Diagnosis and management of acute rheumatic fever

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Literature Review

Diagnosis and management of acute rheumatic fever

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Abstract

Acute rheumatic fever is a nonsuppurative, immune-mediated consequence of group A streptococcal pharyngitis. Recurrent or severe acute rheumatic fever can cause permanent cardiac valve damage and rheumatic heart disease. Universally, the most common major manifestations during the first episode of ARF remain carditis and arthritis. Subclinical carditis now can fulfils a major criterion for ARF in all populations as in revised Jones criteria – AHA 2015. Many of the clinical features of ARF are non-specific, so a wide range of differential diagnoses should be considered. Primary prevention requires accurate recognition and proper antibiotic treatment of GAS pharyngitis. Prevention of recurrent attacks of rheumatic fever (secondary prevention) is the most cost-effective way of preventing further rheumatic heart disease (RHD). Penicillin remains the antibiotic of choice. Intramuscular penicillin is preferred as it is more effective than oral penicillin and results in better compliance.

Keywords : acute rheumatic fever, rheumatic heart disease, GAS pharyngitis
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INTRODUCTION

Acute rheumatic fever (ARF) is a non-suppurative complication following infection by *Streptococcus pyogenes*, or *group A β-hemolytic streptococcal* (GAS) in the tonsillopharynx. This disease can cause symptoms in the joints, skin, subcutaneous tissue, brain, and heart. Damage to the heart valve tissue, otherwise known as rheumatic heart disease (RHD), can become a chronic condition that can result in congestive heart failure, stroke, endocarditis, and death (Carapetis et al., 2005; Cilliers, 2006; Kumar & Tandon, 2013; Seckeler & Hoke, 2011; WHO, 2004).

The incidence and prevalence of ARF and RHD have decreased in developed countries since the early 1900s, but these diseases continue to be a major cause of morbidity and mortality among young people in developing countries. The disease is estimated to occur in up to 30 million children and young adults, and each year an estimated 90,000 people die from this disease (Kumar & Tandon, 2013). The pathophysiology and immune response that underlies the occurrence of ARF is still not properly understood. Clinical manifestations and disease severity in patients are influenced by host susceptibility, virulence of the infecting organism, and favorable environmental factors (Cilliers, 2006; Kaplan, 2005).

Establishing a precise and accurate diagnosis of ARF is very important to do, to avoid over or under diagnoses that can harm the patient. In general, the diagnosis of ARF is established based on clinical manifestations and supported by laboratory tests. Since more than 50 years ago T. Duckett Jones has established criteria to help establish the diagnosis of ARF. These criteria have been revised by the American Heart Association (AHA) (Kumar et al., 2020). Changes made include taking into account the differences in clinical manifestations in the high-risk population, and using echocardiography/Doppler to assess the presence of subclinical carditis. The recent revision of the Jones criteria by the AHA is now considered to be closer to some of the other international guidelines (Gewitz et al., 2015).

Clinicians must be more vigilant in assessing the wide differential diagnosis of the clinical manifestations of ARF, especially in carditis, arthritis, and chorea, so that patients can receive appropriate management. Therefore, this review aims to describe comprehensively about the disease, from the diagnosis to the treatment and prevention.

LITERATURE REVIEW

Epidemiology of Acute Rheumatic Fever

The incidence and prevalence of ARF and RHD began to decline in developing countries since the second half of the 19th century and this decline was influenced by more hygienic environmental conditions, as well as reduced population density. The advent of antibiotics in the 1950s also accelerated this decline. Nonetheless, ARF and RHD remain

the main causes of morbidity and mortality at a young age in many developing countries (Auala et al., 2022; Seckeler & Hoke, 2011). The World Health Organization (WHO) states that there are approximately 0.5 million individuals experiencing ARF each year, and most of them occur in developing countries, where the incidence of ARF is said to exceed 50 cases per 100,000 children. Epidemiological data from many developing countries is still lacking, and it is very possible that the data currently obtained is still far below the actual number (WHO, 2004). The latest data regarding the prevalence of rheumatic fever in Indonesia for the years 1981 - 1990 found 0.3-0.8 among 1000 school children and was much lower than other developing countries (Madiyono, 1998). Much higher rates of 80–100 cases per 100,000 have been documented in several carefully conducted studies in Indigenous populations of Australia and New Zealand (Sudeep & Sredhar, 2013).

The ARF is a disease that can be found in children and young adults. ARF most often occurs in children aged 5-14 years. The first ARF attack is rarely found in children under 5 years of age, and the incidence decreases from the age of 15 years and over, until at the age of 35 years and over the first ARF attack is very rare (Seckeler & Hoke, 2011). Relapses of ARF are common in adolescents and young adults. Relapses of ARF are rarely diagnosed in adults aged 45 years and over. There is no data indicating that there is a difference in the incidence of ARF between men and women (Kaplan, 2005; WHO, 2004).

The highest prevalence of RHD is in the age range of 20-50 years. In several studies stating that the prevalence of PJR was found to be higher in groups of women living in poor and developing countries, researchers linked it to several reasons including genetic and social factors. Currently it is estimated that there are more than 15 million cases of RHD worldwide, with 282,000 new cases, and 233,000 deaths per year3. Subsequent data from studies in Asia show that the number of children with RHD in Asia can reach 1.96-2.21 million individuals. In studies in Asian countries, the burden of RHD was estimated at 10.8-15.9 million individuals, and estimates of RIDs in Asian countries show that the global burden is significantly higher than previous estimates for children and all age groups. RHD mortality in Asian countries in a study is said to be 3.3 percent per year or around 356,000 - 524,000 deaths / year (Carapetis et al., 2005; Kumar et al., 2020; Sudeep & Sredhar, 2013).

Pathophisiology of Acute Rheumatic Fever

Although ARF has been known for over 150 years, a clear understanding of the pathophysiology is still unknown. The infectious role of GAS as an initial event is recognized, and is supported by the occurrence of ARF outbreaks following pharyngitis outbreaks, as well as evidence of elevated antistreptococcal antibodies (ASO) in patients with ARF (Cilliers, 2006; Gewitz et al., 2015; Kaplan, 2005; Kumar et al., 2020; Seckeler & Hoke, 2011).

There are currently three main theoretical hypotheses that have been advanced over the last five decades to explain the streptococcal pathogenesis of ARF. The hypotheses include: (1) direct infection (eg, infection from GAS); (2) the effect of streptococcal toxins (streptolysin O is the most frequently discussed); and (3) the concept of antigenic mimicry or molecular mimicry associated with an abnormal immune response, a hypothesis that is currently more widely accepted (Carapetis et al., 2005; Kaplan, 2005). The clinical manifestations of the response and the severity of the disease in an individual are determined by the susceptibility of the host, the virulence of the infecting organism, and the conducive environment. The theory of molecular mimicry states that antibodies directed against GAS cross-react with tissues in the host. In brief, it appears that a combination of both humoral and cell-mediated immune responses occurs against bacterial antigens, which then cross-react with human tissues, such as those of the heart, joints, skin, and central nervous system, through molecular mimicry. The exact mechanism of initiation of the damage is still unclear. Some of the damage appears to be due to the infiltration of macrophages and T cells that persists for years after the initial event (Auala et al., 2022; Kaplan, 2005).

Not all individuals are susceptible to ARF, and not all GAS strains are capable of causing ARF in susceptible individuals. Approximately 3-5% of individuals from each population are estimated to have a susceptibility to the occurrence of ARF, although until now the individual susceptibility factors are not known with certainty. It is now known that only a few strains of GAS are 'rheumatogenic'. The potential for rheumatogenicity is thought to be determined by the M protein or the antiphagocytic components of the bacterial cell wall (Cunningham, 2000; Woldu & Bloomfield, 2016). M protein is the main virulence factor of Streptococcus and has an important role in the pathogenesis of ARF and RHD. When an individual is infected with a rheumatogenic GAS strain, there is a latency period of approximately 3 weeks before symptoms of ARF appear. By the time symptoms of ARF appear, in general the infecting GAS has already been eradicated from the host by the existing immune response (Arabaci & Ak, 2020; Brouwer et al., 2023).

Diagnosis of Acute Rheumatic Fever

The diagnosis of ARF presents its own clinical challenges for clinicians. Accurate diagnosis is very important. If it is overdiagnosed, the patient will receive unnecessary treatment for a long time. Contrary, if it is underdiagnosed, then ARF will lead to further attacks, therefore causing heart damage and premature death. The diagnosis of ARF remains a clinical decision, because to date there are no specific laboratory tests (Ralph et al., 2020).

The Jones criteria have been used to guide clinicians in making the diagnosis of ARF since 1944, over time the Jones criteria have been modified by the American Heart Association (AHA) in 1992, then reconfirmed at the AHA-sponsored workshop in 2000, and finally the AHA issued the latest revision through the AHA Scientific Statement in 2015 (Gewitz et al., 2015). The current revisions bring the Jones criteria into line with

other international guidelines for the diagnosis of ARF, by defining high-risk populations, and recognizing the differences in clinical presentation in high-risk populations, including the use of Doppler echocardiography as a tool for diagnosing the presence of cardiac involvement (**Table 1**) (Kumar et al., 2020; Reményi et al., 2012).

Tabel 1. Revised Jones criteria (AHA-2015)

a. For all patient populations with evidence of previously GAS infection sebelumnya	
Diagnosis: initial ARF **Diagnosis: recurrent ARF**	2 major criteria or 1 major + 2 minor 2 major criteria or 1 major + 2 minor or 3 minor criteria
b. Major criteria	
Low risk population	**Moderate or high risk population**
• Carditis (clinical and/or subclinical) • Arthritis (only polyarthritis) • Chorea • Erythema marginatum • Subcutaneous nodules	• Carditis (clinical and/or subclinical) • Arthritis (monoarthritis/polyarthritis, polyarthralgia) • Chorea • Erythema marginatum • Subcutaneous nodules
c. Minor criteria	
Low risk population	**High risk population**
• Polyarthralgia • Fever (≥ 38.5◦C) • ESR ≥ 60mm in first hour and/or CRP ≥ 3.0 mg/dL • PR interval lengthening, after accounting for age variability (unless carditis is the major criterion)	• Monoarthralgia • Fever (≥ 38◦C) • ESR ≥ 30mm in first hour and/or CRP ≥ 3.0 mg/dL • PR interval lengthening, after accounting for age variability (unless carditis is the major criterion)

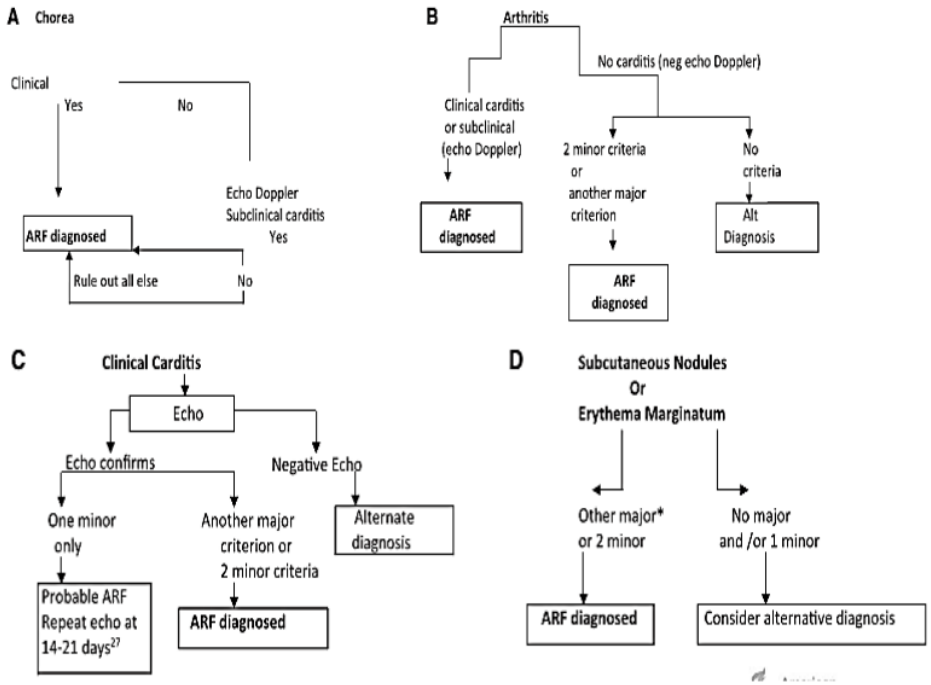
Individuals are said to be at low risk for ARF if they come from a population known to have a low incidence of ARF or RHD (Class IIa; Level of Evidence C). Where good epidemiological data are available, a low-risk population is defined as an area that has an incidence of ARF ≤ 2 per 100,000 school-age children (aged 5-14 years) per year or an all-age prevalence of PJR ≤ 1 per 1000 population per year (Class IIa; Level of Evidence C) (Seckeler & Hoke, 2011). Children of unknown origin from a low-risk population are considered to be at moderate to high risk, depending on their reference population (Class I; Level of Evidence C) (Gewitz et al., 2015).

Evidence that there has been previous GAS infection is very important in the diagnosis of ARF. All major clinical manifestations listed in the Jones criteria must be accompanied

by evidence that an infection from GAS has occurred. Only the clinical manifestations of chorea and indolent carditis did not require evidence of previous GAS infection (**Figure 1**). The 2015 AHA states that if one of the following statements is obtained, it can be used as evidence that a GAS infection has previously occurred: (1) An increase or increase in the titer of anti-streptolysin O (ASO) or other streptococcal antibodies (anti-DNase B) (Class I; Level of Evidence B), the presence of a rise in titer is better evidence than a single titer result; (2) Positive throat culture result for GAS (Class I; Level of Evidence B); and (3) A positive carbohydratete antigen rapid test or rapid antigen detection test (RADT) GAS result in a child who has a clinical presentation strongly supports the presence of streptococcal pharyngitis (Class I; Level of Evidence B)7.

ARF can be found in patients when the first attack (initial) occurs or during repeated attacks (recurrent). The diagnosis of ARF in the first attack is upright when 2 major criteria are met or 1 major criterion with 2 minor criteria, whereas for ARF relapse the criteria that must be met are the same as the criteria for first attack ARF or if major criteria are not found, at least 3 minor criteria must be met7.

Figure 1. Strategy for diagnosing ARF



Under certain conditions, clinicians sometimes encounter cases with clinical presentations that do not meet Jones' criteria, but have strong reasons to suspect ARF as the most likely diagnosis. This is likely to occur in areas with a high incidence of ARF, and areas where tests to confirm GAS infection are not yet available. Such patients can be categorized as "Probable" ARF (Possible Rheumatic Fever). In these circumstances consideration of secondary prophylactic antibiotics for 12 months followed by repeated evaluations, including a careful history, physical examination, and periodic echocardiography may be performed (Class IIa; Level of Evidence C). WHO also has diagnostic criteria for ARF and RHD based on the Jones criteria, it is said that WHO has made diagnostic criteria that focus more on sensitivity than specificity (Table 2).

Tabel 2. Criteria for Diagnosis of ARF and RHD (WHO, 2004, 2020)

Diagnostic category	Criteria
First attack of rheumatic fever	Two majors or one major and two minor plus evidence of infection Streptococcus beta hemolyticus group A previously
Recurrent attacks of rheumatic fever without RHD	Two majors or one major and two minor plus evidence of infection Streptococcus beta hemolyticus group A previously
Recurrent attacks of rheumatic fever with RHD	Two minors plus proof Streptococcus beta hemolyticus infection Group A before
Rheumatic Chorea	No other major criteria are required or evidence of beta Streptococcus infection hemolyticus group A
RHD (pure or combined mitral stenosis with mitral insufficiency and/or aortic valve disorders)	No other criteria are needed for diagnosed as PJR

Clinical Manifestations of Acute Rheumatic Fever

Clinical manifestations in ARF can be divided into 2 groups, namely clinical manifestations that meet major criteria and minor criteria. The most common major clinical manifestations encountered during the first attack were carditis (50-70%) and arthritis (35-66%), followed by chorea (10-30%), then subcutaneous nodules (10%), and erythema marginatum (<6%), which are the least common, but highly specific for ARF (Reményi et al., 2012; WHO, 2004, 2020). Minor clinical manifestations include joint pain, fever, increased C-reactive protein value and sedimentation rate, as well as ECG features in the form of a prolonged PR interval. Because these signs and symptoms are common in many diseases, they are of little use when compared with the minor clinical

manifestations on the Jones criteria. Having a family history of ARF can also increase suspicion of this disease.

Carditis

Pathophysiologically, the endocardium, myocardium and pericardium can all be affected, but rheumatic carditis is almost always associated with valvulitis of the mitral and aortic valves. Therefore, the presence of myocarditis and/or pericarditis alone, without a valvulitis, is not sufficiently strong to be considered rheumatic carditis, and other etiologies must be considered (Cilliers, 2006; Kaplan, 2005; WHO, 2004).

Carditis can be divided into clinical and subclinical. Clinical carditis may be recognized by the presence of an apical holosystolic murmur of mitral regurgitation (with or without an apical mid-diastolic murmur, Carey Coombs). Aortic regurgitation is less common and is characterized by an early diastole murmur at the heart base. In individuals with a previous history of RHD, a change in the character of any pre-existing murmur or the presence of a significant new murmur suggests the presence of carditis (Cilliers, 2006; Gewitz et al., 2015; Kaplan, 2005). Subclinical carditis refers exclusively to conditions in which the classic auscultatory finding of valve dysfunction is absent or not recognized by the clinician, but echocardiography/Doppler examination provides evidence of mitral or aortic valvulitis. The echocardiographic features of valvulitis were made based on specific recommendations for pathological MR/AR. Morphological criteria on echocardiographic examination are also important for the diagnosis and course of ARF and RHD (Ralph et al., 2020; Reményi et al., 2012).

Arthritis

Arthritis is defined as swelling of the joints, followed by two or more of the following: limitation of movement, heat in the joints and joint pain. Usually, the arthritis in ARF is very painful. It often affects the large joints, especially the knees and ankles. Polyarthritis that occurs is usually asymmetrical and migratory (migratory polyarthritis), one joint becomes inflamed while another joint begins to abate, but several joints can also become progressively inflamed, and simultaneously. In addition, arthritis in ARF responds well to salicylates or non-steroidal anti-inflammatory drugs, and usually improves within 3 days of therapy. In general, arthritis in ARF is a symptom that can improve on its own, even without therapy, lasting for approximately 4 weeks. The arthritis in ARF does not result in long-term joint deformity. Arthritis involving only one joint (monoarthritis) is currently a major criterion in the high-risk population for ARF (Gewitz et al., 2015; WHO, 2020).

Polyarthralgia

Polyarthralgia is currently classified as a minor clinical manifestation according to the Jones criteria revised AHA-2015. Polyarthralgia as a major manifestation occurs only in moderate or high-risk populations, and only after careful consideration has been made, and other causes of arthralgia such as autoimmune, viral, or reactive arthropathies have

been excluded (Class IIb; Level of Evidence C). Polyarthralgia in ARF has the same characteristics as polyarthritis in ARF, which is asymmetric, mobile, and affects large joints. If polyarthritis has been found as a major clinical manifestation of ARF, then polyarthralgia cannot be counted as a minor criterion (Gewitz et al., 2015; Ralph et al., 2020; WHO, 2020).

Chorea (Sydenham Chorea)

Chorea may appear with other manifestations of ARF but may also be the only clinical manifestation. Chorea is a neurological disorder characterized by rapid, aimless involuntary movements (often of the hands, feet, tongue, and face) associated with muscle weakness and emotional lability. Movements that arise are not directed and not repetitive but occur suddenly and erratically. These movements disappear during sleep. Most patients with chorea will show improvement in symptoms within a few weeks and almost all patients within 6 months. There are very rare cases where the chorea may persist for 2-3 years (Gerber et al., 2009; Gewitz et al., 2015; Ralph et al., 2020).

Chorea can occur on one side only (hemichorea), and is more common in girls, especially but not always in their teens. Signs that can be used to recognize chorea include: (1) "Milkmaid's grip" (rhythmic squeezing movement when the patient is asked to hold the examiner's finger); (2) "Spooning" (movement of wrist flexion and extension of the fingers when the hand is straightened); (3) "Pronator sign" (rotating movement of the arms and palms outwards, when the hands are held above the head); and (4) Inability to maintain when asked to stick out the tongue. Chorea can occur after a prolonged latency period after GAS infection; therefore, chorea can be the sole criterion for the diagnosis of ARF in the absence of other manifestations, and there is no need for evidence of having been infected with GAS. Chorea has a strong association with carditis, so echocardiographic evaluation is important, even if a heart murmur is not found (Gewitz et al., 2015; Ralph et al., 2020).

Subcutaneous Nodules

Subcutaneous nodules generally appear 1-2 weeks after the appearance of other clinical manifestations and last only 1-2 weeks (rarely more than 1 month). This condition is often found in patients with carditis. These are usually firm, painless nodules, the overlying skin is not inflamed, and vary in size from a few millimeters to several centimeters. The most common location is over the surface of bone or tendons and is best detected by actively palpating for these nodules especially in the areas of the elbows, wrists, knees, nape and spinous processes of the vertebrae {Citation}.

Erythema marginatum

Erythema marginatum is a unique rash, pink in color, appears pale in the center, and has a rounded, wavy border. The rash usually appears on the trunk and upper extremities and rarely affects the face. Heat can trigger the appearance of this rash, and the rash turns pale

when pressed. As with other rashes, erythema marginatum may be more difficult to detect in dark-skinned individuals (Gerber et al., 2009; Gewitz et al., 2015; Ralph et al., 2020).

Differential Diagnosis of ARF

Knowing and considering the differential diagnosis of each major clinical manifestation of ARF is very important in making a precise and accurate diagnosis. **Table 6** lists alternative diagnoses that should be considered when evaluating patients with arthritis, carditis, or chorea (modified from Australian and New Zealand guidelines). Subclinical carditis at this time can be a major criterion for ARF, by passing strict criteria on echocardiographic examination alone without the need for clinical findings, this requires knowledge of caution against other findings that can resemble rheumatic carditis, so that overdiagnosis does not occur, especially in at-risk populations. low. Three of the four criteria used to diagnose pathological mitral valve regurgitation or aortic valve regurgitation (jet length, velocity, and completeness of the Doppler envelope) are affected by systemic blood pressure, and therefore the circulating loading conditions at the time of echocardiographic examination. should also be considered (Gewitz et al., 2015; Ralph et al., 2020; Reményi et al., 2012).

Table 6. Differential Diagnosis in Arthritis, Carditis, and Chorea (Source: Gewitz et al., 2015)

Artritis	Carditis	*Chorea*
• Septic arthritis (including gonococcal) • Autoimmune and connective tissue diseases such as juvenile idiopathic arthritis • Viral arthropathy • Reactive arthropathy • Lyme disease • Sickle cell anemia • Infectious endocarditis • Leukemia or lymphoma • Gout and pseudo-gout • Poststreptococcal reactive arthritis • Henoch-Schonlein purpura	• Physiological regurgitation of the mitral valve • Mitral valve prolapses • Myxomatous mitral valve • Fibroelastoma • Congenital mitral valve disease • Congenital aortic valve disease • Infectious endocarditis • Cardiomyopathy • Viral, or idiopathic, myocarditis • Kawasaki disease	• Drug intoxication • Wilson's disease • Tic disorders • Choreoathetoid cerebral palsy • Encephalitis • Familial chorea (including Huntington disease) • Intracranial tumor • Lyme disease • Hormonal (eg, Lesch-Nyhan, hyperalaninemia) • Antiphospholipid antibody syndrome • Autoimmune: Systemic lupus erythematosus, systemic vasculitis • Sarcoidosis • Hyperthyroidism

Supporting Examination on ARF

In individuals who are suspected of having ARF, the supporting examinations that must be carried out include laboratory examinations, ECG, chest X-rays, and echocardiography (Ralph et al., 2020). The examinations that should be done in diagnosing ARF can be seen in **Table 7**.

Tabel 7. Supporting examination in Suspected Patients with Acute Rheumatic Fever

Recommendations in All Cases	Tests for Alternative Diagnostics, Depending on Clinical Findings
• Blood sedimentation rate (repeated weekly since ARF diagnosis confirmed) • C-reactive protein • Blood culture if fever • Electrocardiography (repeated as needed if the conduction abnormality is more than first degree) • Chest photo, clinically and echocardiography showed carditis • Echocardiography (repeated as needed in 2-4 weeks if equivocal or serious carditis) • Throat smear culture (preferably before antibiotics)-GAS culture	• Serological tests for reactive arthritis • Anti Nuclear Antibody (ANA) for autoimmune arthritis • Repeat blood culture if endocarditis or septic arthritis is suspected • X-rays of joints • Copper, caeruloplasmin, anti-nuclear antibody, drug screen, and head CT/MRI considerations for choreiform movements

Management of ARF

In the acute phase medical management of patients with acute rheumatic fever is divided into 4 parts, namely: 1) management for group A streptococcus, although it does not improve the prognosis within 1 year but can prevent the spread of rheumatogenic strains; 2) general management for acute episodes; 3) heart failure caused by carditis is treated according to heart failure therapy, with monitoring of the possibility of arrhythmias; and 4) administration of prophylactic antibiotics (secondary prevention), the choice of therapy with penicillin, except in patients who are allergic to penicillin (Cilliers, 2006; Kumar et al., 2020; Ralph et al., 2020).

The management for acute episodes including drugs anti-inflammatory are used to control arthritis, fever, and other acute symptoms. Salicylates are the recommended drug and steroids are only used if it doesn't work with the administration of salicylates. Bed rest are recommended especially in patients with carditis. Valproic acid and carbamazepine are now preferred over haloperidol as anti-chorea. Medical administration is only carried out if chorea significantly interferes with daily activities, endangers oneself and those around them, or the patient, family and friends are unable to deal with this condition, a calm environment and reduce stress can reduce symptoms (Ralph et al., 2020).

Prevention in Acute Rheumatic Fever

Primordial Prevention

Primordial prevention consists of improving the socio-economic status of the community, preventing overcrowding, improving nutritional status, ensuring the availability of good medical care, and educating the public about the risk of ARF after getting a throat infection, especially in children under 15 years of age (Kumar et al., 2020).

Primary Prevention

Primary prevention of ARF is carried out by proper identification and administration of appropriate antibiotics for GAS tonsillopharyngitis. The diagnosis of GAS pharyngitis is best made by combining clinical judgment and the results of diagnostic tests. The standard criterion for GAS infection is examination of a throat swab culture. Appropriate administration of antibiotics to patients with throat infections who have symptoms suggestive of GAS infection (pharyngeal exudate and enlarged cervical lymph nodes) can reduce the risk of ARF by 70% (Cilliers, 2006; Gerber et al., 2009; Gewitz et al., 2015; Kaplan, 2005).

The antibiotics recommended for the treatment of GAS are intramuscular benzathine penicillin G and oral penicillin V, except in individuals with a history of penicillin allergy. Until now GAS that is resistant to penicillin has never been found. Patients who have received this antibiotic therapy, 24 hours later can be considered no longer contagious. Erythromycin may be considered in patients on beta-lactam drugs, but have a higher risk of gastrointestinal side effects than other drugs (Class IIb, Level of Evidence B). In addition, there is evidence that several strains of GAS are resistant to erythromycin in several countries in the world, resulting in therapeutic failure. In recent years, rates of macrolide resistance in pharyngeal bacteria in most parts of the United States have been 5% to 8%(Gerber et al., 2009).

Secondary Prevention

The most effective strategy for lowering morbidity and death in underdeveloped nations is secondary prevention. The adoption of echocardiography criteria for diagnosis and follow-up would boost adherence to secondary prevention because there are between 3 and 10 cases of subclinical RHD for every case of clinically diagnosed RHD (Barik, 2018; Katzenellenbogen et al., 2017). In mild RHD, the prophylaxis is necessary for at least 5 years after RHD diagnosis or until age 21 (whichever is longer) if there is no history of ARF and the patient is under 35 years old. In moderate RHD, prophylaxis is necessary for at least 5 years after RHD diagnosis or until age 35 (whichever is longer) if there is no history of ARF and the patient is younger than 35. When RHD is severe, prophylaxis is necessary for at least 5 years after diagnosis or until age 40 (whichever comes first), if there is no known history of ARF (Ralph et al., 2020).

It is known that individuals who have had previous ARF, in which GAS pharyngitis develops, are at increased risk for recurrent attacks of ARF. Repeated attacks may result in a worsening of PJR that developed after the first attack, or occasionally may result in a new onset of PJR, in a patient who did not have cardiac manifestations during the first attack. GAS infection does not need to cause symptoms to trigger a relapse of ARF. In addition, ARF relapses can also occur even when symptoms of GAS infection are treated optimally. Therefore, prevention of recurrent ARF (secondary prevention) requires continuous administration of prophylactic antibiotics. The recommended duration of prophylactic antibiotics for secondary prevention varies based on the clinical manifestations (Al-Jazairi et al., 2017; Gerber et al., 2009; Ralph et al., 2020).

Intramuscular administration of benzathine penicillin G is said to be superior to oral penicillin in terms of preventing ARF relapses, and is given every 4 weeks, or can be every 3 weeks in patients who are proven to have had ARF relapses. There is strong evidence that secondary prevention can reduce the severity of RHD, by inhibiting disease progression. The benefits of long-term intramuscular administration of benzathine penicillin G outweigh the risks of penicillin allergy, which is very rare. Available data indicate that the rate of occurrence of allergic and anaphylactic reactions to intramuscular administration of benzathine penicillin G each month is 3.2% and 0.2%, fatal allergic reactions are said to be very rare. The success of prophylactic oral antibiotics is highly dependent on patient compliance. Secondary prevention with oral therapy is more suitable for patients who have a low risk of recurrent ARF (Cilliers, 2006; Gewitz et al., 2015; Kaplan, 2005; Ralph et al., 2020).

Tertiary Prevention

The therapy of RHD's side effects, such as stroke, infective endocarditis, and arrhythmia, as well as the medical management of heart failure and the surgical management of valve defects are all considered tertiary therapies (Maryland, 2020).

CONCLUSION

Acute rheumatic fever is a non-suppurative complication following infection by *Streptococcus pyogenes*, or group A β-hemolytic streptococcal (GAS) in the tonsillopharynx. The ARF and RHD are still the main causes of morbidity and mortality among young people in developing countries. The most important thing when meeting a patient suspected of ARF is to establish a precise and accurate diagnosis before starting therapy. In 2015 the AHA published a revision of the Jones criteria for ARF, distinguishing several major criteria for low risk and moderate to high-risk groups. Echocardiography has a very important role, especially in recognizing the presence of subclinical carditis which is currently included in the major criteria for ARF. Primary prevention of ARF is carried out by proper identification and administration of appropriate antibiotics for GAS tonsillopharyngitis. Secondary prevention is very

important because it is the most effective way to prevent ARF recurrence which can exacerbate RHD.

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