Acute rheumatic fever (ARF)

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Access this article online

Quick Response Code:

Website: www.innovativepublication.com

DOI: 10.5958/2455-6793.2016.00009.2

DEF: Acute rheumatic fever is an auto immune disorder caused by Group A β hemolytic streptococci (GABHS) infection in the past. It involves principally the heart, joints, central nervous system (CNS), skin and subcutaneous tissues. The usual features in acute phase are-migrating polyarthritis, fever, carditis, Sydenham's chorea, subcutaneous nodules and erythema marginatum which may variably occur at times singly or in various combinations. No single s/s or lab investigations is pathognomic and several combinations –arbitrarily designated- are diagnostic. It subsides over a period of time but may leave behind sequelae in the form of rheumatic heart disease.

Epidemiology

Epidemiology of acute rheumatic fever is closely related to epidemiology of streptococcal upper respiratory infection- (pharyngitis, tonsillitis, scarlet fever and otitis media). Ac rheumatic fever used to be the commonest cause of heart disease in children till about quarter century ago. Improvements in the social parameters of housing and sanitation, more liberal use of antibiotics have all led to marked reduction in its incidence.

Disease affects mainly children of 5-15 years of age, peak incidence for 1st episode being at 6-8 years of age. It is rare below three years of age and also in adults. Younger the patient, more severe the RF; recurrences are also more likely in the young and become rare after 25 years of age. Most recurrences occur within one year of initial attack.

Risk is higher in closed groups like hostels and crowding and dampness in houses. Seasonal fluctuations occur due to seasonal variation in streptococcal infections.

No sex difference for ARF but incidence of chorea and mitral valve disease is higher in females whereas aortic valve disease is more seen in males.

Pathogenesis

A. Evidence of a recent strep infection can be usually obtained
   1. Bacterial isolation from throat at the time of infection preceding ARF
   2. Serological evidence like raised anti streptolysin (ASO) tires.
   3. Association of ARF with outbreaks of streptococcal sore throat
   4. Striking reduction in first attacks of RF when streptococcal infections are treated with penicillin and secondary attacks in patients on continuous antimicrobial prophylaxis.

B. Classic triad of agent, host and environment plays a major role.

1. GABHS has >130 serotypes, some of which are rheumatogenic. m proteins, and several other epitopes of bacteria mimic myocardium (myosin and tropomyosin), heart valves (laminin), synovia (vimentin), skin (keratin) and sub-thalamic and caudate nuclei in brain (lysogangliosides).super-antigenic activity triggered by m protein fragments as well as streptococcal toxins have been implicated in the autoimmune reactivity mediated by b cells and t cells. t cells activated against myosin and bacterial epitopes react to valve tissue. Patients developing RF manifest hyper immune response to GABHS and this correlates with severity of RF.
2. There is genetic susceptibility to risk of developing RF after GABHS pharyngitis- evidenced by 50% risk in those with prior RF. Human leucocyte antigen (HLA)–II alleles & tumor necrosis factor (TNF) –ά and other genetic markers have been identified in susceptible population. In particular, a B cell alloantigen-D8/17 appears to be both sensitive as well as specific in some endemic areas. But, cause effect relationship is unclear.

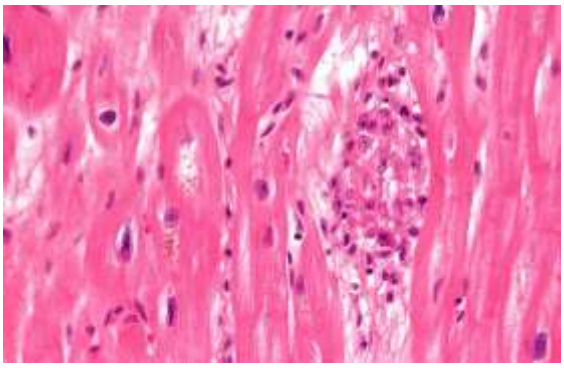
Pathology

Carditis

Exudative phase: First few weeks after onset-fibrinoid degeneration of collagen in left ventricle (LV) and endocardium with lymphocytes, macrophages and in minority of cases plasma cells, polymorphonuclear (PMN) leucocytes, eosinophils and mast cells in infiltrates -there are verrucous vegetation on valve leaflets with extensive edema.

Proliferative phase: lasts one to six month after onset. Aschoff bodies-granulomatous lesion pathognomic for rheumatic carditis are found in valves and all 3-endocardium, myocardium and pericardium.

Scarring → stenotic valve lesions which usually requires years for development.



Aschoff bodies

Arthritis: Manifests by edema, lymphocytic and PMN leucocyte infiltrates and fibrinoid lesions that resolve.

Chorea: Inflammatory lesions recorded in cerebral cortex, cerebellum and basal ganglia.

Aschoff Body doesn't develop in brain & its occurrence in joints is doubtful.

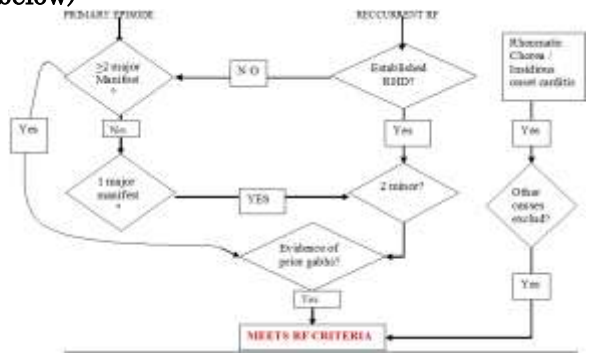
Clinical Features

Latent Period: 1-5 weeks and for chorea 2-6 months.

Rheumatic fever is a multi-system disease, acute manifestations of which may include fever, arthritis, carditis, emotional instability characteristic rash and subcutaneous nodules.

It is by nature recurrent and derives its importance from the fact that it can result in chronic heart disease. Still the leading cause of acquired heart disease in children, particularly among the poor and deprived. *It licks the joints but bites the heart*. Both acute and recurrent attacks are triggered by group A Streptococcal infections – mainly of upper respiratory tract but may be skin as well.

Diagnosis: modified Jones' criteria (diagram below)



Algorithm for diagnosis of aRF incorporating 1992 revision of Jones' criteria + WHO expert consultation report (2002-03). WHO modifications are more sensitive and less specific than AHA criteria.

Jones criteria of 1944 focused on specificity over sensitivity. Major criteria of arthritis, carditis, chorea, subcutaneous nodules and erythema marginatum have remained unchanged since 1st revision in 1956. Minor criteria now include clinical findings of fever, arthralgia & raised ac phase reactants. Evidence of prior GABHS infection was first incorporated in 1965 as an essential criterion.

Subsequent modifications have eliminated nonspecific elements from minor criteria –such as epistaxis, abdominal/ precordial pain, pulmonary findings, raised PR interval, anemia & raised white cell counts.

Only two exceptions for evidence of GABHS are made-chorea as it has long latency period and chronic low grade carditis that may sometimes follow ARF.

Presenting Manifestations

- Onset is often abrupt with fever and arthritis or chest pain and shortness of breath or may be insidious with carditis until a murmur and an enlarged liver are detected. A subtle onset is common in chorea with emotional lability.
- A history of sore throat preceding the illness is obtainable in 50% cases. Sometimes, history of RF for possible earlier attacks or a family case of rheumatic fever or rheumatic heart disease (RHD) may be obtainable as well
- Abdominal pain mimicking acute appendicitis may be the presenting symptom in about 10% cases. It is non-specific and may be due to hepatic congestion, congestive cardiac failure (CHF) or mesenteric lymphadenitis.

Fever: Almost invariable present in early stage except in cases with chorea or if it has been suppressed with drugs. After 1st week, it becomes low grade and persists for 2-4 weeks.

Arthritis of RF characteristically involves large joints, migrates from one to another and does not involve the most distal joint –as small joints of fingers and toes— and the central ones such as hip and spine. Infrequently, temporo-mandibular joint may be involved.

i. Polyarthritis is the earliest and most frequent manifestation of ARF –up to 75% in acute cases. It occurs in first 2-3 weeks of onset of RF and in about ½ to 1/3 cases it is the only manifestation.
ii. During migratory phase, multiple joints can be involved in different stages of inception and resolution. Individual joint involvement usually lasts 1-2 weeks
iii. It is self-limiting but never transient and if untreated will last weeks to months, Poly-arthritis

as a whole resolves in about one month to six weeks and chronic sequelae do not occur except rarely

iv. To be diagnosed as of rheumatic origin, polyarthritis should involve at least 2 joints, associated with at least 2 minor criteria (arthralgia is not a minor criteria if arthritis is present).

v. Pain is intense on pressure or movement, diffuse exquisite tenderness of entire joint, swelling, heat and redness is common. Pain without objective findings (arthralgia) may be present in some joints and frank arthritis in others.

vi. Arthritis may be associated with carditis but the two manifestations appear to be inversely related in severity—patients with severe arthritis have less severe carditis and vice versa.

Carditis

i. Seen in 40-60% of all cases of acute rheumatic fever and leads to rheumatic heart disease with progression dependent on severity of carditis, recurrence of rheumatic fever and use of secondary prophylaxis. It is more common with 1st episode in young infants in whom it be the only major manifestation.

ii. Tachycardia disproportionate to fever, present during sleep and persisting after fever is under control is highly suggestive of carditis.

iii. First heart sound may be muffled, consistent with first degree heart block or both first and second heart sounds may be distant in patients with pericardial effusion.

iv. Carditis typically presents as valvulitis- Significant murmurs are almost always present with rheumatic carditis, most commonly of mitral regurgitation (MR) and less commonly aortic regurgitation (AR). The severity of LV dysfunction appears to correlate with the extent of valvulitis rather than myocardial injury.

v. Neither myocarditis nor pericarditis appear to occur without valvulitis. Carditis typically presents in children with MR and also as AR in 20-40% of cases, but mitral stenosis (MS) is the most frequent valve lesion in adults. Rheumatic tricuspid stenosis (TS) is less common and isolated rheumatic aortic stenosis (AS) is rare. Stenotic lesions are late manifestation and do not develop months to years after the initial or repeated episodes of RF.

vi. Cardiomegaly, pericarditis (with or without friction rub) and congestive cardiac failure may be present. Large effusions are rare. In contrast to adults where CHF is due to altered mechanics, axiomatically any child with rheumatic heart disease in failure must have active carditis. It is usually right sided failure. Pure left heart failure is rare.

vii. In children with RHD, changing murmurs or increasing heart size may be the evidence of progressive or reactivated carditis.

Diagnosis has traditionally been based on MR (at times AR) in heart failure with cardiomegaly in severe cases. There is a linear relationship between the severity of MR during 1st episode of RF and subsequent RHD.

Recurrent episodes of RF lead to very high incidence of carditis. Diagnosis of recurrent carditis has traditionally been based on new cardiac murmurs, pericarditis and increased cardiac silhouette size.

Sydenham's Chorea, rheumatic chorea, St Vitus' dance, Chorea Minor

i. It manifests as involuntary irregular movements, fibrillation of the tongue, and often in pronation called as spooning with external rotation of the hands and abolition of movements with sleep. It is often labelled as milkmaid's grip as fingers slip through. Chorea occurs as sole manifestation in 20% cases. Subclinical carditis can be diagnosed in up to 70% with risk of RHD. Chorea is delayed manifestation of RF, has latency of 1-7 months, and lasts for months to years. Manifestations are immunologically mediated with antibodies to brain tissue. Neurological deficits resolve in about two years' time but recurrences and residual psychiatric disturbances may develop decades later.

ii. It may appear as the only clinical sign and without any lab evidence of inflammation —pure chorea. Diagnosis is made clinically after excluding other causes. Neuro-imaging is not helpful.

iii. It may precede, follow or exist concomitantly with other manifestations including RHD. However, simultaneous occurrence of polyarthritis and chorea is practically unknown.

iv. Interval between chorea and other preceding or following manifestations may be short or a matter of years.

v. Occurs most often in pre-pubertal girls and is rare among adults of either sex. Incidence equal in boys and girls before puberty. Thereafter, female hormones tend to aggravate and chorea incidence increases in post pubertal girls and also exacerbation occurs in pregnancy).

vi. Most striking feature is involuntary purposeless movements, usually bilateral but may be unilateral as well which develop gradually over weeks.

vii. Vary in intensity –from those that can be brought out only on excitation or conscious efforts to those which result in self injury.

viii. Deterioration of hand writing is common and serial samples may be needed to document the course of affliction

ix. General clumsiness-glasses and china are easily broken when the child helps with the dishes; she cannot unbutton her clothes or lace her shoes.

x. Deterioration in speech→ slurred speech. Child may have difficulty in counting rapidly and holding

protruded tongue still which may show twitching/ fibrillatory movements.

xi. Tendency for hyperextended fingers and wrists when holding his /her fingers outstretched. Similarly, palms are outstretched when she holds her arms above the head. Hand grip is weak and on holding it, examiner may detect intermittent muscular contractions or twitching.

xii. Muscular weakness may be present; patellar reflex is hung up type, signs of ataxia, gait hesitancy and angular movements sometimes as hemi-ataxia.

xiii. Emotional lability with inappropriate bursts of crying and laughter may be the first symptoms. There may be irritability, inability to conceptualize in school and explosive mood changes- both short term as well as long term.

Cutaneous Manifestations

i. Both cutaneous manifestations—subcutaneous modules as well as erythema marginatum occur in <10% of cases, and occur in association with carditis.

ii. Subcutaneous nodules are seen as 0.1-1.0 cm diameter protuberances over bony prominences of joints in limbs. They are firm, non-tender, and mostly on the extensor surface of large and small joints, scalp, and bony prominences of spine and scapulae. Skin over the nodules is movable and non-inflamed. They disappear in 1-2 months.

iii. Erythema marginatum is evanescent in nature, seen over trunk, and may persist for months to years. Pink, often slightly raised macules of early stages fade centrally and coalesce to form a serpiginous pattern. There is no itching or discomfort. Usually symmetrical in distribution. Most commonly seen over the protected parts of body.

Laboratory Findings

No specific lab findings for RF.

1. **Acute phase reactants— (erythrocyte sedimentation rate and C-reactive protein):** ESR and CRP are not specific for rheumatic fever but reliable markers for severity and generally correlate well with activity of the disease.

Pitfalls

a. Masking may be induced by anti-inflammatory conditions.

b. They are not useful in objectively documenting the presence or persistence of disease in pure chorea (due to time lag).

c. ESR -increased in anemia and usually decreased in congestive cardiac failure.

d. CRP not affected by anemia but may be positive in any type of heart failure.

2. **Leucocytosis & Anemia:** PNM leukocytosis is often but not always present and so is mild to moderate anemia of ill-defined cause.

3. **Lab evidence of preceding streptococcal Infection:** The most important test.

a. **Usually present** except in chorea.

b. **Group A β hem Strep isolation** is of limited value.

c. **Streptococcal antibody tests** more regularly provide corroborative evidence of recent infection. Baseline antibody levels exhibit age, seasonal and geographic variation and rising anti strep antibody titers (>2 tubes) are more specific.

i. Anti Streptolysin –O (ASO TITRE): This is the most widely used test. About 20% normal children have values >250 Todd units and 10% >320 U. Hence values <250 =N; 250-320= borderline and>320 = +ve. About 80% pts with RF >250 and 60% >320 units. ASO levels increase within one month of streptococcal pharyngitis, plateaus for 3-6 months and then decline

ii. Multiple antibody tests to another streptococcal antigen are often helpful in cases with normal or borderline ASO values, as sometimes in chorea. Anti hyaluronidase (AH) anti streptococcal deoxy-ribonuclease (DNase B), and Nicotinamide-adenonine-dinucleotidase (NADase) or diphosphopyridine- nucleotidase (DPNase) have been developed.

iii. Serial abtibody titers may be useful in identifying new clinical/sub clinical infection which may result in recurrent attacks

iv. Antistrptozyme test (ASTZ): It is a hemagglutination reaction to a concentrate of extracellular streptococcal antigen absorbed on RBC. It's a very sensitive indicator of recent infection & virtually all patients with ARF have titers >200U/ml. Its real value is to rule out RF.

4. **X Ray Examination** useful to document

i. Cardiac enlargement

ii. Pericardial effusion

5. **ECG**

a. Sinus arrhythmia with tachycardia-due to fever, pericarditis or myocarditis

b. 1st degree (prolonged PR interval) or occasionally 2° or 3° AV block in 30% cases, but is not specific and has no correlation with prognosis or subsequent RHD

Differential diagnosis

No single clinical or laboratory sign is pathognomic for ARF. Diagnosis is based on a combination of manifestations and Jones criteria as modified over the years have proved useful. The major manifestations are more likely to be indicative of ARF than the minor ones; for this reason, diagnosis based on two major is stronger than on one major and two minor. Differentials should always be considered and attempted to be ruled out.

1. **Fever, arthritis and +ve acute phase reactants**

a. **Infective** Acute arthritis
Acute osteomyelitis

b. **Reactive** Post streptococcal Reactive arthritis – PSRA
Reiter's disease
Inflammatory bowel disease

c. **Connective tissue** Juvenile immune Arthritis (JIA)
SLE

Main considerations:

1. Post strep reactive arthritis (PSRA) –occurs early after strep pharyngitis without other RF manifestations. It affects smaller joints of upper limbs and is much less responsive to salicylates. These patients should get secondary prophylaxis & followed up for RHD.
2. JIA. There are several features to differentiate;

a. Distribution of joints involved—mainly small joints of fingers.
b. Inflammatory process less painful & joints are less tender *cf.* ARF
c. Involvement is more chronic- lasting weeks to months in the same joint
d. Affected fingers assume spindle shaped appearance
e. Cardiac involvement is rare and involves pericardium and myocardium,

3. Splenomegaly is common.
4. ASO titers are usually not raised.

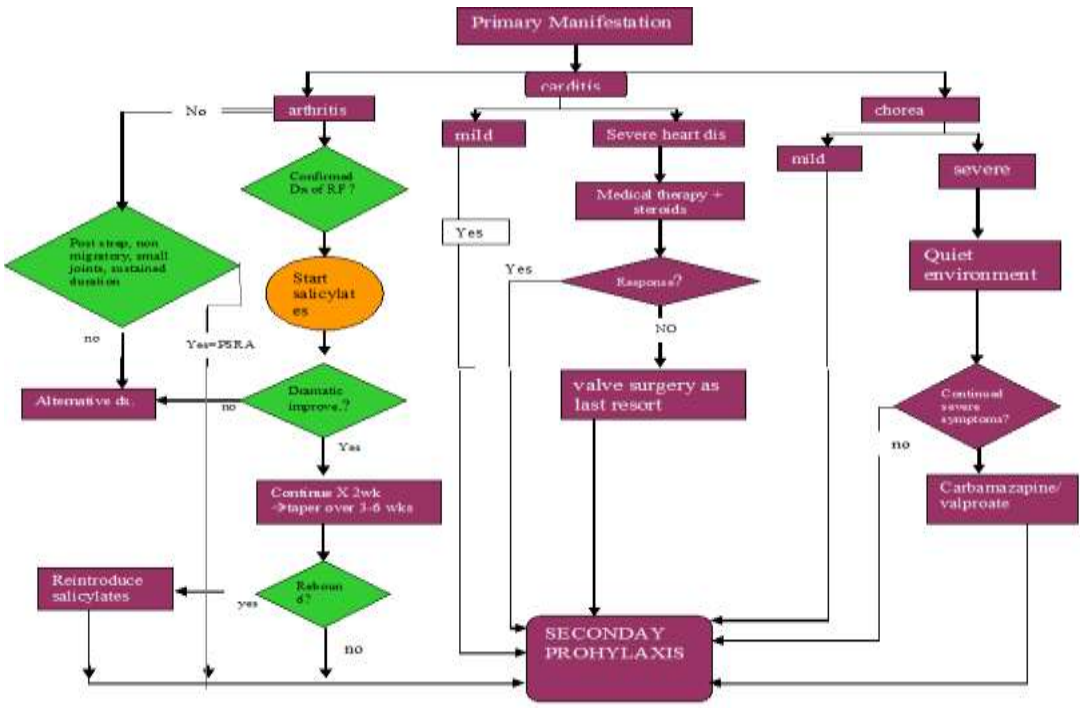
Carditis

1. **Murmur** Physiologic
Mitral valve prolapse
Bicuspid Aortic valve
2. **Cong Heart Dis** VSD
Subvalvular Aortic stenosis
Primum ASD
3. **Viral myocarditis**

Chorea

1. **Familial chorea**
2. **Hormone induced** Oral contraceptives
Pregnancy
Hyperthyroid state
3. **Drug induced** Metochlopramide
Phenothiazines
4. Wilson's disease
5. Atypical seizures
6. PANDAS: (Pediatric Autoimmune Neuropsychiatric Disorder Assoc. with **S**treptococcal infection)

Treatment



Algorithm for management of Rheumatic fever & its primary management. Salicylates have no evidence of effectiveness in carditis or chorea. (Modified from Thatai D, Turi ZG, current guidelines for the treatment of patients with rheumatic fever. Drugs, 1999;57:545).

1. Therapy with salicylates or corticosteroids should **not** be started until a firm diagnosis has been established since it will leave the physician with an unresolvable doubt as the nature of disease process as in some patient's response is never sufficiently specific to warrant a therapeutic trial for a diagnosis.
2. BED REST- is recommended during acute stage.

- strict bed rest with feeding by an attendant is recommended only in cases with CHF or cardiac enlargement.
- Gradual ambulation should be started when the clinical and laboratory signs of acute disease have subsided- may be 7-10 days in children without carditis.Bed rest for 3 weeks to 3 months may be needed in patients with carditis depending on the severity and evidence of progression or stabilization.Prolonged bed rest should be avoided
- After recovery, no restriction of physical activity is ordinarily required. But patients with persistent cardiac enlargement will usually tolerate moderate, not vigorous, exercise only.

3. Digitalis with or without Diuretics

- Should be used when heart failure is present.
- There is no consensus and many physicians use ACE inhibitors like enalapril.

4. Anti-inflammatory Drugs

- Acute signs are quickly suppressed by anti-inflammatory drugs, although course of disease is not influenced.
- Acute phase reactants-ESR- may require several weeks to return to normal
- Corticosteroids are more powerful in bringing acute manifest under control & are drug of choice in acute carditis.
- Aspirin is the drug of choice for joint disease without carditis.

However, there is conflicting evidence of steroids vs. salicylates on residual heart dis.

Doses: Adjust for individual patients to achieve suppression.
Aspirin: 60mg/lb. max 10g per day. If toxicity develops—tinnitus, vertigo and hyperpnoea→ temporarily discontinuance / adjust dose.
Steroids: Prednisolone is preferred over other steroids as it reduces need for low salt diet and added potassium.

- A dose of 2mg/kg /d is sufficient but some clinics use high dose (2.5-4mg/kg/ d) short term (7 day) therapy.

Duration of treatment: In patients with mild disease and no carditis, aspirin can be discontinued in about 10 days or steroids tapered and then stopped after similar time.

- In patients with severe carditis, a prolonged treatment of steroids for 4-6 weeks or longer may be required.

5. Rebounds

- Rebounds occur after discontinuance of aspirin therapy and are even more common after steroid therapy.
- Arthralgia and fever are the usual presentation. At times it may be arthritis and rarely carditis.
- Subclinical rebounds may be detectable only by lab tests—acute phase reactants.
- Most reasonable explanation is that anti-inflammatory drugs have been discontinued before the disease has run its natural course—1-5 weeks for arthritis and 2-6 months or longer in patients with severe carditis.
- The clinical manifestations resolve spontaneously or respond to salicylate therapy. In mild rebounds, do not start any anti-inflammatory drugs.

There is no evidence that anti-inflammatory agents have any effect on erythema marginatum. It is questionable that they influence the disappearance of subcutaneous nodules.

6. Management of chorea

- Steroids cause reduction in duration of symptoms.
- Refractory symptoms can be treated with carbamazepine or valproic acid.
- Empirically anti-seizure and antipsychotic therapy may be used.
- Antibiotic prophylaxis is needed due to high risk of carditis

Symptomatic care includes environment free of noise and bright lights, understanding attendants and protection against tongue biting and other self injury due to violent uncontrollable movements. Complete physical and mental rest is needed since. Side railings of beds needed to prevent fall.

Disease subsides in a few weeks to months; in unusual case it may persist a year or more.

7. Antimicrobial Agents

- Important in prevention of future streptococcal infection which may cause additional cardiac damage.
- They should be prescribed to all patients of acute rheumatic fever including those with chorea. As soon as diagnosis has been made and cultures taken, therapeutic doses of penicillin should be prescribed to eradicate residual group A streptococci and should be followed with continuous prophylaxis.

Prevention

1. **Primary Prevention:** Sine qua non of treat is acute antibiotic treatment to eliminate GBHS from the pharynx and subsequent continuous prophylaxis for secondary prevention. Treatment with antibiotics for 10 days largely eliminates the risk of rheumatic fever and the most cost effective approach.
2. **Secondary Prophylaxis:** Once acute rheumatic fever has manifested, treatment algorithm (as above) varies depending on manifestations of major criteria.
   Long term monitoring is warranted as 50% of carditis cases lead to rheumatic heart dis.

Table 1: Antibiotic treatment of ARF & continuous Prophylaxis (adult doses)

Antibiotic	Dose	Frequency	Duration	Comments	Class
Benzathain Pen G	1.2 million U IM	One time	acutely	↓ compliance Pain	I
Pen V	500mg PO	BD	10d	-	I
Amoxy	1 g PO	Daily	10d	-	I
Pen Allergy					
Narrow spectrum cephalosporins	Varies with drug	Varies with drug	10d	-	I
Clinda	300 mg PO	BD	10d		IIa
Azithro mycin	500 mg PO d1, 250 d2-5	OD	5d	-	IIa
Clarithro	250 mg PO	BD	10d		IIa

Table 2: Secondary prophylaxis in patients with documented ARF (adult doses)

Antibiotic	Dose	Frequency	Comments	Class
Benzathain Pen G	1.2 million U IM	Q 3-4 weeks	↓ compliance Pain	I
Pen V	250 mg PO	BD	-	I
Erythromycin	250 mg PO	BD	-	I
Sulphadiazine	1 gm PO	OD	-	I
Sulphisoxazole	1 gm PO	OP	-	IIa

Duration 5 years to life long. Only in non endemic areas treat for 5 years where no evidence of carditis.
Secondary Prevention

a. Pen G: q 3 weeks in endemic areas with high risk of recurrence as pen concentration is low in 4th wk.
b. Oral: only when

1. Low at risk for recurrence
2. Allergic to penicillin
3. Intolerant to IM injection

Duration depends on patient's age, known RHD, time since last episode of RF, numbers of episodes, family history, occupational exposure and endemicity of area.
Class I recommendation:

- 5 years or 21 years of age of whichever is longer in absence of carditis
- 10 years or 21 years of age for patients with mild or apparently healed carditis
- 10years or till 40 years of age for patients with rheumatic heart disease
- life long –high risk of recurrence of acute rheumatic fever

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