Penicillin for Secondary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease in Acehnese Children

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ABSTRACT

Acute rheumatic fever (ARF) is a sequela of streptococcal infection—typically following 2 to 3 weeks after group A streptococcal pharyngitis—that occurs most commonly in children and has rheumatologic, cardiac, and neurologic manifestations. Rheumatic heart disease (RHD) refers to the long-term cardiac damage caused by either a single severe episode or multiple recurrent episodes of ARF. Secondary prophylaxis with regular intramuscular injections of benzathine penicillin G (BPG) is a key component to prevent ARF and RHD recurrent. This study aimed to evaluate the secondary prophylaxis effectiveness based on the profile of clinical manifestations and blood laboratory findings. The data were collected by interviews, complete blood counts, the anti-streptolysin titer O (ASTO) analysis, the C-reactive protein Assay, electrocardiography, and echocardiography. Data were analyzed using SPSS 18, and the results were presented as the percentage frequency. The samples were 63 patients with ARF and RHD who get secondary prophylaxis, consisting of 32 males (50.8%) and 31 females (49.9%). The echocardiography examination showed that valve regurgitation was more common than valve stenosis, indicating longer P-R interval in 49 subjects (77.7%). Sixty subjects (92.2%) received secondary prophylaxis with BPG injection, and three subjects (4.8%) got Erythromycin oral. The main factor of secondary prophylaxis adherence is pain and injection disliking.

INTRODUCTION

Acute rheumatic fever (ARF) is an illness following an autoimmune response to a group A streptococcus (GAS), or 'Strep A' infection. Strep A bacteria can cause infection in various parts of the body, including the throat (strep throat) and skin (skin sores, pyoderma, impetigo). The severity of the ARF illness can range from very mild, with few of the above symptoms, to severe where the person may be bed-bound due to joint pain or heart failure. Despite the seriousness of the illness, ARF typically leaves no lasting damage to the brain, joints or skin. However, if the heart is involved (acute carditis), damage to the heart valves may remain once the acute carditis has been resolved. This lasting heart valve damage is known as Rheumatic Heart Disease (RHD).[1,2,3]

Acute manifestations of ARF were shown after a GAS infection (group A streptococcus) in the tonsil-pharynx. There is a latent period of about three weeks, causing cardiac valve fibrosis, resulting in hemodynamic disturbances in the RHD.[4] The revised Jones criteria are guidelines to diagnose ARF. The criteria consisted of major criteria: carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules and minor criteria: clinical previous rheumatic fever or rheumatic heart disease, arthralgia, fever and laboratory, acute phase reactions, erythrocyte sedimentation rate, C-reactive protein, leucocytosis, Prolonged P-R interval plus supporting evidence of preceding streptococcal infection (increased ASTO or other streptococcal antibodies, positive throat culture for GAS, and recent scarlet fever). The presence of two major criteria, or of one major and two minor criteria, indicates a high probability of the presence of rheumatic fever if supported by evidence of a preceding streptococcal infection. The absence of the latter should make the diagnosis doubtful, except in situations in which rheumatic fever is first discovered after a long latent period from the antecedent infection (e.g., Sydenham's chorea or low-grade carditis).[2,3,4,5]

The prevention of widespread infections is usually achieved by administering Long acting bacillin (LAB), a penicillin antibiotic injection. There are two methods to prevent the occurrence of ARF or RHD: primary and secondary prophylaxis. Primary prophylaxis is achieved by disrupting the initial transmission of GAS or by blocking the progression of the GAS infection. Antibiotic administration to the individual with streptococcal pharyngitis is the mainstay of primary prophylaxis. In countries with a high incidence of rheumatic fever, antibiotics should be given to individuals with pharyngitis without obtaining throat culture. Penicillin remains the first choice for primary prophylaxis. Other antibiotics used for primary prophylaxis are macrolides and cephalosporins.[5,6] Since the 1980s, the World Health Organization (WHO) has recommended secondary prophylaxis with regular intramuscular injections (3-4 times weekly) of benzathine penicillin G (BPG) to prevent GAS infections and subsequent recurrent episodes of ARF and avoid the progression to cardiac valve damage. The BPG injection continued depending on many factors, including age, time since the last episode of ARF, risk of streptococcal infections in the area and the presence of RHD. Secondary prophylaxis should continue for at least five years after the last episode of ARF or until the age of 18 years (whichever is longer) and for a longer time in cases of carditis or RHD. Patients with a history of penicillin allergy may be managed with Erythromycin 250 mg twice daily. Also, oral penicillin V is alternative

prophylaxis but less popular compared to the first two drugs. [5,6]

Worldwide, ARF is a major cause of acquired heart disease in 5-30 million children and young adults. Of which 90.000 will die each year, and the global mortality is 1-10%, indicating its negative impact on child health.[7,8,9] The incidence of ARF has declined sharply in many developed countries, however, it remains a major problem in developing countries.[10] The prevalence of streptococcal infections in developing countries is linked to some factors, including age; ARF largely affects children between the ages of 5 and 14 years, and initial cases of ARF can affect children even younger than this, gender; ARF is equally common in both males and females, RHD tends to be more common in females, various environmental factors, the socio-economic situation, inadequate health services, untreated or slowly handled throat infections, industrialization, and urbanization.[7,11] In Asia, RHD is estimated to reach 10.8-15.9 million patients with a mortality rate of 356.000–524.000 each year. In 2016, Rodriguez found and reported limited data about the incidence of RHD.[12] The Julius study in 2016 revealed that the prevalence of RHD in Indonesia was 0.3 - 0.8%, with the age range of 5-15 years.[13] Limitations of the data showed the difficulties in handling the problem quickly and accurately. Carapetis reported that treatment and prevention of a post-infection are very important, as this type of disease has a high incidence of mortality.[14]

Molecular mimicry between components of GAS and human heart tissues is the central problem in the pathogenesis of ARF and RHD. Both T and B lymphocytes can recognize pathogenic and self-antigens via four different types of molecular mimicry: (1) identical amino acid sequences, (2) homologous but non-identical sequences, (3) common or similar amino acid sequences of different molecules (proteins, carbohydrates), and (4) structural similarities between the microbe or environmental agent and its host. Among these human proteins, cardiac myosin and vimentin seem to be the major targets of cross-reactive reactions, along with other intracellular valvular proteins.[3,7]

In Aceh - Indonesia, the incidence of ARF and RHD has not been properly recorded since it is difficult to collect data. We have collected data from 63 subjects with ARF and RHD from May 2015 to May 2017. We studied that the factors triggering recurrent ARF and RHD infections were the lack of family support, "non-compliance" and limited access to health care, patient demographic factors (including younger age) pain and injection disliking. Therefore, this study aimed to evaluate secondary prophylaxis and the factors causing the delay for secondary prophylaxis.

METHODS

The sixty-three subjects with ARF and RHD were collected from May 2015 to May 2017. These were children aged 4 to 18 years referred by colleague doctors from all district hospitals in Aceh for treatment at Zainal Abidin Hospital, Banda Aceh – Indonesia, with suspicions of ARF and RHD. The subjects were questioned for information about secondary prophylaxis adherence, and the clinical manifestations and symptoms of ARF can be severe and are described in the Revised Jones Criteria. There are two diagnostic criteria. The ARF Initial criteria are two major or one major with two minor manifestations, and the ARF recurrent criteria are two major or one major with two or three minors. Major criteria include carditis (clinical

and/or subclinical), arthritis (polyarthritis), chorea, *Erythema marginatum*, and subcutaneous nodules, while minor criteria are polyarthralgia, fever (≥38.5° F), sedimentation rate ≥60 mm and/or C-reactive protein (CRP) ≥3.0 mg/dl, and prolonged PR interval (unless carditis is a major criterion) and evidence of antecedent streptococcal infection. The elevated anti-streptococcal antibody titer in serum/ASTO, longer P-R interval in electrocardiography (ECG/Fukuda, Japan) , X-ray examination show cardiomegaly and diagnosis of RHD based on valve damage was conducted by echocardiography (General electric, Japan). Subjects with suspected ARF and RHD were interviewed about the infection compared to the subject's medical records related to their histories of illness, including fever, joint pain and swelling, palpitations, and walking ability. Moreover, the subjects were examined for nutritional status and information about secondary prophylaxis with benzathine penicillin G 600,000 units (BW<30 kg) or 1,200,000 units (BW >30 kg) single intramuscular injection every four weeks or erythromycin 250 mg twice daily for the subject with a history of penicillin allergy.

Complete blood tests, including hemoglobin, hematocrit, blood sedimentation rate, and leukocytes, were carried out on 63 subjects' blood samples to strengthen the diagnosis of ARF and RHD. The anti-streptolysin titer O (ASTO) examination was performed using a semi-quantitative laboratory approach to determine the anti-streptolysin titer O (ASTO) levels. The qualitative assessment of ASTO positive (+) is when agglutination occurs (levels of ≥ 200 IU/ml) or ASTO negative (-) if there is no agglutination. Meanwhile, the semi-quantitative assessment was done by examining the anti-streptolysin antibody titers with the highest dilution, and it showed agglutination.[15] The C-reactive protein (CRP) were examined using the hs-CRP (high sensitivity C reactive protein) assay that used as a marker. The standard reading of CRP values was <1.0 mg/dl, 1-3 mg/dl, and > 3.0 mg/dl, indicating a low risk, moderate risk, and high risk, respectively.[16]

The data were analyzed using SPSS 18, and the results were displayed as a percentage frequency. The ethical clearance committee from the Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia, has approved this study (No: 310/KE/ FK/2015).

RESULTS

We conducted this research for two years (2015 - 2017) in Zainoel Abidin Hospital, Banda Aceh, Aceh – Indonesia. Zainoel Abidin Hospital is a reference hospital for all districts in Aceh Province and the center for the report analysis of ARF and RHD patients. The subject characteristics in Table 1; show that the of RHD patients are more than ARF patients. Its mean, secondary prophylaxis of ARF are important matters to decrease valve damage. Sixty subjects (95.2%) get secondary prophylaxis with Benzathine benzylpenicillin G IM and three subjects (4.2%) with Erythromycin oral, as many as 41 subjects (65.1%) had a recurrent infection. Although most cases occur in children 5 to 15 years of age, the ARF can occur at any age. In our study, the incidence rate was high in the age group ≥ 10 – 15 years, and none of the subjects suffered from malnutrition or poor nutrition.

Table 1. Baseline Characteristics of Subjects in the Study (N=63)

Variable	Frequency	%
ARF	23	36.5
RHD	40	63.5
Sex		
Girls	31	49.2
Boys	32	50.8
Age		
< 10 years	8	12.7
≥ 10 – 15 years	39	61.9
> 15 years	16	25.4
ASTO (IU/ml)		
400	6	9.5
400 – 800	12	19.1
800 – 1200	32	50.8
> 1200	13	20.6
Nutritional status		
Normal	28	44.4
Overweight	31	49.2
Obese	4	6.4
Secondary Prophylaxis		
Benzathine benzylpenicillin G (IM)	60	95.2
Erytromicyn oral	3	4.8
		65.1
Recurrent Infection	41	

Table 2. Characteristics of blood assay

Variable	Frequency %
C-reactive protein positive	50/63 79.4
Leukocytosis	34/ 63 54
Anemia	31/63 49.2
blood sedimentation increased	41/63 65.1

Table 2 shows the blood results of ARF and RHD patients, indicating the C-reactive protein assay of 79. 4%, leukocytosis of 54%, anemia of 49.2%, and blood sedimentation increased by 65.1%. Although there is no nutritional problem in the subjects, Table 2 shows that almost half of the subjects have anemia (31/49.2%).

Table 3. Secondary prophylaxis adherence factors

Variable	Frequency %
Lack of family support	22/63 34.9
Limited access to hospital	8/63 12.7
Pain and injection disliking	31/63 49.2
Health insurance problem	2/63 3.2

Table 3 shows that 31 out of 63 subjects (49.2%) complained of pain and injection disliking. Hence, it can be concluded that this is the main factor for their non-compliance to return on scheduled secondary prophylaxis.

Table 4. Echocardiography and Electrocardiography Finding

Variable	Frequency	%
Echocardiography		
Mitral, Aorta and Tricuspid regurgitation	15/40	37.5
Mitral and Aorta or Mitral and Tricuspid regurgitation	20/40	50
Mitral regurgitation or Mitral stenosis	5/40	12.5
Electrocardiography		
LAE and LVH	40/63	63.5
RAE and RVH	23/63	36.5
P-R interval prolonged	49/63	77.7

DISCUSSION

The ARF and RHD were classified as non-suppurative pharyngeal, caused by group A β-hemolytic Streptococcus.[17] Generally, cases that occurred in developing and developed countries had disproportionate numbers between the incidence of ARF and RHD in each individual sufferer.[18] The progression of RHD, beginning with *S. pyogenes* infection and continuing through ARF and subsequent cardiac valve damage, offers many opportunities to prevent "the next step" in disease prognosis. Thus, it is important to ensure that areas with high rates of ARF and RHD have adequate resources for all of these stages of prevention. These include programs to improve housing and sanitation, antibiotics to treat *S. pyogenes* infection and an *S. pyogenes* vaccine (once developed), a stable supply of high-quality BPG for those diagnosed with ARF, and access to appropriate medical and surgical treatments to treat cardiac damage.[19]

The results revealed no significant difference between the incidence of ARF and RHD based on sex but often found in the age group of 5-15 years old (Table 1), the ARF is equally common in both males and females, RHD tends to be more common in females.[20] Streptococcal infection at an early age is very common because this type of bacteria can reduce the human immunity at that age, caused by poor sanitation, thus affecting the circulation system that can trigger the spread of streptococcus bacteria. In RHD cases, a number of immunity cells are involved, including T lymphocytes as the main effector of the cross-reaction between streptococcus and human cells, such as the response to cytokines.[21] Streptococcal infection also develop neuropsychiatric symptoms or syndrome of pediatric autoimmune neuropsychiatric.[21,22,]

Table 2 shows that the blood test is an important part of the diagnosis for both ARF and RHD. Among its functions is detecting a number of inflammatory components and immune responses leading to RHD. These generally affect the heart valves, which can cause the heart to not pump the blood properly, a condition called RHD.[23,24]

The RHD electrocardiography examination was conducted by examining the cardiac profile based on the clinical analysis.[25] The study results were 63.5% ECG-left ventricle hypertrophy (LVH), 63.5% ECG-left atrial enlargement (LAE), 36.5%ECG-right ventricle hypertrophy (RVH), 36.5% ECG-right ventricle enlargement/RVE, and 74.6% ECG-longer P-R interval. A prolonged P-R interval (first-degree heart block) is the characteristic and useful finding of ARF.

Mitral regurgitation is the most common valvular pathology in RHD; particularly in children and young adults, where pure mitral regurgitation is the most common RHD presentation. Rheumatic mitral regurgitation primarily results from morphological changes that reflect chronic scarring of the mitral valve and mitral valve apparatus. Morphological mitral valve features are well-visualized on standard 2D echocardiography. However, emerging data suggests that 3D echocardiography may improve the sensitivity and specificity of RHD detection in cases of mild valvular involvement and facilitate improved surgical planning for those with advanced disease. Echocardiography can be used to diagnose the abnormal function of the heart chamber. Patients with suspected ARF should have an echocardiogram to confirm clinical findings, grade the severity of valvular regurgitation, evaluate cardiac function, and diagnose any subclinical involvement.[18,26]

The secondary mitral valve prolapse may have resulted from the damage to valvular structures during acute myocardial infection, rheumatic heart disease, or hypertrophic cardiomyopathy (occurred when the muscle mass of the left ventricle of the heart is larger than normal).[26] The mitral valve is the most commonly and severely affected (65 - 70% of patients), followed by the aortic valve (25%), and the tricuspid valve (10%). The fusion of the valve is needed 2-10 years after an episode of acute rheumatic fever, and recurrent episodes may cause progressive damage to the valves. Fusion occurs at the level of the valve commissures, cusps, chorda attachments, or any combination of these.[17-19,] Variables associated with

the severity of the valve disease included the number of previous attacks of rheumatic fever and the length of time between the onset of the disease and the start of therapy.[27,29] The results of our study showed that regurgitation valve damage was common.

The goal of secondary prophylaxis of ARF and RHD is to prevent the recurrence of *S. pyogenes* infection in those previously diagnosed with ARF. The most effective approach to secondary prophylaxis involves the use of BPG, the long-acting depot form of penicillin G. Once BPG is intramuscularly injected, the drug is slowly released from the muscle into the systemic circulation, where it is activated via *in-vivo* hydrolysis and produces prolonged serum concentrations of benzylpenicillin. This prolonged-release BPG formulation is vital for treating and preventing ARF and RHD, where serum concentrations of benzylpenicillin are expected to remain at or above 0.02 µg/ml, the accepted minimum inhibitory concentration (MIC) for preventing *S. pyogenes* colonization and preventing ARF recurrences.[30,31,32] During the study period, it was noted that secondary prophylaxis with widely administered BPG was given. Three subjects did not get BPG injection due to their allergy to this drug. However, many patients do not adhere to this protocol because of pain injection and discomfort. The strategies used to minimize pain included the use of paracetamol-based pain relief. Secondary prevention of recurrent ARF with continuous antibiotic prophylaxis is recommended for patients with a definite history of ARF or a diagnosis of definite RHD. Continuous antimicrobial prophylaxis is recommended because recurrent ARF can be triggered by GAS infection, even if asymptomatic.[30,31,32] The duration of secondary prophylaxis depends on several factors, including the patient's age, the date of their last attack, and, most importantly, the presence and severity of rheumatic heart.[33] The subject of this study will be given secondary prophylaxis for at least five years since the initial diagnosis of ARF or RHD. We will conduct a long-time follow-up study in the subject to assess adherence to secondary prophylaxis.

CONCLUSION
Routine IM benzathine penicillin (once every four weeks) is effective for preventing recurrent rheumatic fever in patients from a high-risk population with rheumatic heart disease. In Aceh, many ARF and RHD patients do not return on schedule due to various reasons.

CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest
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