

Rheumatic Fever: A Review on Pathogenesis, Modified Diagnosis and Pharmacotherapy

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ABSTRACT

Rheumatic fever is one of the common causes of acquired heart disease and has been a burden in countries with low income. It is an autoimmune reaction by the body against an infection caused by group A Streptococcus. As a part of the autoimmune response and repeated infection it damages the cardiac valves and nephrons. Presently it is diagnosed by the modified Jones criteria and bacterial culture is essential for its diagnosis. In recurrent cases, patient develops pancarditis apart from chorea and skin nodules. Diagnosis by microbiological culture, bacitracin susceptibility, rapid antigen detection test, streptococcal antibody test, PCR based diagnosis. The bacterial infection is managed by antimicrobials like penicillin, cephalosporins or macrolides. Other problems are managed symptomatically. Secondary prophylaxis with long-term antimicrobials plays a crucial role in curbing the recurrence of this morbid condition. With the development of newer diagnostic techniques like biosensors and Nano sensors, we can expect an early diagnosis and treatment which could further decrease the morbidity, physical and economic burden in the society.

INTRODUCTION

Rheumatic fever is mostly seen among the children and adolescents which occurs if the individual gets infected by *Streptococcus pyogenes* (group A streptococcus [GAS])^[1]. Most commonly it follows an episode of throat infection by GAS. Rheumatic heart disease is basically a complication of rheumatic fever^[2]. It is an inflammatory condition and if not early in its course there will be progressive calcification and the leaflets of the heart valve will get thickened over time. Connective tissues of heart, joints, brain, and skin are few tissues which commonly gets affected by the GAS.

S. pyogenes is a Gram-positive, anaerobic, non-motile, non-spore forming bacterium which sometimes occurs as long chains of cocci, and occasionally in pairs. The bacteria produce a toxin called as streptolysin which causes hemolysis when mixed in blood agar^[2]. Apart from this, the bacterium has M protein on their surface and their capsule is made up of hyaluronic acid which is responsible for causing hemolysis as well. The M protein and the hyaluronic acid of prevent phagocytosis by making the bacterium unnoticeable as an antigen by the host's defense^[3]. The acute infections which occur due to the bacterium are; pharyngitis, impetigo, cellulitis etc. Following these, the patient further may develop immune-mediated complications such as acute rheumatic fever (ARF) and acute glomerulonephritis^[4,5]. The occurrence rate is usually higher in developing countries and most commonly associated with poverty, poor maintenance of sanitation and overpopulation. Whereas the frequency is comparatively less in developed countries^[6].

PATHOGENESIS

The disease process starts when the *S. pyogenes* bacterium affects an individual which causes an acute episode of pharyngitis. Following the infection, there is an activation of the innate immune system which introduces the *S. pyogenes* antigens to T and B cells. This leads to activation of CD4+ T cells which further activates B cells to produce IgG and IgM antibody. The CD4+ T cells identify Streptococcal M5 protein peptides and generate various inflammatory cytokines such as TNF-alpha, IFN-gamma, IL-10, and IL-4 which can further cause fibrotic valvular lesions^[7]. The *S. pyogenes* bacterium and the human proteins are having a structural similarity which leads to cross-activation of antibodies and at the same time the human proteins are attacked by the T cells. The infected person's peripheral blood lymphocyte gives rise to monoclonal antibodies which cross-reacts with myosin which results in valvular heart disease^[7,8].

Various clinical features which are seen in ARF are “migratory” or “additive” polyarthritis, endocarditis, and Kawasaki Disease. To diagnose the condition of acute rheumatic fever, the Jones criteria was developed in the year of 1944 and served as an indispensable tool for the diagnosis of this autoimmune condition. The Jones criteria include some major criteria like migratory polyarthritis; where all the large joints get involved, mainly the knees, ankles, elbows, and wrists and the joints become warm and swollen. These conditions will be present in the patient for at least a few days to a week and they get healed without any treatment within one month [9-11].

The patient affected with ARF can develop pancarditis which includes the pericardium, epicardium, myocardium, and endocardium [12]. Most commonly the mitral valve gets affected and on the long run, it culminates into mitral regurgitation. After auscultating the patient's chest, a pansystolic murmur can be heard. In severe conditions, diastolic murmur also known as Carey-Coombs murmur can also be heard. If severe valvular regurgitation occurs, it can even end up into cardiomegaly. If the pericardium is extensively involved, then it can unveil pericardial rub [13-15].

Hard, painless, symmetrical subcutaneous nodules over the extensor surface of extremities mainly over the bony prominences are another major manifestation of ARF. These nodules usually stay for up to two weeks. Erythema marginatum can be seen where transient mesh-like bright pink, blanching, non-pruritic macular rash present on trunk and extremities [16].

Another major feature of ARF is Sydenham’s chorea which presents with an involuntary grimace, non-rhythmic, and purposeless movements of the trunk and limbs and an inability to use skeletal muscles in a coordinated manner. During sleep, the chorea symptoms do not occur. Chorea can occur several months after getting the streptococcal infection.

The minor criteria of ARF are, increased C - reactive protein, arthralgia, fever, elevated ESR, prolonged PR interval, anamnesis of rheumatism and leukocytosis.

DIAGNOSTIC CRITERIA

In view of its increased prevalence, in a society of poor and low socio-economic status and keeping in mind its complication early diagnosis and prevention plays an important critical role the various diagnostic modalities are described below. The most important and primary diagnostic criteria as described above are Jones criteria [17,18]. The modified and revised Jones criteria for low-risk populations are summarized in **Table 1**.

The Jones criteria have also been revised for moderate and high-risk populations as summarized in **Table 2**.

For the diagnosis of rheumatic fever, we follow the following criteria as summarized in **Table 3**.

Table 1 demonstrates the occurrence of the 414 patients by age and gender. The majority of cases reported are in age group 5-15 and 62% are below fifteen years of age. The percentage of male affected is 62%.

Table 1. Revised Jones criteria, low-risk populations.

Major Criteria	Minor Criteria
Carditis (clinical and/or subclinical)	Olyarthralgia
Arthritis (polyarthritis)	Fever (≥ 38.5 ° F)
Chorea	Erythrocyte sedimentation rate ≥ 60 mm and/or C-reactive protein (CRP) ≥ 3.0 mg/dl
Erythema marginatum	Prolonged PR interval (unless carditis is a major criterion)
Subcutaneous nodules	

Table 2. Revised Jones criteria, moderate- and high-risk populations.

Major Criteria	Minor Criteria
Carditis (clinical and/or subclinical)	Fever (≥ 38.5 ° F)
Arthritis (monopolyarthritis or polyarthritis, or polyarthralgia)	Erythrocyte sedimentation rate ≥ 30 mm and/or C-reactive protein (CRP) ≥ 3.0 mg/dl
Chorea	Prolonged PR interval (unless carditis is a major criterion)
Erythema marginatum	
Subcutaneous nodules	

Table 3. Diagnosis of ARF with modified Jones criteria.

ARF diagnosis with modified Jones criteria	
Initial episode	2 major criteria, or 1 major plus 2 minor criteria.
Subsequent episode	<ul style="list-style-type: none"> <input type="checkbox"/> With a reliable past history of ARF or established RHD and with documented group A streptococcal infection: 2 major or 1 major and 2 minor or 3 minor manifestations may be enough for a presumptive diagnosis <input type="checkbox"/> When minor manifestations alone are present, the exclusion of other more likely causes of the clinical presentation is recommended before a diagnosis of an ARF recurrence is made

MICROBIOLOGICAL TEST

For the diagnosis of Streptococcal pharyngitis, the streptococcal bacterial species are being cultured on to the horse or sheep blood agar medium and then it is been incubated for at least eighteen hours. Later with the help of gram staining, the diagnosis is confirmed [19].

GRAM STAINING

Due In the year 1884, this test has been developed by Christian Gram and modified by Hucker in 1921. The thick cell wall of the gram-positive bacteria *S. pyogenes* is made up of peptidoglycan which turns the staining medium into a purple color. Yet this diagnostic method is not considered a reliable indicator for diagnosis [20].

BACITRACIN SUSCEPTIBILITY

With a sensitivity of more than 95%, bacitracin susceptibility test is a preferred method to identify Streptococcal pyogenes. Yet, not practiced commonly because group G and C streptococci occasionally give false positive results which could interfere with the diagnosis [21,22].

RAPID ANTIGEN DETECTION TEST (RADT)

A throat culture is done if the individual has got acute pharyngitis, a positive result may denote chronic colonization by *S. pyogenes*. On the other hand, a negative result does not confirm the absence of GAS. For the confirmed diagnosis of GAS, both RADT and throat culture is necessary [23,24].

STREPTOCOCCAL ANTIBODY TESTS

The Anti-streptococcal antibody titers inform regarding the past immunologic incidents that's why it is difficult to consider whether the individual is infected with *S. pyogenes* or not. A raised level of antistreptococcal antibody titers gives us confirmation about the GAS infection of the individual affected with rheumatic fever. Antistreptolysin O and Antideoxyribonuclease B are the frequently used antibody assays [25]. Anti-streptolysin O titers get raised within 1 week and it reaches to the maximum level within 3-6 weeks post-infection [26]. Antideoxyribonuclease B titers get raised within 1-2 week and it reaches to the maximum level within 6-8 weeks post-infection. Streptozyme test is another test which helps in detection of *S. pyogenes* antigen. But, the streptozyme test does not give the exact result for GAS infection [27].

PCR BASED DIAGNOSIS

PCR assay is used for identifying the Streptococcus pyrogenic exotoxin B gene. PCR-based diagnosis is more exact than serology and it also helps in early diagnosis of rheumatic heart disease. A specific genetic marker is used as a specific genetic marker for the diagnosis of GAS [28,29].

MANAGEMENT

Management of joint symptoms

Symptomatic management is the priority treatment of ARF. The backbone of the anti-inflammatory treatment is aspirin. Other NSAIDs which are commonly used for this purpose are, ibuprofen, naproxen. Those with mild joint symptoms may be treated with acetaminophen. Usually, a longer course of treatment should be continued but, some patients require only one to two weeks of treatment [30].

Management of carditis

Individuals with severe carditis are usually treated with corticosteroids. In the case of heart failure, the patient should be provided bed rest, diuretics and fluid restriction should be done. Patients with left ventricular dysfunction can be treated with Angiotensin-converting enzyme inhibitors [31]. The patient should undergo a surgical procedure if he is having mitral or aortic regurgitation associated with chordae tendinae rupture [32]. Valve repair is always a better choice than valve replacement to avoid the long-term anticoagulation treatment which is done if the patient has been treated with mechanical valves [33].

Management of chorea

Valproic acid and carbamazepine are first-line pharmacotherapy for chorea and valproic acid has shown to be more efficacious drug [34]. Yet carbamazepine is sometimes recommended as initial therapy for severe chorea, because of the risk of hepatotoxicity associated with valproic acid [35].

ANTI-STREPTOCOCCAL TREATMENT

Prevention of the first episode of ARF by treating the streptococcal pharyngitis early is called primary prevention. The treatment is summarized in **Table 4** [36].

Table 4. Diagnosis of ARF with modified Jones criteria.

Drug	Special considerations	Body weight	
Phenoxyethylpenicillin	Drug of choice	>40 kg	2-3 MIU/day in 2 divided doses every 12 hours for 10 days
		<40 kg	100,000 to 200,000 IU/kg/day in 2 divided doses every 12 h for 10 days.
Benzylpenicillin	Administered intramuscularly	>40 kg	1.2 MIU, administered intramuscularly at a single dose
		<40 kg	600,000 IU single dose
Cefadroxil	In patients with hypersensitivity to penicillin (except for immediate-type reactions)	>40 kg - 1 g,	1 gm for 10 days.
		<40 kg	30 mg/kg for 10 days.
Erythromycin	Macrolides are indicated in patients	>40 kg	0.2-0.4 g every 6-8 h, for 10 days.
		<40 kg	30-50 mg/kg/day in 3-4 doses, For 10 days.
Clarithromycin	With immediate-type hypersensitivity to beta-lactam	>40 kg	250-500 mg every 12 h for 10 days.
		<40 kg	15 mg/kg/day in 2 doses for 10 days.
Azithromycin	Antibiotics.	>40 kg	500 mg on the first day, then 250 mg for 3 consecutive days
		<40 kg	Single daily dose of 12 mg/kg/day for 5 days or 20 mg/kg/day for 3 days

SECONDARY PROPHYLAXIS

The duration of therapy is dependent on whether the patient has developed carditis or chronic valvular heart disease [37].

Rheumatic fever with carditis and 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-10 years or until age 21 years (whichever is longer).

Rheumatic fever without carditis- 5 years or until age 21 years (whichever is longer).

Pharmacotherapy in secondary prevention

Penicillin G benzathine

Patients weighing 27 kg or less: 600,000 units IM every 4 weeks

Patients weighing more than 27 kg: 1,200,000 units IM every 4 weeks

Penicillin V potassium 250 mg orally twice daily

Sulfadiazine

Patients weighing 27 kg or less: 0.5 g orally once daily

Patients weighing more than 27 kg: 1 g orally once daily

FUTURE DIAGNOSTIC TECHNOLOGIES

DNA-based sensors and nanosensors are novel techniques used for detection and diagnosis of pathogenic diseases. Biosensors are generally defined as an analytical device which can efficiently convert and decode a biological response into a quantifiable and processable signal^[20]. In Biosensors the device which analyses is composed of biological recognition elements. These analyzers are interfaced with a signal transducer which can convert the signals into electrical or optical form. In recent years there has been a huge surge in the usage of DNA biosensors because of their potential relevance in the detection of nucleic acid and recognition of microbes^[38].

CONCLUSION

Rheumatic fever is quite a prevalent condition in the current scenario and understanding the pathogenesis and course of the disease can help us to halt the progression into a chronic one. Early diagnosis and treatment play a crucial role. In near future, with the development of newer diagnostic technologies, we can hope to curb the problem early in its course.

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