INTRODUCTION

Acute rheumatic fever (ARF) is an auto-immune response to bacterial throat infection with group A β haemolytic streptococcus (GAβHS). People with ARF are often in great pain and require hospitalisation. Despite the dramatic nature of the acute episode, ARF leaves no lasting damage to the brain, joints or skin. However, rheumatic heart disease (RHD) may persist. People who have had ARF previously are much more likely than the wider community to have subsequent episodes.[1, 2]

Recurrences of ARF may cause further valve damage, leading to steady worsening of RHD. Although the exact causal pathway is unknown, it seems that some strains of GABHS are "rheumatogenic" and that a small proportion of people in any population (3–5%) have an inherent susceptibility to ARF. While it is widely thought that only upper respiratory tract infection with GABHS can cause ARF, there is evidence that GABHS skin infections may play a role in certain populations.[3, 4]

When a susceptible host is infected with a rheumatogenic GABHS strain, there is a latent period averaging 3 weeks before the symptoms of ARF begin. By the time the symptoms develop, the infecting strain of GABHS has usually been eradicated by the host immune response.[5]

Rheumatic fever is a systemic disease affecting the peri-arteriolar connective tissue and can occur after an untreated GABHS pharyngeal infection. It is believed to be caused by antibody cross-reactivity. This cross-reactivity is a Type II hypersensitivity reaction and is termed molecular mimicry or antigenic mimicry. Usually, self reactive B cells remain anergic in the periphery without T cell co-stimulation. During a Streptococcus infection, mature antigen presenting cells such as B cells present the bacterial antigen to CD4-T cells which differentiate into helper T_2 cells. Helper T_2 cells subsequently activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus. However the antibodies may also react against the myocardium and joints, producing the symptoms of rheumatic fever.[6, 7]

GABHS has a cell wall composed of branched polymers which sometimes contain M protein that are highly antigenic. The antibodies which the immune system generates against the M protein may cross react with cardiac myofiber protein myosin, heart muscle glycogen and smooth muscle cells of arteries, inducing cytokine release and tissue destruction. However, the only proven cross reaction is with perivascular connective tissue. This inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages. Characteristic Aschoff bodies, composed of swollen eosinophilic collagen surrounded by lymphocytes and macrophages can be seen on light microscopy. The larger macrophages may become Aschoff giant cells. Acute rheumatic valvular lesions may also involve a cell-mediated immunity reaction as these lesions predominantly contain T-helper cells and macrophages.[8]

In acute rheumatic fever, these lesions can be found in any layer of the heart and is hence called pancarditis. The inflammation may cause a serofibrinous pericardial exudate described as "bread-and-butter" pericarditis, which usually resolves without sequelae. Involvement of the endocardium typically results in fibrinoid necrosis and verrucae formation along the lines of closure of the left-sided heart valves. Warty projections arise

from the deposition, while subendocardial lesions may induce irregular thickenings called MacCallum plaques .Chronic rheumatic heart disease is characterized by repeated inflammation with fibrinous resolution. The cardinal anatomic changes of the valve include leaflet thickening, commissural fusion and shortening and thickening of the tendinous cords.[8]

If a child gets ARF, he has 50% chance of recurrence. ten percent of children from the family of affected child may develop RF. It is more common in children living in overcrowded poor societies usually between 5-15 years of age, it may rarely start at earlier age (2-3 years), and boy, although people can have recurrent episodes well into their forties. The prevalence of RHD peaks in the third and fourth decades. Therefore, although ARF is a disease with its roots in childhood, its effects are felt throughout adulthood, especially in the young adult years when people might otherwise be at their most productive ages[9, 10].

Epidemiology:

In Egypt, RHD is a significant health problem, with an estimated prevalence of 5.1 per 1000 school child.[9] The impact of disease is aggravated by low public awareness, the lack of appropriate and early diagnosis and the low socioeconomic status of affected families. Poor transport facilities, overburdened clinics and overcrowding also add to the problem.[2]

The burden of ARF in industrialised countries declined dramatically during the 20th century, mainly due to improvements in living standards (and hence reduced transmission of GABHS) and better availability of medical care. In most affluent populations, ARF is now rare. RHD is also rare in younger people in industrialised countries, although it is still seen in some elderly patients, a legacy of ARF half a century earlier. By contrast, ARF and RHD remain common in many developing countries.[11, 12]

A recent review of the global burden of GABHS-related disease estimated that there is a minimum of 15.6 million people with RHD, another1.9 million with a history of ARF but no carditis (still requiring preventive treatment), 470,000 new cases of ARF each year, and over 230,000 deaths due to RHD annually. Almost all cases and deaths occur in developing countries. These figures are all likely to be underestimates of the true burden of the disease[13]

The socioeconomic burden of rheumatic fever

Although rheumatic fever (RF) and its most important sequel, rheumatic heart disease (RHD), are worldwide problems, they are most prevalent in developing countries. In these countries, RF accounts for up to 60% of all cardiovascular disease in children and young adults, and it has the potential to undermine national productivity, since young adults are the most productive segment of the population in these countries.[14] In addition, 67% of school–aged patients drop out of school due to RF, which stifles their ability to realize their full potential.[15]

It is important that an accurate diagnosis of (ARF) is made. Over-diagnosis will result in the individual receiving benzathine penicillin G (BPG) injections unnecessarily

every 3–4 weeks for a minimum of 10 years; and under-diagnosis of ARF may lead to the individual suffering a further attack of ARF, cardiac damage and premature death.[16]

Currently, there is no diagnostic laboratory test for ARF, so diagnosis remains a clinical decision. The pre-test probability for diagnosis of ARF varies according to location and ethnicity. For example, in a region with high compared with low incidence of ARF, a person with fever and arthritis is more likely to have ARF.[17]

The Jones criteria for the diagnosis of ARF were introduced in 1944.The criteria divide the clinical features of ARF into major and minor manifestations, based on their prevalence and specificity. Major manifestations are those that make the diagnosis more likely, whereas minor manifestations are considered to be suggestive, but insufficient on their own, for a diagnosis of ARF. The exception to this is in the diagnosis of recurrent ARF.[18]

The Jones criteria have been periodically modified and updated, the 1992 update is currently the most widely used and quoted version. Each change was made to improve the specificity of the criteria at the expense of sensitivity, largely in response to the falling incidence of ARF in the USA. As a result, the criteria may not be sensitive enough to pick up disease in high-incidence populations, which suggests that the consequences of under-diagnosis are likely to be greater than those of over diagnosis. All cases of suspected ARF should be judged against the most recent version of the Jones criteria, but the criteria need not be rigidly adhered to when ARF is the most likely diagnosis. [19]

An expert group convened by the World Health Organization (WHO) has recently provided additional guidelines as to how the Jones criteria should be applied in primary and recurrent episodes, the diagnosis of rheumatic fever can be made when two of the major criteria, or one major criterion plus two minor criteria, are present along with evidence of preceding GABHS infection:[9]

Major criteria

- **Polyarthritis** : A temporary migrating inflammation of the large joints, usually starting in the legs and migrating upwards.
- **Carditis**: Inflammation of the heart muscle (myocarditis) which can manifest as congestive heart failure with shortness of breath, pericarditis with a rub, or a new heart murmur.
- **Subcutaneous nodules**: Painless, firm collections of collagen fibers over bones or tendons. They commonly appear on the back of the wrist, the outside elbow, and the front of the knees.
- **Erythema marginatum**: A long-lasting reddish rash that begins on the trunk or arms as macules, spreads outward and clears in the middle to form rings, which continue to spread and coalesce with other rings, ultimately taking on a snake-like appearance (serpiginous). This rash typically spares the face and is made worse with heat.
- **Sydenham's chorea** (St. Vitus' dance): A characteristic series of rapid purposeless movements of the face and arms. This can occur very late in the disease for at least three months from onset of throat infection.

Minor criteria

- Fever of 38.2–38.9 °C (101–102 °F)
- Arthralgia: Joint pain without swelling (Cannot be included if polyarthritis is present as a major symptom)
- Raised erythrocyte sedimentation rate or C- reactive protein.
- ECG showing features of 1st degree heart block, such as a prolonged PR interval (Cannot be included if carditis is present as a major symptom).

Evidence of a preceding streptococcal infection: Any one of the following is considered adequate evidence of infection:

- Increased antistreptolysin O titer (ASOT) or other streptococcal antibodies
- Positive throat culture for Group A beta-hemolytic streptococci
- Positive rapid direct Group A strep carbohydrate antigen test
- Recent scarlet fever.

Other less common clinical features: These include abdominal pain, epistaxis, rheumatic pneumonia (pulmonary infiltrates in patients with acute carditis), mild elevations of plasma transaminase levels, microscopic haematuria, pyuria or proteinuria, none of which is specific for ARF.[19]

Manifestations of RHD:

1. May be asymptomatic
2. Evidence of organic murmurs not previously present
3. Carey-coombs mid-diastolic inflow murmur
4. Cardiac enlargement
5. Tachycardia greater than explained by fever and rapid sleeping pulse rate
6. Arrhythmia: 1st degree heart block
7. Congestive heart failure (CHF) in severe cases
8. Pericarditis: pericardial rub or pericardial effusion

All patients with suspected or confirmed ARF should undergo echocardiography, if available, to confirm or refuse the diagnosis of rheumatic carditis. Echocardiographic (echo) evidence of valve damage (subclinical or otherwise), diagnosed by a clinician with experience in ARF and RHD may be included as a major manifestation in the diagnosis of ARF.[20, 21]

Many of the clinical features of ARF are non-specific, so a wide range of differential diagnoses should be considered The most likely alternative possibilities will vary according to location (eg arboviral arthritis is less likely in temperate than tropical climates) and ethnicity (eg some auto-immune conditions may be more or less common in particular ethnic groups).[9, 22]

Differential diagnoses of common major presentations of acute rheumatic fever:

1. **Polyarthritis and fever:**

- Septic arthritis (including gonococcal)
- Connective tissue and other auto-immune disease
- Viral arthropathy
- Reactive arthropathy
- Lyme disease
- Sickle-cell anaemia
- Infective endocarditis
- Leukaemia or lymphoma
- Gout and pseudogout

2. Carditis:

- Innocent murmur
- Mitral valve prolapse
- Congenital heart disease
- Infective endocarditis
- Hypertrophic cardiomyopathy
- Myocarditis — viral or idiopathic
- Pericarditis — viral or idiopathic

3. Chorea:

- Systemic lupus erythematosus
- Drug intoxication
- Wilson's disease
- Tic disorder
- Choreoathetoid cerebral palsy
- Encephalitis
- Familial chorea (including Huntington's)
- Intracranial tumour
- Lyme disease
- Hormonal

Complications of RHD:

1. Cardiac failure (decompensation)
2. Infective endocarditis
3. Arrhythmias, atrial fibrillation
4. Thromboembolism and stroke
5. Recurrence

Management of ARF is formed of 3 main lines:

1. Treatment of GABHS throat infection
2. Anti-inflammatory agents for carditis and arthritis
3. Other supportive measures for CHF, etc

The first step in treating rheumatic fever is to eradicate the bacteria which initially caused the immunologic response. This is usually accomplished with the use of penicillin. For penicillin-allergic patients, there are other options such as erythromycin or azithromycin (10 mg/kg once daily). It is important to make sure that the acute infection is treated, but such treatment won't necessarily change the course of rheumatic fever once the immunologic response has begun. The joint pains are treated with aspirin or aspirin-related medications. It may be necessary to use very high doses to relieve the symptoms. Carditis is treated by high-dose steroids but other cardiac medications may be needed to control the inflammation of the heart. This is a serious condition and is most often initially managed in an acute-care setting such as a hospital. The most difficult and unpredictable symptom to treat is the chorea. It often responds to antipsychotic medications such as haloperidol but may continue for a protracted period. For patients who develop Sydenham's chorea, it can be the most difficult of the symptoms, since it involves involuntary movements and can interfere with daily activities. These individuals must remain on long-term penicillin to prevent recurrence of the strep infection, which has been known to cause recurrence of the chorea.[23, 24]

Rheumatic heart disease: and economic dimensions:

Rheumatic fever (RF) and rheumatic heart disease (RHD) are primarily diseases of childhood and young adulthood. As a result of this epidemiological pattern, RF and RHD have a negative impact on the society by decreasing the capacity of the most productive age groups, as well as limiting future capacity by threatening the physical development of young people. ARF and RHD lead to increased school absenteeism and work absenteeism. The patient and the family bear most of the brunt of these costs, which are shared to some extent by the society as a whole. [13]

Impact of RHD problems are many like health burden on, psychological and social burden, financial burden, schooling achievement this is because poor health generally imposes cost on the society and individuals in terms of reduced ability to enjoy life, earn a living or to work effectively.[13]

Living with heart disease has many physical, emotional, psychosocial and social consequences for children and adolescents. Previous studies reported higher levels of psychological distress and behavioral problems among diseased than those of healthy children and adolescents. Possible related factors may be cardiac status, health-related quality of life, frustration that may occur due to long term use of penicillin and personal factors such as self-esteem or cognitive perceptions of disease severity. Most studies reported that children with heart disease have a reduced Health-related quality of life compared with healthy children.[25]

Prevention:

The primary aims of a RHD prevention program as recommended by WHO[26, 27] are to:

1. Support the uptake and adherence to secondary prophylaxis
2. Improve clinical care and follow up
3. Identify and register new and recurrent cases of ARF
4. Provide education and training for health care providers
5. Provide education and health promotion for clients, families and community
6. promote primary prevention aimed at preventing initial episodes of ARF
7. Use data to monitor patient's outcomes and improve program strategies.

Primary prevention of RF is directed towards young population aged 2-25 years with recurrent GABHS throat and skin infection to avoid development of RF, this involve compliance of patients with adequate treatment with penicillin within 7 days of infection and for a sufficient period (10 days).[13]

Secondary prevention of RF is defined as the continuous administration of specific antibiotics to patients with a previous attack of RF, or well-documented rheumatic heart disease. The purpose is to prevent colonization or infection of the upper respiratory tract with GABHS and the development of recurrent attacks of RF.[13, 28] The most effective antibiotic is penicillin and the most effective method of delivery of penicillin is by 3 or 4 weekly intramuscular injection of **long-acting benzathine benzylpenicillin(LAP)** .[28] Intramuscular benzathine benzylpenicillin reduces streptococcal pharyngitis by 71% to 91% and reduces recurrent rheumatic fever by 87% to 96%.[13]

Secondary prophylaxis can reduce the clinical severity and mortality from RHD and lead to regression of rheumatic heart disease by about 50% to 70% if patients are adherent over a decade. The internationally accepted dosage of benzathine benzylpenicillin is the same as that for eradication of streptococci used during the acute attack. The American Heart Association recommends the same dose for both adults and children of all ages.[29]

Recommendations on the frequency of intramuscular injections and the duration of secondary prophylaxis vary between authorities. The WHO does not specify whether injections should be administered every 3 or 4 weeks. Some experts recommend injections every 3 weeks for patients at high risk (moderate to severe carditis or previous breakthrough case of acute rheumatic fever), based on evidence that suggests that fewer recurrent episodes of acute rheumatic fever occur with this regimen. The duration of secondary prophylaxis is determined by a number of factors, including age, time since last episode of acute rheumatic fever, and severity of disease.[30]

Table (I): Recommended Antibiotics used in secondary prevention of RF according to AHA (American Heart Association):[31, 32]

Antibiotic	Administration	Dose
Benzathine benzyl penicillin	Single IM injection monthly	1.2 MU > 30kg 600 000 U < 30 kg
Phenoxymethyl penicillin (Pen V)	PO daily	250-500mg bd
Erythromycin ethylsuccinate	PO daily	250-500mg bd

Continuous antimicrobial prophylaxis provides the most effective protection from recurrences of rheumatic fever. Because the risk of recurrence depends on many factors, physicians should determine the appropriate duration of prophylaxis on a case-by-case basis while also considering the presence of rheumatic heart disease. Patients who have had rheumatic carditis, with or without valvular disease, are at high risk of recurrences and are likely to have increasingly severe cardiac involvement with each episode. These patients should receive long-term antibiotic prophylaxis well into adulthood, and perhaps for life.[33]

Table (II): Recommended Duration of Secondary Prophylaxis for Rheumatic Fever

Type	Duration after last attack
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	10 years or until age 40 years (whichever is longer); lifetime prophylaxis may be needed
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	10 years or until age 21 years (whichever is longer)
Rheumatic fever without carditis	5 years or until age 21 years (whichever is longer)

In the United States, an injection of penicillin G benzathine every four weeks is the recommended prophylactic regimen for secondary prevention in most circumstances. In certain populations, administration every three weeks is justified because serum drug levels may fall below a protective level before four weeks after the initial dose. A three-week dosing regimen is recommended also for patients who have recurrent acute rheumatic fever despite adherence to a four-week regimen. The advantages of penicillin G benzathine should be weighed against the inconvenience to the patient and the pain of injection, which causes some patients to discontinue prophylaxis.[31]

Successful oral prophylaxis depends on patient adherence to the prescribed regimen. Patients should be given careful, repeated instructions about the importance of compliance to the dosing regimen. Even with optimal patient compliance, the risk of recurrence is higher in patients receiving oral prophylaxis than in those receiving injections of penicillin G benzathine. Therefore, oral regimens are more appropriate for patients at lower risk of recurrent rheumatic fever.[9]