UNIT 1 RHEUMATIC FEVER

Structure

1.0 OBJECTIVES

After reading this unit, you should be able to:

- describe the epidemiology, etiology and pathogenesis of rheumatic fever;
- describe the major and minor criteria of the diagnosis of the acute rheumatic fever; and
- know how to diagnose and treat a patient of acute rheumatic fever.

1.1 INTRODUCTION

Rheumatic fever is an immunologically mediated connective tissue disorder following throat infection with group-A streptococci (GAS). It is characterised by an inflammatory process involving collagen fibrils and the ground substance of the connective tissue. The primary sites of affliction are heart, joints and central nervous system. The salient clinical features are migratory polyarthritis, carditis, chorea and subcutaneous nodules. The saying is "it licks the joint but bites the heart in children and licks the heart and bites the joints in older patients". The most important sequelae of rheumatic fever is rheumatic valvular heart disease, which results in significant morbidity and mortality.

1.2 EPIDEMIOLOGY

The epidemiology of acute rheumatic fever (ARF) is closely connected with that of group-A beta haemolytic streptococcal pharyngitis, both have a maximum incidence in the age group of 5-15 years. In India, the average age at presentation is between 10 and 14 years. However, the early development (under 5 years) of established rheumatic heart disease and rapid progression to mitral stenosis poses a major problem in India and has been labelled as "Juvenile Mitral Stenosis". On occasions, it may occur in older persons as is seen in the epidemics occurring in closed population like military recruits, crowded living conditions and those in contact with

school children. In adults, it is mostly seen in the second and early third decade of life. It is more common in the winter season when the GAS pharyngitis is also on the rise. It still remains a major health problem in developing countries (the incidence being 27-100/100,000/yr).

In the west, there was a peak incidence in the early years of twentieth century, but with socio-economic improvement when overcrowding was reduced and penicillin prophylaxis was started, there was a decline. But again there has been resurgence in USA during the last 2 decades inspite of improved standard of living, improved medical care. This has been attributed to rise of virulent GAS infections. Epidemics of ARF in USA closely followed GAS infections. Also reports from China of Cyclical rise and fall in the incidence of ARF has been noted. Hence the current hypothesis is that there is a cyclical rise and fall of virulent cones of GAS, with respect to time and spread these organisms which results in cyclical outbreaks of ARF. Natural history of rheumatic fever is shown in (Fig. 1.1).

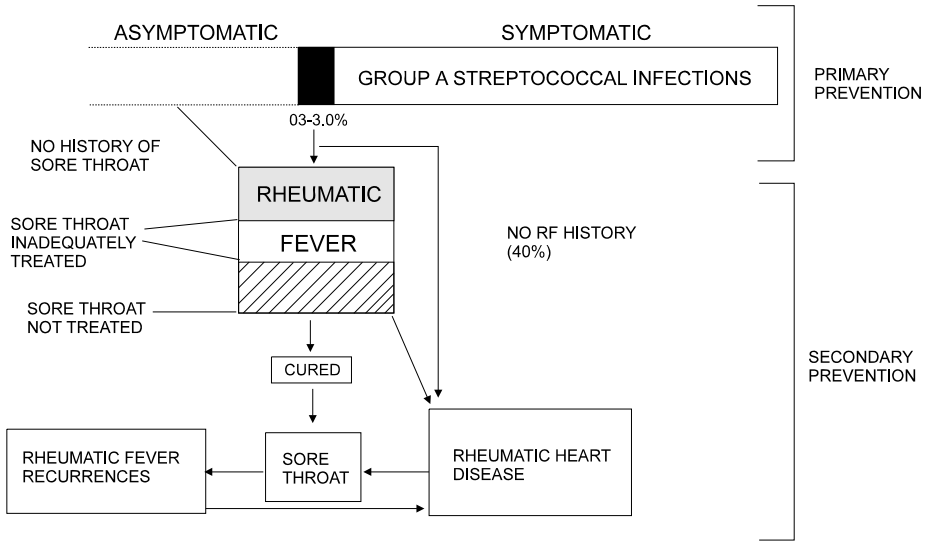

Fig. 1.1: Natural history of Rheumatic Fever

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Check Your Progress 1

1) What is the name of the casuative organism of acute rheumatic fever?

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2) What is the average age of affected by acute rhuematic fever in India?

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1.3 ETIOLOGY

M protein of rheumatogenic GAS has distinct structural characteristics that are akin to human heart tissue, particularly sarcolemmal membrane proteins and cardiac myosin. The major factors that lead to risk of ARF are the severity of the immune response to GAS pharyngitis and persistence of GAS organisms during convalescence. A very small proportion (0.3-3 per cent) of

patients suffering from GAS throat infection ultimately develop ARF and this along with a familial predisposition of ARF points to a genetic susceptibility. Various human leucocyte antigens-HLA DR1/DR2/DR3/DR4/DR7 have been linked to ARF. However, in our Indian patients a genetic linkage to HLA DR3 in patients, with ARF has been demonstrated.

For confirmation of the initial diagnosis of acute rheumatic fever, evidence of prior GAS infection is required. Several rapid GAS antigen tests are available. Majority of these tests has a high degree of specificity but low level of sensitivity in clinical practice.

However, it must be stressed that a negative test does not rule out the GAS infection in the throat. At the same time in presence of a positive antigen test and positive throat culture, it is difficult to distinguish between a recent infection which can be associated with ARF and chronic carrier of GAS infection with ARF. Elevated or rising ASO titres (> 250Todd units in adults and >333 Todd units in children) are more reliable evidence of recent GAS infection than a positive culture or positive rapid antigen test and such titres are also significant for diagnosis.

1.4 PATHOGENESIS

Even though association between GAS pharyngitis and the ARF is fairly well established, the exact pathogenic mechanisms are not clearly understood. However, two mechanisms are postulated.

1) An abnormal immune response of the host to the GAS antigens.

2) Toxic effect of extracellular toxin of GAS on target organs such as synovium, valves, myocardium and brain.

The GAS is a complex micro-organism which produces plenty of somatic and extracellular antigens. Some of our body tissues have antigenic similarities to the GAS antigens with the result that antibodies produced against GAS antigens cross react with these tissue antigens to produce an auto-immune response. The cross reactivity postulation of ARF is supported by following facts:

a) Group specific polysachharide of GAS wall is antigenically akin to glycoprotein found in human and bovine cardiac valves.

b) The somatic antigens of the GAS cell wall and cell membrane are similar to human myocardial sarcolemma.

c) The M protein of GAS cross reacts with human heart tissues particularly sarcolemmal membrane proteins and cardiac myosin as it shares certain common aminoacid sequences.

d) In chorea, antibodies directed against GAS cell membrane cross react with tissues in the caudate nucleus of the brain.

There are two types of immunity:

1) **Humoral Immunity:** Host cross reacting (HCR) antibodies are not only identified against tissue structures form ARF patients (as mentioned above) but are also seen in the sera of patients with previous GAS sorethroat who did not proceed to develop ARF. Therefore, the exact role of those HCR antibodies in the pathogenesis of ARF is not clear.

2) **Cellular Immunity:** During episodes of ARF, various markers of cell mediated immunity (CMI) have been shown to be elevated. These markers are raised CD4/CD8 cell ratio, raised B cell levels, and natural killer cell counts and increase in C3, C4 complements. Aschoff

nodules (a classical marker) in the heart of ARF patients, are due to CMI process. ARF patients with carditis show infiltration by mononuclear phagocytes expressing CD3/CD4 marker proteins. These mediators of CMI seem to be responsible for continuing pancarditis. It is not understood why some persons only suffer from AFR following GAS pharyngitis. It is postulated that there are certain genetic influences that play a role as only 3 per cent of persons develop ARF following GAS sore throat. Monozygotic twins seem to have higher concordance for development of ARF.

The pathologic hallmark of rheumatic carditis (which is always a pancarditis) is the Aschoff body which is typically seen in myocardium. It comprises of a perivascular infiltrate of large cells arranged in a rossette form around an avascular area of fibrinoid necrosis. These Aschoff bodies are usually seen during subacute or chronic phases but not during acute stage of rheumatic carditis. On gross examination, on opening the left atrium, one sees a thickened patch of tissue just above the base of posterior mitral leaflet termed as “MacCallum’s patch”.

Valvulitis is the cardinal lesion that leads to various valvular disorders. There is oedema, cellular infiltration of the valves and the cardiac tendinae causing verrucae formation and hyaline degeneration that results in regurgitant valves. Eventually there is fibrosis and calcification leading to stenotic lesions (mitral, aortic). In large majority cases, fibrinous or fibrinoserous pericarditis is seen. There is generalised vasculitis, i.e., responsible for chorea, pulmonary and renal lesions in ARF. As regards joints, there is serositis which recovers without any deformity.

1.5 CLINICAL FEATURES

The American Heart Association (AHA) has recommended the revised Jones Criteria as a guide for ARF diagnosis. The same have been approved by WHO study group for the diagnosis of initial attack of ARF (Table 1.1). The salient clinical features for the diagnosis of ARF are given in Fig. 1.2. Revised Jones Criteria are (a) Major Criteria (b) Minor Criteria.

Table 1.1: Revised Jones Criteria

Major Manifestations	**Minor Manifestations**
Carditis	A) Clinical findings
Polyarthritis	— Arthralgia
Erythema marginaum	— Fever
Subcutaneous nodules	B) Laboratory findings
Chorea	— Leucocoytosis
	— Raised ESR
	— Raised CRP
	— Prolonged P-R Interval

plus

Supporting Evidence of Antecedent GAS Infection such as positive throat culture or rapid streptococcal antigen test. Elevated or rising ASO or other streptococcal antibodies titre.

Major Criteria

1) ***Carditis***

It has been shown by prospective studies that Rheumatic heart disease (RHD) is linked to the occurrence of carditis during the first episode of ARF. If the first episode is accompanied with carditis, the recurrences also manifest carditis. Around 40 per cent cases of ARF develop carditis and 66 per cent of ARF patients with carditis develop RHD on follow up. During carditis (which is always pancarditis), Carey-Coombs murmur of acute valvulitis is audible. Since mitral regurgitation is the commonest valvular lesion during ARF, one hears a pansystolic murmur and middiastolic flow murmur at mitral area. Basal early diastolic murmur due to aortic regurgitation may be audible. The pulmonary and tricuspid valves are rarely involved. Pericarditis, pericardial effusion and arrhythmias (1st and 3rd degree heart blocks) are other features of rheumatic carditis.

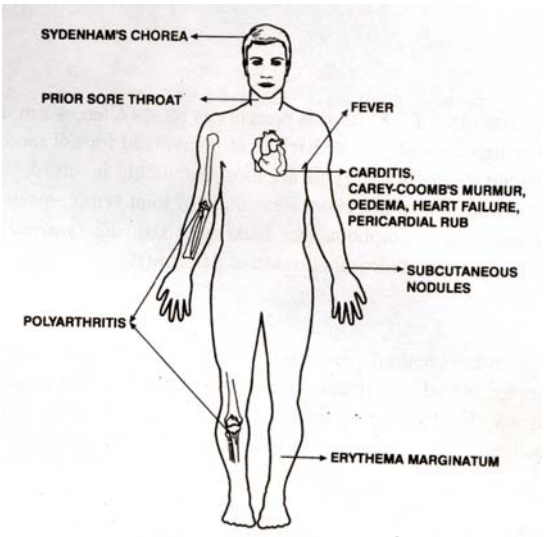

Fig. 1.2: Clinical feature of Rheumatic Fever

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Pericarditis is diagnosed by characteristic chest pain, pericardial rub, typical ECG changes or presence of pericardial fluid on 2D-Echo. Myocarditis presents as tachycardia, distant heart sounds, heart enlargement or signs of congestive cardiac failure (CCF).

2) ***Polyarthritis***

It is the most common (occurring in 75 per cent cases of ARF) manifestation of ARF. It involves large joints, it is typically fleeting in character shifting from one large joint to another. Knees, ankles, elbows and wrists are the common joints involved. There is synovitis and synovial fluid shows polymorph cells. Joint swelling and pain usually resolves in 4-6 weeks and there is no residual deformity of joints.

3) ***Chorea***

It is found in around 20 per cent cases of ARF and it is a late manifestation occurring even 3 months after GAS pharyngeal infection. Chorea is triggered by emotional disturbances with

quasi-purposive involuntary movements involving mostly face and extremities. At times, chorea may be the only manifestation of ARF. Chorea may last for weeks to months.

4) ***Subcutaneous Nodules***

These are found in about 3-6 per cent of cases of ARF. These nodules are typically subcutaneous, firm, painless, freely movable (0.5-2 cm size) and their presence indicates that the patient has carditis. These should be looked on external surfaces of the joints like elbows, knees and spine. These nodules last for about 1 month.

5) ***Erythema Marginatum***

This is a rare manifestation seen in less than 5 per cent of ARF patients. It is erythematous, macular, evanescent, non-pruritic rash with pale centre and serpiginous or rounded borders. The rash occurs mostly on trunk and arms but never on face.

Minor Criteria

These are arthralgia, fever, prolonged PR interval, raised ESR and C-reactive protein levels. In some cases abdominal pain and epistaxis may occur. Other non specific laboratory findings are leucocytosis and anaemia.

Supportive Evidence

One must always look for supportive evidence for antecedent GAS infection in form of positive throat culture, rising ASO titres, and rapid streptococcal antigen tests. Various antibody tests carried out are anti-streptolysin O, anti-deoxyribonuclease B (ADNaseB), anti-nicotinamide adenosine dinucleotidase (ANA Dase), anti-hyaluronidase and anti-streptokinase. When two serum samples taken at 2-4 weeks intervals show a two-fold rise, antibody tests are considered positive. The ASO titres of > 250 Todd units in adults and > 333 Todd Units in children are considered positive. The ASO titres may take upto 4-6 months to return to normal, hence by the time chorea or carditis develops after ARF, ASO titres may have returned to normal. In such situation, one may rely on ADNase B levels, as it remains elevated even beyond 6 months after ARF. Diagnosis of ARF is confirmed if 2 major or one major and 2 minor Jones criteria are present along with a supporting evidence of GAS pharyngitis.

1.6 INVESTIGATION

1) **Complete Blood Count (CBC**)

One may find leucocytosis with predominant polymorphonuclear cellular response in patients of ARF in presence of acute some throat.

2) **Throat Culture**

When patient presents as ARF, one should send throat swab for culture, however, positive throat cultures are uncommon (only 11 per cent). Certain rapid antigen detection kits are available which are specific but sensitivity is low.

3) **Acute Phase Reactants**

ESR and CRP are elevated in almost all patients of arthritis and carditis and rarely in patients with chorea. ESR should be repeated periodically as it is useful in following the course of disease as the level declines as the activity of the rheumatic process subsides.

4) **Streptococcal Antibody Test**

In about 80 per cent of ARF patients, ASO titre is significantly raised. ASO titres vary with age, geographical area and other fevers, which influence frequency of streptococcal infection. ASO titres are at peak usually 2-3 weeks after the streptococcal infection and fall rapidly in the next few months. Acute polyarthritis usually coincides with peak of ASO titre. Hence if ASO titre is normal in presence of arthritis, possibility of ARF is less. Anti-Dnase B and anti-hyaluro-nidase levels are important indicators of recent streptococcal infection.

5) **X-ray Chest**

It is helpful in assessing heart size. One should look for presence of pericarditis, pulmonary oedema or pulmonary congestion.

6) **ECG**

One should look for prolonged PR interval which is indicative of carditis. Also look for evidence of myocarditis in form of sinus tachycardia, QRST changes and AV block.

7) **Echocardiography**

It is very useful in diagnosis of carditis and rheumatic valvular heart disease. It can identify valvular regurgitation not picked clinically. It is useful to assess progress of rheumatic heart disease by serial echocardiography.

8) **Endomyocardial Biopsy (EMB)**

Endomyocardial biopsy helps in understanding that carditis can cause CCF in patients with rheumatic heart disease but frequency of diagnostic features on EMB is found only in 17 per cent cases, hence its routine use is not recommended.

Check Your Progress 2

1) Describe the revised Jones criteria for acute rheumatic fever?

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2) Discuss the pathogenesis and describe the hallmark pathological features of acute rheumatic fever?

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1.7 MANAGEMENT

Differential Diagnosis

Here we discuss differential diagnosis of two cardinal features, Polyarthritis and Rash.

I) ***Polyarthritis***

1) Gonococcal – Therapeutic trial of pencillin may help in diagnosis of gonococcal infection.

2) Viral infections such as rubella and hepatitis B may have polyarthritis.

3) Septic arthritis – Blood cultures may grow organisms.

4) Tuberculosis – It is usually mono-articular.

5) Juvenile rheumatoid arthritis – Here there is small joint involvement which lasts for 6 to 12 weeks and valvular involvement is rare. However, pericarditis alone may be seen. Eventually deformities occur. Rheumatoid factor may be positive.

6) Serum sickness due to drug allergy, e.g., after penicillin injection may present as polyarthritis.

7) Infective endocarditis may mimic ARF as arthritis and carditis are common features. Joint involvement is usually mono-articular affecting large joints. Blood cultures if positive confirm the diagnosis.

8) Henoch Schonlein purpura, inflammatory bowel disease (ulcerative colitis, crohn's diseases), blood disorders (sickle cell anaemia, haemophilia, leukaemias), seronegative arthritis, Takayasu's arteritis may mimick ARF.

II) ***Rash***

Diseases such as Lyme disease and SLE which present with rash may be mistaken for ARF. Lyme disease presents with characteristic rash and arthritis (which appears 1 to 2 months after onset). Juvenile SLE is differentiated by typical skin rash, multiple organ involvement and presence of anti-nuclear antibodies.

Diagnosis

Diagnosis of rheumatic fever is made on basis of various symptoms, signs and results of work up in a case of rheumatic fever (Table 1.2). According to the revised Duckett- Jones criterier, the diagnosis is based upon two or more major clinical manifestations; or and major and two or more minor menifestations. In both cases evidence of previous streptococcal infection is required.

Table 1.2: Work-up in a Case of Acute Rheumatic Fever

Blood	Leucocytosis, raised ESR. C-reative protien (raised) ASO titre (raised > 250 units)
Throat	Throat swab for beta haemolytic streptococci
Chest-X-ray	Enlarged heart
ECG	Increased PR interval (I degree heart block, rarely II and III degree heart block) if pericarditis-low voltage, T-wave inversion
Echocardiography	For valve abnormality, cardiomegaly and pericar dial effusion

Course and Prognosis

The course and ultimate prognosis of ARF is usually directly related to the severity of carditis. The course and prognosis also depends upon recurrence of rheumatic fever. In pre-penicillin era, recurrences of ARF were seen in upto 70 per cent of patients. There is always a tendency to develop rheumatic fever with repeated GAS infections. There is greater chance for recurrence in young children and in the first 3 years after the first attack and in patients with established rheumatic heart disease. If patient had carditis in first attack of ARF, there is always a tendency to have carditis in subsequent attacks. With each recurrence, there is progressive deterioration in valvular lesions and myocardial function. However, if patient is managed well after first attack of ARF and proper prophylaxis is carried out, the recurrent attacks can be prevented. In the UK-USA collaborative study, only 6 per cent of patients with no carditis during first attack of ARF were having murmur after 10 years of first attack. But in patients who developed carditis during first attack of ARF as evidenced by apical systolic murmur, basal diastolic murmurs, CCF, pericarditis, heart disease was present in 30 to 68 per cent at follow up.

Patient is advised bed rest preferably in the hospital. Patient must take bed rest till fever, leucocytosis, ESR, CRP are settled (see Table 1.3 for guidelines of bedrest). If patient develops heart failure due to acute carditis, he should be given digitalis and diuretics with low salt diet. GAS infection should be treated even if throat culture is negative by either single IM injection of benzathine penicillin (1.2 mega units) or oral penicillin for 10 days. If patient is allergic to penicillin, Macrolides or cephalosproins should be given for 10 days. For polyarthritis, high doses of salicylates are used. Aspirin in the dose of 100 mgm/kg/day to maintain a serum level of 20 mg per cent are required. Gradually the dose should be tapered as clinical and laboratory features of inflammation (ESR, CRP) subside.

Table 1.3: Guidelines for Bed Rest

Cardiac Status	Management
No Carditis	2 weeks bed rest and gradual ambulation over 2 weeks
Carditis with no cardiac enlargement	4 weeks bed rest and gradual ambulation over 4 weeks
Carditis with cardiac enlargement	6 weeks bed rest and gradual ambulation over 6 weeks
Carditis with heart failure	Strict bed rest till heart failure is present and gradual ambulation over 3 months

For carditis, also salicylates are beneficial but if there is severe carditis, one may consider corticosteroids. Prednisolone in a dose of 1-2 mgm/kg/day is given. When corticosteroids are tapered, salicylates should be given and then continued for 2 to 4 weeks to prevent rheumatic rebound. Chorea is managed by diazepam or haloperidol.

1.8 PREVENTION

Primary Prevention

Acute GAS pharyngitis should be treated promptly by penicillin or other antibiotics. Indian Council of Medical Research (ICMR) recommends that all cases of pharyngitis must receive penicillin. One need not wait to isolate GAS organisms. A single dose of 1.2 mega units of Benzathine penicillin given IM or a ten day course of oral penicillin V is given. In case of allergy to penicillin, one uses macrolides or cephalosporins.

Table 1.4: Prophylaxis of Rheumatic Fever

Primary Prophylaxis		
Intramuscular	Benzathine penicillin G	12,00,000 U once (6,00,000 U, if weight less than 27 kgs)
Oral	Penicillin V	500 mg bid daily for 10 days
	Erythromycin	250 mg bid daily for 10 days
	Other (Clindamycin, Nafcillin, Ampicillin, Amoxicillin, Cephalexin)	Dose varies
Secondary Prophylaxis		
Intramuscular	Benzathine penicillin G	12,00,000 U every 3-4 weeks
Oral	Penicillin V	250 mg bid daily
	Sulfadiazine	1 gm od (0.5 gm od in children)
	Erythromycin stearate	250 mg bid daily

Secondary Prevention

Benzathine penicillin given every three weeks as IM injection (1.2 mega units) has given the best results. Oral agents (penicillin V) are given in patients with lower risk of rheumatic recurrence. In patients with penicillin allergy, sulphadiazine or erythromycin is used. According to ICMR recommendation, secondary prophylaxis should be carried out till 35 years of age. As per American Heart Association (AHA, 1995), the recommendations vary for secondary rheumatic prophylaxis. In general it is recommended that patients with established rheumatic heart disease, should receive prophylaxis till 10 years after the last episode or 40 years of age, which ever is longer. Some patients who develop post streptococcal reactive arthritis without carditis are given Benzathine penicillin 1.2 mega units ever three weeks for 1 year.

Vaccines for GAS Infections

In developing countries because of poor compliance, poverty, ignorance, primary and secondary prevention strategies are difficult to implement properly. Also in western countries (USA), where there is resurgence of ARF, interest in vaccine development has appeared. However, there are quite a few technical problems in development of vaccines. There are 2 types of vaccines.

I) ***Vaccines Against Virulence Factors Conserved Amongst Various GAS***

Despite antibodies to these conserved antigens, people are affected by multiple serotypes of GAS. Hence there remains a doubt regarding the protective efficacy of antibodies against GAS infections.

II) ***Vaccines Based on Type Specific, Hypervariable N-terminal Regions of M Proteins***

Life long immunity which is protective (25 to 30 years after infection) is achieved by antibodies against the hypervariable N-terminal of M-Protein. Considering this fact, using

recombinant DNA technology, synthetic peptide copies of the hypervariable N-terminal of the M-protein are being manufactured. These synthetic peptides produce only bacterial antibodies without host cross-reactive antibodies. Currently N-terminal synthetic peptides of multiple serotypes of GAS are linked to a carrier protein to produce opsonizing antibodies. Tetra, hexa and octavalent vaccines incorporating M 1, 2, 3, 5, 6, 18, 19 and 24 N-terminal peptides are being evaluated in animals.

Check Your Progress 3

1) How will you manage a patient of acute rheumatic fever with carditis?
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2) Discuss the primary and secondary prophylaxis for acute rheumatic fever.
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1.9 LET US SUM UP

In this unit, you have learnt about the epidemiology, etiology and pathogenesis of acute rheumatic fever. Revised Jones criteria, which have major and minor criteria, are helping to diagnosis of acute rheumatic fever. You have also learnt that penicillin is the drug of choice of acute rheumatic fever and primary and secondary prevention are very much important to prevent the complications of the acute rheumatic fever.

1.10 ANSWERS TO CHECK YOUR PROGRESS

Check Your Progress 1

1) Group A beta hemolytic streptococcal pharyngotis

2) 10 years to 14 years

Check Your Progress 2

1)

Major Criteria	**Minor Criteria**
Carditis	Clinical findings
Polyarthritis	– Arthralgia
Erythema marginatum	– Fever
Subcutaneous nodules	Laboratory findings
Chorea	– Leucocytosis
	– Raised ESR

– Raised CRP

– Prolonged R-R interval

2) The pathologic hallmark of rheumatic carditis (which is always a pancarditis) is the Aschoff body which is typically seen in myocardium. It comprises of a perivascular infiltrate of large cells arranged in a rossette form around an a vascular area of fibrinoid necrosis. These Aschoff bodies are usually seen during subacute or chronic phases but not during acute stage of rheumatic carditis. On gross examination, on opening the left atrium, one sees a thickened patch of tissue just above the base of posterior mitral leaflet termed as "MacCallum's patch".

Valvulitis is the cardinal lesion that leads to various valvular disorders. There is oedema, cellular infiltration of the valves and the cardiac tendinae causing verrucae formation and hyaline degeneration that results in regurgitant valves. Eventually there is fibrosis and calcification leading to stenotic lesions (mitral, aortic). In large majority cases, fibrinous or fibrinoserous pericarditis is seen. There is generalised vasculitis that is responsible for chorea, pulmonary and renal lesions in ARF. As regards joints, there is serositis which recovers without any deformity.

Check Your Progress 3

1) Patient is advised bed rest preferably in the hospital. If patient develops heart failure due to acute carditis, he should be given digitalis and diuretics with low salt diet. GAS infection should be treated even if throat culture is negative by either single IM injection of benzathine penicillin (1.2 mega units) or oral penicillin for 10 days. If patient is allergic to penicillin, Macrolides or cephalosproins should be given for 10 days. For polyarthritis, high doses of salicylates are used.

Aspirin in the dose of 100 mgm/kg/day to maintain a serum level of 20 mg per cent are required. Gradually the dose should be tapered as clinical and laboratory features of inflammation (ESR, CRP) subside.

For carditis, also salicylates are beneficial but if there is severe carditis, one may consider corticosteroids. Prednisolone in a dose of 1-2 mgm/kg/day is given. When corticosteroids are tapered, salicylates should be given and then continued for 2-4 weeks to prevent rheumatic rebound. Chorea is managed by diazepam or haloperidol.

2) **Primary Prophylaxis**

Intramuscular	Benzathine penicillin G	12,00,000 U once (600,000 U, if weight less than 27 kgs)
Oral	Penicillin V	500 mg bid daily for 10 days
	Erythromycin	250 mg qid daily for 10 days
	Others (Clindamycin, Nafcillin, Ampicillin, Amoxicillin, Cephalexin)	Dose varies

Secondary Prophylaxis

Intramuscular	Benzathine penicillin G	12,00,000 U every 3-4 weeks

Oral	Penicillin V	250 mg bid daily
	Sulfadiazine	1 gm od (0.5 gm od in children)
	Erythromycin stearate	250 mg bid daily