TEACHING ARTICLE

RHEUMATIC FEVER

Etsegenet Gedlu*

INTRODUCTION

Acute rheumatic fever (ARF) is one of the nonsuppurative inflammatory responses to a group A Streptococcus pyogenes (GAS) tonsillopharyngitis; usually manifested two to three weeks after the infection. Among patients having GAS tonsillopharyngitis only 3% of them develop acute rheumatic fever (ARF) (1,2). Acute rheumatic fever affects the joints, the heart, the central nervous system, and subcutaneous tissue. All other manifestations of acute rheumatic resolve without sequelae except the carditis. Recurrence of acute rheumatic fever results in severe valvular damage causing rheumatic valvular heart disease. (2,3)

Epidemiology:

Acute rheumatic fever commonly affects children and adolescents aged between 5 years and 15 years. It is very rare before three years of age and is very seldom after the age of 40 years. After recovery from the initial (first) episode of RF, up to 60% of patients develop valvular heart disease with peak prevalence between the age of 25-45 years. In acute rheumatic fever males and females are equally affected while females are at higher risk in developing RVHD with a relative risk of 1.6 to 2.0 compared with males. (4,5)

The burden of rheumatic fever and rheumatic valvular heart disease in the world is highly diverse according to geographical region and socioeconomic status of the country. The annual incidence varies from < 0.5/100, 000 in highly developed countries to > 100/100, 000 in low-income countries. According to the most recent estimates of the global burden of diseases; RHD currently affects 33 million people and it is responsible for 9 million disability-adjusted life years lost and deaths of 275,000 people each year worldwide. More than 80% of deaths occurred in low- and middle-income countries (6-9)

In Ethiopia, recent school and community based studies have shown the prevalence of RHD to be from 14-38/1000, in the age group 4-24 years which is one of the highest in the world (10,11)

Pathogenesis and pathophysiology

After GAS infection of the pharynx, the immune response initiates antibody production against the bacteria and T cell activation to remove the bacteria from the body. In susceptible individuals, due to similarities or molecular mimicry between the host tissue and streptococcal M protein the antibodies trigger delayed abnormal humoral and cellular immune response against the heart, brain, joints, and skin. (12)

*Addis Ababa University. Collage of Health Sciences Department of Pediatrics and Child Health, School of Medicine
Corresponding author: Etsegenet Gedlu, gedlue@gmail.com

The formation of the immune complex and deposition in the joints leads to transient arthritis. Binding of antibodies to the basal ganglion and neuronal cell results in Sydenham chorea. Erythema marginatum and subcutaneous nodule occurs as the result of binding of the antibodies to keratin (12,13)

In the heart, the antibody mediated immune response targets the heart proteins myosin in the myocardium, laminin in the valve endothelium and the basement membrane. The binding of cross reactive antibodies that target valve surfaces lead to inflammation of the valve surface and initiating acute carditis. (fig 1)

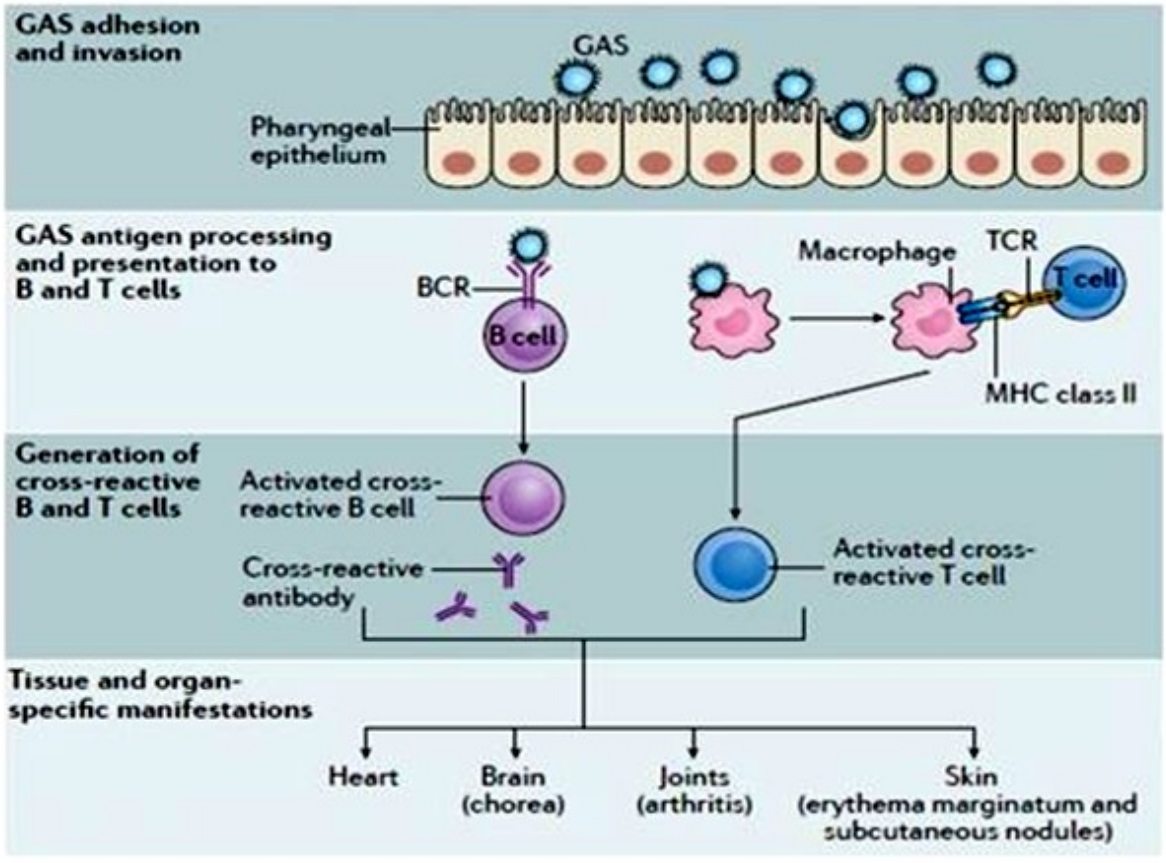

Figure 1.Generation of a cross-reactive immune response in ARF– Following Group, A streptoccocus tonsillopharyngitis

The recurrent Rheumatic fever there will be a change in the valve and valve apparatus which includes dilatation of the valve annuli, fusion, and elongation of the chordae, resulting inadequate coaptation and valvular regurgitation. Further inflammation heals with fibrosis and scarring of leaflets might ultimately lead to valvular stenosis in which the valve becomes narrowed and restrictive and unable to open fully. Figure 2. (12-14)

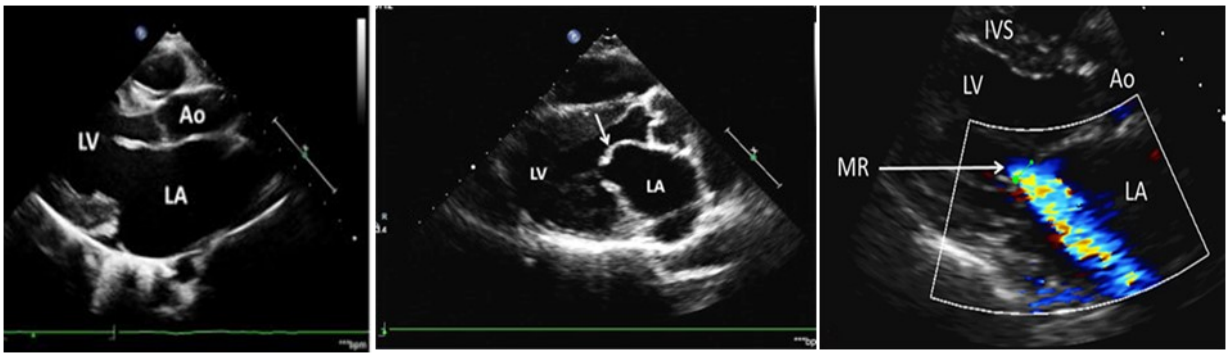

Figure 2. Parasternal View: Mitral valve thickened, clubbed, Sever mitral regurgitation

Clinical presentation
Major Manifestation

Arthritis

Observed in more than 75% of patients; classically described as, a migratory asymmetrical; polyarthritis affecting the large joints such as the knee, ankle elbow, and wrist joints. Severe pain, swelling, limitation of movement, and local heat is characteristics. It is usually self-limiting and shows prompt response with the administration of non-steroidal anti-inflammatory drugs like aspirin. Monoarthritis or non-migratory polyarthritis can occur and has been recently included as major criteria in the high risk population.

Carditis

Is one of the major manifestations of acute rheumatic fever. It occurs in >50% of patients with ARF. The clinical presentation varies from subclinical carditis with no auscultatory finding and valvulitis only detected by echocardiography to severe carditis usually as pan carditis involving pericardium, myocardium, and endocardium with signs of heart failure. The Mitral valve is the commonest valve involved followed by the aortic valve. Both clinical and subclinical carditis is considered as a major criterion for the diagnosis of ARF

Sydenham Chorea

Chorea affects up to 15% of people with rheumatic fever and is more common in females and adolescents. Chorea typically occurs after a longer latent period (up to six months) after a streptococcal infection. It can follow a fluctuating course over many months, occasionally years, before eventually resolving. Clinically it is characterized by behavioral change, gait disturbance, loss of fine and gross motor control with resultant deterioration of handwriting, facial grimacing, fidgetiness, inability to maintain protrusion of the tongue, ” bag of worms”, milkmaids grip, an alternating squeezing and releasing of the fingers and hypotonia. Knee jerk reflex shows a hung up type of response. The purposeless movement is usually observed at rest aggravated by stress and it usually stops during sleep.

Erythema Marginatum

Non-pruritic, erythematous, non-painful maculopapular rash on the trunk and proximal extremities. Lesions often slightly raised that fade centrally, coalesce to form serpiginous patterns and blanches on pressure. They disappear within hours and may appear intermittently within weeks to months. Erythema marginatum is difficult to see in dark skinned children. Local application of heat may help to visualize the lesion. (figure 2)

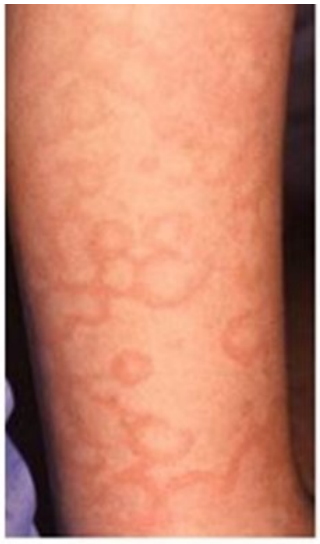

Figure 3.Erythema Marginatum

Subcutaneous nodules

Are small (<2 cm diameter), firm, painless, mobile nodules that occur over the extensor surfaces of elbows, wrists, knees, ankles, and, occasionally, Achilles tendon and spine. Usually, appear during the first weeks of the inflammatory phase and last for about two weeks. Nodules are often found in association with carditis. (Figure 3)

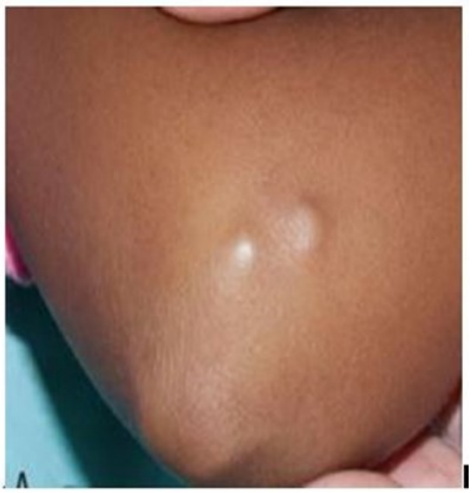

Figure 4.Subcutaneous Nodule

Minor Manifestation

Fever

It is almost invariably present in the early stage, except in patients whose only manifestation is chorea or those receiving salicylates. It often becomes low grade after the first week and may persist at this level for 2-4 weeks. It is one of the minor manifestations of ARF and a single measurement of temperature ≥38 ^{0}c considered as minor criteria in moderate to high risk areas.

Arthralgia

Joint Pain without signs of acute inflammation may occur in some joints. It usually takes a fluctuation course over days to several weeks if untreated but responds dramatically to nonsteroidal anti-inflammatory drugs. In Moderate and high risk populations monoarthralgia is counted as minor criteria while polyarthralgia is a major criterion in the absence of arthritis.

Laboratory Investigations and Imaging

I**. Evidence of preceding streptococcal infection**: Any one of the following can serve as evidence of preceding infection

A. Throat culture: a positive throat culture for group A β-hemolytic streptococcus
B. A positive rapid group A streptococcal carbohydrate antigen test

II**. Streptococcal antibody titer**: Antistreptolysine O (ASO), antideoxyribonuclease (DNAse) titers can rise over several weeks and decline over several months. A titer above the normal or an increment of titer more than twofold, when repeated after two weeks, is diagnostic of a recent streptococcal infection. A rise in titer is better evidence than a single titer result (15)

III. **Acute phase reactants**:

Acute phase proteins are a large and varied group of plasma proteins, which are released into the blood stream in response to a variety of stressors such as inflammation. tissue injury etc. Among the Acute positive reactant proteins; the major proteins are often observed to increase markedly within the first 24–48 h after the triggering event and often exhibit a rapid decline due to their very short half-life. While moderate and minor proteins such as fibrinogen usually increase more slowly and persist for longer, depending on the triggering event (16)

Erythrocyte sedimentation rate (ESR) and C -reactive Protein (CRP) are currently the most commonly used acute-phase markers. Both tests have a high sensitivity but a low specify for rheumatic fever. They may be used to monitor the resolution of inflammation, detect relapse when weaning aspirin, or identify the recurrence of the disease. (12,17)

A. **Erythrocyte Sedimentation Rate (ESR):** The erythrocyte sedimentation rate (ESR) is elevated, and remains elevated for several weeks and may take several months tonormalized. According to the revised Johns criteria, ESR of ≥30mm in the first hour is cut off value to consider as a minor criterion.
B. **C- reactive protein**: Increases rapidly within 4-6 hours of infection or injury. Returns to normal rapidly once condition subsides. A value ≥3mg/dl considered as positive and is used as one of the minor criteria.

IV. **Electrocardiography**: EKG has to be done in all children suspected having ARF. The presence of prolonged PR interval for age considered as one of the minor Jones Criteria in the absence of clinical carditis.

V. Echocardiography: Echocardiographic examination is the main diagnostic tool used for confirmation of the presence of rheumatic valvulitis, severity of regurgitation of the valves, presence of pericardial effusion and evaluation of cardiac function. It becomes very useful in detecting subclinical carditis and monitoring of the progress of the carditis in patients with suspected ARF with no audible murmur (18,19) Table 1

Table 1.Echocardiographic criteria for the diagnosis of subclinical carditis

Pathological mitral regurgitation	**Pathological Aortic regurgitation**
• Seen in at least two views • Jet length ≥2 cm in at least one view • Peak velocity >3 m/s • Pansystolic jet in at least one envelope	• Seen in at least two views • Jet length ≥1 cm in at least one view • Peak velocity >3 m/s • Pan diastolic jet in at least one envelope

Clinical Diagnosis of Acute Rheumatic Fever

The diagnosis of rheumatic fever is based on the revised 2015 Jones' clinical criteria which were modified in three major points mainly; on risk stratification of the patient population, echocardiographic detection of subclinical carditis and joint manifestations as follows: (20)

1**. Risk stratification**: patient population categorized as low and moderate to high risk depending on the burden of the disease of acute rheumatic fever in the country. Countries with the incidence of ARF > 2 per 100,000 school-aged children per year or an all-age prevalence of RHD of > 1 per 1000 population per year considered as moderate to a high risk category. Ethiopia belongs to moderate to high risk category. Low-risk populations are those with ARF incidence ≤2 per 100, 000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.

2. Joint involvement: polyarthritis, monoarthritis, and polyarthralgia considered as major criteria in moderate-risk and high-risk populations.

3. Subclinical carditis: clinical or subclinical carditis qualifies as a major manifestation in both low-risk and high-risk populations. Thus it is recommended, when possible, all patients with confirmed or suspected ARF should undergo echocardiography to evaluate for carditis.In addition to the above three modifications in the major criteria; there is an adjustment on the cut off point for the level of ESR and fever. In high-risk population the ESR level of ≥ 30mm in the first hour and fever of ≥ 380c considered as minor criteria, while ESR of 60 mm and above, fever 38.5 degree and above considered as minor criteria for those low-risk populations.

Acute Rheumatic Fever: One major criterion or one major and two minor criteria, plus laboratory evidence of a recent Group A streptococcal throat infection, are required to confirm the diagnosis of the first episode of acute rheumatic fever. with the exception of chorea.

Recurrence of Rheumatic Fever: In children with a known history of acute rheumatic fever and or rheumatic heart disease diagnosis of recurrence can be made in the presence of a documented group A streptococcal infection with two major or one major and two minor or three minor manifestations. If relying on the presence of 3 minor manifestations, the

diagnosis of recurrent acute rheumatic fever should only be made after other more likely causes have been excluded.

Table 2. The 2015 Modified Jones Criteria for the diagnosis of acute Rheumatic fever for Moderate and High Risk Patient Population

Criteria	**Manifestations**
Major	• Carditis (Clinical and/or subclinical) • Arthritis(including monoarthritis, polyarthritis,or polyarthralgia) • Chorea • Erythema marginatum • Subcutaneous nodules
Minor	• Monoarthralgia • Fever(≥38◦C) • ESR of ≥30mm1st h • CRP of ≥ 3.0 mg/dL • Prolonged PR interval after accounting for age variability(unless carditis is a major criterion)
Evidence of streptococcal infection	• Increased or rising anti streptolysin O titer or other streptococcal antibodies(anti-DNASE) • Throat culture • Antibody titer streptococcal infection
Diagnosis of initial ARF	• Two major • One major and two minor
Diagnosis of recurrence of ARF	• Two major • One major and two minor • Three minor

Management of Acute Rheumatic Fever

Management of acute rheumatic fever is based on the following principles: hospitalization for confirmation of the diagnosis and bed rest, eradication of Group A beta-hemolytic streptococcus infection from the throat, control of acute inflammation, treatment of heart failure, initiation of secondary prophylaxis to prevent recurrence and health education and follow-up. (13,21,22)

1. **Hospitalization**: Despite the severity of initial symptoms; admission is recommended to confirm the diagnosis of acute rheumatic fever and initiation of treatment.
2. **2. Eradication of Group A beta-hemolytic streptococcus infection**: Antibiotic treatment is mandatory even if the

patient has no symptom of acute tonsillo-pharyngitis at initial presentation of ARF. Benzathine penicillin GIM injection has to be given. Make sure the patient has no history of penicillin allergy. In case of penicillin allergy, erythromycin is the drug of choice250 mg bid for ten days for children up to 7 years and 500mg BD or those beyond seven years.

3. Arthritis: A child presented with arthritis without significant carditis can be treated with Aspirin. With a dose of 75 mg per kilogram per day divided 6 hourly after meals for 4 weeks. When there are clinical improvement and reduction of ESR; start tapering the aspirin dose gradually to be completed within the next four to six weeks.

4. Carditis: Steroid is indicated in carditis if there is cardiomegaly, pericarditis or heart failure. Prednisolone is the drug of choice with a dose of 2 mg/kg/day divided into three doses for two weeks followed by tapering of the dose by 5 mg/day every two days. At the starting of tapering of steroid Aspirin should be added at dose of 60mg/kg/day divided four doses for six weeks.

5. Treatment of Heart failure: Heart failure has to be treated with loop diuretics. Furosemide is the common loop diuretic used for heart failure with a dose of 2mg/kg/d in two divided doses. Addition of afterload reduction with Angiotensin-converting enzyme inhibitors (ACEI) is recommended. Captopril initiated with a low dose of 0.1 mg/kg/dose as a test dose. if no hypotension increases the dose gradually possibly over two weeks to 0.5-1,0 mg dose/8hourly depending on the level of blood pressure; with the maximum dose of 2mg/kg/dose.

6. Chorea: Treatment with anti-inflammatory treatment with aspirin or prednisolone is not indicated unless there is an evidence of carditis. In case of moderate to severe chorea treatment has to be started with carbamazepine with a dose of 7-10mg/kg/day divided in to three doses (TID) or valproic acid 15-20mg/kg/day TID and continues 2-4 weeks after the symptom subsides

Prevention of recurrence: Initiate the secondary prophylaxis with a single intramuscular injection of Benzathine penicillin (BPG) to prevent recurrence is a hallmark in the management ARF. BPG has to be given every four weeks.

The recommended dose is similar as depicted for initial treatment of ARF of 600, 000 IU for those children ≥30kg and 1.2 million IU for those who are >30kg. In case of allergy to penicillin oral erythromycin can be substituted with a dose of 250 mg (child < 7years of age) and 500 mg (> 7 years of age) PO BD for the same period.

Duration of secondary prophylaxis

The appropriate duration of secondary prophylaxis is determined by age, the persistence of environmental risk factors, time since the last episode of ARF and potential harm from recurrent ARF. Patients with RF without carditis secondary prophylaxis has to be given up to 25 years of age or 10 years since the last attack of RF whichever comes first while patients with rheumatic valvular heart disease and those who undergo valve repair or replacement has to continue the secondary prophylaxis for life long.

Health Education and Follow up:

Children with ARF/RHD and their caretakers have to be educated about the importance of taking the secondary prophylaxis, the importance of oral hygiene and keeping the regular follow up at the clinic. Patients have to be registered in the RF/RHD registry and have to be provided with a card for documenting administered injections and recording the date of the next appointment.

Complication

Rheumatic valvular disease due to recurrence of acute rheumatic fever is the cause of severe disability and death. Infective endocarditis, arrhythmia, protracted heart failure are common causes responsible for severe disability and death if the valvular damage is left untreated.

Prevention

Improving the socioeconomic condition, increasing access to health care, treatment of tonsillopharyngitis and secondary prophylaxis are major three level strategies to prevent ARF and RHD. (,22,23)

A way Forward

improving the quality of data on the epidemiology and natural history of the disease, establishing prospective RHD registers, Integration of the control efforts into existing child-health programs, providing adequate supplies of high -quality Benzathine penicillin, advocacy in government, nongovernment and community level and considered as a priority for successful ARF/RHD control program.

In addition to the above endeavors, enhancing and coordinating research efforts in identification of potential genetic markers which may help to predict risk of development of ARF, developing biomarkers for early diagnosis and follow up of disease progression, development of a safe, effective vaccine against GAS for primary prevention of ARF, establishment of regional Centers of Excellence equipped with both physical and human resources to deal with prevention and treatment of the disease are some of recommendation mentioned "The Cairo Accord" on Rheumatic Heart Disease – 2017 as a way forward (24)

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