    - the Aboriginal and Torres Strait Islander population is currently experiencing endemic ARF.

- the age-standardised rate per 1000 hospitalisations for ARF or RHD was 7.2 times higher in Aboriginal and Torres Strait Islander peoples compared with the non-Indigenous population (data not shown), with the highest disparity being in the NT.[32] This finding considers the difference in age distribution between the two populations.

Figure 3.5. All hospital admissions for ARF and RHD by Indigenous status, 2011-2012



Source: Unit record data provided by the Australia Institute of Health and Welfare in 2016.
Graphic created by Dr Judith Katzenellenbogen

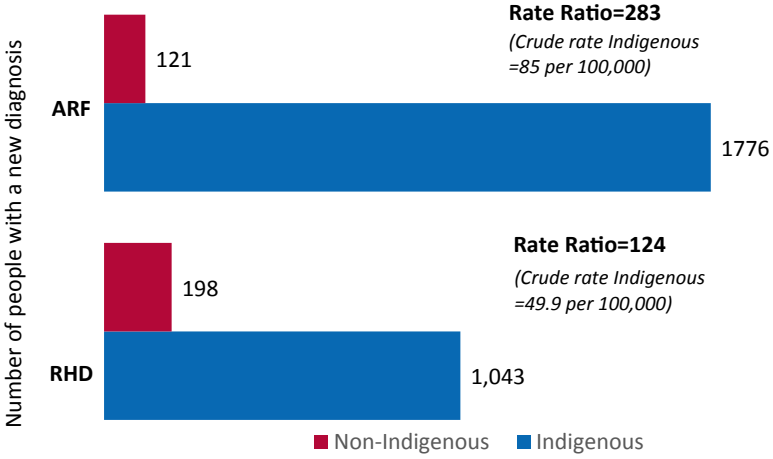
High hospital admission among Aboriginal and Torres Strait Islander young people highlights the need for a health workforce with skills to provide paediatric and adolescent hospital care which meets the needs of Aboriginal and Torres Strait Islander children and their families.

Comparisons of crude rates between Aboriginal and Torres Strait Islanders and non-Indigenous Australians

In this section, numbers reflect numbers of new diagnoses of ARF and RHD, rather than hospitalisation as described in the previous section. The crude ARF incidence (new diagnosis) rates were by far the highest in the NT, likely reflecting a population of very high risk, as well as long-established processes for case ascertainment and registration (data not shown).

- The following section uses jurisdictional RHD control program registrations data to provide information on disease rates. Points to highlight from register data include the following. The overwhelming majority of cases (89%) on RHD registers from SA, NT, QLD and Western Australia as at 31 December 2017 were Aboriginal and Torres Strait Islander people. Six in 10 (61%) were women.
- When using newly registered diagnoses to calculate rates, rates of ARF among Aboriginal and Torres Strait Islander peoples were 283 times higher and RHD rates were 124 times higher than non-Indigenous rates. These (crude) rates do not take into account age differences between Aboriginal and Torres Strait Islander and non-Indigenous populations.
- Females had higher ARF rates than males.
- The rate of ARF diagnoses increased between 2013 and 2017 *(Figure 3.7)*.[32]

Figure 3.6. Number of people with new ARF and RHD diagnoses recorded on ARF/RHD registers in QLD, WA, SA and NT 2013-2017



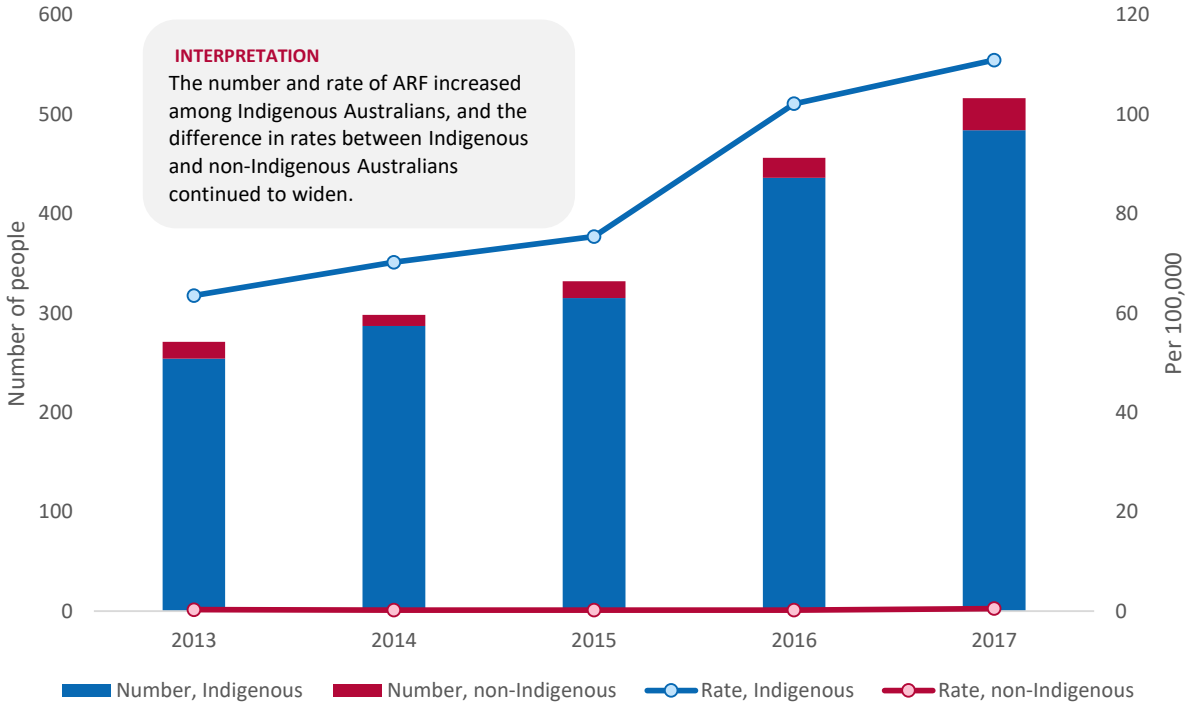
INTERPRETATION

*The vast majority of people registered with new ARF (94%) and RHD (84%) diagnoses are Indigenous.

*The rate of new diagnoses recorded among the Indigenous population is 283 times higher for ARF and 124 times higher for RHD, compared to the non-Indigenous population.

Source: Australian Institute of Health and Welfare 2019. Acute rheumatic fever and rheumatic heart disease in Australia. Cat. no: CVD 86. Canberra.

Figure 3.7. Number and rate of new ARF diagnoses recorded on RHD registers among Australians living in the NT, SA, WA and QLD, 2013–2017



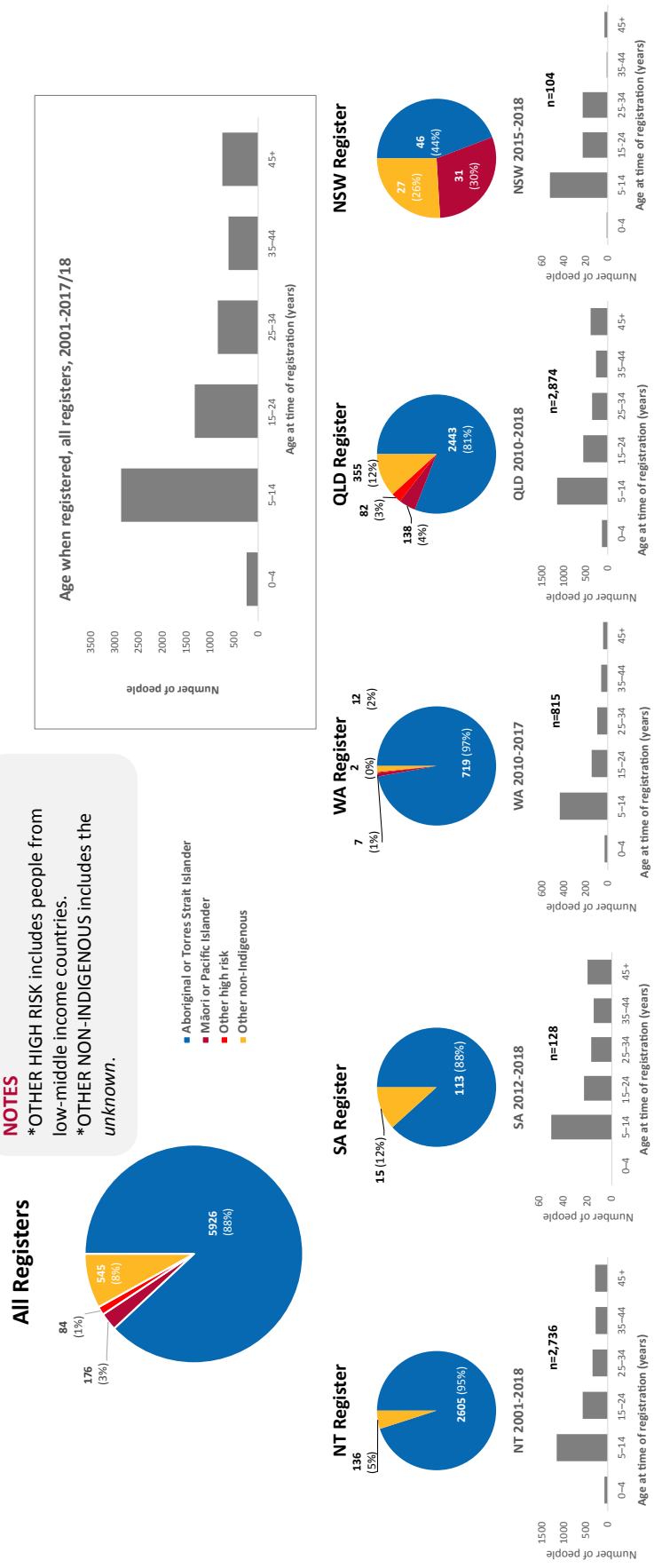
Source: Australian Institute of Health and Welfare 2019. Acute rheumatic fever and rheumatic heart disease in Australia. Cat. no: CVD 86. Canberra.

Registrations by jurisdiction and ethnicity

As at 2017-18, 6660 people with ARF or RHD were recorded on RHD registers in NSW, NT, QLD, SA and WA. This differs from the 2019 AIHW report, which only includes registrations up to 31 December 2017, and does not include NSW registrations.[31]

- The majority (88%) were recorded as being Aboriginal and Torres Strait Islander peoples. Of the remaining 12%:
  - 3% were Māori or other Pacific Islander people;
  - 1% were recorded as being from other high RHD prevalence countries;
  - 8% were recorded as being non-Indigenous Australians.
- For all jurisdictional registers combined, the age at registration peaked in the 5-14 year group, and reduced with age, with 11% registered from the age of 45 years. This profile reflects the age at which people are first registered (most commonly children with ARF who may or may not develop RHD), and is similar for all five jurisdictional registers.
- Registers in the NT and QLD contained equally high numbers of registrants, accounting for 84% of all people registered for ARF or RHD in Australia. This reflects the large at-risk populations in these jurisdictions.
- Registers in SA and NSW contained the smallest numbers of registrants; SA due to the low population numbers and NSW potentially due to the relatively recent establishment of the register and the restricted age range for RHD notification.
- Ethnic distributions varied across the jurisdictions, reflecting the geography of the high-risk populations in Australia. For example:
  - Aboriginal and Torres Strait Islander peoples were the largest group on all registers, however, they comprised 95% of NT registrants, 88% of SA registrants, and only 44% of NSW registrants.
  - Māori and Pacific Islander peoples comprised 30% of those registered in NSW, reflecting the different ethnicity in NSW compared with other jurisdictions.

Figure 3.8. Ethnic and age distribution of people with ARF/RHD on RHD registers: Australia-wide and by jurisdiction (2001-2017/18)



Source: End Rheumatic Heart Disease in Australia: Study of Epidemiology (ERASE) using data supplied by jurisdictional registers for data linkage

Patterns of disease among Aboriginal and Torres Strait Islander peoples

Several data sources have been collated to demonstrate the burden of disease among Aboriginal and Torres Strait Islander peoples. These data sources demonstrate that:

- the burden of disease often spans the majority of a person's lifetime, starting with ARF in childhood, where ongoing active engagement with the healthcare system is needed for many years, and progressing in many cases to RHD and associated heart conditions during adulthood;
- the number of Aboriginal and Torres Strait Islander peoples affected by ARF and RHD appears to be increasing;
- the burden of disease typically develops in childhood among Aboriginal and Torres Strait Islander peoples. The incidence of ARF peaked in the 5-14-year age group, reducing substantially with age and being rare over the age of 35 years *(Figure 3.9)*. In contrast, RHD prevalence increased with age, peaking at 35-44 years. Many of the young people with severe RHD who are hospitalised do not survive to old age;
- in mid-2016, there were 4549 Aboriginal and Torres Strait Islander peoples who had been hospitalised for ARF or RHD since 2001 across the NT, SA, QLD and WA *(Figure 3.10)*. Almost two-thirds of people who had a history of hospitalised ARF since 2001 were under 25 years old;
- this means more than 1% of the Aboriginal and Torres Strait Islander population under 65 years in these jurisdictions combined have a history of ARF or RHD. When considering only the NT and SA combined, this estimate is more than 2% of the population;
- more than one-third of prevalent RHD cases had severe RHD, meaning that these people had also been hospitalised for heart failure or a heart valve procedure;
- 3420 (75%) were hospitalised for RHD (2156 people) or ARF (1264 people) less than 10 years pior to mid-2016, implying that ongoing active engagement with the healthcare system is needed for many years, in keeping with guidelines.

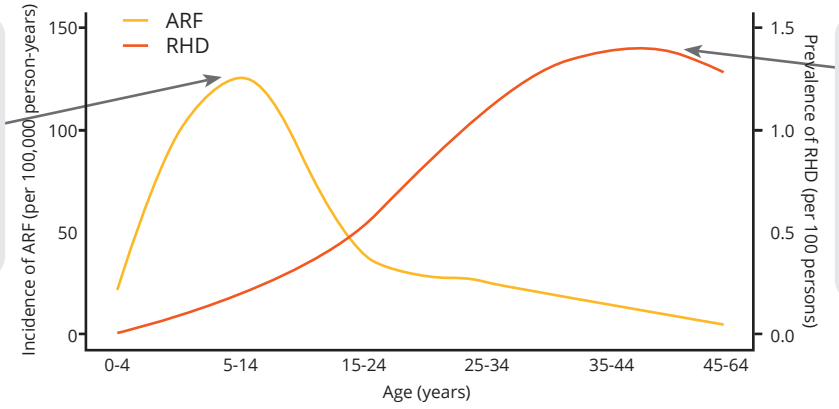
Incidence and prevalence of ARF and RHD by age

For analyses in this section, not all cases on the RHD registers were included because only hospital data were used, and registration data were not linked. Therefore, numbers do not include people who were not admitted to hospital.

Estimates were restricted to Aboriginal and Torres Strait Islander peoples under age 65 years to reflect the ongoing burden among young Indigenous Australians. NSW data were not included.

Figure 3.9. Hospitalised incidence of ARF between 2014 and 2016 and prevalence of RHD in mid-2016 in the NT, QLD, SA and WA

INTERPRETATION
A FIRST EPISODE of ARF *(incidence)* is most common in children aged 5-14 years, and gradually becomes less common as people get older.

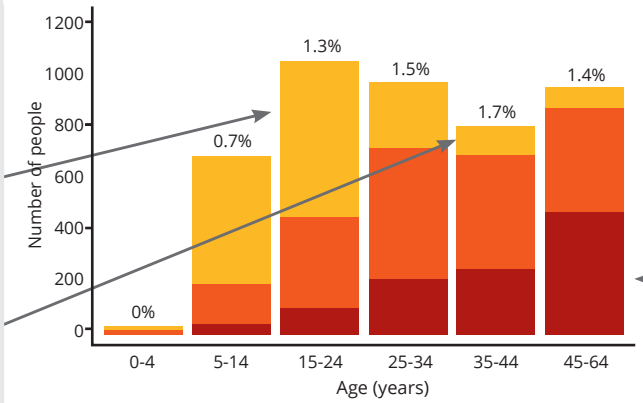


INTERPRETATION
The number of people living with RHD *(prevalence)* steadily increases with age and then starts to decline from the age of 35 years as survival is reduced.

Source: Wyber R, Cannon J, Katzenellenbogen, J. The Cost of Inaction on Rheumatic Heart Disease: The predicted human and financial costs of rheumatic heart disease for Aboriginal and Torres Strait Islander people 2016-2031. The END RHD CRE, Telethon Kids Institute. Perth. 2018

Figure 3.10. Prevalence of ARF and RHD, stratified by severity, among Aboriginal and Torres Strait Islander Australians in the NT, SA, QLD, and WA by age, at mid-2016

INTERPRETATION
This graph shows the age of people (at mid-2016) who were hospitalised for ARF and RHD between 2001 and mid-2016. *Most people were aged between 15-24 years, and this represents 1.3% of the Indigenous population in the four jurisdictions. *However, at 1.7%, a higher percent of the Indigenous population aged 35-44yo have been affected by ARF/RHD compared to any other age group.



NOTE
Episodes of ARF and RHD prior to 2001 are not included.

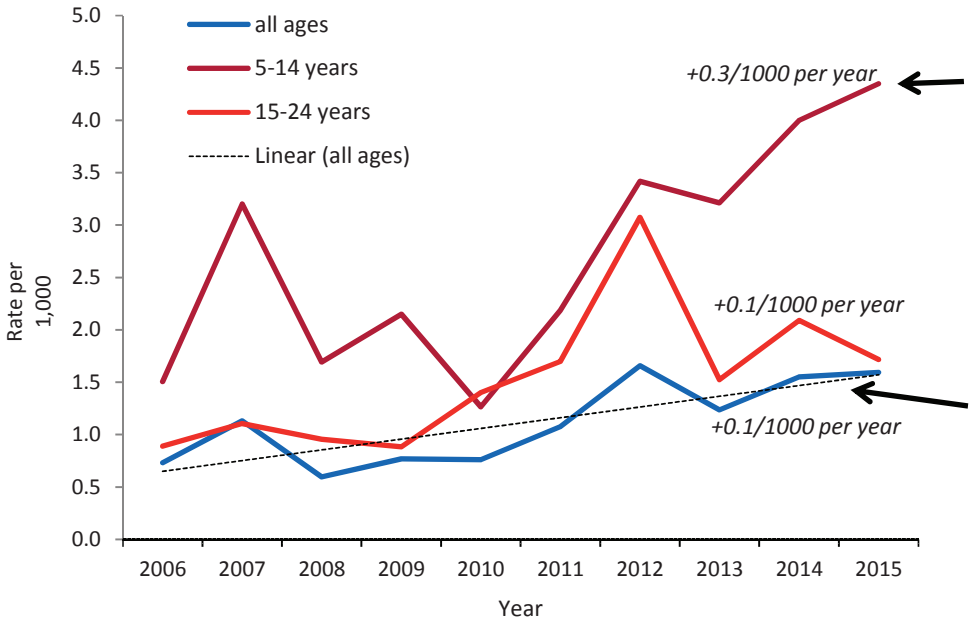
INTERPRETATION
Severe RHD includes people who have been hospitalised with heart failure or for a heart valve procedure between 2001 and 2016. The number and percentage of people with severe RHD increases with age.

Source: Wyber R, Cannon J, Katzenellenbogen, J. The Cost of Inaction on Rheumatic Heart Disease: The predicted human and financial costs of rheumatic heart disease for Aboriginal and Torres Strait Islander people 2016-2031. The END RHD CRE, Telethon Kids Institute. Perth. 2018

Trends in Aboriginal and Torres Strait Islander registration rates in the NT

- ARF incidence (new and recurrent episodes) increased significantly in the NT Aboriginal and Torres Strait Islander population between 2006 and 2015 overall, with the increase highest in the 5-14-year age group. The reason for the increase is unclear but may be due to increased diagnosis and reporting or represent a true increase in ARF.
- In the NT, registration rates of new RHD showed no clear trend over time (data not shown).

Figure 3.11. Incidence (new and recurrent) of ARF in the Northern Territory, Aboriginal and Torres Strait Islander Australians by age group, 2006 to 2015



INTERPRETATION
The INCIDENCE of new and recurrent ARF increased by 0.3 per 1000 children aged 5-14 years in the NT each year (ARF is most common in this group).

The dotted line shows the upward TREND of ARF for all ages as a straight line, increased by 0.1 per 1000 people each year.

Source: Australian Institute of Health and Welfare 2017. Aboriginal and Torres Strait Islander health performance framework 2017: supplementary online tables. Cat. no. WEB 170. Canberra: AIHW.

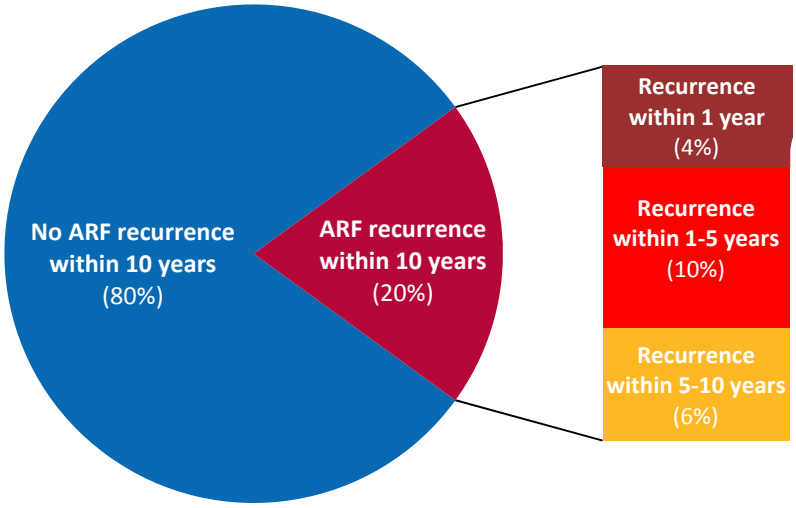
Progression and complications of disease

This section presents data on the progression and complications of ARF and RHD. It shows that:

- people with ARF are prone to a further episode, with one in five (20%) having a recurrent episode within 10 years of their first;
- of these, 4% had their recurrence in the first year, while 10% and 6% had their recurrence within 1-5 years and 5-10 years respectively;
- there is a high risk of valvular damage (RHD) from a recurrent or single severe episode of ARF; more than half of people with ARF progress to RHD within 10 years of their initial ARF episode, and more than one-third of these people develop severe RHD;
- more than one in 10 people are affected by atrial fibrillation or heart failure resulting from RHD.

High recurrence of ARF highlights the need for Australia's primary health care system to strengthen partnerships with people with ARF and their families around disease education, secondary prophylaxis, and management of ongoing risk of ARF.

Figure 3.12. ARF recurrence by time since initial ARF diagnosis: NT 1997-2013



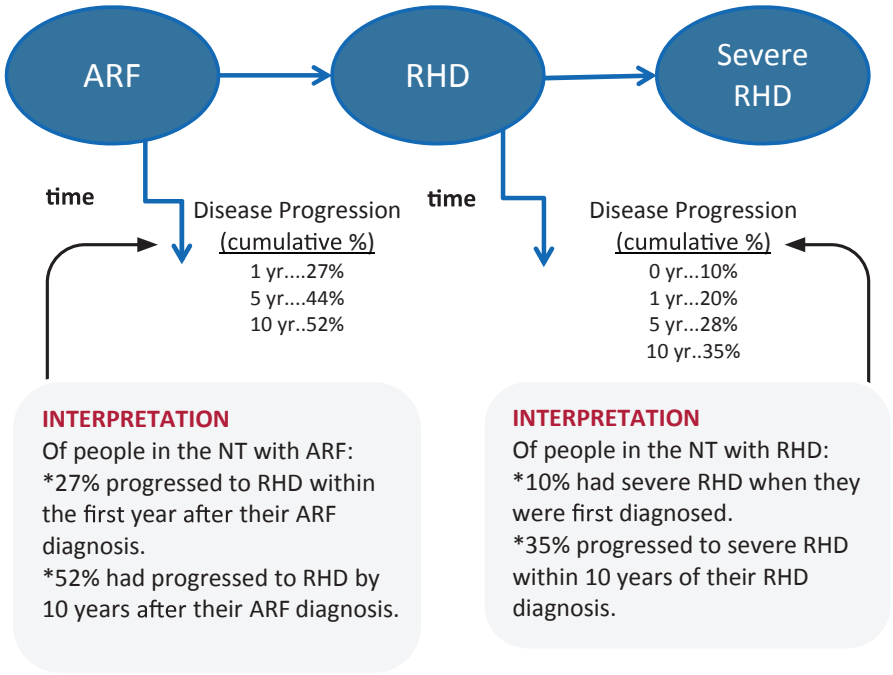
INTERPRETATION
Following a FIRST EPISODE of ARF:
*1 in 5 people will have recurrent ARF within 10 years.
*The majority of recurrences (half) occur between 1 and 5 years after the first episode.

Source: He VYF, Condon JR, Ralph AP, et al. Long-term outcomes from acute rheumatic fever and rheumatic heart disease: A data-linkage and survival analysis approach. Circulation 2016;134:222-32

Progression of ARF to RHD

- More than a quarter (27%) of people experiencing their first ARF episode and free of RHD at that time, developed RHD within a year of their ARF diagnosis. By five years, 44% had developed RHD. More than half (52%) had progressed to RHD within 10 years.
- Among people diagnosed with RHD, 10% had severe RHD when first diagnosed. By one year, that figure had doubled to 20%. By 10 years, more than one-third (35%) had severe RHD.
- These findings highlight opportunities for secondary prevention.

Figure 3.13. Progression of ARF to RHD and RHD to severe RHD, Northern Territory 1997-2013



Source: He VYF, Condon JR, Ralph AP, et al. Long-term outcomes from acute rheumatic fever and rheumatic heart disease: A data-linkage and survival analysis approach. Circulation 2016;134:222-32

Complications of RHD

- The incidence of all adverse outcomes of RHD, except death, was highest in the first year after RHD was diagnosed.
- The incidence of heart failure was the highest of all non-fatal adverse outcomes at all time points. By 10 years, 19% of people with RHD had received a diagnosis of heart failure (data not shown).
- Atrial fibrillation had the second highest incidence in the first year after RHD diagnosis *(Figure 3.13)*. By 10 years, 13% of people with RHD had received a diagnosis of atrial fibrillation (data not shown).
- The incidence of infective endocarditis and stroke was low throughout, with 4% of RHD cases having infective endocarditis and 4% experiencing a stroke within 10 years of RHD diagnosis.
- The death rate increased with time after RHD diagnosis, starting from a low base at one year (0.5%) and reaching 10% by the 10-year mark.

Table 3.1. Incidence rate and cumulative incidence rate (95% CI) of adverse outcomes for RHD patients (n=1248) at intervals after first RHD diagnosis

	Year	Severe RHD ‡	Atrial Fibrillation	Endocarditis	Heart Failure	Stroke	Death
Cumulative incidence (%)†‡	1	20.5 (17.8-23.5)	4.7 (3.4-5.8)	0.9 (0.6-2.0)	8.2 (6.8-9.9)	0.6 (0.3-1.2)	0.5 (0.2-1.1)
	5	28.0 (24.9-31.5)	7.4 (6.0-9.0)	2.2 (1.5-3.2)	12.6 (10.8-14.7)	1.5 (0.9-2.4)	3.8 (2.7-5.1)
	10	34.6 (30.4-39.2)	13.4 (11.2-15.8)	4.0 (2.9-5.6)	18.6 (16.2-21.3)	3.6 (2.5-5.3)	10.3 (8.3-12.6)

† An individual can have one or more of these outcomes.

‡ Only for those with a diagnosis in 2004 or later (n=772)

Source: He VYF, Condon JR, Ralph AP, et al. Long-term outcomes from acute rheumatic fever and rheumatic heart disease: A data-linkage and survival analysis approach. Circulation 2016;134:222-32

Death rates

In this section, Aboriginal and Torres Strait Islander deaths were analysed separately for the NT and the other four jurisdictions combined, while the non-Indigenous data for all five jurisdictions were combined. Most of the analyses included ARF and RHD as underlying causes of death, although the extent to which RHD was coded as an associated cause was also investigated.

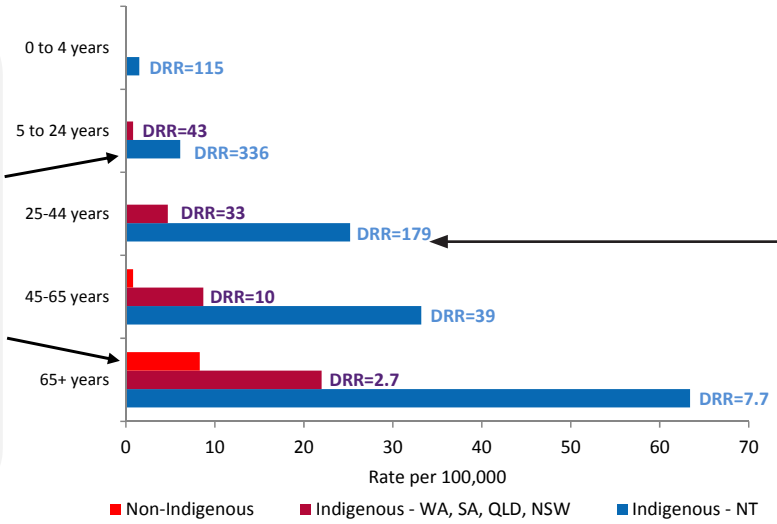
- ARF and RHD death rates among Aboriginal and Torres Strait Islander peoples in the NT were higher at all ages than in the other jurisdictions. Death rates for Aboriginal and Torres Strait Islander peoples were higher than rates for non-Indigenous Australians in all jurisdictions.
- Among non-Indigenous Australians, most deaths occurred in people aged >65 years and more than 80% of deaths were due to RHD as an associated, rather than an underlying cause. In contrast, deaths among Aboriginal and Torres Strait Islander peoples occurred at younger ages and were coded as an underlying cause in more than 60% of cases (data not shown).
- The disparity in RHD death rates (Death Rate Ratios [DRR]) decreased with age, being highest in the 5-24-year age group. Aboriginal and Torres Strait Islander children in the NT had death rates 336 times higher, and Aboriginal and Torres Strait Islander children in other jurisdictions had death rates 43 times higher, than non-Indigenous children.
- RHD death rates in non-Indigenous Australians were low for all age groups except 65+ years.
- Overall, the death rate ratio (Aboriginal and Torres Strait Islander compared with non-Indigenous) was 55 in the NT and 13 in the other four jurisdictions once age and gender were considered (data not shown).
- Over the period 1997 to 2015, death from ARF and RHD in the NT decreased at a more rapid rate for non-Indigenous (7.4% per year) than for Aboriginal and Torres Strait Islander peoples (1.8% per year). Between 1997 and 2005, Aboriginal and Torres Strait Islander peoples in other parts of Australia experienced lower death rates from ARF and RHD than their NT counterparts.
- Aboriginal and Torres Strait Islander peoples with RHD are dying young as a direct consequence of their disease. In contrast, non-Indigenous people with RHD are living longer with their disease and are dying from other or associated causes. Non-Indigenous people are also more likely to be the survivors of a time when RHD was relatively common. People who had severe disease at that time would be less likely to have survived to the current time.
- The AIHW (2019)[31] reports 275 deaths recorded on RHD jurisdictions registers between 2013-2017, of which 80% were Aboriginal and Torres Strait Islander peoples.

Figure 3.14. Age-specific ARF and RHD mortality rates as underlying cause, by Australian jurisdiction and Indigenous status: SA, NT, WA, NSW and QLD 1997-2005

INTERPRETATION

DEATH RATES for ARF and RHD among Indigenous Australians in the NT (blue) are higher than for other jurisdictions (red).

DEATH RATES for ARF and RHD among non-Indigenous Australians (orange) are lowest, and include older people who were affected by ARF and RHD prior to the 1960s.



INTERPRETATION

The DEATH RATE RATIOS (DRR) show how many times higher the death rates for ARF and RHD are for an Indigenous population group, compared with non-Indigenous Australians.

*e.g. For the 25-44 year age group: Indigenous people in the NT died at rates 179 times higher, and Indigenous people in WA, SA, QLD and NSW died at rates 33 times higher, than non-Indigenous people from all jurisdictions combined.

Source: Colquhoun SM, Condon JR, Steer AC, et al. Disparity in mortality from Rheumatic Heart Disease in Indigenous Australians. JAMA 2015;4(7).

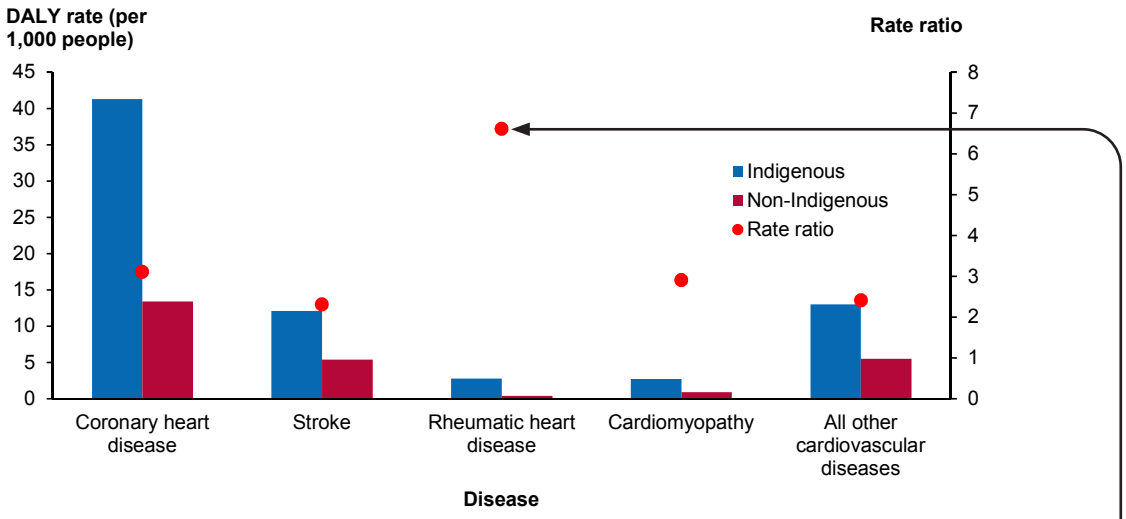
Burden of RHD in Disability-Adjusted Life Years

The Disability-Adjusted Life Year (DALY) is a complex measure of population health that estimates the total years of healthy life lost due to disease and injury. The DALY adds the number of years of life lost to death (YLL, fatal burden) and years of life lost to disability (YLD, non-fatal burden) that is weighted according to the disability for that condition. The Australian Burden of Disease Study[33] used hospital and death data to estimate the burden of ARF and RHD. The approach used does not differentiate between ARF and RHD, thus results reflect the combined ARF and RHD burden. Most of the results in this section focus on Aboriginal and Torres Strait Islander peoples.

- RHD makes a minor contribution to the overall cardiovascular disease (CVD) burden in the Australian population, with non-rheumatic heart disease making a more substantial contribution.
- The high burden of ARF and RHD in the Aboriginal and Torres Strait Islander population is over-shadowed at the national level due to this group being a small proportion of the general population. Consequently, the focus in this section is on the RHD burden in the Aboriginal and Torres Strait Islander population.
- As with other CVDs, the fatal contribution (YLL) is much higher than the non-fatal.
- RHD contributed to a small proportion of all Aboriginal and Torres Strait Islander heart disease burden (5.1%), however, unlike other forms of heart disease it is common among children and young adults.
- The RHD burden due to premature death (fatal burden, 83.6% of total RHD burden) was much greater than the burden from illness/disability (non-fatal burden), although the non-fatal proportion was still higher than that for other CVDs.
- Females contributed 61% of all RHD burden, reflecting the well-documented higher prevalence of RHD among women (data not shown).
- RHD ranked higher among women than among men as a contributor to the overall gap between Aboriginal and Torres Strait Islander and non-Indigenous Australians (data not shown).
- RHD contributed the most DALYs to the CVD burden among Aboriginal and Torres Strait Islander peoples under the age of 20 years (data not shown).
- Once age was considered, the RHD rate in Aboriginal and Torres Strait Islander peoples was 6.6 times higher than that in the non-Indigenous population. This was the highest relative gap among all CVDs and the fifth highest relative gap of all specific diseases reported (data not shown).

High rates of RHD among women highlight the need for a skilled female health workforce, including Aboriginal and Torres Strait Islander Workers, Practitioners, nurses, midwives and doctors.

Figure 3.15. Cardiovascular diseases age-standardised DALY rates (per 1000 people) by disease and Indigenous status, 2011



INTERPRETATION

*The blue charts show the DALY burden rates of different cardiovascular diseases (CVD) for Indigenous Australians.

* The red charts show the rates for non-Indigenous Australians.

* RHD rates are the charts in the middle.

* The Indigenous rates are higher for all types of CVDs.

INTERPRETATION

The orange dots (rate ratios) show how many times higher the Indigenous rates are compared with non-Indigenous rates.

* Here, the Indigenous burden for RHD is 6.6 times higher than the non-Indigenous burden (taking into account age differences between the populations).

Source: AIHW 2016. Australian Burden of Disease Study: Impact and causes of illness and death in Aboriginal and Torres Strait Islander people 2011. Australian Burden of Disease Study Series no 6. Cat.no. BOD 7. Canberra: AIHW.

Projected hospitalisations and medical costs of ARF and RHD

The Cost of Inaction report[34] was based on linked hospital and death data (2001-2016) and external sources, to describe current burden and future burden and cost. The estimations of future RHD burden and costs used several stages of data analysis and were calculated based on:

1. current incidence and prevalence rates;
2. trends in incidence of ARF and RHD;
3. projections of what the population size and distribution will be to 2031;
4. knowledge about the rates of progression from ARF to RHD; and
5. the estimated costs of treatment for the existing and new cases into the future. Estimates assumed that the policies, funding and management of ARF and RHD will stay the same (the status quo).

- 10,211 new cases of ARF or RHD are projected to occur in the NT, SA, QLD and WA between mid-2016 and the year 2031. These cases comprise 4885 and 5326 people who are projected to be hospitalised with ARF or with RHD without a history of ARF, respectively.
- Of the 4885 people projected to be diagnosed with ARF, most of whom will be children aged under 15 years, 2535 are estimated to subsequently progress to RHD.
- 2260 of the people who develop RHD are estimated to be diagnosed with or progress to severe RHD, which includes 1370 people who will require valvular surgery.
- Future medical care for the 3420 people currently with ARF or RHD under active treatment and the 10,211 people projected to develop ARF and RHD between mid-2016 and the year 2031 (considered potentially avoidable) is estimated to cost the Australian health system at least $27 million and $317 million, respectively.[35]
- Children projected to develop ARF between the ages of 5 to 14 years, including those who progress to RHD, will incur the highest medical cost.

A high projection of ARF and RHD in Australia highlights the importance of a skilled health workforce, including an Aboriginal and Torres Strait Islander workforce. It also highlights the need for an equipped and responsive health system.

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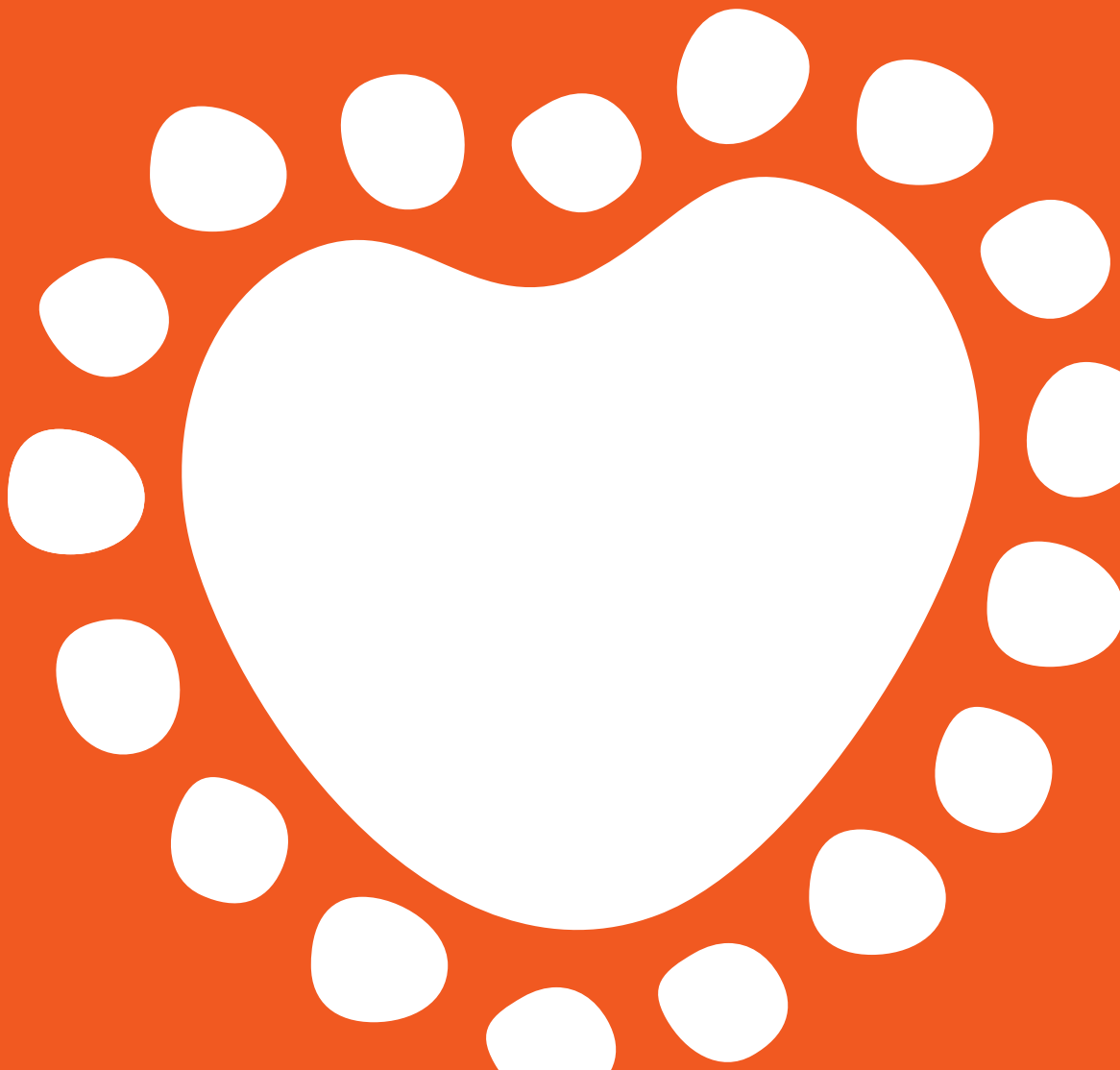
CHAPTER 4

Primordial prevention and social determinants of acute rheumatic fever



Primordial prevention and social determinants of acute rheumatic fever

CHANGES FROM THE SECOND (2012) EDITION

- This is a new chapter.
- The abbreviation used for Group A Streptococcus used in this chapter and throughout the guideline is 'Strep A' (previously 'GAS').

KEY INFORMATION

- The socioeconomic and political factors that influence people's lives can cause structural barriers and inequalities in health. These *social determinants* of health within an Indigenous cultural context have profound impacts on health and wellbeing.
- The circumstances in which people live affect the risk of Group A streptococcus (Strep A) infections, acute rheumatic fever (ARF) and rheumatic heart disease (RHD). Living in overcrowded conditions and having limited access to facilities to wash people, clothes and bedding increase the risk of Strep A infections, ARF and RHD.[1]
- Strep A is a human-only infection with no animal or insect hosts, therefore control strategies comprise modifications of human behaviours and environments.
- Nine Healthy Living Practices were developed in the 1980s by the Nganampa Health Council in South Australia to help prioritise what people need in order to live healthy lives.[2] There is evidence that the Healthy Living Practices can help reduce Strep A infections *(Table 4.1)*.
- While not all Healthy Living Practices apply directly to Strep A, the approach to social determinants of health should be holistic rather than disease-specific.
- There are several approaches to increase access to Healthy Living Practices to reduce the development of Strep A skin and throat infections which lead to ARF and RHD.
- Interventions on living practices applied for ARF and RHD are likely to have an impact on other diseases and conditions.

Table 4.1. Healthy Living Practices and their association with Strep A infections, ARF and RHD

HEALTHY LIVING PRACTICE	ASSOCIATION WITH REDUCING STREP A INFECTIONS	NOTES
1 - Washing people	Strong	Washing of hands and bodies, particularly for children, is clearly associated with a reduction in the risk of Strep A infections.
2 - Washing clothes and bedding	Medium	Washing clothing and bedding is an important way to reduce the risk of Strep A skin infections. • Washing clothes and bedding does not directly reduce the risk of Strep A skin infections. • Washing clothes and bedding can reduce the transmission of scabies mites and lice which can cause skin itch, skin damage and lead to Strep A skin infection.
3 - Removing wastewater safely	Weak	Removing wastewater safely is important to reduce the risk of many infectious diseases. • Wastewater is not a major contributor to the spread of Strep A infections.
4 - Improving nutrition, the ability to store, prepare and cook food	Weak	Improving nutrition is important to improve many health outcomes. • Poor nutrition is not known to be a major risk factor for Strep A infection. • Strep A throat infections can spread through food which has not been cooked or stored properly. This is rare and not a major driver of ARF and RHD in Australia.
5 - Reducing the negative impacts of overcrowding	Strong	Household overcrowding is a major contributor to the burden of Strep A, ARF and RHD. • Efforts to reduce household overcrowding or reduce the risk of overcrowded living circumstances are important.
6 - Reducing the negative effects of animals, insects and vermin	Medium (indirect)	Reducing the rates of skin infestation and damage from animals, insects and scabies are important for reducing the risk of Strep A skin infections. • Strep A only infects humans; dogs and insects do not directly spread Strep A infection. • Animals, insects and scabies mites can cause skin damage which increase the risk of secondary Strep A infection.
7 - Reducing the health impacts of dust	Weak	Dust does not contribute to Strep A infections and does not play a major part in reducing the risk of skin or throat infection.
8 - Controlling the temperature of the living environment	Weak	The risk of Strep A infections may be different in hot, wet weather or cold temperatures when people need to sleep close together for warmth. • The evidence for these associations is variable and there is no clear evidence that controlling household temperature can have a significant impact on Strep A, ARF and RHD risk.
9 - Reducing hazards that cause trauma	Medium	Clean and tidy houses and yards may help reduce Strep A skin infections. • Living in a house with lots of rubbish and debris may increase the risk of skin damage through scratches or abrasions. These can become infected with Strep A.

DISCUSSION

> *"You need to understand the community and the problems that they are facing and then, and only then, you can help them to get rid of RHD."*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

Primordial prevention strategies are focused on the prevention of risk factors and generally address the social determinants of health which increase the risk of Strep A associated disease.[1,3]

Social determinants are defined as 'the circumstances in which people grow, live, work, and age, and the systems put in place to deal with illness. The conditions in which people live and die are, in turn, shaped by political, social, and economic forces'.[4]

Improvements in living conditions have been widely credited for the decreasing burden of ARF and RHD in most developed countries, including Australia.[5,6] Internationally, improvements in living conditions have generally occurred at a population level through economic development, policy and regulatory changes.[5,7,8]

In Australia, the health benefits of economic, social, structural and cultural inclusion have not been realised for many Aboriginal and Torres Strait Islander peoples. The ongoing legacy of colonisation means that social determinants remain the critical components of the gap in health outcomes between Aboriginal and Torres Strait Islander peoples and non-Indigenous Australians.[9] In this regard, the incidence of Strep A infection and ARF are conspicuous markers of disadvantage. It may take some time for all the key factors of this disadvantage to be addressed and remedied. In the meantime, specific strategies are needed to address these underlying drivers of ill health. This includes action on the indirect determinants of health (including racism, discrimination, education and economic exclusion) along with focused action on the direct determinants of health, such as inadequate housing and hygiene infrastructure. Other people in Australia who experience similar social determinants of health which increase the risk of Strep A infections, ARF and RHD include homeless populations, and some marginalised migrant and refugee populations.[10]

Strategies to improve the social determinants of health are likely to have an impact on Strep A transmission and infection. The Healthy Living Practices have been widely adopted as a framework for addressing the links between housing and health for Aboriginal and Torres Strait Islander peoples. Development of the Healthy Living Practices is outlined in *Box 4.1*.

Box 4.1: Development and use of the Healthy Living Practices framework

The Healthy Living Practices framework provides a well-recognised model for considering Strep A risk reduction strategies, developed from a remote Aboriginal community and suitable for direct articulation into existing policy frameworks.

The Nganampa Health Council has provided health services to Aboriginal people in the Anangu Pitjantjatjara Yankunytjatjara (APY) Lands of South Australia since 1983.[11] In the 1980s, Nganampa Health Council Directors called for a project to 'stop people getting sick'.

This initiated *Uwankara Palyanku Kanyintjaku* - a review of Environmental and Public Health in the region funded by the South Australian Minister of Health and jointly conducted by the Nganampa Health Council, South Australia Health Commission and the Aboriginal Health Organisation South Australia (later, AHCSA), in conjunction with technical experts.[2,12]

The review was based on following three main sources of information.

1. field survey of household circumstances of Anangu people in all major communities and selected homelands. This incorporated 90 houses with an average of 8.3 residents;
2. nutrition survey of local dietary practices;
3. analysis of existing data from the health clinics, healthy survey records, housing details and evaluations of previous projects.

Recommendations from the review were intended for use by government and service agencies, Anangu Pitjantjatjara people and communities. The first recommendation of the review was to develop Healthy Living Practices to describe, define and focus on what people need to live healthy lives.

The nine resulting Healthy Living Practices have been widely adopted as a foundation for communities and governments to consider the environmental determinants of health and help guide priorities for action. Dissemination of the framework has been amplified by Healthabitat, guided by the Nganampa Health Council directors.[13] This included development of the *Housing for Health* approach and enshrining the concept of 'no survey without service' promulgated by Dr Fred Hollows.[14]

In 2000-1, Healthabitat received Commonwealth government funding to assess and fix 1000 houses using the Housing for Health process.[14] By March 2002, 792 houses in four jurisdictions had been assessed, with the vast majority of work completed by local Aboriginal staff. Most repairs were able to be completed within the project budget of $3000 per house.[14]

New South Wales subsequently adopted the Housing for Health program and provided jurisdictional funding through the NSW Department of Health in partnership with the Department of Aboriginal Affairs.[13] The NSW Housing for Health program aims to undertake repairs and maintenance of Aboriginal community housing focusing specifically on improving safety and health for residents.[15]

Health outcomes were encouraging. People receiving the Housing for Health intervention had 40% less hospital separations for infectious diseases.[15] Guided by the Healthy Living Practices, the program also demonstrated at least a twofold improvement in the ability to wash people, bedding and homes, and a twofold improvement in the safe removal of waste from homes.[15]

Healthy Living Practices also have been used as a framework for research initiatives (including the Housing Infrastructure and Child Health Study in 10 Northern Territory communities[16]), for the National Indigenous Housing Guide[17] and in reporting on the Aboriginal and Torres Strait Islander Health Performance Framework.[18] The Housing for Health approach was also endorsed by the National Aboriginal and Torres Strait Islander Housing Authority, on behalf of jurisdictional partners in their 2018 submission on the Closing the Gap refresh.[19]

Healthy living practice 1 – washing people

No single approach is effective for promoting washing of hands and bodies. Comprehensive strategies are needed and should be developed by local communities to suit community priorities and preferences.

Washing hands and bodies is directly associated with reducing Strep A infections. People who do not have opportunities for effective washing of their hands and bodies may have increased rates of Strep A. This includes poor access to hardware (taps, sinks and water) and consumables (soap and towels) as well as limited information about the importance of washing to reduce the spread of disease. Social beliefs about hygiene practices or barriers to health behaviours may also reduce handwashing.[12] All these preventative factors often work together in places with a high burden of Strep A infection, ARF and RHD.[20,21]

There is strong evidence from studies in Pakistan that daily handwashing by children with soap and water reduces skin infections.[22,23] Antibacterial soap is no better than regular soap.[22,23] A recent systematic review concluded that daily handwashing can be recommended for treatment and prevention of skin sores in Australia (Level of Evidence GRADE 1A).[24]

Table 4.2. Potential strategies to increase washing of hands and bodies

Health education and health promotion campaigns	Health promotion campaigns encourage people to wash hands and provide information about how and when hands should be washed. Programs promoting handwashing in Australia include social marketing through *No Germs on Me* in the Northern Territory[20,25] and the school-based program *Mister Germ* in Queensland and New South Wales.[26,27] Other programs using local sportspeople or school programs have been used in other parts of Australia.[28,29] However, health promotion campaigns can be effective only if people have adequate facilities for washing. It is important that any health promotion activities are relevant to the population group and are developed in appropriate Aboriginal and Torres Strait Islander languages. Sustained changes in handwashing are more likely to come from community leadership and engagement than short-term health education campaigns.
Providing consumables for washing	Some health promotion programs distribute soap and other products to support washing. The largest of these is the *Squeaky Clean Kids* program in Western Australia.[30] Other initiatives have aimed to produce soaps locally, sometimes including traditional bush medicines.[31,32] No evaluation of whether these approaches increase washing behaviour is yet available.
Promote handwashing in schools	Quality standards require schools and child care providers to reduce the risk of spreading infectious diseases,[33] therefore schools have an important role in providing facilities (including sinks, soap and towels) and promoting handwashing. However, not all schools have soap and handwashing facilities and not all education departments or other governing bodies require the provision of soap at school. Working with local schools to improve handwashing facilities and instruction is an important way to support child health in general, and reduce the risk of Strep A infections.
Access to swimming facilities	Swimming provides a mechanism for washing skin. Ten studies have been conducted in remote Australian communities exploring the impact of community swimming pools on skin health outcomes for Aboriginal and Torres Strait Islander peoples.[34] All prospective studies described a drop in skin sore prevalence and severity (when measured). Although caution is recommended in the interpretation of these outcomes given a lack of control groups, the consistent findings across studies is notable. The authors of the systematic review are calling for further evaluation to assess these results and the possible impact that swimming pools have on skin sores.[34]
Access to shared washing facilities	Some Australian communities have introduced communal shower blocks to make it easier for people to access washing facilities,[35,36] although it is not clear whether this approach increases washing behaviours. No evaluation of the effect of these facilities has been identified.

Healthy living practice 2 – washing clothes and bedding

Washing clothes and bedding is indirectly associated with reducing Strep A infections. However, some people do not have access to the resources they need to wash clothing and bedding. Many households do not own a washing machine or do not have functional laundry plumbing for hot and cold water. The need to purchase detergents may also create a financial barrier to washing clothes and bedding.[37]

There is no evidence that Strep A bacteria are transmitted via clothes or bedding.[38] However, other causes of skin damage (scabies mites [*Sarcoptes scabiei* var. hominis], fleas, lice) may be spread via washable items. These co-infections cause skin disruption which predisposes an individual to Strep A infections (See *Chapter 5. Primary Prevention, Strep A skin infections*).

Transmission of Strep A bacteria from person to person may occur if clothing or bedding is heavily contaminated with body fluids, including pus or serous discharge from skin sores or nasal secretions. Rarely, scabies mites may be spread though clothes or bedding used by someone who has scabies. Scabies transmission through bedding and clothing is more likely from people with crusted scabies and very high mite burden. Fleas, lice and fungal infections may also have some mechanism of transmission through clothes or bedding and cause skin disruption which predisposes to Strep A infections.

Therefore, ensuring that people have facilities to wash clothes and bedding to kill scabies mites and body lice may reduce the rates of Strep A skin infection. Washing clothes and bedding in hot water is an effective method to kill the scabies mites and body lice.

Scabies reduction strategies which do not rely on washing clothes and bedding are reasonable options. Isolating bedding and clothing in a plastic bag or exposing to sunlight for one week is a commonly recommended alternative to washing in order to kill the scabies mite.[49] Recent experiments show that the period of isolation should be at least 3 days in temperate-dry conditions (22°C, 55% relative humidity) and 8 days in warm-humid conditions (26°C, 80% relative humidity).[39] Other resources recommend the sun exposure of blankets and mattresses.[50] This mechanism of killing scabies mites is likely to be through ultraviolet light, heat and dehydration.[51] Previous studies indicate that exposure to temperatures greater than 25°C at low humidity for more than 3-5 days, usually in the absence of an ongoing food supply (i.e. human or animal host), is lethal to scabies mites.[52,53]

Other strategies to increase uptake of washing may include providing washing detergent to families,[37,54] offering education about how to wash clothes and bedding to maximise benefits for skin health, exploring the role of hand-operated washing machines not dependent on electricity and complex maintenance,[55] and mobile laundromat facilities.[56] There is insufficient evidence of the health effect of any of these approaches.

Table 4.3. Strategies for effective parasite removal from clothes and bedding

Scabicidal strategies	Scabies eggs and mites on fomites are killed under the following conditions:[39] • temperature ≥50°C as provided by a hot washing machine or drier • freezing at -10°C for ≥5 hours • isolation of the fomites from human hosts for 3 to 8 days (3 days in temperate-dry conditions and 8 days in warm-humid conditions) Water temperature must be at or above 50°C and exposure for at least 10 minutes to kill 100% of scabies mites and eggs. In cooler water (<50°C) mites and eggs survive. Detergent or Ozone treatment have no killing effect. Dry heat for 30 min (e.g. in a dryer) is another way to eliminate mites and eggs on textiles. Other mechanisms to achieve temperatures ≥50°C including ironing or sunlight exposure may also be effective but have not been proven. When exposed to freezing temperatures of -18°C and -10°C for more than 5 hours, 100% of mites are killed.[39]
Head lice and body lice killing strategies	100% head lice mortality is achieved when:[40] • clothes and bedding are washed at 50°C (with or without detergent); ***or*** • clothes and bedding are tumble-dried at high temperature for more than 40 minutes.
Access to functioning household washing machines	Some programs to help people keep their washing machines working appear to have been effective. For example, the '*Washing machine djäma*' East Arnhem Spin Project included regular servicing of washing machines, facilitating loans for households to purchase new machines, stocking of spare parts in communities for quick repair, training programs for local workers to undertake repairs, and social marketing campaigns. Following inspection, 87 existing machines were repaired across five communities.[41] Other initiatives offer no-interest loans for eligible low-income families which can be used to purchase washing machines.[42] No evaluation of the health impact of this loan program has been conducted. Some studies exploring the provision of washing machines to families as part of healthy skin programs are planned but not yet conducted.[43]
Access to community laundromats	Lack of access to household washing machines has prompted a range of initiatives to build community laundromats, particularly in remote areas. Many laundromats have been built, however there has been little evaluation of the health impacts.[44-46] A contemporary laundromat program was initiated by the Aboriginal Investment Group (AIG) in 2019. The AIG Remote Laundries Project aims to reduce instances of scabies, trachoma and RHD while improving school attendance and contributing to community employment opportunities through the provision of community laundromats. Large converted shipping containers accommodate four washers and dryers linked to soap and water, with room for laundry preparation and folding.[46]
Build, repair and maintain houses which support washing of clothes and bedding	Houses which are well-built and maintained make it easier for people to wash. Poor construction, low-quality materials and poor maintenance of housing are common, particularly in some remote communities.[47] Working with community councils and governments to ensure quality housing according to the National Indigenous Housing Guide can help improve washing facilities.[48]

Healthy living practice 3 – removing wastewater safely

Removing wastewater includes drainage from the bathroom, kitchen and laundry. There is no evidence that wastewater disposal reduces Strep A infection. Likewise, there is no evidence that Strep A is transmitted through contaminated water or human faecal matter.[38]

A study in remote Northern Territory published in 2005 found houses without functional facilities for removing wastewater had higher rates of skin sores.[57] However, this is correlation rather than causation. Skin sores are more common in crowded households.

Housing is a human right[58] and facilities for removing wastewater are fundamental to fulfilling this right.[58] Safe water management is important for preventing a range of infectious diseases and should be part of any comprehensive environmental health approach.

Healthy living practice 4 – improving nutrition, the ability to store, prepare and cook food

It is not clear whether poor nutrition increases the risk of Strep A infections, ARF and RHD.[1] People who have poor nutrition may have reduced immune function which could increase the risk of Strep A infection. On the other hand, the post-infectious consequences of Strep A infection (ARF, RHD and acute post-streptococcal glomerulonephritis [APSGN]) are typified by an abnormal and exaggerated immune response. Improving nutrition is broadly beneficial to health and wellbeing so efforts to improve nutrition are justified. In the meantime, further studies may throw more light on the relationship between nutrition and community levels of Strep A infection, ARF and RHD.

Strep A transmission causing sore throat is possible through contaminated food.[59,60] However, this appears to be rare and is not the major contributor to Strep A infections for Aboriginal and Torres Strait Islander peoples in Australia.

Healthy living practice 5 – reducing the negative impacts of overcrowding

Household crowding sees large numbers of people living in confined environments with limited household resources. However, the impacts of people living together include biological, psychological and cultural determinants.[61] These can have negative and positive implications, particularly as close living is considered a strength in some cultures.[62] On this basis, household crowding could equally be considered 'close living' behaviour.[63]

Reducing the negative impacts of household crowding ('overcrowding') has a strong association with reducing Strep A infections. Living in a crowded household may be associated with some health benefits,[62] but also health risks, including increased risk of Strep A infections, ARF and RHD. The risk of Strep A, ARF, and RHD in crowded households has been shown to be up to 1.7 – 2.8 times higher compared to uncrowded households.[1] However, defining and measuring crowding can be complex and identifying risk to individuals is difficult.[64]

Table 4.4. Strategies to address household crowding

Additional housing	As an isolated strategy, building more houses may not solve the problem of household crowding. For example, building a new house may mean that families move from houses which are not necessarily crowded but do not have functional facilities. Moreover, additional houses with functional facilities may perversely drive crowding if new construction is not coupled with repair and maintenance of existing houses.[65] In the Housing Improvement and Child Health Study, new houses were built in 10 Northern Territory communities between 2004 and 2005, with an average of 11 new houses per community (range: 7–15).[66] No concurrent renovation or hygiene programs were conducted. The construction of new houses did not reduce household crowding (defined as the mean number of people per bedroom in the house on the night before the survey) at a population level. At a household level, reductions in the number of people per bedroom in one study did not statistically reduce the risk of skin infections.[16]
Modified existing housing	In addition to the need for additional houses, it is essential to improve existing housing stock to reduce the functional impact of overcrowding.[65] A variety of programs have attempted to increase access to functional living space, including addition of more bedrooms and verandas and more functional yard space.[65,67] It is not clear whether this has an impact on the risk of skin sores.

Table 4.4. Strategies to address household crowding (continued)

Behaviour change – safe sleeping	Reasonable approaches to reducing bedroom transmission of Strep A could include having a 'safe sleeping zone' around the nose and mouth to reduce upper airways transmission / acquisition of Strep A, avoiding bed sharing, sleeping head-to-toe or sleeping further apart. The specifications for this advice are unknown, including safe sleeping distances. Further research co-designed with communities is needed to identify potential cultural adaptations and define biologic plausibility. Of course, in overcrowded houses, people often sleep on mattresses or blankets in the kitchen, hallway or on the verandas. In the absence of sufficient housing, people living in crowded circumstances may want advice about how to reduce the risks of close contact living. Information about the reality of living with 'big families and small houses' with inadequate infrastructure is clearly needed.[68] One option may be to rearrange bedsharing so that younger people who are at greatest risk of Strep A infection and ARF are not all in one bed together. Historic studies indicated that moving beds further apart reduced the number of new Strep A infections in military barracks.[69] In a New Zealand study of household crowding, 49% of children with ARF shared a bed with other people; conversely only 19% of children who did not have ARF shared a bed with other people.[70] However, the association between bed-sharing and ARF in New Zealand does not appear to be significant in multivariate analysis in a case control study.[71] In New South Wales, children who have had ARF are encouraged to sleep 'head-to-toe' if they are sharing a bed, to reduce people breathing and/or coughing on each other at night to reduce Strep A transmission. However, the effect of this approach is not clear.[72]
Behaviour change – respiratory hygiene	Exposure to respiratory droplets can be reduced by changes in behaviour. Health promotion and school-based education that targets respiratory hygiene (covered coughing/sneezing, use and disposal of tissues for nasal secretions, and clean faces) could help reduce respiratory transmission of Strep A.[73] Covering the mouth when sneezing and coughing reduces the spread of Strep A.[69] Minimising contact with nasal discharge - which can transmit Strep A bacteria - may also reduce Strep A infections.[74] Some respiratory hygiene messages align with the key messages for other diseases, including trachoma where the evidence base for face washing is relatively more developed.[75] It may be possible to align these health promotion goals into comprehensive hygiene messaging which improves hygiene behaviours to reduce the transmission of multiple diseases. The impact of this approach has not yet been evaluated in real world settings for the prevention of Strep A transmission.

Healthy living practice 6 – reducing the negative effects of animals, insects and vermin

Animals, insects and vermin have a range of effects on health outcomes. In some Aboriginal and Torres Strait Islander communities, dogs are recognised as providing protection, companionship and having cultural meaning.[76,77]

Historically, dogs are both companions and hunters for many Aboriginal and Torres Strait Islander communities, however the place of dogs in contemporary society is complex and contested.[77]

Strep A is a human-only pathogen; there is no evidence that Strep A can be transmitted between animals and humans.[38] There is also no evidence that the scabies mites that infest dogs (*Sarcoptes scabiei* var. *canis*) can also infest humans.[78,79] However, dog scabies may rarely cause a temporary skin itch in humans, possibly associated with skin damage.[80] The belief that skin problems in dogs are associated with significant skin infections in humans is widespread but not supported by currently available evidence.[81]

Insect bites cause localised skin itch which can lead to scratching and skin damage. When small bite wounds become infected with Strep A, they often progress to impetigo (skin sores).

Table 4.5. Strategies to reduce the negative effects of animals, insects and vermin

Animal management	A range of animal management programs exist in remote Aboriginal and Torres Strait Islander communities, and are generally focused on improving both animal and human health.[80] Elements to improve human health include education, hygiene and handwashing after contact with dogs, and reducing bed-sharing with dogs. A small number of these programs have been evaluated and show improvement in both human and dog health.[81]
Insect screening	Guidelines for reducing mosquito, midge, and other bites in remote communities include the use of appropriate clothing, mosquito nets and household window screens.[82,83] Recommendations developed for a remote Northern Territory community with a high mosquito burden suggest that '*The best method of avoiding attack at night is to stay inside insect-screened houses*' and that '*Screens should be of the correct mesh, fit tightly and be in good repair*'.[84] However, access to functioning window screening is limited in remote Aboriginal and Torres Strait Islander communities.[85,86] Working to increase household screen access may reduce insect bites and subsequent skin infections. Health promotion campaigns may give people the information they need to protect themselves from biting insects. For example the '*Fight the Bite*' campaign is an initiative of the Western Australia Department of Health, to prevent against mosquito-borne diseases.[82] The program appears to be effective in providing some information to reduce the risk of bites through clothing and insect repellent use.[87]

Healthy living practice 7 – reducing the health impacts of dust

In general, dust is not likely to be a major driver of Strep A skin or throat infection. Strep A is not transmitted through outside environmental dust. The dust inside houses may contain Strep A bacteria but it is not clear whether this dried form of Strep A can subsequently cause infection.[88,89]

Healthy living practice 8 – controlling the temperature of the living environment

Overall, temperature and climate are likely to have an effect on the risk of Strep A infection, with the seasonal variation in rates of Strep A infections reported internationally.[90] In some settings, rates are higher in colder times and are attributed to greater household crowding, while in other settings (including non-tropical parts of Australia), rates are higher in warmer months, attributed to more opportunities for skin breaches e.g. from bare feet.[90] Yet, infection rates appear to be sustained at high levels all year in remote Aboriginal and Torres Strait Islander communities in Australia.[90] In cold climates (such as Australia's central desert area), cold may be a driver of increased bedroom density at night, and thus for increased Strep A transmission.

In New Zealand, public health messaging includes statements such as: 'In a warm, dry home the family may have more space to spread out around the home, rather than having to crowd in the same room. Having more warm rooms and more sleeping spaces available means germs such as strep throat, which can lead to rheumatic fever, are less likely to spread.[91] Therefore low-income home owners affected by ARF in New Zealand are eligible for government-funded household insulation.[92] However, the effectiveness of this strategy for reducing ARF rates or outcomes is unknown.

Healthy living practice 9 – reducing minor trauma

Some people live in houses which are overcrowded, poorly maintained and contain rubbish and debris.[93] This may increase the risk of minor skin damage from cuts and abrasions. This skin damage may become infected with Strep A.

Table 4.6. Strategies to maintain tidy home environments to minimise risk of minor trauma

House and yard tidy days	Several initiatives exist encouraging households to clean up their homes and yards to the benefit of their health. Environmental Health Workers, where available, are encouraged to promote community and yard clean-ups as part of their responsibilities at least annually to prevent the build-up of stagnant water and limit the attraction of vermin.[94] In cyclone-prone regions, the regular removal of unrestrained items such as cars, washing machines and refrigerators is particularly necessary as these items can become projectiles during significant winds.[94] Clean-ups can be encouraged at regular community meetings with additional collection supplies arranged if required.[94] Achieving and maintaining a tidy yard and house can be challenging.[95] Some families with a large number of visitors may not be able to secure the co-operation of visitors or tenants to maintain usual hygiene standards. Other people may be physically unable to maintain a tidy yard, including removing large objects or accessing tools or trailers to complete the work.[95]
Home maker and home management programs	A range of home maker, home management and family support programs have been developed in Australia. Many of these programs focus on keeping the inside of houses clean and tidy by reducing house and yard debris, alongside other health promotion messages.[96] These programs may help reduce minor skin trauma but no health evaluation has demonstrated this in practice.

Culture and workforce considerations to help address social determinants of health in the context of ARF and RHD include:

- **Locally acceptable and feasible strategies to address the social determinants of health.**
- **Dedicated Aboriginal and Torres Strait Islander Environmental Health Workers employed in high-risk communities.**
  - **Environmental health and housing assessment and action for people with Strep A infections.**
- **Culturally appropriate, respectful and practical information and support for reducing risk factors for Strep A infections available where required/requested.**
  - **Hand and body washing promoted by school, education and housing sectors.**
  - **Provision of adequate washing hardware for people, clothes and bedding.**
  - **Health and government services work with community groups to address the environmental and social determinants of health which drive Strep A infections.**
- **Established cross-sector collaboration of departments and activities.**

CASE STUDY

The Murdi Paaki Healthy Housing Worker Program in NSW offers training to Aboriginal and Torres Strait Islander people to develop environmental health, maintenance and construction skills, enabling quick and efficient carpentry, plumbing and electrical repairs to be carried out on homes.[a] Training is delivered by The Batchelor Institute over two years. The aim of the program is to minimise housing and health hardware deterioration and lessen the effects of housing-induced illness and injury.

The Murdi Paaki program addresses the low numbers of skilled tradespeople in rural and remote communities, meaning sewerage, ventilation, hot water and plumbing problems often go unrepaired for extended periods of time, negatively impacting household health. There is a known link between 'Healthy Living Practices' upon which the Murdi Paaki program is based, and child health outcomes, with specific reference to skin disease.[b]

By having a local Aboriginal and Torres Strait Islander workforce to maintain housing, local capacity is developed and there is less reliance on external influence.[c] Local employment, individual self-esteem and labour competitiveness is enhanced, alongside improved living conditions.

Trainees work alongside qualified environmental health staff and tradespeople, guided by a standardised survey tool that systematically assesses criteria within each household. Resources and equipment, including personal protective items are provided.

Several outcomes of the Murdi Paaki have been identified: improved housing maintenance and functionality, with a quicker response to required repairs; an evident intent of stakeholders to ensure further longevity of these homes, increasing the maximum life of remote Aboriginal housing; improved employment prospects for trainees; and increased self-confidence among employees, and a newfound place within the community. Community members also saw value in having an Indigenous worker working within the local community.

This program has several replicable features, including leadership, local coordination and support, relationship and trust, capacity building within the community, and funding and support.[d] The program has succeeded in improving ownership of homes, reducing rates of disrepair and beneficially impacting upon community health.

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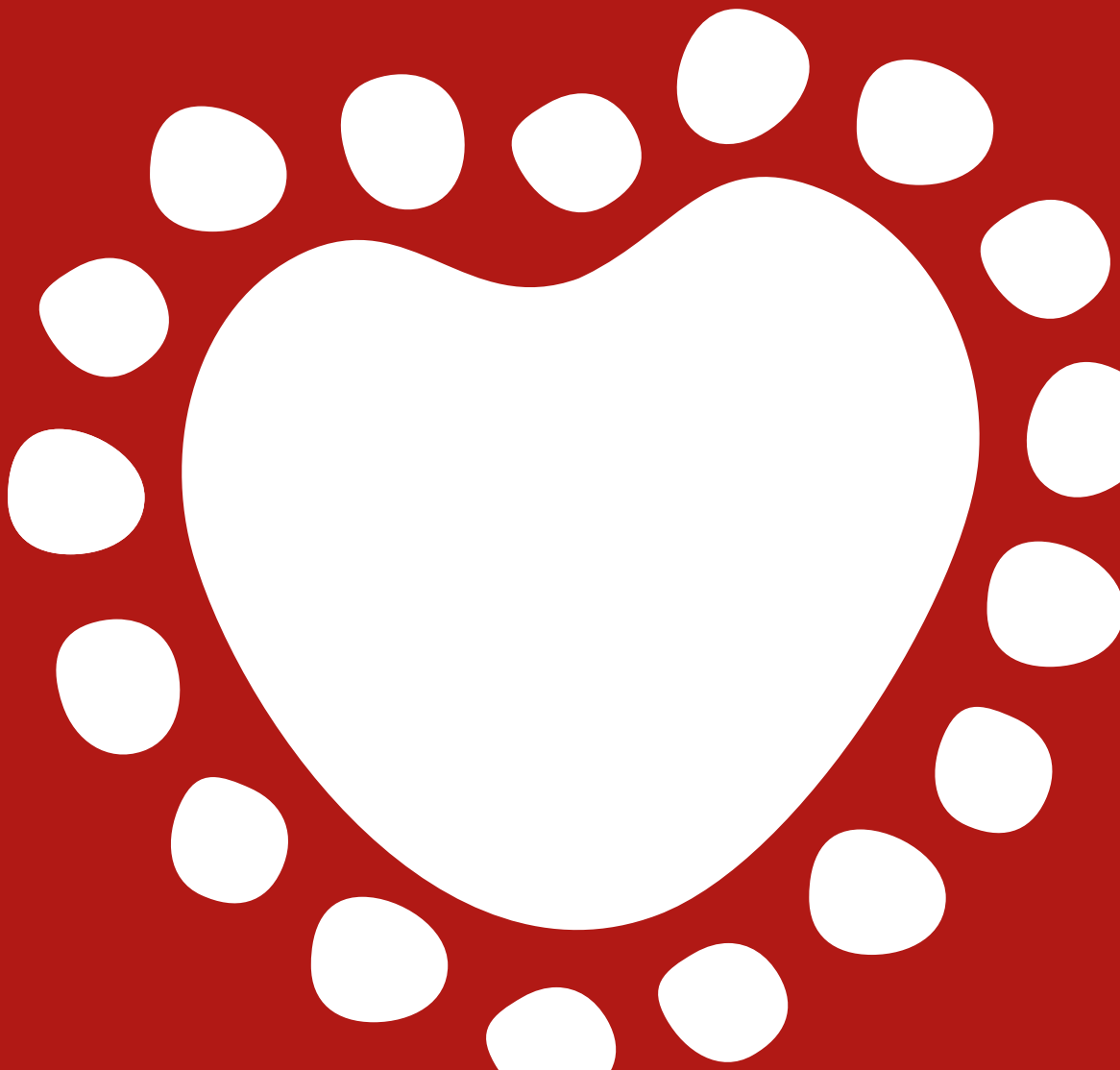
CHAPTER 5

Primary prevention



Primary prevention

CHANGES FROM THE SECOND (2012) EDITION

1. Updated definition of high-risk groups for acute rheumatic fever (ARF).
2. New recommendations for management of Strep A skin infections to prevent ARF.
3. The term *benzathine benzylpenicillin G* (BPG) replaces *benzathine penicillin G.*
4. BPG dosing has been streamlined to three dose bands for simplicity compared to the previously recommended five dose bands *(Table 5.2 and Table 5.3)*.
5. Tablet dosing is provided for use of cotrimoxazole for Strep A impetigo if syrup is in short supply *(Table 5.3)*.

KEY INFORMATION

- Primary prevention of ARF aims to interrupt the link between Strep A infection and the abnormal immune response to Strep A that causes ARF, by early identification and treatment of Strep A infections.
- Strep A has been shown to be associated with up to 37% of throat infections.[1] Strep A is only one cause for tonsillitis. Strep A is present in 10% to 40% of children presenting with a sore throat.[2]
- Treatment of the Strep A sore throat in those at risk of ARF can decrease the subsequent development of ARF by up to two-thirds.[3]
- Not everyone who gets exposed to Strep A becomes symptomatic with a sore throat. Some people may become Strep A carriers.
- Strep A has been shown to be associated with up to 82% of impetigo episodes.[4,5] Strep A impetigo is very common among Aboriginal and Torres Strait Islander children living in remote areas, with almost one in two affected at any one time.[6] Identification, treatment and prevention of Strep A skin infections may help reduce the burden of ARF.
- Individuals already receiving BPG secondary prophylaxis still need active treatment of sore throats or skin sores. This is necessary because the level of penicillin achieved by BPG wanes by about 7 days to reach a prophylactic level which is lower than a required treatment level. If the last BPG dose was ≥7 days ago, provide antibiotic dosing in accordance with *Table 5.2* for sore throat or *Table 5.3* for skin sores.

Table 5.1. Risk groups for primary prevention of ARF

At high risk	Living in an ARF-endemic setting†
	Aboriginal and/or Torres Strait Islander peoples living in rural or remote settings
	Aboriginal and/or Torres Strait Islander peoples, and Māori and/or Pacific Islander peoples living in metropolitan households affected by crowding and/or lower socioeconomic status
	Personal history of ARF/RHD and aged <40 years
May be at high risk	Family or household recent history of ARF/RHD
	Household overcrowding (>2 people per bedroom) or low socioeconomic status
	Migrant or refugee from low- or middle-income country and their children
Additional considerations which increase risk	Prior residence in a high ARF risk setting
	Frequent or recent travel to a high ARF risk setting
	Aged 5-20 years (the peak years for ARF)

† This refers to populations where community ARF/RHD rates are known to be high e.g. ARF incidence >30/100,000 per year in 5–14-year-olds or RHD all-age prevalence >2/1000 *(Figures 3.3 and 3.4)*[7]

Table 5.2. Recommended antibiotic treatment for Strep A sore throat / tonsillitis†

DRUG	DOSE		ROUTE	FREQUENCY
All cases				
Benzathine benzylpenicillin G (BPG)	**Child:**		Deep IM injection	Once
	Weight (kg)	**Dose in IU (mL)**		
	<10	450,000 units (0.9 mL)		
	10 to <20	600,000 units (1.2 mL)		
	≥20	1,200,000 units (2.3 mL)		
	Adult:			
	≥20	1,200,000 units (2.3 mL)		
If IM injection not possible:				
Phenoxymethylpenicillin	**Child:** 15 mg/kg up to 500 mg, bd **Adult:** 500 mg, bd		Oral	For 10 days
For patients with documented hypersensitivity to penicillin e.g. rash				
Cefalexin	**Child:** 25 mg/kg up to 1 g, bd **Adult:** 1 g, bd		Oral	For 10 days
For patients anaphylactic to penicillin				
Azithromycin	**Child:** 12 mg/kg up to 500 mg, daily **Adult:** 500 mg daily		Oral	For 5 days

† Antibiotic treatment indicated for proven Strep A infection, and for people at high risk of ARF presenting with sore throat.

Table 5.3. Recommended antibiotic treatment for Strep A skin sores

DRUG	WEIGHT RANGE	DOSE			ROUTE	FREQU-ENCY
	All children with ≥1 purulent or crusted sore(s)					
Cotrimoxazole (trimethoprim / sulfamethoxazole) 4 mg/kg/dose trimethoprim component	**Weight range**	**Syrup dose (40 mg/5 mL)**	**Tablet dose SS (80/400 mg)** †	**Tablet dose DS (160/800 mg)** †	Oral	Twice daily for 3 days
	3-<6 kg	12 mg (1.5 mL)	N/A	N/A		
	6-<8 kg	24 mg (3 mL)	¼ tablet			
	8-<10 kg	32 mg (4 mL)	½ tablet			
	10-<12 kg	40 mg (5 mL)				
	12-<16 kg	48 mg (6 mL)	¾ tablet			
	16-<20 kg	64 mg (8 mL)				
	20-<25 kg	80 mg (10 mL)	1 tablet	½ tablet		
	25-<32 kg	100 mg (12.5 mL)	1 ½ tablets	¾ tablet		
	32-<40 kg	128 mg (16 mL)				
	≥40kg	160 mg (20 mL)	2 tablets	1 tablet		
Benzathine benzylpenicillin G (BPG)	**Child:** Weight <10 kg 10 to <20 kg ≥20 kg **Adult:** ≥20 kg			 Dose in units (mL) 450,000 units (0.9 mL) 600,000 units (1.2 mL) 1,200,000 units (2.3 mL) 1,200,000 units (2.3 mL)	Deep IM injection	Once

† Cotrimoxazole comes as syrup (40 mg trimethoprim/5 mL) and tablets. The tablets are single strength (SS) (80/400 mg trimethoprim/ sulfamethoxazole) or double strength (DS) (160/800 mg trimethoprim/ sulfamethoxazole). When syrup is unavailable, tablets may be crushed and dissolved in water for small children as per the table above.

IM; intramuscular, BD; twice a day

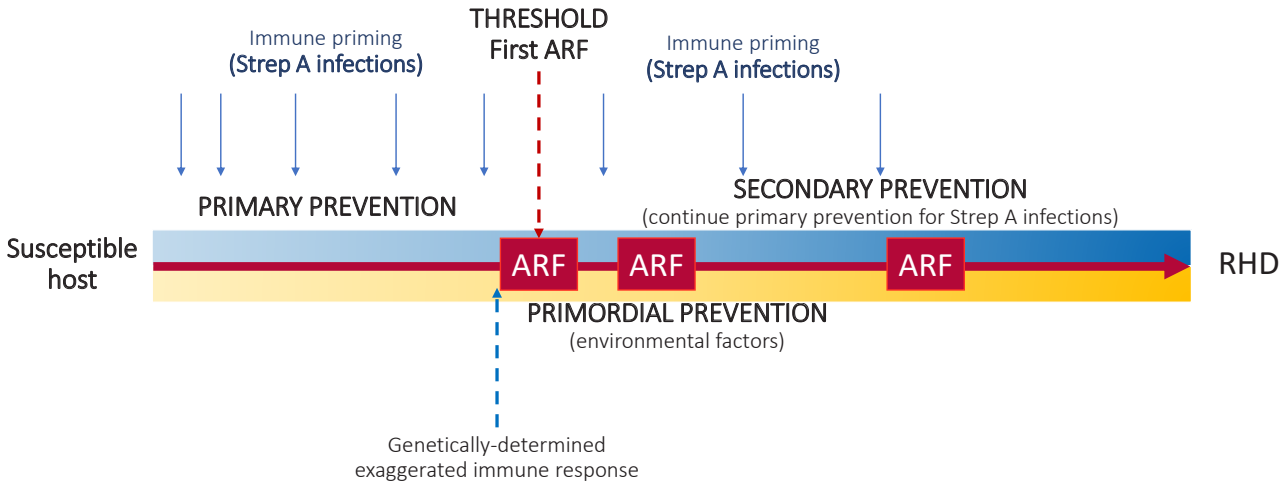
DISCUSSION

"In order to end RHD we need to build a stronger and better Aboriginal workforce in primary health care, one that is supported and valued."

Champion, *RHDAustralia Champions4Change program*, 2019.

Primary prevention of ARF involves the identification and subsequent treatment of Strep A infections in patients at high risk of ARF and RHD. *Figure 5.1* outlines the pathways by which multiple Strep A infections of the throat and / or skin can prime the immune system[8,9] for subsequent development of ARF and RHD. Interrupting this process by identification and treatment of Strep A infections is the key activity of primary prevention. ARF is the result of a specific, abnormal and exaggerated immune response to Strep A.

Figure 5.1. Pathway for ARF and RHD with immune priming



This figure illustrates that primordial prevention must be prioritised at all points to interrupt the pathway towards RHD. Primary prevention activities identify and treat all Strep A infections in high-risk children and are important in preventing the first episode of ARF. Once ARF has been diagnosed, maintenance of consistent, regular secondary antibiotic prophylaxis is implemented, *(Table 10.1)* with primordial and primary prevention activities continuing to operate at the individual and community level.

ARF is preventable. The evidence for this comes from two key observations:

1. On the global level, ARF was previously common around the world. The incidence of ARF dramatically declined in developed countries during the first half of the 20th century. This has been attributed largely to primordial prevention with advances in housing, education, health literacy and employment.[10]
2. In highly controlled settings such as United States military barracks, antibiotic treatment of Strep A throat infection, up to nine days from the onset of symptoms, has been shown to reduce the incidence of ARF.[11-13]

Evidence collected since the early 1900s shows that throat infections (tonsillitis) with Strep A, both clinical and subclinical, precede and cause ARF in specific human hosts. Early research in ARF highlighted the importance of early treatment of Strep A sore throats (up to nine days from the onset of symptoms)[13] for the prevention of ARF. Treatment for Strep A throat infections to prevent ARF is well-evidenced and forms the basis of primary prevention of ARF.[11-13]

The proposal that Strep A skin infection can also lead to ARF dates from the early 2000s.[14] Strep A skin infection is known as impetigo or skin sores. The additional element of identification and treatment for Strep A skin infections as part of primary prevention of ARF is included in this edition based on the following evidence:

1. The median prevalence of Strep A skin sores among Aboriginal and Torres Strait Islander children living in remote settings is 44.5% [interquartile range 34.0 – 49.2%];[6,15]
2. The incidence of Strep A sore throats among remote-dwelling Aboriginal and Torres Strait Islander children is relatively low at ~ 4/100/year;[14]
3. The incidence of ARF among these groups continues to be high; and
4. There is emerging evidence from New Zealand where ARF diagnosis has followed a recent skin infection.[16,17]

Knowing which populations are at elevated risk of ARF and providing early treatment of Strep A infections can prevent ARF and subsequently RHD, from occurring. In Australia, such populations include children aged between five and 20 years who are Aboriginal and Torres Strait Islander, Māori or Pacific Islander, first-generation migrants and refugees from low- and middle-income countries where rates of ARF and RHD are high *(Table 5.1)*.[18] In Australia, more than 90% of new ARF cases are diagnosed in Aboriginal or Torres Strait Islander children.[7] Increased resources and research at primary healthcare service level can improve recognition, prevention and treatment of ARF. Primary prevention relies on all health staff being aware of the risk factors for ARF and providing treatment for all people with sore throats or skin sores who are at high risk of ARF.

Strep A only infects humans and is transferred from person to person; it is not transmitted to humans from insects, dogs, wild animals or water. When people are colonised with Strep A, they do not necessarily become infected but colonised people can pass Strep A on to other people. Infection with Strep A ranges from mild to severe, and even rapidly fatal, for instance invasive Strep A infections with bacteraemia. Many mild infections may be subclinical; and people with mild infections may not seek medical attention. This chapter focuses on identification and treatment of the superficial Strep A infections of sore throat and skin sores as the key strategies of primary prevention of ARF and RHD.

Strep A transmission from person to person is increased when there is household crowding, especially when poorly maintained housing conditions make hygiene difficult. Strep A is especially shared around households where there are children with respiratory infections and skin conditions such as skin sores, scabies and head lice.

Vaccines to prevent Strep A infection have been in various stages of development in several countries since the early 20th century. The large number of Strep A strains makes vaccine development challenging.[19] There are several potential vaccine candidates in the pipeline, including from Australia (See *Chapter 14. New Technologies, Strep A Vaccine Development*).

Strep A throat infections

Colonisation (carriage)

Colonisation or carriage is defined as Strep A cultured from the throat in the absence of symptoms or signs of tonsillitis.[1] Reported throat colonisation rates of Strep A in Australian children vary from <5% in some remote Northern Territory communities[14] to 15% in an urban setting.[20]

Infection (tonsillitis or sore throat)

The acquisition of Strep A (infection) and multiplication of Strep A organisms in the tonsils usually causes clinical symptoms *(Table 5.4)*. This is typically associated with an immunological response i.e. a rise in Strep A serological titres e.g. antistreptolysin O (ASO), anti-DNase B (ADB).

Individuals already receiving BPG secondary prophylaxis still need active treatment of sore throats or skin sores. This is necessary because the level of penicillin achieved by BPG wanes by about 7 days to reach a prophylactic level which is lower than a required treatment level. If the last BPG dose was ≥7 days ago, provide antibiotic dosing in accordance with *Table 5.2* for sore throat or *Table 5.3* for skin sores.

Figure 5.2. Strep A infection of the throat

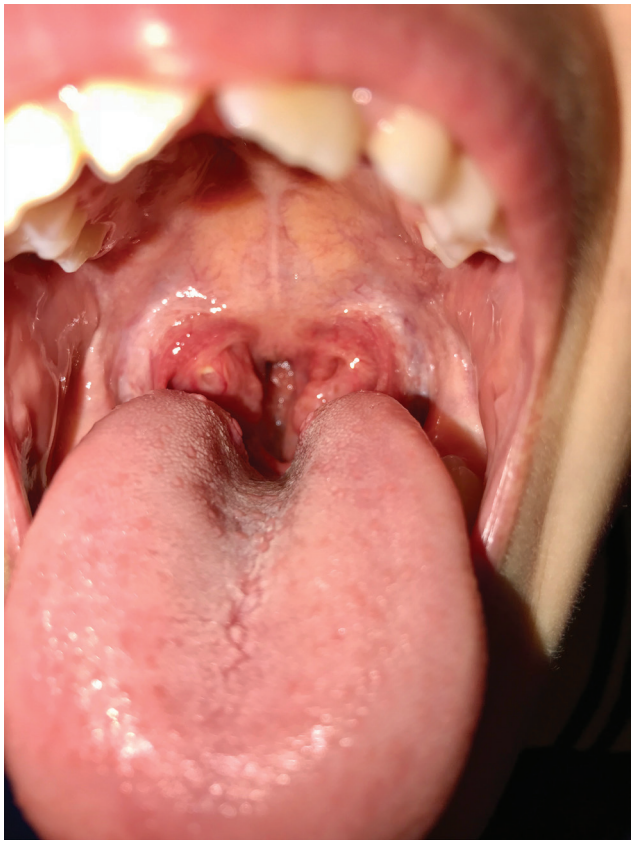


Photo courtesy of Associate Professor Asha Bowen from the Skin Sore Trial[15]

Symptoms and signs

Table 5.4. Symptoms and signs of a sore throat / tonsillitis

Symptoms	Signs
Throat pain / sore throat	Fever (> 38°C)
Difficulty swallowing	Swollen, enlarged tonsils
Not eating as much	Erythematous tonsils with exudate
Not drinking as much	Enlarged, tender cervical lymph nodes
Croaky voice	Absence of cough
Feeling hot	

Symptoms derived from the Aboriginal Sore Throat Story (Sampson C *et al, Australasian Society for Infectious Diseases Annual Scientific Meeting 2019 poster presentation*). Signs derived from the Modified Centor Score.[21]

Where possible, clinicians should consider referral to environmental health, housing or legal services if available and needed, where high risk of ARF has been identified because of homelessness, household crowding, or poor household maintenance.

(See *Chapter 4. Primordial Prevention and Social determinants of ARF*)

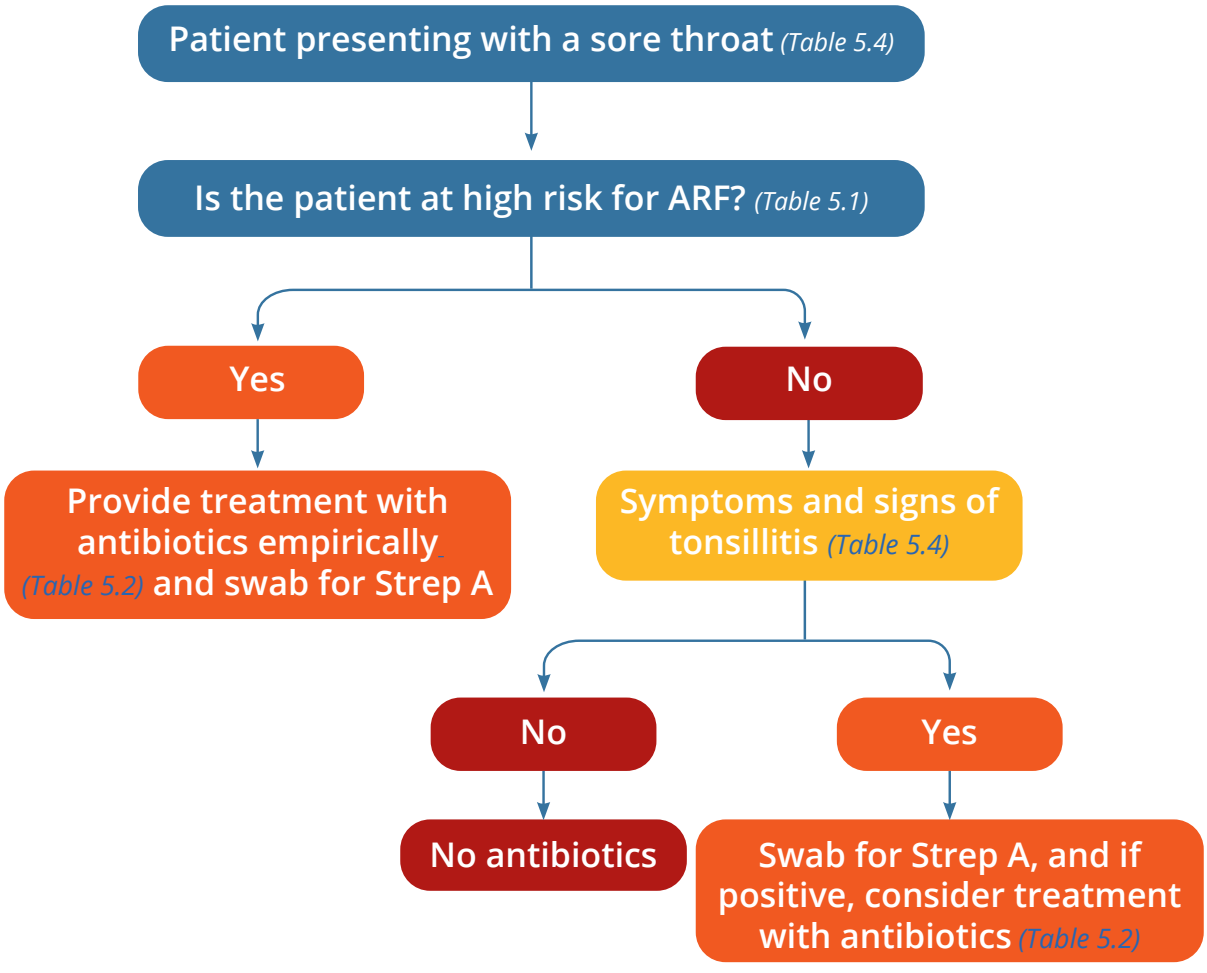
Clinical scoring of sore throats

Several international clinical scoring methods for predicting Strep A tonsillitis are available. Symptoms and signs are collated using a scoring system e.g. Centor Criteria (elevated temperature, tender anterior cervical adenopathy, tonsillar swelling or exudate, absence of cough or upper respiratory symptoms).[22-24] Patients with higher scores are classified as being at greater risk of Strep A infection and are therefore recommended to have a throat swab for culture and/or antibiotic treatment.

None of these clinical scoring methods have been validated in the Australian context where rates of ARF are high; however, research is ongoing. Previous validation studies of such scoring systems internationally have demonstrated relatively low positive and negative predictive values for the subsequent detection of Strep A from throat swab.[21,24]

Whilst this is the case, it is helpful for clinicians to have a diagnostic algorithm to follow in determining whether Strep A tonsillitis is likely. Until new evidence is available, the following algorithm provides guidance *(Figure 5.3)*.

Figure 5.3. Assessment for sore throat



The challenges of treating sore throats

Timely treatment of Strep A sore throats should prevent ARF, however, only some sore throats are caused by Strep A. Antibiotic treatment of all episodes of clinical tonsillitis would expose a significant proportion of patients to unnecessary medication. Depending on the setting, it is likely that only 20–40% of tonsillitis episodes are caused by Strep A.[2,25] The remainder are caused by viruses or by bacteria for which antibiotic treatment is not recommended.

Empirical antibiotic treatment of all Australian children presenting with a sore throat is not recommended. In addition to the unwarranted inconvenience, there is cost and potential risk from adverse medication events, while increasing the pressures that promote antibiotic resistance. However, people presenting with sore throat who are identified as being at high risk of ARF *(Table 5.1)* including people who have a history of confirmed ARF or established RHD, should be treated with antibiotics if they develop a sore throat, irrespective of other clinical features, and irrespective (at present) of any testing using rapid tests or culture for confirmation of Strep A infection.[26]

Awareness of the need for antibiotics to treat sore throats to prevent ARF is an important learning point for all health staff working with populations at high risk of ARF. Health staff will often be more familiar with guidelines that prevent overuse of antibiotics for sore throats.

Strep A skin infections

Skin sores or impetigo

The introduction of Strep A through a break in the skin (e.g. insect bite, scabies, head lice, tinea, minor trauma) can result in the development of skin sores (impetigo/pyoderma). Strep A skin sores are often round or linear, 1-2 cm in size and have pus or a thick crust evident *(Figure 5.4 and Figure 5.5)*. Strep A has been known since the 1970s as the predominant primary pathogen in skin sore development,[27] especially in tropical environments, with reinforcement of this important finding recently.[15,27] There is a clear relationship between the prevalence of skin sores in children and the level of household crowding.[28] Culture recovery of Strep A from skin sores reduces over time until swabs are processed for culture, with treatment and as development of the sores progresses from purulent to crusted. The timing of culture from sores could account for much of the variability in reported skin sore culture rates for Strep A.

Figure 5.4. Progression of impetigo from purulent, inflamed and crusted *(left)*, to crusted *(middle)* to flat and dry *(right)*

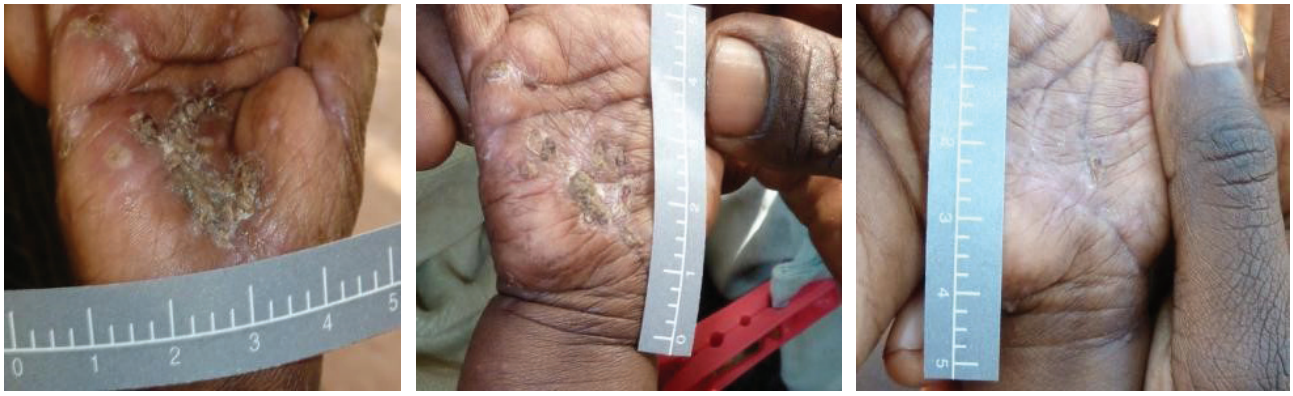
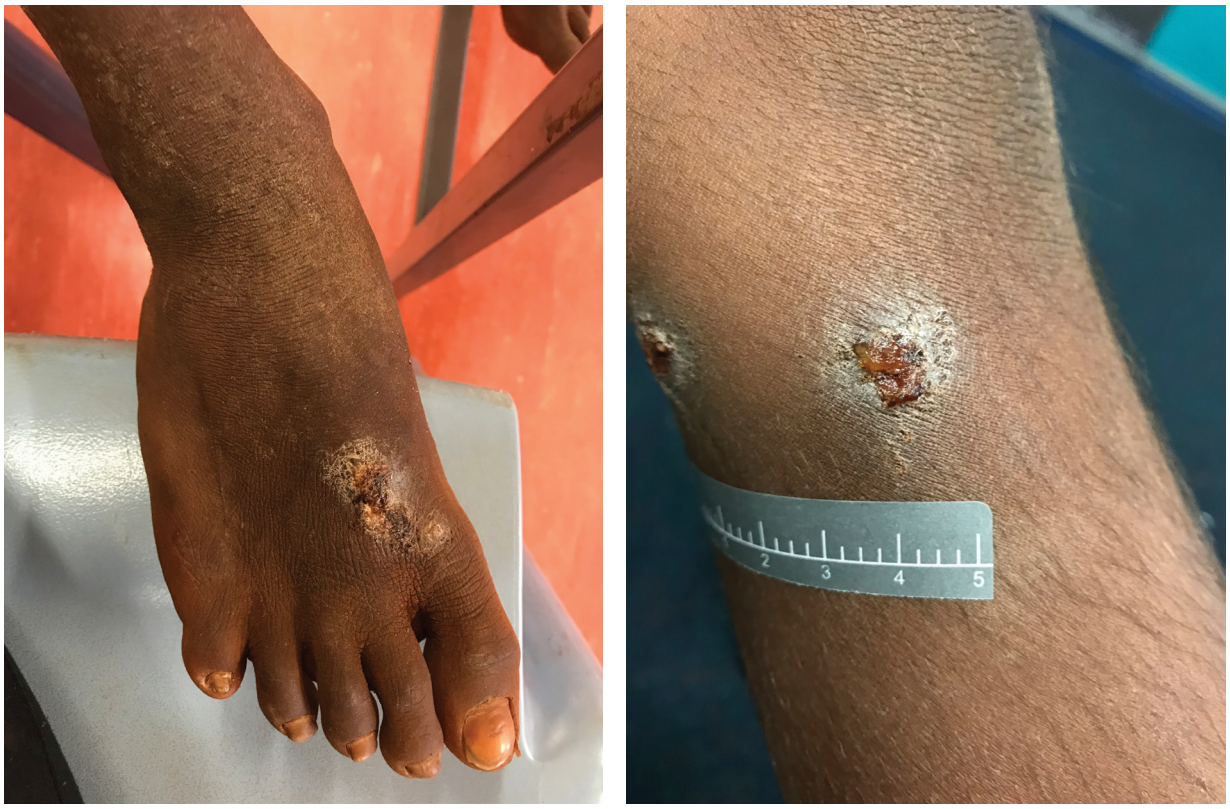


Photo courtesy of Associate Professor Asha Bowen from the Skin Sore Trial[15]

Figure 5.5. Strep A infections of the foot and leg



Photos courtesy of Associate Professor Asha Bowen from the Skin Sore Trial[15]

Antibiotic treatment of skin sores (impetigo)

In some settings,[4,14,29] Strep A skin infection is likely to play a direct and/or indirect role in the development of ARF/RHD. Improved skin health is also likely to have broader health impacts; in regions where there is a high concurrent burden of impetigo and ARF, it is likely that improved skin health activities will reduce the overall burden of Strep A-related diseases, including ARF.

Cotrimoxazole and BPG have been compared in a randomised controlled trial in Australian Aboriginal children. A three-day course of twice-daily or a five-day course of once-daily cotrimoxazole were found to be non-inferior to BPG for treatment of skin sores.[15] Cotrimoxazole had significantly fewer side effects, was well tolerated, and provides a pain-free alternative for treatment of skin sores for children. Work among Aboriginal and Torres Strait Islander groups in Western Australia's Pilbara region found that mothers and grandmothers prefer that treatment options are discussed with them, and they want to be involved in deciding the best solution for their child on each occasion.[30]

There is an ongoing need for culturally appropriate targeted, translational health education.[30] Health promotion material related to the identification and management of Strep A infections should be available for community members and health workers; developed with and by community members in appropriate language and using local metaphors, to increase health literacy and empower decision-making. (See KAMSC patient resources) **Partnerships between the clinic, community and schools to support children with skin sores by providing school-based education on the risk factors and community attitudes towards skin sores are likely to be beneficial.**

Streptococcal serology in high-incidence populations

The high prevalence of Strep A infections (mainly skin sores) in Aboriginal and Torres Strait Islander communities of northern and central Australia produces raised background titres of serum streptococcal antibodies.[31,32] In one study, the median titres of ASO and anti-DNase B in children of three remote Aboriginal communities were 256 and 3172 IU/mL, respectively.[32] Therefore, single measurements of streptococcal antibody serology to determine whether a Strep A infection is recent may be difficult to interpret in this population. However, data from a study in Fiji, which carefully excluded participants with a recent history of Strep A infection, and excluded extreme outlier values, found median and upper limits of normal for ASO and anti-DNase B to be similar to those found in non-Indigenous populations in Australia, and populations in the USA.[33,34] Therefore, the serum streptococcal antibody titres limits outlined in *Table 7.3* should be considered as normal values for both Aboriginal and Torres Strait Islander and non-Indigenous populations.

Strep A rapid diagnostics

Strep A rapid tests include rapid antigen detection tests (RADT) and molecular tests.[35] Current RADT are not as accurate as culture for detecting Strep A[36] and are not commonly used in Australia but are used elsewhere in the world. As RADT are not routinely available in northern Australia, treatment guidelines recommend timely antibiotic treatment for syndromes (sore throat, skin sores) potentially due to Strep A, without need for microbiological confirmation,[37] as microbiological diagnosis is often delayed (due to remoteness from laboratories). These treatment recommendations contrast with guidelines from low-endemic for ARF settings,[38] which discourage antibiotic use unless Strep A tonsillitis is confirmed by culture of a throat swab.

In high-risk populations where clinical follow-up may be difficult, empirical management of sore throat with antibiotics *(Table 5.2)* in those at greatest risk of ARF *(Table 5.1)* is warranted.

Simple, reliable, rapid point-of-care tests for detecting Strep A from throat and skin swabs could improve management[35] and may become more available in coming years. The new generation of rapid molecular tests such as polymerase chain reaction (PCR) may be at least as sensitive as culture, with results available in 5-25 minutes.[39] Some have already been approved for use by non-experts at the point of care to detect Strep A tonsillitis, outside of microbiology laboratories.[40,41]

The utility of clinical scoring systems, RADT and new molecular rapid diagnostic tests in predicting the presence of Strep A versus non-Strep A tonsillitis should be evaluated in Australia, particularly in Aboriginal and Torres Strait Islander communities.

The role of non-A strains of streptococci

Although Strep A is the dominant Streptococcus associated with the pathogenesis of ARF, there is debate about whether other strains of beta-haemolytic streptococci can cause ARF. In particular, group C streptococcus (GCS) and group G streptococcus (GGS) have been discussed in this context, because GCS and GGS can have similar M proteins and virulence factors as those seen in Strep A and can also acquire genetic elements from Strep A through horizontal gene transfer.[14] Given that infections with these organisms can also be associated with raised ASO and anti-DNase B titres,[42,43] their potential role in the pathogenesis of ARF in patients where Strep A is not isolated is worthy of further investigation.

CASE STUDIES

Treatment of Strep A tonsillitis to prevent ARF

Research from the 1950s in the United States military showed that antibiotic treatment of Strep A tonsillitis prevented ARF. Denny *et al*[12] followed 1602 servicemen admitted to hospital for tonsillitis; 798 received penicillin treatment while 804 controls received no treatment, with blinded follow-up three to four weeks after the initial infection. In the treated group, two patients developed definite ARF and two developed probable ARF (4/798, 0.9%). In the control group, 17 developed definite ARF (relative risk [RR] 8.4), and six developed probable ARF (RR 3.0) (23/804, 2.9%). Microbiological clearance of Strep A was higher in the treated group. A later study showed that even when penicillin treatment was delayed until nine days after the onset of illness when acute symptoms had subsided and when near maximal antibody response had occurred, it was still effective in preventing ARF.[13]

Population-based sore throat management

Sore throat management programs may be effective in a broader context than the military trial described, with reduced incidence and prevalence of ARF and RHD in Costa Rica[44] and Cuba[45] following primary prevention programs.[46] In Costa Rica in the 1970s, a program recommended that all people with clinical signs consistent with possible Strep A throat infections be treated empirically with intramuscular BPG.[44] This was associated with a sharp decline in ARF incidence (70/100,000 in the early 1970s, down to 1/100,000 in 1990), but other factors may have facilitated this as the decline commenced before an increased uptake in the use of BPG injections. A substantial decline in the occurrence and severity of ARF/RHD was reported in Cuba, following a 10-year prevention strategy.[45] A multidimensional strategy focused on the development of a registry and recall system for patients with ARF/RHD, and enhanced sore throat management,[47] was associated with an 80% decline in ARF incidence. None of these programs only involved sore throat management - secondary prevention of ARF/RHD, health education for the public and healthcare professionals, epidemiological surveillance, and implementation of a national healthcare plan were all included. The success of these programs is assessable only using historical surveillance data and no control groups exist, so it is difficult to accurately quantify the effectiveness of sore throat management strategies.[44]

The New Zealand Rheumatic Fever Prevention Program (RFPP; 2012–2017)[48] was one of the most ambitious ARF prevention programs ever conducted. It focused on sore throat management in schools using a widespread health promotion campaign. In addition, accessibility of sore throat treatment through primary care was enhanced. This approach reduced the incidence of ARF in a high-risk setting and further analysis will have lessons for improving primary prevention initiatives elsewhere in NZ and internationally.[49,50]

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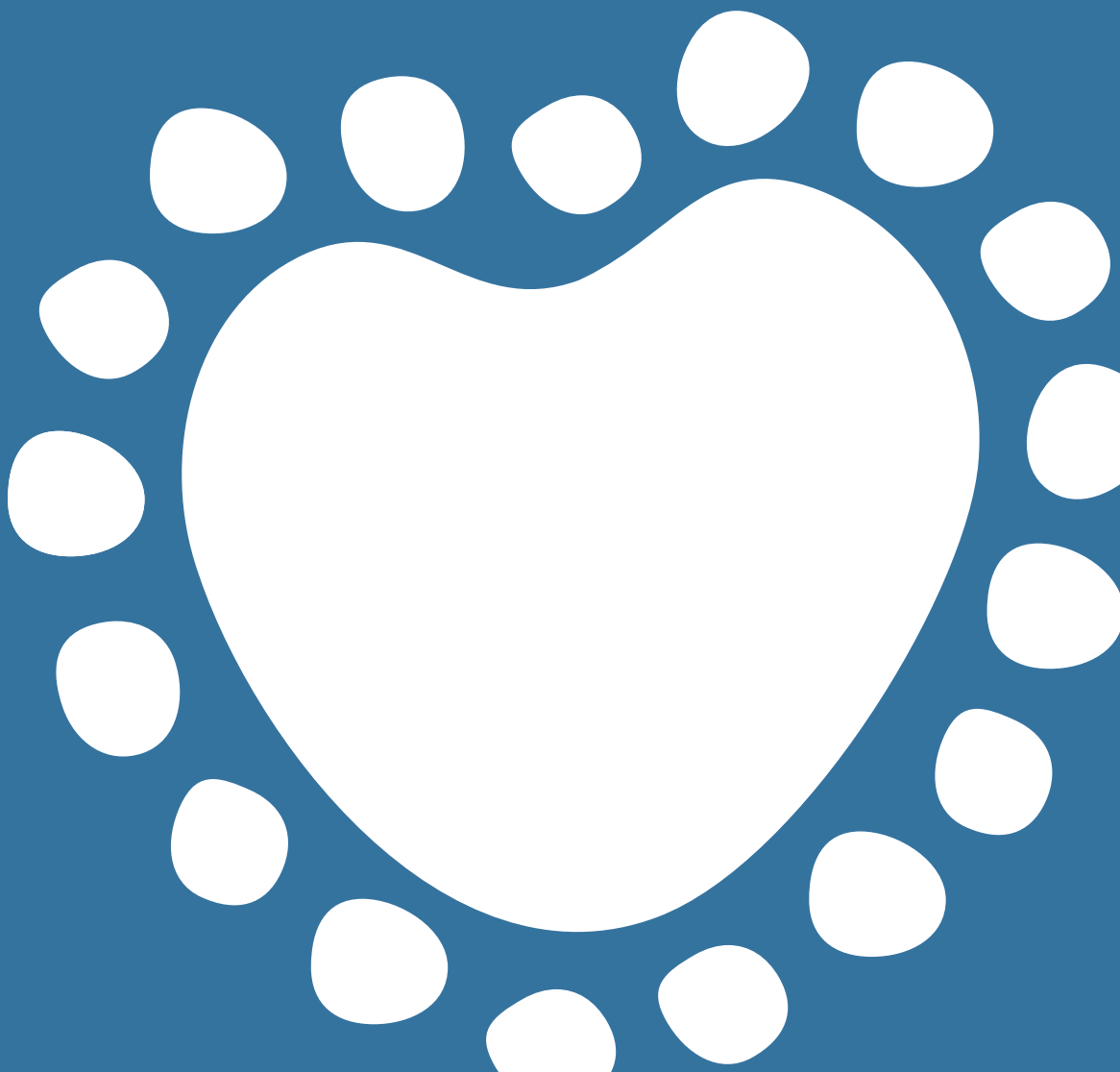
CHAPTER 6

Diagnosis of acute rheumatic fever



Diagnosis of acute rheumatic fever

CHANGES FROM THE SECOND (2012) EDITION

1. In low-risk populations, subclinical carditis is now a major diagnostic criterion.
2. In low-risk populations, erythrocyte sedimentation rate (ESR) as a minor criterion is now **≥60 mm/h** rather than ≥30 mm/h.
3. In low-risk populations, fever as a minor criterion is now **≥38.5°C** rather than ≥38.0°C.
4. For all populations, a definite recurrent episode of acute rheumatic fever (ARF) in a patient with documented history of ARF or rheumatic heart disease (RHD) now requires 2 major, or 1 major **and 2 minor,** or 3 minor criteria, (plus evidence of preceding Strep A infection) rather than 2 major, or 1 major and 1 minor, or 3 minor criteria.

KEY INFORMATION

- Failure to diagnose ARF results is a missed opportunity for secondary prophylaxis with benzathine benzylpenicillin G (BPG), increasing the risk of recurrent ARF and cumulative heart valve damage.
- If clinicians are expecting to find a collection of ARF diagnostic criteria simultaneously in one individual, they are likely to be missing people with mild ARF, such as those who present with joint pain and fever only.
- Patients with sterile joint aspirates should never be treated speculatively for septic arthritis without further investigation, particularly in areas with a high ARF/RHD prevalence.
- Over-diagnosis results in the individual receiving BPG injections unnecessarily and an increased use of health system resources.
- Anyone suspected to have ARF should be admitted to a hospital within 24-72 hours for echocardiography and specialist review.
- Echocardiogram is mandatory for all people with possible or confirmed ARF. Echocardiogram can enable a confirmation of ARF by demonstrating carditis which may not be clinically evident. It is also used to establish a baseline of cardiac status, and to determine whether valve damage (acute carditis or established RHD) is present and if so, to determine the severity.
- Electrocardiogram is also mandatory for all possible or confirmed ARF. While first degree heart block (prolonged P-R interval) is most common, advanced conduction abnormalities (second-degree heart block, complete heart block or accelerated junctional rhythm) occur in approximately 8% of those presenting with ARF *(Figures 6.4 to 6.8)*.
- For each episode, a final diagnosis should be reached and specified as either:
    - definite ARF (confirmed);
    - probable ARF (highly suspected);
    - possible ARF (uncertain);
    - definite ARF recurrence;
    - probable ARF recurrence;
    - possible ARF recurrence; or
    - not ARF.
- The final diagnosis and age of the patient determines the subsequent management recommendations, including need for and duration of secondary prophylaxis with BPG; frequency of follow-up echocardiograms; and frequency of primary care and specialist reviews *(Table 10.2, Table 7.4)*.

Table 6.1. Risk groups for ARF

At high risk	Living in an ARF-endemic setting†
	Aboriginal and/or Torres Strait Islander peoples living in rural or remote settings
	Aboriginal and/or Torres Strait Islander peoples, and Māori and/or Pacific Islander peoples living in metropolitan households affected by crowding and/or lower socioeconomic status
	Personal history of ARF/RHD and aged <40 years
May be at high risk	Family or household recent history of ARF/RHD
	Household overcrowding (>2 people per bedroom) or low socioeconomic status
	Migrant or refugee from low- or middle-income country and their children
Additional considerations which increase risk	Prior residence in a high ARF risk setting
	Frequent or recent travel to a high ARF risk setting
	Aged 5-20 years (the peak years for ARF)

† This refers to populations where community ARF/RHD rates are known to be high e.g. ARF incidence >30/100,000 per year in 5–14-year-olds or RHD all-age prevalence >2/1000 *(Figures 3.3 and 3.4)*.

Table 6.2. 2020 Updated Australian criteria for ARF diagnosis

	HIGH-RISK GROUPS†	LOW-RISK GROUPS
Definite initial episode of ARF	2 major manifestations + evidence of preceding Strep A infection, ***or*** 1 major + 2 minor manifestations + evidence of preceding Strep A infection‡	
Definite recurrent§ episode of ARF in a patient with a documented history of ARF or RHD	2 major manifestations + evidence of preceding Strep A infection, ***or*** 1 major + 2 minor manifestations + evidence of preceding Strep A infection‡, ***or*** 3 minor manifestations + evidence of a preceding Strep A infection‡	
Probable or possible ARF (first episode or recurrence§)	A clinical presentation in which ARF is considered a likely diagnosis but falls short in meeting the criteria by either: • one major or one minor manifestation, ***or*** • no evidence of preceding Strep A infection (streptococcal titres within normal limits or titres not measured) Such cases should be further categorised according to the level of confidence with which the diagnosis is made: • Probable ARF (previously termed 'probable: highly suspected') • Possible ARF (previously termed 'probable: uncertain')	
Major manifestations	Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram) Polyarthritis¶ or aseptic monoarthritis or polyarthralgia Sydenham chorea†† Erythema marginatum‡‡ Subcutaneous nodules	Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram) Polyarthritis¶ Sydenham chorea†† Erythema marginatum‡‡ Subcutaneous nodules
Minor Manifestations	Fever§§ ≥38°C Monoarthralgia¶¶ ESR ≥30 mm/h or CRP ≥30 mg/L Prolonged P-R interval on ECG†††	Fever ≥38.5°C Polyarthralgia or aseptic monoarthritis¶¶ ESR ≥60 mm/h or CRP ≥30 mg/L Prolonged P-R interval on ECG†††

† High-risk groups are those living in communities with high rates of ARF (incidence >30/100,000 per year in 5–14-year-olds) or RHD (all-age prevalence >2/1000). Aboriginal and Torres Strait Islander peoples 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 peoples living in urban settings, Māori and Pacific Islanders, and potentially immigrants from developing countries, may also be at high risk.
‡ Elevated or rising antistreptolysin O or other streptococcal antibody, or a positive throat culture or rapid antigen or nucleic acid test for Strep A infection.
§ Recurrent definite, probable or possible ARF requires a time period of more than 90 days after the onset of symptoms from the previous episode of definite, probable or possible ARF.
¶ A definite history of arthritis is sufficient to satisfy this manifestation. Note that if polyarthritis is present as a major manifestation, polyarthralgia or aseptic monoarthritis cannot be considered an additional minor manifestation in the same person.
†† Chorea does not require other manifestations or evidence of preceding Strep A infection, provided other causes of chorea are excluded.
‡‡ Care should be taken not to label other rashes, particularly non-specific viral exanthems, as erythema marginatum.
§§ In high-risk groups, fever can be considered a minor manifestation based on a reliable history (in the absence of documented temperature) if anti-inflammatory medication has already been administered.
¶¶ If polyarthritis is present as a major criterion, monoarthritis or arthralgia cannot be considered an additional minor manifestation.
††† If carditis is present as a major manifestation, a prolonged P-R interval cannot be considered an additional minor manifestation.

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

Table 6.3. Suggested upper limits of normal (ULN) for serum streptococcal antibody titres in children and adults[1]

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

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

Table 6.4. Upper limits of normal for P-R interval

AGE GROUP (YEARS)	SECONDS
3-11	0.16
12-16	0.18
17+	0.20

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

DISCUSSION

> *"We now know she had some of the symptoms of the fever (acute rheumatic fever) but at the time we had no idea what was going on with her, we put it down to growing pains. We had a lack of understanding about ARF & RHD."*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

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

Difficulties with ARF diagnosis

The diagnosis of ARF relies on health professionals being aware of the diagnostic features, particularly when presentation is delayed or atypical. Populations with the highest incidence of ARF are often the most isolated. A prospective study of ARF in Australian children found that there were delays in both the presentation and referral of patients.[2] There was little difference in the proportion of delayed presentations and delayed referrals between urban/rural areas and remote areas (range: 16–20%). There was also little difference in the median time of delayed presentation and referral between the two geographical locations (14–17 days for all groups). This highlights the importance of:

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

Many medical practitioners and other health staff in Australia have never seen a case of ARF, because the disease has largely disappeared from the affluent and non-Indigenous populations among whom they trained and work. This may partly explain why up to 75% of newly diagnosed cases of RHD in northern Australia have not been previously diagnosed with ARF.[3]

Health staff moving to, and working in, areas with high rates of ARF and RHD (e.g. remote locations) should receive appropriate training on identifying and managing people suspected to have ARF. Regular workforce education should be provided to health staff working with Aboriginal and Torres Strait Islander communities.
(See RHDAustralia eLearning site https://www.rhdaustralia.org.au/e-learning-discussion-forum)

ARF can be difficult to diagnose and presenting symptoms may be subtle. It is therefore strongly recommended that all patients with suspected ARF be admitted to hospital.

Hospitalisation is important for timely blood testing, echocardiography and specialist review, monitoring of fever and joint symptoms, and disease education (with family where possible). Hospitalisation will maximise the likelihood of an accurate diagnosis, ensure prompt and optimal treatment, and formulate a longer-term management plan and clear arrangements for follow-up. Hospitalisation is recommended within 24 hours but may be up to 72 hours in those with less severe illness where there may be logistical difficulties in arranging hospital transfer.

Evolution of the Jones criteria and unifying American and Australian guidelines

The Jones criteria for the diagnosis of ARF were developed in the USA and introduced in 1944.[4] The criteria divide the clinical features of ARF into major and minor manifestations, based on their prevalence and specificity. Major manifestations are those that make the diagnosis more likely, whereas minor manifestations are considered suggestive, but insufficient on their own, for a diagnosis of ARF. The exception to this is in the diagnosis of recurrent ARF, which may be made on minor manifestations alone. The Jones criteria have been periodically modified and updated since 1944. Up to 1992,[5] 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 were sometimes found to be inadequately sensitive to pick up disease in high-incidence populations, where the consequences of under-diagnosis may be greater than those of over-diagnosis. Clinicians caring for Aboriginal and Torres Strait Islander patients were increasingly recognising cases of ARF that did not fulfil the 1992 version of the Jones criteria.[2,6,7]

In 2001, an expert group convened by the World Health Organization (WHO) provided additional guidelines as to how the Jones criteria should be applied in primary and recurrent episodes.[8] In 2006, this was taken further in the first version of the Australian guidelines, which proposed additional criteria for high-risk groups, particularly Aboriginal and Torres Strait Islander peoples.[9] Specifically, subclinical carditis, aseptic monoarthritis and polyarthralgia were included as major manifestations in high-risk groups in the 2006 edition. Subsequently in 2012, monoarthralgia was included as a minor manifestation in the second edition of the Australian guidelines.[10]

In 2015, the American Heart Association (AHA) further revised the Jones criteria to separate moderate-high and low-risk populations, and to include echocardiography as a tool to diagnose cardiac involvement.[11] They noted that the new guidelines aligned more closely with the Australian guidelines and these 2015 re-revised Jones criteria were endorsed by the World Heart Federation.

In this third edition of the Australian guidelines for diagnosis of ARF, minor changes are made to the 2012 Australian guidelines to bring them in alignment with the 2015 AHA revised Jones criteria.[3] The four specific changes to the 2012 Australian guidelines are:

- in low-risk populations, subclinical carditis is now a major criterion;
- in low-risk populations, ESR as a minor criterion is now ≥60 mm rather than ≥30 mm;
- in low-risk populations, fever as a minor criterion is now ≥38.5°C rather than ≥38.0°C;
- for a definite recurrent episode of ARF in a patient with known past ARF or RHD, the requirements are now 2 major, or 1 major and 2 minor, or 3 minor criteria, rather than 2 major, or 1 major and 1 minor, or 3 minor criteria.

These changes mean that the 2020 Australian criteria for diagnosis of ARF are now fully aligned with the 2015 AHA Jones criteria. Assuming other countries take the same approach, this will enable a universal online algorithm to support diagnosis. One issue to note is that in high-risk groups, fever can be considered a minor manifestation based on a reliable history (in the absence of documented temperature) if antipyretic medication has already been administered.

Table 6.5. Evolution of diagnostic criteria for ARF since 1992

MANIFESTATION	AHA 1992	WHO 2003	AUSTRALIA 2006		AUSTRALIA 2012		AUSTRALIA 2020 AHA 2015	
			High Risk	Low Risk	High Risk	Low Risk	High Risk	Low Risk
Carditis	Major	Major	Major		Major		Major	
Subclinical carditis	--	--	Major		Major	--	Major	
Prolonged P-R interval	Minor	Minor	Minor		Minor		Minor	
Polyarthritis	Major	Major	Major		Major		Major	
Polyarthralgia	Minor	Minor	Major	Minor	Major	Minor	Major	Minor
Aseptic monoarthritis	--	--	--	--	Major	Minor	Major	Minor
Monoarthralgia	--	--	--	--	Minor	n/a	Minor	--
Subcutaneous nodules	Major	Major	Major		Major		Major	
Sydenham chorea	Major	Major	Major		Major		Major	
Erythema marginatum	Major	Major	Major		Major		Major	
Fever	Minor	Minor	Minor		Minor		Minor	
							Temp ≥38°C	Temp ≥38.5°C
Raised inflammatory markers	Minor	Minor	Minor		Minor		Minor	
							ESR ≥30 mm/h	ESR ≥60 mm/h
Evidence of recent Group A streptococcal infection	Required	Required	Required		Required		Required	

AHA: American Heart Association. ESR: erythrocyte sedimentation rate. WHO: World Health Organization.

ARF categorised as definite *(confirmed)*, probable *(highly suspected)* or possible *(uncertain)*

The 2006 Australian guidelines suggested that, for patients who did not fulfil the criteria, but in whom the clinician suspected ARF, it would be reasonable to administer a single dose of BPG and perform an echocardiogram within one month, looking for evidence of rheumatic valvular damage.

While patients with suspected ARF may have an alternative diagnosis and not ARF, they may also truly have ARF but not fulfil the criteria for definite (confirmed) ARF for a number of reasons:[7,12-14] atypical presentations with variability from the historical Jones clinical criteria and even from the current less strict criteria; delayed presentation (more than 20% of cases in one study) which can affect both clinical features and laboratory results; and incomplete investigation, missing one or more of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), electrocardiogram (ECG) or streptococcal serology. For example, ESR and/or CRP testing was absent for 19% of 151 children with ARF identified during a national study of ARF in children, and diagnosis was unable to be confirmed for another eight children in whom timely streptococcal serology was not done.[1] The issue of incomplete investigation should be at least partially addressed by adherence to the recommendation of admitting all cases of suspected ARF to hospital for complete diagnostic work-up. Nevertheless, it is important to note that diagnostic capabilities for such investigations may be limited or absent in many low-resource countries or remote settings where ARF and RHD remain major issues *(Table 7.3)*.

The 2012 Australian guidelines included an additional category of probable ARF, to include patients who did not satisfy the criteria for definite (confirmed) ARF but in whom the clinician felt that ARF was the most likely diagnosis. Probable ARF was defined as a clinical presentation that falls short by either one major or one minor manifestation, or the absence of streptococcal serology results, but one in which ARF was considered the most likely diagnosis. It has become clear that while many of these patients most likely did have ARF and some progressed to RHD, the diversity of such presentations includes a substantial number of patients who likely never had ARF. Nevertheless, commencement of secondary prophylaxis with BPG and follow-up echocardiogram is required for all those in this diverse group. To avoid unnecessarily prolonged secondary prophylaxis with BPG, while still emphasising the critical importance of follow-up, the categories of probable (highly suspected) ARF and possible (uncertain) ARF have now been clarified with different management timelines for follow-up and duration of BPG specified for each category *(Table 10.2, Table 7.4)*. For categorising into probable and possible ARF, emphasis is placed on whether ARF is considered the most likely diagnosis and that decision should be made in consultation with a paediatric or medical specialist with experience in the diagnosis of ARF.

Important points about ARF diagnosis in difficult cases

- Patients presenting with monoarthritis should be considered to have septic arthritis until proven otherwise.
- Patients presenting with polyarthritis or polyarthralgia should be thoroughly investigated for alternative diagnoses, including arboviral infections and disseminated gonococcal infection in regions where these diseases are prevalent, as outlined in the notes in *Table 6.2*.
- Make sure all investigations are conducted, both for ARF and for potential differential diagnoses, depending on the clinical presentation.

The management implications of making a diagnosis of probable or possible ARF are outlined in Chapter 7, Management of ARF *(Table 7.4)*.

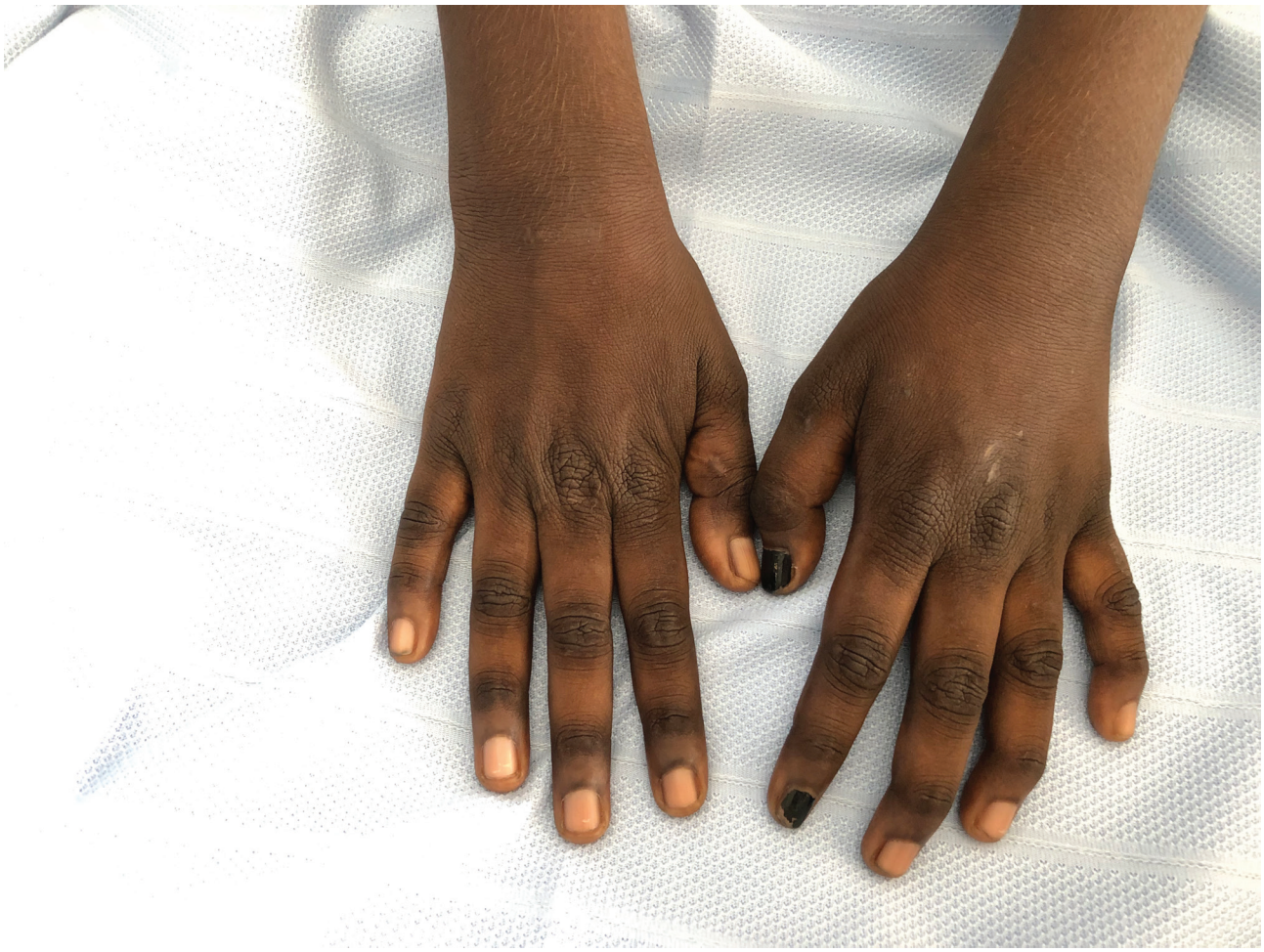
CLINICAL FEATURES OF ARF: MAJOR MANIFESTATIONS

Overview

The nature of ARF presentations is highly diverse and may vary geographically and by ethnicity. Presentations are often subtle and evolve over time. If clinicians are expecting to find a constellation of ARF diagnostic criteria simultaneously in one individual, they are likely to be missing mild cases of ARF, such as those who present with joint pain and fever only. Skin and subcutaneous manifestations are uncommon but do appear to vary in frequency across populations; this may be partly because of greater difficulty appreciating erythema marginatum on deeply pigmented skin.

A comparison of types of presentation between an Australian setting and New Zealand revealed slight differences, with carditis, erythema marginatum and subcutaneous nodules being more common in New Zealand.[10] A much higher rate of arthritis presentations without other major manifestations in Australia may in part reflect differences in diagnostic approaches (polyarthralgia being permitted as a major manifestation in Australia but not New Zealand).

Figure 6.1. Polyarthritis of the fingers demonstrating inter-phalangeal joint swelling



Source: Photo courtesy of Professor Bart Currie, Menzies School of Health Research.

Arthritis

Arthritis is defined as a swollen and hot joint with pain on movement. Arthralgia differs from arthritis in that there is pain on joint movement without evidence of swelling or heat (See *Arthralgia*). Monoarthritis is involvement of a single joint while polyarthritis is involvement of more than one joint, either at the same time or sequentially. 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 most commonly affected, especially the knees and ankles, and symptoms can be transient. Arthritis of the hip is often difficult to diagnose, because objective signs may be limited to a decreased range of movement.

The arthritis is usually extremely painful on movement, often out of proportion to the clinical signs. It is exquisitely responsive to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin. This can be a useful diagnostic feature, as arthritis continuing unabated more than three days after starting NSAID therapy is unlikely to be due to ARF. Equally, withholding NSAIDs in patients with monoarthralgia or monoarthritis, to observe the development of polyarthritis, can also help in confirming a diagnosis of ARF. Paracetamol may be used to relieve pain in children in the interim, or tramadol for more severe pain *(Table 7.1)*.

Because of the migratory and evanescent nature of the arthritis, a reliable history of arthritis, rather than documentation by the clinician, is sufficient to satisfy this manifestation.

ARF should always be considered in the differential diagnosis of patients in high-risk populations presenting with arthritis. Arthritis caused by ARF is not uncommonly initially attributed by a patient and family to a minor traumatic event which may have occurred, such as with sporting activities. In the hospital setting, physicians and surgeons should collaborate when the diagnosis of arthritis is unclear. Joint aspiration for microscopy, culture and molecular testing for *Neisseria gonorrhoeae*, in appropriate clinical circumstances and ages, is recommended. Patients with sterile joint aspirates should never be treated speculatively for septic arthritis without further investigation, particularly in areas with a high ARF/RHD prevalence.[15]

In high-risk populations in Australia, monoarthritis or polyarthralgia are common manifestations of ARF and are often associated with overt or subclinical carditis.[13] While ARF can present as monoarthritis, septic arthritis should initially be ruled out. Monoarthritis was present in 19% of high-risk children with ARF and accounted for 24% of all joint manifestations of ARF in a two-year prospective, national study of ARF in children.[1] Monoarthritis was first included as a major manifestation of ARF for high-risk groups in the 2006 Australian guidelines[16,17] to increase sensitivity in populations at high risk of developing RHD.

In these high-risk populations, aseptic monoarthritis or polyarthralgia may be considered as a major manifestation, in place of polyarthritis *(Table 6.2)*. However, alternative diagnoses should be carefully excluded *(Table 6.8)*.

Patients presenting with monoarthritis should be thoroughly investigated for septic arthritis, as well as rheumatic fever and any other relevant differential diagnoses. Once initial investigations have been sent, including joint aspirate for microscopy and culture (collected appropriately to avoid clotting of the sample), it may be appropriate to treat presumptively with empirical antibiotics appropriate to cover septic arthritis pathogens until an alternative diagnosis, such as rheumatic fever, is confirmed. However, in high-risk populations, such as Aboriginal and Torres Strait Islander communities, ARF should always be considered in the differential diagnosis. Monoarthritis may also be the presenting feature, especially if anti-inflammatory medication is commenced early in the illness prior to other joints becoming inflamed.

Sydenham chorea

This manifestation predominantly affects females, particularly in adolescence.[18,19] It is common in Aboriginal and Torres Strait Islander peoples (between 12%[20] and 28%[19] of ARF presentations in this population). Sydenham 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); https://www.youtube.com/watch?v=A8JYdylPuLU&feature=youtu.be
- 'spooning' (flexion of the wrists and extension of the fingers when the hands are extended); https://www.youtube.com/watch?v=-O4aGtFK2aM&feature=youtu.be
- the 'pronator sign' (turning outwards of the arms and palms when held above the head); https://www.youtube.com/watch?v=Q2u9_m8Hptw
- inability to maintain protrusion of the tongue.

Other examples of Sydenham chorea

https://youtu.be/JPIvvGFn9vM

https://youtu.be/apjTB2NOdYs

https://www.youtube.com/watch?v=4O5IfwOHcXk

https://www.youtube.com/watch?v=VFBOTwmVA0A

Because chorea may occur after a prolonged latent period following Strep A infection,[21-23] 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 also have a mildly elevated ESR (for example 40 mm/h) but have a normal serum CRP level and white cell count.[19,24,25] Chorea is the ARF manifestation most likely to recur, and may occur in pregnancy or with oral contraceptive use. Chorea in a pregnant Aboriginal or Torres Strait Islander woman should be suspected as Sydenham chorea and investigated. The majority of cases resolve within six months (usually within six weeks), although rare cases lasting three years have been documented. Chorea patients have a higher-than-expected prevalence of attention-deficit hyperactivity disorder, anxiety, depression and cognitive dysfunction after they have recovered from the movement disorder, although there is some evidence that attention-deficit hyperactivity disorder and anxiety features are sometimes present before the onset of chorea, suggesting that they may be risk factors, rather than long-term complications.[26-29]

During outbreaks of ARF in the USA in the 1980s, up to 71% of patients with chorea were found to have carditis.[30] Studies in Australia indicate that between 25%[19] and 48%[10] of Aboriginal and Torres Strait Islander peoples with rheumatic chorea have evidence of carditis. Approximately 25% of patients with chorea without detected cardiac involvement also eventually developed RHD in studies from the 1940s and 1980s.[31,32] This highlights the importance of early follow-up echocardiography in all people with ARF, including those without evidence of carditis initially, to detect evolving cardiac pathology. Echocardiography is essential for the assessment of all patients with chorea to assess for carditis and/or RHD, regardless of the presence of cardiac murmurs. 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 with echocardiography for the subsequent development of RHD (See *Chapter 7. Management of ARF, Treatment of Sydenham chorea*).

Carditis

Rheumatic carditis refers to the active inflammation of the endocardium, most importantly the valvular endocardium, with or without involvement of the myocardium and pericardium, that occurs in ARF. While myocarditis[33] and pericarditis[16,34] may occur in ARF, the predominant manifestation of carditis is the involvement of the endocardium presenting as a valvulitis, especially of the mitral and aortic valves.[16,34] The incidence of carditis in initial attacks of ARF varies between 30% and 82%.[8,19,34,35]

The clinical picture of carditis in ARF and the timing of the appearance of cardiac findings are variable. In many patients with ARF, evidence of carditis can be found at presentation, along with fever and arthritis, but in some patients, signs of carditis appear after presentation, usually within the first two to six weeks,[36-38] and repeated examination during admission is therefore important.[39] A less common presentation of rheumatic carditis is the so-called 'insidious onset' or 'indolent' carditis. This mode of presentation was described in the USA in the first half of the twentieth century, and is characterised by a subacute illness of several weeks in children aged under six years with mild or no fever, few joint symptoms and relatively severe cardiac involvement. Insidious onset carditis may be under recognised in Aboriginal and Torres Strait Islander children, in which case, it could potentially explain some cases of RHD presenting without a documented history of ARF. However, such presentations in themselves do not constitute definitive evidence of insidious onset carditis, since prior discreet episodes of ARF may have occurred but were not diagnosed.

There are four clinical findings of carditis that are commensurate with the nature and degree of cardiac involvement. They are, in order of decreasing frequency:

- significant murmur;
- cardiac enlargement;
- cardiac decompensation; and
- pericardial friction rub or effusion.

In addition, evidence of valvulitis on echocardiogram is now considered a manifestation of carditis in Australia and internationally.[3]

A significant organic (pathological) murmur as a sign of valvulitis is the most common clinical manifestation of rheumatic carditis. However, contemporary studies show that reliance on auscultation, at least in established RHD, is highly unreliable.[40] Valvulitis most commonly affects the mitral valve, leading to mitral regurgitation (MR), although with prolonged or recurrent disease scarring, may lead to stenotic lesions (See *Chapter 8. Diagnosis of RHD, Mitral valve disease*).[41] MR presents clinically as an apical blowing, holosystolic (pansystolic) murmur. The presence of an associated mid-diastolic flow murmur (Carey Coombs murmur) implies significant mitral valve regurgitation; however, it must be differentiated from the diastolic murmur of mitral stenosis (MS), which is often preceded by an opening snap. The Carey Coombs murmur disappears if the mitral valvulitis improves. Aortic valvulitis manifests as aortic regurgitation (AR) and is characterised by a decrescendo early diastolic murmur heard at the base of the heart (aortic area) or left sternal edge, accentuated by the patient sitting forward in held expiration (See *Chapter 8. Diagnosis of RHD, Aortic valve disease*).

During the first episode of ARF, carditis is often but not always mild,[35,42] and echocardiographic findings may precede clinical evolution of a murmur.[39,43,44] Given that even moderate valvular lesions can go undetected by auscultation,[39] echocardiographic evidence alone is sufficient to confirm valvulitis in the setting of ARF.

Cardiac enlargement can be detected clinically by the displacement of the apical impulse and confirmed on echocardiography or chest X-ray. Cardiac failure in ARF results from valvular dysfunction, secondary to severe valvulitis, and is not due to primary myocarditis.[36,44,45] Cardiac decompensation occurs in less than 10% of patients during their first episode,[41,42,46-48] and is more common in patients with recurrent attacks of ARF.[41,42,46,49] The physical findings of heart failure are variable, and depend on the severity of disease and age of the patient. Findings of heart failure in younger children can be subtle, and may include tachypnoea, resting tachycardia, displaced apex beat, basal crepitations, hepatomegaly and facial puffiness. In older patients, the more classical findings of frank pulmonary oedema, raised jugular venous pressure and bipedal oedema may be elicited.

Pericarditis is uncommon in ARF, and is rarely, if ever, an isolated finding.[50-52] Pericarditis should be suspected in patients with ARF who have chest pain. The main clinical finding of pericarditis is a friction rub, which is characterised by a superficial scratching or grating sound on auscultation of the precordium. A pericardial

effusion may also be present, and is suspected if there is muffling of the heart sounds. If pericarditis is present, the friction rub may obscure valvular murmurs.

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

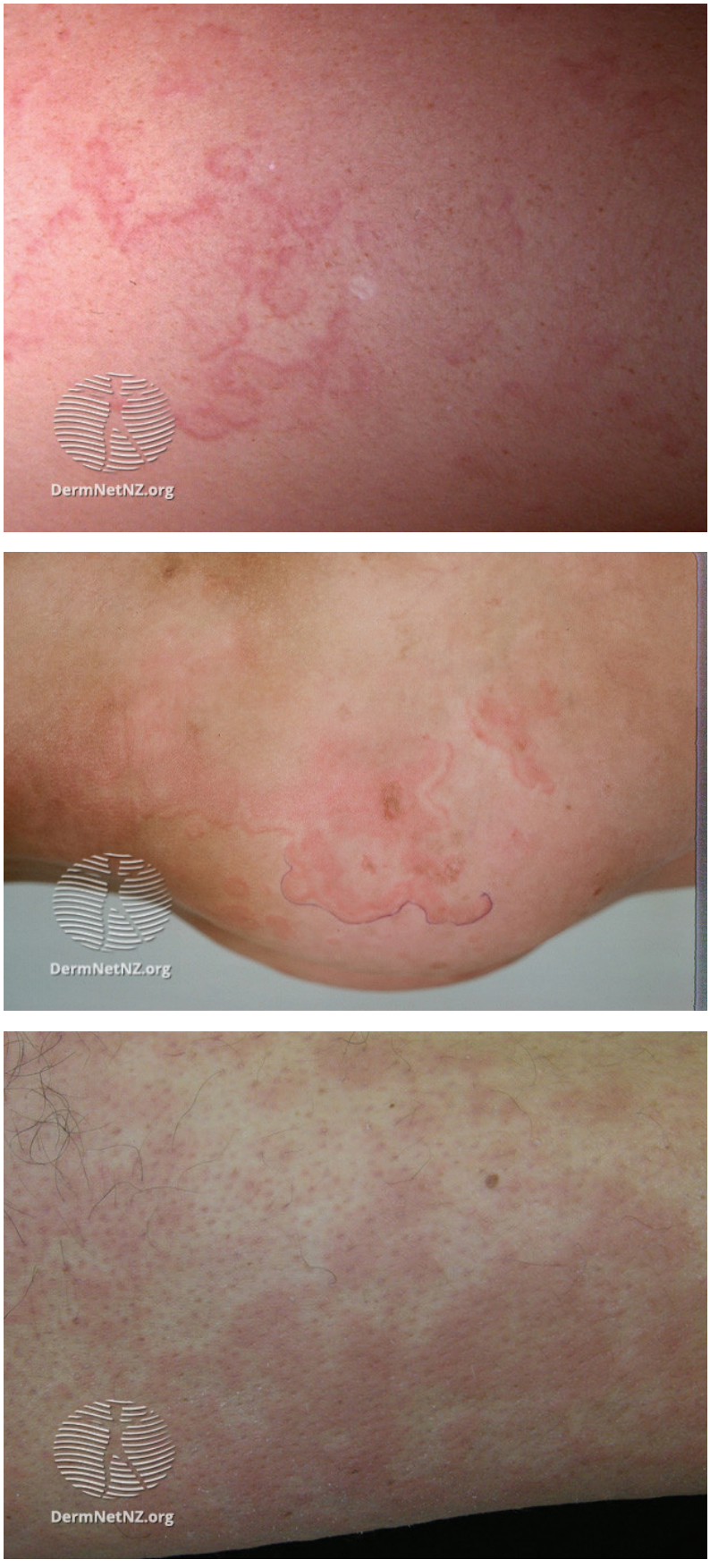
Subcutaneous nodules

These are very rare (less than 2% of cases) but are considered highly specific manifestations of ARF.[13] Nodules are usually 0.5–2 cm in diameter, round, firm, freely mobile and painless nodules that occur in crops of up to 12 over the elbows, wrists, knees, ankles, Achilles tendon, occiput and posterior spinal processes of the vertebrae. They tend to appear one to two weeks after the onset of other symptoms, last only one to two weeks (rarely more than a month) and are strongly associated with carditis.

Erythema marginatum

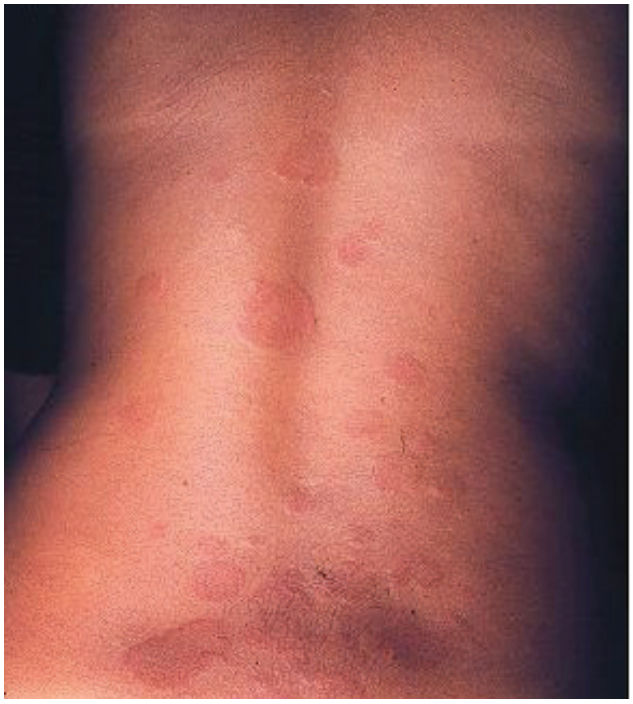
Erythema marginatum is also rare, being reported in less than 2% of cases.[10] As with subcutaneous nodules, erythema marginatum is considered highly specific for ARF.

Figure 6.2 Erythema marginatum



Source: DermNet, (New Zealand) at https://creativecommons.org/licenses/by-nc-nd/3.0/nz/legalcode.

Figure 6.3. Erythema marginatum on the back



This image of the back of a patient with ARF shows the characteristic rash, erythema marginatum. Note the erythematous lesions with pale centers and rounded or serpiginous margins.

Reproduced with permission from: Binotto MA, Guilherme L, Tanaka AC. Rheumatic fever. Images Paediatric Cardiology 2002; 11:12. Copyright © 2002 Images in Paediatric Cardiology. Graphic 50841 Version 2.0

It occurs as bright pink macules or papules that blanch under pressure and spread outwards in a circular or serpiginous pattern. It is rapidly evanescent (that is, waxes and wanes during the course of a day). The lesions are not itchy or painful, and occur on the trunk and proximal extremities, but almost never on the face. The rash can be difficult to detect in dark-skinned people, so close inspection is required. 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 6.6* outlines the key points in identifying major manifestations of ARF.

Table 6.6. Key points in identifying major manifestations of ARF

Manifestation	Points for diagnosis
Arthritis	Most common presenting symptom of ARF Usually extremely painful Polyarthritis (or polyarthralgia) is usually asymmetrical and migratory but can be additive Monoarthritis may be a presenting feature in high-risk populations Large joints are usually affected, especially knees and ankles Should respond within three days of starting NSAID therapy, including aspirin
Sydenham chorea	Present in up to one-quarter of ARF presentations, particularly females, and predominantly in adolescence Consists of jerky, uncoordinated movements, especially affecting the hands, feet, tongue and face, disappears during sleep Echocardiography is essential for all patients with chorea
Carditis	Usually presents clinically as an apical holosystolic (pansystolic) murmur (MR), and/or an early diastolic murmur at the base of the heart or left sternal edge (AR) May only be detected using echocardiography (subclinical carditis)
Subcutaneous nodules	Rare, but highly specific, manifestations of ARF in Aboriginal and Torres Strait Islander peoples, 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 and Torres Strait Islander peoples, but highly specific for ARF Occurs as circular patterns of bright pink macules or papules on the trunk and proximal extremities

NSAID, non-steroidal anti-inflammatory drug; MR, mitral regurgitation; AR, aortic regurgitation.

CLINICAL FEATURES OF ARF: MINOR MANIFESTATIONS

Arthralgia

Arthralgia differs from arthritis in that there is pain on joint movement without evidence of swelling or heat.

In high-risk groups, polyarthralgia can be considered a major manifestation and monoarthralgia can be considered a minor manifestation. In low-risk groups, polyarthralgia can be a minor manifestation.

Arthralgia is a non-specific symptom, and usually occurs in the same pattern as rheumatic polyarthritis (migratory, asymmetrical, with large joints more commonly affected). The pain is usually out of proportion to clinical findings and is associated with movement. While it may be undetectable at rest, lower limb arthralgia can be elicited by noting a limp when asking the patient to walk, and upper limb arthralgia can be elicited by noting movement restriction when asking the patient to undertake a movement such as reaching behind their head. Alternative diagnoses should be considered in a patient with arthralgia, especially if it is not typical of ARF. *(Table 6.8)*

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[5,53] but lower peak temperatures have been described more recently.

In Aboriginal and Torres Strait Islander peoples and others in high-risk groups, defining fever as a temperature greater than 38°C results in improved sensitivity for the diagnosis of ARF.[13] However, in low-risk groups, fever remains defined as ≥38.5°C rather than ≥38.0°C *(Table 6.2)*.[3] One issue to note is that in high-risk groups, fever can be considered a minor manifestation based on a reliable history (in the absence of documented temperature), especially if antipyretic medication has already been administered. Fever, like arthritis and arthralgia, is usually quickly responsive to aspirin or other NSAID therapy.

Elevated acute-phase reactants

Some clinicians have reported normal CRP with elevated ESR, suggesting that CRP is not a good substitute for ESR.

Typically, ARF patients have a raised serum CRP level and/or ESR. The peripheral white blood cell (WBC) count is <15×109 /L in 75% of patients, so an elevated WBC is an insensitive marker of inflammation in ARF.[13] Further analysis of these data demonstrated that less than 4% of patients with confirmed ARF, excluding chorea, had both a serum CRP level of <30 mg/L and an ESR of <30 mm/h. *(J Carapetis, unpublished data)*

Therefore, it is recommended that for high-risk groups, a serum CRP level of ≥30 mg/L or ESR of ≥30 mm/h is needed to satisfy the minor manifestation of elevated acute-phase reactants. For low-risk groups, the ESR cut-off has been changed to align with the 2015 AHA revised Jones criteria of a serum CRP level of ≥30 mg/L or ESR of ≥60 mm/h. The serum CRP concentration rises more rapidly than the ESR, and falls more rapidly with resolution of the attack. The ESR may remain elevated for three to six months, despite symptoms resolving within a much shorter period.

Prolonged P-R interval and other rhythm abnormalities

All patients with suspected and confirmed ARF should have an ECG.

Some healthy people show a prolonged P-R interval on ECG; however, one 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, but sometimes faster (when the rate of the atrioventricular junctional pacemaker exceeds that of the sinus node, resulting in an accelerated junctional rhythm).[52,54] Accelerated junctional rhythm also can occur without a prolonged P-R interval. Second-degree, and even complete heart block, can occur in ARF, and if associated with a slow ventricular rate, may give the false impression that carditis is not significant. In a resurgence of ARF in the USA into the 1990s, 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.[34] In a recent large study from New Zealand, advanced conduction abnormalities (second-degree heart block, complete heart block or accelerated junctional rhythm) occurred in 8% of those presenting with ARF.[55]

Therefore, an ECG should be performed in all cases of suspected ARF. If a prolonged P-R interval is detected, the ECG should be repeated after one and two weeks, and if still abnormal, it should be repeated again at one and two 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. The ULN for P-R interval for age groups are provided in *Table 6.4*.[56]

Figure 6.4. Normal Sinus Rhythm

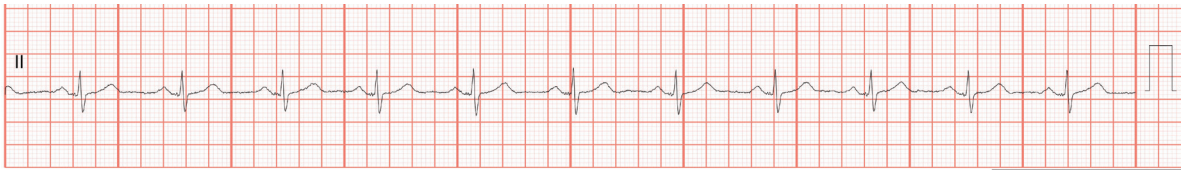


Figure 6.5. First degree heart block

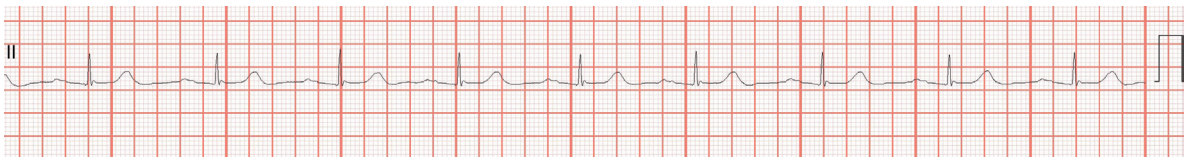


Figure 6.6. Second degree heart block

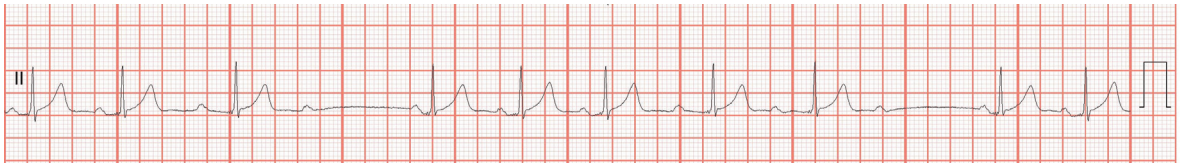


Figure 6.7. Third degree (complete) heart block

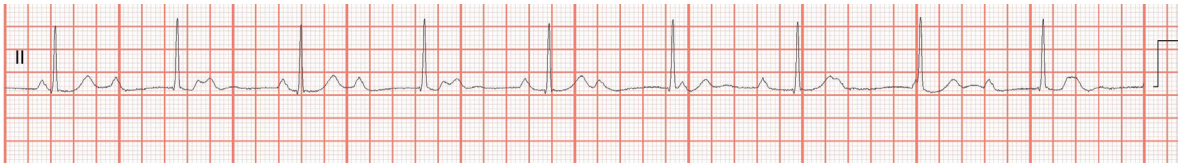
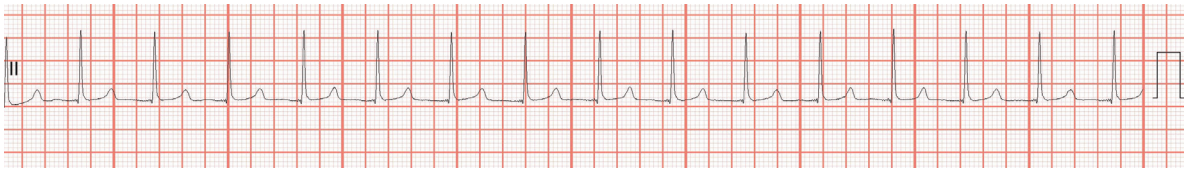


Figure 6.8. Accelerated junctional rhythm



OTHER LESS COMMON FEATURES OF ARF

Other less common clinical features include abdominal pain, epistaxis, mild elevations of plasma transaminase levels, and microscopic haematuria, pyuria or proteinuria. Acute post-streptococcal glomerulonephritis (APSGN) has been described to occur at the same time as ARF but this is very uncommon.[57] Some patients with acute carditis also present with pulmonary infiltrates on chest radiography and have been labelled as having 'rheumatic pneumonia'. This is probably a misnomer, as it likely represents unilateral pulmonary oedema in patients with fulminant carditis with ruptured chordae tendinae.[58,59] *Table 6.7* includes the key points in identifying minor manifestations of ARF.

Table 6.7. Key points in identifying minor manifestations of ARF

MANIFESTATION	POINTS FOR IDENTIFICATION
Arthralgia	Suggestive of 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 (which can be low-grade and transient) Oral, tympanic or rectal temperature ≥38°C (high-risk groups) or ≥38.5°C (low-risk groups) on/after admission or documented with a reliable history during the current illness (high-risk groups only), should be considered as fever
Elevated acute-phase reactants	Serum CRP level of ≥30 mg/L (both high-risk and low-risk groups) or ESR of ≥30 mm/h (high-risk groups) or ≥60 mm/h (low-risk groups) meets this diagnostic criterion
ECG	If a prolonged P-R interval or a more advanced conduction abnormality is detected, the ECG should be repeated to see if it returns to normal If the P-R interval or a more advanced conduction abnormality has returned to normal, ARF becomes a more likely diagnosis

ECG, electrocardiogram; ESR, erythrocyte sedimentation rate.

EVIDENCE OF STREPTOCOCCAL A INFECTION

Strep A is isolated from throat swabs in less than 10% of ARF cases in New Zealand,[60] and less than 5% of cases in Aboriginal and Torres Strait Islander peoples.[13] Molecular methods of Strep A detection, discussed below, appear to be more sensitive, and have a future potential role in diagnosis (See *Streptococcus A rapid diagnostics*).[61] Streptococcal antibody titres are currently crucial in confirming the diagnosis. The most commonly used tests are the plasma ASO and the anti-DNase B titres. Previous data suggest that a rise in the ASO titre occurs in 75–80% of untreated Strep A pharyngeal infections, and that the addition of anti-DNase B titre increases the sensitivity of testing.[62] ASO and antiDNase B antibody responses can be elicited by all beta-haemolytic streptococci rather than being confined to Group A streptococci. Streptococcal serology results can lack sensitivity and specificity, and longitudinal changes are not always in keeping with expectations.[10,63] Nevertheless, while research is underway to identify more clinically useful serological markers of Strep A infection,[64] ASO and the anti-DNase B comprise critical components of the diagnosis of ARF.

The serum ASO titre usually rises within one to two weeks, and reaches a maximum at about three to six weeks after infection, while the serum anti-DNase B titre can take up to six to eight weeks to reach a maximum.[65] The rate of decline of these antibodies varies enormously, with the ASO titre starting to fall six to eight weeks, and the anti-DNase B titre three months after infection.[66] In the absence of re-infection, the ASO titre usually approaches pre-infection levels after 6–12 months, whereas the anti-DNase B titre tends to remain elevated for longer and sometimes indefinitely during childhood, especially in communities with high rates of Strep A skin infections.[67]

Single antibody titres are often misleading, and sequential samples more accurately define occurrence and time of infection.[57] To confirm a current Strep A infection, ideally it is recommended that the titre be determined in the acute phase, and then in the convalescent phase 14–28 days later, with a positive result defined as a rise in titre of twofold or more.[68] However, relying on rising titres in paired sera is often not useful in ARF diagnosis. Because of the delay of one to five weeks between Strep A infection and the onset of symptoms of ARF, the ASO and often the anti-DNase B titres are already elevated at presentation. Moreover, it is sometimes impractical to draw a second blood sample if the patient has been discharged.

Therefore, it is generally accepted that if only a single specimen is available, a titre greater than the ULN at initial testing be considered presumptive evidence of a preceding Strep A infection. The ULN for Strep A serology has been defined by separating the upper 20% from the lower 80% of the group distribution in a dichotomous fashion.[68-70] The choice of the 80th centile cut-off for the ULN is based on the observation that more than 80–90% of patients with ARF have Strep A titres that are above the 80th centile of healthy controls with no clinical evidence of recent streptococcal infection.[68,69]

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

A study of 424 adults and children in Fiji, a population with a similar epidemiology of Strep A infection to Aboriginal and Torres Strait Islander peoples, including a high prevalence of Strep A skin infections, provides ULN for Strep A serology applicable to the Australian context across all ages *(Table 6.3)*.[71]

STREPTOCOCCUS A RAPID DIAGNOSTICS

A simple, reliable, rapid point-of-care test for detecting Strep A from throat and skin swabs will improve the management of throat and skin infections and diagnosis of ARF.[55]

Strep A rapid tests include rapid antigen detection tests (RADT) and molecular tests. Current RADT are not as accurate as culture for detecting Strep A[72] but are still an important diagnostic tool for Strep A pharyngitis in some countries. However, these rapid tests currently have limited use in children and in public health interventions for control of ARF and RHD. Where RADT are used, clinical practice guidelines recommend a negative test is followed by a backup throat swab culture.[73]

STREPTOCOCCAL SEROLOGY IN HIGH-INCIDENCE POPULATIONS

The high prevalence of Strep A infections (mainly pyoderma) in Aboriginal and Torres Strait Islander communities of northern and central Australia often causes very high background titres of serum streptococcal antibodies.[74,75] All cases of suspected ARF should have elevated serum streptococcal serology demonstrated to enable confirmation of a diagnosis of ARF *(Table 6.3)*.

If the initial titre is above the ULN, there is no need to repeat serology. If the initial titre is below the ULN for age, testing should be repeated 10–14 days later *(Table 6.3)*.

DIFFERENTIAL DIAGNOSIS

Many of the clinical features of ARF are non-specific, so a wide range of differential diagnoses should be considered *(Table 6.8)*.[76]

The most likely alternative possibilities will vary according to location (e.g. arboviral arthritis is less likely in temperate than tropical climates) and ethnicity (e.g. some autoimmune conditions may be more or less common in particular ethnic groups).

Table 6.8. Differential diagnoses of common major presentations of ARF

PRESENTATION		
Polyarthritis and fever	**Carditis**	**Sydenham chorea**
Septic arthritis (including disseminated gonococcal infection)†	Innocent murmur	Systemic lupus erythematosus
Connective tissue and other autoimmune disease‡	Mitral valve prolapse	Drug intoxication
Viral arthropathy§	Congenital heart disease	Wilson's disease
Reactive arthropathy§	Infective endocarditis	Tic disorder††
Lyme disease¶	Hypertrophic cardiomyopathy	Choreoathetoid cerebral palsy
Sickle cell anaemia	Myocarditis: viral or idiopathic	Encephalitis
Infective endocarditis§§	Pericarditis: viral or idiopathic	Familial chorea (including Huntington's)
Leukaemia or lymphoma		Intracranial tumour
Gout and pseudo-gout		Lyme disease¶
		Hormonal‡‡

† Gonorrhoea should be actively sought in all potentially sexually active cases. Tests for gonorrhoea include microscopy and culture and polymerase chain reaction (PCR) of joint aspirate, endocervical swab, or first-pass urine/self-collected vaginal swabs in cases where endocervical PCR is not possible.

‡ Includes rheumatoid arthritis, juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis and sarcoidosis. Note that systemic lupus erythematosus occurs at a significantly higher rate in the northern Australian Aboriginal population than in the non-Aboriginal population.[77]

§ Ross River Virus, Barmah Forest Virus, Mycoplasma, cytomegalovirus, Epstein–Barr virus, parvovirus, chlamydia, hepatitis, rubella vaccination, and *Yersinia* spp. and other gastrointestinal pathogens.

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

†† Tourette's syndrome and possibly including PANDAS (paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection).

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

§§ Ensure separate sets of blood cultures are collected and stigmata of endocarditis are investigated (See *Chapter 11. Management of RHD, Prevention of infective endocarditis*).

SYNDROMES THAT MAY BE CONFUSED WITH ARF

Post-streptococcal reactive arthritis

Some patients present with arthritis not typical of ARF, but with evidence of recent streptococcal infection (group A, or groups C and G, that is *Streptococcus dysgalactiae* subsp. *equisimilis*), and are said to have post-streptococcal reactive arthritis. In these cases, the arthritis may affect joints such as the small joints of the hand that are not so commonly affected in ARF. The arthritis is less responsive to anti-inflammatory treatment and may be more prone to relapse after cessation of anti-inflammatory treatment.[78] These patients are said not to be at risk of carditis,[79] and therefore, do not require secondary prophylaxis. However, some patients diagnosed with post-streptococcal reactive arthritis have developed later episodes of ARF, indicating that the initial diagnosis should have been atypical ARF.

It is therefore 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. Patients diagnosed with post-streptococcal reactive arthritis should receive secondary prophylaxis for at least five years (high-risk populations), or at least one year (low-risk populations). Echocardiography should be used to confirm the absence of valvular damage in all of these patients from both high- and low-risk populations, both before making the diagnosis and before discontinuing secondary prophylaxis.

Paediatric autoimmune neuropsychiatric disorders associated with Strep A infections

Some cases of chorea are mild or atypical, and may be confused with motor tics, or the involuntary jerks of Tourette's syndrome. There may be overlap between Sydenham chorea and these conditions. Indeed, obsessive–compulsive features have been found at increased frequency in long-term follow-up studies of patients with ARF and RHD.[80,81] The term 'paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections' (PANDAS) refers to a subgroup of children with tic or obsessive–compulsive disorders, whose symptoms may develop or worsen following Strep A infection, and who are said to be at no risk of cardiac valvular damage.[82,83]

However, the evidence supporting PANDAS as a distinct disease entity has been questioned,[84,85] with a follow-up study in PANDAS and non-PANDAS patients with tic and obsessive–compulsive disorders failing to find any exacerbations of symptoms associated with streptococcal infections in PANDAS patients.[85] Hence, in high-risk populations, clinicians should rarely, if ever, make a diagnosis of PANDAS, and should rather err on the side of diagnosis of ARF and provision of secondary prophylaxis. Echocardiograms are essential for such circumstances and the diagnosis of PANDAS should only be made by clinicians if they have excluded echocardiographic evidence of valvular damage and other features of ARF, and have documented exacerbations of neuropsychiatric symptoms with clear evidence of recurrent Strep A infections.[81] If ARF is excluded, secondary prophylaxis is not needed but such patients should be carefully followed up to ensure that they do not develop carditis in the long term.

ECHOCARDIOGRAPHY AND ARF

All patients with suspected and confirmed ARF (with or without an audible murmur) should have an echocardiogram:

- to confirm the presence of acute valvulitis;
- to assess severity of valvulitis and cardiac function status;
- to establish the presence of pre-existing, undiagnosed RHD;
- as a baseline for future monitoring of disease progression and/or recurrent ARF.

Before the introduction of echocardiography, the diagnosis of rheumatic carditis relied on clinical evidence of valvulitis, supported by ECG or radiographic evidence of cardiomegaly. Echocardiography is more sensitive and specific for acute rheumatic carditis than auscultation,[16,39,44] and it is therefore mandatory that all patients with suspected or definite ARF should undergo echocardiography. With the advent of portable machines and specialist outreach services, echocardiography should be available to all Australians, including those living in remote settings.

- In patients with definite ARF, echocardiography can confirm the presence, severity and aetiology of valvular regurgitation. It can identify additional valve involvement (without an associated detectable murmur), pericardial effusion, and assess cardiac size and function *(Table 6.9)*.
- In patients with suspected ARF, reliance on the clinical finding of a murmur may result in misclassification of congenital heart disease, or even of physiological (functional) murmurs, as rheumatic carditis. The likelihood of misclassification has increased in recent years, as most clinicians' auscultatory skills have become less proficient.[8] Poor sensitivity and specificity of auscultation by healthcare providers also has been shown in established RHD.[11]
- In patients with suspected ARF without a clinically significant murmur, echocardiography can identify subclinical valvular damage that is likely to be rheumatic, thus increasing the likelihood that the presentation is due to ARF. Subclinical carditis is now acceptable as a major manifestation of ARF in both high-risk and low-risk groups *(Table 6.5)*.[3]

In 2012, under the auspices of the World Heart Federation, an international consortium published minimal criteria for a diagnosis of RHD on echocardiography.[86] Those criteria did not specifically address the differentiation between acute carditis and chronic RHD. The same criteria are recommended for defining pathological regurgitation in the acute phase, as in the chronic phase *(Table 8.2)*.

Morphological changes to the valve, however, are often minimal in acute carditis, as these take time to develop and may be somewhat different than those found in chronic RHD.[35,47,87,88] Many cases of ARF are recurrent ARF occurring on the background of chronic RHD, and acute and chronic changes can then co-exist.

- Pathological regurgitation of the mitral or aortic valve (in the absence of an alternative diagnosis, such as bicuspid aortic or mitral valve prolapse) is sufficient to fulfil the minimal echocardiographic criteria of acute carditis in the setting of suspected or proven ARF.
- The presence of additional morphological changes to the mitral or aortic valve increases the confidence with which the diagnosis can be made.
- Morphological changes of the mitral or aortic valve, in the absence of pathological valvular regurgitation, are not sufficient to diagnose acute rheumatic carditis. Such cases should be followed with repeat echocardiography after four to six weeks to detect evolving acute carditis *(Table 8.2)*.

Table 6.9. Uses of echocardiography in ARF

Valvulitis
Define the severity of mitral, aortic and/or tricuspid regurgitation.
Define the severity of mixed valve disease (mixed stenotic and regurgitant).
Identify subclinical evidence of rheumatic valve damage.
Visualise valvular anatomy and define mechanism of regurgitation (prolapse, flail leaflet, annular dilatation etc).
Cardiac function
Assess left ventricular size and function.
Pericarditis
Confirm the presence of a pericardial effusion.
Reveal inaudible or subclinical valvular regurgitation in the presence of a friction rub.
Exclude other forms of cardiac murmur
Identify congenital heart disease, such as bicuspid aortic valve and congenital mitral valve anomalies, as the cause for a pathological murmur.
Confirm normal valvular function and morphology in the presence of flow or innocent murmurs.

VALVULITIS: MINIMAL ECHOCARDIOGRAPHIC CRITERIA FOR PATHOLOGICAL REGURGITATION

ARF most commonly affects the left-sided cardiac valves, and regurgitation is frequently mild during the first episode.[35,42] Severe aortic or mitral regurgitation, however, does occur in approximately 10% of patients at first presentation.[47] If valvulitis is not found at presentation, it may appear within two weeks,[39] and usually within six weeks.[47] Valvular regurgitation can be accurately graded with continuous-wave and colour Doppler echocardiography as nil, physiological, mild, moderate or severe for both rheumatic[39] and non-rheumatic valve disease.[89-92]

The minimal criteria for a diagnosis of pathological regurgitation for the aortic and mitral valve are summarised in *Table 6.9*.[86] To be classified as pathological on colour Doppler, the regurgitant jet must extend substantially beyond the valvular closure-line (by 2 cm for MR, and by 1cm for AR), and be visualised from two views, although it only has to meet the required jet length in one view. On continuous-wave Doppler, the regurgitant jet must be high velocity and pan-diastolic (for AR) or pan-systolic (for MR). These criteria can distinguish a small colour jet of physiological regurgitation in a normal child from pathological regurgitation.[90-97]

Regurgitation of the right-sided cardiac valves (tricuspid and pulmonary valve) is extremely rare without aortic or mitral valve involvement.[98] For this reason, a diagnosis of carditis should not be based on purely right-sided regurgitation alone. Although pulmonary and/or 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.[90]

Table 6.10. Minimal echocardiographic criteria to allow a diagnosis of pathological valvular regurgitation

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

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

AR, aortic regurgitation; MR, mitral regurgitation.

MORPHOLOGICAL CHANGES ASSOCIATED WITH RHEUMATIC CARDITIS

Acute rheumatic carditis is characterised by annular dilation and chordal elongation leading to anterior, and less commonly, posterior mitral valve prolapse.[88] Chordal rupture can also occur and result in a flail leaflet and significant MR.[16,88,99-101] Beading or nodularity of the leaflet tips can also be noted during an episode of ARF.[16,35] More chronic anatomic or morphological changes include leaflet and chordal thickening, chordal and commissural fusion of the mitral valve, restricted leaflet motion and later calcification.[101] Evolution to mitral stenosis (MS) is rarely observed in young children in Australia[102] but is more commonly seen in adolescents and adults. The experienced echocardiographic operator can use these morphological features as supportive evidence of a rheumatic aetiology of valvulitis *(Table 8.2)*.

ECHOCARDIOGRAPHY IN ARF RECURRENCES

In a patient with established RHD, the diagnosis of acute carditis during a recurrence of ARF relies on the accurate documentation of the cardiac findings before the recurrence, so that new clinical or echocardiographic features can be confirmed. New findings may include worsening severity of an existing valve lesion or affliction of an additional valve.

LEFT VENTRICULAR SIZE AND FUNCTION

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 LV function (e.g. single-plane ellipse and Simpson's methods of discs).[45] Impairment of systolic function and LV/left atrium dilation only occurs in the setting of significant valvular dysfunction.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Many cardiac surgical centres now routinely use three-dimensional echocardiography (3DE) to further evaluate RHD, both in its acute and chronic phases.[103] It facilitates more detailed assessment of the mechanism of regurgitation, and hence, aids surgical decision-making.

EVIDENCE OF SUBCLINICAL RHEUMATIC VALVE DAMAGE

Subclinical rheumatic carditis that is silent on auscultation, but detectable by echocardiography, has been recognised worldwide as a manifestation of ARF.[34,39,44,104-117] This echocardiographic finding has been incorporated as a major diagnostic criterion for ARF in the Australian and the New Zealand guidelines[118] for high-risk ARF populations since 2006. *(Table 6.5)* It was subsequently incorporated as a major diagnostic criterion for ARF for both high-risk and low-risk groups in the 2015 AHA revised Jones criteria with which this edition of the Australian guidelines now aligns.[3] This is supported by data indicating that the course of subclinical carditis[116,117] appears similar to that of mild carditis with an audible murmur.[41,117]

A systematic review in 2007 estimated the prevalence of subclinical carditis as 17% among those with ARF.[116] Echocardiographic findings persisted or progressed in 45% of cases.[116] A study from North Queensland reported that 71% of their patients with subclinical carditis had a long-term valvular consequence.[14] This indicates importance of prescription of and adherence to secondary antibiotic prophylaxis after detection of subclinical carditis. Complete echocardiographic resolution of mild clinical carditis can be expected within five years in two-thirds of patients with high levels of adherence to secondary prophylaxis.[41]

CASE STUDY

Sam's Story

Background

Sam is a nine-year-old Aboriginal boy who lives in a rural community in Western Australia. One day he noticed that he had strange movements in his hands which caused him to drop things; his speech was mumbled, and he was tired all the time. His mother was worried and took him to the hospital believing he had ARF. She recognised the symptoms from her own experience with ARF as a young woman.

Hospitalisation

Sam stayed in hospital for a few months; *"I know it was a long time because I missed Christmas and the start of the school year. I was scared and upset because the doctors did not listen to my mum when she said it was rheumatic fever. The doctors even took my appendix out, but the appendix had nothing wrong with it."*

Sam had been exhibiting signs of Sydenham chorea associated with ARF and, after many tests, he was eventually also diagnosed with RHD, with echocardiogram showing heart valve damage.

Living with RHD

The lengthy hospital admission and delayed diagnosis resulted in long-lasting social, emotional and health effects.

"I regret not getting the proper treatment sooner. I couldn't even hold a pen properly and I had trouble reading. Sometimes I still get my words muddled and this makes me shame (embarrassed). I missed a lot of school and opportunities like going to boarding school down south with my cousin. The school thought I was dumb and put me in the learning difficulties class."

Sam never had any problems with schooling before his illness. He is determined to show people that he can still do amazing things. *"It was hard seeing my mum so upset, I try to protect her now from getting upset about my illness. There are family pressures too, because sometimes my brothers and sisters think I get special treatment."*

Sam wants to stay positive and does not let RHD get him down.

"I like to set my own challenges like learning to play the trumpet and trying harder at sports, and I want to go to the clinic by myself one day to get my needles to give my mum a break. When I get mumbled words, I stop and just listen to my friends talking and when my hands get all shaky I hold on to something."

Discussion

A delayed or missed diagnosis of ARF can have serious consequences for the patient and the family. This extends to family and social relationships, work and schooling, missed opportunity and an increased reliance on health services.

Health staff need to be aware of ARF in populations that are at high risk; symptoms can be subtle.

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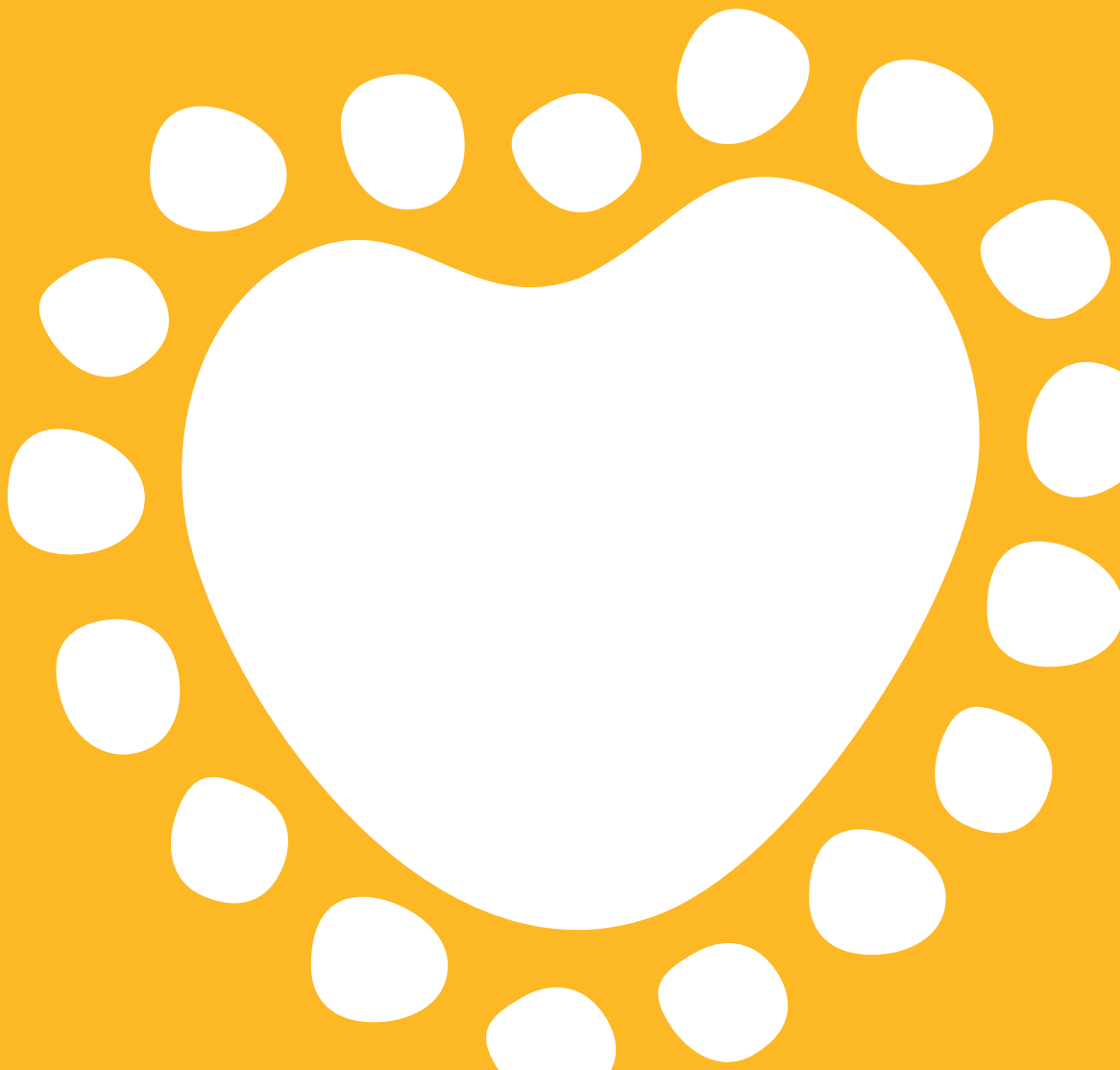
CHAPTER 7

Management of acute rheumatic fever



Management of acute rheumatic fever

CHANGES FROM THE SECOND (2012) EDITION

1. *Probable ARF – 'Highly suspected'* has now been renamed **Probable ARF**.
2. *Probable ARF – 'Uncertain'* has now been renamed **Possible ARF**.
3. The Priority definitions in the 'priority classification system' for presence and severity of RHD have changed to align with appropriate timing of follow-up.
4. Non-steroidal anti-inflammatory drugs are recommended ahead of aspirin in children requiring anti-inflammatory treatment.
5. Expanded therapeutic approaches for Sydenham chorea are provided.

KEY INFORMATION

- People suspected to have acute rheumatic fever (ARF) should be referred as soon as possible for investigations (including echocardiography), treatment and education.
- Admission to a hospital with echocardiography services is strongly recommended in order to facilitate correct diagnosis. Echocardiographic findings inform the management plan including recommended duration of secondary prophylaxis.
- While the diagnosis is uncertain, giving salicylate and non-steroidal anti-inflammatory drug (NSAID) therapy should be deferred because they might mask symptom evolution, and thereby impede correct diagnosis.
- 'Suspected ARF' is a term that applies during diagnostic workup. For each ARF episode, a final diagnosis should be reached and specified as either:
    - definite ARF (initial or recurrence);
    - probable ARF (initial or recurrence);
    - possible ARF (initial or recurrence);
    - not ARF.
- For definite ARF, a 'priority' grade based on the presence and severity of any accompanying RHD should also be provided, using the revised priority classification *(Table 7.4)*. The priority determines which care plan to use, including frequency of medical reviews and echocardiograms.
- People diagnosed with ARF should be:
    - notified to the local Disease Control Unit or Public Health Unit in accordance with jurisdictional legislation *(Table 13.1)*; and
    - registered with the jurisdictional RHD Control Program, with details of their secondary prophylaxis requirements *(Table 13.2)*.
- The pillars of management are eradication of the inciting infection using penicillin (or an alternative if allergic to penicillin) and management of symptoms with analgesic / antipyretic agents as needed.

Table 7.1. Medications used for acute rheumatic fever

INDICATION	MEDICATION OPTIONS LISTED IN ORDER OF PREFERENCE	COMMENT
Eradication of inciting streptococcal infection	1. Benzathine benzylpenicillin G (BPG) 1,200,000 units (child <20 kg: 600,000 units; ≥20 kg: 1,200,000 units) IMI single dose ***or*** 2. Phenoxymethylpenicillin 500 mg (child: 15 mg/kg up to 500 mg) orally 12-hourly for 10 days	Streptococcal infection may not be evident by the time ARF manifests (e.g. cultures often negative) but eradication therapy for possible persisting streptococci is recommended nonetheless. Intramuscular penicillin is preferred due to better adherence and its ongoing use in secondary prophylaxis.
	3. *Penicillin hypersensitivity (non-severe)*: cefalexin 1 g (child: 25 mg/kg up to 1 g) orally, 12-hourly for 10 days	Between 3 and 30% of Group A Streptococcus isolates internationally are resistant to macrolide antibiotics (e.g. azithromycin).
	4. *Immediate penicillin hypersensitivity*: azithromycin 500 mg (child: 12 mg/kg up to 500 mg) orally daily for 5 days	
Initial analgesia while awaiting diagnostic confirmation: mild-moderate pain	Paracetamol 1000 mg (child 15 mg/kg) orally, 4-hourly up to a maximum of 60 mg/kg/day or 4000 mg/day	Preferred initial analgesia during diagnostic uncertainty, to avoid the masking effect that anti-inflammatory use can have on migratory joint symptoms, fever and inflammatory markers.
Initial analgesia while awaiting diagnostic confirmation: severe pain	Tramadol immediate-release 50 to 100 mg (child 1 to 2 mg/kg) orally, 4-hourly up to a maximum of 400 mg/day	As above but for severe pain. Note safety warnings to avoid tramadol (or codeine) in children aged <12 years due to variable metabolism; therefore, use only when strong analgesia is essential and cautious monitoring is available.
Symptomatic management of arthritis/arthralgia after confirmation of ARF diagnosis	1. Naproxen immediate-release 250-500 mg (child 10–20 mg/kg/day) orally twice daily, up to a maximum of 1250 mg daily ***or*** 2. Ibuprofen 200-400 mg (child 5-10 mg/kg) orally three times daily, up to a maximum of 2400 mg daily ***or*** 3. Aspirin adults and children 50-60 mg/kg/day orally, in four to five divided doses. Dose can be escalated up to a maximum of 80-100 mg/kg/day in four to five divided doses.	Naproxen may be safer than aspirin, and convenient due to twice daily dosing and the capability oral suspension. Ibuprofen is well tolerated and readily available but data and experience with its use is less in ARF than naproxen. The dose of NSAIDS needed for ARF is generally higher than the dose recommended for other conditions, therefore it may be appropriate to commence at the higher dose range. Due to the rare possibility of Reye's syndrome in children, aspirin may need to be ceased during intercurrent acute viral illness, and influenza vaccination is strongly recommended.
Symptomatic management of moderate to severe chorea *(Table 7.6)*	1. Carbamazepine 3.5 to 10 mg/kg per dose orally, twice daily 2. Sodium valproate 7.5 to 10 mg/kg per dose orally, twice daily	Treatment of Sydenham chorea should be considered if movements interfere substantially with normal activities.

Chapter 7 MANAGEMENT OF ACUTE RHEUMATIC FEVER

Table 7.1. Medications used for acute rheumatic fever (continued)

INDICATION	MEDICATION OPTIONS LISTED IN ORDER OF PREFERENCE	COMMENT
Symptomatic management of very severe chorea / *chorea paralytica* *(Table 7.6)*	In addition to an anticonvulsant agent, consider adding corticosteroid: Prednisone/prednisolone 1 to 2 mg/kg up to a maximum of 80 mg orally, once daily or in divided doses	
Symptomatic management of carditis	Paediatric dosing: Furosemide (frusemide) 1 to 2 mg/kg orally as a single dose, then 0.5 to 1 mg/kg (to a maximum of 6 mg/kg) orally, 6- to 24-hourly Spironolactone 1 to 3 mg/kg (initially) up to 100 mg orally, daily in 1 to 3 divided doses. Round dose to a multiple of 6.25 mg (a quarter of a 25 mg tablet). Enalapril 0.1 mg/kg orally, daily in 1 or 2 divided doses increased gradually over 2 weeks to a maximum of 1 mg/kg orally, daily in 1 or 2 divided doses, other ACE inhibitors (captopril, lisinopril, ramipril, perindopril)	Treatment of heart failure may be required in severe, acute carditis. Seek advice from a specialist cardiologist. Choice of ACE inhibitor will vary depending on the clinical situation. Seek advice from a specialist cardiologist.
	Adult dosing: Furosemide (frusemide) 20–40 mg oral or intravenous as a single dose followed by 20–40 mg oral or intravenous 8–12 hourly. Ongoing dose adjustment based on clinical progression and renal function. Spironolactone may be added for patients having limited or no response to loop diuretic, 12.5–25 mg spironolactone orally daily Nitrate therapy may be added for patients having limited or no response to diuretic therapy, whose systolic blood pressure is greater than 90 mmHg. Intravenous or topical glyceryl trinitrate may be used. ACE inhibitor is recommended in patients with moderate or severe left ventricular systolic dysfunction, unless contraindicated	The management of acute carditis follows the same principles as the management of acute heart failure. This table gives a guide to the initial management of acute heart failure due to acute carditis in adults. Seeking advice from a specialist cardiologist early is strongly recommended.
	Digoxin 15 micrograms/kg orally, as a single dose, then 5 micrograms/kg after 6 hours, then 3–5 micrograms/kg (adult: 125–250 micrograms) orally, daily	Digoxin is rarely used in the treatment of acute carditis. Seek advice from a specialist cardiologist.
Disease-modifying (immunomodulatory) treatments	Prednisone/prednisolone 1 to 2 mg/kg up to a maximum of 80 mg orally, once daily or in divided doses	Considered for use in selected cases of severe carditis, despite meta-analyses in which overall benefit was not evident.

IMI, intramuscular injection; NSAID, non-steroidal anti-inflammatory drug; ACE, Angiotensin-converting enzyme

DISCUSSION

> *"The use of traditional healers to complement western medicine is important to Aboriginal and Torres Strait Islander peoples with ARF or RHD."*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

The priority in the first few days after a person presents with suspected ARF is confirmation of the diagnosis. The priorities in managing ARF are outlined in *Table 7.2*.

Healthcare providers who have trained and worked in settings where ARF is rare may underestimate the importance and urgency of accurate diagnosis and prompt treatment, which includes admission to hospital. This highlights the need for new medical and nursing staff in hospitals and primary care settings in these high-burden regions to undergo education about ARF and RHD. Education should be embedded into clinical orientation programs, including systems for regular clinical updates.

The guidance in this chapter relates to individuals who present with features suggestive of ARF. RHD detected during screening is described in *Management of Rheumatic Heart Disease*.

PRE-HOSPITAL MANAGEMENT OF SUSPECTED ARF

The diagnosis of ARF is often not evident on first presentation to a primary care centre, since symptoms may evolve over several weeks. Primary care clinicians require a high degree of suspicion for ARF; presentations can be very subtle. The majority of RHD diagnoses are made in individuals whose prior ARF episodes have never been recognised (in the Northern Territory, around 75% of RHD cases),[1] illustrating the high proportion of people with ARF who either do not present to primary care services, or do present and are misdiagnosed. Retrospective chart reviews reveal that individuals with RHD often have presented to health services with joint pain or unexplained fever which would have met criteria for possible, probable or definite ARF *(unpublished)*. Had the patient been referred to hospital for echocardiogram, ECG, blood tests and close monitoring of symptom evolution, and a diagnosis of ARF made, then secondary prophylaxis could have been instituted to avert the development or mitigate the severity of RHD.

A first dose of benzathine benzylpenicillin G (BPG) should be given (or alternative oral antibiotic regimen commenced) prior to hospitalisation to individuals with suspected ARF. If fever is documented, blood cultures should be obtained prior to antibiotic administration since alternative diagnosis such as septic arthritis or endocarditis may be present.

The arthritis, arthralgia and fever of ARF respond to NSAIDs.[2-4] However, early administration of NSAIDs may mask the development of migratory polyarthritis or fever. Until the diagnosis is confirmed, it is therefore recommended that joint pain be treated with paracetamol.[5] This approach may still mask a fever meeting diagnostic criteria of ≥38°C, but fever tends to occur early in the illness and hence is likely to be evident prior to commencing antipyretic analgesics. A history of subjective fever is also sufficient as a minor Jones criterion *(Table 7.2)*. Severe joint pain may require escalation of analgesia e.g. to tramadol, but there are significant safety concerns with use of this agent in children aged under 12 years.[6]

Occasionally, when the diagnosis has already been confirmed and the patient is not unwell (e.g. mild arthralgia or mild recurrent Sydenham chorea in a child with no other symptoms or signs), outpatient management may be appropriate if a timely echocardiogram is also

able to be obtained (i.e. within 4 weeks of symptom onset). While hospitalisation is strongly recommended for the reasons outlined below, in some cases management in the community may be more patient-centred and sensitive to cultural needs. In such cases, health staff must ensure accurate documentation of history and examination findings including vital sign monitoring (regular temperature, pulse rate and rhythm, respiratory rate and blood pressure). Video recording after obtaining patient / guardian consent of examination findings e.g. to demonstrate joint examination findings or chorea, can be a helpful way of providing accurate information to the consulting off-site advising doctor. Appropriate investigations, treatment, health education and patient registration must all be completed, and consultation with an expert is essential. ESR testing can be challenging in remote communities but can help make the diagnosis of ARF if elevated when CRP is not meeting the threshold. Collect into the correct tube required by the pathology service and this can be stored at 4°C for up to 24 hours before processing.

People managed in the community should have an integrated care plan that includes nursing, medical, and allied health involvement, with consideration for tradition and culture, and which is centred on the needs of the patient. Timely echocardiography is essential for all people with suspected ARF.

All suspected and confirmed new and recurrent ARF episodes should be reported by the treating Medical Officer to the local Disease Control Unit according to local legislation for notifiable conditions *(Table 13.1)*.

HOSPITAL MANAGEMENT OF ARF

Where available, hospital-based Aboriginal and Torres Strait Islander health staff and Aboriginal Liaison Officers should be engaged at the time of admission for Aboriginal and Torres Strait Islander patients.

Patients with suspected ARF (first episode or recurrence) should be hospitalised as soon as possible after the onset of symptoms.[5] This ensures that investigations are performed, especially echocardiography, ECG, inflammatory markers, streptococcal serology, and investigation that may be indicated to exclude differential diagnoses *(Table 7.2)*. Hospitalisation also provides an opportunity for clinical observation and regular temperature charting for a period prior to commencing anti-inflammatory analgesics, to confirm the diagnosis. In cases of mild ARF, it is common for symptoms to have resolved by the time the individual reaches hospital, emphasising the importance of clinical history obtained from the individual, their family and the community primary care staff.

Health literacy and beliefs among Aboriginal and Torres Strait Islander peoples around health can impact the potential for an accurate diagnosis. From a cultural perspective, it is important that the most appropriate person(s) provide details about the medical history. This may not be the patient. Communication between the healthcare provider and the patient and family should be conducted in a language and setting in which clear and accurate information can be safely relayed.

Table 7.2. Priorities in managing ARF in the acute setting

ADMISSION TO HOSPITAL	
Admit all patients suspected to have ARF	
DETERMINE THE DIAGNOSIS	
The diagnosis is determined based on • Understanding of epidemiological risk • History obtained from primary care staff and/or patient and their family • Clinical observation prior to anti-inflammatory treatment: use paracetamol (first line) during this time if required for fever or joint pain • Investigations *(Table 7.3)* • Follow up findings ○ The final diagnosis may not be clear until several months after the acute episode; e.g. if Jones criteria are not met for a diagnosis of definite ARF but a follow up echocardiogram confirms rheumatic valvular changes not visible at the outset, then the diagnosis shifts from possible or probable to definite ARF	
TREATMENT	
All cases	Provision of supportive, culturally safe care Antibiotic management using pain avoidance techniques for delivery of intramuscular injection *(Table 7.1)* Influenza vaccine - annual influenza vaccination is part of the long-term care plan but needs to be considered acutely as a strategy to reduce the risk of Reye's syndrome for children receiving aspirin
Arthritis and fever	Paracetamol (first line) until diagnosis confirmed Naproxen, ibuprofen or aspirin once diagnosis confirmed, if arthritis or severe arthralgia present Mild arthralgia and fever may respond to paracetamol alone
Sydenham chorea	No pharmacological treatment for mild cases Anticonvulsant such as carbamazepine or sodium valproate if symptoms are debilitating or impacting significantly on function *(Table 7.1)* Stepwise use of other agents as per text below *(Figure 7.1)* . Evidence base is limited
Carditis/ heart failure	Bed rest, with mobilisation as symptoms permit Anti-failure medication as required *(Table 7.1)* Corticosteroids for severe carditis or pericarditis with effusion *(Tables 7.1 and 7.5)* Valve surgery for life-threatening acute carditis (rare)

Table 7.2. Priorities in managing ARF in the acute setting (continued)

LONG-TERM PREVENTIVE MEASURES AND DISCHARGE PLANNING

Prepare for discharge to primary care facility and follow-up

- Notify case to the jurisdictional ARF/RHD register (where it exists) *(Table 13.1)*
- Contact the patient's local primary care service and community pharmacist
- Provide a discharge letter to the patient or family, the primary care service and community pharmacist including information about:
  - ARF diagnosis (possible, probable, definite);
  - priority classification of RHD if also present (Priority 1, 2 or 3) *(Table 11.2)*;
  - a recommended care plan summary based on disease priority classification *(Table 7.4)*;
  - date of last BPG administration ;
  - required frequency of BPG, and the due date of next dose;
  - date of next medical appointment;
  - date of next echocardiogram;
  - information about vaccinations administered in hospital;
  - relevant contraception information and/or pregnancy planning for women.
- Arrange dental review and ongoing dental care to reduce risk of endocarditis

Family and community engagement

- Involve family in care
- Engage interpreters for patients and families whose first language is not English
- Provide education that is culturally appropriate and age-appropriate
- With consent from family, notify school (for school-aged children) to encourage support for ongoing care
- Acknowledge the significance of a chronic disease diagnosis in childhood, including the need for linkage with peer-support networks, psychological support, ongoing education, transition care as the individual ages, and self-management support. Where indicated, engage adolescent support services *(Table 11.4)*.

Five priorities during hospitalisation

1. Classify as either:
   - definite ARF (initial or recurrence);
   - probable ARF (initial or recurrence);
   - possible ARF (initial or recurrence);
   - not ARF.
2. Notify the case to the local Disease Control Unit in accordance with jurisdictional legislation *(Table 13.1)*.
3. Register the patient with the jurisdictional RHD Control Program and provide details of secondary prophylaxis requirements *(Table 13.2)*.
4. Provide education for the patient and their family (including for ARF recurrence).
5. Commence secondary prophylaxis: *(Table 10.1)*
   a. Ensure that the secondary prophylaxis regimen has been commenced prior to discharge, even if an alternative oral antibiotic regimen has been given for treatment of Strep A infection.
      i. Only one dose of BPG needs to be given, so the dose should not be repeated if it has been given already for Strep A eradication.
   b. The second dose of BPG should be scheduled to be given 21-28 days after the first dose (no later than 28 days).
   c. In the case of ARF recurrence, ensure secondary prophylaxis is given as required, and the register is notified as per jurisdictional protocol.

Principles of management of ARF are shown in *Table 7.2* and clinical evaluation and monitoring in *Table 7.3*.

Table 7.3. Testing and monitoring of ARF in the acute setting

Investigations	Always request:
	• Electrocardiogram (ECG)
	• Echocardiogram
	• Full blood count (FBC)
	• Erythrocyte sedimentation rate (ESR)
	• C-reactive protein (CRP)
	• Streptococcal serology (anti-streptolysin O and anti-DNase B)
	In relevant situations:
	• Throat swab
	• Skin sore swab
	• Blood cultures
	• Synovial fluid aspirate
	  ○ ensure sample does not clot by using correct tubes which have been well mixed and transported promptly to the laboratory
	  ○ include request for cell count, microscopy, culture and gonococcal polymerase chain reaction (PCR)
	• Pregnancy test
	• Creatinine test (UEC [urea, electrolytes, creatinine]) since NSAIDS can affect renal function
	Tests to exclude alternative diagnoses, depending on clinical presentation and locally endemic infections:
	• Autoantibodies, double-stranded DNA, anti-cyclic citrullinated peptide (anti-CCP) antibodies
	• Urine for *Neisseria gonorrhoeae* molecular test
	• Urine for *Chlamydia trachomatis* molecular test
	• Serological or other testing for viral hepatitis, Yersinia spp, cytomegalovirus (CMV), parvovirus B19, respiratory viruses, Ross River virus, Barmah Forest virus

Clinical observations	Temperature, pulse, respiratory rate, blood pressure 4 times daily On occasions of rapid or irregular pulse, ensure ECG is recorded Thorough skin examination for skin sores, erythema marginatum, subcutaneous nodules Regular assessment of joints
Diet	Standard healthy diet Early dietary advice if overweight (especially if in heart failure), to avoid further weight gain. Consider testing lipids, HbA1c. Weekly weight
If clinical carditis is present	Document cardiac symptoms and signs Include sleeping pulse in regular nursing observations (e.g. 0200 hours), as long as this can be done without waking the patient Individuals with heart failure or severe acute valve disease should be encouraged to rest in bed and avoid exertion until symptoms are improving Daily weight and fluid balance chart Weekly echocardiograms in severe acute valvulitis while patient is hospitalised, if able

Education

Effective communication supports self-management. Poor communication is a significant barrier to care, particularly if there are language, cultural or social barriers. For Aboriginal and Torres Strait Islander peoples, clinical yarning has been used in clinical consultations to build rapport and trust between patients and healthcare providers. It is a conversational, relaxed, open-ended style of communication that allows storytelling to understand a patient's health issue within the context of their life, and to communicate health information. It marries a cultural base – a consultation style that is culturally congruent with Aboriginal ways of communicating – to traditional biomedical knowledge.[7]

Hospitalisation offers an important opportunity to provide education for patients and families, using culturally appropriate educational materials in the patient's first language. RHDAustralia has an online archive of video, audio and written resources translated into common Australian Aboriginal languages (See HealthInfoNet, KAMSC and RHDA resources).

Further education by local health staff to reinforce information about ARF is of critical importance once the patient has returned home. Evidence from a study conducted with Northern Territory Aboriginal peoples with a history of ARF or RHD shows that most initial education provided by healthcare providers did not result in any knowledge being imparted.[8] Genuine knowledge transfer occurs when information is repeated over time, in the person's first language, and in a culturally appropriate way – such as in an environment in which the person feels comfortable, drawing on local learning styles such as the use of metaphor to explain medical concepts.[9] It is also facilitated if the health professions work in collaboration with Aboriginal Health Workers, Aboriginal Health Practitioners and Aboriginal Liaison Officers to provide in-person support to allow people and their families to ask questions and alleviate the concerns.[10]

Aboriginal and Torres Strait Islander health staff often greet, triage, treat and support patients in primary care settings. Education, training, and empowerment of the Aboriginal and Torres Strait Islander health workforce will enable them to support patients and their families in line with clinical best practice.

Management of possible and probable ARF

Patients with ARF not fulfilling definite criteria are categorised as having **possible** or **probable ARF**, and treatment recommendations differ substantially. The distinction between possible and probable ARF depends to a certain extent on what the clinician thinks is most likely to be the diagnosis. In addition to the definitions provided in the ARF Diagnosis chapter, (See *Chapter 6. Diagnosis of ARF, ARF categorised as definite, probable & possible*) clinical judgement is needed in assigning a diagnostic category. For instance, in a high-risk individual with recurrent episodes of possible ARF over several years in whom other diagnoses have been excluded, it may be appropriate to make a diagnosis of probable rather than possible ARF.

The proportion of individuals with probable ARF who progress to definite ARF and/or RHD is unclear pending further studies, but clinical anecdotes illustrate an important subset of individuals who do progress. Therefore, the conservative approach is to ensure that people with **probable ARF** receive the same secondary prophylaxis regimen as people with definite ARF without RHD (Priority 3); that is, BPG for five years or until age 21, whichever is longer *(Table 10.2)*.

The recommendation in **possible ARF** is for 12 months of BPG only, with ongoing review for another 12 months thereafter *(Table 10.2)*. Clinical discretion should apply when considering extension of the duration of secondary prophylaxis in high-risk individuals, such as people with a strong family history of RHD and significant epidemiological risk factors *(Table 7.1)*. Assigning people with possible ARF to 12 months of treatment is a strategy that balances risks (personal and healthcare system costs of 28-day BPG injections) against benefits (avoiding further streptococcal infections during the highest-risk period for ARF recurrences, which is in the first 12 months after initial ARF).[11] It has been shown that regular BPG for ARF prophylaxis is associated with reduced mortality overall.[12] This highlights that for people living in high-risk settings where communicable penicillin-susceptible childhood diseases are common, including people who have not had ARF, there may be benefits of penicillin beyond ARF prevention alone.

Management according to priority classification

A priority classification system to grade disease severity has been in use in Australia for several decades for individuals diagnosed with ARF or RHD. This determines general principles of the care plan appropriate for that individual. This system was initiated in the Northern Territory in 2001 as a clinical tool to help healthcare providers recognise which patients required closest follow up, and to appropriately allocate resources according to need. Modifications to the priority classification system have been made, including further revisions in the current edition of the guideline. Management of ARF should align with the priority classification, which should be assigned in accordance with *Table 7.4*.

Table 7.4. Priority classification and recommended follow-up (updated March 2022)

DIAGNOSIS	RECOMMENDED FOLLOW-UP PLAN†
Priority 1 Severe RHD‡ High risk post-valve surgical patients§ ≥ 3 episodes of ARF within the last 5 years Pregnant women with RHD (of any severity) may be considered Priority 1 for the duration of the pregnancy Children ≤ 5 years of age with ARF or RHD	Specialist review: at least 6 monthly Echocardiogram: at least 6 monthly Medical review: at least 6 monthly Pregnant: see *Figure 12.1 for care pathway* Dental review: within 3 months of diagnosis, then 6 monthly
Priority 2 Moderate RHD‡ Moderate risk post-valve surgical patients§	Specialist review: yearly Echocardiogram: yearly Medical review: 6 monthly Dental review: within 3 months of diagnosis, then 6 monthly
Priority 3 Mild RHD‡ ARF (probable or definite) without RHD, currently prescribed secondary prophylaxis Low risk post-valve surgical patients§	Specialist review: 1 – 3 yearly Echocardiogram: children ≤ 21 years: 1-2 yearly, > 21 years: 2-3 yearly Medical review: yearly Dental review: yearly
Borderline RHD currently prescribed secondary prophylaxis	Medical review: 1-2 years after diagnosis, and 1-2 years after ceasing secondary prophylaxis Echocardiogram: 1-2 years after diagnosis, and 1-2 years after ceasing secondary prophylaxis
Priority 4 History of ARF (possible, probable or definite) and completed secondary prophylaxis Borderline RHD not on secondary prophylaxis Resolved RHD and completed secondary prophylaxis	Specialist referral and echocardiogram: 1 year, 3 years and 5 years post cessation of secondary prophylaxis *(or following diagnosis in the case of Borderline RHD not on secondary prophylaxis)* Medical review: yearly until discharge from specialist care and then as required Dental review: yearly or as required

† Frequency should be tailored to the individual following specialist assessment. All patients should be given influenza vaccine annually and have completed pneumococcal vaccinations as per Australian Immunisation Handbook. Intervals for medical and specialist review and echocardiography are a guide and may vary for specific individuals. Medical and dental reviews may be combined with general health check-up. People with RHD require endocarditis prevention as indicated. (See *Chapter 11. Management of RHD, Prevention of infective endocarditis*).

‡ See *Table 10.2* for definitions of RHD severity.

§ While post-surgical RHD is by definition severe RHD, post-surgical risk varies for individuals due to age, type of surgery, recurrence of ARF, adherence with secondary prophylaxis and other factors. Priority category for post-surgical RHD varies as listed in this Priority classification table and should be determined by specialist cardiologist/paediatrician/physician. (See *Chapter 11. Management of RHD, Monitoring following valve surgery*).

ANTIBIOTIC TREATMENT

People presenting with definite, probable or possible ARF require antibiotics for treatment of persisting streptococcal infection or asymptomatic respiratory tract carriage.

Controlled studies have failed to show that treating ARF with large doses of penicillin affects the outcome of rheumatic valvular lesions one year later.[13,14] Despite this, most authorities recommend a course of penicillin, even if bacterial cultures for Strep A are negative, to ensure eradication of streptococci that may persist, for example in the upper respiratory tract. Although streptococci may not be present in high enough numbers to be culturable from the throat by the time of ARF presentation, findings from a recent study suggest that pathogenic Strep A may still be detectable in the throat using molecular tests which are more sensitive than culture (See *Chapter 6. Diagnosis of ARF, Streptococcal A rapid diagnostics*).[15]

Strep A (Streptococcus pyogenes) isolates are almost universally susceptible to penicillin and related beta lactam antibiotics, e.g. cephalosporins. The organism appears to lack capacity to express beta-lactamase that would confer resistance.[16] Mutations in penicillin-binding proteins conferring decreased susceptibility to some beta lactam antibiotics but not penicillin have been reported, but very rarely, and never in Australia.[17]

Strep A can, however, readily become resistant to macrolide antibiotics (azithromycin, roxithromycin, erythromycin etc) with marked geographical variation; e.g. 3% in some Australian studies, 30% in studies from Italy and South Korea.[16,18] Resistance to macrolide antibiotics generally also confers resistance to clindamycin.

Treatment of fever

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

Treatment of arthritis and arthralgia

Salicylates (aspirin) have traditionally been recommended as first-line treatment, because of the extensive historical experience with their use in ARF and an established evidence base.[5,19,20] However, there is increasing clinical experience with other NSAID therapy, particularly naproxen[21-24] and ibuprofen. These agents are now used in preference to aspirin in childhood inflammatory conditions (with the exception of Kawasaki disease) and have less toxicity than high-dose aspirin.[21,24]

Anti-inflammatory therapy should be commenced in patients with arthritis or severe arthralgia once the diagnosis of ARF has been made. In such cases, paracetamol should be used instead for initial pain relief *(Table 7.1)*.

The arthritis of ARF has been shown in controlled trials to respond dramatically to salicylate or other NSAID therapy,[2-4] often within hours, and almost always within three days. If the symptoms and signs do not remit substantially within several days of commencing regular anti-inflammatory medication at an appropriate dose, alternative diagnoses should also be considered. Having noted this, anecdotal experience especially of adults with ARF indicates that while improvement has occurred, limping and other functional impairment may persist for weeks.

The duration of treatment is dictated by the clinical response and improvement in inflammatory markers (ESR, CRP). Many patients need anti-inflammatory therapy for only one to two weeks (i.e. anti-inflammatory therapy can be stopped at two weeks if the patient is pain free with improved inflammatory markers). In some patients, joint symptoms may recur following the cessation of regular anti-inflammatory treatment (so-called 'rebound phenomenon'[25]); this does not indicate ARF recurrence, and can be treated with another course of anti-inflammatory therapy.[26] Clinical practice differs in relation to the duration of anti-inflammatory therapy. Many

patients have symptoms for a short duration only (less than one week) and only require symptomatic treatment with anti-inflammatory therapy for that period. Some patients who have persisting joint symptoms may require regular anti-inflammatory therapy for up to six weeks. In such cases, the anti-inflammatory dose can often be reduced after the initial one to two weeks.[27-29] As the dose is reduced, rebound symptoms may occur, as described earlier, and can be treated with a brief course of higher-dose anti-inflammatory therapy. The majority of ARF episodes have fully subsided within six weeks, and 90% resolve within 12 weeks.

Approximately 1 in 10 patients will have joint symptoms persisting for more than three months.

Some clinicians are guided by inflammatory markers as well as symptoms in determining duration of NSAID therapy but there is no evidence that this changes outcome, and no parameters have been established for threshold CRP and ESR levels to guide cessation.

Naproxen and Ibuprofen

The effectiveness of naproxen has been reported in a small retrospective review of 19 patients in the year 2000,[21] in open-label comparative study of naproxen and aspirin in 33 children in 2003,[22] and a large retrospective cohort study of 338 children in 2016.[21] In the open-label comparative study, efficacy was similar to aspirin, but gastrointestinal adverse effects were fewer with naproxen.[22] Similarly, in the large retrospective cohort, significantly fewer ARF patients who received naproxen developed gastric pain or hepatoxicity.[21] Thus, naproxen is advocated as a safer alternative to aspirin.[21,22] Naproxen also has the advantage of twice-daily dosing and is available in Australia as a suspension. Ibuprofen is a readily available NSAID and has also been used successfully in ARF at a dose of 30 mg/kg/day divided into three doses, although there are no published data to support its use in ARF.

Aspirin

Aspirin, when used, should be started at a dose of 50–60 mg/kg/day, up to a maximum of 80–100 mg/kg/day (4–8 g/day in adults) in four to five divided doses. If there is an incomplete response within two weeks, the dose may be increased to 125 mg/kg/day. At high doses, the patient should be carefully observed for features of salicylate toxicity (tinnitus, headache, hyperpnoea), gastritis and bleeding. Proton pump inhibitor (PPI) therapy may provide some gastric protection. If salicylate toxicity occurs, substitution with naproxen or ibuprofen should be considered, or the aspirin dose can be reduced to 60–70 mg/kg/day once symptoms are controlled, for the remainder of a several-week-long course.[28,30,31] There is a risk of Reye syndrome (encephalopathy with liver toxicity) in children receiving salicylates, particularly those who have an intercurrent viral infection such as influenza. Hepatotoxicity has also been described in up to 10% of children with ARF receiving high-dose aspirin therapy.[23] Annual influenza vaccination is part of the standard care plan for individuals with ARF or RHD of any priority classification but needs to be part of the acute management strategy for children prescribed aspirin during the influenza season.

Treatment of carditis and heart failure

An urgent cardiology assessment with chest X-ray and echocardiogram 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 cardiac failure, corticosteroids can be considered (detailed below), and angiotensin-converting enzyme (ACE) inhibitors may be used, particularly if aortic regurgitation is present, for their role in afterload reduction.[19] Digoxin is usually reserved for patients with supraventricular tachycardias, and may be associated with excess mortality.[32] There is little experience with beta blockers in heart failure due to acute rheumatic carditis, and their use is not recommended. Nitrate therapy may be added for patients having limited or no response to diuretic therapy, whose systolic blood pressure is greater than 90 mmHg. Intravenous or topical glyceryl trinitrate may be used (See *Chapter 11. Management of RHD, Management of RHD complications*).

Corticosteroids for carditis

The use of corticosteroids and other anti-inflammatory medications in rheumatic carditis has been studied in two meta-analyses.[33,34] These studies were performed more than 40 years ago, preceded the availability of echocardiography, and did not use drugs that are in common use today. The meta-analyses failed to suggest any benefit of corticosteroids or intravenous immunoglobulin (IVIg) over placebo, or of corticosteroids over salicylates, in reducing the risk of long-term heart disease.

Also, the available evidence suggests that salicylates do not decrease the incidence of residual RHD.[2,4] Therefore, salicylates are not recommended to treat carditis.

Corticosteroids may be considered for patients with heart failure in whom acute cardiac surgery is not indicated. This recommendation is not supported by evidence but is made because many clinicians believe that corticosteroids may lead to a more rapid resolution of cardiac compromise, and even be lifesaving in severe acute carditis.[34,35] Some clinicians believe corticosteroid therapy can play a useful role in severe rheumatic carditis, particularly in rheumatic pericardial effusions, advanced atrioventricular (AV) block and/or when cardiac dimensions are increasing. If corticosteroids are used at immunosuppressive doses/durations *(Table 7.5)*, screening for latent infections is required, followed by appropriate management of latent infections and prevention of opportunistic infections *(Table 7.5)*.

Meta-analyses indicate a lack of benefit of corticosteroids in altering RHD outcome. However, all studies were performed prior to the availability of echocardiography. Expert opinion recommends their use in carditis causing heart failure.

Corticosteroids are effective in reducing symptoms including pain associated with pericarditis; NSAIDs can usually be ceased.

Proton pump inhibitors should be considered prophylactically with corticosteroids e.g. if long courses are anticipated or NSAIDs cannot be ceased.

Screening for, and management of, latent infections is required prior to or at commencement of immunosuppressive doses of steroids.

If corticosteroids are used, the drug of choice is oral prednisone or prednisolone (1–2 mg/kg/day, to a maximum of 80 mg once daily or in divided doses). Intravenous methylprednisolone may be given in very severe cases. If one week or less of treatment is required, the medication can be ceased when heart failure is controlled, and inflammatory markers improve. For longer courses (usually no more than three 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. Mild to moderate carditis without cardiac failure does not warrant specific pharmacological treatment.

Table 7.5. Prevention of opportunistic infections in immunosuppressed individuals

Corticosteroid regimens used in ARF
Prednisone ***or*** prednisolone, 1–2 mg/kg/day, to a maximum of 80 mg once daily ***or*** in divided doses Intravenous methylprednisolone may be given in very severe cases
Corticosteroid regimens considered immunosuppressive
High dose pulsed corticosteroids In adults, prednisolone (or equivalent): ≥10 mg/day for ≥ 4 weeks ***or*** >20 mg/day for ≥2 weeks ***or*** total cumulative dose of 7 mg/kg within 1 month In children, prednisolone (or equivalent): >0.5 mg/kg/day for ≥2 weeks
Examples of screening tests required prior to commencing immunosuppressive doses of corticosteroid medication†
Tuberculosis: interferon gamma release assay ***or*** Tuberculin Skin Test (TST/Mantoux test) **Hepatitis B:** Hepatitis B serology with HBsAg, HBcAb and HBsAb. In patients with either a positive HBsAg ***or*** HBcAb, a hepatitis B DNA PCR should be ordered **Hepatitis C:** Hepatitis C antibody. If positive, an HCV RNA viral load and genotype should be ordered **HIV serology** **Melioidosis:** Melioidosis serology. If positive (an indirect haemagglutination titre of ≥ 1:40), swabs for melioidosis culture should be taken from throat, rectum and any wounds. Blood, urine and sputum (if any) should also be collected for melioidosis culture and a chest X-ray performed. If cultures are positive, full treatment is required **Strongyloidiasis:** Serology and if serology is positive ***or*** eosinophilia is present, also perform stool microscopy (single stool as a minimum, but 3 preferable). Treat with ivermectin **Scabies:** Examine skin for evidence of scabies infection, with or without associated pyoderma **Review of immunisation history:** provide any required immunisations when clinically appropriate to do so
Prevention and management of latent and opportunistic infections
Follow local guidelines regarding recommended actions guided by above results Avoid live viral vaccines (e.g. measles/mumps/rubella, varicella) which are contraindicated in individuals receiving immunosuppressive doses / durations of corticosteroids

† Depends on local epidemiology. Examples provided here are relevant to tropical northern Australia.
HBsAg, Hepatitis B surface antigen; HBcAb, Hepatitis B core antibody; HBsAb, Hepatitis B surface antibody; PCR; Polymerase chain reaction; RNA, Ribonucleic acid.

The potential major adverse effects of short courses of corticosteroids, including gastrointestinal bleeding and worsening of heart failure due to fluid retention, should be considered before they are used. Proton pump inhibitors should be considered prophylactically with steroids. Stress corticosteroid dosing should be considered for those with acute illness while on weaning doses of prednisone.

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

Role of surgery for ARF

Surgery is usually deferred until active inflammation of the heart has subsided. Valve leaflet or the rare occurrence of chordae tendineae rupture leads to severe regurgitation, necessitating emergency surgery. This can be safely performed by experienced surgeons, although the risk of adverse outcomes appears to be slightly higher than when surgery is performed after active inflammation has resolved.[36]

Valve replacement, rather than repair, is usually performed during the acute episode, because of the technical difficulties of repairing friable, inflamed valvular tissue. Nevertheless, highly 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 a shorter duration of carditis, fewer relapses and less cardiomegaly.[37] Strict bed rest is no longer routinely recommended for 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 four weeks. Some clinicians also use serum CRP and ESR as a guide to return to exercise. Patients with milder or no carditis should rest only as long as necessary to manage other symptoms, such as joint pain.

Treatment of Sydenham chorea

Table 7.6. Summary of Sydenham chorea management strategies

MANIFESTATION	DESCRIPTION	MANAGEMENT
All cases of Sydenham chorea	All	Antibiotic treatment of the preceding streptococcal infection *(Table 7.1)*
Mild chorea	Involuntary movements, incoordination and psychiatric features	Supportive measures: calm environment, avoidance of over-stimulation, rest, education about the condition
Moderate to severe chorea	Functional impairment, unsteady gait, difficulty attending to feeding and other self-care activities	Supportive measures plus anticonvulsant therapy with carbamazepine or sodium valproate. Some clinicians add risperidone or haloperidol when the response to anticonvulsant therapy is poor, but the evidence base is limited.
Very severe, refractory chorea and chorea paralytica	Persisting, significant functional impairment, bedbound due to falls risk or motor incapacity	Above measures plus corticosteroids If persisting symptoms, consider intravenous immunoglobulin therapy or plasma exchange

Sydenham chorea is a neuropsychiatric manifestation of ARF characterised variably by chorea, decreased muscle tone, and psychiatric and behavioural symptoms such as obsessive-compulsive symptoms and hyperactivity.

Most cases of Sydenham chorea are mild, and resolve spontaneously within a few weeks, and almost all cases resolve within six months.[38] Rarely, symptoms may last two to three years with fluctuations in severity, particularly during times of stress or intercurrent illness.[39,40] Mild or moderate chorea does not require pharmacotherapy but benefits from rest and a calm environment. Overstimulation or stress can exacerbate the symptoms. Hospitalisation can be useful in confirming the diagnosis and ensuring an opportunity for education and disease notification as well as reducing the stress that families face in dealing with abnormal movements and emotional lability, or if children have significant functional impairment (for example, unable to eat, unsteady gait at risk of falls or injury). Aspirin does not influence the effect or duration of rheumatic chorea.[41,42]

Treatments to reduce the degree of choreiform movements chiefly comprise anti-convulsant medications. An algorithm for the additive, step-wise use of anti-convulsant medications, neuroleptic agents, corticosteroids and experimental therapies, has been suggested.[43] Given the limited evidence base, this algorithm is not reproduced here, but the elements are discussed below.

Grading the severity of chorea

Severity ranges from very subtle choreiform movements to the patient being bed-bound. For clinical purposes, symptoms can be categorised as **mild** if involuntary moments or incoordination do not significantly interfere with daily activities; **moderate-severe** if there is functional impairment, unsteady gait, or difficulty attending to self-care activities; and **very severe** is there is persisting, significant impairment despite commencement of treatment. *Chorea paralytica* refers to most severe Sydenham chorea causing profound muscular atonia resulting in the patient being bed-bound, dysphagia and dysarthria.

For research purposes, response to therapy can be formally rated using the Universidade Federal de Minas Gerais (UFMG) Sydenham's Chorea Rating Scale (USCRS).[44,45] This tool provides a scale to grade the performance of daily living activities, behavioural abnormalities, and motor function of subjects with Sydenham chorea.

Differential diagnoses of chorea

Other causes of chorea such as systemic lupus erythematosus (SLE) or chorea gravidarum must be excluded. Some populations hyperendemic for ARF also have high rates of SLE, which mimics not only the joint symptoms of ARF, but also Sydenham chorea.[46] However, in high ARF-risk populations, most chorea presentations in children will be due to ARF, and neuroimaging is not needed routinely.[47]

Anti-convulsant agents

Carbamazepine is generally recommended as the first-line agent due to its preferable safety profile, followed by sodium valproate.[48,49] Haloperidol (a dopamine agonist) was previously considered the first-line medical treatment for chorea but is no longer recommended due to potential extra-pyramidal side effects, to which Sydenham chorea patients appear especially vulnerable.[43] A small (n=18), prospective comparison of carbamazepine, sodium valproate and haloperidol concluded that sodium valproate was the most effective.[50] Another small study (n=24) indicated that carbamazepine and sodium valproate had similar efficacy.[49] On balance, due to the potential for liver toxicity with sodium valproate, and teratogenicity, carbamazepine is preferred first line. Sodium valproate should be avoided in pregnant women and all women of childbearing age. A single case report from South America describes successful use of levetiracetam for Sydenham chorea.[51] Levetiracetam also appears effective in other forms of chorea.[52] This agent could be an attractive option due to its favourable side-effect profile but requires further investigation.[43]

A response to treatment may not be seen for one to two weeks, and successful medication may only reduce, but not eliminate, the symptoms of Sydenham chorea. Medication should be continued for two to four weeks after chorea has subsided, and then withdrawn. Recurrences of chorea during the ARF episode (i.e. within 3 months) are usually mild and can be managed conservatively or with commencement of medication as necessary.

Neuroleptic agents

In other settings, chlorpromazine has been reported as the preferred first-line agent for Sydenham chorea,[44] and other neuroleptic agents such as risperidone are recommended as an add-on agent for people failing anti-convulsant therapy.[43] Experience with these agents is limited in Australasia and generally, cases needing escalation of treatment beyond anticonvulsants receive corticosteroids as second-line treatment.

Corticosteroids for chorea

Low-quality evidence and expert reviews recommend the use of corticosteroids for severe chorea. A review in 2017 identified 12 case reports and series and one comparative trial which included a total of 77 patients with Sydenham chorea who received steroids.[43] Seventy-six of the 77 individuals reportedly benefited, leading to the overall conclusion that steroids are an effective treatment of chorea. The trial reported faster time to reduction in chorea activity (one versus two weeks) and faster time to complete remission (54 versus 120 days) in 22 people treated with high-dose (2 mg/kg) prednisone compared with 15 individuals treated with placebo.[53] Examples of a case report and case series suggesting therapeutic success with corticosteroids (IV methylprednisolone and/or oral corticosteroid therapy) include a report of chorea paralytica,[54] and a series of five individuals with Sydenham chorea of varying severity,[55] all of whom were reported to improve after commencement of steroids.

If immunosuppressive medication is used in an individual with ARF, a pre-immunosuppression screen is needed, followed by appropriate management of latent infections and prevention of opportunistic infections *(Table 7.5)*.

Other immunomodulatory agents for Sydenham chorea

A small study of intravenous immunoglobulin (IVIg) suggested more rapid recovery from chorea than placebo.[56] A systematic review of IVIg[57] identified two randomised, controlled trials with 38 participants.[58,59] Compared with other immunomodulatory therapies (steroids and plasma exchange), short-term benefit was seen with IVIg and the side-effect profile is favourable. The authors concluded that use of a single 2 g/kg dose of IVIg in children with moderate-severe chorea associated with significant impairment, is reasonable. Expert advice also describes the use of IVIg 1 g/kg daily for 2 days or 400 mg/kg for 5 days as alternative dosing regimens. In addition to these trials there are also case reports of successful IVIg use in severe chorea.[57] If IVIg is used, it should be noted that this may inhibit the immune response to some vaccines; there should be a delay in giving some vaccines afterwards (See Australian Immunisation Handbook).

Plasmapheresis (plasma exchange), which aims to remove antineuronal antibodies, has been trialled as an experimental immunotherapy in Sydenham chorea. A case report and one of the above-mentioned trials suggested that plasmapheresis can be successful for patients who have failed steroid therapy,[60] or can affect a faster resolution of chorea symptoms than steroids.[58]

Given the low-quality evidence base for experimental therapies, these are reserved for refractory cases.

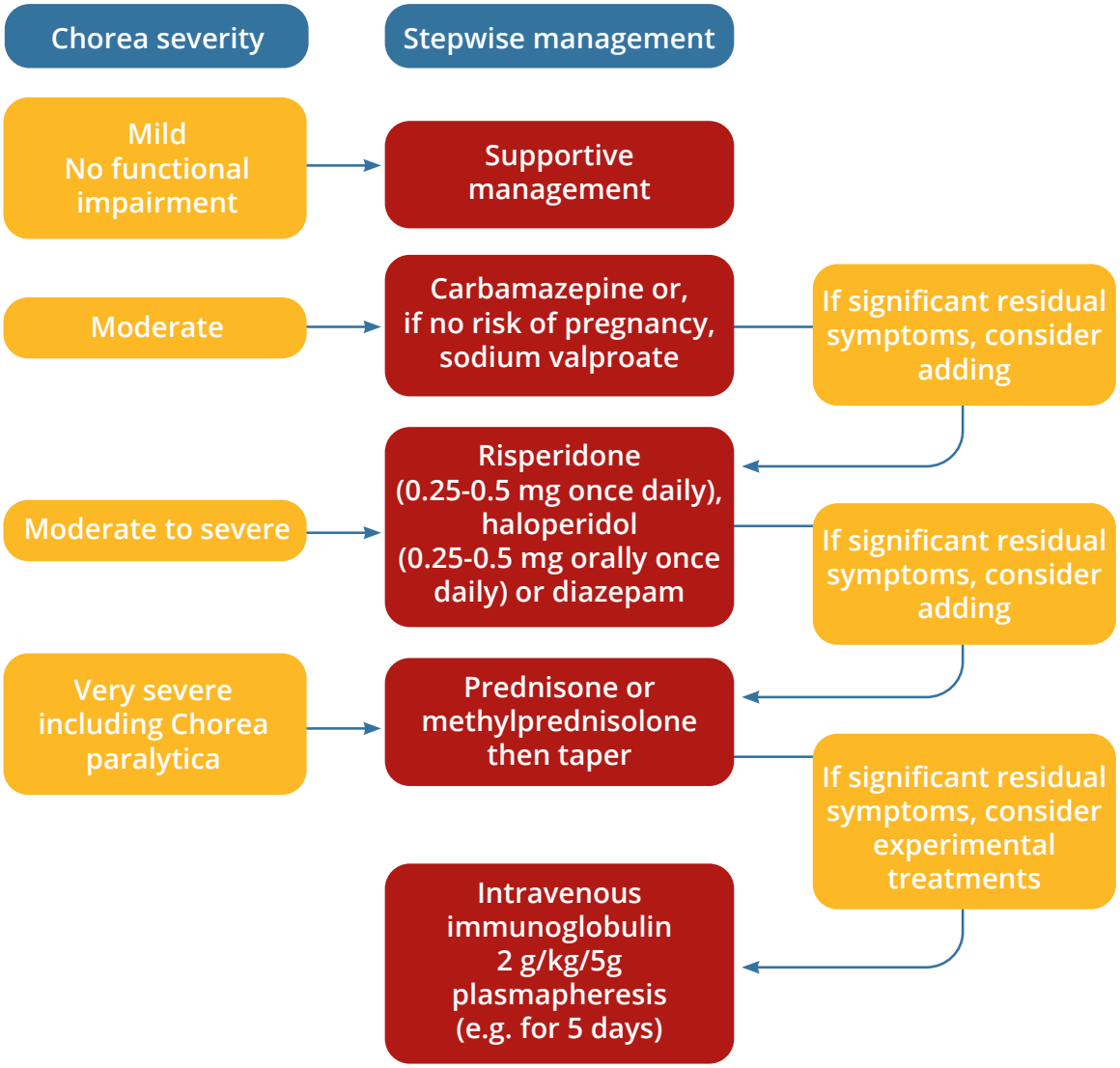
A suggested algorithm for the approach to treatment for Sydenham chorea was developed by Dean and Singer.[43] A modified version is presented in *Figure 7.1*.

While additive therapy may be of benefit, the risks of polypharmacy, especially drowsiness from the combination of anticonvulsants and neuroleptic agents, need to be balanced against the severity of the chorea. Operational research to report on the outcome of different approaches is needed.

Monitoring response of Sydenham chorea symptoms to therapy

Response to therapy can be formally rated using the Universidade Federal de Minas Gerais (UFMG) Sydenham's Chorea Rating Scale (USCRS).[44,45] This research tool was designed to provide a detailed quantitative description of the performance of daily living activities, behavioural abnormalities, and motor function of subjects with Sydenham chorea. The scale comprises 27 items scored from 0 (no symptom or sign) to 4 (severe disability or finding).

Figure 7.1. Hierarchy of therapeutic options for management of Sydenham chorea



Adapted from Shannon L. Dean, Harvey S. Singer Treatment of Sydenham Chorea: A Review of the Current Evidence Tremor Other Hyperkinet Mov (N Y) 2017; 7: 456.

MONITORING AND PROGRESS OF ARF

The time course of ARF symptoms is highly variable within a given manifestation and across different manifestations. Clinical experience in northern Australia is that many individuals with the most common presentation of fever and low grade joint symptoms are asymptomatic by the time they reach hospital. However, an estimated 10% of individuals have persisting joint symptoms more than three months after the start of an ARF episode, despite appropriate treatment. Chorea usually resolves spontaneously within a few weeks, almost all within six months,[38] but rarely, can persist for years.[39,40]

Recurrences of symptoms within 3 months of an ARF diagnosis are considered to be part of the same ARF episode, not a recurrence. See discussion of the rebound phenomenon in the *Treatment of Arthritis and Arthralgia* section.

Frequency of laboratory tests

Once the diagnosis has been confirmed and treatment commenced, inflammatory markers (ESR, CRP) should be measured once or twice weekly initially, then every one to two weeks, including after discharge, until they have been normal for one month. There is no evidence to support this; it is the general approach taken by those who regularly care for people with ARF. Salicylate levels may also be monitored, if the facilities are available, but most cases can be managed without this information.

Echocardiography should be repeated within a month if the initial diagnosis was not clear, carditis was severe, pericardial effusion was present or whenever a change in cardiovascular examination findings, such as resting heart rate, blood pressure or auscultatory findings, is detected. Access to echocardiography can be very limited in remote areas where the majority of ARF cases occur. Cases of severe carditis with heart failure may need more frequent echocardiographic assessments, ECG and chest X-rays, according to their clinical course *(Table 7.4)*.

Discharge from hospital

Discharge from hospital is a critical point in the patient journey. A health management plan should be developed in partnership with the hospital medical officer, nurse, Aboriginal Liaison Officer, and the patient and family. Where possible, the first outpatient medical appointment should be booked prior to hospital discharge.

Planning for discharge and follow-up should consider the presence and severity of cardiac valve damage and the potential for ongoing valvulitis due to continuing rheumatic inflammation, which sometimes leads to cardiac failure appearing, or worsening, in the weeks after discharge. Normally, discharge should only be considered for patients who are asymptomatic or only mildly symptomatic, in whom the manifestations of ARF have stabilised, and in whom inflammatory markers (particularly CRP) are clearly improving. If patients come from remote communities or other settings with infrequent access to medical care, it is advisable to discuss discharge timing with the patient, family and local primary healthcare team. Particularly in those with significant carditis, it is prudent to wait until inflammatory markers are near-normal. Most ARF patients with no, or only mild, carditis can be discharged from hospital within two weeks. Those with moderate or severe carditis may require longer admission. (See *Treatment of arthritis and arthralgia* with regards to duration of NSAIDs and rebound phenomenon)

Regardless of the timing of discharge, follow-up by the local medical practitioner or community clinic should be scheduled for within a week of discharge, when clinical evaluation *(Table 7.3)* and repeat CRP should be undertaken to exclude evidence of recrudescence. Planning follow up before discharge is critical to optimise long-term outcomes. This involves coordination between the community clinic, specialist services and the community pharmacy, in consultation with the patient and family. Most fatalities from ARF and RHD among young Aboriginal and Torres

Strait Islander peoples occur in circumstances where such coordination has been difficult or inadequate.

The hospital medical practitioner should provide a written discharge summary and 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.

Patients and their families should be provided with clear information about how secondary prophylaxis works, and the risk of recurrent ARF and its consequences if they do not receive treatment as prescribed. This may require an interpreter, language-appropriate written material, and culturally appropriate conversation.

Patients require clear information about where they can receive secondary prophylaxis, details about the date and location of future appointments, and contact details for their local health centre or hospital.

Patients and families should be encouraged to phone or visit their local health service or hospital if they have any questions concerning their follow-up or secondary prophylaxis.

COMMENCEMENT OF LONG-TERM PREVENTATIVE MEASURES

Secondary prevention

By the time of hospital discharge, ensure that patients and their families have a good understanding of how to reduce the future risk of ARF recurrence.

Long-term care is very important, and there are often many care providers involved. The ongoing social and economic circumstances in which some Aboriginal and Torres Strait peoples live often require support beyond the health system. Culturally appropriate education for patients, families and communities needs to be ongoing, and tailored to changing needs over time. Self-management support should be provided by primary care staff, acknowledging that a new diagnosis of ARF is an important chronic disease diagnosis for a young person and their family. People with ARF need close engagement with the health system for many years.

Commencement of secondary prevention activities for ARF includes antibiotic prophylaxis, plus a suite of measures to reduce an individual's risk of Strep A infection (e.g. hygiene measures), or consequences of Strep A infection (early recognition and treatment).

Organising dental checks and ongoing dental care 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 7.2)*
(See *Chapter 11. Management of RHD, Prevention of infective endocarditis*).

Immunisations

Ensure routine immunisations are up to date and if not, administer these at discharge from hospital.

Annual influenza immunisation is advised for all patients with ARF/RHD, and especially important in the following groups including people with severe carditis, people taking aspirin, and pregnant women. Influenza immunisation is not funded by the Australian Government for non-Indigenous people with ARF unless they are pregnant.

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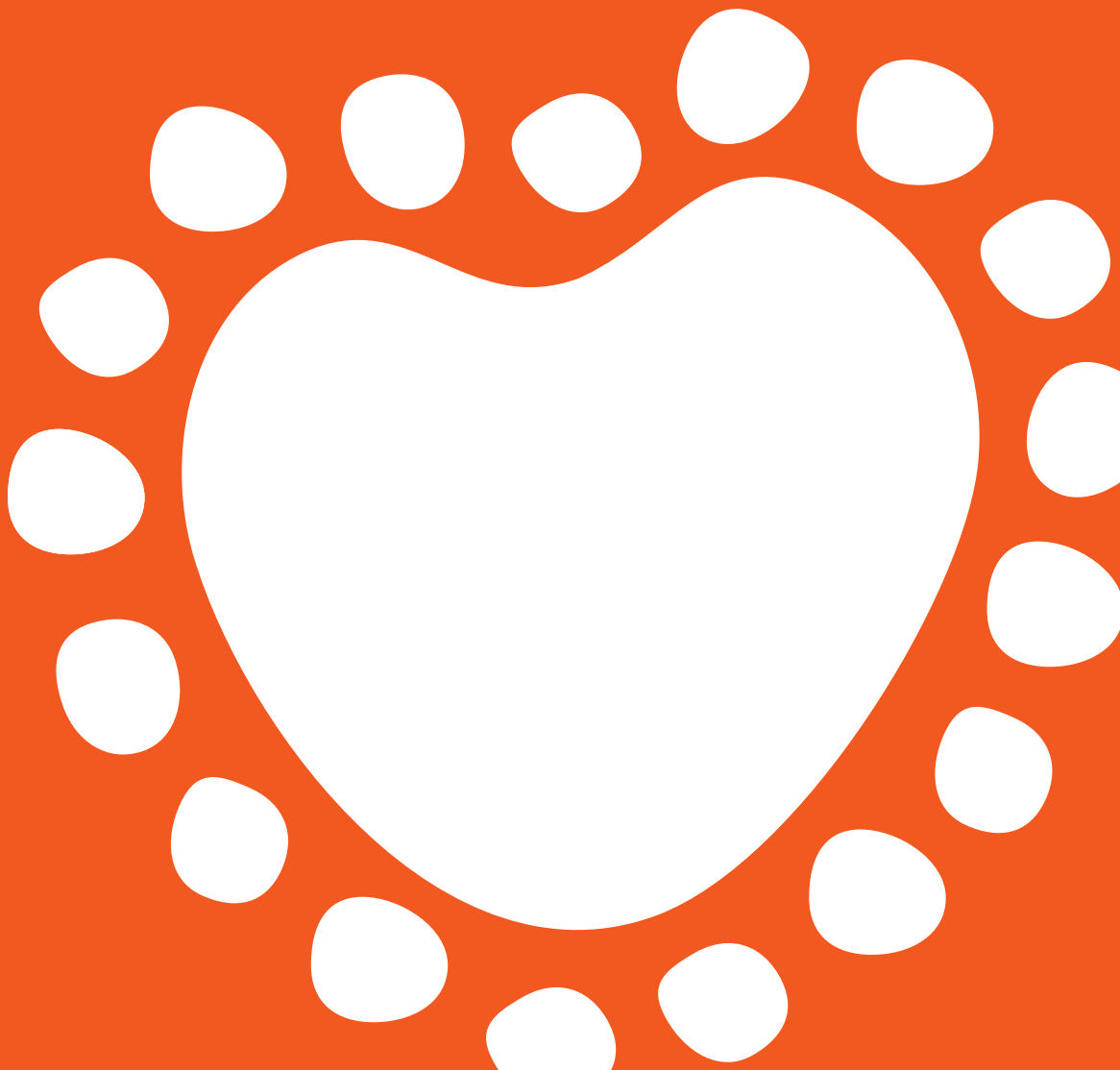
CHAPTER 8

Diagnosis of rheumatic heart disease



Diagnosis of rheumatic heart disease

CHANGES FROM THE SECOND (2012) EDITION

1. The World Heart Federation guidelines for the diagnosis of RHD, which were developed and validated in multiple populations including high and low prevalence groups, inform this chapter.
2. The echocardiographic features of severity have been aligned with updated international guidelines for valvular heart disease (European Society of Cardiology 2017 and American Heart Association/American College of Cardiology 2014).
3. Exercise stress testing is recommended with echocardiography to determine severity of RHD and planning for intervention.
4. A new section on distinguishing RHD from other valvular pathology is provided.
5. An update on new echocardiography technology including hand-held and portable echocardiogram machines and their role in RHD diagnosis is provided.

KEY INFORMATION

- In Australia, approximately 87% of rheumatic heart disease (RHD) occurs in Aboriginal and Torres Strait Islander peoples (depending on the dataset used).
- RHD has a female predominance of 2:1 and the prevalence peaks in the third and fourth decade of life.
- RHD should be considered in individuals from high-risk populations *(Table 6.1)* with reduced exercise tolerance or breathlessness (Level of Evidence GRADE 1C) noting that most RHD is asymptomatic.
- Reduced exercise tolerance or breathlessness in a pregnant woman from a high-risk population should not be attributed to pregnancy or anaemia; consider and investigate for RHD.
- Exercise testing or stress echocardiography is recommended when severity of symptoms and echocardiographic findings are discordant (Level of Evidence GRADE 1B).
- Transoesophageal echocardiography may help clarify valve morphology and severity to plan surgical intervention or when transthoracic echo is inconclusive (Level of Evidence GRADE 1B).
- The WHF guidelines on echocardiographic diagnosis provide criteria to distinguish pathological RHD from physiological changes in children and adults (Level of Evidence GRADE 1B) *(Table 8.5)*.
- The mitral valve is the most common valve involved in RHD.
- Many adult patients will have mixed or multi-valvular disease.
- Symptoms may not reflect severity of disease. Many patients will appear asymptomatic until advanced stages of disease develop.
- Patients may present with complications of valve disease including stroke, heart failure or arrhythmia.

Table 8.1. Clinical features of common valve lesions

VALVE LESION	SYMPTOMS	SIGNS	COMPLICATIONS
Mitral regurgitation (MR)	Mild-moderate: Asymptomatic Dyspnoea on exertion Fatigue Weakness Orthopnoea, paroxysmal nocturnal dyspnoea	Mid/pan-systolic murmur at apex, radiating laterally (occasionally medially/ posteriorly) Displaced apex beat in severe MR	Congestive cardiac failure Atrial arrhythmia Pulmonary hypertension
Mitral stenosis (MS)	Exertional dyspnoea (symptoms sensitive to increase in heart rate) Orthopnoea, paroxysmal nocturnal dyspnoea Haemoptysis	Low-pitch, diastolic murmur at apex with patient in left lateral position Murmur duration correlates with severity	Atrial arrhythmia Pulmonary hypertension Systemic embolism (stroke, peripheral arterial occlusion)
Aortic regurgitation (AR)	Mild-moderate: Asymptomatic Dyspnoea on exertion Angina Orthopnoea, paroxysmal nocturnal dyspnoea	Blowing decrescendo diastolic murmur at left sternal edge Systolic murmur due to increased flow Mitral diastolic murmur (Austin Flint) Wide pulse pressure	Congestive cardiac failure
Aortic stenosis (AS)	Dyspnoea, angina, presyncope and syncope all associated with exertion	Ejection systolic murmur over aortic region, radiating to neck Slow-rising pulse	Heart failure with preserved or reduced ejection fraction Atrial arrhythmia
Tricuspid regurgitation (TR)	Peripheral oedema Abdominal distention and discomfort	Pan-systolic murmur at left parasternal edge Elevated jugular venous pressure (JVP) with prominent V-waves. Pulsatile liver Right ventricular heave	Right-sided heart failure
Tricuspid stenosis (TS)	Fatigue Abdominal discomfort Anorexia	Soft, high-pitch diastolic murmur at left parasternal edge Abdominal ascites Hepatomegaly Giant A-waves in JVP	Anasarca Hepatomegaly and hepatic dysfunction

Table 8.2. Echocardiographic features of RHD

CHARACTERISTIC FEATURES	MARKERS OF SEVERE DISEASE
Mitral valve features • Prolapse of anterior leaflet • Thickened leaflet tips • Restricted posterior leaflet • Chordal thickening • Leaflet calcification • Diastolic doming of anterior leaflet ("dog leg" or "hockey stick" appearance)	**Mitral regurgitation** • Central jet > 40% of LA • Holosystolic eccentric jet • Vena contracta ≥ 0.7 cm • Regurgitant volume ≥ 60 mL • Regurgitant fraction ≥ 50% • ERO ≥ 0.40 cm^2 **Mitral stenosis:** • Valve area ≤ 1.5cm^2 • Diastolic pressure half-time ≥ 150 ms • Mean pressure gradient ≥ 10 mmHg
Aortic valve features • Cusp prolapse • Cusp thickening • Rolled cusp edges • Cusp restriction • Cusp fibrosis, retraction, calcification • Dilated aortic root	**Aortic regurgitation** • Jet width ≥ 65% of LVOT • Vena contracta ≥ 0.6 cm • Holodiastolic flow reversal in the proximal abdominal aorta • Regurgitant volume ≥ 60 mL/beat • Regurgitant fraction ≥ 50%; • ERO ≥ 0.3 cm^2 • Evidence of LV dilatation **Aortic stenosis**† • Aortic valve Vmax ≥ 4 m/s • Mean pressure gradient ≥ 40 mmHg • Valve area ≤ 1.0 cm^2
Tricuspid valve features • Leaflet thickening, calcification • Leaflet restriction, retraction • Chordal shortening	**Tricuspid regurgitation** • Central jet area ≥ 10.0 cm^2 • Vena contracta width ≥ 0.7 cm • CW jet density and contour: dense, triangular with early peak • Systolic flow reversal in hepatic vein **Tricuspid stenosis** • Pressure half-time ≥ 190 ms • Valve area ≤ 1.0 cm^2

† Scenarios of low-flow, low-gradient and normal flow, low-gradient severe AS exist. Expert input is advised.

LA, left atrium; ERO, Effective regurgitant orifice; LVOT, Left Ventricular Outflow Tract; LV, left ventricular; CW, Continuous wave;

Table 8.3. Role of cardiac investigations in the diagnosis of RHD

INVESTIGATION	ROLE
Transthoracic echocardiography† (TTE)	Baseline investigation Assessment of valve pathology Assessment of cardiac function and chamber size Surveillance of valve pathology and cardiac function over time
Transoesophageal echocardiography (TOE)	Pre-surgical planning Anatomical assessment for valve repair Exclusion of LA thrombus and significant MR prior to percutaneous balloon mitral valvuloplasty Assessment of valve severity when TTE non-confirmatory
Electrocardiogram†	Identify arrhythmias that may complicate RHD (e.g. atrial fibrillation) Identify structural changes of RHD (e.g. left ventricular hypertrophy, p-mitrale)
Exercise stress test	Objective assessment when valve severity discordant from symptoms
Stress echocardiogram	Objective assessment when valve severity discordant from symptoms Use in MS for assessing change in gradient and pulmonary arterial systolic pressure with exercise
Right heart catheterisation	Assessment of valve severity in cases when TTE/TOE is non-confirmatory Assessment and classification of pulmonary hypertension in setting of valvular disease
Coronary angiography	Exclude concomitant coronary disease pre-surgery (over age 25 years)
Computed tomography coronary angiogram	Exclude concomitant coronary disease pre-surgery (younger than 25 years)
Cardiac magnetic resonance imaging	Role in assessing aetiology of cardiomyopathy and quantifying chamber size and function Quantification of regurgitant volumes
Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and anti-streptococcal titres†	In cases of newly diagnosed RHD to exclude possible ARF episode
B-type natriuretic peptide (BNP), pro-NT BNP	Role in assessment of heart failure presentation (See NHFA/CSANZ heart failure guidelines)

† Compulsory in diagnostic work-up

Table 8.4. Morphological features of RHD

VALVE	MORPHOLOGICAL FEATURES†
Mitral valve	AMVL thickening ≥3 mm (age specific)‡
	Chordal thickening
	Restricted leaflet motion§
	Excessive leaflet tip motion during systole¶
Aortic valve	Irregular or focal thickening††
	Coaptation defect
	Restricted leaflet motion
	Leaflet prolapse

†Minimal diagnostic criteria to differentiate normal from rheumatic

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

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

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

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

Table 8.5. 2012 World Heart Federation criteria for echocardiographic diagnosis of RHD

Echocardiographic criteria for individuals aged ≤20 years

Definite RHD (either A, B, C or D):

- A) Pathological MR and at least two morphological features of RHD of the MV
- B) MS mean gradient, ≥4 mmHg (note: congenital mitral valve anomalies must be excluded)
- C) Pathological AR and at least two morphological features of RHD of the AV
- D) Borderline disease of both the AV and MV†

Borderline RHD (either A, B, or C):

- A) At least two morphological features of RHD of the MV without pathological MR or MS
- B) Pathological MR
- C) Pathological AR

Normal echocardiographic findings (all of A, B, C, and D):

- A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR)
- B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR)
- C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
- D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation

Echocardiographic criteria for individuals aged >20 years

Definite RHD (either A, B, C, or D):

- A) Pathological MR and at least two morphological features of RHD of the MV
- B) MS mean gradient, ≥4 mmHg
- C) Pathological AR and at least two morphological features of RHD of the AV, only in individuals aged <35 years
- D) Pathological AR and at least two morphological features of RHD of the MV

† Combined AR and MR in high-prevalence regions and in the absence of congenital heart disease is regarded as rheumatic.
AR, aortic regurgitation; MR, mitral regurgitation; MS, mitral stenosis.

Box 8.1. Echocardiography machine settings

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

Figure 8.1a. Rheumatic mitral valve; appearance with harmonics 'on', note anterior mitral valve thickness. Harmonics should be turned off *(Table 8.4 footnote and Box 8.1)*

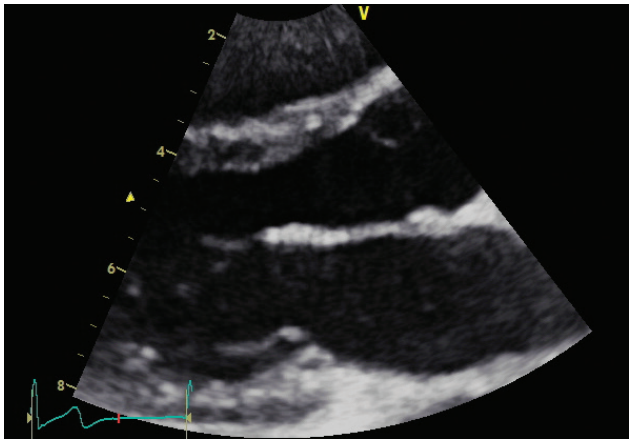


Figure 8.1b. Rheumatic mitral valve; appearance with harmonics 'off', note anterior mitral valve thickness

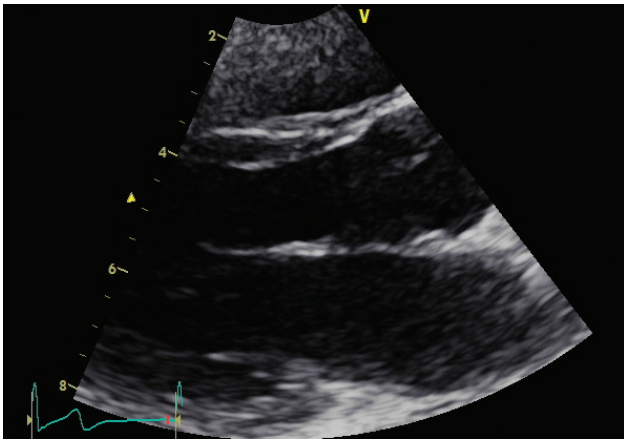
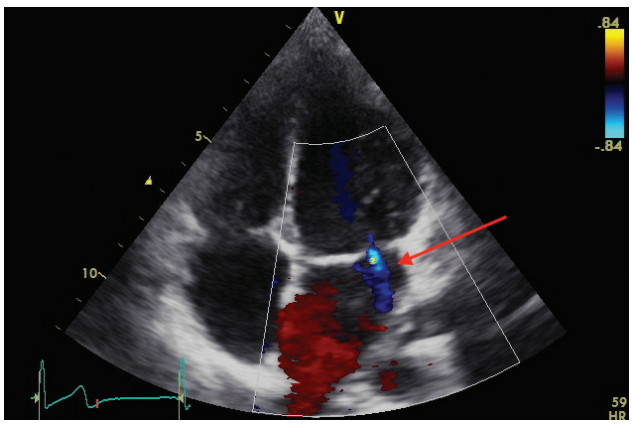


Table 8.6. Criteria for pathological regurgitation

Pathological mitral regurgitation	Seen in two views In at least one view, jet length ≥ 2cm† Peak velocity ≥ 3 m/s Pan-systolic jet in at least one envelope
Pathological aortic regurgitation	Seen in two views In at least one view, jet length ≥ 1cm† Peak velocity ≥ 3 m/s Pan-diastolic jet in at least one envelope

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

Figure 8.2. Rheumatic mitral valve; mitral regurgitant jet needs to measure at least 2 cm on colour doppler to meet RHD diagnostic criteria for pathological regurgitation (red arrow; See *Table 8.6*)



DISCUSSION

> *"Just because you have RHD does not mean you have to stop living. Drive RHD. Don't let RHD drive you."*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

Echocardiography is the gold standard diagnostic tool for RHD and should be performed in any patient suspected of having RHD (Level of Evidence GRADE 1A).

RHD is often asymptomatic. Critical symptoms that should raise the suspicion of RHD are breathlessness or reduced exercise tolerance, especially in a pregnant woman from a high-risk setting.

The diagnosis of RHD often occurs late and in the advanced stages of disease when patients are most symptomatic.[1] This may include presentations with complications of valve dysfunction, including arrhythmias, stroke, infective endocarditis or maternal complications of pregnancy.[1] There is a significant latent period of asymptomatic valvular heart disease and the majority of patients do not have a documented history of ARF.[1] In Australia, more than 87% of RHD cases occur in Aboriginal and Torres Strait Islander populations.[2] Consideration of a possible RHD diagnosis in high-risk populations is imperative *(Table 6.1)*; diagnosis in the early stages of disease has the best chance to inhibit progression through delivery of secondary prophylaxis and prevent complications through appropriately timed medical and surgical intervention.

Aboriginal and Torres Strait Islander peoples with RHD often present to the health system in an advanced stage of disease.

Communication and knowledge transfer between the health workforce and people at high risk of RHD are critical for timely and accurate diagnosis.

Interpreters and family members should be engaged to support people with RHD where indicated; to help relay information on behalf of the patient, and to help explain diagnostic testing and procedures.

Aboriginal and Torres Strait Islander health staff (including Aboriginal Liaison Officers, Aboriginal Health Workers and Aboriginal Health Practitioners) should be engaged as early as possible to support patients and their families.

Cultural and language appropriate resources can assist with timely and accurate diagnosis.

Health assessments and enhanced primary care should be incorporated into health services for Aboriginal and Torres Strait Islander peoples. This includes care planning and team care arrangements.

Natural history of RHD

The natural history of RHD was documented in the pre-penicillin and pre-echocardiography era (up to the 1950s) by Bland and Duckett Jones.[3] They observed 87 patients with ARF who had clinical signs of isolated rheumatic MR for 20 years. They found that in one-third of their patients, MR resolved; in one-third it persisted; and in one-third it progressed to severe disease, MS or resulted in death. Following the wide availability of penicillin in the 1950s, Tompkins *et al* reported that 70% of their patients with MR had no clinical evidence of heart disease at nine years after initial diagnosis.[4] This clinical resolution of MR in two-thirds of patients on secondary prophylaxis within 5–10 years of diagnosis is also supported by the findings of Kassem and Lue.[5,6]

The progression to mitral stenosis is variable. In some populations, there is often a latent period of 20–40 years between episodes of ARF and a presentation with MS.[7,8] In the Aboriginal and Torres Strait Islander population, MS progresses rapidly, and patients become symptomatic at a young age, although this is rare below 10 years of age. Approximately 30% of Aboriginal people with RHD in the Northern Territory aged 10–19 years have MS, and the mean age of all patients with MS is 33 years.[9] In India, this trend is more marked, where MS is common in children aged under 10 years. This rapid progression may be due to undetected recurrences of ARF. Once MS becomes symptomatic, the long-term prognosis without cardiac intervention is poor, with 10-year survival ranging from 34% to 61%.[7,8,10,11] The progression of RHD and the need for subsequent intervention is related to the severity of disease at diagnosis and the presence of ARF recurrences.[5,12-14] Australian RHD register data show that of people with severe disease, 50% require surgery within two years and 10% die within six years.[15]

Diagnostic aspects of RHD

A thorough and comprehensive clinical assessment is vital in a patient with possible RHD. This provides information regarding severity of symptoms and clinical signs of valve disease and related complications. However, echocardiography is the gold standard diagnostic tool; *(Table 8.5)* it is substantially more accurate than clinical auscultation and should be made available to all people with RHD, regardless of their location (Level of Evidence GRADE 1A).[16]

Clinical assessment of RHD

It is important to note that many patients with RHD will be asymptomatic or at least appear asymptomatic. Furthermore, the majority of patients with RHD have no documented history of ARF.[1] Assessment of medical history and current symptoms can be challenging due to language barriers, cultural factors and some patients may self-regulate their physical activity and thus not report symptoms, despite advancing disease.

It is also important to note that many patients will have either mixed valvular disease (e.g. mitral regurgitation and mitral stenosis) or multi-valvular disease (e.g. aortic regurgitation and mitral regurgitation). In adults, mixed and multi-valvular disease are the most common presentations of RHD.[17,18] Although there may be a dominant lesion responsible for symptoms, clinical presentation can relate to both. Both mixed and multi-valvular disease will affect the echocardiographic assessment of lesion severity. Mixed moderate valve disease may have a similar prognosis to severe single valve disease, making management decisions challenging.[19,20]

There is considerable overlap in symptomatology for different valvular lesions. Exercise limitation, dyspnoea and fatigue can occur with any more advanced valve lesions. Other symptoms are specific to the type and severity of valve lesions *(Table 8.1)*.

Aside from symptoms directly due to valvular disease, patients may also present with symptoms reflecting complications of RHD. These most commonly include congestive heart failure, atrial fibrillation, pulmonary hypertension, predominant right heart failure, stroke, or other systemic thromboembolism.[1,17]

Heart failure may result from acute valvulitis in children and younger adults as well as any chronic severe valve lesions, particularly mitral and aortic regurgitation. Symptoms include exercise intolerance, and shortness of breath on exertion in mild and moderate cases and at rest in advanced disease. Paroxysmal nocturnal dyspnoea, orthopnoea and peripheral oedema may develop in more advanced disease.

Atrial fibrillation (AF) is more commonly associated with mitral valve disease and subsequent left atrial dilatation in older adolescent and adult populations.[21] It is rarely seen in children below the age of 15 years but becomes more common between 15-25 years of age. In younger adults, it is usually symptomatic and associated with a high ventricular rate. Those with mitral stenosis are particularly

vulnerable and new-onset AF may be the first clinical presentation of advanced disease, precipitating acute decompensation due to the tachyarrhythmia. In these cases, patients may present with acute pulmonary oedema, haemoptysis, hypotension and cardiogenic shock. Subacute symptoms of AF include exercise intolerance and palpitations.

Pulmonary hypertension may develop as a consequence of left ventricular (LV) systolic dysfunction in the setting of valvular disease or directly due to mitral valve disease, particularly mitral stenosis.[22] It may be difficult to distinguish symptoms of the primary valve disease or LV dysfunction from those of pulmonary hypertension. Furthermore, pulmonary hypertension may occur in this population due to other pathology, such as rheumatological disorders. In these cases, further investigations including serological markers and right heart catheterisation may be useful to distinguish the predominant pathology.

Unfortunately, stroke and other systemic arterial embolisation remain an uncommon but tragic first presentation of RHD.[1] This usually reflects mitral stenosis with or without the complication of atrial fibrillation. RHD should be considered in any young patient from a high-risk population *(Table 6.1)* presenting with stroke or arterial thromboembolism.

Clinical features of specific valve lesions

Mitral valve disease

The mitral valve is the most commonly involved valve in RHD.[17] Examples of echocardiographic images of rheumatic mitral valve pathology are shown in *Figure 8.1* to *Figure 8.7*. Acute valvulitis and subsequent early RHD is characterised by pure mitral regurgitation (MR).[17] With recurrent episodes of ARF and subsequent fibrosis and scarring, mixed mitral valve disease develops. This is the most common RHD valve lesion seen in the adult population,[17] while pure mitral stenosis is uncommon.

In patients with mild to moderate MR, the left ventricular apex will not be displaced, and there will be a mid- or pan-systolic murmur heard best at the apex, which may radiate laterally or medially, depending on the direction of the regurgitant jet *(Table 8.1)*.[23] Patients with moderate or more severe MR will have an apex beat displaced to the anterior or mid-axillary line, and a loud pan-systolic murmur maximal at the apex. There may be an associated diastolic murmur of MS or a mid-diastolic murmur from increased trans-mitral flow.

The murmur of mitral stenosis (MS) is a low-pitched, diastolic rumble heard best at the apex, with the patient in the left lateral position. It may be difficult to hear, especially if the ventricular rate is rapid. This murmur may be particularly difficult to detect in the resting patient and manoeuvres such as leg raises to increase heart rate and trans-mitral flow may aid in accentuating the murmur. The duration of the murmur correlates with the severity of MS. If the patient is in sinus rhythm, there will be presystolic accentuation, but this is lost once AF occurs. It may be possible to palpate a right ventricular heave in the left parasternal region due to right ventricular systolic hypertension resulting from elevated pulmonary pressures from significant mitral stenosis.

Figure 8.3. Rheumatic mitral valve; thickened and restricted posterior leaflet (red arrow), thickened anterior leaflet tip with diastolic doming (yellow arrow) resulting in stenosis

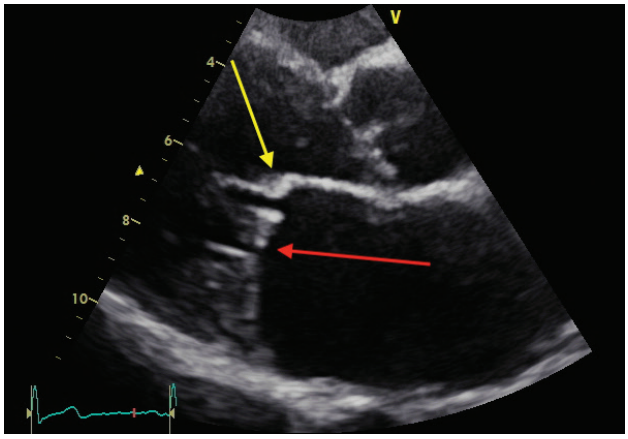


Figure 8.4. Rheumatic mitral valve; restricted posterior leaflet with loss of coaptation (red arrow) leads to eccentric posteriorly directed regurgitation

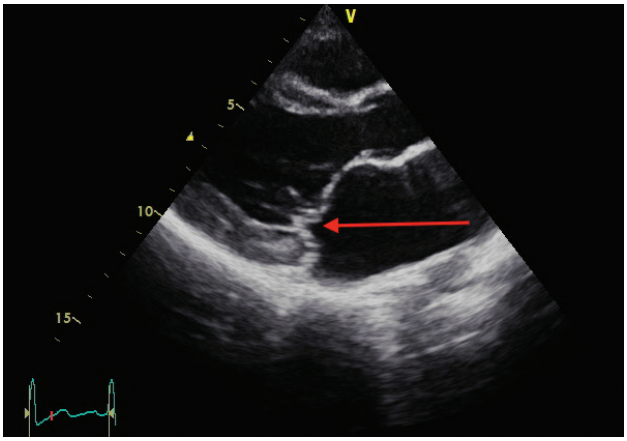


Figure 8.5. Rheumatic mitral valve; significant bileaflet thickening and calcification (yellow arrow) with fused commissure (red arrow) resulting in reduced orifice area

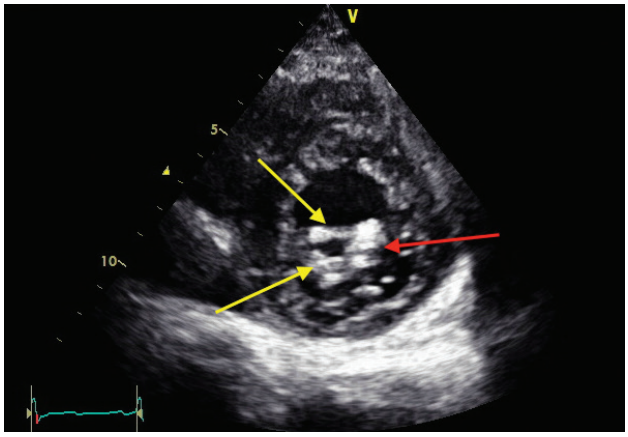


Figure 8.6. Rheumatic mitral valve; mitral regurgitation due to RHD is commonly eccentric with a posteriorly directed jet seen on colour doppler (red arrows)

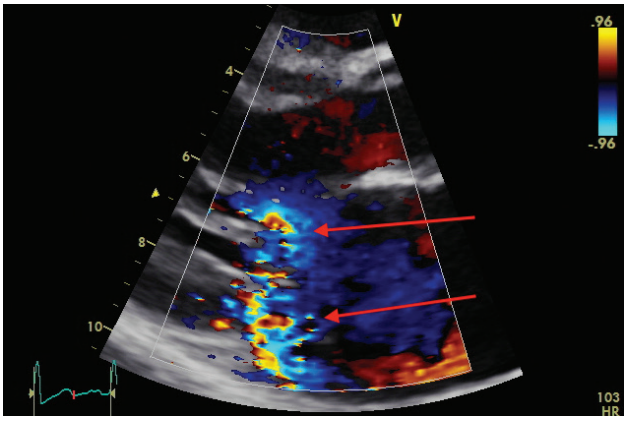
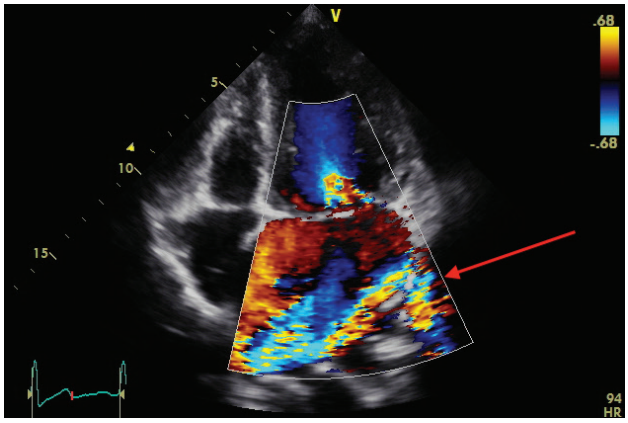


Figure 8.7. Rheumatic mitral valve; severe eccentric mitral regurgitation demonstrated with colour doppler. The regurgitation follows the posterior wall and fills multiple pulmonary veins (red arrow)



Aortic valve disease

Rheumatic aortic valve disease is less common than mitral valve disease and rarely occurs in isolation. The typical lesion is AR. Examples of echocardiographic images of rheumatic aortic valve pathology are shown in *Figures 8.8* to *8.11*. Aortic valve disease may be due to other conditions in addition to RHD, and the probability of these conditions (including connective tissue disease, aortitis and hypertension) increases with age.[24] RHD is a rare cause of AS and therefore other causes, including degenerative and bicuspid aortic valve, should be excluded prior to labelling the valve rheumatic.

The typical murmur of AR is a diastolic, blowing decrescendo murmur best heard at the left sternal border, with the patient sitting upright at the end of expiration *(Table 8.1)*. The length of the murmur correlates with severity (except in acute aortic valvulitis), with more severe cases producing a pan-diastolic murmur. There is usually an associated systolic murmur, even in the absence of AS, due to the increased forward flow across the aortic valve, and in occasional cases, a mitral diastolic (Austin Flint) murmur. Examination may reveal a forceful LV apical impulse, which may be displaced laterally and downwards. A water-hammer pulse at the brachial artery and a collapsing carotid pulse are clinical indications of at least moderate AR.

The characteristic clinical finding in AS is a loud, mid-systolic ejection murmur, best heard in the aortic area, radiating to the neck and the apex.[25] In patients with haemodynamically significant AS, useful physical signs are a slowed and reduced carotid pulse upstroke, and the presence of a thrill in the suprasternal notch.

Figure 8.8. Mixed rheumatic valve disease; aortic cusp thickening and rolled edges (yellow arrow), thickened anterior mitral valve leaflet (red arrow)

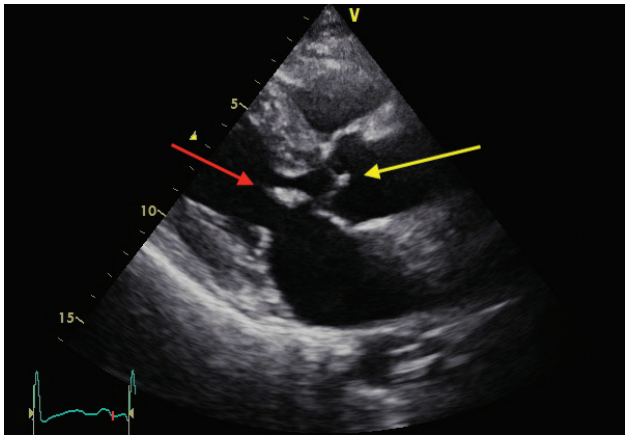


Figure 8.9. Rheumatic aortic valve; cusp thickening and restriction (red arrow)

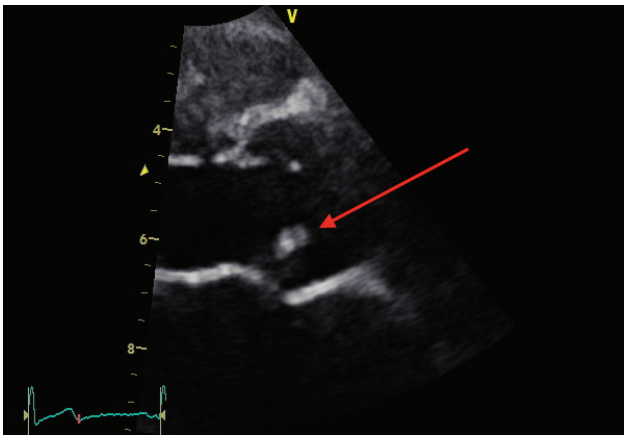


Figure 8.10. Rheumatic aortic valve; restricted cusp with rolled edges (red arrow)

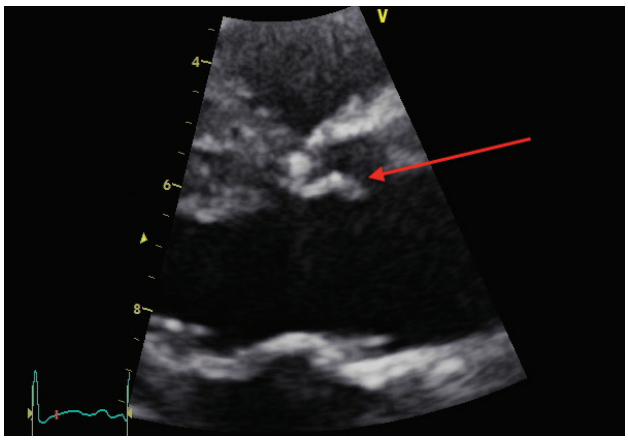
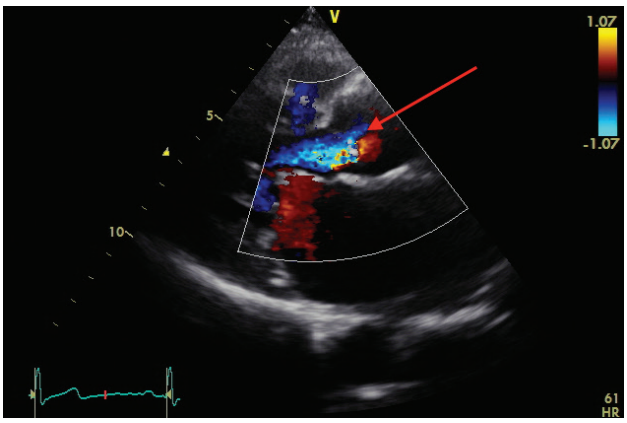


Figure 8.11. Rheumatic aortic valve with colour doppler demonstrating regurgitation



Tricuspid valve disease

Classical teaching advises that tricuspid regurgitation (TR) is best distinguished by the associated peripheral signs. These include prominent V waves in the jugular venous waveform, with a steep y descent and systolic hepatic pulsation with hepatomegaly. The murmur of TR may be difficult to auscultate, particularly if there is concomitant MR. The murmur is mid- or pan-systolic heard at the left sternal border, which may increase on inspiration. Tricuspid stenosis is rare but, if present, is nearly always due to RHD. A soft, high-pitched diastolic murmur may be heard at the left lower sternal edge. Like TR, tricuspid stenosis may be identified by other associated signs which include abdominal distention, ascites, hepatomegaly, profound peripheral oedema and giant A-waves in the jugular venous waveform.

Echocardiography and RHD diagnosis

Echocardiography is the primary clinical tool for the detection and diagnosis of RHD.

All patients with murmurs suggestive of possible valve disease, or a history of ARF, require echocardiography (Level of Evidence GRADE 1A). This will detect any valvular lesion and allow assessment of its severity and of cardiac function. Serial echocardiography plays a crucial role in the diagnosis and follow-up of rheumatic valve disease, allowing objective monitoring of any change in the severity of valve lesions, left and right chamber sizes, ventricular function, and any increase in pulmonary artery pressure. These objective echocardiographic data are essential in helping to determine the timing of any possible intervention.

The WHF guideline on the echocardiographic diagnosis of RHD *(Table 8.5)* provides diagnostic criteria for identifying and distinguishing RHD in both children and adults.[24] The WHF guideline aims to:

a) make echocardiography reporting simple, reproducible and consistent worldwide, and hence, to facilitate echocardiographic screening for RHD, specifically in school-aged children;

b) aid physicians with the diagnosis of RHD in those patients who do not have a documented history of ARF. The criteria were modified so that they are also applicable to adult patients >20 years of age.

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

The WHF recommends two echocardiographic categories of RHD in individuals ≤20 years of age: 'definite RHD' and 'borderline RHD', based on evidence derived from numerous studies (Level of Evidence GRADE 1C).[24] The borderline RHD category was established to improve the sensitivity of the test for individuals from regions with a high prevalence of RHD (i.e. high-risk populations), and who, due to their young age, may not have had sufficient time to develop the full echocardiographic manifestations of RHD.[26,27] The borderline RHD category is not applicable to patients who are considered to be at low risk of RHD (Level of Evidence GRADE 1C). In individuals who are aged over 20 years, minor age-related or degenerative changes[28-30] may overlap with what is defined as borderline RHD on echocardiography. Therefore, the borderline RHD category is not indicated in adults beyond 20 years of age (Level of Evidence GRADE 1C).

Criteria for morphological features of RHD and pathological regurgitation are detailed in *Table 8.4* and *Table 8.6* respectively. Trivial regurgitation of the mitral or aortic valves - that does not meet all four criteria for pathological regurgitation - is common,[31-34] and should be considered normal or physiological (Level of Evidence GRADE 1C) (*Table 8.5* and *Table 8.6*). The same can be said for isolated morphological changes, such as valvular thickening, that occurs without pathological stenosis or regurgitation (Level of Evidence GRADE 1C).[35]

Distinguishing RHD from other valve pathology

Although the echocardiographic features of RHD are quite distinctive, it is important to distinguish them from other forms of valve pathology. Functional mitral regurgitation refers to MR occurring in the presence of a structurally normal valve apparatus.[36] This may result from dilated cardiomyopathy in which there is apical displacement of the papillary muscles resulting in tethering of both leaflets apically, thus limiting normal coaptation. This typically causes a central regurgitation jet. Ischaemia may result in MR, most commonly seen in inferior wall ischaemia or infarction resulting in restricted motion of the posterior mitral valve leaflet and tethering of normal motion. This typically results in an eccentric, posteriorly directed regurgitant jet but can be distinguished from rheumatic disease as the valve leaflets themselves are thin and freely mobile. Degenerative disease of both the mitral and aortic valve becomes more common with age and is a more common cause of aortic stenosis than RHD. Degenerative changes typically involve diffuse leaflet or cusp thickening with calcification that is predominantly at the annulus and leaflet base. Mitral valve annular calcification may be associated with left ventricular inflow obstruction. In rheumatic valve disease, this process commences at the leaflet tips. Myxomatous mitral valve disease may be confused with RHD in its appearance of leaflet thickening with or without leaflet prolapse. However, myxomatous disease may have significant redundant leaflet tissue and lack the typical leaflet restriction and tethering seen in more advanced rheumatic mitral valve disease. Finally, carcinoid syndrome can present with tricuspid stenosis with marked leaflet thickening and restriction. This may be distinguished from RHD due to the lack of left-sided valve involvement.

Specific valve features on echocardiography

A summary of valve characteristics and parameters are found in *Table 8.2*.

Mitral valve disease

Early RHD is distinguished by pure mitral regurgitation. With chronicity, mixed mitral valve disease develops followed by predominant stenotic lesion in older adults. The two-dimensional (2D) echocardiographic images of the rheumatic mitral valve are quite characteristic, and can help confirm a diagnosis of RHD. The main echocardiographic feature of pure mitral regurgitation in young people is overriding or prolapse of the anterior (less commonly of the posterior) mitral valve leaflet, due to elongation of chordae leading to a typically posteriorly directed jet.[27,37,38] In more severe cases, chordal rupture can lead to flail leaflet.[38] Dilatation of the posterior mitral annulus, although not specific to RHD, is also a common finding.[37,38]

Valvular thickening, chordal thickening and tethering of either or both leaflets can be present, even in mild disease, and is the predominant mechanism of MR in the adult population.[39] The combination of valvular thickening, restricted leaflet motion and doming gives rise to the characteristic 'dog leg' (or 'hockey stick') appearance of the anterior mitral leaflet. This abnormality is especially common if there is a degree of associated mitral stenosis. Leaflet and annular calcification tends to be a late development, and is unusual in young patients.

Rheumatic mitral regurgitation is often associated with eccentric jets, making accurate quantification difficult. Continuous-wave and colour flow mapping in the left atrium allows a semiquantitative estimate of the severity of the central mitral regurgitant jet. This is done by grading the area of the regurgitant jet in relation to the area of the left atrium, and by examining the spectral intensity of the jet by continuous Doppler.[31] Milder degrees of regurgitation may be missed, unless 'sweeping' scans of the left atrium and mitral valve from parasternal and apical windows are used. The WHF guideline outlines how to differentiate trivial/physiological regurgitation from pathologic regurgitation. Complete Doppler assessment, including E wave velocity, pulmonary vein sampling and measurement of flow convergence radius, enables more accurate evaluation of severity. Quantitative assessment of mitral regurgitation includes calculating regurgitant volume and effective regurgitant orifice area. However, these calculations may be inaccurate due to the eccentricity or multiplicity of regurgitant jets *(Table 8.2)*.

Mitral stenosis severity is best determined by planimetry of the mitral valve area. This allows for dynamic changes relating to loading situations and heart rate. Planimetry is measured in the parasternal short axis view in mid diastole at the leaflet tips and therefore requires adequate 2D imaging. The use of three-dimensional (3D) echo may improve accuracy of this measurement. The calculated mitral valve area from the diastolic

pressure half-time is also recommended, although it is important to note that this is influenced by left ventricular and left atrial compliance.[40] Continuous-wave Doppler trans-mitral gradient has been the main stay of severity assessment previously. This continues to be used during invasive measures of mitral valve area and pre- and post- percutaneous balloon mitral valvuloplasty. However, this measurement is acutely dependent on trans-valvular flow and diastolic filling period, and can vary greatly with changes in heart rate, circulating volume or the presence of mitral regurgitation. Left ventricular systolic function is usually preserved even in severe mitral stenosis. However, significant left atrial dilatation can develop as well as pulmonary hypertension and associated right ventricular dilatation and dysfunction.

2D echo features aid in determining appropriateness for percutaneous balloon mitral valvuloplasty. While several scoring systems exist, the Wilkins score[41] based on four echocardiographic criteria – leaflet thickening, leaflet mobility, leaflet calcification, and sub valvular thickening and calcification – is most commonly employed, with a lower score predicting a more promising outcome.

Aortic valve disease

Morphological rheumatic changes of the aortic valve consist initially of cusp prolapse. With time, the cusps become thick and the edges roll, resulting in a coaptation defect. This typically results in aortic regurgitation or mixed aortic valve disease, as opposed to pure aortic stenosis which is rarely due to RHD. Isolated rheumatic aortic valve disease is rare in the adult population, however 2–10% of children will have isolated AR.[42] The extent of AR is examined with colour flow mapping in the left ventricle.[43,44] The spatial extent of the colour flow jet in the LV outflow tract is an approximate guide to the severity of AR. If the area is at least two-thirds or more of the LV outflow tract, the regurgitation is in the moderate to severe range. The depth of the jet in the left ventricle is also of some value, although it may be obscured by turbulent mitral valve inflow, particularly in cases of associated MS.

Further assessment of AR includes pressure half-time of the regurgitation jet with a measurement of >500 m/s usually indicating mild regurgitation, whilst <200 m/s is consistent with severe AR. However, additional factors, such as heart rate and LV end-diastolic pressure, can affect pressure half-time.[43,44] Complete quantification of AR may include calculation of regurgitation volume, flow convergence measurement and regurgitation orifice area as well as measurement of left ventricular dimensions. A useful method for assessing the severity of AR is to sample diastolic flow in the descending thoracic aorta from the suprasternal notch position. The length and velocity of the reversed flow is proportional to the severity of regurgitation. Pan-diastolic-reversed flow, particularly with increased velocity, is indicative of moderate or severe regurgitation, while in more severe cases, there may be reversal of diastolic flow in the abdominal aorta.

RHD is a rare cause of aortic stenosis and therefore other aetiology should be excluded. 2D echocardiography demonstrates thickened and restricted aortic valve cusps, often with visible calcification of the cusps. The peak and mean velocity across the valve can be measured and are the most commonly used marker for severity. The aortic valve orifice area can also be calculated to help determine severity, and is especially useful when the LV function is reduced, making the aortic velocity gradient less reliable.[45] In these circumstances, an aortic valve orifice area <1 cm^2 indicates severe disease. Left ventricular size and systolic function can be assessed quantitatively and are usually preserved even in very late disease.

Right-sided valve disease

Tricuspid valve regurgitation in RHD more commonly occurs as a complication of left-sided valve disease and subsequent pulmonary hypertension and right ventricular dilatation. However, primary tricuspid valve RHD can also occur. In these cases, the most frequent findings are retraction of the leaflet free edge with thickening, calcified foci and some degree of fusion and thickening of the commissures and sub-valvular apparatus. Tricuspid stenosis features are like those of MS and there may be thickening and leaflet restriction, with doming of the tricuspid valve leaflets. The severity of regurgitation is assessed by Doppler and colour flow mapping whilst measurement of trans-valvular gradient and pressure half-time gives data to quantify severity of stenosis.

Adjunctive investigation in RHD diagnosis

Transoesophageal echocardiography

In adults, transoesophageal echocardiography (TOE) has several roles. It can help clarify severity and mechanism of valve lesions, particularly in cases of mixed and multi-valvular disease. This is particularly important in pre-surgical planning and may aid in determining appropriateness for valve repair rather than replacement (Level of Evidence GRADE 1B). In cases of mitral stenosis, TOE is used to exclude left atrial appendage and left atrial thrombus prior to percutaneous balloon mitral valvuloplasty and 3D TOE can be used to clarify mitral valve area by planimetry in cases of poor transthoracic imaging. It is also used to investigate for infective endocarditis in patients with rheumatic valve disease.

In children, TOE is reserved for guidance during or just prior to cardiac surgery. This is due to the need for a general anaesthetic to perform TOE in children.

Exercise stress testing and stress echocardiography

Exercise stress testing is useful in cases where symptoms are discordant to echocardiographic data (Level of Evidence GRADE 1B). This applies particularly in patients who deny symptoms despite severe valvular heart disease. In these cases, exercise testing may give objective evidence of true exercise tolerance, either induce symptoms or conversely prove lack of symptoms. This data may be used to support appropriate timing of intervention. Stress echocardiography may provide further information in cases of mitral stenosis. Due to the influence of heart rate and left atrial compliance, some patients may report only exercise-induced symptoms despite echo demonstrating non-severe stenosis. In these cases, stress echocardiography may be helpful as significant elevation in pulmonary artery pressure (≥60 mmHg) and trans-mitral gradient (>15 mmHg in exercise and 18 mmHg with dobutamine) is associated with poor outcomes and supports consideration of early intervention.

Angiography and right heart catheterisation

Coronary angiography is indicated prior to valve surgery to exclude concurrent coronary disease requiring intervention (Level of Evidence GRADE 1C). The choice of invasive coronary angiography versus computed tomography (CT) coronary angiography is determined by the likelihood of patients having established disease and access to testing. In the Aboriginal and Torres Strait Islander population, invasive angiography is recommended in those over the age of 25 years (Level of Evidence GRADE 2C).

Right heart catheterisation may aid in clarifying valve lesion severity when echocardiographic data are inconclusive (Level of Evidence GRADE 1C).[40,46,47] It also may be used to determine the predominant cause of pulmonary hypertension when there is clinical ambiguity (Level of Evidence GRADE 1C).[48]

New echocardiography technology and its role in diagnosis

Since its development in 2012, the WHF guideline[49] *(Table 8.5)* has been used across many countries in various echocardiographic screening studies. Their sensitivity and specificity in high- and low-risk populations have been clarified.[49,50] During this time, there has been significant development of portable and hand-held echocardiography technology. At the time the WHF criteria were developed, hand-held technology had limited functionality and therefore the WHF criteria were not for application with these machines. However, the capacity of hand-held machines has progressed significantly, and this had led to their use in screening studies. Importantly, there remain limitations of the WHF criteria for hand-held echo. A study by Beaton *et al*[51] demonstrated that, compared to standard echocardiography, hand-held echo was highly sensitive and specific when performed by an expert operator. However, it was limited in regard to certain aspects of the WHF criteria, including morphological abnormalities. As such, researchers have suggested modifications to the WHF criteria to better accommodate findings from hand-held echo. Further simplification of echo diagnosis for RHD has also been studied. The use of single echocardiographic criteria that can be assessed by portable echo machines, hand-held devices, and operators with limited training, have shown promise. A 2012 study assessed the use of a single echocardiographic view on a standard echo machine and compared an MR jet ≥2.0 cm versus a modified criteria, demonstrating a positive predictive value of 92%, although four out of 15 cases of RHD were missed.[52] A more recent study performed in East Timor utilising a modified parasternal view involving a whole sweep through the heart showed 100% sensitivity and 95% specificity for borderline and definite RHD in a paediatric population when performed by a cardiologist on a portable standard echocardiogram machine.[53] Although this research shows substantial promise for translation to ubiquitous use of hand-held machines for the diagnosis of RHD, at this stage it remains predominantly a research tool. However, it is likely that hand-held echo will become mainstream once technology advances further and research supports accurate and high-quality diagnostic criteria.

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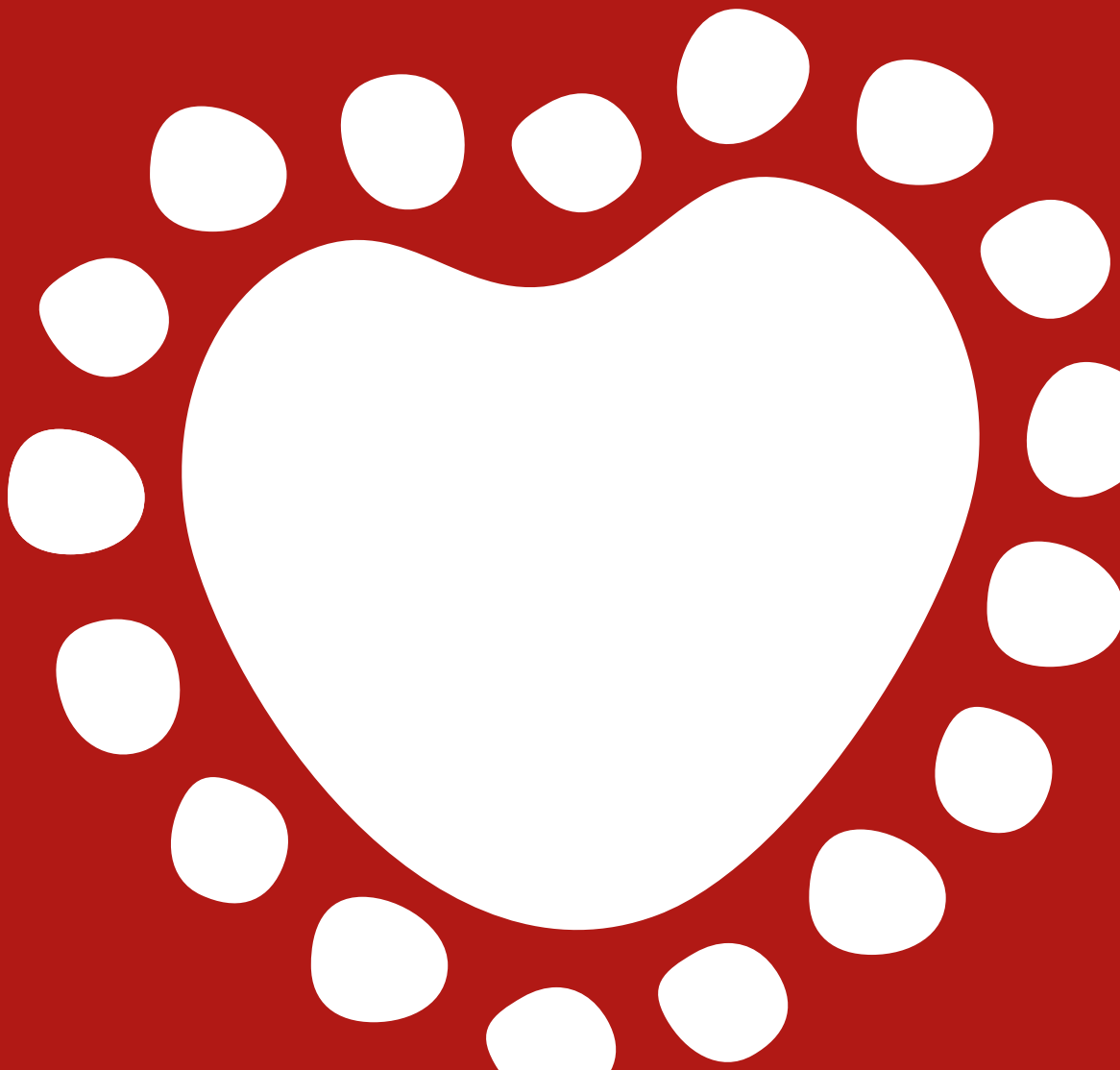
CHAPTER 9

Screening for rheumatic heart disease



Screening for rheumatic heart disease

CHANGES FROM THE SECOND (2012) EDITION

This is a new chapter.

KEY INFORMATION

- Echocardiographic screening for rheumatic heart disease (RHD) has been widely used internationally, often in a research setting or to estimate burden of disease.
- Screening procedures have evolved over time, using different technologies and using operators with varying levels of expertise.
- Population-based screening using auscultation is not accurate for detecting undiagnosed RHD so is not recommended.
- Screening using echocardiography can accurately detect previously undiagnosed RHD.
- Echocardiographic screening for RHD meets some, but not all, of the standard public health criteria for community screening for disease *(Table 9.2)*. In particular, the impact of secondary prophylaxis on disease trajectory is not well defined.
- There remains insufficient evidence to support routine, population-level echocardiographic screening for RHD in Australia as a method of disease detection and control.
- Targeted screening of particular highest-risk groups may be appropriate under certain circumstances; factors to take into consideration are presented in this chapter.
- Screening activities may be effectively used to estimate disease prevalence, and have the potential to improve community awareness, foster local champions and galvanise support for better RHD control.

DISCUSSION

> *"Your whole life changes. I felt like my whole life just stopped but after that day in his room, I thought, I can't sit here and not do anything, especially knowing that there's other young people going through the same thing."*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

General principles of screening

Screening is a public health strategy that aims to identify asymptomatic individuals with latent forms of disease. Disease screening programs aim to improve patient outcomes by intervening with effective treatment during this latent period.

Table 9.1. Definitions of RHD

Latent RHD	Asymptomatic RHD diagnosed through echocardiographic screening which may be clinical (pathological murmur) or subclinical (no clinical signs)
Subclinical RHD	RHD without audible murmur or other clinical symptoms or signs.† Subclinical RHD is only diagnosed by echocardiography and is typically less advanced than clinical RHD
Clinical RHD	RHD with clinical symptoms or signs including pathological heart murmur. Echocardiography is required to confirm the diagnosis

† Detection of a murmur without echocardiography has been shown to be poorly sensitive and specific for the diagnosis of RHD.

In the case of RHD, it is established that effectively delivered secondary prophylaxis can reduce the progression of disease in clinically-diagnosed acute rheumatic fever (ARF) or RHD by preventing ARF recurrence,[1] and may allow for improvement (regression) or resolution of early RHD. In well-resourced settings, early diagnosis of severe RHD also provides the opportunity for earlier surgical intervention and improved surgical outcomes.[2,3]

For a disease to be considered suitable for screening at a population level, there are several criteria which must be satisfied.[4,5] RHD satisfies several, but not all criteria *(Table 9.2)*.

Table 9.2. Suitability of early RHD for screening (updated March 2022)

CRITERION	RELEVANCE FOR RHD
Evidence of a significant burden of disease	The prevalence of RHD among Aboriginal and Torres Strait Islander peoples in northern Australia is one of the highest in the world,[6,7] RHD is a cause of significant morbidity and mortality in this population.[8]
Condition must have a latent stage	RHD has an asymptomatic phase when valvular damage can be detected before symptoms are evident.
The latent stage must be detectable by simple, accessible and sensitive tests	Echocardiography is highly accurate at detecting early, asymptomatic RHD. The predictive value of echocardiography for RHD screening depends on the screening protocol used, the screening device used, the operator and the population screened. Echocardiography is a painless, non-invasive procedure which appears to be acceptable in Aboriginal and Torres Strait Islander communities where it has been used.[7]
The early stage of disease must be treatable with adequate therapy	The natural history of latent RHD is unclear but may be similar to the history of clinically diagnosed ARF, with similar degrees of valvular dysfunction.[9] Early evidence from cohort studies suggests that some screen-detected valve lesions improve (regress), some remain stable, and some progress to clinically significant RHD. The factors influencing risk and rate of this regression or progression are not well understood. The World Heart Federation (WHF) criteria for echocardiography diagnosis define two categories of subclinical RHD: borderline RHD and definite RHD. In general, asymptomatic people with definite RHD on screening echo, and people with borderline RHD from high-risk settings, are presumed to be at risk of valve disease progression and should receive secondary prophylaxis *(Table 10.2)*.[10, 11]
Early intervention must improve prognosis	The clinical benefit of early diagnosis of RHD through echocardiography screening remains unclear. A small number of high-quality, longitudinal studies have been conducted but clear effects on improved prognosis have not yet been demonstrated, as these studies were not coupled with effective secondary prophylaxis delivery.

Adapted from The END RHD Centre for Research Excellence 'Endgame Strategy' https://endrhd.telethonkids.org.au/our-research/the-endgame-strategy/

Brief history of RHD screening

The importance of early RHD detection has long been recognised. The World Health Organization initiated pilot mass screening using cardiac auscultation in the 1980s, but these programs were not sustained.[12] While initial screening protocols relied on auscultation for the detection of heart murmurs, the emergence and adoption of echocardiography has conclusively demonstrated that auscultation is inaccurate for detection of latent RHD, and should no longer be used.[6,13-15] (Auscultation remains an important tool in the clinical setting, but has limited diagnostic utility for screening) Echocardiography has been shown to detect approximately 10 times as many cases of latent RHD, compared to auscultation, revealing a much greater burden of disease than previously estimated.[16] More than 20 countries have now undertaken echocardiographic screening activities to estimate the burden of RHD.

There have been significant advances in ultrasound technology, including the development of small portable echocardiogram devices and the advent of handheld machines. Improved portability makes screening more accessible in remote communities, including in clinics, schools and homes. Research has also explored training non-expert operators (nurses, community health workers) to obtain the limited images required to detect RHD.[7,17,18] The results of these studies are promising, and may offer a more accessible and cost-effective way to screen for RHD. Such an initiative also has the potential to provide local employment opportunities, empowering communities affected by RHD.

World Heart Federation diagnostic criteria for RHD

As the use of echocardiography for RHD screening became more widespread, the need for standardised diagnostic criteria was recognised. In 2012, the WHF published its guideline for the echocardiographic diagnosis of RHD in the absence of a previous history of ARF *(Table 8.5)*.[19] These criteria were the first evidence-based definitions that included both morphological features *(Table 8.4)* and functional aspects of mitral and aortic valve disease due to rheumatic carditis *(Table 8.6)*. The WHF criteria are now widely accepted as the reference standard for RHD diagnosis in patients without a history of ARF and provide clear diagnostic criteria for *definite* and *borderline* RHD as well as features of an echocardiogram classified as *normal*.

Natural history of screen-detected RHD

Echocardiographic screening allows the detection of valvular changes before clinical symptoms develop. However, uncertainty remains regarding the natural history of mild abnormalities in individuals without a prior history of ARF. Further, it is unclear whether screening and commencement of secondary prophylaxis for mild valvular changes provide a better prognosis than no intervention.

Some natural history data from echo screening studies which have used the WHF criteria are now available.[7,20-22] These data have several limitations, including short duration of follow-up (from 4-60 months), small cohorts, variable implementation of secondary prophylaxis and variable definitions of progression/regression of valve changes.

Results of follow-up studies demonstrate the heterogeneity of this group, with some participants progressing, some regressing, and many others remaining stable.[7,20-22] Only two studies have specifically looked at the risk of ARF in those with screening-detected mild RHD, and results are also inconclusive, due to variable uptake of secondary prophylaxis.[21,23]

In a large cohort of latent RHD describing 227 children from Uganda, 10% of children with borderline RHD showed progression, while 25% of children with mild definite RHD showed progression over a median of 2.3 years.[24] Comparatively, 45% of children with mild definite RHD demonstrated improvement in echocardiographic findings in that period. Children with moderate/severe RHD at time of

screening did substantially worse; an observation consistent with data from Fiji showing that >80% of this group demonstrated persistence or progression of RHD, including death.[17] The authors propose that children with screen-detected, moderate/severe RHD be considered as 'missed clinical RHD', and treated in accordance with local recommendations for clinically detected RHD.

Amongst the mild RHD cases, it is not currently possible to confidently predict which individuals are more likely to progress or regress. The Ugandan study suggested that younger age at diagnosis, and the presence of pathological aortic regurgitation or morphological mitral valve features at diagnosis were independent risk factors for unfavourable outcomes but these criteria for progression have not been replicated in all cohorts.[21,25]

Globally, there has been uncertainty regarding whether secondary antibiotic prophylaxis is beneficial for borderline and mild definite RHD cases detected through screening, and the most appropriate clinical management strategy for these individuals has been unclear. A randomised control trial to determine the impact of secondary prophylaxis on the progression of latent RHD was published in 2022.[11] There was a significant difference between the two groups with 3 (0.8%) children in the prophylaxis group having echocardiographic progression at two years, compared with 33 (8.2%) in the control group. These results support the use of secondary prophylaxis for the treatment of latent RHD.

Potential approaches to implementation of RHD screening with echocardiography

Until a clear benefit of earlier intervention can be demonstrated, there remains insufficient evidence to recommend widespread, population-based screening for RHD in Australia. In the meantime, screening activities are being undertaken in different settings, and the rest of this chapter outlines factors to be taken into consideration when considering a program of screening with echocardiogram, including recommendations about the management of screen-detected RHD.

(See *Recommendations of management of echocardiogram screening-detected RHD*)

Target population

Whilst widespread, population-based screening for RHD is not currently recommended, but it may be appropriate to consider screening in some high-risk populations. Screening activities can be targeted to those who are most likely to benefit from earlier detection and treatment of disease. In Australia, it is assumed that all Aboriginal and Torres Strait Islander peoples living in rural or remote areas are at high-risk but regional data would suggest that risk can be further stratified within this heterogeneous cohort,[6] with some communities demonstrating 'hyper-endemic' rates of disease.[7]

The potential contribution of RHD screening is shown in the Burden of ARF and RHD chapter *(Figure 3.2)*.

The optimal age and frequency of screening has not been determined. Globally, the most common approach to date has been to use school-aged cohorts, typically aged 5-15 years. While a school-based screening approach has practical advantages, vulnerable children (including those not attending school) may not be adequately reached, and alternative ways of accessing this group need to be considered.

Another high-risk group that may benefit from screening is pregnant women at risk of RHD,

given the significantly increased demands on the cardiovascular system during pregnancy and delivery (See *Chapter 12. Women and Girls with RHD, Screening*). International studies have demonstrated a high burden of previously undetected disease, and an association with adverse fetal and maternal outcomes.[11,18,26,27]

Different models of screening

Varying models of echocardiographic screening have been undertaken internationally; key differences are summarised in *Table 9.3*.

Table 9.3. Models of echocardiographic screening

	CARDIAC EXPERT MODEL *(Cardiologist, Physician)*	TECHNICAL EXPERT MODEL *(Cardiac sonographer)*		NON-EXPERT MODEL† *(Trained local health worker)*	
		Direct support	**Indirect support**	**Direct support**	**Indirect support**
Screening personnel	Cardiologist	Cardiac sonographer	Cardiac sonographer	Briefly trained healthcare worker	Briefly trained healthcare worker
Diagnostic confirmation	Cardiologist	On-site cardiologist	Off-site cardiologist	On-site cardiologist	Off-site cardiologist
Availability of staff	✓	✓✓	✓✓✓	✓✓	✓✓✓
Echocardiographic equipment	Portable	Portable	Portable	Handheld	Handheld
Screening protocol	Abbreviated Full screen Comprehensive	Abbreviated Full screen Comprehensive	Abbreviated Full screen Comprehensive	Abbreviated	Abbreviated
Sensitivity of RHD detection	✓✓✓	✓✓✓	✓✓✓	✓✓	✓
Specificity of RHD detection	✓✓✓	✓✓✓	✓✓✓	✓✓	✓
Detection of congenital heart defects	✓✓✓	✓✓✓	✓✓✓	✓	-
Time to confirm diagnosis	Immediate	Immediate	Delayed	Immediate	Delayed

† Operators with limited training using handheld devices have lower sensitivity and specificity than qualified technicians using portable machines; a greater proportion will require a subsequent definitive scan by an expert, increasing the final cost.

Personnel

Historically, screening programs have relied on expert teams, frequently led by cardiologists providing direct, on-site support. As screening has evolved in resource-limited settings, shortage of physicians has led to increasing interest in training non-expert operators (nurses, community health workers) to undertake echocardiography screening. Teams have been variable in terms of personnel, including:

- cardiac expert model (cardiologist or physician with echocardiography expertise performs screening and diagnosis);[7,18]
- technical expert model (cardiac sonographer with on-site or off-site cardiologist support for diagnostic confirmation);[6]
- non-expert model (briefly trained health worker with on-site or off-site cardiologist support for diagnostic confirmation).[7,28,29]

Local healthcare workers have established relationships within the community and a connection with language and culture. Use of briefly-trained healthcare workers recognises these qualities and builds community capacity.

Whilst most training of non-experts requires face-to-face instruction and demonstration, freely available online training packages have also been developed and implemented with success.[30]

Task-shifting is appealing where availability of expertly trained operators is limited, however individuals with abnormal screens still require cardiology review. For example, screen-positivity is estimated to be about 10-30%, depending on protocols, resulting in a large number of children requiring a repeat echocardiogram for diagnostic confirmation.[13,31] Models requiring off-site expert review face certain challenges including delays in diagnostic confirmation, delays in decisions regarding treatment, and potentially loss to follow-up prior to treatment instigation. Positive screening results may lead to anxiety, and exclusion from daily activities whilst awaiting diagnostic assessment. Technologies including cloud-servers permit same-day expert review of studies, which enables immediate decision-making. While this is particularly useful for screening performed in remote areas, there are slow internet connections and limited access to mobile phone reception in some areas.

Equipment

Ultrasound technology has continued to evolve, with increasing processing power in smaller consoles, providing different options for RHD screening *(Table 9.4)*. Portability and functionality (including the ability to perform Doppler imaging), 2D image resolution, screen size, battery capacity, storage of images (including file format), and the ability to transfer images are important considerations.[10] Equipment quality has a direct impact on the accuracy of study outcomes.

Despite superior imaging quality, traditional large-format machines are usually not appropriate for screening due to their cumbersome size and lack of portability. Portable echocardiography machines have reduced in size and have sophisticated functions, but they remain expensive. Hand-held ultrasound devices and newer ultrasound probes that are compatible with smartphones and tablets are more affordable, portable and provide adequate image quality.[32] However, many of these devices are limited by lack of pulse-wave and continuous wave Doppler, precluding the application of the 2012 WHF diagnostic criteria. Modified criteria for handheld devices have been used in research settings.[25,28,33,34]

Table 9.4. General specifications and functionality of different categories of echocardiogram machines

SPECIFICATION	HIGH-END MACHINE	PORTABLE MACHINE	HAND-HELD MACHINE
Technical capabilities			
-2D Image Quality	+++	+++	+++
-Colour Doppler	+++	+++	++
-Pulsed Wave/ Continuous Wave Doppler	+++	+++	-
-Measurements – linear	+++	+++	+
-Measurements – volume	+++	+++	-
Affordability	+	++	+++
Console size and portability	-	++	+++
Screen size/resolution	+++	++	++
Battery capacity	-	++	++
Additional probes	+++	++	-/+
Storage and transfer of images	+++	++	++

+++: superior quality, ++: good quality, +: limited quality, -/+: quality not determined, -: unavailable

Screening protocols

The choice of screening protocol will depend on the goals of the screening activity and the resources available. Application of the full 2012 WHF criteria *(Table 8.5)* requires more time and a higher level of training, and is usually limited to cardiologists and cardiac sonographers with specialised equipment. This approach is effectively employing a diagnostic-standard evaluation as a screening test, which is accurate but resource-intensive.

An alternative is a two-stage screening approach, using a brief, abbreviated screening test with either a portable or handheld machine. Several groups have evaluated the performance of simplified screening protocols using limited views, obtained by operators with varying levels of training, comparing single echocardiographic criteria (e.g. mitral regurgitation jet length ≥2cm, presence of any aortic regurgitation) with the WHF criteria.[28,35,36-38] Sensitivity for the detection of any RHD (borderline or definite) varies from 75 - 85% and specificity 80 -90%.

Whichever protocol is used, appropriate sensitivity and specificity thresholds need to be defined and may vary between settings. High sensitivity is usually considered to be the priority in a screening context, to ensure cases are not missed and to maximise the potential benefit of early intervention. High specificity also can be advantageous to reduce the number of false positive screens, of importance where resources are scarce, to ensure resources for diagnostic confirmation and ongoing treatment are effectively targeted.

Diagnostic confirmation

If a two-stage screening model is used, each *positive* or *abnormal* echocardiogram will require diagnostic confirmation and treatment decisions to be made by a cardiologist. This might be achievable using the available screening images, or a second, more detailed echocardiogram may be required. The latter increases complexity and the risk of loss to follow-up if the cardiologist is off-site rather than part of the screening team. Following cardiologist review of the images and/or patient, a diagnosis of definite or borderline RHD (or congenital heart disease), and treatment and follow-up recommendations should be made *(Tables 10.2 and 11.2)*.

Echocardiographic screening performed by experienced cardiac sonographers has the added benefit of detecting previously undiagnosed congenital heart defects which may also benefit from cardiology review and intervention. The prevalence of incidental congenital heart disease detected during echo screening for RHD is consistently around 1%,[6,13,18] and a management pathway for these cases needs to be available.

Recommendations for management of echocardiogram screening-detected RHD

Whilst there remains uncertainty regarding natural history and risk factors for progression of latent RHD, decisions need to be made regarding treatment and follow-up in settings where screening is already taking place.

If screening detects moderate or severe valvular changes of RHD, these individuals should be managed according to standard recommendations for moderate or severe RHD *(Table 11.2)*.[17,24]

If screening detects mild definite RHD, expert consensus recommends that these individuals should be offered secondary prophylaxis according to the recommendation for their age, and follow-up as per local clinical guidelines for mild RHD *(Tables 10.2 and 11.2)*.

For individuals meeting criteria for borderline RHD, recommendations regarding prophylaxis vary according to local practice, and patient and clinician preference. However, secondary prophylaxis is recommended for 2 years for individuals with borderline RHD who live in high RHD-risk settings. Prophylaxis should only be ceased if there is no probable or definite ARF within the previous 10 years, and there is normalisation of echocardiogram findings at 2 years or anytime thereafter. Medical review with repeat echocardiogram should be repeated 1-2 years after ceasing secondary prophylaxis.

Management should include culturally appropriate patient and family education, reinforcing the importance of symptoms of possible Strep A infection or ARF, and presenting early to a health facility for investigation and treatment *(Table 11.2)*.

Non-technical considerations

A number of further issues need careful consideration before commencing screening activities for RHD. This is not an exhaustive list, but highlights challenges that have been faced by different groups who have undertaken screening for RHD in different international settings.

Table 9.5. Considerations for screening

ETHICAL CONSIDERATIONS	
Availability of treatment	• Is there a reliable supply of BPG and a means of administering it for potentially many years? • Is immediate cardiac medical and/or surgical treatment available for severe RHD or congenital heart disease detected by screening?
Culturally appropriate, informed consent	• Are educational resources available in local language? • Should interpreters be used and are they available? • Who is the most appropriate person to provide consent? • How is consent obtained? • Are the potential impacts of a positive screening test able to be conveyed with the chosen consenting procedure?
WORKFORCE CONSIDERATIONS	
Resources available to conduct screening	• Who will perform the screening? • Who will perform the usual duties of that person(s) if they are assigned to screening activities? • Is additional training required? • Who will provide that training? • Will it be sustainable? • Who will maintain quality standards? • Is there support for community-based workers?
Resources available to confirm diagnosis	• Is there access to rapid cardiology review of abnormal screens? • Is there capacity within local cardiology services to review individuals with abnormal screens if needed? • How will the result and recommendations be transmitted to the patient and local health service?
Resources available to provide education	• Do local health facilities have the capacity to deliver education to people found with RHD and their families? • Is there capacity to support Aboriginal Health Staff to provide education and support
Resources available to treat confirmed cases	• Do local health facilities have capacity to provide ongoing secondary prophylaxis? • Is there capacity within the local primary healthcare and cardiology services to provide ongoing clinical follow-up? • Is there an RHD register/control program to monitor follow-up?
ECONOMIC CONSIDERATIONS	

Additional resources will be required	• Cost of resources required will depend on screening model used
	  ○ Equipment
	  ○ Staff, including training
	  ○ Travel

Cost effectiveness is affected by many variables[39]	• Cost effectiveness will increase as the number of new cases detected per population screened increases; i.e.
	  ○ in high-prevalence populations (high pre-test probability)
	  ○ in settings with poor disease surveillance (resource-poor settings)
	  ○ if large cohorts can be screened at one time (e.g. large target population, high screening attendance)
	• Factors that make screening less cost effective include:
	  ○ High number of screens requiring cardiology review (poor specificity of the screening test/model)
	  ○ High travel costs associated with remoteness†

† Combining screening activities in rural and remote areas with specialist cardiology visits may reduce costs and result in timely diagnosis and treatment planning.

Potential benefits of screening

Benefits at an individual level

If an individual is diagnosed with definite RHD through screening, they will have the opportunity to receive secondary prophylaxis which may prevent their progression to clinical disease. In a minority of cases, screening may also detect moderate or severe RHD requiring urgent medical or surgical treatment and lead to improved outcomes.

These potential benefits to the individual assume that screen-detected disease will benefit from earlier treatment, and are dependent upon a functioning health system, which is able to deliver the necessary treatments.

Benefits at a community level

RHD screening activities, particularly when conducted at scale within communities, have been effective at raising community awareness about the disease and providing opportunities for community education. These activities may lead to changes in health-seeking behaviour. Community engagement, trust, cultural safety, education delivered in first language, and local governance and ownership are factors that are likely to increase the long-term impact of a program.[40] The Australian experience in the Pedrino study, found that the community embraced RHD screening. Local RHD champions were identified who were vital to the success of the screening activity and as ongoing advocates for RHD control.

Benefits at a health-system level

Echocardiographic screening is the most accurate method to estimate the prevalence and burden of RHD. High-quality, local disease data is a powerful tool that can be used for local community planning, advocacy and government engagement, and is essential to enable rational health policy decision-making. Local data should be provided to community for interpretation based on principles of data sovereignty and data governance.

If interventions for screen-detected RHD are subsequently shown to alter the trajectory of disease and improve patient outcomes, there are likely to be considerable economic benefits from reduced morbidity and mortality, and improved productivity.

Potential risks of screening

Risks to the individual

If an individual is identified by screening as having RHD requiring secondary prophylaxis and/or medical or surgical treatment, but cannot access or be provided with that care, then there is no benefit from screening. This is more likely to be the case in resource-poor settings, and raises obvious ethical questions about the appropriateness of screening in this instance.

Limited data are available about the impact of echocardiographic screening for RHD on asymptomatic children and their communities. One inherent risk of screening is that of misdiagnosis – a false positive screening test, even if subsequent diagnostic evaluation is normal – may create health-related anxiety, and has been reported to adversely impact quality of life, despite a lack of symptoms.[41] Appropriate counselling and education in communities can mitigate the impact.[41,42]

Perhaps the greatest risk of echocardiogram screening is the potential for over-diagnosis of 'disease' resulting in over-treatment. Secondary prophylaxis is onerous, and the impact of four-weekly intramuscular injections and regular specialist follow-up for potentially many years is significant; for individuals, families and health staff. Understanding the impact of BPG prophylaxis on the trajectory of subclinical RHD (mild definite and borderline) is the most important priority in determining the potential utility of large-scale echocardiogram screening for RHD.

Risks to the health system

Population-based screening programs require infrastructure and additional, ongoing resources. How health resources are allocated is a decision for public health policy. In some settings, the opportunity costs of screening have been raised as a concern: human resources devoted to echocardiography screening may reduce capacity to deliver other strategies to prevent new cases of Strep A infection and ARF, or to deliver clinical care to individuals already known to have RHD. The cost to the health system of screening and delivering secondary prophylaxis to those who may not actually need it cannot be quantified until the natural history of screen-detected RHD is better understood.

CASE STUDIES

South Australian Childhood RHD Screening Project (SACRHD), 2016-2018

SACRHD, conducted by the South Australian Health and Medical Research Institute, reached 2077 Aboriginal and Torres Strait Islander children across South Australia for echocardiography screening by accredited cardiac sonographers. The aims of the study were to:

- determine the prevalence of RHD among Aboriginal children in South Australia; and
- evaluate the suitability of cloud technology in transferring echocardiographic images.

Children were enrolled primarily through schools, and male and female sonographers were used where necessary in line with cultural expectations, and an Aboriginal research assistant led community engagement in traditional areas.

Scans noted by sonographers as being suspicious for RHD were uploaded to a cloud server, often from very remote locations, for review by an off-site paediatric cardiologist. Seven (0.3%) children were identified to have definite RHD and 17 (0.8%) with borderline RHD. Several children were also identified with congenital heart disease. All children were referred to paediatric cardiology services.

The use of accredited cardiac sonographers to perform echocardiographic screening for RHD was efficient and reduced demands on local cardiologists. The use of cloud technology for scan transfer from regional and remote areas to central specialist services enabled the study team to provide timely feedback to families, schools and local health services. A low prevalence of RHD was found in this population.

Pedrino Screening Research Project, 2017-2018

Pedrino, a study based out of the Menzies School of Health Research in the Northern Territory, conducted echocardiographic screening of 1975 children in Timor-Leste (urban and regional settings), and 615 Aboriginal children in Maningrida, a remote community in the Northern Territory. The study was designed to investigate an ultra-abbreviated echocardiography protocol, using briefly trained non-expert health workers, as well as to determine the burden of RHD in the communities screened.

Investigators found that the briefly trained health worker approach used in the study was not adequately sensitive to detect definite RHD. Further studies are underway to refine the approach to training and investigate newer technologies for portable handheld echocardiography. The study demonstrated an extremely high prevalence of definite RHD in the Maningrida cohort (32/615; 5.2%),[7] and detected a high proportion of previously undiagnosed cases, including severe cases requiring surgical management, illustrating the potential impact of active case finding in hyper-endemic settings such as this.

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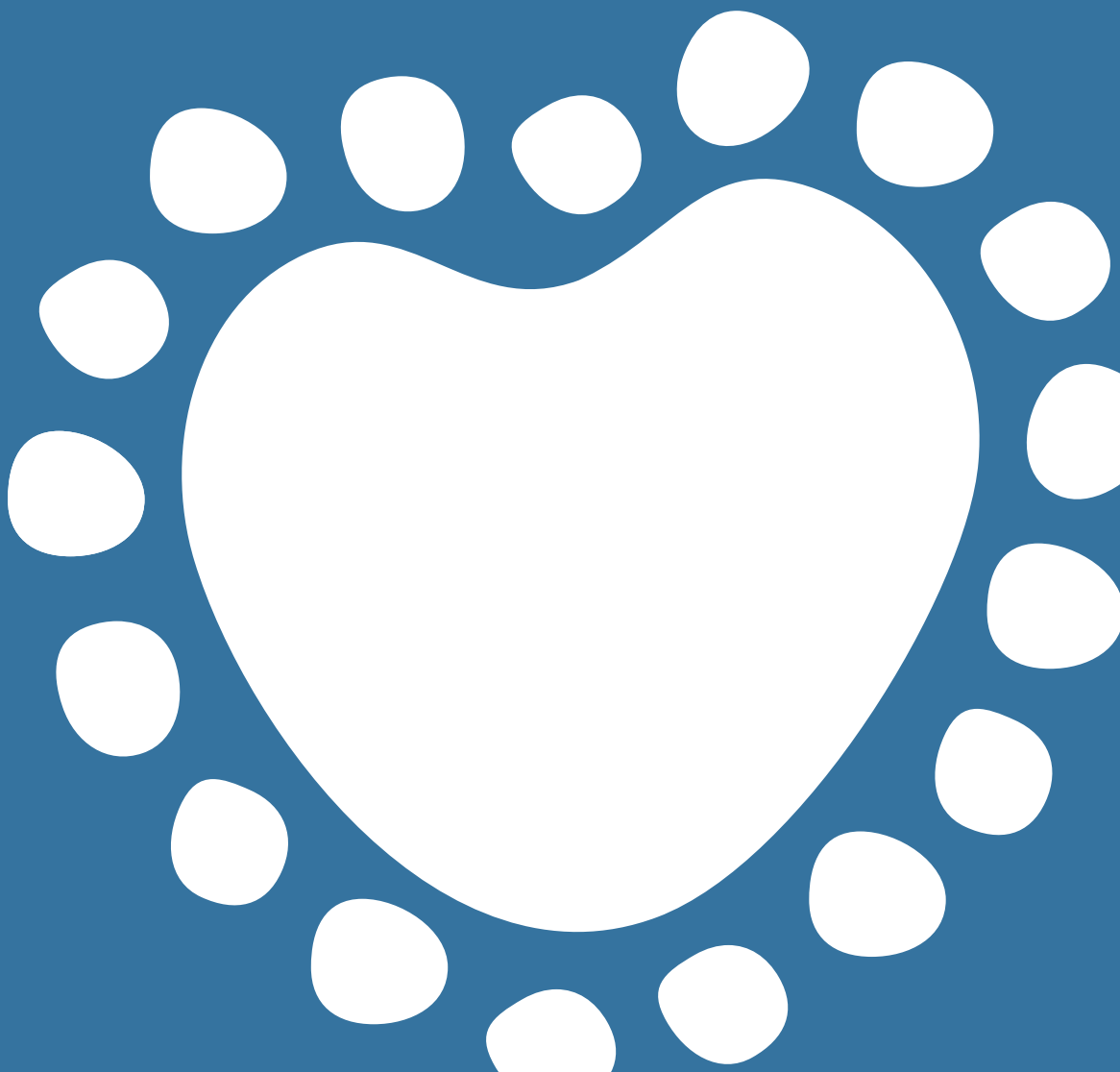
CHAPTER 10

Secondary prophylaxis



Secondary prophylaxis

CHANGES FROM THE SECOND (2012) EDITION

1. The new term *benzathine benzylpenicillin G* (BPG) replaces *benzathine penicillin G.*
2. Doses are provided in units - not milligrams (mg) - for BPG in response to Therapeutic Goods Administration requirements for labelling.
3. Guidance for the ventrogluteal injection site is provided.
4. New approaches to managing injection pain, fear and distress are provided, including the option of medically prescribed lidocaine (lignocaine) and procedural sedation.
5. New recommendations for the duration of secondary prophylaxis are described.
6. A focus on the responsibility of health services to provide a culturally safe service, and for staff to be culturally competent in the management of secondary prophylaxis, is emphasised.
7. Calculation of *days at risk* (which is the best predictor of ARF recurrence) as well as *percent delivery* of BPG injections (which is easier to calculate and comprehend) are both recommended for RHD control program reporting.

KEY INFORMATION

- Secondary prophylaxis of acute rheumatic fever (ARF) is the consistent and regular administration of antibiotics to people who have had ARF or rheumatic heart disease (RHD), to prevent future group A beta-haemolytic streptococcus (Strep A) infections and the recurrence of ARF.
- Long-acting *benzathine benzylpenicillin* G (BPG) used for ARF prophylaxis should not be confused with short-acting *benzylpenicillin.*
- Strep A is fully sensitive to penicillin. Failures of penicillin secondary prophylaxis (i.e. breakthrough ARF recurrence despite receiving all prophylaxis with no *days at risk*) are not thought to be attributable to organism resistance but rather, to low serum or tissue concentrations of penicillin due to individual host differences in pharmacokinetic-pharmacodynamic properties.
- BPG injections should be delivered no later than 28 days after the last injection (or 21 days for those prescribed a 21-day regimen) *(Table 10.1)*.
- Doses of BPG for the treatment of Strep A infection (i.e. primary prevention, *Tables 5.2* and *5.3*) differ slightly from doses of BPG for regular secondary prophylaxis. For example, small children under the age of five living in high-risk settings who frequently develop Strep A infections but rarely develop ARF, are recommended to receive weight-adjusted dosing to avoid excessively large BPG doses. A simpler strategy of two dose options with a single weight cut-off at 20 kg is used for secondary prophylaxis of ARF for pragmatic reasons *(Table 10.1)*.

Table 10.1. Recommended antibiotic regimens for secondary prophylaxis

ANTIBIOTIC	DOSE	ROUTE	FREQUENCY
First line			
Benzathine benzylpenicillin G (BPG)	1,200,000 units (≥20 kg) 600,000 units (<20 kg)†	Deep intramuscular injection	Every 28 days‡ Every 21 days for selected groups§
Second line (if IM route is not possible or consistently declined)			
Phenoxymethylpenicillin (penicillin V)	250 mg	Oral	Twice a day
Following documented penicillin allergy			
Erythromycin	250 mg	Oral	Twice a day

† For children weighing less than 10 kg, a dose of 600,000 units is still generally recommended but seek paediatric advice for careful planning of the regimen of secondary prophylaxis.

‡ People on 28-day regimens can be recalled from 21 days to help ensure that injections are given by day 28.

§ BPG given every 21 days may be considered for a) patients who have breakthrough ARF despite complete adherence to a 28-day regimen, or b) are at high risk of adverse consequences if ARF occurs (have severe RHD or a history of heart valve surgery).

Table 10.2. Recommended duration of secondary prophylaxis (updated March 2022)

DIAGNOSIS	DEFINITION	DURATION of PROPHYLAXIS	CONDITIONS for CEASING PROPHYLAXIS[†]	TIMING of ECHO-CARDIOGRAPHY AFTER CESSATION[‡]
Possible ARF (no cardiac involvement)	Incomplete features of ARF with normal echocardiogram and normal ECG[§] throughout ARF episode	12 months (then reassess)	No signs and symptoms of ARF within the previous 12 months Normal echocardiogram	At 1 year
Probable ARF	Highly suspected ARF with normal echocardiogram	Minimum of 5 years after most recent episode of probable ARF, or until age 21 years (whichever is longer)	No probable or definite ARF within the previous 5 years Normal echocardiogram	At 1, 3 and 5 years
Definite ARF (no cardiac involvement)	ARF with normal echocardiogram and normal ECG[§] throughout ARF episode	Minimum of 5 years after most recent episode of ARF, or until age 21 years (whichever is longer)	No probable or definite ARF within the previous 5 years Normal echocardiogram	At 1, 3 and 5 years
Definite ARF (with cardiac involvement)	ARF with carditis or RHD on echocardiogram, or with atrioventricular conduction abnormality on ECG[§] during ARF episode	According to relevant RHD severity		
Borderline RHD (this diagnosis applies to people ≤20 years of age only)	Borderline RHD on echocardiogram without a documented history of ARF	In a high-risk setting: Minimum of 2 years following diagnosis of borderline RHD *If borderline RHD still present at 2 years continue for further 2 years and reassess. Consider specialist input*	No probable or definite ARF within the previous 10 years Normalisation of echocardiogram after a minimum of 2 years follow up	Medical review and repeat echocardiogram at 1-2 years after diagnosis, and 1-2 years after stopping secondary prophylaxis
Mild RHD[††]	Echocardiogram showing: Mild regurgitation or mild stenosis of a single valve OR Atrioventricular conduction abnormality on ECG[§] during ARF episode	If documented history of ARF: Minimum of 10 years after the most recent episode of ARF, or until age 21 years (whichever is longer) If NO documented history of ARF and aged <35 years:[‡‡] Minimum of 5 years following diagnosis of RHD or until age 21 years (whichever is longer)	No probable or definite ARF within the previous 10 years, no progression of RHD Stable echocardiographic features for 2 years	At 1, 3 and 5 years

Table 10.2. Recommended duration of secondary prophylaxis - Update January 2022 (continued)

DIAGNOSIS	DEFINITION	DURATION of PROPHYLAXIS	CONDITIONS for CEASING PROPHYLAXIS†	TIMING of ECHO-CARDIOGRAPHY AFTER CESSATION‡
Moderate RHD†† §§	Echocardiogram showing: Moderate regurgitation or moderate stenosis of a single valve OR Combined mild regurgitation and/or mild stenosis of one or more valves Examples: • Mild mitral regurgitation and mild mitral stenosis • Mild mitral regurgitation and mild aortic regurgitation	If documented history of ARF: Minimum of 10 years after the most recent episode of ARF or until age 35 years (whichever is longer) If no documented history of ARF and aged <35 years:‡‡ Minimum of 5 years following diagnosis of RHD or until age 35 years (whichever is longer)	No probable or definite ARF within the previous 10 years Stable echocardiographic features for 2 years	Initially every 12 months
Severe RHD§§ ¶¶	Echocardiogram showing: Severe regurgitation or severe stenosis of any valve OR Combined moderate regurgitation and/or moderate stenosis of one or more valves Examples: • Moderate mitral regurgitation and moderate mitral stenosis • Moderate mitral stenosis and moderate aortic regurgitation OR Past or impending valve repair or prosthetic valve replacement‡‡‡	If documented history of ARF: Minimum of 10 years after the most recent episode of ARF or until age 40 years (whichever is longer) If no documented history of ARF:††† Minimum of 5 years following diagnosis of RHD or until age 40 years (whichever is longer)	Stable valvular disease / cardiac function on serial echocardiogram for 3 years OR Patient or family preference to cease due to advancing age and/or end of life care	Initially every 6 months

† All people receiving secondary prophylaxis require a comprehensive clinical assessment and echocardiogram prior to cessation. Risk factors including future exposure to high Strep A burden environments need to be considered.

‡ Echocardiography may be more frequent based on clinical status and specialist review.

§ Normal ECG means no atrioventricular (AV) conduction abnormality during the ARF episode - including first-degree heart block, second degree heart block, third-degree (complete) heart block and accelerated junctional rhythm.

†† Prophylaxis may be considered for longer in women considering pregnancy who live in high-risk circumstances for ARF.

‡‡ If diagnosed with mild or moderate RHD aged ≥35 years (without ARF), secondary prophylaxis is not required.

§§ Rarely, moderate or severe RHD may improve on echocardiogram without valve surgery. In these cases, the conditions for ceasing prophylaxis can change to follow the most relevant severity category. For instance, if moderate RHD improves to mild on echocardiogram, recommendations for mild RHD can then be instigated.

¶¶ Risk of ARF recurrence is low in people aged ≥40 years, however, lifelong secondary prophylaxis is usually recommended for patients who have had, or are likely to need, heart valve surgery.

††† If diagnosed with severe RHD aged ≥40 years (without ARF), specialist input is required to determine the need for secondary prophylaxis.

‡‡‡Priority classification is variable, see *Table 7.4* and *Table 11.2* for clarification

DISCUSSION

"I've been travelling a lot now, for sport and work. I've been to many different communities, but I never forget about this needle. No matter where I go, I never think, "I'll wait till I go back [home]", nah, wherever I go I just get it."

Champion, *RHDAustralia Champions4Change program*, 2019.

Overview

The term *secondary prevention* is a broader concept than *secondary prophylaxis*. Secondary prevention includes antibiotic use as well as activities to limit Strep A infections, or treat infection early if it does arise, among individuals at risk of recurrent ARF. Secondary prevention broadly includes a range of organisational-level factors and environmental and socio-political actions that help improve resourcing and awareness of the problems associated with disease prevention.

Secondary prophylaxis antibiotic therapy goes beyond giving needles. It should include cultural and workforce considerations which place the patient at the centre of care.

Specifically, secondary prevention should include:

- strategies aimed at improving the delivery of secondary prophylaxis;
- the provision of culturally appropriate and accessible patient, family and community education about ARF and RHD;
- support for patients and families to engage in self-management or community group-management of treatment regimens;
- coordination of, and collaboration between, available health services and schools;
- culturally competent, structured, and sustained routine care and follow-up;
- the establishment of local, regional and national RHD control programs;
- advocacy for necessary and appropriate resources for all people at risk of, or living with, ARF and RHD.

Secondary prophylaxis specifically refers to consistent and regular antibiotic therapy delivered to people with a history of ARF and RHD to prevent recurrences of ARF. This approach is a cost-effective RHD control strategy at both community and population level for global ARF/RHD control.[1-3]

Locally tailored interventions provided within a framework of cultural, environmental and social factors related to the treatment, the patient, and the health service have been shown to significantly improve secondary prophylaxis delivery.[4]

Pharmacological therapy

1,200,000 units of BPG is administered to all persons weighing 20 kg or more, and 600,000 units is administered to children weighing less than 20 kg.

BPG is available as Bicillin-LA™ in Australia.

BPG is an Australian Schedule 4 class medicine supplied in boxes of 10 syringes.[5]

Local name variations in use across Australia include 'LA Bicillin', 'LAB', 'BLA' and 'Bicillin'.

Recommended secondary prophylaxis dosage

The internationally accepted standard dose of BPG for the secondary prevention of ARF in adults is 1,200,000 units.[6,7] The dose for children is less clear, with variations across international guidelines regarding the precise weight limit for a lower dose of 600,000 units.[6,8] For example, the World Health Organization (WHO)[6] and New Zealand guidelines[9] recommend 600,000 units for children weighing <30 kg, while the American Heart Association (AHA) recommends the 600,000 units dose for children weighing ≤27 kg.[8]

Pharmacokinetics

Serum penicillin levels may be low or undetectable at 28 days following a dose of 1,200,000 units.[10] Analysis of data from the Northern Territory RHD register has shown some recurrences despite timely delivery of all injections on the 28-day regimen and in rare instances, on the 21-day regimen, revealing the complexities of interpreting the pharmacokinetics and the Strep A environment.[11] A study of BPG pharmacokinetics in children and adolescents in 2019 showed that few patients will achieve the widely accepted penicillin serum concentration of ≥0.02 mg/L for the majority of time between injections if the recommended dosage is used. One proposed explanation for the lower-than-expected concentration was inadvertent injection into subcutaneous or adipose tissue rather than into muscle, since Body Mass Index was identified as a significant determinant of penicillin concentration after injection.[12] Previous studies of BPG pharmacokinetics in children suggested that higher per kg doses are required to achieve sustained penicillin concentrations in serum and urine, and that 600,000 units is insufficient for most children weighing less than 27 kg.[13,14] Nevertheless, the intramuscular penicillin regimen remains the most effective pharmacological strategy for ARF prevention despite these limitations.[15]

Frequency of injections

Injection frequency is sometimes referred to as 'monthly', 'four-weekly' or 'moon-cycle'; however, these terms can be interpreted inconsistently, therefore the use of 'four weekly' or '28-day regimen' is preferred.

BPG is routinely recommended every 28 days to maintain prolonged, low-level benzylpenicillin concentrations.[12] A 21-day antibiotic regimen may be considered by a medical specialist for a small proportion of patients who have breakthrough ARF despite receiving the 28-day regimen, or are at high risk of adverse consequences if ARF occurs.[6,16,17]

Indications for 21-day BPG regimen:

- people diagnosed with definite, recurrent ARF, despite complete adherence to a 28-day regimen *(Table 10.1)*;
- consider in people at high epidemiological risk of Strep A infection who have moderate or severe RHD, or a history of heart valve surgery.

Duration of secondary prophylaxis after ARF

Before ceasing secondary prophylaxis, it must be confirmed that there is no symptomatic deterioration, and that any existing valve lesions are stable. This must include consultation with a clinical specialist, and echocardiographic assessment.

Recommendations on the duration of secondary prophylaxis are made by balancing the risk of ARF recurrence and its consequences to the patient, against the difficulties associated with delivering and receiving regular BPG.

- **Risk of ARF recurrence:** ARF recurrences are most likely to occur in the first year after ARF diagnosis, with the risk continuing to decrease over the subsequent 5-10 years *(Figure 3.12)*.[8] A Northern Territory study in 2016 found that the recurrence rate in the first year after ARF diagnosis was 4.5%, the cumulative five-year recurrence rate was 12.5%, and the ongoing risk after 10 years was very low. The other determinant of ARF risk is patient age, with recurrences being less common after the age of 21.[18,19]
- **Potential consequences to the patient of ARF recurrence:** Many ARF recurrences are 'mimetic' (mimicking the first episode). Therefore, if rheumatic carditis occurs with the first ARF, carditis is likely to be present in ARF recurrences in that individual. The fact that many cases are not mimetic (e.g. the risk of future carditis and RHD is still high after an ARF presentation with arthritis or chorea only) is the reason that secondary prophylaxis is provided for anyone who has had ARF. Nevertheless, ARF recurrence carries a more serious risk for patients who already have significant valve damage.

The presence or absence of RHD is a determinant of secondary prophylaxis duration *(Table 10.2)*. The presence of severe RHD may also prompt the treating clinician to prescribe a more frequent BPG regimen.

- **Personal and health system costs of BPG**: The benefit to risk ratio falls with each passing year after the most recent ARF episode, and as the patient ages. BPG has side effects and costs, and is burdensome to patients, families and health systems, and should not be continued when the likelihood of ARF recurrence, and therefore benefit to the individual, is low.

These considerations are balanced in developing guidance on the duration of secondary prophylaxis, which is recommended for 5-10 years depending on cardiac involvement or not, or until age 21, whichever comes later *(Table 10.2)*.

Ceasing secondary prophylaxis *(Table 10.2)* is a decision between patients and their medical specialist, based on disease history, echocardiogram results, clinical features, social, economic and environmental circumstances, and the likelihood of ongoing exposure to Strep A. The patient's local healthcare team should also be involved, because they are likely to be aware of any social circumstances and ongoing risk exposure which may influence the decision.

Rationale for revision of secondary prophylaxis duration

The recommended duration of secondary prophylaxis has shifted in this guideline from 10 years[20] to five years in selected patients *(Table 10.2)*. However, the existing recommendation to continue until age 21, if that comes later than the 5 to 10-year period, still applies. The implication of this change is that patients aged ≥16 years at the time of their ARF diagnosis, who did not have cardiac involvement and have normal follow-up echocardiography, can cease treatment earlier under the current recommendations.

This reflects the knowledge that the likelihood of an older individual developing RHD, when the last ARF episode was five or more years ago and did not affect the heart, is very low. These guidelines are still relatively conservative (safe) when compared with WHO guidelines that recommend secondary prophylaxis for five years after last ARF or until age 18 years in patients without proven carditis.[6] Regional variations in international guidelines are summarised elsewhere.[21]

Ascertaining whether cardiac involvement is present

Rheumatic carditis can have acute clinical, ECG and echocardiographic findings. A normal echocardiogram especially if done early in the illness, does not exclude carditis. Changes in electrical conduction due to cardiac inflammation may be evident in the absence of visible valve changes. The most common electrical conduction abnormality is first-degree heart block (seen on ECG as prolongation of the P-R interval); but other conduction abnormalities such as accelerated junctional rhythm are also well recognised. While not included as a minor Jones criterion, these cardiac arrhythmias should be considered during diagnostic decisions. Examples of electrical conduction abnormalities associated with ARF are shown in *Chapter 6. Diagnosis of ARF chapter Figures 6.4 to 6.8*.

ECG findings during an ARF episode should therefore be used to help inform decision-making on secondary prophylaxis duration *(Table 10.2)*.

Duration of secondary prophylaxis after RHD diagnosis

In instances where the date of an ARF occurrence is unavailable - that is, RHD is diagnosed in the absence of any recognised ARF episode – the recommended duration of secondary prophylaxis is for 5-10 years after RHD diagnosis depending on RHD severity, or until age 21, whichever is longer. If the person is aged over 35 years at the time of RHD diagnosis and there is no history of ARF, then no secondary prophylaxis is recommended *(Table 10.2)*. The diagnosis of RHD in the absence of recognised ARF is common; an estimated 60% of RHD diagnoses in the Northern Territory occur in people without prior recognised ARF, reflecting the challenges in recognition of this condition.

Oral versus intramuscular secondary prophylaxis

Oral penicillin is not as effective as BPG at preventing Strep A infections and subsequent recurrences of ARF[6,22,23] because oral administration achieves less predictable serum penicillin concentrations.[24] Twice-daily oral regimens are also more difficult to adhere to over many years of prescribed therapy.[25] Treatment with non-penicillin regimens or patients with a documented penicillin allergy is discussed below (See *Penicillin allergy and reaction*).

Oral penicillin should be reserved for patients who experience bleeding problems following injection, and for those who consistently decline intramuscular BPG despite attempts to identify and address the barriers to injections. (See *Managing injection and pain and distress*)

If a patient is provided with oral penicillin, the consequences of missed doses must be clearly emphasised, and the patient carefully monitored for Strep A infections and recurring symptoms of ARF.

Interruptions to the supply of BPG have occurred in the past due to stock outages; this poses significant risks to patients.[26,27] Since there is no adequate injectable alternative to BPG, oral penicillin should be prescribed in the short-term, with regular conversations with patients and their families about the importance of taking all tablets as prescribed, and the need to return to BPG injections as soon as they become available.

Monitoring oral prophylaxis

Monitoring oral prophylaxis over many years is difficult. An oral regimen should be supported by effective communication with the patient, and with people who are strongly connected with the patient. Everyone needs to understand the short- and long-term risks of not taking oral prophylaxis as prescribed, including recurrent ARF and the development or worsening of RHD, and the impact that this can have on quality of life, and on future pregnancies for women *(Table 12.1)*.

Injection sites and techniques

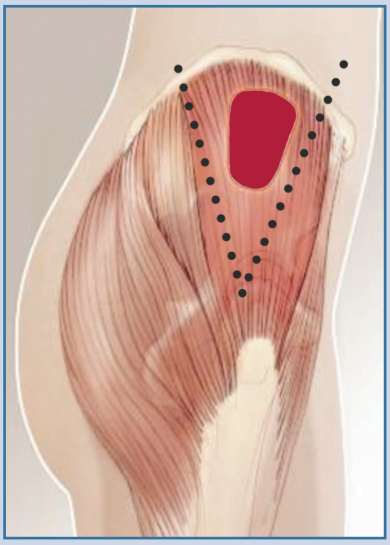
Health staff administering BPG injections need to be able to accurately identify each injection site using bony landmarks, and be familiar with potential complications inherent to each site.[28]

As with all medications, clinicians should check and confirm that the medicine, patient, dose, frequency, indication, and duration of therapy are consistent with the patient's prescription and local protocol for administration.

Recommended injection sites for BPG

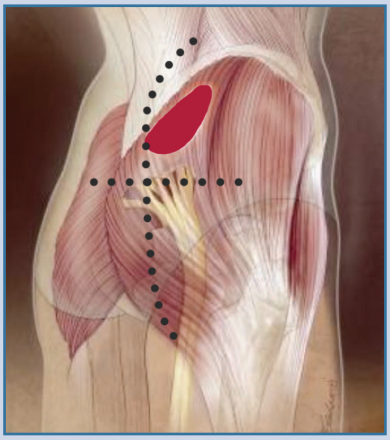
- The ventrogluteal site is emerging as a preferred site for intramuscular injection.[29,30]
- The dorsogluteal site (upper out quadrant of the buttock) is associated with risk of sciatic nerve injury, and this site must be used with caution.[31]
- The vastus lateralis (lateral thigh) is an acceptable site for BPG injection.
- The deltoid muscle of the arm is not recommended for BPG administration.

VENTROGLUTEAL SITE



1. Place the patient in a side-lying position.
2. Using your right hand on the patient's left hip; or left hand on the patient's right hip:
   a) With the palm of your hand, locate the greater trochanter of the femur.
   b) Place your index finger towards the front or anterior superior iliac spine, and fan the middle finger as far along the iliac crest as you can reach. (The thumb should always be pointed toward the front of the leg.)
3. The injection site is in the middle of the triangle between the middle and index fingers.
4. Remove your fingers prior to inserting the needle.

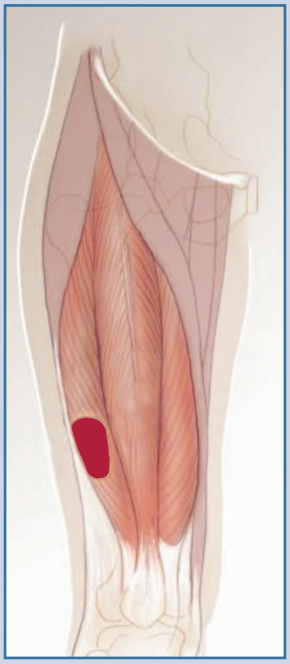
DORSOGLUTEAL SITE



CAUTION - Injections into the dorsogluteal muscle have been associated with sciatic nerve injury.

1. Place the patient in a prone (face down) position, or lying on the side. Some patients may prefer standing up. Patients with valve disease at risk of cardiac decompensation must lie down (See *Non-allergic penicillin reactions*).
2. The site for injection can be identified by either:
   a) dividing the buttock into four quadrants, selecting the upper outer quadrant;
   b) drawing an imaginary diagonal line from the posterior superior iliac spine to the greater trochanter. From the middle of the line move up and out.

VASTUS LATERALIS INJECTION SITE



1. Place the patient in a supine (on back) or sitting position. Patients with valve disease at risk of cardiac decompensation must lie down (See *Non-allergic penicillin reactions*).
2. Place one hand on patient's thigh against greater trochanter, the other hand against the lateral femoral condyle near the knee.
3. Visualise a rectangle between the hands across the thigh.
4. The correct injection site is the middle third of the anterolateral thigh.

Managing injection pain and distress

Patients of all ages should have control over how and where they receive their injection, to enhance their sense of control and wellbeing. Injections should be delivered by culturally competent health staff in a culturally safe environment, with the aim of making each injection procedure as positive for the patient and family as possible.

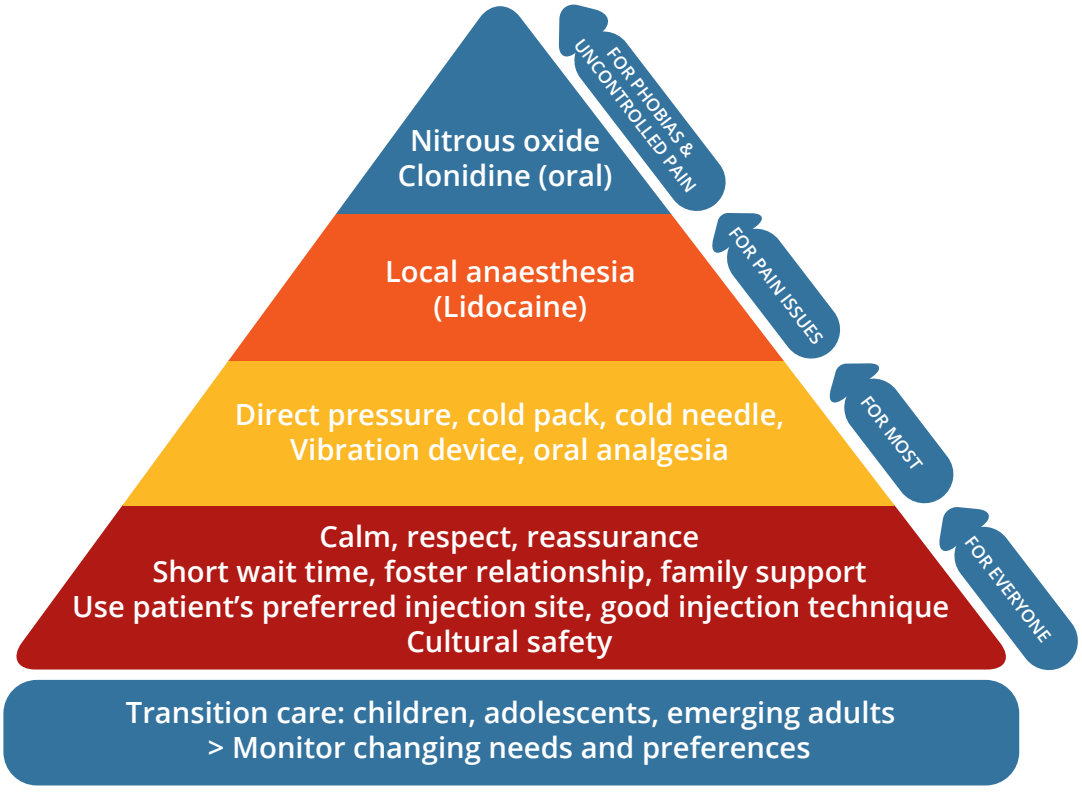
Receiving injections in schools, homes, and places of employment are acceptable alternatives to primary care settings.

Intramuscular BPG injections are painful. Most people do not get used to repeated painful procedures without psychological or pharmaceutical intervention.[32,33] Targeted strategies are required for managing pain; particularly for children, given the young age of many patients on secondary prophylaxis and the long-term nature of the regimen. Pain, fear and distress associated with the first injection can affect patients' expectations of future injections. Also, the patient's prior experiences of pain should be discussed before the first injection. Restraint (restrictive physical intervention) should not be used when administering secondary prophylaxis to children, because psychological effects from restraint can occur for children, their families, and clinicians.[34]

Non-pharmacological techniques and analgesia for procedure-related pain in children are described in Australian Therapeutic Guidelines. Pain management policies for BPG injections *(Figure 10.1)* include:

- non-pharmacological strategies for everyone;[35]
- timely or preventative procedural interventions and analgesia if pain is an issue;
- protocols for procedural sedation for people with phobias or uncontrolled pain.[36]

Figure 10.1. Strategies for injection managing pain, fear and distress



Non-pharmacological strategies

The following patient-centred strategies are part of the standard approach for all patients receiving BPG injections:

- a patient-focussed, culturally safe environment;
- respect for the patient's preference for pharmacological pain management strategies and site for injection (within the guidelines for appropriate delivery site);
- relationship-based and relationship-strengthening activities such as use of incentives and rewards;
- family or support person involvement during injection procedures;
- minimal waiting time for injection;
- best practice injection technique;
- allowing skin swabbed with alcohol to dry before injecting;
- distraction during injection with electronic games, videos etc;[37]
- injecting slowly.

The *gate theory of pain* proposes that a patient's interpretation of pain can be interrupted by applying direct stimulus at or near the injection site.[38] There are several non-pharmaceutical pain-blocking techniques and devices available in this category, including:

- firm pressure to the site for at least 10 seconds immediately before injecting;
- ice pack applied to the site before injecting;
- use of ice and vibration (e.g. Buzzy®, a vibrating ice pack) directly adjacent to the injection site during injection;[39,40]
- use of other medical devices to provide distracting stimuli to the skin (e.g. Shot Blocker, a piece of plastic shaped to fit around an injection site and press the skin with multiple, small, blunt bumps to 'saturate sensory nerves');[41]
- refrigerating the needle prior to injection delivery.[42]

Pharmacological strategies: analgesia

There are several pharmacological strategies for managing injection pain. Pharmacological options for managing injection pain and distress should be discussed with patients and their families, and reviewed regularly to monitor changing needs and preferences *(Figure 10.1)*. Pharmacological strategies include:

- oral paracetamol before injection and at appropriate time intervals afterwards as required;
- anaesthetic spray before injection;
- lidocaine (lignocaine) injected with BPG;
- nitrous oxide (Entonox) during the injection procedure;
- oral clonidine prior to injection (for children and adolescents who are highly distressed with the injections despite use of other strategies).

Pharmacological interventions should be accessible to all patients depending on their level of pain and distress, and should be only used as part of an individual care plan. Prescriptions, clinical scope of practice, local protocols and supply of medications and medical gases should be expended as needed.

Lidocaine-Claris (lignocaine) is a sodium-channel-blocking drug. It is quick-acting and lasts 60 to 90 minutes. When used with BPG injections, it is reported to significantly reduce pain during injection and in the first 24 hours after injection.[39,43] Lidocaine is recommended in New Zealand (0.25 mL of 2% lidocaine)[9] and Fiji (up to 1.0 mL of 1% lidocaine)[44] as a pain management option for people who experience moderate to severe pain during and after BPG injection.[45] A trial of interventions in New Zealand among children aged 13 years or younger included using either lidocaine alone, or lidocaine with Buzzy®. Results showed a greater reduction in pain when lidocaine and Buzzy® were used together, and the fear of injection among these children was also reduced.[39] Anecdotal reports suggest that unexpected vibration such as provided by Buzzy® can cause alarm, therefore it needs to be introduced with care (e.g. demonstrate on one's own hand first before allowing the child to hold it, then using it at the injection site).

Lidocaine can also be administered as a spray or cream to anaesthetise the skin, but this is not effective in anaesthetising lower dermal or fat layers.

Administering BPG injection with lidocaine (lignocaine)

Lidocaine is contraindicated in people with the following:

- **known hypersensitivity to local anaesthetics of the amide type;**
- **second- or third-degree heart block.**

Lidocaine is relatively contraindicated in people with bradycardia and hypovolaemia

Addition of local anaesthetic to a pre-filled BPG syringe had previously not been recommended due to the potential for biohazard injury in handling sharps. Additionally, the manufacturer noted that there was inadequate data on the rate of absorption, efficacy, and safety of an admixture of Bicillin L-A® with lidocaine, and therefore they could not recommend the addition of lidocaine. However, these concerns are outweighed by the proven benefit to the patient in pain reduction.[39,43]

A strategy to deliver lidocaine with BPG is to transfer the contents of the pre-filled BPG syringe to a new syringe, draw lidocaine into the new syringe tip, then administer using the new syringe so that the lidocaine is injected first.

Equipment

- Pre-filled BPG syringe
- 3 mL syringe
- 2 drawing-up needles
- 21 g needle

Preparation

1. Attach a drawing-up needle to a 3 mL syringe.
2. Draw the required contents of BPG from the pre-filled syringe into the 3mL syringe (2.3 mL for 1,200,000-unit dose and 1.17 mL for 600,000-unit dose).
3. Using a new needle, draw up 0.5 mL of 1% lidocaine **or** 0.25 mL of 2% lidocaine into the tip of the 3mL syringe.
4. Avoid mixing to keep the lidocaine in the tip of the syringe.
5. Push plunger up carefully to remove any air in the syringe.
6. Remove the drawing-up needle.
7. Attach IM needle (e.g. 21 gauge) to the syringe to administer injection.

(Adapted from Heart Foundation New Zealand, 2014)[9]

Table 10.3. Considerations for using lidocaine (lignocaine)

CLINICAL FACTORS	PATIENT FACTORS
Lidocaine can be offered as part of a multi-faceted approach to managing injection pain.†	Consider the impact of introducing lidocaine for a patient who is already receiving BPG injections without lidocaine.
Lidocaine should only be used following discussion between the doctor and the patient, and with input from family and other health staff.	• Addition of lidocaine results in an increased volume to be administered.‡
Lidocaine needs to be ordered on a medication chart according to local protocol.	Consider the impact of not providing lidocaine to a patient regularly receives lidocaine.
Lidocaine is compatible with penicillin and does not affect its chemical composition.[43]	• The pain of an injection without lidocaine may influence the patient's approach to future injections.
Low-dose lidocaine is safe during pregnancy.[46-48]	Confirm use of lidocaine with the patient prior to each injection.
• Lidocaine crosses the placenta, however there is no evidence that it causes fetal malformations or other significant side effects.	• Ongoing use of lidocaine should be determined by the patient.
Low-dose lidocaine can be administered to women who are breastfeeding.[43,46,49]	
• Lidocaine is excreted into breastmilk in small amounts. Given the small amount of lidocaine used with BPG injection, the amount excreted into breastmilk to which the baby is exposed is minimal. Lidocaine is unlikely to cause adverse effects in breastfeeding babies.	

† Recommendations for the use of lidocaine (lignocaine) with BPG vary across Australia's jurisdictions; some recommend against adding lidocaine, and some recommend against decanting, mixing, or diluting during intramuscular injection preparation.

‡ The formulations of BPG vary globally, with powder formulations for reconstitution and/or larger volume injections required in some countries.

Pharmacological strategies: sedation

Sedation may be necessary when distress remains significant despite using other measures to manage pain, fear and distress. When sedation is needed, use the least intrusive route and lightest sedation necessary.

Pre-mixed nitrous oxide (Entonox®) can be used for short-duration procedural pain and anxiety reduction related to BPG injection, where use of other non-pharmacological and pharmacological strategies has failed.[50] While this agent has favourable qualities making it suitable for use during BPG injection, it is not available in many community settings. A procurement process would be required for health services wishing to offer this option. Pre-mixed nitrous oxide, an S4 (restricted) medicine, is a gas mixture of 50% nitrous oxide and 50% oxygen which is self-administered using a mouthpiece or mask. It must be used on prescription only and with sound knowledge of potential adverse effects, which include loss of consciousness if used incorrectly.[50] Prolonged exposure can lead to bone marrow suppression, and it should not be used in children aged <4 years, or in older children who are unable to self-administer. The clinic room in which nitrous oxide gas is used must be well-ventilated. There are no published data on the efficacy of pre-mixed nitrous oxide in improving the acceptability of BPG injection.

Oral clonidine is an alpha-2 adrenergic receptor agonist with broad cardiovascular and central nervous system effects in children and adults, including analgesia and sedation. Clonidine produces sedation by decreasing sympathetic nervous system activity and the level of arousal due to inhibition of central nervous system alpha-2 receptors. The result is 'a calm patient who can be easily aroused to full consciousness'.[51] Immediate-release clonidine has rapid oral absorption, reaching a peak concentration within 60-90 minutes. These features make clonidine an attractive option for use for BPG injection in a monitored primary- or tertiary-care setting. However, drug effects also include dry mouth, bradycardia and hypotension. Individuals with RHD may not tolerate hypotension or bradycardia; clonidine may be contraindicated in such cases, so discussion with the child's specialist would be required, and in all instances, close monitoring is required. The recommended starting dose is 3 micrograms/kg.[51,52] Unpublished case reports describe the successful use of clonidine using a clearly documented protocol in Australia to treat severe needle phobia and anxiety, with oral administration 60 minutes prior to BPG injection, accompanied by blood pressure at least every 10 minutes and continuous pulse oximetry monitoring (*Table 10.4*).

Table 10.4. Clonidine use for BPG injection[53]

Staffing requirements: two clinicians at least one of whom is trained in Paediatric Basic Life support

Equipment: pulse oximeter, sphygmomanometer, oxygen, bag and mask

Preparation: fasting for 6 hours for food and milk; fasting for 1 hour for clear fluids (water, cordial, clear apple juice)

Monitoring: continuous pulse oximetry, and frequent monitoring of vital signs and level of consciousness.

Baseline observations:

- heart rate
- oxygen saturation
- blood pressure
- respiratory rate
- level of consciousness using the 'alert, verbal, pain, unresponsive' (AVPU) score

1. Procedural coaching – provide a clear explanation in a calm environment to the patient and their carer about the role of clonidine, the expected effect to improve the experience of the BPG injection, potential side effects, the monitoring that will occur, and the post-procedure requirements.	
2. Give clonidine 3 micrograms/kg orally, 60 minutes prior to BPG injection.	• Paracetamol or a nonsteroidal anti-inflammatory agent can be administered simultaneously. • Seat the patient with the carer and keep carer with patient until observation period is over. • Give BPG with lidocaine when patient is sufficiently calm or drowsy, usually maximally noted around 60 – 90 minutes post clonidine administration (See *Administering BPG injection with lidocaine (lignocaine)*) • Provide continuous pulse oximetry and 10 minutely HR, BP, pulse rate and RR from time clonidine given until drowsiness mostly resolves, patient is easily rousable to voice and vital signs normalise. Discharge from clinic. • If no drowsiness has occurred by 90 minutes and vital signs are normal, it is reasonable to cease continuous monitoring and do a final set of observations at two hours.
3. Re-dosing of clonidine for subsequent BPG doses	Adjust next clonidine dose according to the response to 3 micrograms/kg. For example, reduce to 2 micrograms/kg if excessive drowsiness (e.g. needing respiratory support or oxygen) or unacceptable haemodynamic effects occurred with the 3 microgram/kg; increase to 4 microgram/kg if lower dose was inadequately effective.

Penicillin allergy and reaction

The global rates of allergic and anaphylactic reactions to BPG are 3.2% and 0.2% respectively, and fatal reactions in clinical practice are exceptionally rare.[6,54-56] Most patients labelled as allergic to penicillins are not truly allergic when appropriately stratified for risk and re-challenged.[32,57]

Patients commencing secondary prophylaxis who have a documented reaction or allergy to penicillin should be referred to an allergist or immunologist to verify the type and severity of the response, and to determine if there is an absolute contraindication to penicillin. Options include skin testing for patients with immunoglobulin E-mediated reactions[58] and/or a supervised drug challenge for patients with non-severe delayed reactions. Most patients who report a penicillin allergy can safely tolerate a penicillin challenge. Penicillin desensitisation is not practical, because it would have to be repeated before each dose of BPG.[58,59]

When patients report an allergy to penicillin, it is important to cross-reference the clinical history of past reactions, and review the medical record for associations between administration and symptoms, preferably using an antibiotic allergy assessment tool. For example, the tool described by Devchand *et al*[60] can help assign someone to a category of being likely or unlikely to have true penicillin intolerance or true immediate penicillin hypersensitivity. If a confirmed immediate and severe allergic reaction to penicillin is revealed,[61] (e.g. anaphylaxis, Stevens-Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) a non-beta lactam antimicrobial such as erythromycin should be used instead *(Table 10.1)*.[6,17]

Reactions resulting from BPG injections are most likely to occur within 15 minutes of administration, so the patient should be observed for 15 minutes after administration of the first dose or if there is concern about a potential reaction. Anaphylaxis can include respiratory symptoms such as wheeze or stridor, cardiovascular symptoms such as tachycardia and sustained hypotension, skin symptoms such as itching and weals, gastrointestinal symptoms such as abdominal cramps, nausea and vomiting, and neurological symptoms such as severe anxiety and distress.

Rapid intramuscular administration of adrenaline is the first line for anaphylaxis treatment. Observe local protocols for managing anaphylaxis, including first aid.

Non-allergic penicillin reactions

Mild to moderate adverse reactions to BPG not comprising allergy, such as fever and malaise, are described. In qualitative work from the Northern Territory, the majority of individuals receiving regular BPG did not experience side effects, although a small number described feeling generally unwell afterwards, requiring bed rest.[32]

Concerns internationally about risks of severe or fatal reactions to BPG have in some settings caused reluctance to prescribe BPG.[62] However, an investigation of case reports of severe and fatal adverse events associated with BPG administration for RHD prophylaxis from African and Asian settings indicated that anaphylaxis is unlikely to be a major cause of adverse reactions to BPG.[63] The authors reviewed the likely diagnosis in each case, considering potential alternative explanations: anaphylaxis, impurities or contamination of BPG products, inadvertent intravascular administration of BPG, or underlying structural cardiac disease itself predisposing to adverse outcomes. They concluded that the most likely explanation was the latter, whereby individuals with severe valvular disease may develop severe, sometimes fatal, compromise in response to receiving BPG injections. Mitral valve disease is a risk factor for arrhythmias and sudden cardiac death; pain or fear of BPG administration could drive a physiological response causing decompensation or arrhythmic events, and vasovagal hypotension/syncope. Vasovagal syncope is a well-described response to intramuscular injection, which could also contribute, particularly in patients with severe valvular disease.[63]

Correct administration of BPG is important, especially for people with severe RHD.

BPG injections should be administered by people trained in intramuscular injections and identification of anatomical landmarks, which minimise the risk of intravascular administration (See *Recommended injection sites for BPG*).

In Australia, adverse events associated with the administration of medicines should be reported to the Therapeutic Goods Administration and to the manufacturer, and details recorded in the clinical notes and provided to the patient/carer. There is no increased risk of developing allergies to penicillin with prolonged BPG use.

To minimise the risk and impact of adverse events with BPG:

- **Employ strategies to reduce the pain of BPG injections, particularly in people with advanced heart valve disease** *(Figure 10.1)*.
- **Prepare the injection according to the manufacturer's instructions.**
- **Check the patient's allergy status prior to administration.**
- **Administer the injection slowly.**
- **Advise the patient, and their parent or carer, about which adverse events are common and of relatively minor significance and how to manage them (e.g. pain, tenderness, low-grade fever), and which are serious and should be reported to staff and managed (e.g. swelling, heat and increased pain at site, feeling significantly unwell).**
- **Adrenaline (epinephrine) should always be available (ideally in appropriately dosed pre-filled syringes) when BPG injections are delivered.**
- **All secondary prophylaxis programs should have a mechanism for reporting adverse drug reactions to BPG. (In Australia, to the Therapeutic Goods Administration)**

Special considerations

Pregnancy and breastfeeding

Penicillin and erythromycin are safe for mother and child during pregnancy and breastfeeding and should continue if indicated *(Table 12.2)*.

Penicillins cross the placenta in low concentrations, and can be detected in amniotic fluid, however there is no evidence that penicillins have any teratogenic effects on the fetus.[64] The importance of continuing secondary prophylaxis during pregnancy, which is a time of higher cardiac risk, should be discussed with the woman and her family prior to a planned pregnancy, and as soon as possible during an unplanned pregnancy *(Table 12.1)*.

Following heart valve surgery

Surgery does not affect the risk of Strep A infections or recurrent ARF. Therefore, secondary prophylaxis must be continued following surgery.

The aim of heart valve surgery is to improve cardiac function and patient wellbeing by repairing or replacing damaged heart valves. The potential for cardiac damage from recurrent ARF is increased after surgery, particularly if mechanical heart valves have been used to replace damaged valves. Unlike tissue valves, mechanical valves are not able to expand with carditis, and the surrounding tissue is more likely to tear and dislodge. If patients are discharged from hospital with oral penicillin, they should recommence BPG as soon as is practical.

Patients who require heart valve surgery for non-rheumatic heart valve disease and who are not at high risk of ARF, are not indicated for secondary prophylaxis.

Bleeding disorders

Bleeding complications from BPG injections in patients receiving anticoagulation therapy in Australia are rare.[65] Therefore, BPG injections should be continued in patients receiving anticoagulation unless there is evidence of uncontrolled bleeding or the international normalised ratio (INR) is greater than 4.5.[66] If INR is >4.5 and secondary prophylaxis is due, administer oral penicillin until the INR has reduced, and BPG can be resumed.

Multidisciplinary patient-centred care

Patient education

Patients and their families should be provided with clear information about how secondary prophylaxis works, and the risk of recurrent ARF and its consequences if they do not receive treatment as prescribed. This may require an interpreter, language-appropriate written material, and culturally appropriate conversation.

Patient-related factors to consider and appropriately respond to include level of health literacy, experiences of pain (including previous experience with BPG injections), knowledge and beliefs about secondary prophylaxis, expectations of health services, and recognition of ARF recurrence.

Multidisciplinary teams should provide clear and consistent health messaging to patients about the importance of secondary prophylaxis, and its role in preventing recurrent ARF and avoiding or delaying the development of RHD. Provision of culturally appropriate education is emphasised at the time of diagnosis (See *Chapter 7. Management of ARF, Education*), however, effective, engaging and age-appropriate educational opportunities need to be repeated. Each time the patient and family encounter the health system for secondary prophylaxis is an opportunity to provide relevant education. This should include:

- respecting and acknowledging the family's beliefs about what causes disease;
- opportunities for two-way knowledge exchange;
- use of trained interpreters to aid communication between clinicians and their patients where English is not the primary language;
- information about ARF and RHD, the reason for BPG injections, and the importance of receiving each injection;
- discussions about the patient's injection experience, duration of the prescribed regimen and proposed cease date (date to cease may change based on recurrent ARF and RHD status) *(Table 10.2)*;
- discussions about recognising and responding to Strep A infections, and symptoms of ARF.

A range of resources are available to guide health education, supporting people of different ages, gender and language. (See HealthInfoNet, KAMSC and RHDA resources)

Adolescent care

Most people receiving secondary prophylaxis injections will be pre-teens, adolescents and young adults *(Table 10.2)*. Several studies have shown delivery of secondary prophylaxis decreases when children reach adolescence[67-69] so a good understanding by the health workforce of adolescent health needs around ARF, RHD and secondary prophylaxis is essential.

Chronic illness in children and adults can have lifelong physical and psychological impacts. ARF even without RHD is a 'chronic disease' due to the long-term nature of secondary prophylaxis, and the complicated care plan and engagement with the health system.[69] Health services that acknowledge adolescent health needs and embrace the concept of 'transition care' are likely to achieve better delivery of secondary prophylaxis.[70] Child and adolescent-friendly spaces within health services are a tangible way of supporting this. Tracking the development of children and adolescents within a clinic's RHD program, including how they are coping with their injections and what they understand about their condition, helps to provide responsive health care *(Table 11.4)*. Unpublished data from Australia indicate that local community patient navigators or RHD support people are beneficial for both patients and clinicians. A study is also underway in New Zealand to investigate the role of care navigators.[71]

Measuring BPG injection adherence

Delivery of BPG for individual patients can be measured as a percentage, and calculated as follows:

$$\text{Percent (\%) delivered} = \frac{\text{number of doses administered}}{\text{number of doses recommended}} \times 100$$

This can be expressed as an annual measure, or shorter if the patient has not yet been receiving BPG for 12 months.

While percent delivery of prescribed BPG injections is the simplest way to calculate injections delivered/received and is easy to comprehend, the measure does not take account of dose timing. 100% delivery can be achieved by someone on a 28-day regimen who receives 13 doses in 12 months, yet they may have had some doses delivered at short intervals while having substantial breaks between other doses, leaving the person vulnerable to Strep A infection and ARF recurrence. Therefore, to estimate an individual's adherence more precisely, a calculation of *days at risk* provides a better estimate.

Days at risk for a 28-day BPG regimen = number of days after 28 days that the next BPG dose was administered.

If the BPG administration date is considered as *day 1*, the next BPG dose is due on *day 29*. If the next BPG dose is given late, the first day at risk is *day 29* and all subsequent days before the next dose administration date are counted as days at risk.

In a comparison of the association between different measures of injection delivery and ARF recurrence risk, total *days at risk* was the strongest predictor of ARF recurrence.[72] It is recommended that calculation of *days at risk* be included in program reporting as well as *percent delivered*. The reason to calculate and report both is that while *days at risk* is more precise and more predictive of ARF recurrence risk, it is difficult to calculate and interpret. *Percent delivered* is a more comprehensible measure which is easy to calculate.

Recall for injection

Depending on social circumstances and methods used for reminders, patients may benefit from receiving recall reminders in the week leading up to their next due date for BPG. This is, from day 21 for people receiving a 28-day regimen and from day 14 for people receiving a 21-day regimen. This minimises the risk of injections being delivered late. Over-dosage due to early administration is not of concern, since the serum concentrations achieved are low. Calculation of *days at risk* for ARF recurrence allows healthcare services to be alerted to late doses to ensure patient recall.

To minimise days at risk, patients prescribed a 28-day regimen should be recalled between day 21 and 28 to allow adequate time for patients to attend for their injection.

Local knowledge should be sought to document in advance the locations where patients are likely to live and visit for social, economic, cultural and other reasons. Health service networking between these sites should be intentional and collaborative around delivery of secondary prophylaxis.

Patient and family support strategies

Secondary prophylaxis support strategies should be informed by local knowledge of barriers to treatment. Some factors vary widely from one health service to another (wait times, triage processes, accessibility of the clinic); other factors are universal (the time commitment required to attend clinic, needle-related factors). Support can be broadly categorised into health centre-related approaches, community-level approaches, patient-level approaches and treatment-specific approaches.
(See Treatment Tracker app and Take Heart app)

Table 10.5. Strategies to improve the delivery of secondary prophylaxis

SUPPORT CATEGORY	EXAMPLES OF STRATEGIES
Health centre-related approaches	• Health services prioritise secondary prophylaxis delivery and are skilled in its delivery • Health services provide culturally safe care • Pro-active, register-based recall systems are used to ensure patients are recalled for their next dose and given adequate notice • Outreach (home-based / school-based) injection delivery is provided when feasible
Community-level approaches	• Community awareness-raising events are supported • Peer support groups are developed (e.g. Champions4Change)

Patient-level approaches	• Self-management support with family and community engagement is provided
	• ARF and RHD educational materials are suitable for the target audience e.g. in the patient's local language; provided in audio or video format
	• BPG dose reminder systems are used, such as:
	  ○ Smartphone application
	  ○ Electronic or paper calendar
	  ○ Phase of moon strategy (e.g. remember needle is due on full moon or new moon)
	• Incentives are considered

Condition and therapy-specific approaches	• Validated methods such as 'transition care' are used to support chronic care management from childhood through to adolescence and adulthood • Non-pharmacological techniques are employed to improve the experience of BPG injection • Pharmacological techniques are used when needed, and in addition to non-pharmacological approaches

RHD program oversight

Wherever possible, patients should be offered the opportunity to receive their injections at a location of their choice (e.g. the health service, home, workplace, school).

Culturally competent, experienced staff should be appointed to deliver local secondary prophylaxis programs, and staff who are competent to administer BPG injections to children and adolescents should be identified. Clinician expertise and confidence in administering BPG injections can be improved and maintained by continuing professional development, observing local protocols for injection delivery, and by working directly with patients and their preferences.

In a health system environment of frequent clinician turnover and high deployment of agency staff, health service managers have a responsibility to ensure governance and oversight of local RHD portfolios and to promote a whole-of-team approach to delivery of secondary prophylaxis.

Administration of each injection needs to be recorded at primary care level, and reported to the jurisdictional RHD register (where it exists) *(Table 13.1)*. Information on BPG delivery should be recorded in a centralised database, so that health staff can monitor injection delivery and make informed clinical decisions. This is especially important in settings where multiple patient information systems are used in parallel.

Patients require clear information about where they can receive secondary prophylaxis, details about the date and location of future appointments, and contact details for their local health centre or hospital. Patients and families should be encouraged to phone or visit their local health service or hospital if they have any questions concerning their follow-up or secondary prophylaxis.

Unsuccessful secondary prophylaxis delivery

Unsuccessful secondary prophylaxis delivery can be defined as:

- *short term,* where the patient misses or declines 1-2 scheduled injections;
- *medium term,* during which the patient misses or declines scheduled injections for a period of months;
- *enduring,* when the patient rejects secondary prophylaxis as a treatment method.

Where patients miss or decline injections in the short or medium term, health staff and Aboriginal and Torres Strait Islander Community Workers should work with the patient and family to identify and address any manageable factors that may be contributing to unsuccessful secondary prophylaxis delivery *(Table 10.5)*.

Where patients reject secondary prophylaxis as a treatment method to prevent ARF, a high level of support is required. A multidisciplinary supportive network should be engaged to ensure that the patient is aware of the risks of non-treatment, and regular patient monitoring should be scheduled to determine ongoing risk of Strep A infections, recurrent ARF, and the development or progress of RHD. Patients should continue to be offered secondary prophylaxis treatment as indicated.

Patients who miss or decline secondary prophylaxis should be encouraged to engage with treatment, while being monitored closely to determine ongoing risk of ARF and cardiac status.

CASE STUDY

Secondary Prophylaxis Delivery in RHD: Benefits of a Collaborative Approach

Background

Nganampa Health Council (Nganampa) is an Aboriginal-owned and controlled health service providing healthcare for the Anangu people of the Anangu Pitjantjatjara Yankunytjatjara (APY) Lands in remote north-western South Australia. Nganampa Heath Council has co-written and approved the use of this case study. In response to the National Chronic Disease Strategy,[a] Nganampa introduced a Chronic Disease Program to help improve outcomes for people living with chronic disease.

In 2010, about 60 people across APY communities were prescribed secondary prophylaxis but only ~60-65% of doses were being delivered each year. Access to specialist services was poor, with many patients overdue for routine care including echocardiograms and cardiology review. There were issues around health literacy, staff awareness of the importance of secondary prophylaxis, and management planning. Coordination with other health services was not reliable. An opportunity existed to improve healthcare and secondary prophylaxis delivery for people with ARF and RHD.

Strategies

With the benefit of additional funding, a systematic process was introduced to provide structured, coordinated care for people with ARF and RHD. This was facilitated by Nganampa having both a population register and a computerised patient information management system; key resources for its healthcare delivery. The new process includes:

- A dedicated RHD coordinator with local knowledge, appointed to oversee case management, provide education and support for patients, families and health staff, and able to visit patients scheduled for surgery in Adelaide.
- A partnership between Nganampa, the SA and NT RHD Control Programs and Alice Springs Hospital, to improve coordination of patient care.
- Regular visiting specialist cardiology services.
- RHD Management Plans developed and regularly updated for each patient. A one-page summary can be printed to accompany the patient on visits to other health services.
- A calendar depicting local people to help engage patients and their families around RHD and encourage them to attend the health service.

Significant changes were also made to secondary prophylaxis delivery.

- Central Australian Rural Practitioners Association (CARPA) guidelines recommend that BPG injections be administered between 21 and (no later than) 28 days after last dose.[b] The electronic recall was therefore changed to start at 21 days to reduce the potential for overdue injections.
- New patients are entered on to the RHD register as soon as possible, and BPG injections are entered onto the register by the coordinator each week.
- Weekly lists of patients requiring injections are produced from the database by Nganampa health staff in each clinic.
- A summary of people overdue for injection by more than a week is sent to each clinic.
- A summary of transient patients overdue for injection is sent to SA RHD register at least monthly for follow-up support (noting that injections could be received elsewhere).
- Health promotion around the importance of secondary prophylaxis is conducted regularly for health staff and the community.

Outcomes

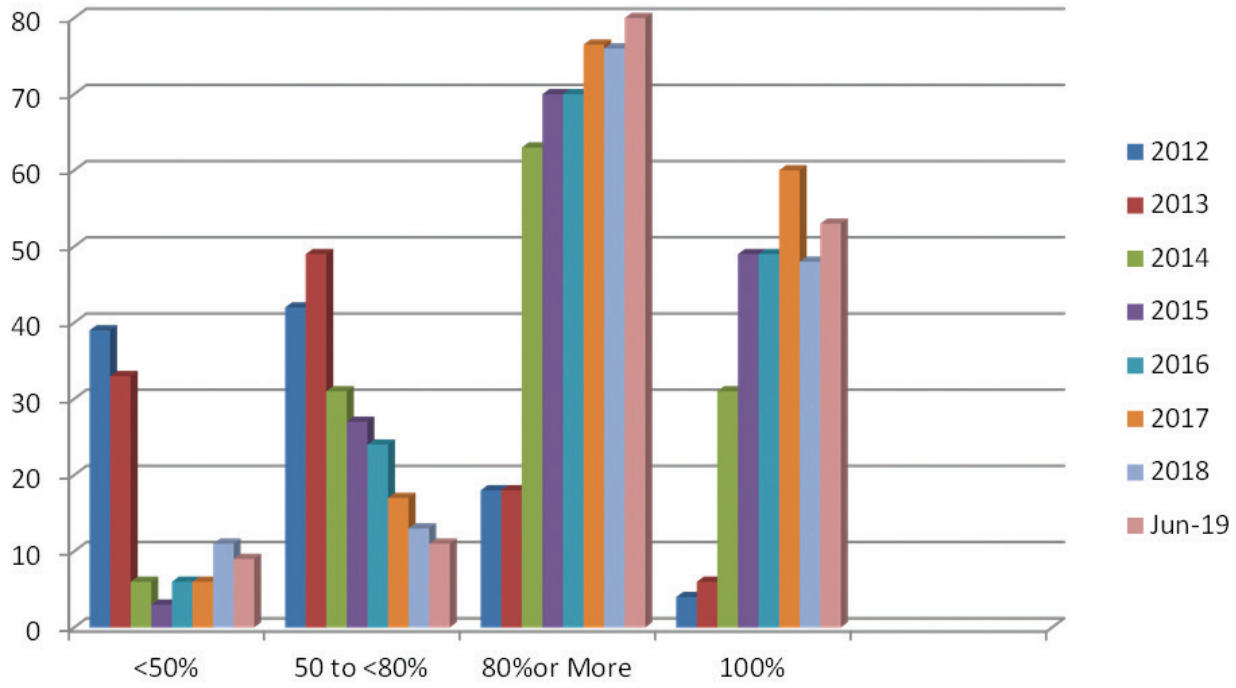
Following the introduction of these initiatives, there was a marked rise in secondary prophylaxis delivery rates which has been sustained, and gradually improved, for nearly six years. Between 2012 and 2019, the proportion of people who received <50% of prescribed injections fell from 39% to 9%, and the proportion who received 100% has risen from 4% to 53%. By mid-2019, 80% of all patients on RHD prophylaxis were receiving >80% of their injections *(Table 10.2)*. This sustained improvement is especially impressive given that there was a 60% increase (from 28 in 2012 to 45 in 2019) in the number of people prescribed secondary prophylaxis.

Reducing the injection recall period from 28 days to 21 days has made a particularly important contribution.

The introduction of regular cardiology visits to the APY communities has helped raise awareness of the disease and reduce the number of people overdue for echocardiography or cardiology review.

Increasingly effective interstate and inter-organisation coordination is reflected by the high prophylaxis adherence rates for cross-border patients who receive treatment at several clinics. In the year to 30 June 2019, there were 15 cross-border patients who had BPG injections at Nganampa clinics. Four of these still attained 100% adherence across several health centres (one having visited five different health centres over a large geographic area). Two others received >80% of prescribed doses, another seven received 50-80% and only two received <50%.

Figure 10.2. Proportion of prescribed BPG injections delivered to people with ARF and RHD across the APY Lands from 2012 to June 2019



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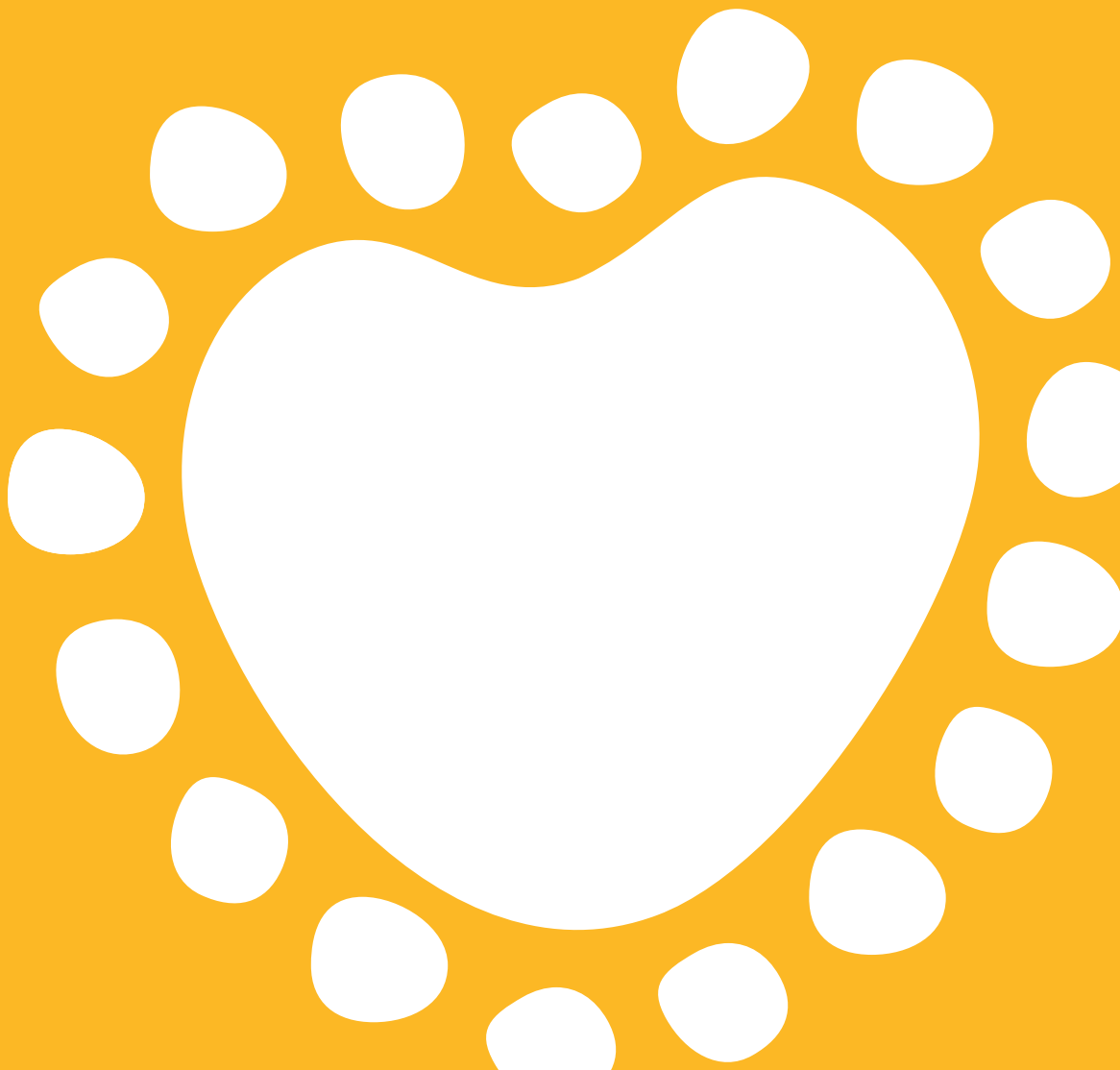
CHAPTER 11

Management of rheumatic heart disease



Management of rheumatic heart disease

CHANGES FROM THE SECOND (2012) EDITION

1. The Priority definitions in the 'priority classification system' for presence and severity of rheumatic heart disease (RHD) have changed to align with appropriate timing of follow-up.
2. The new option of transcatheter valve replacement may influence choice of valve replacement in younger individuals.
3. A focus on transition from paediatric to adult services is included.
4. The role of non-vitamin K antagonist oral anticoagulants in RHD is described.
5. Definition of non-valvular atrial fibrillation in the setting of RHD and the role of CHA_2DS_2-VA score to determine thromboembolic risk are detailed.
6. Antibiotic prophylaxis to prevent infective endocarditis following dental procedures now comprises amoxicillin instead of clindamycin, even for people on regular penicillin-based treatment (e.g. regular benzathine benzylpenicillin G (BPG)), in keeping with revisions to the Australian Therapeutic Guidelines: Antibiotic.
7. Prophylaxis for endocarditis is now recommended for all people with RHD rather than being restricted to only high-risk populations with RHD (See *Table 11.5*)

KEY INFORMATION

- Secondary prophylaxis is an integral aspect of the management of RHD.
- RHD is a notifiable disease in Western Australia, South Australia, Northern Territory, Queensland and New South Wales (in NSW, for people aged <35 years).
- Anticoagulation in RHD:
    - Non-vitamin K antagonist oral anticoagulants (NOACs) are appropriate for patients with RHD and atrial fibrillation (AF) with an elevated CHA_2DS_2-VA score, except in those with moderate or greater mitral stenosis *(Table 11.1)*.
    - For patients with moderate or greater mitral stenosis and atrial fibrillation, warfarin is currently the only indicated oral anticoagulant.
    - Patients with a mechanical valve prosthesis require anticoagulation with warfarin, clexane or heparin.
- All patients with RHD should have access to specialist paediatric and adult cardiology services.
- Coordinated transition from paediatric to adult services is imperative for young patients with ARF and RHD.
- Aboriginal Health Workers, Aboriginal Health Practitioners and remote-area nurses should be consulted prior to surgery to provide an understanding of the patient's personal, social, economic and cultural situation that will likely determine which surgical option is best suited to that individual.
- Early engagement of a multidisciplinary heart team is essential in determining the appropriate choice and timing of intervention for patients with RHD.
- The decision between repair, bioprosthetic and/or mechanical valve replacement needs to take into consideration the age at first operation, risks of anticoagulation, adherence, future pregnancy, and durability of valve repair and prosthesis.

- Choice of valve replacement for RHD:
  - Mechanical valve: proven durability, requires lifelong anticoagulation.
  - Bioprosthetic valve: does not require lifelong anticoagulation, limited durability, may enable future valve-in-valve procedure.
- Complications of RHD include atrial fibrillation, heart failure, thromboembolic events, pulmonary hypertension, prosthetic valve thrombosis and death.
- Mixed and multi-valvular disease is common in RHD and requires more frequent surveillance and follow-up.
- Regular oral healthcare and education may reduce the long-term risk of infective endocarditis (IE) for patients with RHD.
- Aboriginal and Torres Strait Islander peoples with RHD should receive IE antibiotic prophylaxis for high-risk procedures.

Table 11.1. The CHA_2DS_2-VA score is used to determine thromboembolic risk and guide use of anticoagulation in patients with non-valvular atrial fibrillation

CRITERIA	POINTS†
Age	65-74yrs = 1, ≥75yrs = 2
Congestive heart failure	1
Hypertension	1
Stroke/ transient ischaemic attack/ thromboembolic event	2
Vascular disease	1
Diabetes mellitus	1

† A score of ≥ 2 in the setting of non-valvular atrial fibrillation is an indication for anticoagulation. Anticoagulation should be considered in individuals with a score of 1. Anticoagulation is not recommended in individuals with a score of 0.[1]

Table 11.2. Priority classification and recommended follow-up (updated March 2022)

DIAGNOSIS	RECOMMENDED FOLLOW-UP PLAN†
Priority 1 Severe RHD‡ High risk post-valve surgical patients§ ≥ 3 episodes of ARF within the last 5 years Pregnant women with RHD (of any severity) may be considered Priority 1 for the duration of the pregnancy Children ≤ 5 years of age with ARF or RHD	Specialist review: at least 6 monthly Echocardiogram: at least 6 monthly Medical review: at least 6 monthly Pregnant: see *Figure 12.1 for care pathway* Dental review: within 3 months of diagnosis, then 6 monthly
Priority 2 Moderate RHD‡ Moderate risk post-valve surgical patients§	Specialist review: yearly Echocardiogram: yearly Medical review: 6 monthly Dental review: within 3 months of diagnosis, then 6 monthly
Priority 3 Mild RHD‡ ARF (probable or definite) without RHD, currently prescribed secondary prophylaxis Low risk post-valve surgical patients§	Specialist review: 1 – 3 yearly Echocardiogram: children ≤ 21 years: 1-2 yearly, > 21 years: 2-3 yearly Medical review: yearly Dental review: yearly
Borderline RHD currently prescribed secondary prophylaxis	Medical review: 1-2 years after diagnosis, and 1-2 years after ceasing secondary prophylaxis Echocardiogram: 1-2 years after diagnosis, and 1-2 years after ceasing secondary prophylaxis
Priority 4 History of ARF (possible, probable or definite) and completed secondary prophylaxis Borderline RHD not on secondary prophylaxis Resolved RHD and completed secondary prophylaxis	Specialist referral and echocardiogram: 1 year, 3 years and 5 years post cessation of secondary prophylaxis *(or following diagnosis in the case of Borderline RHD not on secondary prophylaxis)* Medical review: yearly until discharge from specialist care and then as required Dental review: yearly or as required

† Frequency should be tailored to the individual following specialist assessment. All patients should be given influenza vaccine annually and have completed pneumococcal vaccinations as per Australian Immunisation Handbook. Intervals for medical and specialist review and echocardiography are a guide and may vary for specific individuals. Medical and dental reviews may be combined with general health check-up. People with RHD require endocarditis prevention as indicated. (See *Chapter 11. Management of RHD, Prevention of infective endocarditis*).

‡ See *Table 10.2* for definitions of RHD severity.

§ While post-surgical RHD is by definition severe RHD, post-surgical risk varies for individuals due to age, type of surgery, recurrence of ARF, adherence with secondary prophylaxis and other factors. Priority category for post-surgical RHD varies as listed in this Priority classification table and should be determined by specialist cardiologist/paediatrician/physician. (See *Chapter 11. Management of RHD, Monitoring following valve surgery*).

Table 11.3. Summary of medical and surgical management options that may be considered for specific advanced valve disease

VALVE DISEASE	MEDICAL THERAPY	INDICATIONS FOR CONSIDERATION OF INTERVENTION & REFERRAL TO HEART TEAM	VALVE INTERVENTION
Mitral Regurgitation (MR)	ACE inhibitor, beta-blocker and diuretic therapy in setting of heart failure. Antihypertensive medication in setting of hypertension.	Symptomatic severe MR Asymptomatic severe MR and: • LVEF ≤60% ***or*** • LVESD ≥40 mm ***or*** • New-onset AF ***or*** • New PASP ≥50 mmHg ***or*** • Child with enlarged indexed heart size	Valve repair (preferred intervention). If unable to be repaired, surgical valve replacement: • Bioprosthetic valve ***or*** • Mechanical valve
Mitral Stenosis (MS)	Beta-blockers (AF or sinus rhythm) or ivabradine (sinus rhythm) for symptom relief. Diuretics if evidence of pulmonary oedema/ congestion. Anticoagulation with warfarin if AF or high-risk features for thromboembolism present (See *Monitoring anticoagulation*).	Symptomatic severe MS Asymptomatic severe MS and: • significantly elevated trans-mitral gradient or elevated PASP on EST ***or*** • New PASP ≥50 mmHg ***or*** • New-onset AF ***or*** • Cardio-embolic stroke	Percutaneous balloon mitral valvuloplasty (PBMV) if anatomically suitable. Closed or open surgical mitral valvotomy. Surgical valve replacement if not suitable for PBMV: • Bioprosthetic valve ***or*** • Mechanical valve
Aortic Regurgitation (AR)	Vasodilator therapy with ACE inhibitor, angiotensin receptor blocker or dihydropyridine calcium channel antagonist for symptom relief. Antihypertensive medication in setting of hypertension.	Symptomatic severe AR Asymptomatic severe AR and: • LVEF <50% ***or*** • LVEDD >70 mm ***or*** • LVESD >50 mm ***or*** • Child with enlarged indexed heart size	Aortic valve repair, if technically feasible. Surgical valve replacement: • Mechanical valve ***or*** • Bioprosthetic valve ***or*** • Homograft valve ***or*** • Ross procedure

Table 11.3. Summary of medical and surgical management options that may be considered for specific advanced valve disease (continued)

VALVE DISEASE	MEDICAL THERAPY	INDICATIONS FOR CONSIDERATION OF INTERVENTION & REFERRAL TO HEART TEAM	VALVE INTERVENTION
Aortic Stenosis (AS)	Antihypertensive medication in setting of hypertension Cautious use of diuretic and afterload reduction in those with heart failure	Symptomatic severe AS Asymptomatic severe AS and: • LVEF <50% ***or*** • Abnormal EST ***or*** • Mean PG ≥60 mmHg ***or*** • Vmax ≥5 m/s ***or*** • PASP ≥60 mmHg	Surgical valve replacement or transcatheter valve replacement Decision based on surgical risk, age, anatomical assessment and heart team opinion
Tricuspid Regurgitation (TR)	Diuretic therapy for symptom relief from right heart failure and congestion	Severe primary TR Symptomatic severe secondary TR and absence of severe RV or LV dysfunction or severe pulmonary hypertension Asymptomatic or mildly symptomatic severe secondary TR with evidence of progressive RV dilatation or dysfunction Secondary moderate TR with annular dilatation in patients presenting for left-sided valve procedure	Valve repair / annuloplasty (preferred intervention) Surgical valve replacement: • Bioprosthetic valve ***or*** • Mechanical valve
Tricuspid Stenosis (TS)	Diuretic therapy for symptom relief from right heart failure and congestion	Symptomatic severe TS	Surgical valve replacement: • Bioprosthetic valve ***or*** • Mechanical valve

(Grading of evidence-based recommendation available in relevant valve disease section)

PASP: Pulmonary artery systolic pressure, AF: Atrial fibrillation, EST: Exercise stress test, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, PG: Pressure gradient, RV: Right ventricle.

DISCUSSION

> *"I was walking by his room and the door was open. He was standing there, looking in the mirror with his shirt off, staring at the scar running up the middle of his chest. He was just standing there crying. I said to him, 'What's wrong? What's wrong? I can't do anything to help if you won't tell me what's wrong with you.' He said, 'I hate the way I look, I hate this scar'."*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

Access to care

Access to specialist physician, paediatrician or cardiologist

The highest burden of RHD in Australia is within the Aboriginal and Torres Strait Islander population, many of whom live in rural and remote locations. It can be difficult and expensive for people living in remote areas to access specialist cardiac services, which are predominantly located in major towns and cities. Although there has been an expansion in specialist outreach services in Australia through programs such as Medical Specialist Outreach Assistance and Indigenous Outreach Assistance, access to adult and paediatric specialist care remains inadequate in many rural and remote areas.[2,3] Consistency of visiting specialists to remote communities is crucial, because it allows for therapeutic relationships to be developed in often culturally diverse and geographically challenging environments.

Visiting clinical services call for improved health literacy, effective clinical interactions and communication, functional two-way learning, local care navigation and patient support, shared decision making, and cultural safety.

Successful models of care have been developed in various remote locations across Australia. Cardiology outreach teams may consist of a specialist cardiologist, doctors-in-training, Aboriginal health staff and clinical nurse educators. The various models have been shown to be successful and impactful regarding the cardiac care of people living in rural and remote Australia.[3,4] Furthermore, telehealth consultation may improve access to specialist care[5,6] and is likely to be most effective when combined with face-to-face consultations. Ensuring adequate access to specialist services is vital to the management of RHD.[4]

Access to comprehensive cardiac services

The interventional cardiology and cardiothoracic surgical management of RHD in Australia is challenging. The number of patients undergoing procedures for RHD is relatively low compared with other forms of heart valve disease. Furthermore, there are social, cultural and geographical complexities that impact on the delivery of patient care. This means that few cardiothoracic and cardiology services have the opportunity to obtain the necessary experience and skill sets to maintain a high level of expertise. The rapid progression of transcatheter and percutaneous valve intervention technology has led to the need for a multidisciplinary team approach in order to determine the best treatment for individual patients. This has led to the development of heart teams which have been shown to improve patient outcomes.[7,8] A heart team for RHD should include people with expertise in rheumatic and valvular heart disease such as cardiologists, cardiac surgeons, anaesthetists, allied health staff and, when indicated, intensive care physicians, infectious disease physicians and obstetricians.[8] Given the described challenges, it is recommended that the surgical management of RHD for Aboriginal and Torres Strait Islander peoples be concentrated in select locations in order to develop centres of excellence.

Of vital importance in Australia is the inclusion of Aboriginal Health Workers, Aboriginal Health Practitioners, Aboriginal Liaison Officers, and educators who are familiar with patients' social and cultural backgrounds. Early engagement of the heart team at dedicated centres of excellence is essential in determining the appropriate choice and timing of intervention for patients with RHD.

Accessible care for Aboriginal and Torres Strait Islander adolescents

The peak burden of ARF and RHD occurs in adolescents and young adults. It is therefore essential that primary care services are developmentally appropriate and accessible to young people. The World Health Organization (WHO) has defined eight standards for ensuring accessible and quality healthcare for adolescents *(Table 11.4)*.

Primary healthcare services need to be culturally competent. Key features of a quality consultation with a young person include appropriate engagement, including language and the use of interpreters as needed; assuring confidentiality, trust and respect; and moving beyond the presenting complaint to explore broader aspects of health and wellbeing.

Engaging adolescents involves building rapport, trust and involving them in decisions about their health. This includes making a point of speaking with them rather than to their accompanying parent or guardian, and if possible, offering to see the young person alone as part of the consultation. Confidentiality is a particular barrier to young people accessing healthcare. Many adolescents will forgo healthcare around sensitive issues without a guarantee of confidentiality.[9] Additionally, with increasing maturity, young people have the right to make independent decisions and receive confidential healthcare.[10] Assuring confidentiality, and explaining when it may need to be breached, is critical. A quality consultation for a young person may involve exploring beyond the primary health issue. Other concerns may impact adversely on, or be more important to, the young person than RHD. Finally, it is important to use plain language to explain the diagnosis, and if possible, involve the young person in developing a management plan because this will likely enable better adherence and long-term engagement.

Transition from paediatric to adult cardiology services and care providers

The lack of well-coordinated transition of care can put patients at risk of being lost to follow-up, and suffering preventable and significant morbidity. Cardiac services providing care for young people with RHD need to develop structured transition programs to prevent these avoidable negative outcomes.

Good transition care is well-planned and has a strong focus on building health literacy. Young people should be involved in the transition planning with adult specialists. They should be able to describe their condition, medications and treatments, follow-up schedule, and access help if required. Given these tasks, transition planning should begin early, perhaps years before the actual transfer of care occurs. Transition checklists and tools can assist in care planning.

Primary healthcare providers, particularly Aboriginal Health Workers, Aboriginal Health Practitioners and general practitioners, play an important role in providing continuity of care during the period of transition and transfer. A further consideration is that adult specialist services may provide a different scope of services than those provided by paediatric services. This may be particularly relevant in considering the transition needs of young people living with complex comorbidities and transition may involve several other care providers in addition to cardiologists.

Cultural considerations that relate to men's and women's business should be observed, especially when contraception and family planning is introduced.

Table 11.4. Standards for quality healthcare for adolescents[11]

Adolescents' health literacy	**Standard 1**. The health facility implements systems to ensure that adolescents are knowledgeable about their own health, and they know where and when to obtain health services. *Communication needs to be in the young person's first language.*
Community support	**Standard 2**. The health facility implements systems to ensure that parents, guardians and other community members and community organisations recognise the value of providing health services to adolescents and support provision and utilisation of services by adolescents. *Some communities have strong and active youth programs.*
Appropriate package of services	**Standard 3**. The health facility provides a package of information, counselling, diagnostic, treatment and care services that fulfils the needs of all adolescents. Services are provided in the facility and through referral linkages and outreach.
Providers' competencies	**Standard 4**. Healthcare providers demonstrate the cultural and technical competence required to provide effective health services to adolescents. Both healthcare providers and support staff respect, protect and fulfil adolescents' rights to information, privacy, confidentiality, non-discrimination, non-judgmental attitude and respect.
Facility characteristics	**Standard 5.** The health facility has convenient operating hours, a welcoming, safe, friendly and clean environment, and maintains privacy and confidentiality. It has the equipment, medicines, supplies and technology needed to ensure effective service provision to adolescents.
Equity and non-discrimination	**Standard 6.** The health facility provides quality services to all adolescents irrespective of their ability to pay, age, sex, marital status, education level, ethnic origin, sexual orientation or other characteristics. *There needs to be reference to men's and women's business and services that reflect this.*
Data and quality improvement	**Standard 7.** The health facility collects, analyses and uses data on service utilisation and quality of care, disaggregated by age and sex, to support quality improvement. Health facility staff are supported to participate in continuous quality improvement.
Adolescents' participation	**Standard 8.** Adolescents are involved in the planning, monitoring and evaluation of health services and in decisions regarding their own care, as well as in certain appropriate aspects of service provision.

This table has been adapted to include Aboriginal and Torres Strait Islander cultural considerations.

Secondary prevention with penicillin prophylaxis

A fundamental goal in long-term management of RHD is to prevent ARF recurrences and progression of disease with secondary antibiotic prophylaxis *(Table 10.1)*. In cases of mild RHD, continuous antibiotic prophylaxis may also result in the resolution of heart disease.[12] Carditis following the first episode of ARF is often mild,[13,14] and with secondary prophylaxis, the majority of people with mild disease at diagnosis have no detectable disease within 5–10 years.[14-17]

Those with moderate or severe disease at first presentation, and those who suffer from recurrent ARF, have poorer long-term outcomes, with a greater need for cardiac surgical intervention.[14,15,18] Patients with severe RHD at initial presentation can avoid cardiac surgery, providing there is a high level of adherence to secondary prophylaxis.[19]

OVERVIEW OF MANAGEMENT OF VALVE DISEASE

Medical management of valve disease

Many patients with RHD will have less than severe valvular disease which is asymptomatic or minimally symptomatic. These patients require routine follow-up to monitor for recurrence of ARF, progression of valve pathology and symptoms, and administration of secondary prophylaxis. Regular interaction with health services provides opportunity for preventative health care and continued education. Recommended follow-up periods are outlined in *Table 11.2*.

Medical therapy plays a role in both preventing and treating complications of more advanced disease. Complications of RHD include atrial fibrillation, heart failure, endocarditis and thromboembolic events.[20] There is limited evidence regarding medical management of RHD, with a large focus on procedural intervention.[21,22] However, medical therapy can play a crucial role in preventing complications and ensuring that patients undergo procedural intervention at the most appropriate time.

Surgical management of valve disease

Surgical and percutaneous management of RHD is consistent with international valvular heart disease guidelines regarding indication, timing and choice of intervention.[7,8] The recommendations in this chapter are not an exhaustive list of indications for valve intervention but rather a summary relevant to patients with RHD. The final decision regarding surgical or percutaneous valve procedures should be made by the heart team who can appropriately apply international guidelines to the context of patients with RHD in Australia.

Surgical repair of rheumatic valvular disease is technically more difficult than non-rheumatic pathologies.[23,24] However, where possible, the mitral and aortic valves should be repaired, rather than replaced with prosthetic valves, especially for children and young adults.[8,25] There is increasing interest in conservation of native valve tissue in surgery for aortic valve disease but this is less well established compared to mitral valve repair techniques.[26,27] In certain cases of rheumatic disease, earlier intervention, as compared to international guidelines, may be recommended when valve repair is likely to be achieved and provide a durable long-term outcome. Additionally, selective repair of the mitral valve with conservative management of other valves with moderate disease may be suggested, understanding that the patient is likely to require redo surgery in the future and thus enabling a less complicated subsequent operation.

There are significant challenges regarding valve replacement in younger patients, including rapid prosthesis degeneration, management of anticoagulation – particularly in women of child-bearing age, due to concerns of warfarin use during pregnancy *(Table 12.2)* – and young patients outgrowing a prosthesis.

If a valve is not able to be repaired, a decision between bioprosthetic and mechanical valve prosthesis needs to be made before the patient undergoes surgery, with consideration of adherence, geography, access to specialist follow-up, and cultural factors.

A bioprosthetic valve prosthesis has the benefit of not requiring long-term anticoagulation. However, it will have a limited durability, particularly in younger patients, resulting in an increased likelihood of repeat surgery.[28]

In the era of transcatheter valve implantation, valve-in-valve procedures may offer suitable options for the replacement of a degenerated bioprosthetic valve, to avoid repeat sternotomy.[29,30] A valve-in-valve procedure refers to percutaneous implantation of a transcatheter heart valve within an existing degenerated surgical (bioprosthetic) heart valve.

Since the 1990s, there has been a steep rise in the use of bioprosthetic valves.[31] Mechanical valve prostheses have the benefit of durability,

however lifelong anticoagulation is required. The main complications of mechanical valves are bleeding, thromboembolic events, and valve thrombosis, usually due to problems with anticoagulation adherence.[31-33] Where possible, mechanical valves should be reserved for adult patients who are likely to be able to manage daily warfarin and routine follow-up. Long-term propensity-matched data comparing bioprosthetic versus mechanical prostheses have shown either equivalent survival or superiority of mechanical valves.[31,32,34] All valve prostheses are at risk of other complications such as endocarditis, thrombosis, dehiscence and haemolysis.

A woman of child-bearing years who is in sinus rhythm but not suitable for valve repair, may need to be considered for bioprosthetic valve replacement to avoid the hazards of anticoagulation during pregnancy.

Australian experience in valvular intervention for RHD

There are limited data available regarding the long-term outcomes of rheumatic valve surgery in Australia.[24,28,35-37] Patients with RHD tend to be younger and are more likely to be female compared to people undergoing surgery for non-RHD-related valve disease.[38] Surgical registry data suggest there has been an increasing trend in the use of bioprosthetic valves for RHD surgery.[38] This shows five and ten-year mortality following RHD valve surgery is 15% and 25% respectively. A small cohort study of valve surgery performed between 1992 and 2004 in Aboriginal and Torres Strait Islander patients reported freedom from reoperation at five years of 88%.[37] More recently, published data for mitral valve repair in children demonstrated 100% success of repair with very good survival rates to 15 years.[21] However, 72% had valve repair deterioration over the same time frame, highlighting the lifelong burden of RHD in a young population, including the need for repeat interventions. Data on redo cardiac surgery suggest that median time to requiring repeat valve surgery is six years amongst Aboriginal and Torres Strait Islander patients with prior valve repair or replacement.[28] The morbidity associated with redo surgery in this cohort was lower for those with prior valve repair as compared to replacement. Recently published single-centre experience of transcatheter valve implantation within failing bioprosthetic mitral prostheses revealed encouraging results.[30] Long-term follow-up studies in Australia have shown a significantly poorer outcome for Aboriginal and Torres Strait Islander patients who have undergone valve surgery compared to non-Indigenous patients.[36,37,39] There are likely many factors contributing to this, including recurrence of ARF, problems with medication delivery, difficulties in providing follow-up specialist care to patients who may live in rural or remote communities, inadequate health literacy, and cultural and language barriers.[36,37,39,40]

Remote-area nurses, Aboriginal Health Workers and Aboriginal Health Practitioners should be consulted prior to surgery to provide an understanding of the patient's personal, social, economic and cultural situation that will likely determine which surgical option is best suited to that individual.

Patient resources and education

The overrepresentation of Aboriginal and Torres Strait Islander peoples requiring rheumatic valve surgery[24,35] emphasises the need to provide a surgical and interventional cardiology service that incorporates appropriate resources to inform patients, their families, and the Aboriginal and Torres Strait Islander health workforce that supports them. Such resources should include relevant disease information, discussion and informed consent regarding the risks and implications of valve intervention procedures. Interpreters should be available when required, and written and visual resources should be provided in a patient's primary language. This helps ensure that the patient, their family and the surgical service understand the effect of the agreed treatment on future childbearing and physical and work activities, and the capacity for anticoagulation and long-term follow-up. A close partnership between the multidisciplinary primary healthcare team and specialist services is a prerequisite for the optimal care of patients with RHD.

Aboriginal Hospital Liaison Officers should be involved in care as early as possible, to help arrange accommodation and transport, and provide support with social and economic circumstances that could impede care.

Box 11.1. Factors to consider in selecting the nature and timing of valve interventions

Age at first operation, continued growth in children

For women – future pregnancy and associated risk *(Table 12.1)*

Patient preference

Adherence to regular BPG injections

Access to anticoagulation monitoring and medications

Adherence with medical therapy and anticoagulation

Access to specialist follow-up – especially if previous valve repair

Presence and severity of mixed and multi-valve disease

Acceptability of redo surgery

Comorbidities that would preclude patients from redo surgery

Appropriateness for redo surgery using percutaneous valve-in-valve options

Secondary indication for anticoagulation (e.g. AF)

Contraindications to anticoagulation
(e.g. prior significant bleeding complications or bleeding conditions)

Access to primary healthcare services

When discussing valve choice with Aboriginal and Torres Strait Islander peoples, the following factors remain important:

- **family support;**
- **patient preference and lifestyle;**
- **culturally appropriate communication;**
- **interpreters being used where English is not the preferred language;**
- **involvement of the patient's local health care providers with knowledge of the patient and available health care services.**

MANAGEMENT OF VALVULAR HEART DISEASE

Mitral regurgitation

Medical management

Limited evidence from small studies of medical management of non-rheumatic primary mitral regurgitation shows conflicting results.[7,22] Traditionally, vasodilator drug therapy is considered potentially beneficial in primary significant MR. However, there is no evidence to support this in patients who are normotensive with preserved left ventricular systolic function (Level of Evidence GRADE 2B).[7]

For adults with mitral regurgitation and left ventricular systolic impairment, recommended management is described in the Guideline for Prevention, Detection and Management of Heart Failure in Australia, including ACE inhibitors and beta-blockers (Level of Evidence GRADE 1A).[2,41] Diuretic therapy is recommended in patients with clinical volume-overload.[41] For adults with MR and hypertension, anti-hypertensive agents should be used in accordance with the Australian Guideline for the diagnosis and management of hypertension in adults, including early use of ACE inhibitors (Level of Evidence GRADE 1A).[7]

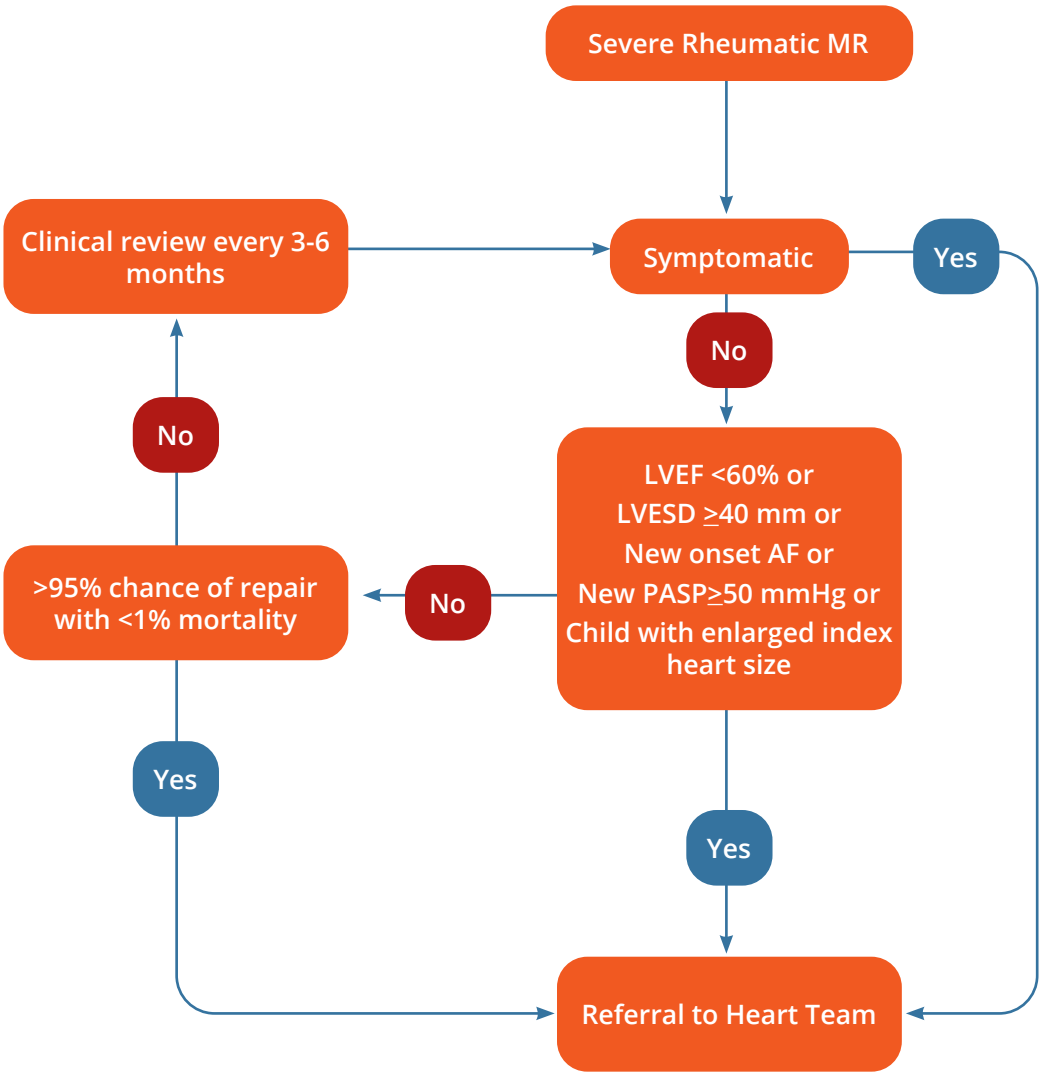
Indications for surgery

Patients with severe MR and preserved LV systolic function who are symptomatic should be automatically referred for surgical management[7,8] (Level of Evidence GRADE 1B) *(Figure 11.1)*. Patients who develop left ventricular dilatation (adults LVESD ≥40 mm) or impaired systolic function (ejection fraction [EF] ≥30% - <60%) have an increased surgical risk, less likelihood of restoring normal systolic function, and increased risk of late heart failure and death (Level of Evidence GRADE 1B).[42-44] This also applies to people with significant pulmonary hypertension (pulmonary artery systolic pressure >50 mmHg)[43] and preoperative AF (Level of Evidence GRADE 2B).[45-47] A critical LV end-systolic dimension has not been identified in children, however data suggest that surgery could be considered if LVESD or LVES volume Z score > +2.0 and is highly recommended if Z score > +3.0 (Level of Evidence GRADE 1C).[48] Therefore, it is recommended that in severe chronic MR, patients should be recommended for surgery once the above parameters are approached, rather than reached, regardless of symptomatic status.[7,8] This is especially important in children and young people in whom a high rate of successful repair, rather than replacement, is the aim. Patients with severe MR and severely impaired left ventricular systolic function (EF <30%) have poorer outcomes post-surgery. Whilst the threshold for intervention for children and adolescence is lower, valve intervention for adults in this group is only indicated in those with symptoms refractory to medical therapy (Level of Evidence GRADE 2C).[7,8]

The recommended guidelines in *Figure 11.1* should be applied with a degree of flexibility. For example, patients with significant MR, favourable anatomy and good adherence with secondary prophylaxis, who do not meet the above criteria, may be considered for early surgery in centres with low perioperative mortality and high rates of successful mitral valve repair (Level of Evidence GRADE 2C).[8]

As indications for surgery in asymptomatic patients are not always clear, it is important that patients with asymptomatic moderate or severe MR are referred to specialist heart teams early, so appropriate care plans can be arranged. This should take into consideration the clinical and echocardiographic findings, the patient's individual circumstances and findings of exercise testing (Level of Evidence GRADE 1B).[7,8,21]

Figure 11.1. Rheumatic mitral regurgitation: indications for intervention



Mitral valve repair

The operation of choice for dominant or pure rheumatic MR is mitral valve repair (Level of Evidence GRADE 1B).[25,49-51] Mitral valve repair has a lower operative risk and provides better preservation of LV systolic function.[52,53] Although there have been no randomised, comparative trials, more recent surgical experience has shown that the long-term results of mitral valve repair are at least equivalent or superior to those of mitral valve replacement in RHD.[24,25,35,51,54,55] This is attributable to avoidance of complications of anticoagulation and infection, with several series demonstrating similar durability to bioprosthetic valves.[56]

Valve repair for rheumatic MR is more technically demanding than repair of a degenerative mitral valve, and the long-term results are not as good.[57,58] Nevertheless, very acceptable results have been obtained in surgical centres that perform these operations regularly.[24,59,60] Centres specialising in repair of rheumatic MR in the paediatric population should aim to provide 100% success rates.[24]

In adults, the late reoperation rate is higher with mitral valve repair than bioprosthetic valve replacement, although in experienced centres, reoperation can be carried out at low risk.[58] It is also higher in the Aboriginal and Torres Strait Islander populations than in other populations.[28,36,37] Long-term results will be affected by valve morphology, surgeon experience, age at first operation, and ARF recurrences.[61-63] Active carditis at the time of surgery is likely a major predictor of late valve failure and therefore, if clinically reasonable, surgery should be delayed until the ARF episode subsides.[59] Reoperation may require mitral valve replacement, but initial valve repair can delay the need for long-term anticoagulation for many years.

Bioprosthetic mitral valve replacement

Some patients with rheumatic MR will not be suitable for valve repair due to particular valve morphology, including significant leaflet retraction, fibrosis or calcification. In these cases, valve replacement may be needed. Considerations for mechanical versus bioprosthetic valves are discussed earlier. After bioprosthetic valve replacement, most patients in sinus rhythm can be managed with only three months of anticoagulation (Level of Evidence GRADE 1B).[64] The major disadvantage of bioprosthetic valves is their limited durability, especially in younger patients. It has previously been documented that structural valve degeneration occurs earlier, and is more common with mitral bioprosthetic valves than aortic bioprosthetic valves in younger patients.[65] More recent work looking at bioprosthetic valve replacement in young people with RHD from India has shown promising long-term event-free survival of 93% to 16 years.[66] Australian experience has shown that Aboriginal and Torres Strait Islander peoples required reoperation at a median of 6.5 years following initial bioprosthetic valve replacement and at a median age of 29.5 years.[28]

Mechanical mitral valve replacement

The advantage of mechanical valve prostheses is their long-term durability with low rates of failure.[31,67] However, lifelong anticoagulation with warfarin is necessary (Level of Evidence GRADE 1A). Older patients who demonstrate good adherence with medical therapy may benefit from a mechanical prosthesis, avoiding the need for repeat surgery. Patients with tilting disc or bileaflet valves in the mitral position require a slightly higher target international normalised ratio (INR) of 3 (range: 2.5–3.5), compared to those in the aortic position (INR range 2–3).[7]

Mitral stenosis

Medical management

Significant mitral stenosis (MS) is associated with atrial arrhythmias, thromboembolic complications and congestive heart failure.[20,68]

MS results in impaired left ventricular filling and elevated left atrial pressure, both of which are exacerbated by a rapid heart rate due to anaemia, pregnancy, exercise or tachyarrhythmia. This exacerbation can occur even in patients below the threshold for intervention on the valve.[69] A reduction in heart rate may reduce symptoms, even in patients in sinus rhythm (Level of Evidence GRADE 1C).[70] This can be achieved using beta-blockers, which significantly improve symptoms.[71] Ivabradine, an agent used in heart failure that lowers the resting heart rate through its inhibiting effect on the cardiac pacemaker If current,[72] has similar efficacy to metoprolol in MS with an improvement in haemodynamics, exercise performance and dyspnoea.[70] As such, ivabradine may be used for symptom management in MS when beta-blockers are contraindicated or not tolerated or where an adequate reduction in heart rate cannot be achieved with beta-blockers alone. There is limited evidence for its use in the paediatric population and therefore caution and discussion with a paediatric cardiologist are recommended.[73] However, due to its mechanism of action, ivabradine is not useful in atrial fibrillation. For patients with pulmonary congestion or right heart dysfunction secondary to significant mitral stenosis, diuretics may be used for symptomatic relief (Level of Evidence GRADE 1C).[41] Anticoagulation in the setting of mitral stenosis is discussed in the *Management of Anticoagulation* section later in this chapter.

Indications for intervention

The indication for intervention is progressive symptoms associated with documented evidence of severe MS (Adults: mitral orifice area ≤1.5 cm^2, trans-mitral pressure half-time ≥150 ms, mean trans-mitral gradient ≥10 mmHg. Children: mitral orifice area ≤1.5 cm^2, PASP ≥50 mmHg) (Level of Evidence GRADE 1A).[7,8] Asymptomatic patients usually do not need intervention, unless there is a history of thromboembolism, paroxysmal AF or significant pulmonary hypertension (PASP >50 mmHg) (Level of Evidence GRADE 2B).[7,8] If the presence of symptoms is difficult to elicit then exercise testing with or without echocardiography can be useful. Limited exercise tolerance for age as well as significant elevation in trans-mitral mean gradient (>15 mmHg) or pulmonary artery systolic pressure (>60 mmHg) measured by echocardiography may indicate the need for intervention (Level of Evidence GRADE 2B).[7] Patients with severe MS in combination with significant mitral regurgitation or in heavily calcified valves not amenable to percutaneous treatment should be referred for consideration of surgical management.

Percutaneous balloon mitral valvuloplasty

The treatment of choice for dominant or pure mitral stenosis is PBMV *(Figure 11.2)* (Level of Evidence GRADE 1A).[7,8,74-76] PBMV involves a balloon catheter being inserted via the femoral vein and placed in the left atrium, via a transseptal puncture technique. The balloon is positioned across the stenotic mitral valve and inflated, thereby spitting the fused commissures. Invasive pressure measurements are performed before, during and after balloon deployment to determine success of the procedure.

The short- and medium-term results are comparable to surgical valvuloplasty.[77,78] However, PBMV is much less invasive, usually requiring only one night in hospital, considerably cheaper and has less associated morbidity than mitral valve surgery.[68] Mitral valve gradient usually reduces significantly with improvement in orifice area following balloon valvuloplasty, 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.[75,76,79,80] Repeat valvuloplasty can be performed if restenosis leads to symptom recurrence, especially if the predominant mechanism of restenosis is commissural fusion.

Patients with pure or dominant MS requiring intervention should be referred for PBMV to a high-volume centre.[74] Early referral is recommended for younger patients, since they have the most favourable valve morphology and the best long-term results. Echocardiographic criteria contribute to case selection.[81] This includes consideration of valve mobility, thickening, calcification and subvalvular involvement. 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 for PBMV.[81] Significant calcification and subvalvular thickening are associated with worse outcomes following PBMV. A large left atrial thrombus is a contraindication to PBMV. However, it can often be performed safely in the presence of a small, stable thrombus in the left atrial appendage.[82]

PBMV is ideally suited to managing MS in pregnancy, where the risk of surgery and associated fetal loss is high.

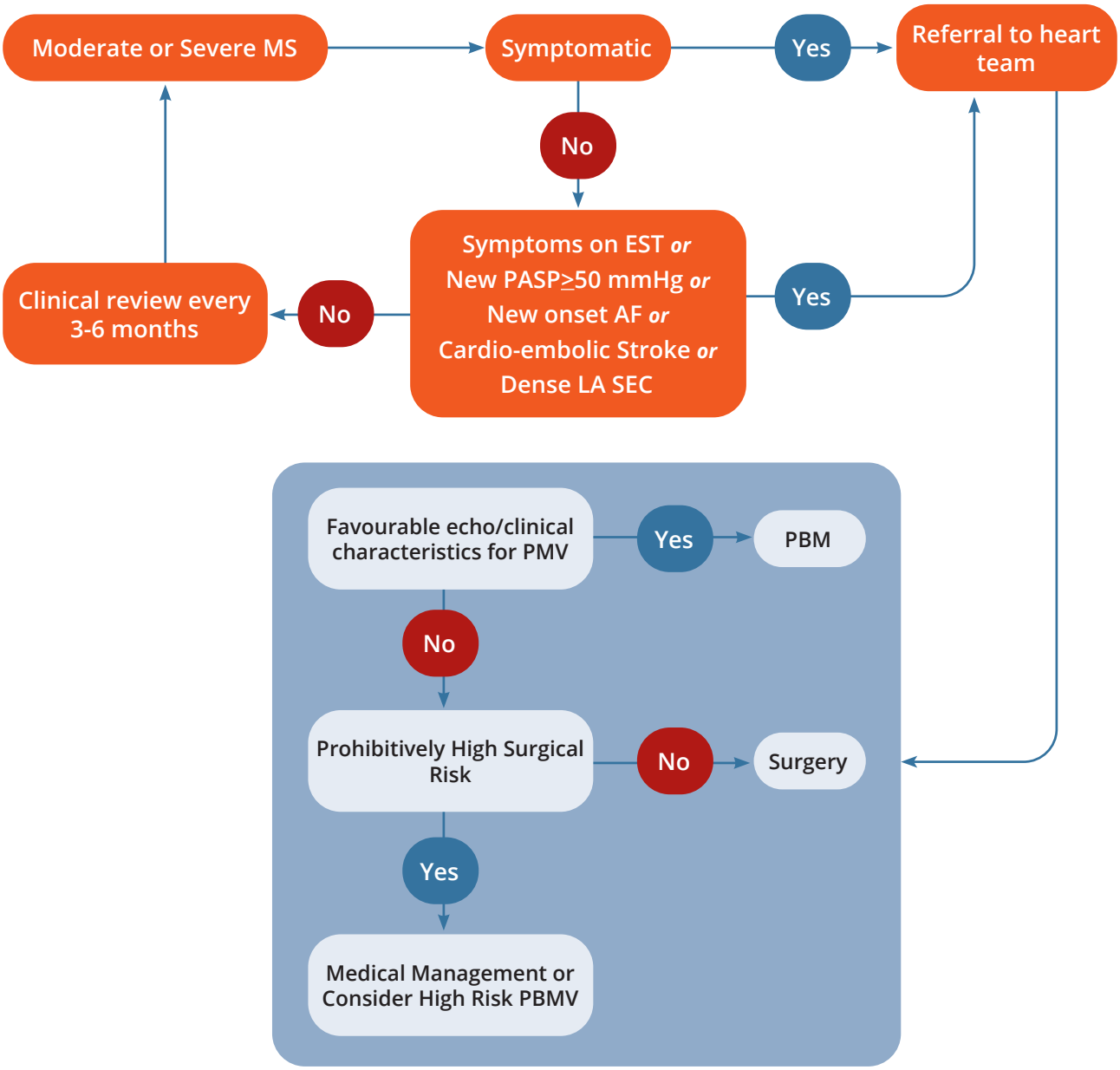
The most serious complication of the procedure is tearing of the mitral valve leaflets and/or subvalvular apparatus, causing severe mitral regurgitation.[83,84] Other rare complications are cardiac tamponade and systemic embolism.

Surgical management

PBMV has largely replaced surgical mitral commissuroplasty and commissurotomy.[68,79] 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, especially if patients are in sinus rhythm (Level of Evidence GRADE 1C). 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, or in those with significant mixed mitral valve disease (Level of Evidence GRADE 1B).[7,8] Refer to *Mitral regurgitation* section for choice of valve prosthesis.

Figure 11.2. Rheumatic mitral stenosis: indications for intervention



Aortic regurgitation

Medical management

In patients with significant, asymptomatic aortic regurgitation, vasodilator therapy has been demonstrated to reduce LV dilatation and regurgitant fraction.[52,85] This has the potential to slow the progression of LV dilatation, delaying the need for surgery.[86] However, randomised studies have been limited and findings are inconsistent.[86-88] Most evidence involves the use of dihydropyridine calcium channel antagonists with smaller studies including ACE inhibitors or aldosterone receptor antagonists.[85-87] In adult patients with significant aortic regurgitation and systemic hypertension, vasodilator therapy is recommended (Level of Evidence GRADE 1B).[7] In patients with significant symptomatic AR with or without impaired LV systolic function, vasodilator therapy may aid in symptoms (Level of Evidence GRADE 2B).[87,88] Medical therapy is not a substitute for surgical intervention for severe AR. However, medical therapy is appropriate in patients considered to be at very high surgical risk or in those who decline surgery (Level of Evidence GRADE 1C).[7]

Indications for surgery

Patients with symptomatic severe aortic regurgitation (AR) should be referred for surgery, regardless of left ventricular systolic function (Level of Evidence GRADE 1B) *(Figure 11.3)*. [8,89,90] Asymptomatic patients with reduced systolic function (LVEF <50%) should be referred as soon as possible for valve surgery, as long-term studies suggest that progression of heart failure and death occur in up to 25% of these patients per year (Level of Evidence GRADE 1B).[91,92]

Patients with equivocal symptoms should undergo exercise testing to assess functional capacity and symptomatic response (Level of Evidence GRADE 2B).[89]

For patients with normal LV systolic function without symptoms, surgery should be delayed for as long as possible.[52] Surgery should be considered in asymptomatic patients with severe AR and preserved left ventricular systolic function with severely dilated left ventricle (Adults: LVEDD > 70 mm, LVESD > 50 mm. Children: LVESD Z score > +4.0) (Level of Evidence GRADE 2B).[8,48,93]

Choice of operation

The options for aortic valve surgery include repair or replacement. Aortic valve replacement options include mechanical prosthesis, a stented or stentless bioprosthesis, or an aortic homograft.[65,94] Another less common surgical option is the *Ross procedure*.

Mechanical valve replacement

Mechanical tilting disc/bileaflet prostheses have excellent long-term durability, with favourable long-term outcomes, if INR can be maintained.[31,67] If patients already have chronic AF requiring anticoagulation, the valve of choice is a mechanical valve prosthesis. However, in young patients, it is often not possible to fit an adult-sized prosthesis and further surgery may be required following a growth spurt. Patients with a newer tilting disc/bileaflet mechanical aortic valve can usually be anticoagulated to a lower INR (2–3) than was needed with the earlier-generation caged ball/disc valves, because of a lower risk of thromboembolism, especially in the aortic position.[64]

Bioprosthetic valve replacement

Replacement with a bioprosthesis has the advantage of avoiding long-term anticoagulation. The main disadvantage is their limited durability in younger patients with long-term data suggesting approximately 50% deterioration at 10-15 years in those aged <65 years.[65,95,96]

With the advent of transcatheter aortic valve replacements, a bioprosthetic valve replacement has the added advantage of permitting future transcatheter aortic valve implantation (TAVI) to occur as a valve-in-valve procedure. These procedures are associated with a lower risk of mortality and morbidity compared to redo operations, especially when able to be performed by a trans-femoral artery approach.[28,97]

Aortic valve repair

Experience with repairing the rheumatic aortic valve is limited.[98-101] The Carpentier group in Paris has pioneered this approach, reporting a 92% freedom from reoperation at five years with cusp augmentation techniques.[100] Repair is best in the early stages of rheumatic valvular disease when the cusps are thin and pliable, and often associated with more durable outcomes in children. There is limited experience with aortic valve repair in Australia.[26] Despite concern about the durability of repair, it may be the procedure of choice in some children at high-volume centres, because there are limited alternatives in this age group. The valve morphology, including leaflet retraction and volume loss, seen in Aboriginal and Torres Strait Islander adults makes repair more challenging.

Homograft valve replacement

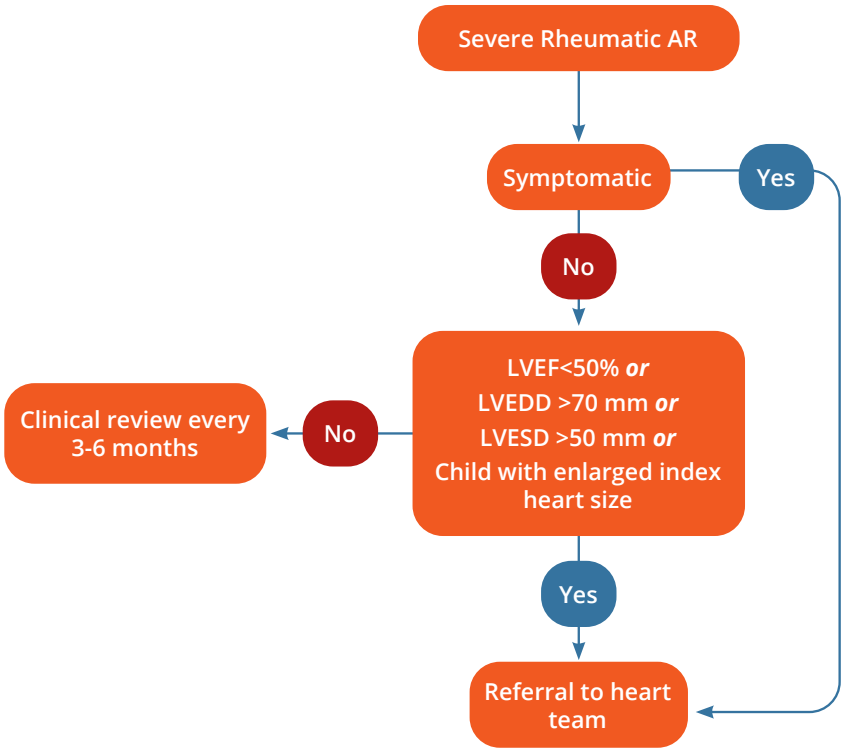
Homograft valve replacements are subject to structural deterioration, often with associated calcification.[102-104] They do have the advantage of haemodynamics identical to that of a native aortic valve and the avoidance of anticoagulant therapy. One large follow-up study of aortic homografts found a 10- and 20-year freedom from tissue failure (development of significant valve degeneration) of 62% and 18%, respectively.[104] A more contemporary single-centre experience demonstrated that 30% of patients were alive without reoperation out to 20 years follow-up.[102] Difficulties in obtaining donor homografts and the significantly increased complexity of reoperation in many of these patients has led to this procedure becoming less favoured in recent years, especially in younger patients.

Ross procedure

Another alternative for aortic valve surgery is the Ross procedure,[105,106] which uses a pulmonary autograft for valve replacement and a homograft for pulmonary valve replacement. The surgery is more complex, so has slightly higher risk. It is best suited for the aortic valve in later stages of rheumatic disease, when leaflets are thickened and retracted. It has the theoretical advantages of the valve 'growing' in younger patients and anticoagulation not being required.

However, ARF recurrence can involve the neo-aortic valve (pulmonary autograft), causing regurgitation. Late follow-up has also shown that some patients may develop significant AR, especially after five years, and require reoperation.[107] In younger patients, structural degeneration of the pulmonary homograft, usually manifesting as pulmonary stenosis, remains a problem.[108] The need for late reoperation, which is often quite complex, is the principal limitation of the Ross procedure.[109]

Figure 11.3. Rheumatic aortic regurgitation: indications for intervention



Aortic stenosis

Medical management

Patients with aortic stenosis (AS) do not usually become symptomatic until a severe systolic gradient develops. Initially, symptoms include exertional dyspnoea and fatigue, but syncope and angina can also occur. Many patients may remain asymptomatic despite haemodynamically significant AS. Once symptoms develop, prognosis is poor without intervention.[110,111] Patients with asymptomatic AS and hypertension should be treated as per standard guidelines, with frequent monitoring for side effects (Level of Evidence GRADE 1B).[7] Antihypertensive or diuretic use in patients who are normotensive, have clinical heart failure or have small LV cavity size should be used cautiously and with appropriate haemodynamic monitoring (Level of Evidence GRADE 1C).[7,112,113]

Indications for intervention

Aortic valve replacement (AVR) is recommended for severe symptomatic AS (mean pressure gradient ≥40 mmHg, aortic valve area ≤1cm^2, Vmax ≥4 m/sec) (Level of Evidence GRADE 1B).[7,8] This can be performed using either a transcatheter or surgical approach. It should be undertaken in all patients with severe stenosis once they have developed symptoms.[7,8] Patients with moderate gradients with severely reduced aortic valve area should have further imaging including transoesophageal echocardiogram (TOE), CT or invasive haemodynamics to determine whether there is low-flow, low-gradient severe AS (Level of Evidence GRADE 2B).[7] In those with significantly impaired LV systolic function, dobutamine stress echo may help determine true severe AS from pseudo-severe AS (Level of Evidence GRADE 2B).[7,8] Exercise stress testing may help determine effort tolerance and symptomatic status and therefore guide timing of intervention.[7] Asymptomatic patients with severe aortic stenosis and impaired left ventricular systolic function (LVEF < 50%) should be referred for surgery. Patients with asymptomatic critical/very severe aortic stenosis, defined by a mean pressure gradient >50 mmHg or Vmax >5.5 m/sec, can be considered for surgery (Level of Evidence GRADE 1C).[114,115]

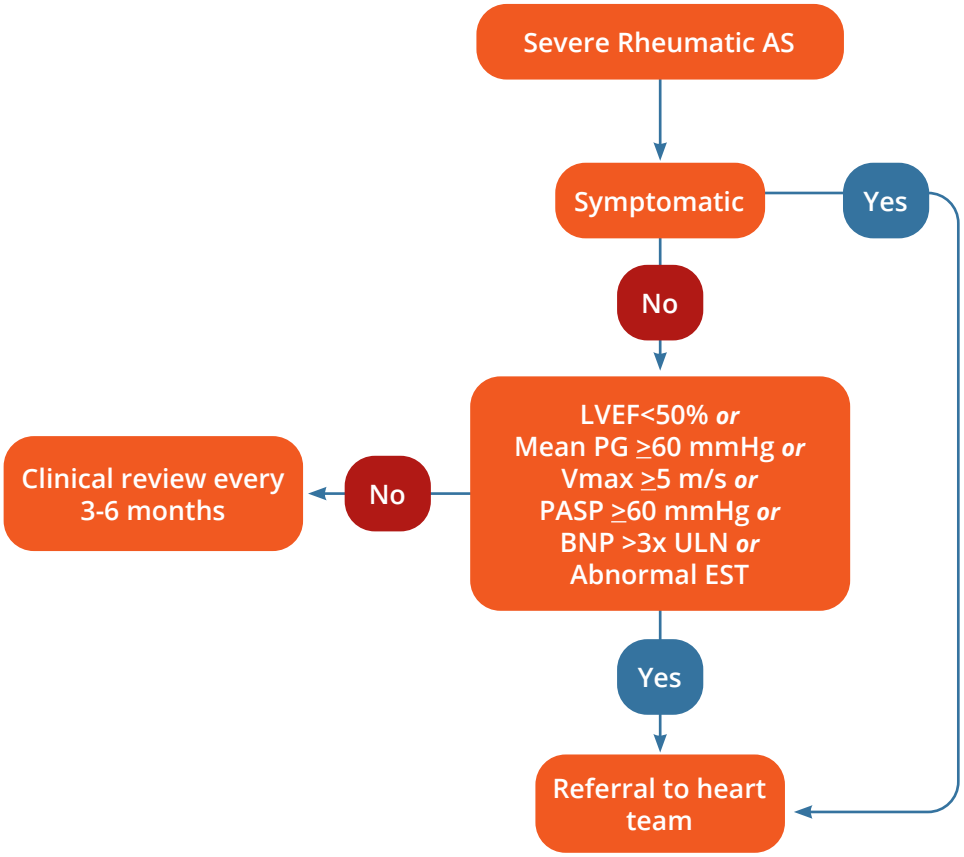
Choice of intervention

Surgery for AS includes replacement with a mechanical or bioprosthetic prosthesis or a homograft valve.[65,94] Transcatheter aortic valve implantation (TAVI) is an additional therapeutic option for patients with isolated AS who are at significant surgical risk. Surgical risk is defined by specific scoring systems that take into account anatomical and clinical parameters.[116,117] TAVI is a minimally invasive technique to replace an aortic valve with a bioprosthetic valve. It involves a valve being placed within the native valve via the femoral or subclavian artery or direct aortic approach. Outcomes using this technique are similar to outcomes for surgical bioprostheses for patients with severe AS at intermediate or high surgical risk (Level of Evidence GRADE 1B).[118,119] There is emerging evidence that at least short-term outcomes also support TAVI in low-risk populations.[119,120] The durability of TAVI compared to bioprosthetic AVR appears similar at 5-10 years follow-up, however longer-term data are needed.[121,122] At this stage, TAVI has limited role in patients with RHD because predominant AS is rare in RHD and patients with RHD are typically younger than the traditional TAVI cohort with different valve morphology, therefore making extrapolation of results difficult.

Aortic valvuloplasty

Percutaneous balloon aortic valvuloplasty (BAV)[123,124] may reduce severe AS to moderate stenosis but usually leaves a significant residual gradient. The procedure may entail substantial morbidity and mortality, particularly in older patients.[125] Follow-up studies have shown that initial improvement is usually not maintained after a few months.[126] Medium-term mortality remains high if definitive valve intervention is not performed.[126-128] There is a high restenosis rate in calcific valvular disease, however no evidence basis exists for rheumatic aortic stenosis.[123] BAV may be considered in symptomatic and haemodynamically unstable patients as a bridge to definitive surgical or transcatheter intervention (Level of Evidence GRADE 2C).[8]

Figure 11.4. Rheumatic aortic stenosis: indications for intervention



TRICUSPID VALVE DISEASE

Medical management

Significant tricuspid regurgitation (TR) is associated with right heart failure symptoms including peripheral oedema, congestive hepatomegaly and, in more severe cases, intestinal oedema and anorexia. Symptomatic relief is provided through use of diuretic therapy (frusemide, spironolactone) in those with volume overload (Level of Evidence GRADE 1C).[7]

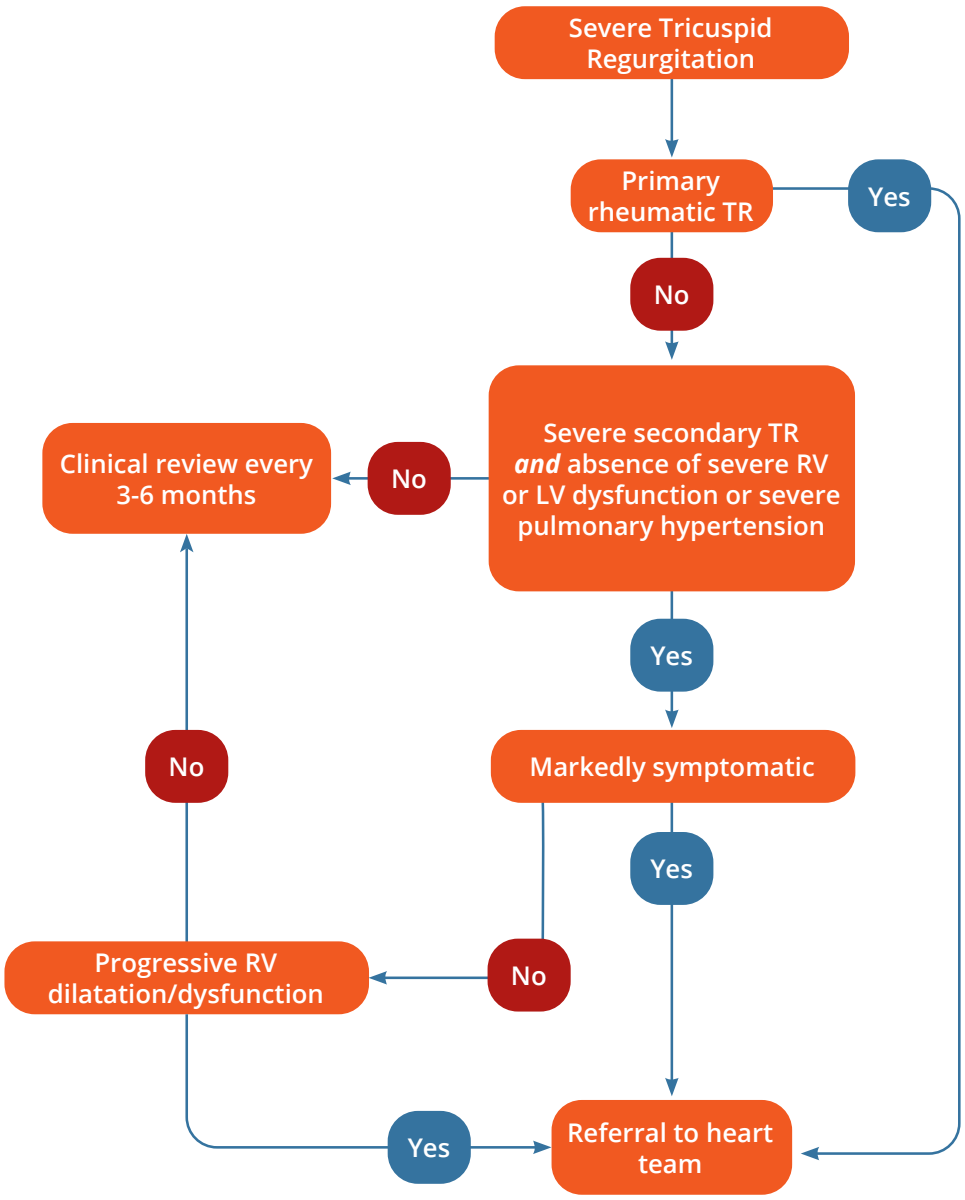
Surgical management

Tricuspid valve disease in RHD is most commonly secondary (functional) regurgitation due to progressive right ventricular dilatation and dysfunction as a result of left-sided valvular disease. Less commonly, primary rheumatic tricuspid valve disease may occur, presenting as regurgitation or stenosis.[8,21] Severe TR is associated with poor long-term prognosis.[129] In most cases, a repair is preferred over

replacement as the latter is associated with greater surgical risk and long-term morbidity and mortality.[8,130] In the setting of secondary severe TR, tricuspid valve repair during left-sided valve surgery does not add to peri-operative mortality and may prevent right heart deterioration (Level of Evidence GRADE 1C).[131,132] Delayed or repeat surgery for secondary TR is associated with significant mortality, due to irreversible right heart dysfunction.[129]

Severe symptomatic primary TR should be treated with surgical intervention (Level of Evidence GRADE 1C).[7,8] Severe tricuspid stenosis should be treated with surgery if either symptomatic or in the setting of left-sided valve surgery (Level of Evidence GRADE 1C).[7,8] Intervention for minimally symptomatic severe primary or secondary TR may be warranted in the setting of progressive right ventricular dysfunction to prevent irreversible impairment (Level of Evidence GRADE 2B).[7,8] Functional progressive TR of moderate severity may be considered for surgery at the time of a left-sided valve procedure (Level of Evidence GRADE 2C)[7] whereas mild functional TR and moderate TR with stable annular dimensions may be managed conservatively. There are limited long term data regarding percutaneous balloon valvuloplasty for tricuspid stenosis.[7] However, this option may be considered by the heart team in select cases, such as patients deemed high surgical risk (Level of Evidence GRADE 2D). Tricuspid valve replacement may be necessary in the setting of fibrotic or calcified rheumatic tricuspid valve disease. In this case, a discussion of mechanical or bioprosthetic valve replacement is necessary. A mechanical prosthesis in the tricuspid position is at higher risk of thrombotic complications due to the relatively lower pressures of the right heart.

Figure 11.5. Tricuspid regurgitation in the setting of RHD: indication for intervention



MIXED AND MULTI-VALVULAR DISEASE

The mitral valve is affected in more than 90% of RHD cases and commonly presents with mixed mitral valve disease. In more than half of cases, both mitral and aortic valves are involved.[20] Stages of multi-valvular disease will vary, with the mitral valve disease often more advanced than aortic valve disease.

Despite the predominance of multi-valvular and mixed valvular disease in RHD, there is no clear evidence on the timing of surgery in these cases. Clinical symptoms and the nature of the predominant lesion should therefore dictate the medical management and timing of cardiac intervention (Level of Evidence GRADE 1C).

Earlier surgery is preferred to avoid post-operative left ventricular dysfunction (Level of Evidence GRADE 2C).[48] The presence of mixed valvular disease may place limitations on non-invasive and invasive measures of valvular disease severity due to the haemodynamic effects each lesion may have on the other.[133] For example, mixed rheumatic mitral valve disease with predominant MR may result in left ventricular remodelling and a significantly elevated gradient across the valve despite the valve area remaining large. Conversely, in mixed MR and AS, the MR may result in under-estimation of the AS severity due to relatively reduced flow, and therefore gradient, across the aortic valve. Multimodality imaging evaluation is encouraged to determine anatomical and physiological severity. This should include TOE, exercise stress testing, stress echocardiography and cardiac MRI. These should be used particularly in cases with multiple valvular lesions, atypical symptoms or discordant clinical and echocardiographic information.

There are limited data regarding the outcomes of mixed or multi-valvular disease, particularly when lesions are less than severe.[134] Some research suggests that mixed moderate valvular disease may have a similar prognosis to severe single pathology disease.[135] Intervention in these cases needs to be based on thorough assessment of anatomy, haemodynamics and patient symptoms and comorbidities. Timing and choice of intervention should be determined by a heart team with expertise in RHD. For example, it is not unreasonable to consider isolated mitral valve repair and conservative management of moderate aortic disease (especially AR), knowing further surgery will be required in the future. More frequent surveillance of mixed or multi-valvular disease may be necessary.

MONITORING FOLLOWING VALVE SURGERY

There are several key points regarding patient follow-up after valvular intervention. Adherence to secondary penicillin prophylaxis is vital in preventing recurrence of ARF. In patients with mechanical prostheses, lifelong anticoagulation requires routine and regular monitoring of INR and management of anticoagulation surrounding other future invasive procedures. Due to their relatively limited long-term durability, bioprosthetic valves will require regular review and echocardiography. Similarly, valve repairs will require regular follow-up to identify early and late failure. It is important to note that patients vary in their short and long-term outcomes following valvular intervention.

Children and young adults remain at the highest risk of recurrence of ARF and recurrent valve injury so require closer follow-up.

Older patients with mechanical prosthesis who demonstrate adequate management on anticoagulation and remain clinically stable may benefit from less frequent review *(Figure 11.2)*.

Strict adherence to secondary prophylaxis following cardiac surgery is vital to prevent valve failure due to the recurrence of ARF. Regular echocardiographic studies are also required to monitor valve repairs and prostheses to detect any deterioration, thus enabling appropriate and timely management.

MANAGEMENT OF THROMBOEMBOLIC RISK AND ANTICOAGULATION

Patients living with RHD may have several indications for anticoagulation. These indications include: atrial fibrillation and atrial flutter with an elevated thromboembolic risk; significant mitral stenosis with other risk factors for thromboembolism; and post valve surgery, including mechanical valve replacement. Each of these scenarios will be addressed here.

Atrial fibrillation and atrial flutter

Since the publication of the second edition of the Australian Rheumatic Heart Disease guidelines in 2012, the role of non-vitamin K antagonist oral anticoagulants (NOACs) – also known as novel oral anticoagulants – has been established in the setting of atrial fibrillation or atrial flutter with elevated thromboembolic risk as assessed by the CHA_2DS_2-VASc score.[1,136] The 2018 Australian guidelines for the management of atrial fibrillation elected to remove gender from the scoring system due to the lack of evidence supporting the increased risk attributed to females. This has resulted in the adoption of the CHA_2DS_2-VA score *(Table 11.1)* rather than the previous CHA_2DS_2-VASc score.[1] A score of ≥2 points is associated with significantly elevated risk of thromboembolic event that can be reduced with the use of therapeutic anticoagulation (Level of Evidence GRADE 1A). Anticoagulation should be considered in individuals with a score of 1 (Level of Evidence GRADE 1B). Anticoagulation is not recommended in individuals with a score of 0 (Level of Evidence GRADE 2B).

NOACs have been shown to be equivalent or superior to warfarin for thromboembolic events and safety.[137-139] In these landmark trials, AF was described as "non-valvular". This term has caused confusion in clinical practice; however, "valvular" in this context refers specifically to moderate or greater mitral stenosis (MS) or prosthetic valve replacements. Patients with these pathologies were excluded from the NOACs trials. Patients with other forms of valvular disease, including clinically significant regurgitation and non-mitral valve stenosis, were represented in smaller numbers within these studies. Later publications interrogating these specific cohorts suggest similar benefits to the larger trial populations.[140,141]

It is reasonable to recommended non-vitamin K antagonist oral anticoagulants (e.g. rivaroxaban, apixaban) in patients with AF and elevated CHA_2DS_2-VA score even if valvular disease is present, provided there is no mitral stenosis of moderate or greater severity, and no mechanical valve replacement.[136]

Evidence to support the use of NOACs in patients with bioprosthetic valve replacements and AF is limited, with very few of these patients represented in trials and as such warfarin is the default option in this group.[8] NOACs may be used in cases where it is preferred over warfarin for specific clinical reasons after being discussed with the relevant specialist. Patients with atrial fibrillation and moderate or severe mitral stenosis (regardless of CHA_2DS_2-VA score) or mechanical valve prostheses should be treated with warfarin (Level of Evidence GRADE 1B).[136]

Mitral stenosis

Significant mitral stenosis is a cause of atrial fibrillation and elevated thromboembolic risk, regardless of CHA_2DS_2-VA score. As mentioned above, these patients were excluded from the major NOACs trials. As such, warfarin (a vitamin K antagonist) remains the only oral anticoagulant for the management of patients with atrial fibrillation and moderate or greater MS. There is a single registry-based study which suggests that NOACs may be safe and effective in patients with significant mitral stenosis.[142] However, further evidence is needed before changing guideline recommendations. For patients in sinus rhythm and no history of atrial fibrillation, anticoagulation is indicated if there is a history of thromboembolic event or thrombus visualised within the left atrium (LA) or left atrial appendage (Level of Evidence GRADE 1B).[7] Furthermore, it should be considered in those with significant spontaneous echo-contrast seen within the LA on echocardiography or significantly dilated LA (Level of Evidence GRADE 2C).[7,8] Warfarin is recommended in these latter cohorts also, due to lack of evidence supporting the use of NOACs.[8] Their use in patients with significant mitral stenosis may be considered for specific cases where warfarin is contraindicated, and adherence has been demonstrated (Level of Evidence GRADE 2D). In such circumstances, discussion with a cardiologist is strongly advised. Aspirin in combination with anticoagulation may have a role in specific circumstances and again discussion with a specialist is advised.

Prosthetic valve replacement

Warfarin remains the only option for anticoagulation following implantation of a mechanical valve replacement (Level of Evidence GRADE 1A). A study of non-vitamin K antagonist oral anticoagulants (NOACs) in mechanical valve replacement was stopped prematurely due to increased harm driven by thromboembolic events in the NOACs arm.[143]

Target INR may vary depending on valve prosthesis location (e.g. 2–3 for mechanical aortic valves and 2.5–3.5 for mechanical mitral valves. Patients receiving a bioprosthetic valve replacement may be treated with anticoagulation (warfarin) for the first one to three months post-surgery, as this has been demonstrated to be the highest risk period for thromboembolic events (Level of Evidence GRADE 1C).[8] This practice may vary between institutions and therefore discussion with local cardiothoracic and cardiology services is advised. Enoxaparin or heparin may be used in cases of sub-therapeutic INR or if bridging is needed for patients with mechanical valves.

Monitoring anticoagulation

The major limitation of warfarin is the requirement for monitoring its therapeutic effect (INR) in the form of regular blood tests. Both under-anticoagulation and over-anticoagulation can lead to a life-threatening event. Dosing requirements are variable, as warfarin interacts with many commonly used medications and foods. Difficulties also may arise because of language and cultural barriers, mobility of the population, and remoteness from pathology services. For these reasons, achieving satisfactory anticoagulation is often a challenge.[144] Point-of-care INR testing is available for patients remote from regular pathology services, and this can improve anticoagulation management.[145]

MANAGEMENT OF RHD COMPLICATIONS

Heart failure

Heart failure (congestive cardiac failure) is a clinical presentation where the heart is either unable to pump blood at the rate required for organ function or can only do so with an elevated diastolic filling pressure. It may be associated with reduced or preserved ejection fraction on imaging, respectively termed 'heart failure with reduced ejection fraction' (HF-REF) or 'heart failure with preserved ejection fraction' (HF-PEF).[41] The clinical presentation of heart failure varies widely, from mild symptoms of peripheral oedema or reduced exercise tolerance through to pronounced pulmonary congestion or fulminant cardiogenic shock.

A thorough clinical assessment is imperative in all patients presenting with possible heart failure, particularly in younger patients who may compensate well, therefore masking the severity of the disease.

The aetiology of heart failure may be due to the rheumatic valvular disease itself or other pathologies such as concomitant coronary heart disease, hypertension or another form of cardiomyopathy. Specific to RHD, heart failure may be due to a volume loaded and dilated left ventricle (LV) secondary to regurgitant lesions (e.g. AR, MR), or associated with development of tachycardia and atrial arrhythmias (e.g. atrial fibrillation), particularly in mitral stenosis. While management of these precipitants may be beneficial in the longer term, acute management of decompensated heart failure is often necessary.

The majority of evidence-based therapy has been developed for HF-REF, whereas a paucity of efficacious treatment options are available for HF-PEF. Management of acute decompensated heart failure includes appropriate use of investigations and management of precipitating causes. In patients with RHD, this may include new-onset tachyarrhythmia, coronary ischaemia, sepsis, anaemia, non-adherence with medical therapy or pregnancy. Haemodynamic monitoring may be necessary. Diuretic therapy is recommended to reduce congestion (Level of Evidence GRADE 1C).[41] Negatively inotropic agents, such as beta-blockers, may need to be withheld during acute congestive heart failure. Afterload reduction with vasodilator therapy (i.e. intravenous/topical nitrates) can be of benefit in those with a systolic blood pressure ≥90 mmHg (Level of Evidence GRADE 2C).[41] Inotropic therapy may be necessary in those with progressive hypotension, congestion or cardiogenic shock refractory to earlier treatments (Level of Evidence GRADE 2C).[41]

Management of chronic heart failure includes lifestyle, behaviour, medical and device-based treatments. The appropriate use of these therapies and details regarding acute heart failure management are outlined in the Australian clinical guidelines for the management of heart failure (2018).[41]

Pulmonary hypertension

Left heart disease can result in pulmonary hypertension (PH). Common causes include left ventricular failure (both HF-REF and HF-PEF) or valvular heart disease. In the setting of RHD, any valve disease of significant severity resulting in abnormal left ventricular function may lead to pulmonary hypertension. Of particular note, mitral stenosis may result in significant pulmonary hypertension due to elevated filling pressures and reduced left atrial compliance, even in the setting of preserved LV systolic function. Although the exact mechanism of pulmonary hypertension is not known, it is thought that the pulmonary venous congestion results in a cascade of metabolic responses leading to abnormal pulmonary vascular remodelling.[146] Furthermore, patients may have concomitant pulmonary hypertension due to another pathology, such as autoimmune disease. The correct classification of PH is vital as this determines treatment options.[146] Clinical assessment in combination with echocardiography is used to determine the likely cause of PH, including identification of reversible factors.[146] Right heart catheterisation plays a role in determining severity of disease and may aid in distinguishing types of PH and identifying response to treatment. Treatment of PH complicating left heart disease is focused on management and reversal of the underlying cardiac pathology (Level of Evidence GRADE 1B). This may include medical management of heart failure or procedural intervention of valve disease.[146] Early identification of PH due to RHD is

vital to enable appropriate timing of intervention in order to prevent irreversible complications of PH.[7,8] Pulmonary arterial hypertension therapies are not recommended in PH due to left heart disease (Level of Evidence GRADE 1C).[146]

Atrial fibrillation

Atrial fibrillation is a common complication of RHD, particularly mitral stenosis.[20] Patients who develop AF with a rapid ventricular rate may develop acute heart failure, including pulmonary oedema, and require intravenous diuretic therapy. The ventricular rate in AF is best slowed with rate-controlling medications such as beta-blockers, digoxin and non-dihydropyridine calcium channel antagonists (diltiazem, verapamil). Rhythm-controlling agents such as flecainide, sotalol or amiodarone may play a role in maintaining sinus rhythm in selected patients. However, the long-term use of these agents should be avoided in younger patients due to adverse effects.[136]

If a direct current cardioversion is being considered as a treatment for new-onset AF (≤48 hours duration), TOE is recommended in those at high risk of thromboembolic complications, including significant mitral stenosis, severely dilated left atrium, evidence of thrombus or spontaneous echo-contrast on a transthoracic echocardiogram (TTE), or prior thromboembolic event. Although four weeks of therapeutic anticoagulation is usually considered adequate to reduce the risk of embolism in non-valvular AF cohorts, no evidence for safe cardioversion without TOE exists in patients with moderate or severe MS.[147,148]

Detailed discussion of other management strategies for atrial fibrillation, including ablation and surgical procedures, can be found in the Australian clinical guidelines for the diagnosis and management of atrial fibrillation, 2018.[1]

Prosthetic valve thrombosis

Prosthetic valve thrombosis is an uncommon but serious complication following valve surgery. Australian data demonstrate the high morbidity and mortality associated with valve thrombosis.[149] It is most commonly associated with inadequate anticoagulation in the setting of a mechanical prosthesis.[149] The diagnosis should be considered in any patient with a history of valve replacement presenting with symptoms of congestive heart failure or cardiogenic shock. Early cardiologist involvement is crucial. Urgent surgery is recommended in critically ill patients with mechanical valve thrombosis (Level of Evidence GRADE 1C).[8] In locations where surgery is not immediately available or considered too high risk, thrombolysis should be considered (Level of Evidence GRADE 2C).[8] For patients with thrombosis affecting a bioprosthetic valve, anticoagulation should be trialled before considering repeat surgery (Level of Evidence GRADE 1C).[8]

PREVENTION OF INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) - infection of the endocardial aspect of the heart, most commonly the heart valves - carries high morbidity and mortality.[150,151] It most commonly affects previously damaged or prosthetic valves, which is why RHD poses a major risk for IE. Common bacterial pathogens include *Staphylococcus aureus*, organisms of the *viridans* group of Streptococci, *Enterococcus* species and coagulase-negative Staphylococci.[150,151] Risk factors for development of bacteraemia with these pathogens, in turn causing IE, include dental and other invasive procedures, intravenous drug use, haemodialysis, immunosuppression and indwelling intravascular/invasive devices or catheters.[150] IE complicating RHD is an important adverse event following prosthetic valve replacement.[22,150]

In a study from northern Australia, the rate of endocarditis was found to be 6.5 per 100,000 person-years, being more common in people with RHD (relative risk 58) or people of Indigenous status (relative risk 2.0).[152]

There was significant controversy during the decade from 2008 on the need to give antibiotic prophylaxis for dental procedures. The evidence that peri-procedural antibiotic prophylaxis prevents IE was considered poor quality. Therefore, guidelines committees internationally recommended that antibiotic prophylaxis not be given except to highest risk individuals. While Australia has continued to recommend IE prophylaxis for high-risk individuals undergoing certain procedures, in 2008 the United Kingdom's National Institute for Health and Care Excellence (NICE) recommended that dentists stop its use completely.[153] In 2015, an observational study in The Lancet showed that antibiotic prophylaxis prescribing in England had reduced by 89% since the NICE guideline change, and the incidence of IE had increased significantly.[154] The European Society of Cardiology then concluded 'the weight of evidence and opinion is now in favour of the efficacy and usefulness of antibiotic prophylaxis in preventing IE in those at high-risk' and that 'the risk of not giving antibiotic prophylaxis outweighed any risk of giving it'.[155]

The Australian Therapeutic Guideline recommendations for the use of prophylactic antibiotics for the prevention of IE have evolved over recent editions to the current version which provides clarity and more comprehensive advice regarding the specifics of who is at risk and what procedures are considered risk procedures.[156]

Antibiotic prophylaxis is recommended only in individuals meeting both of the following criteria:

- **Have a cardiac condition associated with an increased risk of developing infective endocarditis and the highest risk of adverse outcomes from endocarditis.**
- **Are undergoing a procedure associated with a high risk of bacteraemia that is associated with endocarditis.**

The following general recommendations are made to prevent IE in those at risk:

- Regular, routine dental examination and scaling.
- Timely treatment of all bacterial infections.
- Avoidance of intravascular catheters and invasive procedures, unless necessary.
- Strict adherence to protocols for managing central and peripheral intravenous devices.
- Active discouragement of tattooing, piercing and intravenous drug use.

Table 11.5. Cardiac conditions and procedures for which infective endocarditis prophylaxis is recommended

Endocarditis prophylaxis is recommended ONLY for patients with the following cardiac conditions who are undergoing a procedure listed below.[† ‡]

CARDIAC CONDITIONS	PROCEDURES[¶]
Prosthetic cardiac valve, including transcatheter-implanted prosthesis or homograph Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords Previous infective endocarditis Congenital heart disease but only if it involves: • unrepaired cyanotic defects, including palliative shunts and conduits • repaired defects with residual defects at or adjacent to the site of a prosthetic patch or device (which inhibit endothelialisation) Rheumatic heart disease in all populations	**Dental procedures.** Only those involving manipulation of the gingival or periapical tissue or perforation of the oral mucosa (e.g. extraction, implant placement, biopsy, remove of soft tissue or bone, subgingival scaling and root planing, replanting avulsed teeth). **Dermatological and musculoskeletal procedures.** Only those involving infected skin, skin structures or musculoskeletal tissues. **Respiratory tract or ear, nose and throat procedures.** Only for tonsillectomy or adenoidectomy, or invasive respiratory tract or ear, nose and throat procedures to treat an established infection (e.g. drainage of abscess). **Genitourinary and gastrointestinal tract procedures.** Only if surgical antibiotic prophylaxis is required or for patients with an established infection.

Adapted from Australian Therapeutic Guidelines: Prevention of Infective Endocarditis, 2019.

† Endocarditis prophylaxis is not recommended for patients with forms of valvular or structural heart disease not listed in this table, including patients with mitral valve prolapse, septal defects or cardiac implantable electronic devices.

‡ Patients with a heart transplant who have developed cardiac valvulopathy may also be at high risk of adverse outcomes from endocarditis. Consult with patient's cardiologist for specific recommendations.

¶ Endocarditis prophylaxis is not recommended for procedures other than those listed above. However, surgical prophylaxis may be indicated if endocarditis prophylaxis is not.

The presentation of infective endocarditis often includes non-specific symptoms and signs including fever, rigors, malaise, anorexia, weight loss, myalgias, arthralgias, night sweats and abdominal pain.[150] A cardiac murmur is common, noted in the majority of patients.[150] Peripheral embolic lesions including splinter haemorrhages are not uncommon but classical Janeway lesions, Osler's nodes and Roth spots are less common.[150] Patients may present with complications of the disease, including acute severe valvular dysfunction, heart failure and deep embolic complications such as stroke, deep organ septic emboli or abscess.[151] It is imperative that patients at high risk of IE with unexplained fever or non-specific symptoms are investigated for infective endocarditis.[151] Blood tests including blood cultures should be taken prior to the administration of antibiotics.

Antibiotic prophylaxis to reduce endocarditis risk

For patients taking long-term BPG injections for secondary prevention of ARF, it is the consensus view of the Antibiotic Expert Groups that amoxicillin is still appropriate for endocarditis prophylaxis (Level of Evidence GRADE 2D) *(Table 11.6)*.[156] This is a departure from the previous guidelines[157] which recommended the use of clindamycin as the first-line approach for people receiving long-term penicillin therapy. The rationale is that, while the level of penicillin achieved with BPG prophylaxis is not adequate as peri-procedural prophylaxis to prevent bacteraemia from mouth organisms, the amoxicillin susceptibility of viridans streptococci in the oral flora is not significantly affected by the by the penicillin prophylaxis. However, for patients currently taking or who have recently taken a course of other beta-lactam therapy (not BPG), evidence suggests that the amoxicillin susceptibility of viridans streptococci may be affected. Therefore, a non–beta-lactam antibiotic, such as clindamycin, may be considered for prophylaxis in this setting.

Table 11.6. Antibiotics for infective endocarditis prophylaxis

DRUG	ROUTE	TIME BEFORE PROCEDURE
For endocarditis prophylaxis, use:		
Amoxicillin 2 g *(child: 50 mg/kg up to 2 g)*	oral	60 minutes before the procedure
If oral administration is not possible, use:		
Amoxicillin 2 g *(child: 50 mg/kg up to 2 g)*	intramuscular	30 minutes before the procedure, ***or***
Amoxicillin 2 g *(child: 50 mg/kg up to 2 g)*	intravenous	within 60 minutes before the procedure, ***or***
Ampicillin 2 g *(child: 50 mg/kg up to 2 g)*	intramuscular	30 minutes before the procedure, ***or***
Ampicillin 2 g *(child: 50 mg/kg up to 2 g)*	intravenous	within 60 minutes before the procedure
For patients with delayed non-severe hypersensitivity to penicillins, cefalexin can be used in most cases.† Use:		
Cefalexin 2 g *(child: 50 mg/kg up to 2 g)*	oral	60 minutes before the procedure
If oral administration is not possible, use:		
Cefazolin 2 g *(child: 30 mg/kg up to 2 g)*	intramuscular	30 minutes before the procedure, ***or***
Cefazolin 2 g *(child: 30 mg/kg up to 2 g)*	intravenous	within 60 minutes before the procedure
For patients with immediate (severe or non-severe) or delayed severe hypersensitivity to penicillins,† use:		
Clindamycin‡ 600 mg *(child: 20 mg/kg up to 600 mg)*	oral	60-120 minutes before the procedure
If oral administration is not possible, use:		
Clindamycin‡ 600 mg *(child: 20 mg/kg up to 600 mg)*	intravenous	within 120 minutes before the procedure

† See Therapeutic Guidelines: Antimicrobial hypersensitivity / Management of patients reporting hypersensitivity to penicillins.

‡ There is some evidence that moxifloxacin may be used as an alternative to clindamycin for patients with immediate (severe) or non-severe or delayed hypersensitivity to penicillins but this has not been validated.

Oral health and RHD

Oral health is an important element of care for people living with RHD. Poor oral health, particularly the presence of dental caries, is associated with increased risk of infective endocarditis (IE) complicating RHD.[158]

Common dental pathologies and pre-surgical assessment

Common dental conditions seen in patients requiring cardiac surgery are untreated dental caries, high levels of plaque and gingival inflammation, retained roots and poorly controlled periodontitis.[159] There is correlation between people with severe RHD and poor oral health, which places these individuals at high risk for IE.[160] Aboriginal and Torres Strait Islander peoples, particularly those in rural and remote areas, suffer from poorer oral health than non-Indigenous Australians.[161] Poor oral health is associated with higher risk of significant bacteraemia and therefore maintaining good oral health and hygiene is likely to have a greater positive impact than antibiotic prophylaxis during dental procedures.[158]

All people with ARF and RHD need regular dental review to reduce the risk of IE (Level of Evidence GRADE 2D). Patients requiring cardiac intervention for RHD need a comprehensive dental consultation prior to surgery (Level of Evidence GRADE 2D).

Dental review preceding cardiac surgery comprises detailed treatment planning for caries stabilisation, management of active periodontal disease, and elimination of any odontogenic infection supported with appropriate radiography. Treatment includes extraction of any teeth with poor prognosis from dental caries, filling of restorable teeth, treatment of moderate to severe periodontitis and stabilisation of periodontal or gingival health. Patients should also receive age- and culturally appropriate education to improve oral hygiene practice in the longer term.

Access to dental care

Oral health services in rural and remote areas are usually provided by visiting oral healthcare professionals. The short duration and limited frequency of visits result in a low level of access to oral health services for people living in many rural and remote communities. Oral health services provided are usually limited to general services, and do not include specialist care or more complex procedures. The need to travel to regional centres for urgent dental care is common.

Effective communication between dental services and local healthcare centres or referring GPs is important to ensure that patients can access dental services in their community when available. Treatment required over multiple appointments can be difficult. Patients should be made aware of the number of appointments required for treatment. Reminders and transport should be arranged to ensure that treatment is timely, particularly ahead of scheduled cardiac surgery.

CASE STUDY

Surgery journey

Patients living in rural and remote areas who need to access cardiothoracic and interventional cardiology services are required to travel to major tertiary hospitals. These tertiary centres are often located a significant distance from the patient's home; away from family and familiar community support services. Primary care services located across rural and remote Australia have shaped effective referral relationships with tertiary centres, specialist cardiothoracic surgeons and cardiologists. *Table 11.7* provides an example of the journey for surgery – from pre-surgical assessment through to follow-up after hospital discharge. The information provided here can be used to help patients and families understand what is involved during the surgical journey, from the time that a recommendation for operation is made through to the journey home after the initial recovery period.

This is a guide only; hospital management can vary between institutions.

The cultural and language differences between some Aboriginal and Torres Strait Islander patients and the personnel encountered along the surgery journey may be significant.

At every stage:

- **Aboriginal and Torres Strait Islander health staff need to be included in the process and involved with the patient.**
- **The level of patient and escort health literacy needs to be considered.**
- **The patient, and relevant family and escorts, need to be involved in all discussions and decisions.**
- **Appropriate, trained interpreters need to be employed as required, to bridge language differences and facilitate informed consent for investigations and procedures.**
- **The system's capacity for cultural competence needs be considered, and addressed as indicated.**

STAGE	PERSONNEL	MANAGEMENT	SYSTEM FACTORS	CONSIDERATIONS	PATIENT CARE
Assessment for heart valve surgery *OUTCOMES: Patient indicated or not indicated for surgery, based on severity of disease, symptoms, and ongoing risk to health* *Patient and family are adequately informed so that they can agree to or refuse surgery (if indicated)*	Paediatrician/ Physician Cardiologist Cardiothoracic surgeon Local primary healthcare staff • GP • AHW, AHP • Nurse	Review by cardiologist & cardiothoracic surgeon • Medical history • Symptoms and impact on daily living • Treatment (including secondary prophylaxis delivery) Discussion around risks and benefits of surgery Refer to heart team†	Timely access to surgical consultation (particularly for people in rural and remote areas) Communication between local cardiology services and cardiothoracic surgeons Engagement with local primary care service to ensure appropriate follow-up, prescription of secondary prophylaxis, involvement of dental and/or indicated allied health services Advanced allocation of surgery date (+/- 3 months)	Understanding the importance of surgical intervention Community consent for surgery to proceed (where indicated) Implications of future planned pregnancies Implications of travel from remote areas Work, education, financial and family implications of taking time for surgery	Involvement by proposed escort as early as possible Stories from other people who have had surgery
Pre-operative clinical preparation *OUTCOMES: Clinical preparation completed prior to surgery* *Clinical preparation planning sensitive to the patient's capacity to attend and accept assessments and treatments*	Paediatrician/ Physician Cardiologist Local primary healthcare staff • GP • AHW, AHP • Local Cardiac Coordinator • Nurse/ Midwife	Team, patient, family discussion: • pre- and post-operative testing and care including surgical equipment, attachments, procedures • heart valve options (repair vs replacement, tissue vs mechanical) • risks and benefits of long-term anticoagulation Transthoracic echocardiogram +/- transoesophageal echocardiogram (for mitral valve disease) Coronary angiogram (if aged >30 years) Biochemistry analysis/ complete blood exam Urine culture Multidrug resistant organism screening (i.e. MRSA/VRE/CRE) Skin assessment and treatment (fungal infections/ rash/open wounds) Oral health assessment and treatment (dental caries, gum disease) Other chronic conditions stabilised (e.g. diabetes, hypertension) Medication review (e.g. anticoagulant therapy ceased 5-7 days before surgery) Informed consent for surgery	Access to investigation and interventional services Treatments completed (e.g. skin conditions, dental work) as indicated Timing of investigations and tests as close to surgery date as possible (preferably within 1 month of surgery date) Test results communicated to surgical facility Capacity of local health staff to provide detailed and accurate information Capacity to provide education over multiple sessions Coordinated input from local health staff to aid in determining valve choice options and medication delivery Capacity to arrange appointments so that regional travel and inconvenience is minimised	Capacity to attend for multiple assessments and treatments Understanding the importance of pre-operative preparation (particularly if lengthy or complex) Patient, family, escort overwhelmed	Transport to attend appointments Clear communications about assessments and treatments Appointments arranged to reduce regional travel and inconvenience

Chapter 11 MANAGEMENT OF RHEUMATIC HEART DISEASE

Table 11.7. Patient surgery journey (continued)

STAGE	PERSONNEL	MANAGEMENT	SYSTEM FACTORS	CONSIDERATIONS	PATIENT CARE
Travel planning *OUTCOMES: Return travel and accommodation secured for patient and appropriate escort* *Patient and escort have a clear understanding of travel arrangements and their responsibilities related to travel*	GP ALO Local Cardiac Coordinator Nurse/ Midwife Patient Travel Officer	All flights, accommodation, and transfers from patient's home to surgical facility and return home	Capacity to include escort in travel and accommodation Timing of connecting flights and transfers Access to money (e.g. use of basics card, location of ATM)	Availability of appropriate escort at time of travel Arrangements (and issues) related to substitute family care and leave from school or work (where indicated) Remoteness of home, and additional transfers required Money and appropriate clothing and other requirements available for patient and escort	Travel details provided to local primary care facility and family at home Planned communication (sharing phone numbers, out-of-hours contacts) between patient, escort and health service/home
Travel to surgical facility[‡] *OUTCOME: Smooth transfer between home (or regional health facility) and cardiothoracic surgery facility*	Regional aeromedical staff Commercial airline staff Airport staff Road transport drivers (bus, taxi, rail) Hotel, hostel, outreach services staff		Travel processing times and transfers Long drives and flights Overnight travel arrangements Access to hospital from hostel accommodation Availability of hospital (units, rooms) accommodation Transit staff capacity to communicate with patient and escort effectively	Unfamiliar and/ or uncomfortable travel Unfamiliar and/ or uncomfortable weather conditions Cultural isolation (being away from family, friends, and traditional Lands) Personal isolation (no escort available)	Trained support staff to send and receive patient and escort Well-planned travel arrangements, including patient and escort education Planned communication (sharing phone numbers, out-of-hours contacts) between patient, escort and travel organiser

Table 11.7. Patient surgery journey (continued)

STAGE	PERSONNEL	MANAGEMENT	SYSTEM FACTORS	CONSIDERATIONS	PATIENT CARE
Preparation for surgery – surgical assessment and planning	Cardiothoracic surgical team (consultant surgeon, surgical registrars) AHW, AHP ALO Nurse Clinical pharmacist	Review of recent tests and treatments (clinical preparation) Clinical measurements: • repeat biochemistry, complete blood picture, coagulation studies • blood group & cross match • ECG • CXR (repeated and compared to previous) • other imaging as required (CT Chest (if reoperation), Carotid Duplex Ultrasound) Team, patient, escort discussion: • pre- and post-operative testing and care including equipment and personal attachments • surgery procedure and associated risks • post-operative treatment plan Signed consent form for surgery Medication review, including cessation of anticoagulant therapy (if indicated)	Established process for surgery Capacity to incorporate patient, escort care preferences Capacity for escort to accompany patient to theatre Support for escort during surgery	Unfamiliar healthcare environment and routine Concern about surgery (procedure, pain, scarring) Concern about anaesthesia (process, risks) Concern about future health and capacity for independence Patient, escort overwhelmed	Escort and Aboriginal and Torres Strait Islander health staff included in all discussions Activities available to patient and escort in between appointments and tests
Preparation for surgery - anaesthetic risk assessment and planning	Anaesthetist AHW, AHP ALO	Clinical assessment • medical history, including existing anaesthetic risk • physical examination of mouth, throat, teeth • auscultation (lung and heart sounds) • need for transfusion Anaesthetist, patient, escort discussion: • anaesthetic process and care of patient under anaesthesia • premedication, fasting prior to surgery, post-operative pain management Consent to anaesthesia	Capacity to incorporate patient, escort care preferences Introduction and orientation to theatre environment Capacity to provide clear instruction about pain relief options post-surgery		
Preparation for surgery – cardiothoracic ward *OUTCOMES: Patient prepared for surgery according to hospital protocol* *Preparation for surgery is culturally safe and acceptable to the patient and escort*	Nurse AHW, AHP Physiotherapist	Antibacterial body wash and shave Oral fasting for 8-10 hours before surgery Premedication Intravenous line insertion Nurse, physiotherapist, patient, escort discussion: • post-operative mobilisation plans • deep breathing and coughing exercises (demonstrated use of *triflo* device)	Capacity to incorporate patient, escort care preferences and to communicate this clearly between ward and theatre staff		

Chapter 11 MANAGEMENT OF RHEUMATIC HEART DISEASE

Table 11.7. Patient surgery journey (continued)

STAGE	PERSONNEL	MANAGEMENT	SYSTEM FACTORS	CONSIDERATIONS	PATIENT CARE
Surgery[§] *OUTCOME:* *Surgery completed as planned*	Cardiothoracic surgeon Anaesthetist Theatre Nurses Perfusionist (operates the *Heart-lung machine*)	Surgical antibiotic protocol Heart valve repair/replacement Central venous catheter insertion Urinary catheter insertion Cardio-pulmonary bypass (not indicated for transcatheter procedure	Clear communication and handover within the team	Patient, escort overwhelmed by operating theatre environment, surgical masks and equipment	Escort and/or Aboriginal Liaison Officer support through to operating theatre Welcoming and supporting surgical team *NOTE: Cardiothoracic surgeon talks to the escort or other relevant patient contacts immediately after surgery*
Intensive care[¶] ***(24-48 hours after surgery)***	Cardiothoracic surgeon AHP Intensive Care Team • Intensivist • Nurse • Physiotherapist Clinical pharmacist	Daily cardiothoracic review Surgical antibiotic protocol Routine monitoring and management • respiratory support (ventilation) • haemodynamic management • heart function/status • nutrition/hydration • pain management • CXR, ECG, echocardiogram • blood tests – biochemistry, haemoglobin • passive movement and mobilisation	Clear communication and handover within the team Capacity to provide culturally safe (intimate personal) care Capacity to include escort	Unfamiliar healthcare environment and routine Pain and fear (and unfamiliar with pain relief options) Cultural isolation (being away from family, friends, and traditional Lands) Concerns about lack of privacy Patient, escort overwhelmed (potentially unsure of expectations from hospital staff) Increasing independence with mobility and self-care Cultural considerations around pain management	Escort involvement in patient care (if appropriate) Access to phone and/or video to communicate directly with family and friends at home Culturally appropriate care - appropriate staff available to conduct male and female procedures *NOTE: AHP provides regular updates to local primary healthcare team and family at home* *NOTE: AHP accompanies escort to visit patient during intensive care admission. They also advocate for the patient while under intensive care, and provide ongoing support to the escort and others associated with the patient*
Post-surgery ward-based care ***(day 2-5 after surgery)***	Cardiothoracic surgeon ALO AHW, AHP Nurse Cardiac rehabilitation Physiotherapist Clinical pharmacist	Daily cardiothoracic review Routine monitoring and management: • monitoring vital signs • daily weight Blood tests as indicated: • daily INR • haemoglobin • troponin Wound management Pain management Deep breathing & coughing exercises **DAY 2** Removal of urinary catheter Light diet and oral fluids as tolerated First shower and/or sit out of bed Physiotherapist review (sit out of bed/shower)	Capacity to provide culturally safe (intimate personal) care Capacity for clear communication and clinical handover Planning for discharge from ward Capacity to plan discharge with local primary healthcare team		

Table 11.7. Patient surgery journey (continued)

STAGE	PERSONNEL	MANAGEMENT	SYSTEM FACTORS	CONSIDERATIONS	PATIENT CARE
		DAY 3-5 Removal central venous catheter Removal temporary pacing wires (if used) Increased physical mobility as tolerated Commence team, patient, escort discussions: • discharge planning • care after discharge Cardiac rehabilitation review			
Post-surgery ward-based care ***(day 5 after surgery to discharge)***	Cardiothoracic surgeon ALO AHW, AHP Nurse Cardiac rehabilitation Physiotherapist Clinical pharmacist Social worker (if indicated)	Daily cardiothoracic review Routine monitoring and management: • monitoring vital signs • daily weight Blood tests as indicated: • daily INR • haemoglobin • troponin Normal diet as tolerated Wound management Pain management Deep breathing & coughing exercises Continue team, patient, escort discussions: • discharge planning • care after discharge Cardiac rehabilitation review			
Hospital Discharge Planning[††] ***(discharge on day 5 or 6 post-surgery)***	Nurse AHW, AHP ALO Cardiac Rehabilitation Physiotherapist Pharmacist	Comprehensive discharge report to primary healthcare service and local cardiologist Team, patient, escort discussion: • what to expect after surgery (diet, wound care, sleeping, mental health, energy levels, constipation) • guidelines for mobility, pain management, medications, driving etc. • infective endocarditis prevention (formal prophylaxis and management of small infections) Cardiac rehabilitation review prior to discharge Medication review, including discharge medications Future appointment bookings: • Hospital in the Home • INR AHP contact information provided	Established process for discharge Clear communication and handover within the team Capacity to incorporate patient, escort care preferences Capacity to involve local primary healthcare team during discharge planning Visit from *Hospital in the Home*	Uncertainty about support after hospital discharge	Written information to guide patient through the post-discharge period *NOTE: ALO assists with Centrelink, finances, travel arrangements, transport to and from hospital*

Chapter 11 MANAGEMENT OF RHEUMATIC HEART DISEASE

Table 11.7. Patient surgery journey (continued)

STAGE	PERSONNEL	MANAGEMENT	SYSTEM FACTORS	CONSIDERATIONS	PATIENT CARE
Residential Convalescence ***(for 1 week prior to travel home)***	Nurse AHW, AHP ALO Cardiac rehabilitation	Indirect support with daily living Hospital in the Home nurse visit (including INR if required) Surgical review prior to travel home – AHP in attendance	Access to hospital Access to local facilities (shops, public transport) Access to ALO for guidance and support	Unfamiliar metropolitan environment Post-operative pain or complications	Support to navigate metropolitan environment Transport to hospital Clear instruction for expectations during this period 24-hour contact for clinical support Access to money for food, and entertainment
Travel home *OUTCOME:* *Smooth transfer between cardiothoracic surgery hospital and home (or regional health facility)*	See: *Travel to surgical facility (above)*	Transfer between metropolitan residential facility and home.	See: *Travel to surgical facility* (above)		

The term *escort* is used to describe the person or people who accompany the patient to hospital. The escort/s may be family members, friends, or community representatives.
† A heart team for RHD should include people with expertise in rheumatic and valvular heart disease such as cardiologists, cardiac surgeons, anaesthetists, allied health staff and, when indicated, intensive care physicians, infectious disease physicians and obstetricians (as indicated).
‡ Cardiothoracic surgical facilities are based in tertiary hospitals in Perth, Adelaide, Brisbane, Melbourne and Sydney.
§ Cardiothoracic (open heart) surgery usually takes between 3-5 hours; transcatheter surgery usually takes about 1-5 hours.
¶ Patients with complications and complex comorbidities may need to stay in the intensive care unit for an extended period.
†† Elements of hospital discharge planning should commence at admission to hospital.

GP, General Practitioner; AHW, Aboriginal Health Worker; AHP, Aboriginal Health Practitioner; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant enterococci; CRE, carbapenem-resistant Enterobacteriaceae; ALO, Aboriginal Liaison Officer; ECG, electrocardiogram; CXR, chest x-ray; CT, computed tomography (scan); INR, International Normalised Ratio

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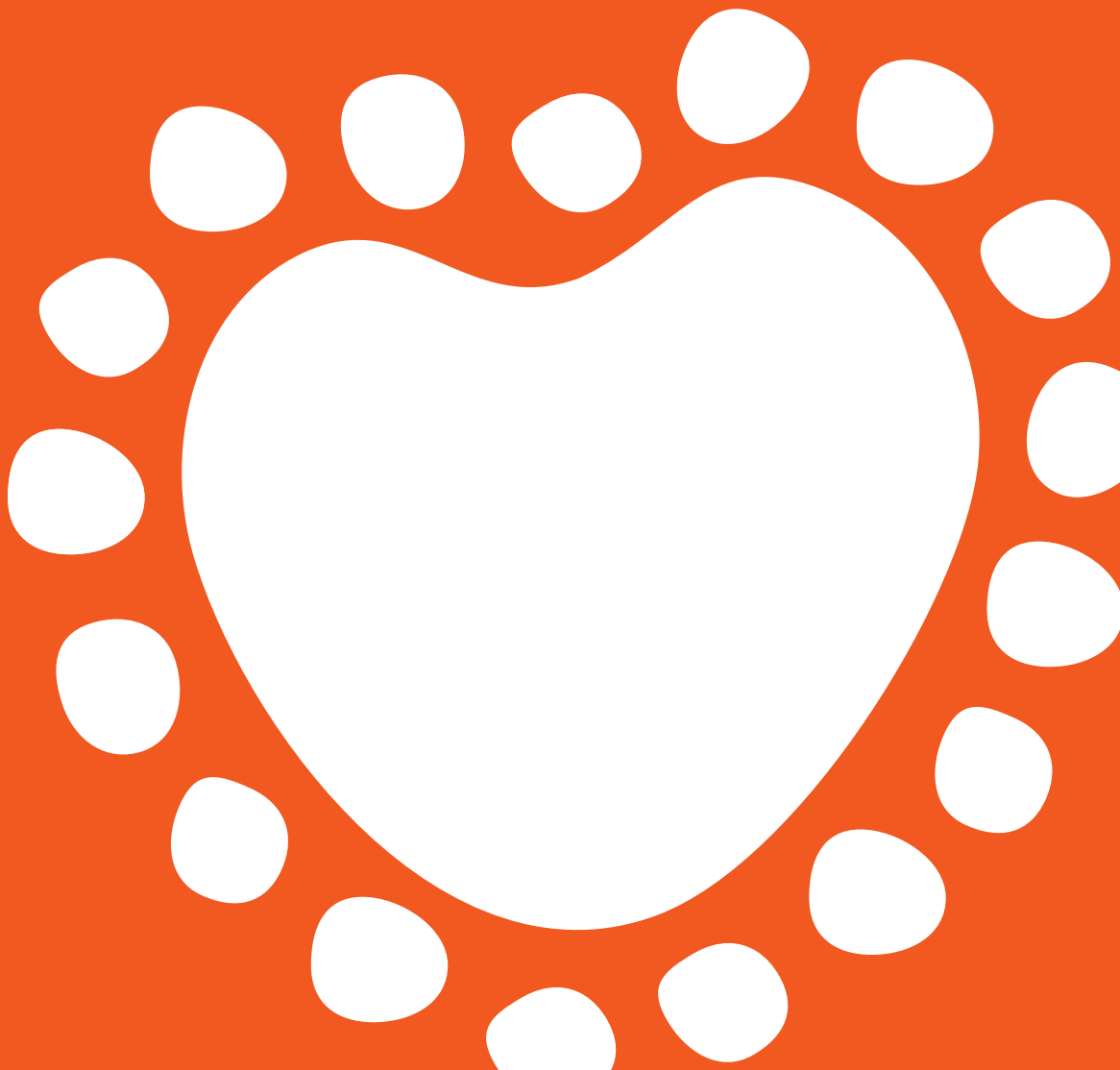
CHAPTER 12

Women and girls with rheumatic heart disease



Women and girls with rheumatic heart disease

CHANGES FROM THE SECOND (2012) EDITION

1. The ***Women and Girls with RHD*** (previously *RHD in Pregnancy*) section has been substantially revised and extended to incorporate a whole-of-life approach.
2. A new section on transition to adult care, reproductive health, and preconception care is provided.
3. Discussion around the need and strategies for a well-planned pregnancy and delivery are updated.
4. Anticoagulation during pregnancy and impact in reproductive health has been revised and expanded.
5. Care pathways for women and girls with rheumatic heart disease (RHD) are provided, including a referral algorithm in pregnancy.

KEY INFORMATION

- Effective multidisciplinary, community-centred care that is age-appropriate, encompasses reproductive health as well as cardiac and other health care and continues through the lifespan.
- Many women with RHD can safely conceive and have children. In the Northern Territory, 2-3% of Aboriginal pregnant women each year have RHD. Women with mild RHD may be able to birth on Country.
- Pre-conception diagnosis of RHD allows optimisation of management including surgical management, before pregnancy.
- Recommended contraceptives are long-acting reversible contraceptives (intra-uterine contraceptive device or etonogestrel implant such as *Nexplanon*). Oestrogen-containing contraceptives are associated with elevated risk of thrombosis and should be avoided.
- Women with RHD contemplating pregnancy or who are pregnant require coordinated health care. Aim to avoid multiple appointments incurring high travel costs and requiring time away from children and from community.
- Anticoagulation is needed for all women and girls with mechanical prosthetic valves to prevent stroke and other thromboembolic disease and may be needed for atrial fibrillation depending on thromboembolic risk assessment. All anticoagulants pose risks in pregnancy. Risks to the mother include both antepartum and post-partum haemorrhage. Risks to the fetus include teratogenicity and stillbirth (warfarin). An approach to balancing risks and benefits is provided.
- Women with valve lesions posing problems in pregnancy (moderate or greater mitral stenosis, severe mitral or aortic regurgitation, severe aortic stenosis, pulmonary hypertension or heart failure) are at high risk with elevated chance of cardiac events during pregnancy and adverse fetal outcomes. They require specialist care and close monitoring.
- A left ventricular ejection fraction of <30% or reduced systolic function with New York Heart Association (NYHA) class III/IV symptoms is associated with high risk of maternal morbidity or mortality, and pregnancy is strongly discouraged.
- A pregnant or post-partum woman at higher risk of or diagnosed with RHD who presents with breathlessness, orthopnoea, wheeze or worsening fatigue should be investigated with an echocardiogram.
- When low molecular weight heparin is used in pregnancy to replace warfarin, monitoring of anti-Xa levels and appropriate dose adjustment is essential.
- Normal vaginal delivery is preferred. Epidural anaesthesia - after appropriately-timed short-term cessation of anticoagulation – may be indicated to reduce tachycardia and hypertension that can precipitate acute heart failure during delivery.

ASPECT	DETAILS	GRADE
TRANSITION TO ADULT CARDIAC CARE & PRECONCEPTION CARE		
Transition to adult cardiac care	Begins at adolescence. Include paediatric and adult cardiology teams, family planning, primary health services with the adolescent girl and her family.	1C 2B
Reproductive health & contraception	Refer to obstetrician/gynaecologist and/or family planning clinic (may be done through Aboriginal and Torres Strait Islander child and family programs) as relevant. Promote effective contraception for all girls and women, especially if pregnancy poses a risk. Avoid oestrogen-containing contraceptives.	1C 1B
Preconception care (PCC) & planning pregnancy	Full assessment and echocardiogram. Assess co-morbidities. Check vaccination status, rubella/varicella immunity and cervical screening. Review medications, especially warfarin or ACE inhibitors/angiotensin receptor blockers (ARBs). Consider a wallet card with RHD alert and key points related to care requirements and medications.	1C 1A 2C
Surgery & other interventions pre-pregnancy	Consider choices (prosthetic type/repair/PBMV) in context of future pregnancy and associated risk. Discussion with adolescent/woman, her family and appropriate primary health services together with specialist. Pre-pregnancy intervention recommended in patients with asymptomatic severe or symptomatic mitral stenosis (MS), symptomatic severe aortic stenosis (AS) or symptomatic severe valve disease.	1C 1B
DURING PREGNANCY		
Diagnosis of RHD in pregnancy	Attentive history-taking and careful cardiovascular examination. Low threshold for echocardiogram and cardiac referral in at-risk populations.	1C 1C
Integrated care	Includes cardiac (or obstetric physician), obstetric, anaesthetic, midwifery, primary health teams, Aboriginal health service, Māori, Pacific Islanders or refugee health workforce support (other disciplines/sectors as relevant) with women and family. Incorporate Birthing on Country models of care principles.	1C

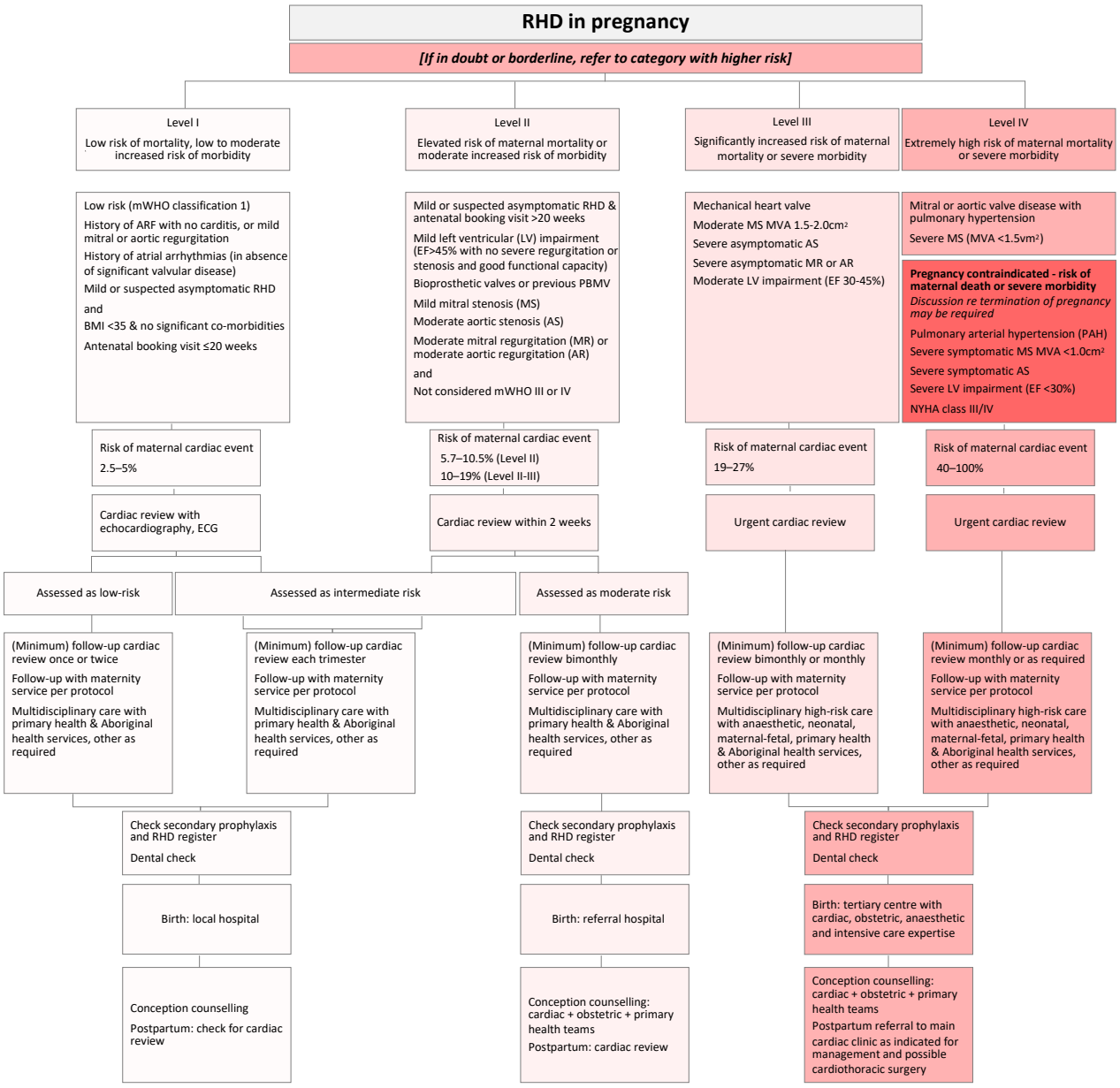
Table 12.1. Summary – Care pathways for women and girls with RHD (continued)

ASPECT	DETAILS	GRADE
Cardiac risk assessment & general principles of care	Clinical risk assessment at booking and as required during pregnancy. Baseline echocardiography at booking and as required during pregnancy according to risk *(Figure 12.1)*. Anaesthetic assessment. Treatment in specialised centres by a multi-disciplinary pregnancy heart team for high-risk patients. Appropriate anticoagulation regimen where relevant. Interpreter services as required. Dental review. Assessment of social circumstances. Facilitate access to care depending on individual needs. Develop comprehensive birth plan as early as possible. Review/modify as needed. Discuss contraception: identify women who may desire tubal ligation at caesarean section or intrauterine device insertion at time of delivery.	1C 1C 1C 1C 2B 2B 2C 2C 1C 2C
Identify as high risk	Prior cardiac event (heart failure, transient ischaemic attack, stroke, arrhythmia) or events during pregnancy. Decreased left ventricular systolic function. Moderate or severe aortic and/or mitral stenosis. Pulmonary hypertension (PH). Mechanical valve prostheses or cardiac disorder requiring anticoagulation. Current heart failure or arrhythmia.	
RHD Register	Ensure the woman is on RHD Register in relevant jurisdictions. If not (or if not sure), contact RHD Register.	2B
Secondary prophylaxis	Check if woman needs to be on secondary prophylaxis (usually 3-4 weekly benzathine benzylpenicillin G [BPG] injection) to prevent further rheumatic fever infection. If she is currently on regimen, check when next injection/oral antibiotic is due. Safe in pregnancy for mother and baby so should continue where prescribed.	1A
Mechanical heart valves & anticoagulation	High maternal and fetal risk. Discussion early in first trimester but ideally preconception to avoid warfarin in early pregnancy. Risk of warfarin embryopathy in first trimester. Risk of warfarin fetopathy in second and third trimesters. Highest risk of maternal thromboembolic complications with poor adherence to anticoagulation and/or monitoring, lack of appropriate multidisciplinary expertise especially when transitioning between different anticoagulant therapies.	1A 1C 1A 1A 1C

Table 12.1. Summary – Care pathways for women and girls with RHD (continued)

ASPECT	DETAILS	GRADE
Red flags	Symptoms and signs requiring urgent medical assessment: • new onset or progressive breathlessness or cough • need to sleep sitting up (orthopnoea) • significant reduction in exercise tolerance • syncope or presyncope (light headedness) • persistently fast heart rate (tachycardia) • wheeze and/or leg oedema	1C
LABOUR & BIRTH		
Labour & birth	Multi-disciplinary team approach (for Aboriginal and Torres Strait Islander women, include the Aboriginal Liaison Officer). Individualised birth plan taking account of cardiovascular and obstetric issues. Vaginal birth recommended unless obstetric and/or cardiovascular conditions preclude. Requirement for intrapartum intensive or invasive monitoring should be individualised depending of severity of underlying valvular disease. Follow anticoagulation protocol where relevant. Routine antibiotic prophylaxis for bacterial endocarditis not recommended and antibiotics should be given as per local obstetric indications. Aim for early epidural analgesia when tachycardia or hypertension may not be well tolerated because of maternal valvular disease. Oxytocin: administer slowly by infusion in third stage of labour. Avoid ergometrine in severe RHD, unless life-threatening bleeding.	2B 1C 2C 1A 1A 2C 2C 2C
POST-PARTUM & POST-DISCHARGE		
Post-partum	Consider need for diuretic therapy to assist with haemodynamic shifts post-partum. Follow anticoagulation protocol where relevant. Investigate post-partum/ post-discharge dyspnoea or new-onset cough promptly. Encourage breastfeeding and review safety of cardiac medications with lactation. Discuss family planning and contraception.	2C 1A 1A 1C 2C
Post-discharge	Follow-up cardiac review according to priority. Clinical communication follow-up with primary health services/GP/Aboriginal Medical Service and other relevant services. Maintain high degree of suspicion for presentation of dyspnoea.	1C 2C 1C
Information for health services & women	RHDAustralia Treatment Tracker reminder app. 'Sharing a Heartbeat' Parts 1 & 2 short films and posters – for women and health services. RHDAustralia 'e-learning modules modules (including RHD in Pregnancy).	

Figure 12.1. Care pathways and referral algorithm for pregnant women with RHD



Adapted with permission from Regitz-Zagrosek (2018), and Sliwa (2014)[1,2]

Abbreviations: Modified World Health Organization (mWHO); mitral regurgitation (MR); aortic regurgitation (AR); tricuspid regurgitation (TR); left ventricular (LV); pulmonary hypertension (PH); aortic stenosis (AS); mitral stenosis (MS); pulmonary arterial hypertension (PAH); mitral valve area (MVA); ejection fraction (EF).

Mild RHD: MVA >2 cm² AND EF=50-70% AND mitral/aortic/tricuspid regurgitation = none or mild AND no AS.

PAH: LV filling pressure <15 mmHg & pulmonary vascular resistance >3 Wood units

Significant co-morbidities include diabetes, BMI >35, chronic kidney disease, drug and/or alcohol dependency.

Risk of maternal cardiac event: according to modified World Health Organization classification of maternal cardiovascular risk adapted from Regitz-Zagrosek (2018).[1]

DISCUSSION

> *"There's a need to make more informative resources for RHD clients. I felt there was a lack of information for young women in regard to pregnancy and having RHD. Young women and girls want answers to questions like, 'am I putting myself at risk if I want to have a baby?'"*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

OVERVIEW

Rheumatic heart disease (RHD) is twice as common in women as in men.[3-7] In high-risk communities it is not uncommon for RHD to exist across multiple generations, with an additional burden of managing care and prevention in families, particularly where women are the primary caregivers. The 2018 World Health Assembly resolution recognises this, with a call to align RHD strategies with existing women's, children's and adolescent health programs.[8]

A woman's journey with RHD often starts well before pregnancy. Decisions during childhood about treatment interventions for RHD, such as surgery and anticoagulation, may be required. These decisions will have lifelong consequences. Health services must assume that an adolescent girl or woman will wish to become pregnant at some point in her life and assist her to make an informed choice against an often complex and challenging clinical background. Conversations about treatment and pregnancy planning with the adolescent/woman, her caregiver, other family and partner as appropriate to age and circumstance should begin in adolescence and continue through reproductive years.

Pregnancy for women with RHD may reveal clinical symptoms in previously undiagnosed cardiovascular disease, resulting in complications and adverse outcomes for mother and baby.[9]

However, pregnancy also provides an important opportunity to re-engage with cardiovascular and RHD services. Optimal care, including early review and regular monitoring, reduces risk in pregnancy and can minimise maternal and fetal complications.[1,9,10] Women with mild RHD who receive appropriate care and reviews often have uncomplicated pregnancies, giving birth to a healthy baby at their local hospital. This chapter outlines core standards in the spectrum of whole-of-life care, including transition to adult cardiac care; sexual and reproductive health; preconception counselling, valvular lesions in pregnancy, surgery and other interventions; antenatal care including risk assessment; medications including anticoagulation; labour and birth; post-partum and post-discharge care.

These standards require a woman-centred, multi-disciplinary approach that is underpinned by a shared understanding of the impact of RHD with women and their families. They take account of culture and community practice: consistent with good maternity care.[11] As well as health literacy for women, girls and communities about the impact of RHD particularly in pregnancy, this chapter emphasises education and knowledge for the health workforce including primary health as well as tertiary care.

The clinical recommendations in this chapter provide broad principles of care that will vary according to level and type of health service, severity of RHD, and a woman's personal health circumstances and wishes. Most women with RHD in Australia are Aboriginal and/or Torres Strait Islander (78% of women in a recent study of RHD in pregnancy).[9] Good care acknowledges the importance that Birthing on Country holds for Aboriginal and Torres Strait Islander women, which in turn can impact directly on pregnancy outcomes.[11-16] It takes an individualised approach: an Aboriginal woman living in Perth is likely to have different needs to a Torres Strait Islander

woman on remote Badu Island. Their needs are shaped by their own situation, as well as cultural beliefs and practices, language, history, and place of residence.[17] This is similarly true for other high-risk populations – including Māori and Pacific Islander women residing in Australia, and women migrating to Australia from resource-poor countries.

Recommendations are intended to facilitate decision-making. However, the final decisions concerning an individual must be made by the treating health professional(s) in consultation with the adolescent girl/woman, caregivers and family as appropriate, and in accordance with local hospital and health district protocols.

The care of women with other cardiovascular conditions such as coronary artery disease, cardiomyopathies and aortopathies may also be high risk requiring specialist input but are not covered in these guidelines.

Lastly, this and other guidelines addressing RHD during pregnancy are mostly based on case series and observational studies, often part of broader studies of all-valvular or all-cardiovascular disease. Existing literature on preconception and reproductive health care is predominantly focused on congenital heart disease rather than RHD. Specific research to test the evidence is required to strengthen the rigour of recommendations, better understand the effects of pregnancy and choose the best individualised plan for ongoing care.

Transitional care

Transition to adult reproductive health and preconception care

Planning for adulthood includes reproductive health and preconception care as well as the transition to adult cardiovascular care. Consultations should involve the cardiology (or obstetric physician) and obstetric specialists, primary health team and other disciplines such as the midwife, Aboriginal child and family teams, Aboriginal Health Practitioner or Māori or refugee health workforce support, interpreter (as required) and family members as requested. Other intersectoral collaboration with, for example, school staff (particularly where a girl is at boarding school) may be required to support care plans for adolescents with RHD. All aim for a shared understanding of recommendations, concerns and care plans.

Obstetric and related care can be frightening for some young women. Check their preference of who should attend (partner, parent, health care worker), including if female health staff should conduct the examination.

As with all other RHD care, the transition to adulthood, reproductive health and preconception care considers social as well as clinical context. (See *Jamaya's Story*) Two-way communication between a known primary care provider(s) and specialist(s), accompanied by discussion with the adolescent girl/woman and her team, may be the best way to promote a shared understanding of needs and risks, so informed decisions can be made. This is particularly important where English is a second language and/or there is low health literacy.

Transition to adult cardiovascular care

Collaboration between paediatric and adult cardiovascular care should commence in early adolescence. Primary health services play a crucial role by providing individualised continuity of care and helping to educate both the girl/adolescent/young adult and her family/carer. This will need re-assessment as she matures and reproductive/cardiac health needs change.[18]

It should not be assumed that everything discussed regarding care will be understood and remembered (See *Dee's Story*). There are numerous studies that show women with heart disease display a significant lack of accurate contraception and pregnancy knowledge.[18-21] Taking responsibility for health choices should be encouraged in a scaffolded fashion according to age and maturity level. While there is no known research specifically on the transition to adulthood for adolescent girls with RHD, studies exploring the impact of other chronic diseases,[22] ARF,[23] and congenital heart disease[24] in school-age children all emphasise the need for intersectoral collaboration including mentoring and/or a local support person and school staff as appropriate, in addition to family and health services.[25]

Pregnancy and childbirth in women with RHD need to be considered in the context of the risk that it brings. Care planning should support choices for future potential pregnancy as much as possible, addressing the possible need for cardiac valve surgery and its consequences.

(See *Preconception care and planning, Prosthetic heart valve considerations and Anticoagulation therapy*).

Pre-pregnancy

Contraception and reproductive health

Choosing a contraception method must consider risk and efficacy from a cardiac perspective as well as the usual considerations of reproductive health provision in a safe, respectful environment.[26,27]

All girls, adolescents and women should receive counselling regarding risk and discussion about the optimal timing of pregnancy, to improve the chances of an uncomplicated pregnancy.[28] As for other aspects of care pathways, these conversations should include clinical providers, the Aboriginal Health Practitioner, the adolescent or woman's family and interpreter according to wishes and need. Check with the woman regarding her partner being present: apart from personal preference, Women's Business may preclude partner involvement in discussions. Respect this choice wherever possible with the gender of clinical care providers.

In high-risk girls, adolescents and women who may need future cardiac intervention or surgery, the use of long-acting reversible contraception (Intra-Uterine Contraceptive Device (IUCD) including Mirena or etonogestrel implant such as *Nexplanon*) should be strongly encouraged if there is a risk of pregnancy.[28] Oestrogen-containing contraceptives are associated with a higher risk of thrombosis and should be avoided.[29-31]

High-risk cardiovascular disease requires discussion about the safety of any pregnancy. Tubal ligation may be considered if women agree that they do not wish to have (any more) children. This typically needs several discussions which should not take place in emergency settings.

Anticoagulation requires specific contraceptive and reproductive health considerations. Intramuscular injections can be safely provided if the international normalised ratio (INR) is ≤1.5 (See *Chapter 10. Secondary Prophylaxis, Special considerations; bleeding disorders*). By inference, contraceptive implant insertion is likely also to be safe up to an INR of 1.5 but waiting until the INR has decreased to the recommended reference range is recommended to reduce bleeding and bruising risk. The increased effect of warfarin in the presence of oral contraceptives may require more frequent INR monitoring.[32] The increased risk of bleeding associated with nonsteroidal anti-inflammatory drugs such as Ibuprofen contraindicates its use in dysmenorrhoea or menorrhagia.[32] Tranexamic acid may be used

where other treatments have failed. In severe circumstances of menorrhagia an endometrial ablation may be considered (concomitant contraception will still be required) in women where fertility is not desired or recommended, or family is complete. Refer to a gynaecologist for further discussion of individualised treatment.

Contraceptive choice should also consider living circumstances. Girls and women living remotely in particular may face challenges such as privacy, maintaining hygiene in crowded houses with poorly functioning home health-hardware and access to sanitary products.

Preconception care and planning

The overall aim of preconception care (PCC) is to improve health status and optimise pregnancy outcome through identifying and reducing risk before conception occurs.[33] It addresses the maternal and infant mortality and morbidity that exists disproportionately in marginalised communities: highly relevant for women with RHD.[34] There are few studies specifically on PCC for women with RHD, although there is increasing literature for women with all-cardiovascular disease,[1,34] particularly congenital heart disease.[18] There is a growing suite of educational resources including short films in multiple languages highlighting the impact of RHD for women:[35] helpful for health services as well as women. (See *Jamaya's Story*)

Preconception assessment includes a full history and examination, with functional assessment, a detailed echocardiographic study and possible exercise testing.[1] Check if there are any other health problems that need to be addressed, particularly iron deficiency anaemia or other chronic diseases such as diabetes.[26] Follow up on cervical screening, vaccination status (including influenza), rubella/varicella immunity, folic acid and iodine supplements.[26,36,37]

PCC provides a good opportunity to discuss why a visit to the local health centre or doctor soon after the first missed period and regular antenatal review is so important.[26]

Medication considerations pre-pregnancy

PCC includes consideration of medications not safe in pregnancy and planning for any necessary medication withdrawal or substitution.

Pregnant women with mechanical valves are at a very high risk, as all anticoagulant options carry maternal and/or fetal risks. *(Table 12.2)* (See *Prosthetic heart valve considerations and Anticoagulation therapy*).

Pregnancy planning and risk

If a woman is already symptomatic with moderate or severe RHD, or has asymptomatic clinically significant mitral stenosis (MS), interventional therapy such as Percutaneous Balloon Mitral Valvuloplasty (PBMV) or surgery prior to pregnancy is likely to be required, to avoid the risk of life-threatening complications. Consider and discuss the risks and benefits of options for all surgical interventions, including mechanical prostheses, bioprostheses and repair.[38]

Some women with severe RHD may be advised against becoming pregnant. They need to be able to discuss and make choices about risks associated with pregnancy. Final decision-making lies with women and must be respected, even if it differs from medical advice.[20]

There are few studies on the lived experience of RHD in pregnancy. Fear and vulnerability for women are common themes identified in studies of all-cardiovascular disease in pregnancy.[39] By contrast, a study of Aboriginal women's journeys with RHD in the Northern Territory found that self-care and awareness of the impact of RHD in pregnancy competed with basic concerns such as food security and complex social challenges.[40] Other concerns identified relate to financial burden of disease, fear of abandonment and social stigma.[21] All studies identified the need for responsive, respectful care that supported shared decision-making.

During pregnancy

Antenatal care

Multi-disciplinary care with early antenatal review for women with RHD contributes to the likelihood of safe pregnancy.[1,2,9,10,41-44] However, the type and degree of this care will vary according to individual risk. In high-risk women, multi-disciplinary care is required, including obstetric/obstetric physician, cardiac, neonatology, fetal and anaesthetic specialisations. In contrast, if a thorough assessment indicates low risk, women may be referred to their local hospital for antenatal care and birth. For most women this is a preferred option, preventing the dislocation of birthing long distances away from Country and better supporting a women-focused holistic model of care throughout pregnancy and postpartum.[45]

In many cases, the first point of contact of care will be with the midwife, Aboriginal Health Practitioner, nurse, GPs or other remote primary care provider. These services play a critical role in conducting early reviews in pregnancy and providing continuity of care.

Optimal health care for women with RHD must take place in a secure environment with culturally aware and competent practitioners.[26,40] When available, Aboriginal Mothers and Babies (AMB) health services and other strength-based partnership programs such as the Australian Nurse Family Partnership Program should be offered as an integral part of care. Evaluations of these programs for Aboriginal and Torres Strait Islander women have consistently shown success in improving uptake (and timing) of antenatal care as well as supporting other healthcare interventions.[17,46-52]

Aboriginal Mothers and Babies health services are Australian jurisdiction-based programs where midwives partner with Aboriginal Health Workers and Aboriginal Health Practitioners to provide culturally appropriate holistic support and care throughout pregnancy. They are known by various names across Australia: NSW Aboriginal Maternal Infant Health Services (AMIHS); SA Aboriginal Maternal and Infant Care (AMIC); NT Midwifery Group Practice; QLD Mums and Bubs.

General principles of care and access to services

Is an interpreter needed? In the Northern Territory, where 2-3% of Aboriginal women journey through pregnancy each year with RHD,[53] 42% of residents do not speak English at home.[54] Interpreter services support health service providers to understand women's wishes and informed decision-making by women and their families.

Can the girl/woman hear satisfactorily in conversation? Aboriginal and Torres Strait Islander children experience some of the highest rates of chronic otitis media in the world, with associated risk of hearing loss as an adult.[55]

A dental check and any required treatment for teeth decay or gum disease[56] should be done as early as possible in pregnancy to minimise the risk of bacterial infection.

Continuity of care

Women with multiple co-morbidities interact with many health care providers throughout the course of pregnancy. This can be confusing and frustrating and may impact on quality of care, discharge planning and follow-up.[57,58] As far as possible, continuity of care should include specific known care provider(s) throughout pregnancy and post-partum (See *Alicia's Story*).

Antenatal care that supports the particular needs of rural and remote women in accessing services[11,59] also helps reduce cardiac risk. Remote communities may only have a cardiology team visit once or twice a year. This may affect access to an early cardiology review during pregnancy, without travelling considerable distances. Coordinate investigations/reviews and provide active measures such as appointment reminders and transport, to minimise long-distance travel and assist young women to maintain antenatal contact.[51] The use of telehealth services can facilitate an early cardiology review and timing of further investigations. Prompt clinical communication and handover to all relevant health services throughout pregnancy and post-partum is essential.[53,56,60]

Cardiovascular physiology during pregnancy

The first presentation of RHD may be during pregnancy or in the early post-partum period. A high index of suspicion and early diagnosis, along with appropriate follow-up, are key elements to a successful outcome for mother and child.[18]

Pregnancy is associated with a 40–50% increase in cardiac output and workload which exacerbates pre-existing valvular disease. These haemodynamic changes begin during the first trimester, with continued impact through to post-partum. Systemic blood pressure decreases in first trimester and increases towards pre-gestational levels prior to term. Because of this hyper-dynamic circulation, innocent, soft mid-systolic murmurs are common during pregnancy, particularly along the left sternal border. However, in high-risk populations, all women with a murmur (or regardless of the presence or absence of murmur in some settings) (See *Screening*) should be investigated clinically (e.g. using a six-minute walk test or other assessment of exertional capacity) and with an echocardiogram.

Labour and delivery are associated with significant demands on the cardiovascular system, with pain, anxiety and uterine contractions leading to increased heart rate and blood pressure. With birth, there is a relief of caval pressure and return of circulating volume from uterine contraction to the systemic circulation, with an associated risk of precipitating heart failure post-partum, particularly in the first 24 to 48 hours. Haemodynamics continue to normalise over the following two weeks, reaching normal, non-pregnant levels at up to 24 weeks.

In severe RHD, women often do not achieve the required cardiovascular response to pregnancy, sometimes resulting in a relatively low cardiac output state with significant functional impairment. These are the high-risk patients who may have no cardiovascular reserve to cope with the additional demands of labour, delivery and complications of pregnancy.

Failure to increase cardiac output with advancing pregnancy is also a risk for neonatal events including pre-term birth and low birth weight, neonatal respiratory distress and death.[61]

Screening

There is growing recognition of the importance of early echocardiographic screening of all pregnant women in high-risk populations.[62,63] One cross-sectional study in Eritrea showed a high prevalence of subclinical RHD[64] and a large Ugandan longitudinal study is in progress using existing infrastructure to screen pregnant women and follow outcomes.[65] This study found pre-existing cardiovascular disease (nearly 90% due to RHD which was unknown pre-pregnancy in all but 3% of women) was responsible for a substantial risk of adverse maternal outcomes in low-resource settings.[66]

A cardiovascular risk assessment should be obtained in all pregnant women, with or without symptoms per pregnancy guidelines.[11,18] Attentive history-taking for RHD is required particularly in high-risk populations. While individuals may be unaware of their RHD diagnosis, they may recall regular penicillin injections, previous echocardiograms, prolonged hospital admissions especially with symptoms of ARF, or other family members with ARF/RHD. An echocardiogram should be performed as part of this evaluation in populations at high risk of RHD, with a low threshold for cardiac referral.

Cardiac risk assessment

Appropriate and early antenatal risk assessment helps determine the appropriate level of care that women will require during pregnancy. Available risk prediction scores[1,43] are mostly based on heterogeneous groups of women in pregnancy with congenital and valvular cardiac disease and international registries. The modified World Health Organization classification of maternal cardiovascular risk (mWHO) provides reliable risk assessment and associated recommendations of level of specialist care management required for the pregnancy.[1] The mWHO has been applied in low-resource settings for suspected and known maternal cardiovascular disease with good results.[2]

A retrospective analysis of 95 pregnancy outcomes in 54 women with RHD who were mostly Aboriginal and Torres Strait Islander was undertaken at a regional north Queensland centre.[42] A modified cardiac risk assessment score[67] based on an index developed for mixed-aetiology maternal heart disease was applied. Findings suggested that women with a score of 0 according to this cardiac risk scoring system could safely birth their child in a non-tertiary hospital.[42] Notably, four patients in the study were first diagnosed with RHD after developing acute pulmonary oedema during the peripartum period, emphasising this as an ongoing critical risk period.[42]

Figure 12.1 details the predictors of risk in a pregnant woman with RHD and provides guidance on decision-making regarding birthing from the perspective of maternal and cardiac health.[1,2,42,43,68-70]

Cardiac risk factors must be seen in an overall cardiac context. A prior cardiac event (heart failure, transient ischaemic attack, stroke, arrhythmia) or cardiac medications prior to pregnancy are all predictors of risk. Any degree of reduced left ventricular systolic function in the presence of severe MR carries a high risk of maternal heart failure, morbidity and possible mortality. Similarly, in combined aortic regurgitation AR/MR, the combination of the moderate lesions may be associated with a higher risk of heart failure.

Self-reporting of functional NYHA status may not be reliable. Exercise testing in women may provide additional risk stratification, as can a stress echocardiogram in MR and AR, however its use to predict outcomes in pregnancy is not established.[71]

Women with severe RHD or otherwise assessed as high risk require ongoing review at a tertiary centre with intensive care, obstetric/cardiology and anaesthetic services.

Further risk stratification can be performed with baseline and serial B-type natriuretic peptide (BNP) levels. BNP levels <100 pg/mL at 20 weeks' gestation, or on serial assessment, have been associated with a high negative predictive value for maternal cardiac events.[72,73] However, the haemodynamic changes throughout pregnancy, and BNP levels reflecting one point in time, suggest larger studies are required. Routine access to BNP testing and regular echo services may be difficult outside of major centres.

A pregnant or post-partum woman at higher risk of or diagnosed with RHD who presents with breathlessness, orthopnoea, wheeze or worsening fatigue should be investigated with an echocardiogram.

Risk assessment for women with RHD during pregnancy includes their individual circumstances, preference of where to give birth, engagement with medical services, adherence with medical therapies, co-morbidities and access to services as well as the degree of severity of RHD. It takes account of non-clinical factors as well as other co-morbidities. Barclay *et al*, in their assessment of risk related to pregnancy and childbirth in rural and remote Australia, suggest that social (cultural, social and financial) risks can exacerbate clinical factors and compound overall risk.[73] An extended definition has been proposed that considers the full range of risks and their interaction, and recognises the importance of Birthing on Country.[14,16,74]

Birthing on Country - why it matters for women with RHD

Birthing on Country addresses the integral connection between birthing, land (country) and place of belonging for Aboriginal and Torres Strait Islander women. The term is often not well understood. The Birthing on Country position statement describes it as '...a metaphor for the best start in life for Aboriginal and Torres Strait Islander babies and their families' which provides an appropriate transition to motherhood and parenting, and an integrated, holistic and culturally appropriate model of care for all.[13]

Birthing on Country models can be described as maternity services that are designed, developed, delivered and evaluated with and for Aboriginal and Torres Strait Islander women that encompass the following:

- community based and governed;
- provide for inclusion of traditional practices;
- involve connections with land and country;
- incorporate a holistic definition of health;
- value Aboriginal and/or Torres Strait Islander as well as other ways of knowing and learning; and
- encompass risk assessment and service delivery and are culturally competent.

These principles underpin care pathways that promote optimal outcomes for women with RHD and their babies and should be incorporated into all aspects of care.

Birthing on Country models can be incorporated into any setting,[13] including urban as well as regional and remote Australia.

Termination of pregnancy

Termination of pregnancy (TOP) may occur according to a woman's preference or if medically indicated such Level III or IV RHD in pregnancy severity *(Figure 12.1)*. The choice of medical versus surgical TOP will depend on gestation, the woman's choice, her cardiac condition and operator experience. Both medical and surgical procedures are effective, with similar rates of major complications in women with cardiovascular disease.[1,75,76] The greater need for unanticipated intervention favours the surgical approach in high-risk women.[1]

Provide the termination service as close to home as possible, with known health care providers who can provide continuity of care. Financial costs can be a significant barrier where only private clinics are available, requiring long distance travel to the closest centre. If medical termination is chosen, close observation and back-up expertise is essential should a failed medical abortion require subsequent surgical intervention.

High-risk patients should receive care in a tertiary centre. Refer to cardiac guidelines,[1] jurisdictional/hospital abortion guidelines/legislation and recommendations.[26,77] In most Australian states and territories, the same laws governing consent and confidentiality will apply in the case of a young woman seeking termination, as with any other form of health care. Check where parental/guardian consent or court order may be required.[26,78-80]

Termination of pregnancy may be emotionally traumatic, particularly where it is medically advised. An individualised approach is guided by the same principles of care as in pregnancy to support decision-making.[77] Consider additional support that may be required, such as accommodation, childcare, transport and pre/post-abortion counselling, which would involve recommendations for surgery and discussions about contraception and future pregnancy risk.

Specific cardiac valve lesions and complications

Mitral/aortic regurgitation

Single lesion mild/MR and AR are generally well tolerated during pregnancy.[1,81] The increase in blood volume and cardiac output in pregnancy increases left ventricular (LV) volume overload but the decrease in systemic vascular resistance partly compensates for this. However, combined rheumatic aortic and mitral disease as well as mixed valve disease may be under-represented in studies, and an individual approach to pregnancy risk must always be considered.

Mitral stenosis

Mitral stenosis (MS) that is asymptomatic before pregnancy may be poorly tolerated in pregnancy because the fixed stenotic mitral valve limits the required increase in cardiac output of advancing pregnancy. Mild MS may be well tolerated but a decline in functional class and development of heart failure has been reported in up to 15% of women.[82,83] Women diagnosed or presenting late in pregnancy have an increased risk of complications.[9,84] Women with moderate or severe MS often show a functional deterioration in pregnancy which will require treatment.

A pre-pregnancy functional status of NYHA >1 is an independent predictor for adverse events but women with MS are often asymptomatic until faced with the increased cardiac work of pregnancy.[83] A reduction in functional state is often gradual so the first diagnosis of MS in pregnancy may be with severe symptoms including acute heart failure. Mitral valve area (MVA) by accurate planimetry is used as the reference value in determining severity, as it is independent of cardiac output, which increases in pregnancy along with increased mitral valve gradient.

In patients with mild or moderate symptoms during pregnancy, medical therapy with beta blockers and diuretics may be sufficient. The development of atrial fibrillation (AF) with rapid ventricular rates may precipitate acute heart failure, requiring emergency treatment, including use of beta blockers for rate control. Digoxin can be added to beta-blocker therapy for rate control in AF if required.[1] In patients with severe MS, the prophylactic use of beta blockers should be considered to reduce the risk of rapid ventricular rates if AF develops.[38,85]

Consider PBMV prior to pregnancy for women with moderate-severe MS (orifice area <1.5 cm2), even if asymptomatic or mildly symptomatic.

There are very high rates of heart failure (up to 50%) in women with severe MS which can persist post-partum, with significant risks of acute pulmonary oedema, atrial arrhythmias, stroke or need for intervention during pregnancy, as well as fetal risks.[83]

Indications for PBMV during pregnancy include NYHA class III or IV symptoms (despite medical therapy), MVA <1–1.5 cm^2, suitable valve characteristics[86] and no atrial thrombus.[87-89] The exact timing of the procedure requires a multi-disciplinary team consultation.[89,90]

There is a small risk of traumatic MR resulting from PBMV, however this can usually be managed medically, without the need for surgery until after pregnancy. The haemodynamic effects of lesions as well as functional status should guide risk stratification and medical therapies.

Atrial fibrillation in mitral stenosis

AF is poorly tolerated in MS and associated with a very high risk of atrial thrombus, requiring anticoagulation (See *Anticoagulation therapy*) as well as rate control. Anticoagulation also may be considered for women in sinus rhythm with very severe left atrial dilatation, spontaneous echo contrast on echo, or heart failure, as the risks of AF and thrombus formation are much higher. Beta blockers are recommended as first-line therapy for rate control. Digoxin may be added for additional rate control if required.[85,91] Higher than standard digoxin doses may be needed due to protein binding. Beta blockers have been well studied in pregnancy and are considered relatively safe *(Table 12.2)*.[92]

Direct current cardioversion should be used to restore sinus rhythm when the tachy-arrhythmia is causing cardiac symptoms and haemodynamic instability.[85,91] Trans-oesophageal echocardiogram (TOE) directed cardioversion should be used as per current guideline, considering anaesthetic risk and likelihood of success.

Aortic stenosis

Isolated severe rheumatic aortic stenosis (AS) is rare. It may be seen with bioprosthetic valve degeneration and is associated with a significant risk of adverse maternal and fetal outcomes.[43] Heart failure can occur during pregnancy in initially asymptomatic women but is more common in those with pre-pregnancy symptoms. Severe AS is associated with low birth weight and higher rates of caesarean sections.[93]

In asymptomatic women with AS, exercise testing is recommended to assess functional status and haemodynamic response preferably before pregnancy, or in early pregnancy. An abnormal blood pressure response to stress is associated with an increase in cardiac events and poor prognosis.[38]

Aortic valve area is the preferred measure of AS grade in combination with aortic valve gradient, as the increased cardiac output that occurs during pregnancy is associated with increased aortic gradients.[93,94]

Tricuspid regurgitation

Tricuspid regurgitation (TR) is usually secondary to left heart valvular disease in RHD and may be associated with pulmonary hypertension. Severe TR with right ventricular dysfunction may be associated with heart failure and atrial arrhythmias in pregnancy. It can usually be managed with diuretic therapy alone, with management directed as appropriate for left heart disease, and surgery performed at the time of aortic or mitral surgery pre- or post-partum.

Left ventricular systolic dysfunction

In RHD, the impact of impaired left ventricular (LV) function is variable according to the valve lesion. In women with severe MR, hyperdynamic systolic function (high ejection fraction (EF)) is expected. An LVEF <60% in these patients is a sign of LV decompensation and may be poorly tolerated.

In general, an LVEF <30% or reduced systolic function with NYHA class III/IV symptoms is associated with a high risk of maternal morbidity and possible mortality, and pregnancy is strongly discouraged.[67,95] In contrast, mild LV systolic dysfunction has a better prognosis.

Heart failure medications

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), and ivabradine are all contraindicated in pregnancy and should be stopped as soon as pregnancy is confirmed.

Hydralazine and nitrates may be used as alternative agents in the absence of ACE inhibitors/ARBs. Loop diuretics are given for clinical evidence of heart failure, with cautious monitoring due to risks of reduction in placental blood flow. Beta blockers should be continued or introduced once the patient is euvolemic.

Post-partum, all heart failure therapies should be re-introduced *(Table 12.2)*. Safety in lactation advice is shown in *Table 12.2*.

Pulmonary hypertension

Idiopathic pulmonary arterial hypertension is known to be associated with high rates of morbidity and mortality in pregnancy. There are few data available on pulmonary hypertension (PH) secondary to left heart disease in pregnancy. Hospitalisation, frequently due to heart failure, is common in women with significant pulmonary hypertension (>50 mmHg) secondary to left heart disease. Heart failure often occurs late in the second trimester, early third trimester or in the post-partum period due to the changing haemodynamic demands[70] Emergency caesarean-section rates and rates of early delivery are higher.[96] Outcomes with mild pulmonary hypertension (pulmonary artery systolic pressure <45-50 mmHg) are better than those with moderate, or severe (pulmonary artery systolic pressure >50 mmHg). Morbidity increases with worsening symptoms and severity of pulmonary hypertension.

Ergometrine and prostaglandin F analogues are contraindicated in pulmonary hypertension due to the effects of pulmonary vasoconstriction.[97]

Other cardiac risk

Pre-eclampsia in women with RHD is a medical emergency. The associated vasoconstriction, hypertension and pulmonary oedema which can occur exacerbates valvular heart disease and is associated with a significantly increased risk of heart failure.[70]

Prosthetic heart valve considerations

The choice of valve prosthesis in adolescents and women requires careful judgement of the need for later reoperation and associated mortality and morbidity risks. While a mechanical heart valve is extremely durable, these valves require lifelong anticoagulation with vitamin K antagonists (VKA) warfarin, which may potentially harm the fetus.

Tissue or bioprosthetic valves have the major advantage of not requiring anticoagulation if the patient is in sinus rhythm. However, bioprosthetic valve replacement inevitably leads to reoperation later in life because of structural valve degeneration (SVD). This may occur as early as two to three years after the initial valve replacement and has been reported as high as 50% of people at 10 years and in 90% at 15 years.[98] Higher rates of deterioration occur in the mitral position compared with aortic or tricuspid bioprosthetic valve replacement.[99] Due to the higher rate of SVD in young people, annual review with echocardiography is recommended. While some reports had originally suggested a more rapid deterioration of bioprostheses following pregnancy, this was not seen in other studies,100 and is confounded by a younger population at higher risk for SVD.[99]

Most women with normally functioning bioprosthetic valves tolerate the haemodynamic changes of pregnancy well, in the absence of other significant risk factors. However, heart failure or atrial arrhythmias may develop, especially if the LV function is impaired or there is significant left atrial dilatation.

Anticoagulation therapy

Anticoagulation is required for all girls and women with mechanical prosthetic valves, and may be required with atrial fibrillation, depending on thromboembolic risk.

Pregnant women with mechanical heart valves are a very high-risk group, in whom all anticoagulation options carry significant maternal and/or fetal risks (WHO risk classification III). The choice of anticoagulation involves balancing those risks *(Table 12.2)*.

Fetal risk with warfarin

Warfarin embryopathy is characterised by nasal or mid-facial hypoplasia and epiphyseal stippling leading to limb deformities. The risk of embryopathy beyond six weeks' gestation is approximately 5-8%,[101,102] although higher rates have been reported.[103,104] Warfarin fetopathy due to use of this agent in the second and third trimesters can cause bleeding in an over-anticoagulated fetus, leading to stillbirth or neurological conditions such as optic atrophy and intracranial haemorrhage.

A dose-dependent effect of warfarin on rates of embryopathy has not been established but fetal loss and stillbirth escalate with increasing doses of warfarin during pregnancy.[1,104-107] Fetal risks were similar with low dose (<5 mg daily) warfarin to those of women taking Low molecular weight heparin (LMWH) throughout pregnancy.[105,108]

Despite these recommendations, it is important to counsel the woman that there is no safe dose of warfarin;[106,107,109] however, there is clear maternal benefit with lower thromboembolic events[1,102] than LMWH.

Be aware that many women know that warfarin can have adverse effects in their unborn child and may not take it during pregnancy.

Taking no anticoagulant in pregnancy poses the highest risk to a woman and her infant.

Use of low molecular weight heparin

LMWH is associated with significantly better fetal outcomes (up to 95% live birth rates),[102,110] at the expense of increased maternal thromboembolic complications. All women on LMWH should have access to facilities to monitor anti-Xa levels and expertise for dose adjustment[56] given complications seen with sub-therapeutic levels.

LMWH is administered subcutaneously every 12 hours with anti-Xa monitoring. In pregnancy, an initial dose of 1 mg/kg twice daily is recommended; however, the dose must be adjusted to maintain a trough (pre-dose) anti-Xa level of 0.6-0.7 U/mL. Peak levels 3-4 hours post-dose should be 1.0–1.2 U/mL and should not exceed 1.5 U/mL. Both peak and trough levels should be performed, as therapeutic peak anti-Xa levels do not guarantee therapeutic trough levels, leading to thrombotic events.[111-114]

LMWH dose changes, guided by anti-Xa levels, are usually required in pregnancy[111,114] in response to physiological changes. Weight-based dosing alone without monitoring will lead to insufficient anticoagulation.[113] Where dose adjustments are required, increase or decrease by increments of 10 mg twice daily. Monitor peak and trough anti-Xa levels every three days until in the appropriate range and stable. The subsequent frequency of monitoring should be guided by the treating physician, but monthly testing would be the recommended minimum.

Sequential treatment with LMWH use in first trimester to avoid risks of warfarin embryopathy, followed by VKA/warfarin treatment in second and third trimesters to provide the best maternal protection, is often used and is outlined below.

Aspirin

Low-dose aspirin is recommended in combination with anticoagulation in mechanical prostheses.[94,115-118]

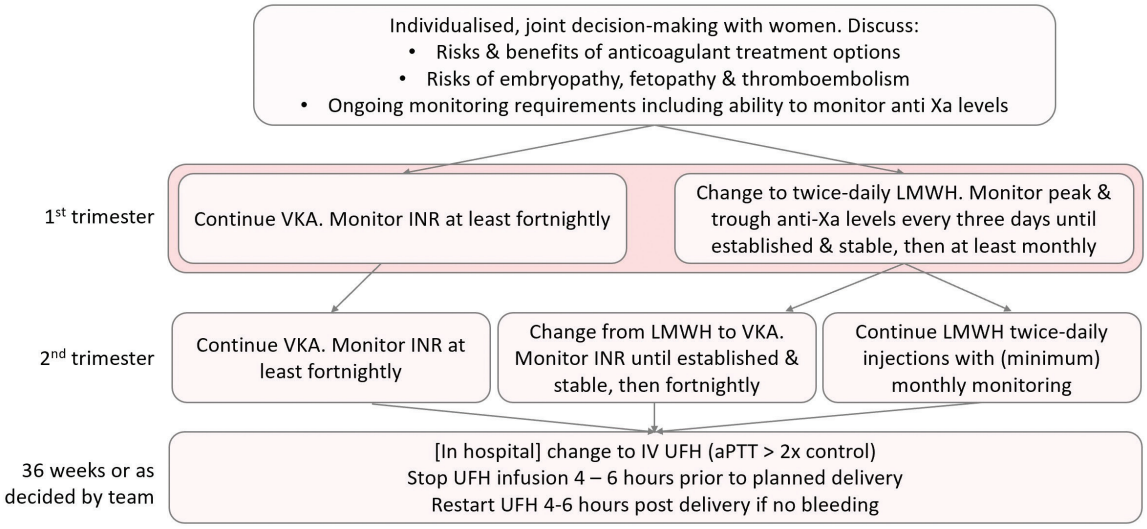
Direct Oral Anticoagulants (rivaroxaban, dabigatran, apixaban) should not be used for anticoagulation in any patient with mechanical prosthetic valves.

Clinical recommendations for anticoagulation in pregnancy

There are limited good-quality studies available on anticoagulant options, and no randomised comparative studies have been (or are likely to be) performed. Literature reviews have been undertaken to provide best practice guidance.[102,105,106,119,120] There is a choice of three recommended anticoagulant regimens during pregnancy for patients with mechanical prostheses (Level of Evidence GRADE 2C): *(Figure 12.2)*

1. Low molecular weight heparin (LMWH, enoxaparin) throughout pregnancy
2. LMWH in first trimester; warfarin (Vitamin K antagonist – VKA) in second and third trimesters; peripartum switch to LMWH/ unfractionated heparin (UFH)
3. Warfarin throughout pregnancy.

Figure 12.2. Anticoagulation pathways for pregnant women on Vitamin K antagonist (VKA) regimen



VKA: Vitamin K antagonist (eg Warfarin, Acenocoumarol); LMWH (Low Molecular Weight Heparin); UFH (Unfractionated heparin)

Balancing risk

Balancing maternal and fetal risks and individualising the preferred method of anticoagulation is best done by a team with expertise in prosthetic valve and anticoagulation management in pregnancy.[109] This risk is compounded by gaps in expert care and variable anticoagulant monitoring. Each management strategy should be discussed with the woman so that she can make a truly informed choice, including the option of not continuing the pregnancy or alternatively, risking personal health in favour of the child.

Early involvement of an anaesthetist concerning anticoagulation decisions is essential, since there are formal obstetric anaesthesia guidelines that determine the timing of cessation and recommencement of anticoagulation when regional anaesthetic techniques are used in labour, especially epidural analgesia.

Once a joint treatment plan on anticoagulation has been decided, close clinical follow-up and a birth plan are essential.[102] There is an increased risk for thrombotic complications transitioning between different anticoagulant therapies, and strict monitoring of all therapies is required. Irrespective of the anticoagulation regimen chosen, the highest risk of maternal events and poor outcomes relates to sub-therapeutic anticoagulation.

Any woman requiring anticoagulation should have access to routine and appropriate monitoring of anticoagulation as close to home as possible, including point-of-care monitoring for patients in rural and remote settings.[56] Where this is not available, early referral to a centre with expertise for review is essential.

Vaginal delivery is recommended for anticoagulated women in the absence of obstetric indications if there is no significant prosthetic valve dysfunction or other significant cardiac indication. If caesarean delivery is necessary for fetal or maternal indications, care is required with post-partum anticoagulant management.

Mechanical valve thrombosis

Mechanical valve thrombosis is a life-threatening complication of inadequate anticoagulation in pregnancy. It usually results in varying degrees of valve obstruction, with or without regurgitation, with consequent heart failure, arrhythmias, shock and/or embolisation such as stroke. It is a medical emergency and if suspected, patients need immediate transfer to a centre that can at a minimum provide TOE guided thrombolysis, or if required, cardiac surgery. The most experience is with fibrinolytic treatment with tPA (Alteplase), traditionally given as an infusion of 50-100 mg over five hours,[121] however smaller doses of 25 mg over five hours can be effective if bleeding risk is high and have been reported in pregnant populations.[122] If there is a very high bleeding risk and the patient is NYHA class I or II, consider a heparin infusion at therapeutic dose with further management guided by haemodynamic stability and imaging findings. Streptokinase is not considered as effective in populations where there is endemic streptococcal infection.[123,124] Follow-up transthoracic echo is usually adequate in assessing valve recovery. Further thrombolysis dosing can be used if valve function has not normalised (Level of Evidence GRADE 1C) and if the benefit is thought to outweigh the risk after clinical assessment and detailed imaging. Ongoing therapeutic anticoagulation is essential, with review of the previous regime. The risk of thromboembolic events, major bleeding and re-thrombosis are important considerations and management decisions should be made by a multi-disciplinary team.

Cardiac surgery during pregnancy

When medical management during pregnancy fails, options are early delivery (beyond 28 weeks gestation) or surgical intervention during pregnancy (which is associated with increased risk of fetal loss).

Rarely, very severe maternal cardiac valvular disease cannot be managed by medical therapy alone and early delivery is required if the fetus is viable, to allow optimal maternal management and relief from the haemodynamic demands of pregnancy. Cardiac surgery during pregnancy is recommended when medical therapies or interventional procedures fail and there is a risk to the mother's life. It is associated with a high risk of fetal loss (~20%) and morbidity, including late developmental delays in the child. The decision must be made on an individual basis in consultation with relevant specialists in centres with expertise. Beyond 28 weeks' gestation, delivery before surgery should be considered.[1,125,126]

Other drugs in pregnancy and lactation

Safety of all prescribed pharmaceuticals in pregnancy and lactations needs close attention *(Table 12.2)*. Breastfeeding should be encouraged to promote better long-term health for infant and mother, and facilitate bonding. There can be variations in safety between cardiac drugs of the same class. Medications where there is greater experience in pregnancy are noted in the relevant sections in this chapter (See *Heart failure medications and Medications to treat post-partum haemorrhage*). Refer to the usual resources for comprehensive detail before prescribing during pregnancy and lactation. There are also several online resources for reviewing safety and use, as well as pregnancy guidelines and reviews.[1,127]

Infant Risk Centre (Texas Tech University Health Sciences Centre)
The Australian categorisation system for prescribing medicines in pregnancy (Therapeutic Goods Administration)
Drugs and lactation database (LacMed, National Institutes of Health)
Drug safety in lactation (MEDAFE, New Zealand Medicines and Medical Devices Safety Authority)

Secondary prophylaxis (BPG injections, oral penicillin and erythromycin) are safe during pregnancy and breastfeeding, and should continue if indicated (Level of Evidence Grade 1A). The importance of continuing secondary prophylaxis during a time of higher risk should be discussed with the woman and her family prior to a planned pregnancy, or as soon as possible during an unplanned pregnancy.

Labour, birth and the post-partum period

Method of birth

Vaginal birth is associated with less blood loss, lower risk of infection, less venous thromboembolic complications and is advised for most women with RHD.[1] In most patients with heart failure controlled with medication, vaginal delivery is recommended if obstetric factors are favourable, with adequate heart rate control and analgesia.[84] A caesarean section is usually recommended for women on oral anticoagulant therapy presenting in pre-term labour, or those with high-risk aortopathies, severe heart failure or severe pulmonary hypertension**.** However, individual management approaches are determined by the multi-disciplinary team. Maternal deterioration with failure to respond to medical therapies may require premature delivery for maternal safety.[1]

During labour, cardiac output increases as heart rate and blood pressure rise. An inability to increase cardiac output secondary to moderate/severe RHD (particularly obstructive left sided lesions) may lead to pulmonary oedema. Early epidural administration will help minimise tachycardia, by limiting pain and hypertensive responses that may precipitate heart failure.

The increased systemic vascular resistance and venous return with labour and birth often necessitate the use of diuretic therapy in women with significant valvular disease. Peri-delivery and post-partum care in an intensive-care setting may be required for high-risk women.

Infective endocarditis prophylaxis

Currently, there is insufficient evidence to recommend extra antibiotic prophylaxis against endocarditis during vaginal delivery or caesarean section in addition to the standard antibiotics recommended in Therapeutic Guidelines: Antibiotic for surgical prophylaxis for caesarean section or for prolonged labour or premature rupture of the membranes.[1,128,129]

Medications to treat post-partum haemorrhage

Oxytocin and carbetocin can cause vasodilatation, resulting in hypotension and reflex tachycardia and has been associated with coronary vasoconstriction. Cautious use including limiting boluses and using a continuous slow infusion is generally tolerated.

Ergometrine, an α-adrenergic receptor agonist, may cause coronary vasospasm, pulmonary vasoconstriction and hypertension. Depending on the severity of RHD, it should be avoided, particularly if the woman has pulmonary hypertension.

Carboprost, a smooth muscle contractor, should be avoided. It may cause hypertension, increased pulmonary vascular resistance and severe bronchospasm in asthmatics. Misoprostol, a prostaglandin E1 analogue, is better tolerated.[127]

In general anaesthesia, eliminating or reducing volatile anaesthetic use and converting to intravenous anaesthesia can remove the negative effect of volatiles on uterine tone.

Calcium gluconate or chloride supplementation will increase uterine tone and is often required to offset citrate effects with blood product administration, however, observe caution with transient cardiac and vascular effects if administered as a bolus.

Management strategies must be balanced against maternal risk and life-threatening bleeding.

Pre-discharge

Discharge plan

Review the discharge plan with the woman (and partner/family as wished), including treatment, medication, future management plans and future conception planning. Ensure that discussions are culturally sensitive, empowering and are in the patient's first language.

Conception planning

Discussion with women regarding cardiovascular health, future pregnancy risk and inter-pregnancy planning should take place before discharge and followed up in the primary health setting. A minimum interval of 24 months until attempting a subsequent pregnancy is normally recommended.[130,131] (See *Alicia's Story and Jamaya's Story*)

A shared understanding about risk and preference promotes informed decisions about pregnancy planning and contraception. Long-acting reversible contraception can be inserted prior to discharge, after discussion with the woman (See *Contraception and reproductive health*).

RHD Register and secondary prophylaxis

Check the woman is on the RHD Register in relevant jurisdictions and confirm the date for her next secondary prophylaxis dose (if applicable). Where a mother has RHD, her children will often have an increased risk of ARF/RHD.

Post-discharge

A vital aspect of preconception care is the post-partum and inter-pregnancy periods. High-risk women should be referred to tertiary care centres with required expertise.[132]

Early involvement of primary care services is crucial to ensure a smooth transition post-partum.[18] Information about the woman's treatment, medication, future management plans and conception planning should reach her specialist and primary care provider(s) including Aboriginal Mothers and Babies health services and referring hospital (where relevant) within 48 hours of discharge.[56] This will include clear information regarding RHD diagnosis, treatments and interventions, pregnancy and birth, routine recall plans and specific information about non-routine care requirements.[53,60] All women without a designated GP or primary care provider should be integrated into a community program for home- or centre-based therapy and education following hospital discharge and be assisted to access appropriate primary care services.[56]

DRUGS	CLASSIFICATION	AUSTRALIAN CLASSIFICATION	PLACENTA PERMEABLE	BREASTMILK EXCRETION	CLINICAL USE
Anticoagulation (See also Clinical recommendations for anticoagulation in pregnancy)					
Warfarin	Vitamin K antagonist	D	Yes	Yes	**Pregnancy: *Fetal risk.*** Relatively contraindicated. Associated with embryopathy (1st trimester exposure) and fetopathy (second and third trimester use), fetal bleeding, fetal loss. **Breastfeeding:** considered safe. Very low levels expressed in breastmilk.
Low molecular weight heparin	Heparin	C	No	No	**Pregnancy: *Maternal risk***. Increased maternal thromboembolic risk. Considered safe to fetus. **Breastfeeding:** Considered safe.
Unfractionated heparin	Heparin	C	No	No	Refer to *Clinical recommendations for anticoagulation in pregnancy* section
Aspirin	Antiplatelet	C	Yes	Yes	**Pregnancy:** Low dose recommended (75-100 mg). Higher doses associated with bleeding, premature closure of patent ductus arteriosus teratogenicity. **Breastfeeding:** Low-dose aspirin considered safe.
Thrombolytics		B1/C	Yes	Yes	**Pregnancy: *Fetal risk.*** Relatively contraindicated, with use limited to life-threatening risk to mother and per prosthetic valve management guidelines.
Rivaroxaban, dabigatran, apixaban	Non-vitamin K antagonist oral anticoagulants (NOACs)	C	Yes	Yes	**Pregnancy:** Contraindicated **Breastfeeding:** Contraindicated
Antihypertensives and antiarrhythmics; Diuretics					
Metoprolol	Beta blocker (ß1 selective)	C	Yes	Yes	**Pregnancy:** Preferred beta blocker. Relative safety. Class effect of fetal bradycardia, intrauterine growth restriction (IUGR), hypoglycaemia. Increased pregnancy dose frequently required. **Breastfeeding:** Minimal excretion in breastmilk, undetectable levels in neonate.

Table 12.2. Medications in pregnancy and lactation (continued)

DRUGS	CLASSIFICATION	AUSTRALIAN CLASSIFICATION	PLACENTA PERMEABLE	BREASTMILK EXCRETION	CLINICAL USE
Labetalol	ß/ß blocker	C	Yes	Yes	**Pregnancy:** Extensive experience in pregnancy, however displays similar class effects with feta bradycardia, hypoglycaemia & IUGR. **Breastfeeding:** Low levels expressed in breastmilk.
Bisoprolol	Beta blocker (ß1 selective)	C	Yes	Yes	**Pregnancy:** Class effect risks of fetal bradycardia, hypoglycaemia. **Breastfeeding:** Appears safe for use in breastfeeding in small studies.
Carvedilol	Beta blocker	C	Yes	Yes	**Pregnancy:** No human data available. Preference for alternative beta blockers e.g. Metoprolol. **Breastfeeding**: Increased mortality in animal studies, inadequate human data. Other beta blockers preferred.
Atenolol	Beta blocker	C	Yes	Yes	**Pregnancy:** ***Fetal risk.*** Associated with higher rates of IUGR and possible birth defects. Alternative beta blockers recommended. **Breastfeeding:** Recommendation to avoid in breastfeeding if alternative agents available.
Ivabradine	If channel blocker	D	Yes	Yes	**Pregnancy:** ***Fetal risk.*** Inadequate human data. Teratogenic in animal studies. **Breastfeeding:** Inadequate human data. Contraindicated.
Sotalol	Antiarrhythmic	B	Yes	Yes	**Pregnancy:** Bradycardia and hypoglycaemia. **Breastfeeding:** Extensive excretion in breastmilk, avoid where possible.
Amiodarone	Antiarrhythmic (class III)	D	Yes	Yes	**Pregnancy:** ***Fetal risk.*** Relatively contraindicated in pregnancy as can cause fetal thyroid, mild neurological and congenital abnormalities. Use if maternal life-threatening arrhythmias cannot be treated with alternative agents. **Breastfeeding:** Expressed in breastmilk in unpredictable levels, breastfeeding not recommended.[127,133]
Flecainide	Antiarrhythmic (class IC)	B3	Yes	Yes	**Pregnancy:** Appears safe in small studies. **Breastfeeding:** Limited data. Clinically insignificant breastmilk levels <200 mg.

Table 12.2. Medications in pregnancy and lactation (continued)

DRUGS	CLASSIFICATION	AUSTRALIAN CLASSIFICATION	PLACENTA PERMEABLE	BREASTMILK EXCRETION	CLINICAL USE
Diltiazem	*Calcium channel blocker*	*C*	*Yes*	*Yes*	**Pregnancy:** ***Fetal risk.*** Teratogenic in animal studies. **Breastfeeding:** Limited data, low levels expressed in breastmilk.
Verapamil	*Calcium channel blocker*	*C*	*Yes*	*Yes*	**Pregnancy:** Limited data. Appears relatively safe. Recommended as second- line treatment if beta blockers fail or not tolerated. **Breastfeeding:** Limited data, not associated with adverse outcomes.
Digoxin	*Cardiac glycoside*	*A*	*Yes*	*Yes*	**Pregnancy:** Appears safe in pregnancy, however digoxin intoxication associated with fetal death. Digoxin serum levels in pregnancy not reliable. **Breastfeeding:** Low levels expressed in breastmilk.
ACE inhibitors; Angiotensin receptor blockers or neprilysin inhibitors	*ACE inhibitors; Angiotensin receptor blockers or neprilysin inhibitors*	*D*	*Yes*	*Yes*	**Pregnancy:** ***Contraindicated. Fetal risk.*** Associated with renal tubular dysplasia, IUGR, lung hypoplasia, oligohydramnios, skull ossification disorders, joint abnormalities, fetal death. **Breastfeeding:** Enalapril and captopril assessed in small studies: considered safe. Others not well studied.
Frusemide	Loop diuretic	C	Yes	Yes	**Pregnancy:** ***Fetal and neonatal risk.*** Associated with oligohydramnios, electrolyte imbalance. Lowest dose for clinical effect recommended. **Breastfeeding:** Safe. Milk production can be reduced.
Spironolactone Eplerenone	Aldosterone antagonist	D	Yes	Yes	**Pregnancy:** ***Fetal risk.*** Contraindicated in pregnancy: congenital and antiandrogen effects. **Breastfeeding:** Very low levels expressed in breastfeeding, limited data suggest safety.
Secondary prophylaxis					
Benzathine benzylpenicillin G (BPG)	Antibiotic	AB	Yes	Yes	**Pregnancy:** No adverse fetal effects reported. Continue injections every 3-4 weeks as prescribed. **Breastfeeding:** Considered safe.
Erythromycin	*Antibiotic: oral substitute for BPG*	*AB*	*Yes*	*Yes*	**Pregnancy:** No fetal adverse effects reported. Continue regimen as prescribed. **Breastfeeding:** Considered safe.

Australian classification for medicines in pregnancy

A: Drugs which have been taken by a large number of pregnant women without proven increase in frequency of malformations or harmful effects on the fetus observed. **B1:** Drugs which have been taken by only a limited number of women without an increase in the frequency of malformations or harmful effects on the fetus observed. **B2:** Drugs which have been taken by only a limited number of pregnant women without an increase in the frequency of malformations or harmful effects on the fetus observed, and animal studies are inadequate or lacking. **B3:** As previous but studies in animals show an increased occurrence of fetal damage, the significance of which is uncertain in humans. **C:** Drugs which, owing to their pharmacological effects, have cause or are suspected of causing harmful effects on the human fetus or neonate without causing malformations. **D:** Drugs which have caused, or are suspected to have caused, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. **X:** Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.[134]

CASE STUDIES

These stories highlight principles of care. Names and details have been changed.

Alicia's Story

Background: Alicia is a 28-year-old Wiradjuri woman first diagnosed with RHD 33 weeks into her second pregnancy after presenting in heart failure with severe rheumatic mitral stenosis and pulmonary hypertension. She and her baby survived and subsequently moved to a different Local Health District with no cardiac or post-partum follow-up and no access to existing medical information after discharge.

Pregnancy: Alicia was not well in her next (third) pregnancy. She attended the local Emergency Department via ambulance a few times from 29 weeks' gestation with shortness of breath, wheeze and tiredness. She was treated for asthma and a respiratory infection and then went home.

At 32 weeks' gestation, Alicia had a home visit from the Aboriginal Mothers and Babies (AMB) team, who found her extremely short of breath with pitting oedema and a moist audible wheeze. This time she agreed to hospital admission. Midwife concerns that Alicia's symptoms could be cardiac-related were followed by a physician review that confirmed Alicia was again in heart failure caused by RHD. She was transferred to a tertiary centre at 34 weeks and treated for severe pulmonary oedema. At 36 weeks' gestation, Alicia had a premature vaginal birth. Her premature baby was admitted to neonatal intensive care with an Apgar of 7. Alicia and baby were discharged home with follow-up by the AMB team. Before discharge, after discussion between Alicia, obstetrician, cardiologist and AMB team, Alicia had *Nexplanon* inserted.

Discussion: It is common for some Aboriginal women to move between communities, regions and hospitals, making their pregnancy journey more difficult, particularly if important medical information is missed. Alicia's RHD was not picked up despite it being diagnosed in a previous pregnancy. There were gaps in clinical communication and assessment. The journey is also complicated by women moving between Aboriginal Community Controlled Services and mainstream services.

Electronic information about the woman's diagnosis, treatment, medication and future management plans should reach the patient's primary care provider(s) and referring hospital (where appropriate) within 48 hours of discharge. The clinical communication must include clear information regarding RHD diagnosis, recall plans and care requirements with access between health districts and sites. Consider a medical bracelet or wallet card with RHD alert and key points related to care routine.

Encourage health providers to maintain a high degree of suspicion of cardiac disease, where there is persistent or worsening breathlessness, tiredness and/or wheeze in pregnancy.

Alicia's children will be at higher risk of Strep A infection and ARF. Discuss this with the mother and about working with her children's health services.

Alicia did not engage with maternity or cardiac services. Could earlier involvement with the Aboriginal Mothers and Babies team have made a difference? Wherever available and relevant, offer and actively refer to specific antenatal programs and services for Aboriginal and Torres Strait Islander women; these improve early antenatal care uptake. If this is not available, promote the local Aboriginal Medical Service with an Aboriginal Health Worker or Aboriginal Health Practitioner as part of the woman's care pathway.

Dee's Story

Background: Twenty-four-year-old Dee lives in a remote community in northern Australia. She speaks Kriol, with English as a second language. Dee had a mechanical valve replacement at 13 years of age after being diagnosed with severe rheumatic mitral stenosis and now takes warfarin anticoagulation ≤5 mg). After being away from community for a few weeks without medication, Dee took double her dose for a few days 'to catch up'. Dee's most recent echo was three years ago.

Pregnancy: After her first pregnancy with Codie (now six years old), Dee believed she couldn't get pregnant again because of her cardiac disease. However, for about a month Dee *felt* pregnant and recently noticed a small vaginal blood loss. The obstetrician who cared for Dee during her first pregnancy was in town, so Dee visited the clinic. Urine and blood tests confirmed a pregnancy - estimated at 22 weeks' gestation. Dee was surprised. *"I didn't think I could get pregnant,"* she said. *"I was told that I couldn't get pregnant because of that RHD."*

The obstetrician consulted with a cardiac colleague and Dee was flown to the nearest tertiary centre for urgent cardiac review, echocardiogram and fetal ultrasound. Her INR blood clotting times) was 3 ± 0.4.

The fetal ultrasound suggested nasal hypoplasia consistent with warfarin embryopathy. Dee's vaginal blood loss increased. Sadly, she gave birth to a stillborn baby with warfarin-induced fetal intracranial haemorrhage.

Discussion: Anticoagulation in pregnancy carries high maternal and fetal risk.

Dee does not fully understand the relationship between RHD and becoming pregnant, or the risk of pregnancy on her cardiac health. Skilful education and discussion with appropriate interpreter services should be part of ongoing care for women with RHD.

In this instance, the trauma of losing her baby creates an added dimension of grief.

Cultural factors need to be considered regarding the death and burial of her baby, and how she and her family will cope with the loss.

Conversations and education should take place for all women with RHD. In high-risk women, the use of contraception with a low failure rate should be strongly encouraged and monitored. Oestrogen-containing contraceptives are associated with a higher risk of thrombosis.

Any woman receiving anticoagulation should have access to routine anticoagulation monitoring as close to home as possible, with appropriate health service expertise.

Naomi's Story

Background: Naomi is a 19-year-old who lives in a remote community and was visibly pregnant with her second child. She had recently moved to the area and had not received any antenatal care. She was unsure how long she would stay in town because she lived between several communities.

Ebony is a local Aboriginal Health Worker who met Naomi by chance. Ebony spoke to Naomi about the Aboriginal Mothers and Babies program and offered a home visit to Naomi. But she declined because she was worried about other people at the house hearing her business. Ebony then offered a pick-up appointment.

Pregnancy: Naomi attended the first antenatal visit with her daughter. Her fundal measurement indicated 33 weeks' gestation. Naomi denied all previous illnesses including cardiac conditions but did mention that she'd had anaemia and a previous blood transfusion. The midwife arranged a visit with the obstetrician at the nearest birthing facility for further investigations and antenatal care.

Naomi attended the obstetric appointment with Ebony. This time, Naomi remembered she 'had two holes in the heart'. On examination, a cardiac murmur was heard, although Naomi didn't remember having rheumatic fever as a child or receiving any treatment. The obstetrician organised an immediate echocardiogram, which showed mild RHD.

Naomi attended a subsequent cardiac review with Ebony, where she commenced four-weekly BPG injections and agreed to be registered with the RHD Control Program. The multi-disciplinary team met to discuss her birth plan. Naomi wanted to stay in town to have her baby, and her low cardiac risk score suggested that – pending a satisfactory cardiac review at 37 weeks – she could have her baby at the local hospital rather than be transferred for higher-level care.

At 39 weeks' gestation, Naomi gave birth to another healthy daughter. She decided to stay in this town and was scheduled to have a follow-up review in six weeks. Naomi agreed to have her history shared with the Aboriginal Health Service at the other community where she lives.

Discussion: Women may not remember having rheumatic fever.

Skilful and respectful consultation, with time allowed for responses, should include questions about sore throat, skin sores, regular injections and heart history. Also ask about family history – have any siblings or kids had ARF or treatment for sore throats/skin sores? Think RHD in high-risk populations.

It is important to have an Aboriginal Health Worker or Aboriginal Health Practitioner in discussions for cultural support and to assist in understanding. Aboriginal and Torres Strait Islander women may live in complex social situations. Home visits may be uncomfortable, inconvenient or stressful for them, so offer alternative venues wherever possible.

Access to services includes consideration of transport and accommodation access – particularly in remote and regional areas, streamlining appointments, access, provision of support person and/or interpreter where required.

Jamaya's Story

Background: Jamaya is a Wirangu nation young woman from rural South Australia. She was diagnosed with ARF at five years of age. She received support from her grandmother and the local Aboriginal Medical Service (AMS) for her three-weekly BPG injections over the years. At age 17, Jamaya had been with her partner for a couple of years. She had recently stopped using contraception and thought she may be pregnant.

Jamaya attended her annual cardiac appointment with visiting paediatric cardiologist Dr Ken, accompanied by partner Todd. She was comfortable with Dr Ken: she had been under his care for the past 12 years. She was excited at the possibility of being pregnant, but she and Todd were both a bit nervous about how Jamaya's heart would cope.

Pregnancy: A full cardiac assessment was performed including history, examination and functional assessment. The echocardiogram showed mild RHD. A dating scan confirmed pregnancy of nine weeks' gestation. Blood tests showed mild anaemia but were otherwise normal.

It was agreed that Jamaya would have her care transferred to the adult cardiologist based at a regional hospital. Her cardiac status remained unchanged and at the follow-up appointment with the adult cardiologist, they discussed the birth plan.

Jamaya stressed she did not want to leave her grandmother. Jamaya and Todd chose a Shared Maternity Care model, with her general practitioner (GP), the Aboriginal Mothers and Babies midwife and Aboriginal Health Practitioner providing antenatal care. Assuming there were no complications, they wanted to give birth at the local town hospital and for the baby to be born on Country. Jamaya would see the cardiologist once more and knew if her condition changed, to contact the AMS or her Aboriginal Mothers and Baby team. Her cardiologist consulted with the hospital obstetrician who agreed with this plan.

Pregnancy was uneventful. Jamaya's anaemia was managed with iron supplements, she continued her secondary prophylaxis, and had a dental procedure for tooth decay. A second echocardiogram showed mild mitral regurgitation that had not worsened.

At 38 weeks, Jamaya had a normal vaginal birth with no complications. Afterwards, she confided in her midwife that she didn't want another baby 'for ages' and an Nexplanon contraceptive device was inserted. Jamaya went home where she lived with Todd and her grandmother, with follow-up from Child and Family Health services and her local GP.

Discussion: Women known to have RHD should be assessed as early as possible before pregnancy, including a full history and examination, with functional assessment and an echocardiographic study.

Birthing on Country is culturally significant for many women, and if safe to do so, it can be achieved with the proper care and coordination.

Transitioning from a child to adult can be frightening, and it is important that this is acknowledged and considered when changing from paediatric services to adult services.

Emphasise that – whether pregnancy is intended and especially where it is not recommended – women should attend the health service as early as possible, and not avoid check-up through embarrassment or shame.

Secondary prophylaxis where indicated, should continue throughout pregnancy.

A dental care check and good oral hygiene reduce potential sources of bacterial infection including infective endocarditis, particularly in women with mechanical heart valves.

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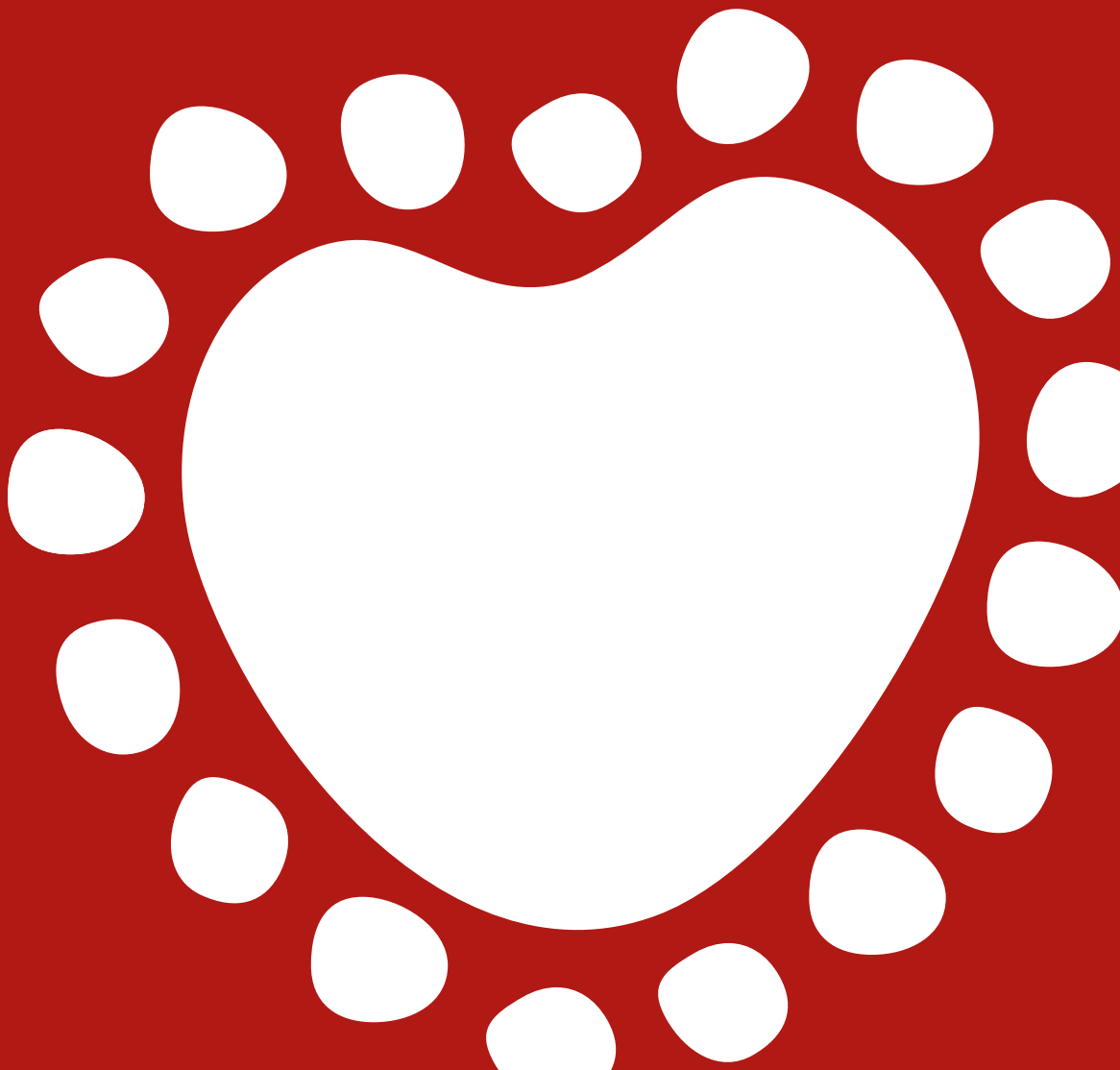
CHAPTER 13

Rheumatic heart disease control programs



Rheumatic heart disease control programs

CHANGES FROM THE SECOND (2012) EDITION

1. This chapter has been significantly expanded.
2. Legislated notification requirements for acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in Australian jurisdictions are described.
3. A recommended dataset for ARF and RHD is no longer included.

KEY INFORMATION

- Comprehensive RHD control programs which span action on the social and environmental determinants of health, and primary and secondary prevention of ARF, can provide effective approaches to reducing the burden of RHD.[1,2]
- A key aim of RHD control programs is to maintain a register and recall system for secondary prophylaxis and clinical management.
- RHD control programs:
    - support patient care by maintaining a skilled health workforce, promoting culturally appropriate care, supporting education and health promotion for patients and communities and working with patients and primary healthcare staff to optimise delivery of secondary prophylaxis
    - promote primary prevention aimed at preventing initial episodes of ARF
    - provide jurisdiction-wide data for epidemiological reporting.

Box 13.1. Recommended elements of RHD control programs[3]

Commitment from national, regional and local organisations, particularly to ensure long-term funding and governance support.

An effective program advisory committee that includes Aboriginal and Torres Strait Islander health service organisations and members from the Aboriginal and Torres Strait Islander health workforce, medical specialists, general practitioners, epidemiologists, nurses, public health practitioners, and relevant community representatives.

The ability to find new cases of ARF and RHD and to assess and monitor the burden of disease.

An electronic patient register that contains data elements to support quality patient management, and internal and external reporting requirements.

Advocacy for improved environmental health.

Support for delivery of primary antibiotic treatment and secondary antibiotic prophylaxis delivered within the framework of primary healthcare.

Planning and advocacy for a stable supply of benzathine benzylpenicillin G (BPG), and the establishment of plans for sustainable secondary prophylaxis in the event of supply limitations.

A commitment to partnerships between clinicians and public health services to support the needs of people with ARF and RHD and the community.

Education and training for the health workforce, and supported health education for patients, families and communities.

Activities guided by locally relevant, evidence-based guidelines.

Legislation and/or regulations warranting the notification of ARF and RHD supported by public health surveillance activities at the State or Territory level.

A mechanism for monitoring disease, delivery of secondary prophylaxis, and ongoing care.

Evaluation of patient management and program activities.

DISCUSSION

> *"I just get organised and coordinate my needles with the nearest clinics or the CDC. I've had injections while working in Mataranka, Katherine, Bulman, Lajamanu, Palmerston, Robertson River, and Minyerri. I've even had a nurse come out and give me an injection in the carpark of my trade school."*
>
> Champion, *RHDAustralia Champions4Change program*, 2019.

Program model

Register-based control programs reduce recurrence of ARF, decrease hospitalisations, and help to avoid costly and life-threatening heart surgery for young Aboriginal and Torres Strait Islander peoples. However, ARF and RHD can only be eliminated by addressing underlying environmental risk factors, and by providing timely and effective healthcare to ensure that throat and skin infections do not progress to ARF.[4]

The World Health Organization (WHO) recommends a coordinated, public health approach where there are substantial populations with ARF or RHD.[3] RHD control programs aim to improve timely diagnosis and the delivery of secondary prophylaxis, which is the most cost-effective approach to RHD control.[3,5] RHD programs are also well-placed to advocate for, and support, activities aimed at preventing ARF and RHD (primordial prevention) *(Table 4.1)*.

A dedicated coordinating team is critical to the success of the jurisdictional RHD control program. Combined capacity should include skills in data management and reporting, education and training, basic epidemiology and clinical medicine. To ensure that the program continues to function well despite staffing changes, program activities must be integrated into the established public health system.

Program implementation should be stepwise;6 starting in one or more defined areas to test whether the structure and processes are appropriate within the local context, with gradual extension of the program to regional and statewide coverage. RHD control programs should aim to support existing healthcare services and be managed in line with local healthcare frameworks.

Registers and recall systems

Indigenous peoples worldwide are reaffirming their sovereignty rights around the collection and use of medical and personal data that describes themselves or their living circumstances. In Australia, many Aboriginal leaders and academic institutes are calling for a national approach to data sovereignty and data governance.[7]

The right to own, collaborate, analyse and use data is reflected in the United Nations Rights of the Indigenous Peoples.[8] Data related to ARF and RHD are collected locally and aggregated nationally, with an emphasis on rates and prevalence of disease. Under a data sovereignty and data governance approach, local communities would be more active in determining which data should be collected, and how and who it should be shared with. This approach allows community ownership, empowerment, collaboration and partnerships to occur. Data presented back to communities would also help make sense of the data from a different lens and worldview.

ARF/RHD registers are an important component of comprehensive RHD control programs, and a key element of RHD control at individual, community and national levels.[1,2] Contemporary, local evaluation of the impact of RHD control programs is difficult due to the lack of appropriate comparative groups, and because programs activities (improving the detection and reporting of ARF and RHD) inherently have the effect of increasing case notifications at least in the short term. However, at different historical times and in various geographical settings, register-based programs have been shown to:

- improve case detection;[9,10,11,12-14]
- increase adherence to secondary prophylaxis;[13,14]
- reduce recurrences of ARF;[13-18]
- decrease hospitalisations from ARF/RHD.[13,14]

Ideally, ARF/RHD registers should be linked to local, primary care registers and into a national disease reporting system. This may be a centralised, dedicated database, or part of a more comprehensive chronic disease register maintained by program staff. Satellite registers, including clinic-based patient management systems and secondary prophylaxis injection books that are managed by dedicated staff, can link or report into regional registers. All patient registers should maintain patient confidentiality, conform to privacy legislation, and be established with relevant approvals.

In addition to reporting on disease epidemiology and providing other information necessary to monitor program activities, registers should provide individual and community reports and recall lists for visiting specialists and primary healthcare staff. Registers may also provide reports to funders and researchers.

Registry data can be used to contribute to epidemiological knowledge of ARF and RHD by linking with population denominator data to allow calculation of ARF prospective incidence and RHD prevalence data.

RHD control programs in the Australian context

An Aboriginal and Torres Strait Islander workforce should be embedded into the RHD control program, to provide guidance and support to program activities, and to help translate health promotion into culture and practice. Further consideration should be given to partnering with local Aboriginal and Torres Strait Islander health programs and organisations to facilitate disease control across social and cultural pathways.

RHD control activities have been established in Australia since 1997. From 2009, most funding has been provided through the Australian Government's *Rheumatic Fever Strategy* which includes State-based register and control programs, and a national support unit, *RHDAustralia*.[4]

Programs in the Northern Territory (NT), South Australia (SA), Queensland (QLD) and Western Australia (WA) are funded under the National Partnership Agreement.[19] These agreements outline improved detection, monitoring and management of ARF and RHD through:

- improved clinical care, including improved delivery of and adherence to secondary prophylaxis antibiotics;
- provision of education and training for healthcare providers, individuals, families and communities;
- collection and provision of agreed data annually to the Australian Institute of Health and Welfare (AIHW) for national monitoring and reporting of ARF and RHD, and measuring program effectiveness in the detection and management of ARF and RHD;
- maintenance of a dedicated statewide patient register and recall system for ARF and RHD.

The New South Wales (NSW) program is funded by the NSW Government, and its aims align with the other programs.[20]

Australia's first register-based RHD control program was established in the NT's Top End in 1997.[21] A second NT program was established

in Central Australia in 2000, and the Top End and Central Australia programs have since amalgamated to form a territory-wide program. The NT program provides Clinical Nurse Specialists across two regional divisions in the Top End and another in the Central Australia and Barkly region. The program delivers hospital-based patient support and education, and supports specialist outreach visits to remote communities.

An RHD Register and Control Program was established in QLD in 2009 under the National Partnership Agreement with the Rheumatic Fever Strategy. The program includes both clinical and non-clinical staff and provides a service across the State.

The program in WA was established in Broome in 2009 and managed by the Kimberley Population Health Unit. Since July 2017, the program has been based in Perth, and managed by the WA Country Health Service, Population Health. The WA program focuses on providing leadership, clinical support, education, and active follow-up of people with ARF and RHD. A regional funding allocation to the Kimberley, Goldfields, Pilbara and Midwest regions enables the employment of clinical nurses who coordinate care at a local level and engage with local health service providers.

The SA program was established in Adelaide in 2010. A dedicated nurse also coordinates patient care and cardiology outreach for people with ARF and RHD living in the Anangu Pitjantjatjara Yankunytjatjara (APY) Lands across northern SA.

The NSW program was established in 2015, with a register commencing the following year. A coordinator provides support in each local health district. The program focuses on raising awareness about ARF and RHD among primary healthcare providers, including the Aboriginal Community Controlled Health sector and networks representing people from the Pacific region. The NSW program also works with established environmental health programs to improve housing for Aboriginal and Torres Strait Islander peoples.

Legislated notification of ARF and RHD

The National Notifiable Diseases Surveillance System (NNDSS) was established in Australia in 1990 to coordinate surveillance of communicable diseases.[22] Notifications are legislated in each jurisdiction in line with local legislation.

Diseases may be nationally notifiable or may be notifiable only in specific States and Territories. National and jurisdictional legislation applies to diseases becoming notifiable, and to the process of enrolling people in RHD registers.

ARF and RHD have been designated notifiable diseases in several Australian jurisdictions *(Table 13.1)*. Also see the Series of National Guidelines document for ARF and RHD

https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-arf-rhd.htm

The notification process comprises notification of demographic, clinical and diagnostic data by clinicians, which differs from most other notifiable conditions where notifications are made by laboratories. Lack of awareness by clinicians of the need to notify, or of the process to do so, can result in missed opportunities for inclusion of ARF or RHD cases in registers. Furthermore, notification by clinicians requires contact with different agencies in some jurisdictions (e.g. the RHD Register and the Notifiable Diseases database), and multiple agencies for cross-border patients *(Table 13.2)*. This may pose a barrier to enrolling people on registers, resulting in further missed opportunities for inclusion as well as delivery of coordinated care.

It may be possible to simplify notification of ARF and RHD at a jurisdictional level by mapping notification pathways, and seeking opportunities to increase capacity for online notification and ARF data reporting from different sources (e.g. primary healthcare facilities, laboratory providers and hospital admissions).

Table 13.1. Evolution of ARF and RHD notification and RHD program establishment in Australia

	NT	QLD	WA	SA	NSW	VIC, TAS, ACT
RHD Control Program	1997†	2009	2009	2010	2015	✘
ARF/RHD Register	1997	2006	2009	2012	2016	✘
Confirmed (definite) ARF notifiable	1996	1999	2007	2016	2015	✘
Probable ARF notifiable	2019	✘	2015	2016	2015	✘
Possible ARF notifiable	✘	✘	2015	2016	✘	✘
Confirmed RHD notifiable	2019	2018	2015	2016	2015‡	✘
Borderline RHD notifiable	✘	2018	2015	2016	✘	✘

† The Top End Control Program was established in Darwin in 1997, and expanded in 2000 to include the whole NT.

‡ Notification of RHD only in persons aged less than 35 years.

Table 13.2. Processes for notification and inclusion on registers, as at December 2019

JURISDICTION	NOTIFICATION PROCESS	PATIENT CONSENT
NSW	Medical practitioner or hospital CEO notifies the NSW Public Health Unit by telephone, or by completing and submitting a notification form.[23]	Notification – consent not required. Register – informed, opt-in consent.
SA	1. Medical practitioner notifies the SA Communicable Disease Control Branch by telephone or by completing and submitting a notification form within three days of suspecting or confirming a diagnosis (online form option available). ***and*** 2. Medical practitioner notifies the SA RHD Register by telephone, or by completing and submitting a notification form.[24]	Consent not required.†
QLD	Medical practitioners, medical superintendents (or delegates) notify the QLD RHD Register and Control Program by completing and submitting an ARF notification form or RHD notification form.	Consent not required.‡
NT	Medical practitioner notifies the relevant Public Health Unit at first suspicion, by completing and submitting a notification form.	Consent not required.
WA	Medical practitioner notifies the WA RHD Register and Control Program by completing and submitting a notification form together with copies of diagnostic tests (including echocardiogram) and copies of each medical specialist's report (secure file transfer options available).¶	Consent not required.§

†Consent was required for all patients prior to 2019. From 2019 an opt-out option is available.

‡ Consent was required for patients with RHD registered prior to 2018

§ Notification required within 30 days of the medical specialist report.

¶ An individual can request in writing to the Chief Health Officer that there only be limited disclosure of identifying information on the register.

Discussion about the suitability of ARF as a nationally notifiable disease in Australia has been underway for many years.[25] National notification was considered by the Communicable Diseases Network Australia (CDNA) in 2010, however this was not implemented.

RHD meets fewer of the CDNA criteria for notification than ARF but there are good reasons for considering its candidacy. Almost half of Aboriginal and Torres Strait Islander peoples living with RHD would not be identified by relying on ARF notification alone, because ARF diagnoses in people with established RHD have often been missed.

In a 2015 review, ARF and RHD both met the threshold for national notification to be considered further.[26] Incorporating ARF into the NNDSS would mandate a standardised national approach to notification with a potential range of benefits: clinicians working across different jurisdictions would be familiar with a standardised approach to notification, and case reporting could be managed across jurisdiction boundaries. Registered patients who move across jurisdictional boundaries may be less likely lost to follow-up.

The development of a national register also has been considered for some years. Several reviews have recommended a national register, including the Audit and Best Practice for Chronic Disease 2 study in 2016.[27] However, local registers have been established due to the staggered timing of program development and variations for legislated notification *(Table 13.1)*.

ARF and RHD surveillance

Surveillance of ARF usually depends on case identification from healthcare providers who report cases to registers through established notification channels *(Table 13.2)*. Historically, this has underestimated the burden of disease, due to inaccuracies and incompleteness.[28]

A three-year study of ARF in Australian children between October 2007 and December 2010 also demonstrated under-reporting. The study was conducted by the Menzies School of Health Research in conjunction with the Australian Paediatric Surveillance Unit (APSU).[29] The APSU notification mechanism relies on voluntary reporting from clinicians working in paediatrics and child health. The voluntary nature of reporting, together with the lack of core data for some reported cases, resulted in an underestimate when compared with the number of cases reported on registers in the same period.[29]

Ideally, active surveillance should be used to expand on passive surveillance.[30] This requires mechanisms to identify new cases of ARF and RHD, and to update information about known cases. In under-resourced settings, the deficiencies of passive surveillance are exacerbated by the high turnover of hospital and primary care staff and lack of awareness of ARF and RHD among many healthcare providers. Therefore, processes should be automated where possible.

A diverse range of activities has been used for active ARF and RHD data capture to inform the registers. Examples include hospital separation data, specialist and radiological reports, automated alerting of registered patients on presentation to hospital, review of patients' presenting complaints, and community and staff education aimed at improving case identification. In the NT, data are also sought from reports generated from primary care electronic health information systems. Active case finding of RHD may include systematic echocardiographic screening in settings with high rates of disease *(Table 9.2)*.

Active case finding for RHD and improved diagnosis of ARF causes an increase in apparent disease rates as previously undetected, unnotified cases are identified. Therefore, successful RHD control programs can be associated with increases in reported disease rates while simultaneously having population-level benefits by linking newly-detected cases to treatment.

Similarly, improved and coordinated access to specialist care may also result in higher rates of valvular surgery (a proxy measure for RHD severity and therefore, control program performance, where the aim is to decrease the numbers of people needing surgery) in the initial years after commencing an RHD control program.

Evaluating RHD control

Key reporting indicators for RHD control programs are shown in *Table 13.3*. General recommended measures to track program performance include:

- Rates of disease occurrence (ARF and RHD numbers and population-adjusted rates respectively).
- Delivery of secondary prophylaxis for individuals and per community for the group prescribed ARF secondary prophylaxis, using the metrics of *percent delivery of prescribed BPG infections* and *days at risk* (See *Chapter 10. Secondary Prophylaxis, Measuring BPG injection adherence*).
- ARF recurrence rate and as a proportion of all ARF cases.
- Indicators of satisfactory care specified in best-practice guidelines.
- Disability attributable to ARF and RHD.
- Deaths among people with ARF and RHD, including cause of death where possible.

Further consideration should be given to assessment of the quality and reach of patient care, including:

- the delivery of specialist cardiology services;
- availability and accessibility of echocardiography and dental care;
- trends in need for cardiac surgery;
- medical and surgical referral practices and structures;
- patient support and appropriate follow-up processes;
- transition from paediatric to adult services.

RHD programs should be evaluated on how well they identify people with ARF and RHD and support the health system to provide appropriate care. Monitoring should be conducted at regular intervals on:

1. Which program activities are being undertaken.
2. The extent to which program objectives are being met.
3. Progress towards the program goal.[1]

An independent evaluation of the Australian Rheumatic Fever Strategy and associated program activity was conducted in 2016.[4] Overall, the evaluation reported multiple successes including improved monitoring and surveillance of ARF and RHD, increased awareness of the disease among the health workforce, and improved secondary prophylaxis delivery in some areas. Recommendations included continued, longer-term funding to enable the programs to:

- broaden efforts around primordial and primary prevention of ARF while continuing to improve secondary prevention;
- further develop the registers;
- streamline data sharing for national epidemiological reporting;
- strengthen clinical education.

The availability of, and support for, routine primary healthcare is essential for preventing ARF and controlling RHD. Indicators used to evaluate RHD control should be relevant, structured, measurable, routinely available and affordable. They should not overburden primary healthcare providers, and should lead to improved clinical results.

Most people in Australia enrolled on ARF/RHD registers are Aboriginal and Torres Strait Islander peoples *(Figure 3.8)*. This is mostly attributable to the recognised differential disease burden but partly attributable to reporting practices which deliberately or accidentally exclude people with RHD above a certain age (who are more likely to be non-Indigenous) (See *Chapter 3. Burden of ARF and RHD, Demographic distribution of ARF and RHD*), or from low risk populations in Australia *(Table 13.1 footnote)*. Reporting for ARF and RHD should support accountability in measuring progress towards agreed outcomes, and should be accessible to Aboriginal and Torres Strait Islander communities and healthcare organisations, in line with the Council of Australian Governments (COAG) Implementation Principles of 2019.[31]

Key performance indicators

Key reporting indicators to monitor and report ARF and RHD activity vary both within Australia and internationally. Issues with availability and accuracy of data, and with denominators for rate calculations, caution against recommending complex reporting requirements.

RHDAustralia's vision is that no child dies in Australia as a result of acute rheumatic fever and its complications.

This vision has been adopted into the National Health and Medical Research Council End RHD Centre of Research Excellence Endgame report. (https://endrhd.telethonkids.org.au/our-research/the-endgame-strategy/).

Other parameters that have been useful are outlined in *Table 13.3*.

Table 13.3. Key reporting indicators

1.1 Yearly ARF incidence by episode type, age group and	1.1.1	Sex
	1.1.2	Ethnicity
1.2 Yearly ARF recurrences	1.2.1	Proportion of all ARF episodes
	1.2.2	Rate per 100 patient-years for patients prescribed prophylaxis (both oral and BPG)
1.3 Yearly RHD point prevalence by age group and	1.3.1	Sex
	1.3.2	Ethnicity
	1.3.3	Severity classification
1.4 Proportion of people receiving secondary prophylaxis each year[32]	1.4.1	80-100%
	1.4.2	40-79%
	1.4.3	0-39%

For consistency, the same frequency of reporting, and the same definitions and methods for calculation should be used across regions and jurisdictions. The true picture of ARF and RHD within Australia and the progress of RHD control regionally and nationally, will only be possible with national legislated notification of ARF and RHD and a national data collection and reporting system.

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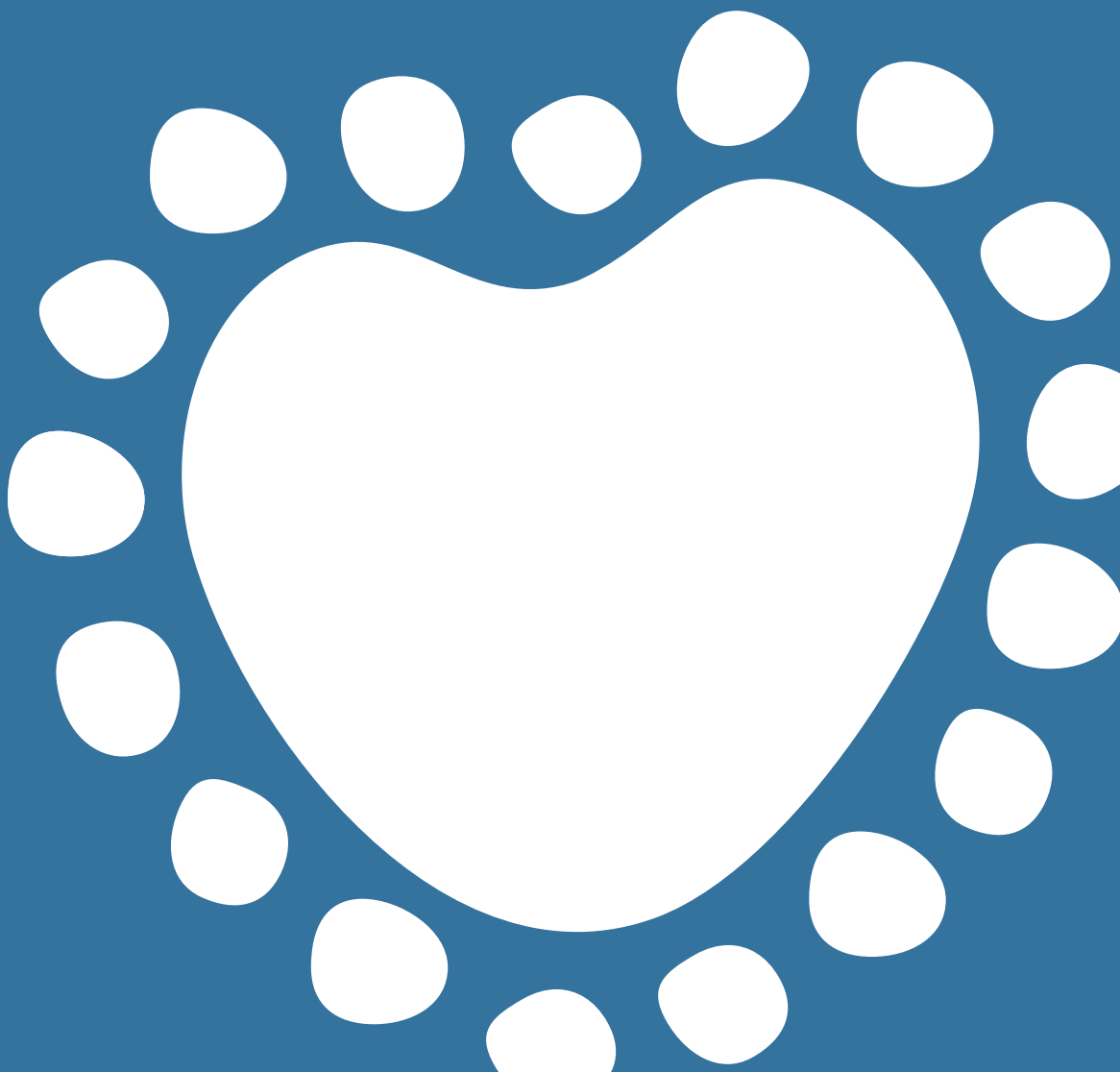
CHAPTER 14

New technologies



New technologies

CHANGES FROM THE SECOND (2012) EDITION

This is a new chapter.

KEY INFORMATION

- This chapter reviews research underway in Australasia which aims to discover better alternatives to benzathine benzylpenicillin G (BPG), develop a Strep A vaccine, and develop a diagnostic test for ARF.
- Research is underway to determine whether a penicillin depot (implant) may be a future reality. Development is dependent on answering existing knowledge gaps relating to lowest effective dose of penicillin against Strep A and ideal route of delivery.
- Funding initiatives, including a 2019 Australian Government grant, aim to fast-track development of a Strep A vaccine, with the goal of being able to commence field trials to assess efficacy and safety within 5 years from 2019. Challenges with Strep A vaccine development include the need to cover hundreds of different Strep A types, and to avoid immune complications that could trigger ARF-like outcomes.
- Diagnostic tests for autoimmune disease usually rely on disease-specific antibodies and other immune markers such as complement levels, but no diagnostic test for ARF has yet been discovered. Research is underway to determine if biomarkers (measurable molecules, genes, immune or other markers which can identify a disease process) measurable in blood may be discoverable which distinguish ARF from non-ARF presentations. If a distinguishing biomarker profile is discovered, then it may be possible to develop an ARF diagnostic test suitable for use in clinical diagnostic laboratories.

DISCUSSION

Community engagement is critically important to ensure that Aboriginal and Torres Strait Islander peoples are actively engaged in decisions about priorities and directions for research. Research into ARF and RHD must align with community needs, with consultation of community members about project design and implementation.

PENICILLIN DELIVERY

Long-acting penicillin, in the form of intramuscular BPG injections, has been an integral part of preventing recurrent acute rheumatic fever (ARF) since the 1950s. This unique depot injection has been shown to have detectable levels in humans for up to four weeks,[1,2] and is tolerated in most people requiring secondary prevention for ARF.[3,4] For more than 60 years, the Strep A bacteria have remained sensitive to penicillin; there have been no documented penicillin-resistant strains of Strep A (See *Chapter 7. Management of ARF, Antibiotic treatment*). Non-penicillin antibiotics are used for individuals with a penicillin allergy, however they are generally considered inferior, and resistance can develop.[5,6]

Research into better understanding the pathogenesis of Strep A and ARF has been extensive.[7] However, little has changed with regards to the type, dose and frequency of penicillin used since early studies demonstrated intramuscular penicillin to be superior to other antibiotics for secondary prevention.[5]

Despite the long-term effectiveness of penicillin in managing ARF, there have been significant issues. A relatively small market for BPG and low financial profit margins have resulted in a lack of innovation from manufacturers. Stock shortages of the pre-filled syringe product (Bicillin L-A®) across Australia at different times have required a temporary switch to powdered alternatives used in other parts of the world.[8] While there have been changes in recommended injection administration technique to manage pain and distress of injections with some effect,[9,10] the penicillin preparation itself has remained largely unchanged since its development.[11]

Most of the antibiotic comparison studies were conducted in the 1950s and consisted of cohorts of Caucasian children, which is a vastly different population to that most commonly affected by ARF today.[12,13] Further studies in the 1990s and 2000s highlighted significant differences in blood concentrations between individuals without clear explanation.[1,14] Early lab studies (*in vitro*) attempting reformulation showed some promise with a nanoparticle impregnated with penicillin. An attempt to develop a long-acting penicillin implant prototype in Australia since 2000 has been largely unsuccessful, owing to several key barriers and highlighting a poor understanding of the basic science around BPG injections.[15,16] Further work is underway to explore other possible delivery devices.

A more acceptable method of secondary prophylaxis is required to more effectively manage the pain, distress and inconvenience of the regular intramuscular injections, while effectively preventing recurrent ARF.

Several key questions about penicillin delivery remain to be answered:

- Is there a difference in how penicillin is metabolised in individuals from different racial groups?
- Does weight or body mass index (BMI) have an impact on the required dose?
- Are there alternative ways to administer penicillin?
- What is the minimum required dose that will prevent ARF in everyone?
- Do patients, families and health staff have a preferred method of delivery?

Several studies are underway to help answer these questions.

1. An urban-based pharmacokinetic study in Perth in 2017 assessed penicillin levels in predominately Aboriginal children and adolescents.[2] Results indicated that size and shape of the individual had a significant impact on the way the body processed the penicillin. It illustrated that several individuals with higher BMI were possibly receiving their injections into subcutaneous fatty tissue rather than into the muscle as intended. Those with a higher BMI (≥25kg/m^2), had a detectable penicillin level (half-life, $t_{1/2}$) almost double ($t_{1/2}$ increased by up to 86%), suggesting that subcutaneous administration was occurring and may be an ideal route of administration for reformulation. Interestingly, some individuals never reached the traditional 0.02 mg/L 'concentration of protection', yet did not have Strep A infection, suggesting that a lower concentration of penicillin may be protective against Strep A (e.g. 0.01 mg/L).[2] These unexpected findings require further investigation before a change in current dose or frequency can be recommended.
2. A clinical trial was conducted by the Telethon Kids Institute and partners in Western Australia in 2018 with the aim of confirming the findings of the above study, in addition to determining the safety and pain (tolerability) of penicillin injected subcutaneously.[17] Participants included young adults without rheumatic heart disease (RHD). Ultrasound technology was used to confirm correct location of injections, either into the muscle or in the fatty tissue

below the skin. Using specifically developed minimally invasive blood sampling,[18] the researchers measured penicillin levels in the blood over six-week periods. Differences in penicillin concentration or pain rating between the two routes of injection (into muscle versus into subcutaneous fatty tissue) may allow for a new route of administration with the current formulation that is less painful. This knowledge will be essential for the longer-term goal of penicillin reformulation.

Blood levels of penicillin considered protective against Strep A are interpreted from laboratory tests, and current dosing regimens usually provide adequate protection against Strep A and recurrent ARF.[19,20] However, demonstration of the true protective level of penicillin in people (*in vivo*) is much more difficult. There has not been the technology to test *in vivo* whether a reduction in penicillin concentration will continue to be protective.

3. The development of a human challenge model for Strep A infection[21] has been a significant breakthrough. A team at the Murdoch Children's Research Institute in Melbourne has been able to expose healthy individuals to Strep A (Strep A 'challenge') to develop a sore throat. With this controlled infection model, it will be possible to establish the true minimum protective penicillin level against Strep A, rather than assume from laboratory values. If this protective level can be identified, and is found to be lower than the previously determined concentration of 0.02 mg/L, it will allow for smaller implants to be developed, a major barrier identified preventing reformulation.[15]

Together, these studies will help ensure that a penicillin reformulation is effective and acceptable to patients and health systems.

Whilst the science is important, it is recognised that patient-centred treatment is essential for long-term BPG delivery. To that end, several qualitative studies are investigating patient/family/clinician preference for a penicillin reformulation with collaborators in New Zealand.[22]

STREP A VACCINE DEVELOPMENT

Vaccines are a safe and effective way of reducing and eliminating illnesses caused by bacteria such as meningitis (brain infection) and pneumonia (lung infection) due to *Haemophilus influenzae* type B, *Streptococcus pneumoniae,* and *Neisseria meningitidis*.[23]

Strep A vaccines have been studied since the 1920s.[24] As well as reducing pharyngitis ('strep throat'), impetigo (skin sores), ARF and RHD,[25] an effective Strep A vaccine given in early childhood would prevent other Strep A diseases including post-streptococcal glomerulonephritis (kidney disease), cellulitis (skin infection), severe and frequently fatal invasive disease including bacteraemia (blood infection), toxic shock syndrome, necrotising fasciitis, and infections in pregnant women and newborn babies.[26,27] Aboriginal and Torres Strait Islander peoples experience these conditions at a much higher rate than non-Indigenous Australians, and are therefore most likely to benefit from a vaccine.[28-30] By preventing disease across the Strep A spectrum, a vaccine would also reduce the non-communicable disease burden of Strep A diseases, including complications of RHD and its management such as heart failure, stroke and infective endocarditis.

In addition to providing primary prevention of Strep A infection, a vaccine administered to people with pre-existing ARF or RHD could provide effective secondary prevention of ARF. Other medical approaches to primary prevention such as antibiotic treatment for Strep throat and skin infections have not been able to achieve large and sustainable reductions in the subsequent development of ARF or RHD.[31]

In the longer term, reducing ARF and RHD through vaccination of high-risk populations will help eliminate the disease. In the short term, offering vaccination to those at risk will reduce the impact of ARF and RHD on individuals, families and communities. A successful vaccine will be an important part of ending RHD in Australia, eliminating RHD as a global public health problem, and would be a game-changer for control of all conditions associated with Strep A. Protection from a vaccine would likely be long-lasting, and certainly much longer than the protection provided from a single dose of BPG.

Development of a Strep A vaccine is the most attractive opportunity for a single medical intervention to substantially reduce the global burden of RHD. Science has identified many

vaccine targets (antigens) on the Strep A bacteria with promising results in laboratory and animal studies.[32,33] Unfortunately, there have been scientific, regulatory and commercial obstacles which have delayed the progress of a vaccine, and almost a century later there is no safe and reliable human Strep A vaccine available.[34] However, there has been an upsurge in interest from the World Health Organization (WHO) and other major international public health bodies and funders, vaccine developers, and regulators discussing and planning ways to overcome obstacles.[35] Strep A vaccine development was promoted in the WHO's 2018 Resolution on Rheumatic Fever and Rheumatic Heart Disease.[36]

In early 2019, the WHO published a *GAS Vaccine Research and Development Technology Roadmap* and *Preferred Product Characteristics* for GAS (Strep A) vaccines.[37-39] Through the Australian and New Zealand government-funded Coalition to Advance Vaccines Against Group A Streptococcus (CANVAS)[40] and other initiatives, Australian leadership has been crucial to promoting development of a vaccine, achieving global consensus on the way forward, and building new models to test vaccines. This includes an Australian-based controlled human infection ('human challenge') model of Strep A pharyngitis to test the ability of vaccines to protect healthy adult volunteers before starting large clinical field trials. [21,35,41]

In 2019 the Australian Federal Government, through the Medical Research Future Fund, committed $35 million to the Australian Strep A Vaccine Initiative coordinated by Telethon Kids Institute and Murdoch Children's Research Institute (MCRI), with the goal of fast-tracking Strep A vaccine development towards large field trials within five years.[42,43] Australian leadership in Strep A vaccine development will help ensure that the benefits of a vaccine ultimately reach Australian populations at highest risk of ARF and RHD. British biomedical research foundation the Wellcome Trust has granted $2.25 million to MCRI and the International Vaccine Institute in Seoul, Korea, to coordinate global Strep A vaccine development efforts.[44,45]

BIOMARKERS FOR DIAGNOSIS OF ARF

There is no specific laboratory test for the diagnosis of ARF. The modified Jones criteria include recommendations for measuring general markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), together with streptococcal serology (ASO and anti-DNase B). Streptococcal serology provides evidence of a preceding Strep A infection but is not a measurable indicator (biomarker) for ARF risk.[46,47] The identification of disease markers that are specific for ARF could aid in making a diagnosis, classifying the case and monitoring disease progression.[48]

Research to identify biomarkers for ARF has been gaining momentum, including the application of 'omics' technology.[49] There are reports of proteomics being used to map the proteins associated with mitral stenosis in RHD[50,51] and molecular library approaches to identify potential autoantigens in ARF sera.[52] A 2018 study of ARF blood samples collected from Aboriginal children made use of cytokine arrays, flow cytometry and transcriptomics.[53] This broad profiling approach led to the identification of a dysregulated cytokine axis (IL-β and GM-CSF) in these patients. Collectively, these studies demonstrate that it is feasible to apply 'omics' approaches to ARF and, despite being limited in sample size, suggest it will be possible to identify biomarkers that can distinguish ARF from non-ARF cases.

The START study (**S**earching for a **T**echnology-Driven **A**cute **R**heumatic Fever **T**est) is a larger-scale trans-Tasman study aiming to identify ARF biomarkers. (*unpublished*) This study commenced in 2019 and is led by the Telethon Kids Institute in Perth. Blood samples from individuals with ARF and controls in Darwin in northern Australia and Auckland in New Zealand will be subject to transcriptomics, metabolomics, mass cytometry (CyTOF) and high content protein array analysis. If a panel of ARF specific biomarkers can be identified, these would need to be converted into assays suitable for use in clinical diagnostic laboratories. Technology platforms that enable multiplex testing, such as bead-based immunoassays, are a likely solution. Feasibility for bead-based multiplex testing in ARF has been demonstrated for streptococcal serology.[54] Expanded multiplex assays incorporating ARF specific biomarkers have the potential to dramatically improve the efficiency and accuracy of ARF diagnosis.

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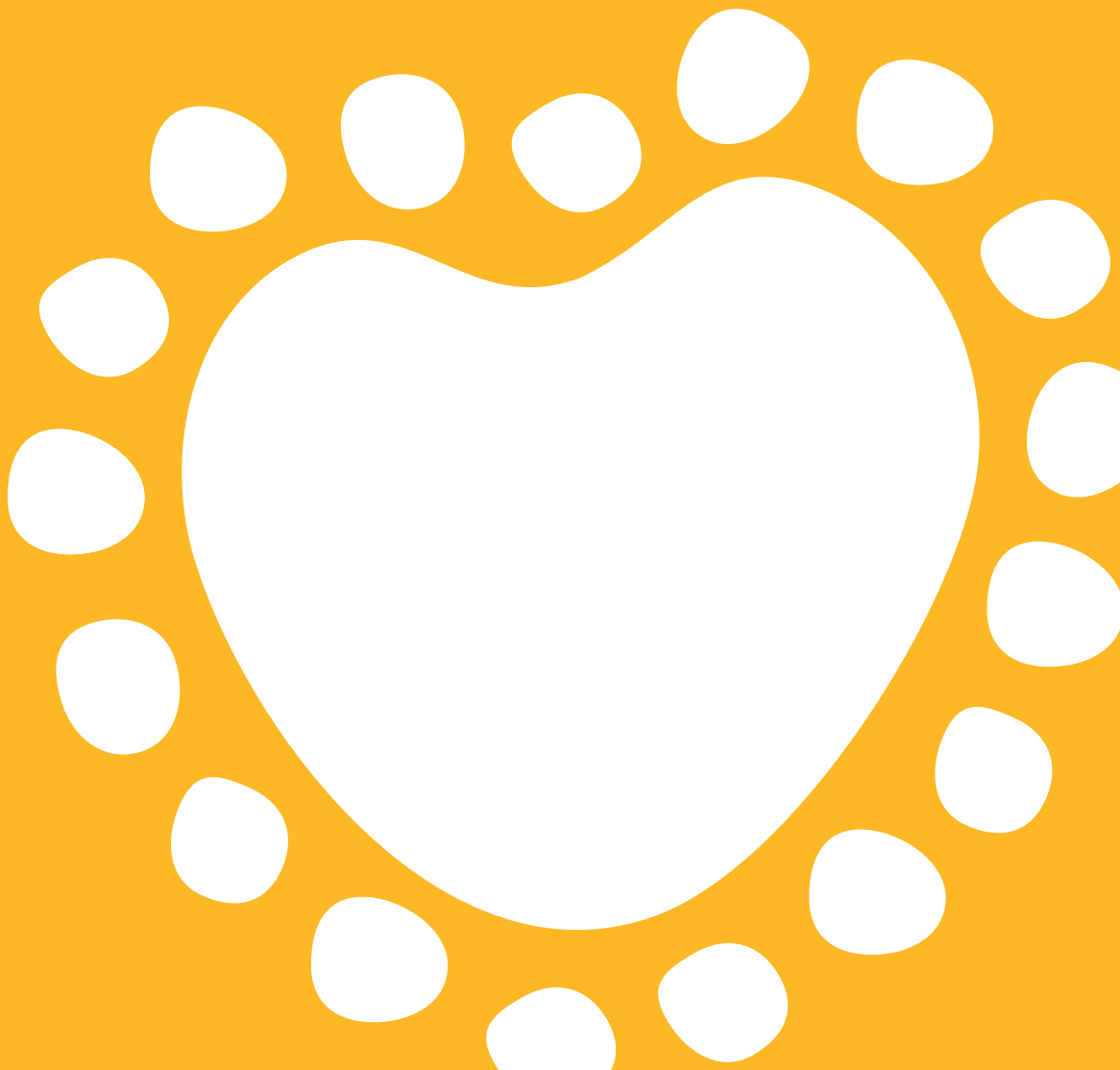
Acronyms and abbreveiations

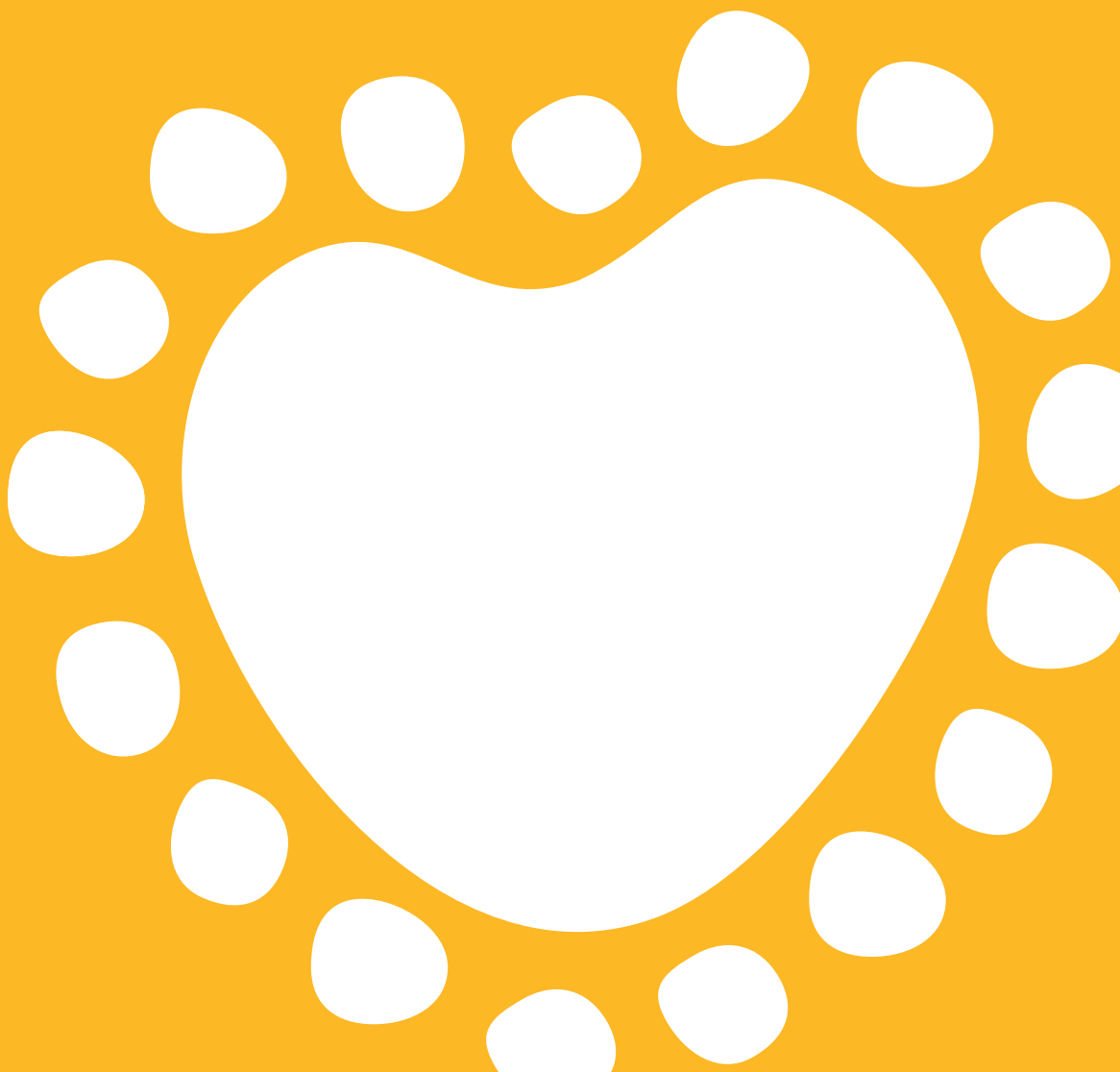


Acronyms and abbreviations

2DE	Two-dimensional echocardiography
3DE	Three-dimensional echocardiography
ACE	Angiotensin-converting enzyme
ADB	Antideoxyribonuclease B / Anti-DNase B (titre)
AF	Atrial fibrillation
AHA	American Heart Association
AHP	Aboriginal Health Practitioner
AHW	Aboriginal Health Worker
AIHW	Australian Institute of Health and Welfare
AMB	Aboriginal Mothers and Babies (team)
AMS	Aboriginal Medical Service
AMVL	Anterior mitral valve leaflet
anti-CCP	Anti-cyclic citrullinated peptide
APSGN	Acute post-streptococcal glomerulonephritis
APSU	Australian Paediatric Surveillance Unit
APVU	Alert, verbal, pain, unresponsive (score)
AR	Aortic regurgitation
ARB	Angiotensin receptor blockers
ARF	Acute rheumatic fever
ARNI	Angiotensin receptor neprilysin inhibitor
AS	Aortic stenosis
ASO	Antistreptolysin O (titre)
AV	Advanced atrioventricular
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
BMI	Body mass index
BNP	B-type natriuretic peptide
BPG	Benzathine benzylpenicillin G
CANVAS	Coalition to Advance Vaccines Against Group A Streptococcus
CARPA	Central Australian Rural Practitioners Association
CDNA	Communicable Diseases Network Australia
CMV	Cytomegalovirus
COAG	Council of Australian Governments
CRE	Carbapenem-resistant enterobacteriaceae
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
CW	Continuous wave
CyTOF	Mass cytometry
DALY	Disability-adjusted life year

DRR	Death rate ratio
ECG	Electrocardiogram
EF	Ejection fraction
ERO	Effective regurgitant orifice
ESR	Erythrocyte sedimentation rate
EST	Exercise stress test
FBC	Full blood count
GAS	Group A streptococcus
GBD	Global burden of disease
GCS	Group C streptococcus
GGS	Group G streptococcus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HF-PEF	Heart failure with preserved election fraction
HF-REF	Heart failure with reduced ejection fraction
ICD	International Classification of Diseases
IE	Infective endocarditis
IMI	Intramuscular injection
INR	International normalised ratio
IU	International units
IUCD	Intra-uterine contraceptive device
IUGR	Intrauterine growth restriction
IVIg	Intravenous immunoglobulin
JVP	Jugular venous pressure
LA	Left atrium
LMWH	Low molecular weight heparin
LV	Left ventricular
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
MRA	Mineralocorticoid receptor antagonist
MRSA	Methicillin-resistant staphylococcus aureus
MS	Mitral stenosis
MVA	Mitral valve area
mWHO	Modified World Health Organization classification of maternal cardiovascular risk
NNDSS	National Notifiable Diseases Surveillance System

NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association (Functional Classification)
P1	Priority 1
P2	Priority 2
P3	Priority 3
P4	Priority 4
PAH	Pulmonary arterial hypertension
PANDAS	Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection
PASP	Pulmonary artery systolic pressure
PBMV	Percutaneous balloon mitral valvuloplasty
PCR	Polymerase chain reaction
PG	Pressure gradient
PH	Pulmonary hypertension
PPI	Proton pump inhibitor
RADT	Rapid antigen detection tests
RHD	Rheumatic heart disease
RNA	Ribonucleic acid
RR	Relative risk
RV	Right ventricle
SLE	Systemic lupus erythematosus
Strep A	Group A streptococcus
TAVI	Transcatheter aortic valve implantation
TOE	Transoesophageal echocardiography
TOP	Termination of pregnancy
TR	Tricuspid regurgitation
TS	Tricuspid stenosis
TTE	Transthoracic echocardiography
U	Unit/s
UEC	Urea, electrolytes, creatinine
UFH	Unfractionated heparin
ULN	Upper limits of normal
VKA	Vitamin K antagonist
VRE	Vancomycin-resistant enterococci
WBC	White blood cell
WHO	World Health Organization
YLD	Years of life lost to disability
YLL	Years of life lost to death



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