View Point

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Consensus Statement of Cardiac Society of Nepal on Diagnosis, Management and Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease in Nepal

Deewakar Sharma[1], Dipanker Prajapati[2], Urmila Shakya[3], Manish Shrestha[3], Samir Shakya[4], Navin Chandra Gautam[5], Reeju Manandhar[2], Kunjang Sherpa[6], Man Bahadur KC[1], Prakash Raj Regmi[7], Chandra Mani Poudel[4], Chandra Mani Adhikari[2], Ratna Mani Gajurel[4], Bijoy G Rajbanshi[8].

[1] Department of Cardiology, Hospital for Advanced Medicine and Surgery (HAMS), Kathmandu
[2] Department of Cardiology, Shahid Gangalal National Heart Centre, Kathmandu
[3] Department of Pediatric Cardiology, Shahid Gangalal National Heart Centre, Kathmandu
[4] Department of Cardiology, Manmohan Cardiothoracic and Vascular Centre, Kathmandu
[5] Department of Cardiac Surgery, Shahid Gangalal National Heart Centre, Kathmandu
[6] Department of Cardiology, National Academy of Medical Sciences, Kathmandu
[7] Nepal Heart Foundation, Kathmandu.
[8] Department of Cardio Thoracic and Vascular Surgery, Nepal Mediciti Hospital, Lalitpur

Corresponding Author: Deewakar Sharma
Department of Cardiology,
Hospital for Advanced Medicine and Surgery (HAMS), Kathmandu, Nepal
Email: deewakarsharma71@gmail.com
ORCID ID NO: 0000-0002-6396-3424

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Abstract

The prevalence of rheumatic heart disease is still significant in Nepal, especially in rural areas. It is an important preventable cause of morbidity and mortality in children and young adults. Diagnosis of rheumatic heart disease and acute rheumatic fever is based on clinical, laboratory, and echocardiographic criteria. Diagnosis and management criteria need to be locally relevant and practical to our context for implementation at the national level. The Cardiac Society of Nepal initiated the development of consensus document with aim of providing a reasonable and practical format of diagnosis and management. We hope this document will be helpful for physicians, pediatricians and cardiologists of the country to diagnose and treat acute rheumatic fever and RHD.

Keywords: Acute Rheumatic Fever, Consensus document, Rheumatic Heart Disease, Nepal.

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Introduction

Acute Rheumatic Fever (ARF) is an autoimmune disease consequence to Group A beta-hemolytic streptococci (GAS) related pharyngitis. Skin infections caused by streptococcus has also been implicated in certain population. It most commonly occurs in the age group of 5 to 15 years.[1] It is mostly associated with poverty, overcrowding, malnutrition, and limited access to healthcare. Incidence is decreasing in developed countries like North America and Western Europe (<0.1/1000). However, it is still high in Eastern Europe, the Middle East, Asia, Africa, Australia, and New Zealand with an incidence rate of >0.1/1000.[2]

Data on burden of Rheumatic Heart Disease (RHD) in Nepal is limited. In studies done in the nineties and early 2000s among school-going children of Kathmandu valley, the prevalence of RHD ranged from 1.2 to 1.35 per 1000.[3-5] After a decade, a larger study done on nearly 35000 school-going children within the Kathmandu valley revealed the prevalence of RHD to be 0.9 per thousand, indicating the burden has slightly decreased in Kathmandu valley, probably due to improvement in healthcare facilities, living standard and preventive efforts.[6] However, studies conducted outside Kathmandu valley reported the prevalence to be above one per thousand.[7] A recent study conducted in Jajarkot, a rural and underdeveloped region of Nepal revealed the prevalence of 7.32 per 1000 school children. This data suggests that the magnitude of the problem is still huge in rural Nepal.[8] All these studies were on auscultation detected murmur followed by echocardiography. Thus these studies might have missed subclinical RHD.A study conducted in the eastern part of Nepal in 2015, diagnosed with clinical and echocardiographic evaluation revealed the prevalence of borderline and definite RHD to be 10.2 per 1000 children. It also showed incidence remaining stable at 1.1 per 1000 children per year.[9] This study indicated that the burden of the disease might be much larger than previously anticipated. A study conducted in Pokhara revealed the prevalence of GAS infection and clinical Pharyngitis among school children to be 7.2% and 25.3% respectively.[10]

The decline of ARF and RHD in developed countries is mainly due to the introduction of antibiotics in the 1940s along with improvement in socioeconomic standards, less overcrowding in houses, and improved access to medical care.[11] Some developing countries have recently reported decreased incidence due to the implementation of comprehensive public health programs for primary and secondary prevention of rheumatic fever.[12] Primary prevention appears to reduce the attack rate by as much as 80%.[13] The priority of primary and secondary intervention cannot be more emphasized. The development of evidence-based

guidelines at the national level by a multidisciplinary group, with the involvement of local stakeholders and adaptation to the local context by local practitioners, is recommended for improved comprehensive RHD care and prevention. Good quality clinical practice guidelines provide recommendations based on current best-evidence summaries, informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options, and are intended to improve the quality and outcomes of patient care.[14]

This document aims to provide a consensus statement on the diagnosis and management of ARF and RHD in Nepal. The task force consisting of writing committee members was formed by the Cardiac Society of Nepal (CSN) executive committee which included cardiologists, pediatric cardiologists, and cardiac surgeons. The document was developed after an extensive review of available scientific literature, multiple roundtable discussions, and meetings by writing committee members. This document was also extensively reviewed by independent review committee formed by the Cardiac Society of Nepal. It was finally endorsed by the executive committee of CSN 2021-2023.This consensus document might be a stepping stone toward forming recommendation guidelines that will result in a better outcome for RHD prevention in Nepal.

Diagnosis and Management of Streptococcal Tonsillopharyngitis

GAS tonsillopharyngitis is the preceding event for acute ARF. Prompt diagnosis and appropriate treatment of GAS tonsillopharyngitis play an important role in the prevention of an initial attack of ARF. This refers to the primary prevention of ARF.[15]

Acute tonsillopharyngitis is more often caused by viruses than bacteria. Due to overlapping clinical features, clinical differentiation of viral or non-Streptococcal tonsillopharyngitis from GAS infection is challenging. Clinical diagnosis of GAS tonsillopharyngitis may be based on some clinical predictive rules, which include clinical features like a) sore throat, b) fever, c) enlarged tonsils with exudates and pus points, d) presence of tender anterior cervical lymphadenopathy and e) absence of rhinorrhea and cough. However, none of these clinical manifestations are specific enough to diagnose GAS tonsillopharyngitis.

The gold standard for diagnosis of GAS tonsillopharyngitis is a throat swab culture. A rapid antigen diagnostic test (RADT) based on a throat swab is an alternative method for diagnosing GAS tonsillopharyngitis. Either of these tests should be done based on local availability.[16]

Anti-Streptolysin O (ASO) and antideoxyribonuclease antibodies reflect past and not current GAS infection. Therefore, they should not be used to diagnose current GAS tonsillopharyngitis.

Treatment of GAS tonsillopharyngitis (Primary Prevention)

The aim of treatment of GAS tonsillopharyngitis with antibiotics is to eradicate GAS infection before it can trigger an immune response leading to ARF. Penicillin is the drug of choice for the treatment of GAS tonsillopharyngitis. GAS resistance to penicillin has not been reported. It is most effective if penicillin is started within 9 days of the onset of acute illness.

A single intramuscular injection of Benzathine Penicillin G (BPG) is the preferred agent. However, due to pain and discomfort caused by intramuscular injection, children and their parents are unwilling to take BPG injections in the real world for primary prevention. In this context, we recommend oral phenoxymethyl penicillin as a primary agent to treat GAS tonsillopharyngitis. Other effective drugs used for the treatment of GAS tonsillopharyngitis are mentioned in table 1. In patients with known minor hypersensitivity to penicillin, cephalosporins are the better options. In those with a history of angioedema, hypotension, or anaphylaxis following BPG injection administration, macrolide antibiotics should be given.[17]

American Heart Association(AHA) recommends treatment of all sore throat with antibiotics only after microbiological confirmation of GAS infection.[18] However, in view of the high endemicity of RHD and lack of resources for microbiological testing in our setup,[19] we recommend antibiotic treatment of sore throat with clinical suspicion of GAS infection (based on clinical predictive rules).

Table 1: Antibiotics used in the treatment of GAS tonsillopharyngitis

Agent	Dose	Route	Duration
Benzathine Penicillin G	For ≤ 27 kg: 600000 U single dose For > 27 kg: 1200000 U single dose	Intramuscular	Once
Phenoxy Methyl Penicillin (Penicillin V)	For ≤ 27 kg: 250 mg 8 hourly For > 27 kg: 500 mg 8 hourly	Oral	10 days
Amoxycillin	Children: 10-15 mg/kg/dose 8 hourly Adult: 500mg 8 hourly	Oral	10 days
For individuals allergic to Penicillin			
Cephalexin / Cefadroxil	Adult: 500mg twice daily Child: 25-50mg/Kg twice daily	Oral	10 days
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days
Clarithromycin	15 mg/kg/day divided in 2 doses (maximum 250 mg BID)	Oral	10 days

Diagnosis of ARF

At present, diagnosis of ARF is made using the Revised Jones Criteria based on major and minor criteria supported by evidence of preceding GAS infection as recommended by AHA in 2015 (Table 2).[20] We recommend the same criteria in our setup as well. The Revised Jones criteria propose different diagnostic parameters for low-risk and moderate to a high-risk population. As ARF incidence of >2 per 100,000 school-age children per year or all-age RHD incidence of >2 per 1000 population is categorized as moderate to this high-risk category, it is recommended that we should follow this criteria proposed for our population. This includes criteria like polyarthralgia, low-grade fever, and only slightly increased acute phase reactants which are more common in our population. If the recommended major and/or minor criteria are met along with evidence of preceding GAS infection, which is an essential criterion, diagnosis can be established.

Table 2: Diagnosis of Acute Rheumatic Fever

A. Essential criteria (Evidence of preceding GAS infection) *Any one of the following* • *ASO titre> 400 IU or more than cut-offs by age* • *A rising ASO titre defined as a twofold or greater difference between titres measured at presentation and when convalescent (2-4 weeks later generally).* • *Anti-deoxyribonuclease B (normal values AntiDNase B titre 1:60 in preschool, 1:480 in school children & 1:340 in adults)* • *A positive throat swab for group A streptococcus at presentation.*
Diagnosis: **Initial ARF-** 2 major or 1 major plus 2 minor manifestations Diagnosis: **Recurrent ARF**- 2 major or 1 major and 2 minor or 3 minor manifestations
B. Major criteria
Carditis (clinical and/or subclinical)
Arthritis (polyarthritis/monoarthritis/polyarthralgia)
Sydenham's Chorea (ARF can be diagnosed on the basis of chorea without other manifestations or evidence of GAS infection, maybe only late symptom, duration ranging from 1–2 weeks to 2–3 years. Around 30% of patients with chorea may present as subclinical carditis.)
Erythema marginatum
Subcutaneous nodules
C. Minor criteria
Monoarthralgia
Fever (≥38°C)
ESR≥ 30mm in the first hour and/or CRP≥3.0mg/dl
Prolonged PR interval after accounting for age variability (unless carditis is a major criterion) *(Normal upper range of PR interval: 3-12 years: 0.16 sec, 12-14 y: 0.18 sec, >17 y: 0.2 sec)*
Raised blood WBC count for age

Clinical Conditions

1. **Recurrent ARF:** A new episode of rheumatic fever following another GAS infection; which occurs after 8 weeks following stopping treatment.
2. **Subclinical Carditis:** When the clinical examination is normal but the echocardiogram is abnormal.
3. **Indolent Carditis:** Carditis of slow progression or insidious onset; the patient usually presents months after ARF. It is very common in our country.

Rheumatic Heart Disease

RHD is a condition of permanent heart valve damage due to repeated episodes of ARF. Once ARF occurs, there is a very high rate of recurrence and the valve damage becomes evident. Recurrence of ARF is the most important factor that determines the severity and prognosis of RHD. Early diagnosis of RHD is very important so that secondary prophylaxis can be started as soon as possible to prevent the progression of valve damage. Echocardiography is the main diagnostic test to confirm the diagnosis of RHD. The degree of cardiac involvement is quite variable, ranging from very mild, subclinical valvulitis to severe carditis with significant acute mitral and/or aortic regurgitation resulting in heart failure. The acute rheumatic cardiac involvement may resolve or persist and evolve as chronic rheumatic valvular disease, with cardiac symptoms developing years after the initial episode. Chronic mitral regurgitation is the most common form of RHD in children and young adults. The next most commonly affected valve is the aortic valve.

Types of RHD

RHD can be divided broadly into clinical and subclinical RHD.

- **Clinical RHD:** In clinical RHD, patients usually develop symptoms and have murmurs during cardiac auscultation.
- **Subclinical RHD:** Subclinical RHD is diagnosed only with echocardiography. On auscultation, patients do not present with a heart murmur. These are silent cases and are easily missed in the community. Echocardiography screening is useful in the diagnosis of such cases.

Diagnosis of RHD

History, signs and symptoms including heart murmurs on auscultation, Electrocardiogram (ECG), Chest X-ray, Laboratory investigations like ASO titre, C-reactive protein (CRP), etc. are important for the diagnosis of RHD. However, echocardiography is considered the gold standard test for diagnosis of RHD. We recommend World Heart Federation(WHF) criteria for the diagnosis of RHD.[21] (Table 3-5). Echocardiography also provides other important diagnostic and prognostic information like types of valvular lesions, disease severity, cardiac chamber dilatation, cardiac function, pulmonary artery pressure, etc., which are used for clinical decision makings.

Table 3: Morphological features of RHD

Features in the Mitral Valve (MV)

- Anterior mitral valve leaflet (AMVL) thickening ≥3 mm (age-specific)
  AMVL thickness should be measured during diastole at the 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 ≥2.0 MHz.
  Abnormal thickening of the AMVL is age-specific and defined as follows: ≥3 mm for individuals aged ≤20 years; ≥4 mm for individuals aged 21–40 years; ≥5 mm for individuals aged >40 years. Valve thickness measurements obtained using harmonic imaging should be cautiously interpreted and a thickness up to 4 mm should be considered normal in those aged ≤20 years.
- Chordal thickening
- Restricted leaflet motion
  Restricted leaflet motion of either the anterior or the posterior MV leaflet is usually the result of chordal shortening or fusion, commissural fusion, or leaflet thickening.
- Excessive leaflet tip motion during systole
  Excessive leaflet tip motion is the result of elongation of the primary chordae, and is defined as displacement of the tip or edge of an involved leaflet towards the left atrium resulting in abnormal coaptation and regurgitation. Excessive leaflet tip motion does not need to meet the standard echocardiographic definition of MV prolapse disease, as that refers to a different disease process. This feature applies to only those aged <35 years. In the presence of a flail MV leaflet in the young (≤20 years), this single morphological feature is sufficient to meet the morphological criteria for RHD (that is, where the criteria state "at least two morphological features of RHD of the MV" a flail leaflet in a person aged ≤20 years is sufficient).

Features in the Aortic Valve (AV)

- Irregular or focal thickening
- In the parasternal short axis view, the right and noncoronary aortic cusp closure line often appears echogenic (thickened) in healthy individuals and this should be considered normal.
- Coaptation defect
- Restricted leaflet motion
- Prolapse

Table 4. Criteria for Pathological Regurgitation

Pathological Mitral Regurgitation (MR)
(All four Doppler echocardiographic criteria must be met)

- Seen in two views
- In at least one view, jet length ≥2 cm
- A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red).
- Velocity ≥3 m/s for one complete envelope
- Pan-systolic jet in at least one envelope

Pathological Aortic Regurgitation (AR)
(All four Doppler echocardiographic criteria must be met)

- Seen in two views
- In at least one view, jet length ≥1 cm
- A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red).
- Velocity ≥3 m/s in early diastole
- Pan-diastolic jet in at least one envelope

Table 5. 2012 World Heart Federation(WHF) criteria for echocardiographic diagnosis of RHD[21]

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. Mitral Stenosis (MS) mean gradient ≥4 mmHg
   Congenital MV anomalies must be excluded. Furthermore, inflow obstruction due to nonrheumatic mitral annular calcification must be excluded in adults.
C. Pathological AR and at least two morphological features of RHD of the AV
   Bicuspid AV, dilated aortic root, and hypertension must be excluded.
D. Borderline disease of both the AV and MV
   Combined AR and MR in high prevalence regions and in the absence of congenital heart disease is regarded as rheumatic.

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
Congenital MV anomalies must be excluded. Furthermore, inflow obstruction due to nonrheumatic mitral annular calcification must be excluded in adults.
C. Pathological AR and at least two morphological features of RHD of the AV, only in individuals aged <35 years
Bicuspid AV, dilated aortic root, and hypertension must be excluded.
D. Pathological AR and at least two morphological features of RHD of the MV

Management of ARF

Management includes treatment of acute illness and prevention of recurrence of rheumatic fever (secondary prevention).

Treatment of Acute Illness

- Hospitalization for Moderate to Severe Carditis, Severe Arthritis or Chorea.
- Antibiotic to eradicate GAS infection and prevent future reinfection,
- Anti-inflammatory therapy for symptomatic relief. (Table 6)
- Management of heart failure if present.
- Management of Chorea if present. (Table 7)
- Supportive treatment.

All cases of ARF should receive an Antibiotic - Injection BPG is the first-line antibiotic recommended for ARF (Tables 1, 8). This serves as the first dose of penicillin prophylaxis as well.[22-24] If BPG cannot be used; other antibiotics should be used as mentioned in table 1.

Table 6: Anti-inflammatory therapy for symptomatic relief [24,25]

Aspirin

- Aspirin is the first line agent for ARF with or without mild carditis.
- Starting dose of Aspirin is 50-60 mg/kg/day for children (maximum 100mg/kg/day) and 6-8 gm/day for adults in 4 divided doses (QID) for 4 weeks.
- Taper the dose once symptoms are resolved and the acute phase reactants (ESR, CRP) decrease.
- Total duration of treatment is 12 weeks or should be individualized depending upon the severity of illness.

Naproxen: If Aspirin intolerance is detected:
Dose: 10-20mg/kg/day

Steroids (prednisolone):

Prednisolone is indicated in the following situations and it may be lifesaving in fulminant carditis.

1. Patients who do not tolerate Aspirin.
2. Patients who do not improve with Aspirin.
3. Patients with moderate to severe carditis.

Dose and treatment duration of Prednisolone:

- 1-2mg/kg/day for 2 weeks.
- Then start to taper by 5mg every 2-3 days.
- While tapering steroid, overlap with Aspirin (initial dose 60mg/kg/day in 4 divided doses)

Continue Aspirin for 4~6 weeks after tapering off Prednisolone.

Table 7: Treatment of Chorea[24,25]

Mild-Moderate cases do not need medication. For severe cases, Haloperidol or Carbamazepine or Valproic acid can be given. Carbamazepine: 3.5 -10mg/kg /dose PO BID Sodium Valproate: 7.5-10mg/kg/dose PO BID Haloperidol: 0.25 - 0.5mg/day PO BID ~TID Continue treatment till 2-4 weeks after clinical improvement.

Secondary prevention of ARF

Recurrent GAS tonsillopharyngitis may cause repeated attacks of ARF which may lead to further damage to the heart valves. Thus, treatment aimed at prevention of recurrences of GAS tonsillopharyngitis, recurrences of ARF, and progression of heart valve damage with proper antibiotics for a long duration is known as secondary prevention of ARF. Secondary prevention is absolutely necessary for symptomatic definite RHD and "subclinical definite RHD". It is also recommended in patients with borderline RHD in resource-limited areas where the prevalence of RHD is high with inadequate access to valve surgery (Tables 8 and 9).[26-29]

We recommend BPG injection as the preferred agent for secondary prevention of ARF in the vast majority of patients due to its efficacy. If BPG cannot be used, other drugs as mentioned in Table 8 should be considered.[29] Duration for secondary long-term prophylaxis against rheumatic fever is recommended as shown in table 9.[29]

Table 8: Antibiotics used in Secondary prevention of RHD

Drug	Dose	Route / Frequency of dose
Inj. Benzathine Penicillin G (deep IM) -Contraindicated if Penicillin allergy present	Body weight > 27 Kg: 1.2 million units Body weight <27 Kg: 0.6 million units	IM / Every 21 days
Phenoxy Methyl Penicillin (Penicillin V) - Contraindicated if Penicillin allergy present	Body weight > 27 Kg: 250mg Body weight <27 Kg: 125mg	PO / twice a day, daily
Erythromycin(Oral) - Contraindicated in liver disease	Body weight > 27 Kg: 250mg Body weight <27 Kg: 125mg	PO / twice a day, daily

Table 9: Duration of Secondary prophylaxis[29]

Categories	Duration
ARF with no proven carditis	Minimum of 5 years after last ARF episode or until age 21 years(whichever is longer)
Carditis without residual valve involvement	Minimum of 10 years after last ARF episode or until age 25 years(whichever is longer)
Carditis with residual valvular heart disease	Up to 40 years of age
Carditis with residual severe valvular heart disease Post intervention or cardiac surgery	Up to 40 years of age (or Lifelong if needed)

Management of cardiac complications: Congestive Heart failure (CHF), Arrhythmias, Endocarditis, Thromboembolism

Management of CHF

CHF in ARF: Bed rest, salt and fluid restriction, standard heart failure medications such as diuretics, vasodilators [Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs)], and beta-blockers (when patient is euvolemic) are recommended for symptomatic relief of heart failure. Corticosteroids are reserved for heart failure with NYHA class IV not responding to NSAIDs if surgery is not indicated or unavailable. Surgery for intractable heart failure associated with severe mitral or aortic regurgitation is preferably deferred until the ARF has resolved.

CHF in chronic RHD: Management of CHF in RHD in young patients mostly follows the principles of heart failure management as per the guidelines in adults. Although guidelines are in favor of either surgical or catheter-based therapy for severe or symptomatic valvular heart disease, pharmacological management is needed for improving symptoms and stabilizing patients till definitive management can be performed.[30-33] The principal strategies for the management of CHF in RHD are as follows:

Supportive management- includes restriction of physical activities, and salt and fluid restriction to reduce symptoms. Treat concomitant anemia with iron and/or blood transfusion as indicated. Monitor weight and fluid balance.

Pharmacological Management- *Moderate to Severe Mitral Regurgitation (MR):* Management includes diuretics (loop diuretics and spironolactone) to reduce preload and vasodilator therapy (ACE inhibitors and ARBs) to reduce afterload. Additionally, digoxin and beta-blockers may be considered.

Mitral Stenosis (MS): Diuretics (Loop diuretics, aldosterone blockers, potassium sparing diuretic and thiazides) are indicated to reduce preload. However, it should be used cautiously to avoid over diuresis which can reduce cardiac output. Similarly, beta-blockers, calcium channel blocker and digoxin can be used to reduce heart rate which improves LV filling and reduce left atrial pressure.

Aortic regurgitation (AR): ACE inhibitors/ ARBs can be used along with diuretics for symptomatic improvement. Concomitant hypertension should be managed adequately.

Arrhythmia

Atrial fibrillation (AF) is a frequent complication of ARF and RHD. It is most commonly associated with mixed mitral valve disease(MS/MR) and tricuspid regurgitation.[34,35] It can cause acute decompensation of heart failure and thromboembolic complications like stroke and acute limb ischemia. Management of AF involves three main aspects which include rate control, rhythm control and anticoagulation.[25,30] Drugs used in the management of AF are shown in Table 10.

Table 10: Strategies for the management of AF

Strategies	Drugs
Rate control – for hemodynamically stable patients with chronic AF and fast AV conduction	Beta-blockers, Calcium channel blockers, Digoxin
Rhythm control – for hemodynamically unstable patients with AF of recent onset	Electrical cardioversion Pharmacological cardioversion – Amiodarone

Infective Endocarditis (IE)

It is a devastating complication of RHD with high mortality rates up to 30% at 1 year.[36] In the few studies from Low and Middle-Income Countries (LMICs), RHD was found to be the underlying valve disease in 5.4% to77% of cases.[37] Management of endocarditis involves prophylaxis and treatment of endocarditis. Antibiotic prophylaxis is recommended for high-risk dental procedures which involve manipulation of the gingival or periapical region or perforation of the oral mucosa. Antibiotic prophylaxis is required in patients with RHD if the patient has a previous history of infective endocarditis or prosthetic valve replacement.

Antimicrobial therapy is the cornerstone in treating IE. Empirical therapy with a combination of antibiotics based on clinical and epidemiological clues to the etiology can be started till the culture sensitivity reports are available.[30] As >80% of IE are caused by staphylococcus, streptococcus and enterococcus, initial antimicrobial therapy should cover all these organisms. These can be covered with a combination of ceftriaxone, gentamycin and/ or vancomycin. Once the culture sensitivity report is available appropriate antibiotics can be initiated.

Emergency surgery is needed in IE patients with aortic or mitral native valve endocarditis with severe regurgitation, obstruction or fistula causing refractory pulmonary edema or cardiogenic shock. Urgent surgery in IE patients is needed in patients with severe CHF, uncontrolled infection such as left-sided IE caused by Staphylococcus aureus, fungal or other highly resistant organisms, uncontrolled infection despite optimum antimicrobial therapy, locally uncontrolled infection (Abscess, false aneurysm, fistula, and enlarging vegetation) and for prevention of embolism with persistent vegetation greater than 10 mm after one or more embolic episode despite appropriate antibiotic therapy and in right-sided I.E, refractory right-sided heart failure and/or vegetation size greater than 20mm with recurrent pulmonary embolism.[30]

Management of Chronic RHD

Diuretics relieve pulmonary congestion, peripheral edema, and symptoms of dyspnea. Beta-blocker, non-dihydropyridine calcium channel blockers and digitalis are useful to control ventricular rate in patients with AF. Anticoagulation is indicated in the patient with AF and Left Atrial/Left Atrial Appendage (LA/LAA) clots. Management of individual lesions based on ACC/AHA guidelines are summarized below.[30]

Mitral Stenosis

The type of intervention is either percutaneous transvenous mitral commissurotomy (PTMC) or surgery, as well as its timing, should be decided based on clinical characteristics, anatomy of the valve and subvalvular apparatus, and local expertise.

Indications for intervention PTMC or Mitral Valve Replacement (MVR) for MS is

1. Symptomatic severe rheumatic mitral stenosis (Stage D) with valve area less than or equal to 1.5 square cm.
2. Asymptomatic patients (Stage C) with PASP >50mg Hg and new AF, and progressive MS with MVA > 1.5 square cm.

Suitable valve anatomy should be subjected to PTMC if not contraindicated. Contraindications for PTMC are severely calcified valve, LA/LAA clot and more than mild MR.

Mitral stenosis of less severity can be treated medically.

Mitral Regurgitation

Indications of intervention (repair or replacement) for MR are:

1. Symptomatic severe MR (stage D), regardless of Left Ventricle (LV) function.
2. Asymptomatic severe MR (Stage C2) with LV systolic dysfunction Left Ventricular Ejection Fraction (LVEF) < 60% or End Systolic Dimension (ESD) > 40mm
3. Asymptomatic normal LV function severe MR (stage C1) LVEF >60%, ESD<40mm, accompanied by a progressive increase in LV size or decrease in LVEF on at least 3 studies.

Mitral regurgitation of less severity can be treated medically with diuretics, vasodilators, ACE inhibitors and digoxin as indicated and need regular follow-up.

Aortic Stenosis

Indications of AVR for AS

1. Symptomatic severe AS (Stage D1) Maximum Velocity (Vmax) > 4m/s or Mean Pressure Gradient > 40mmHg.
2. Symptomatic Severe AS V max > 4m/s and AVA < 1.0 cm^2
3. Symptomatic Severe AS (stage D2) Vmax > 4 m/s, with LVEF < 50%
4. Symptomatic Severe AS (Stage D3) AVA < 0.6cm^2 /m^2 and Stroke Volume Index (SVI) 35ml/m^2 irrespective of LVEF
5. Asymptomatic severe AS (Stage C) V max > 4m/s with LVEF <50% or abnormal exercise stress test
6. Moderate Aortic Stenosis (Stage B) V max 3-3.9 m/s, when concomitant cardiac surgery is planned for other lesions

Aortic stenosis of less severity is treated conservatively and kept under regular follow-up.

Aortic Regurgitation

Indications of AVR for Aortic Regurgitation are

1. Severe AR symptomatic (Stage D)
2. Severe AR asymptomatic (stage C), LVEF < 55% (Stage C2), concomitant with other cardiac surgery, LVEF 55% and Left Ventricle End Systolic Dimension (LVESD) >50 mm Hg, progressive decrease in LVEF to 55%-60% or increase in Left Ventricle End Diastolic Dimension (LVEDD) to > 65mm on at least 3 studies.

Vasodilators such as Angiotensin-converting enzyme inhibitors (ACE-I) and ARBs help to control hypertension and help alleviate symptoms. AR of less severity is treated medically with ACE-I, ARB, diuretics, etc. as needed and kept under regular follow-up.

Choice of Prosthesis

Patients under 50 years of age are usually advised for metallic prostheses. An individualized decision should be made for patients of 50-60 years of age regarding the choice of either a mechanical or biological prosthesis with consideration of patients factors. Patients above 60 years of age should be considered for the bioprosthetic valve.

Anticoagulants choice and management of anticoagulation in prosthetic heart valves are mentioned in Table 11 and in patients with Atrial Fibrillation are mentioned in Table 12.

Table 11: Anticoagulation for Prosthetic Heart Valves

Valve	Recommended INR
Mechanical Valve (lifelong anticoagulation)	2.5 -3.5
Mitral Prosthetic Valve	2.0 -3.0
Aortic Prosthetic Valve	
Bioprosthetic Valve (only for 3 months if no other indications)	
In mitral and aortic position	2.0-3.0
Prosthetic annuloplasty rings	2.0-3.0

Aspirin is indicated in patients after valve surgery for lifelong if not contraindicated.

Table 12: Anticoagulation for Atrial Fibrillation

Anticoagulation– for all patients in Atrial Fibrillation	Warfarin to achieve INR of 2-3
For patients in non-valvular Atrial Fibrillation (AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair)30	Warfarin or Novel Oral Anti Coagulants (NOACs) can be used

Management of adverse effects of BPG

Patients with ARF require antibiotic prophylaxis to prevent recurrent infection from GAS organism and progression to the cardiac involvement. BPG given intramuscularly every 3-4 weeks apart is the most preferred regimen used in the majority of the patients with ARF and RHD.[38] However, there is a growing body of evidence that patients with RHD who have severe valvular heart disease with or without reduced ventricular function may be dying from cardiovascular compromise following BPG injections, which are being attributed to vasovagal syncope with coronary hypo-perfusion rather than anaphylaxis. As these deaths appear predominantly hemodynamic, a painful BPG injection maybe responsible for hypotension, decreased coronary perfusion, ventricular arrhythmias, and death in a patient with significant existing cardiovascular compromise.

The authors of this consensus document also hold a similar opinion as such phenomenon has been observed in their clinical practice as well. For patients with elevated risk (with severe valve disease), in whom the risk of adverse reaction to BPG, specifically cardiovascular compromise, may outweigh its theoretical benefit, oral prophylaxis is being strongly considered as per the latest advisory released by ACC/AHA. We also recommend oral penicillin in a few high-risk patients with severe valve disease with CHF in whom cardiovascular compromise is likely following penicillin injection, especially in a small clinical setup where advance management may not be possible in case of any mishaps. For all other patients without severe valvular heart disease, BPG injection is still considered the most preferred agent for primary and secondary prevention as the true risk of anaphylaxis following a BPG injection is lower than previously assumed.

The incidences of allergic and anaphylactic reactions to BPG injection are reported to be 3.2% and 0.2% respectively and the fatal reactions are rare. In a report published in Nepal, only 65 allergic reactions (5 anaphylaxis and 60 minor allergic reactions) and 8 vasovagal reactions were documented out of 77,300 BPG injections given to 4712 patients over a period of 32 months without any reported death. Hence, the anaphylaxis rate was 0.1% or 0.7/10000 injections.[33,39,40] and vasovagal reaction was noted in 0.16%. The long-term benefits of BPG therapy in preventing ARF far outweigh the risk of a serious allergic reaction. The skin test is recommended before the first penicillin injection and with a change in batch number and brand.[40,41,42]

Signs and symptoms of cardiovascular compromise and anaphylaxis

Signs of a cardiovascular response often occur immediately after administration of BPG and can include low BP, slow heart rate, and fainting, all of which may lead to low blood flow to the heart, irregular heart rhythm and sudden cardiac death. Signs of anaphylaxis after BPG injection are usually slightly delayed after the injection, even up to an hour later, and include coughing, respiratory distress, wheezing, rapid heart rate, low BP that does not respond to a position change, fainting, itching, and redness at the injection site, conjunctivitis; or swelling of eyes, lips, tongue, mouth, face, or extremities agitation; convulsions; acute change in mental status.[33]

Management: Measures to reduce the pain during BPG injection, injection administration in the supine position and letting the patient eat and drink 30-60 minutes before injection may help to reduce vasovagal reactions and cardiovascular compromise following BPG injections. If it occurs despite precautions, it should be managed following standard ACLS algorithms. Anaphylactic reactions are the most severe and potentially life-threatening dramatic conditions seen in penicillin allergy. Acute treatment is based on international guidelines and recommendations.

Adherence to secondary prophylaxis with BPG injection is reduced due to injection pain and safety concerns. To address these issues we recommend practice measures for safe injection BPG delivery (table 13) and minimizing injection pain (table 14).[43]

Table 13: Recommendations on safe Benzathine Penicillin injection delivery

1. Take consent from the patient or his/her relative before the first penicillin injection, with a change in batch number and brand.
2. Record the brand name and batch number of the BPG.
3. Reconstitute the BPG powder with 3.5 ml of sterile distilled water.
4. Use 2 separate needles: 1 for pricking the vial and the other for injecting into the patient.
5. Use a 10 ml syringe and 21-G needle for deep intramuscular injection.
6. Patient should lie down on trolley or bed on abdomen with head resting on a pillow in a comfortable and relaxed position. In hospital settings, beds should be portable to rush the patient to the intensive care unit in case of emergency.
7. Inject BPG deep intramuscularly in the upper outer quadrant of the buttock.
8. Stay prepared for the treatment of possible adverse effects. Penicillin injection rooms should have emergency care kit boxes with all necessary medicines and instruments.

   The following medicines and instruments should be ready for emergency use:

   a. Adrenaline injection: l ampoule pre-loaded into the syringe.
   b. Atropine injection.
   c. Dexamethasone and antihistamine injection.
   d. Intubation set.
   e. Suction machine.

Table 14: Recommendations for minimizing the pain of BPG injection

1. Shake the powdered BPG vial after adding 3.5 ml of distilled water until the powder dissolves and an opaque, viscous, suspension is formed with a final volume of 5.0 ml.
2. Use a 21-G taper cut needle for intramuscular injection.
3. Properly select the injection site and apply finger pressure for 10 s.
4. Stretch the skin at the injection site with the thumb and index finger.
5. Inject the liquid medicine at a 90-degree angle with a taper cut needle tip facing downward in a vertical plane, which will cause minimum nerve end damage.
6. Never double prick with the same needle.
7. Push the syringe slowly, applying sufficient pressure in a gradually increasing manner to allow the crystals in the viscous medicine to flow smoothly. It may take up to 1 min to push 5.0 ml of solution.
8. Distract the attention of the patient away from the injection.
9. Maintain the injection delivery room temperature below 30 C. In hot air and on moist skin, the injections are more painful.
10. Apply an ice pack in case of pain immediately after injection.
11. Mix 0.5 to 1.0 ml of 1% lignocaine with the BPG solution for reducing pain if all other techniques fail.

Prevention and follow-up

Rheumatic heart disease is a chronic condition and it impacts not only individuals but families, communities and governments too. Therefore effective comprehensive RHD control program encompasses prevention, diagnosis and treatment of RHD to reduce the burden of the disease. These programs should include awareness raising, active surveillance, proper advocacy and effective preventive measures. These programs should be effectively described, designed, implemented and frequently evaluated and should include a collection of the burden of disease data, fostering government engagement, community education, development of an RF/RHD register and medical management of existing cases of RHD.

Due to the chronic nature of the disease, RHD patients should be regularly followed up. The recommendation for the follow-up has been modified from the 2020 Australian ARF and RHD guidelines.[24]

Table 15: Recommended Follow-up

Severe RHD High-risk post-valve surgical patients ≥ 3 episodes of ARF within the last 5 years Pregnant women with RHD (of any severity) Children ≤ 5 years of age with ARF or RHD	Specialist review: at least 6 monthly Echocardiogram: at least 6 monthly Dental review: within 3 months of diagnosis, then 6 monthly
Moderate RHD Moderate risk post-valve surgical patients	Specialist review: yearly Echocardiogram: yearly Dental review: within 3 months of diagnosis, then 6 monthly
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 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
History of ARF (possible, probable or definite) and completed secondary prophylaxis Resolved RHD and completed secondary prophylaxis	Specialist referral and echocardiogram: 1 year, 3 years and 5 years post cessation of secondary prophylaxis Dental review: yearly or as required

Pregnancy and RHD

The hemodynamic burden of RHD may pose significant challenges during pregnancy and delivery. Pre-pregnancy counseling allows discussion of the risks of pregnancy for the mother and fetus. Women with severe valve disease who become pregnant are at an elevated risk of heart failure (HF), arrhythmia, and other cardiac disorders along with an increase in cardiac morbidity and mortality. We recommend following AHA guidelines for the management of pregnant RHD patients.[30]

The effects of cardiac medications on the fetus must be understood so that the appropriate risks and benefits can be weighed. The use of beta-blockers with beta-1 selectivity avoids the beta-2 effects on uterine relaxation. The incidence of fetal growth retardation is lower with metoprolol than with atenolol in pregnancy Diuretics can alleviate the effects of volume overload in pregnant women with RHD and HF symptoms. However, the reduction of volume overload must be balanced against the reduction in placental blood flow associated with diuretics. ACE inhibitors and ARBs are strongly associated with fetal malformations when used by women during pregnancy and hence, are contraindicated.

Regurgitant valve lesions are generally better tolerated during pregnancy than stenotic ones. Valve surgery is reasonable only in pregnant women with severe valve regurgitation with NYHA class IV HF symptoms refractory to medical therapy. High-risk features for the development of HF during pregnancy in patients with MR include depressed LV systolic function and pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg).

Severe rheumatic MS presents a significant risk of maternal adverse outcomes during pregnancy. In asymptomatic women with severe rheumatic MS (mitral valve area ≤1.5 cm^2) and favorable valve morphology who are considering pregnancy, PTMC results in an increase in the mitral valve area and reduction in transmitral gradient, which makes the patient more resilient to the hemodynamic load of pregnancy. However, it is a high-risk procedure during pregnancy for both the mother and the fetus and should be performed only if there is a hemodynamic deterioration or if there are severe NYHA class III or IV HF symptoms, preferably during the second trimester.

Patients with severe AS may develop progressive HF or sudden hemodynamic deterioration during the stress of pregnancy. Both open heart surgery and percutaneous balloon dilation of the aortic valve are high-risk procedures during pregnancy for both the mother and the fetus and should be performed only if there is a hemodynamic deterioration or if there are severe NYHA class III or IV HF symptoms.

For patients with prosthetic valves, no anticoagulation strategy is optimally safe for both the mother and the fetus. Warfarin is safest for the mother but crosses the placenta and can cause fetal intracranial hemorrhage; fetal loss; and teratogenicity, particularly at doses >5 mg/d and when given during the first trimester, keeping in mind that the warfarin dose needed to maintain a therapeutic INR may change during pregnancy. Neither Unfractionated Heparin (UFH) nor Low-molecular-weight heparin (LMWH) crosses the placenta, but each is associated with higher rates of maternal complications than are seen with warfarin. Counseling and shared decision-making allow for a woman and her physician to choose the best therapy including anticoagulation to achieve the woman's goals. Secondary prophylaxis should be continued during pregnancy. Safe delivery should be prioritized preferably in multi-specialty hospitals.

Conclusion

This consensus document outlines the guidance for the diagnosis, management and prevention of acute rheumatic fever and rheumatic heart disease in Nepal. However, there still exists controversies regarding management which need further outcome research in our population. Till then, this document will help in reducing the burden as well as address the current inequities in acute rheumatic fever and rheumatic heart disease care in the country.

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