

Consensus Guidelines on Pediatric Acute Rheumatic Fever and Rheumatic Heart Disease

WORKING GROUP ON PEDIATRIC ACUTE RHEUMATIC FEVER AND CARDIOLOGY CHAPTER OF INDIAN ACADEMY OF PEDIATRICS

ABSTRACT

Justification: Acute rheumatic fever and rheumatic chronic valvular heart disease is an important preventable cause of morbidity and mortality in suburban and rural India. Its diagnosis is based on clinical criteria. These criteria need verification and revision in the Indian context. Furthermore, there are glaring differences in management protocols available in literature. These facts prompted Indian Academy of Pediatrics to review the management of rheumatic fever. **Process:** Management of Rheumatic fever was reviewed and recommendation was formulated at national consultative meeting on 20th May 2007 at New Delhi. **Objectives:** To formulate uniform guidelines on management of acute rheumatic fever and rheumatic heart disease in the Indian context. Guidelines were formulated for the management of streptococcal pharyngitis, acute rheumatic fever and its cardiac complication as well as secondary prophylaxis for recurrent episodes. **Recommendations:** (1) Streptococcal eradication with appropriate antibiotics (Benzathine penicillin single dose or penicillin V oral or azithromycin). (2) Diagnosis of rheumatic fever based on Jones criteria. (3) Control inflammatory process with aspirin with or without steroids (total duration of treatment of 12 weeks). (4) Treatment of chorea according to severity (therapy to continue for 2-3 weeks after clinical improvement). (5) Protocol for managing cardiac complication like valvular heart disease, congestive heart failure and atrial fibrillation. (6) Secondary prophylaxis with benzathine penicillin and management of anaphylaxis.

Keywords: Acute rheumatic fever, Guidelines, India, Practice, Rheumatic heart disease.

INTRODUCTION

Acute rheumatic fever is a non-suppurative complication of group A beta hemolytic streptococcal (GABHS) sore throat. It affects joints, skin, subcutaneous tissue, brain and heart(1). Except heart, all other effects are reversible, needing only symptomatic relief during the episodes. Cardiac complications are significant in absence of secondary prophylaxis and culminate into chronic and life threatening valvular heart disease(2).

Correspondence to: Dr Smita Mishra, Convener, National Consultative Meeting on Pediatric ARF/RHD. Pediatric Cardiologist, Max Heart & Vascular Institute, Saket, New Delhi, India. E mail: smi1@rediffmail.com

These Guidelines were formulated at National Consultative Meeting on 20th May, 2007, IMA Hall, New Delhi, under IAP Vision 2007.

Prevalence of acute rheumatic fever and rheumatic heart disease (RHD) in Indian population varies from 0.5 /1000 to 11/1000 in various studies. The disease actually has its roots in childhood (5-15 yr)(1-6). Till now any clear-cut guidelines on the subject in Indian scenario are nonexistent. Therefore, Indian Academy of Pediatrics took the initiative and convened a national consultative meeting at IMA Hall, New Delhi on 20th May 2007.

AIMS AND OBJECTIVES

This consultative meeting was convened to bring uniformity in approach on management of acute rheumatic fever and rheumatic heart disease in the Indian context. The objectives were to frame practice guidelines for:

- (i) diagnosis and management of streptococcal pharyngitis;

- (ii) diagnosis and management of acute rheumatic fever;
- (iii) management of cardiac complications of rheumatic fever;
- (iv) care of native and prosthetic valve, endocarditis prophylaxis, and anticoagulation; and
- (v) secondary prophylaxis of rheumatic fever.

Formulation of Guidelines was based on online national survey conducted by central IAP before the consensus meet to obtain pediatricians' input; experience from ICMR projects (Jai-Vigyan Mission Mode Project–Indian Council of Medical Research); available published literature (National/International); and experience from premier institutes of India represented by faculty members.

Level of Evidence

- Class I:* General agreement exists
- Class II:* Reasonable agreement, but conflicting evidence/ divergence of opinion
- Class IIa:* Weight of evidence/opinion in favor
- Class IIb:* Credibility less well established, but most agree
- Class III:* Intervention not indicated, may be harmful

RECOMMENDATIONS

1. MANAGEMENT OF STREPTOCOCCAL PHARYNGITIS

Group A beta hemolytic streptococcal (GABHS) sore throat is the first event in the natural history of acute rheumatic fever. It should be diagnosed, differentiated from non streptococcal pharyngitis and treated. Onset of symptoms is sudden. Clinically patient has high fever, sore throat with pustules, strawberry tongue, petechiae on palate and tender anterior cervical lymph nodes. The following investigations should be done: throat culture, rapid streptococcal antigen test, antistreptolysin O (ASO), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and complete blood counts. Antimicrobials to be used for GABHS pharyngitis are detailed in **Table I**. Tetracycline, sulfonamide and chloramphenicol should not to be used to treat GABHS pharyngitis because of widespread prevalence of drug resistance(7-12).

2. MANAGEMENT OF ACUTE RHEUMATIC FEVER

Diagnosis

Diagnosis is based on recognition of major and minor criteria supported by evidence of preceding streptococcal infection (**Table II**)(4,11-20).

First episode: Two major or one major and two minor criteria plus supportive evidence of previous streptococcal throat infection.

TABLE I DRUGS FOR THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS AND SECONDARY PROPHYLAXIS

Drugs	Dose	Sore-throat treatment (duration)	Secondary prophylaxis (interval)*
Benzathine Penicillin G (deep IM inj)	1.2 million unit (> 27 Kg) after sensitivity test (AST)	single dose**	21d
	0.6 million unit (<27 Kg) (after sensitivity test) contraindication: penicillin allergy	single dose**	15d
Penicillin-V (oral)	children: 250 mg qid	10d	twice a day
	adult: 500 mg tid contraindication: penicillin allergy	10d	twice a day
Azithromycin (oral)	12.5 mg/kg/day once daily	5	not recommended
Cephalexin (oral)	15-20 mg/kg/dose bid	10d	not recommended
Erythromycin (oral)	20 mg/kg/dose max 500 mg contraindication : liver disorder	not recommended	twice a day

* see text for duration of secondary prophylaxis and references. ** only one dose is sufficient for GABHS pharyngitis.

TABLE II DIAGNOSIS OF RHEUMATIC FEVER

Clinical and laboratory Criteria	Supportive evidence of preceding streptococcal infection (essential except for diagnosis of Chorea)
<i>Major criteria (more specific)</i>	Anti streptolysin O
– Carditis	ASO titer: >333 unit for children and > 250 for adults.
– Polyarthritits	Anti-deoxyribonuclease B
– Chorea	(normal values Anti DNase B titer 1:60 unit in preschool, 1:480 units in school children & 1:340 in adults)
– Subcutaneous nodule	
– Erythema marginatum	
<i>Minor criteria (less specific)</i>	<i>History of (within previous 45 days)</i>
– Fever	– streptococcal sore throat
– Polyarthralgia	– scarlet fever
– ESR, CRP, polymorphonuclear leukocytosis (follow standard laboratory values)	– positive throat culture
– *ECG: Prolonged PR interval	– positive rapid streptococcal antigen detection test

*Normal upper range; – PR Interval: 3-12 yrs: 0.16sec; 12-14 y: 0.18 sec; >17y: 0.20 sec)

Recurrence in a patient without established heart disease: Two major or one major and two minor criteria + supportive evidence of previous streptococcal throat infection.

Recurrence in a patient with established heart disease: Two minor criteria and supportive evidence of previous streptococcal throat infection.

Rheumatic chorea and insidious onset rheumatic carditis: No requirement of other major manifestations or supportive evidence of streptococcal sore throat infection

Indicators of recurrence of rheumatic fever in established heart disease:

- (i) new murmur / change in pre-existing murmur;
- (ii) pericardial rub (and other evidence of pericarditis); and
- (iii) unexplained congestive heart failure (CHF), including cardiomegaly.

Terminology

Recurrence: A new episode of rheumatic fever following another GABHS infection; occurring after 8 week following stopping treatment.

Rebound: Manifestations of rheumatic fever occurring within 4-6 wk of stopping treatment or while tapering drugs.

Relapse: Worsening of rheumatic fever while under treatment and often with carditis.

Sub clinical carditis: When clinical examination is normal but echocardiogram is abnormal. Around 30 percent of patients having chorea present as sub clinical carditis.

Indolent carditis: It is a common entity in our country. Patient presents with persistent features of CHF, murmur and cardiomegaly. There are no or very few features of carditis.

Investigation

To establish the diagnosis, relevant tests include throat culture, rapid streptococcal antigen test, ASO, ESR, CRP, hemoglobin, complete blood count, platelet count, chest X-ray and electrocardiogram (ECG)(18,19). Echocardiography is not mandatory to establish the diagnosis of rheumatic fever although it is an important role in detection of sub-clinical carditis(16,17).

Treatment

General measures and symptomatic relief:

According to clinical status, treatment for pain relief should be given (codeine or paracetamol till diagnosis is confirmed and aspirin after the diagnosis is confirmed). Hospitalization is needed for moderate to severe carditis, severe arthritis or chorea. Rest is individualized according to symptoms. For arthritis, rest for two weeks is adequate. Carditis without congestive heart failure (CHF) needs 4-6 weeks of rest. In cases of CHF, rest must be continued till the CHF is controlled. Appropriate diet is a must for a growing child with cardiac involvement(12,18,19,30).

Management of inflammatory process—therapy to be continued for 12 weeks:

Total duration of anti-inflammatory therapy after the diagnosis of acute rheumatic fever is established, must be 12 weeks (**Table III**). All anti-inflammatory drugs may cause gastrointestinal bleeds. Steroids may lead to cushingoid facies and flaring up of dormant infections. Aspirin may cause tinnitus. For side effects, monitoring is needed. Aspirin and steroids are primarily used to control inflammation. Naproxen and methylprednisolone can be used alternatively(12,18,19,21-24).

Management of chorea: Mild chorea is treated with quiet environment, and sedatives like oral phenobarbitone or diazepam. If there is no response, then one may use haloperidol (0.25-0.5 mg/kg/d), sodium valproate (15 mg/kg/day), or carbamazepine (7-20 mg/kg/d) may be used. Resistant cases can be treated with plasmapheresis or pimozide(25-28). Treatment should be continued for 2-4 weeks after clinical improvement. If there are laboratory features of rheumatic activity (ESR, CRP, ASO), anti-inflammatory drugs must be given (**Table III**).

3. MANAGEMENT OF CARDIAC COMPLICATIONS

Management of congestive heart failure: Restrict physical activities to reduce or eliminate symptoms. Monitor the weight and fluid balance (input/output charting). Treat anemia with iron and/or packed cells, as and when indicated. **Table IV** enlists the drugs and their dosages, recommended to control CHF(18,29,30).

Atrial fibrillation: Usually accompanies chronic valvular disease. It may cause acute decompensation and thromboembolism. Drugs recommended for control of atrial fibrillation are listed in **Table V** (18,30,31).

4. INTERVENTIONS IN VALVULAR HEART DISEASE

Patients, who are symptomatic, have ventricular dysfunction or have severe involvement of valve according to clinical and echocardiographic evaluation, would need intervention according to lesion(12,18,30,32-35):

A. **Mitral stenosis:** Suitable cases with pure mitral stenosis must be treated with balloon mitral valvuloplasty (BMV). The patients unsuitable for BMV may need valve repair or replacement.

B. **Mitral regurgitation:** Acute rheumatic fever with acute severe mitral regurgitation and uncontrolled congestive heart failure, secondary to chordal rupture, is a class I indication for urgent surgical intervention. Symptomatic chronic MR is treated with either valve repair or replacement.

C. **Aortic stenosis:** Isolated aortic stenosis is rare. Treatment with ballooning procedures is usually not helpful. Surgical intervention is done in symptomatic patients.

D. **Aortic regurgitation:** Aortic regurgitation presenting as isolated or combined lesion, is treated with prosthetic valve replacement.

Endocarditis and thromboembolism: Chronic valvular disease predisposes for endocarditis, thrombus formation and subsequent systemic thromboembolic events in patients with diseased native or prosthetic valves.

Endocarditis: Detailed management is beyond the scope of this article(12,18,36). Benzathine penicillin is not recommended for endocarditis prophylaxis, hence, separate antibiotic protocols must be used before catheterization or any surgical intervention. For unexplained fever, blood culture using at least three samples of blood from three different sites, at the interval of half to one hour and echocardiography is recommended in addition to routine blood examination, urine examination, X-ray

TABLE III DRUGS FOR CONTROL OF INFLAMMATION IN ACUTE RHEUMATIC FEVER

Inflammation	Doses
<i>Arthritis ± mild carditis</i> Aspirin*	<p>Regime I Starting doses: children 100 mg/kg/day for 2-3 weeks adult 6-8g/day - divide in 4-5 doses Tapering doses :once symptoms resolved, taper to 60-70 mg/kg/day. For older children 50 mg/kg/day (Level of evidence : Class I)</p> <p>Regime II 50 to 60 mg//kg /day for total 12 weeks (Level of evidence-Class Ib)</p>
Naproxen*(If aspirin intolerance detected) No response to aspirin in four days	10-20 mg/kg/day Switch over to steroid. Rule out other conditions like chronic inflammatory/ myelo-proliferative disorders before switching over to steroids.
<i>Moderate to severe carditis</i> Steroids*	<p>Regime I Prednisolone: 2mg/kg/d, maximum 80mg/day till ESR normalizes -usually 2 weeks. Taper over 2-4 weeks, reduce dose by 2.5-5mg every 3rd day. start aspirin 50-75mg/kg/d simultaneously, to complete total 12 weeks. (Level of evidence : Class I)</p> <p>Regime II Prednisolone same doses × 3-4 weeks. taper slowly to cover total period of 10-12 weeks (Level of evidence-Class IIb)</p>
<i>Non responders</i> Methyl Prednisolone (Intravenous)	If no response to oral steroid therapy then start IV methyl prednisolone 30mg/kg/day for 3 days

* Consider antacids. Avoid gastric irritants. Allow frequent feeding. Medicines must not be taken on empty stomach.

TABLE IV DRUGS AND DOSAGES FOR HEART FAILURE

Drug	Dose
Digoxin	30 mcg/kg total digitalization dose, 7.5 mcg/kg /day maintenance dose (Evidence level : Class I)
Diuretics	Frusamide 0.5 - 2 mg/kg/day, Metolazone:0.2-0.4 mg/kg/day. Adults 2.5-10 mg/day (Evidence level: Class I)
ACE inhibitors	Captopril: 0.25 mg/kg: Test dose, build up doses from 1.5 mg/day to 3 mg/kg/day in three divided doses (Evidence level Class I)
Sodium nitroprusside	(uncontrolled CHF) 0.5-10 mcg/kg/min infusion, monitor cyanide level. (Evidence level: Class I)
Inotropes	Dobutamine: 2-20 mcg/kg/min infusion; Dopamine: 2-20 mcg/kg/min infusion; Milrinone: 0.5-1 mcg/kg/min infusion (Evidence level: Class I)
Surgery	Severe mitral regurgitation due to chordal rupture leading to refractory CHF (Evidence level: Class I)

TABLE V MANAGEMENT OF ATRIAL FIBRILLATION

Usually associated with chronic valvular heart disease.

Clinical presentation: irregularly irregular pulse.

ECG: Fibrillatory wave.

Rate control	(hemodynamically stable, untreated patients of rheumatic heart disease having chronic AF with fast AV conduction) Digoxin*, Ca++ channel blocker*, beta blockers (Evidence level: Class I)
Rhythm control	(hemodynamically unstable patients of chronic RHD having AF of recent onset), Cardioversion** (level of evidence: Class I), Amiodarone infusion (Level of evidence: IIa)
Anticoagulant	Warfarin to achieve INR of 2-3 (level of evidence: Class I) Avoid vitamin K containing food like green leafy vegetables

* Before starting the treatment rule out accessory pathways (AP) as these drugs may slow down AV conduction and increase ventricular rate due to faster conduction via AP; ** Rule out left atrial clot and start anticoagulant before cardio version.

chest and other relevant investigations. Endocarditis prophylaxis and management include (i) adequate use of antibiotics only on pediatrician's advice and avoidance of self prescription; and (ii) family counseling regarding dental hygiene and other precautions.

Treatment of endocarditis needs prolonged administration of recommended IV antibiotics. Duration differs according to status of patient (with native or prosthetic valve) and the type of organism.

Anticoagulation: Therapy is indicated in the patients with atrial fibrillation or history of embolization and following the prosthetic or bioprosthetic valve replacement (**Table VI**)(18,37).

5. SECONDARY PROPHYLAXIS

Secondary prevention of rheumatic fever is defined as the continuous administration of specific antibiotics to patients with a previous attack of rheumatic fever, or documented RHD(12). The purpose is to prevent colonization or infection of the upper respiratory tract with group A beta-hemolytic streptococci and the development of recurrent attacks of rheumatic fever. Secondary prophylaxis should be started only after establishing the diagnosis of acute rheumatic fever(38-40). Isolated ASO titre is not a criteria to start secondary prophylaxis. After surgery or intervention secondary prophylaxis should be continued.

Duration of secondary prophylaxis

- (i) No carditis: 5 years/18yrs of age, whichever is longer.
- (ii) Mild to moderate carditis and healed carditis: 10 yrs/25 yrs of age, whichever is longer.
- (iii) Severe disease or post intervention patients: Life long. One may opt for secondary prophylaxis up to the age of 40 years (**Table I**).

Drugs recommended for secondary prophylaxis (Table I)

6. MANAGEMENT OF ANAPHYLAXIS

Sensitivity testing for penicillin: Ideally sensitivity test has to be done with major and minor allergen supplied separately (not available in India). Benzathine penicillin is unsuitable for skin test for various reasons. Intradermal test must be done with both benzyl penicillin and control saline (0.02-0.05 ml at volar surface of forearm or lateral surface of arm). Positive test is indicated by formation of a wheal, 2 mm more than control or 4 mm more than initial edema (test time 20-30 min).

Anaphylaxis: This is a reactionary involvement of many systems, best treated by adrenalin (IM/SC/IV) and not steroids. It needs weight appropriate administration of fluid. In severely affected cases a prolonged cardiopulmonary resuscitation is usually

TABLE VI ANTICOAGULATION FOR PROSTHETIC HEART VALVES

Valve	Recommended INR
Mechanical Valve (life long anticoagulation)	
Mitral Prosthetic Valve	2.5-3.5
Aortic Prosthetic valve	2.0-3.0
Bioprosthesis (Only for 3 month in absence of additional indications)	
In mitral or aortic position	2.0-3.0
Prosthetic annuloplasty rings	2.0-3.0

INR: International Normalized Ratio = $(x/y)z$, where x = Prothrombin Time of sample (sec), y = Mean Normal Prothrombin Time (sec); z = [ISI of Thromboplastin]

fruitful. Mechanical ventilation must be done if required. Diuretics may be detrimental even if used in pulmonary edema (36,37).

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Writing Committee: Anita Saxena, R Krishna Kumar, Rani Prem Kumar Gera, S Radhakrishnan, Smita Mishra, Z Ahmed.

Advisory Committee: A Gupta, J Singh, M Sharma, R K Agarwal, R Tandon, Simi Manocha, Y K Mishra.

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KEY MESSAGES

- In absence of effective streptococcal vaccine, early detection of GABHS pharyngitis and its treatment is only way to primary prophylaxis.
- WHO criteria (updated 2001) are recommended for diagnosis. Echocardiography can help in recognizing sub-clinical carditis. It is not included as a separate criteria.
- High ASLO titre, in absence of other Jone's criteria must not be given either anti inflammatory treatment or long term secondary prophylaxis.
- Aspirin is drug of choice for anti inflammatory treatment of arthritis and mild carditis. Major cardiac involvement needs treatment with steroids. Duration of treatment must be 12 weeks.
- Benzathine penicillin based secondary prophylaxis must be re-emphasized for prevention of cardiac complications.
- With the wider availability of valve repair/replacement procedures, pediatricians need to be aware of the indications for and problems related to valvular surgery.

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