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Complete Atrioventricular Block in Acute Rheumatic Fever with Clinical Presentation of Syncope and Abdominal Pain: A Case Report

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A B S T R A C T

Acute rheumatic fever (ARF) is a systemic inflammatory disease following group A streptococcus infection that can affect various organs, including the heart. The most common cardiac manifestation is pancarditis, which can cause various arrhythmias. Complete atrioventricular (AV) block is a rare cardiac complication of ARF, especially in adult patients. We report the case of a 30 year old man who came to the emergency room with the main complaint of abdominal pain, nausea, vomiting, and a history of syncope. He also had a history of fever and joint pain. Physical examination and electrocardiogram (ECG) showed complete AV block. The patient was admitted to the ICU and given medical therapy for ARF and complete AV block. After several days of treatment, his complete AV block recovered to sinus rhythm, and his clinical symptoms improved. This case report highlights the importance of considering ARF as a differential diagnosis in young adult patients with complete AV block and systemic symptoms. Fast and appropriate treatment can improve the patient's prognosis.

1. Introduction

Acute rheumatic fever (ARF) is a systemic inflammatory disease following group A streptococcus infection that has been a global health scourge for centuries. Although advances in antibiotic treatment have reduced the incidence and prevalence of ARF in developed countries, the disease remains a significant health problem in developing countries, including Indonesia. The disease burden of ARF lies not only in the acute morbidity it causes but also in the long-term complications that can affect various organs, especially the heart. One of the most feared heart complications in ARF is rheumatic carditis, which is inflammation of the heart lining that can involve the endocardium, myocardium, or pericardium. Rheumatic carditis can cause a variety of structural and functional heart abnormalities, including valve regurgitation, valve stenosis, and heart rhythm disturbances. Heart rhythm disturbances in ARF can range from mild, asymptomatic arrhythmias to severe, life-threatening arrhythmias, such as complete atrioventricular (AV) block. A complete AV block is a disturbance of the heart's electrical conduction in which electrical impulses from the atria cannot reach the ventricles. This results in a loss of synchronization between atrial and ventricular contractions, which can lead to decreased cardiac output and symptoms such as syncope, dizziness, and fatigue. Complete AV block can be caused by a variety of factors, including ischemic heart disease, cardiomyopathy, congenital

heart disease, and inflammatory diseases such as ARF. In ARF, a complete AV block usually occurs due to inflammation of the AV node or bundle of His, which is part of the heart's electrical conduction system. This inflammation can interfere with the transmission of electrical impulses from the atria to the ventricles, causing complete AV block. Although complete AV block is a rare cardiac complication of ARF, it can have serious consequences for the patient.[1-3]

The incidence of complete AV block in ARF varies depending on the population studied and the diagnostic method used. Several studies report an incidence of complete AV block in ARF of approximately 1-5%. Complete AV block is more common in children than in adults. This may be due to differences in the immunological response to streptococcal infection and differences in cardiac structure between children and adults. The diagnosis of complete AV block in ARF is made based on the history, physical examination, and supporting examinations such as electrocardiogram (ECG) and echocardiography. A careful history may reveal symptoms such as syncope, dizziness, and fatigue, as well as a history of fever, joint pain, and previous streptococcal infection. Physical examination may show signs of heart failure, such as edema, hepatomegaly, and rales on lung auscultation.[4,5]

ECG is an important examination to identify a complete AV block. On the ECG, complete AV block is characterized by the absence of a connection between the P wave (which represents atrial depolarization) and the QRS complex (which represents ventricular depolarization). In addition, the ECG can show the presence of a junctional or ventricular discharge rhythm, which is a compensatory cardiac mechanism to maintain cardiac output in conditions of complete AV block. Echocardiography can also provide useful information in the diagnosis and management of complete AV block in ARF. Echocardiography can assess heart function, the presence of structural abnormalities such as valve regurgitation, and the presence of signs of inflammation in the heart. In addition, echocardiography can help determine the etiology of complete AV block, whether caused by ARF or another condition.[6,7]

Treatment for complete AV block in ARF includes medical therapy for ARF and therapy for complete AV block. Medical therapy for ARF includes antibiotics to eradicate streptococcal infections and anti-inflammatory drugs to reduce inflammation. The antibiotic commonly used is penicillin, while the anti-inflammatory drugs often used are aspirin or steroids. Therapy for complete AV block can include drugs to improve AV conduction or implantation of a temporary or permanent pacemaker. Drugs that can be used to improve AV conduction include atropine and isoproterenol. However, the effects of these drugs are usually temporary and cannot be relied upon in the long term. Therefore, implantation of a temporary or permanent pacemaker is often necessary to treat persistent or life-threatening complete AV block. The prognosis for complete AV block in ARF is generally good, especially if treated quickly and appropriately. Most patients with complete AV block in ARF will recover completely with medical therapy. However, in some cases, complete AV block can persist and require permanent pacemaker implantation. Factors that can influence the prognosis of complete AV block in ARF include the patient's age, the severity of the AV block, the presence of other cardiac complications, and response to therapy.[5,6] This case report aims to provide a clearer picture of the clinical manifestations, diagnosis, and treatment of complete AV block in ARF, especially in young adult patients. Apart from that, it is also hoped that this case report will increase clinician awareness of rare cardiac complications in ARF so that earlier and more appropriate diagnosis and treatment can be carried out.

2. Case Presentation

A 30-year-old man, with no previous history of heart disease, came to the emergency room (ER) with

the main complaint of severe abdominal pain in the epigastric area, accompanied by nausea and vomiting that lasted for two days. This complaint was exacerbated by the two syncopal episodes he experienced at home on the same day. In addition, the patient also reported a mild fever for the last three days and pain in his left elbow for a week. The patient had no history of recent upper respiratory tract infections, but he admitted to frequently experiencing heart palpitations that had never been checked before. The patient had worked as a cruise ship crew member for the past eight months, sharing a cramped sleeping cabin with three co-workers. His work history and crowded living environment increased his risk of exposure to various pathogens, including group A streptococcus bacteria, the main cause of acute rheumatic fever (ARF). On physical examination, the patient appeared moderately ill with a body temperature of 37.2°C. His blood pressure was recorded at 100/80 mmHg, and his respiratory rate was 18 breaths per minute. Cardiac auscultation did not reveal a murmur, but abdominal examination revealed tenderness in the epigastric region without signs of peritonitis. An electrocardiogram (ECG) showed bradycardia with a heart rate of 46 beats per minute and a complete AV block with normal QRS complexes, indicating a junctional discharge rhythm. This ECG finding is very worrying because a complete AV block can be life-threatening if not treated immediately (Figure 1). The patient was immediately transferred to the intensive care unit (ICU) for further monitoring and treatment.

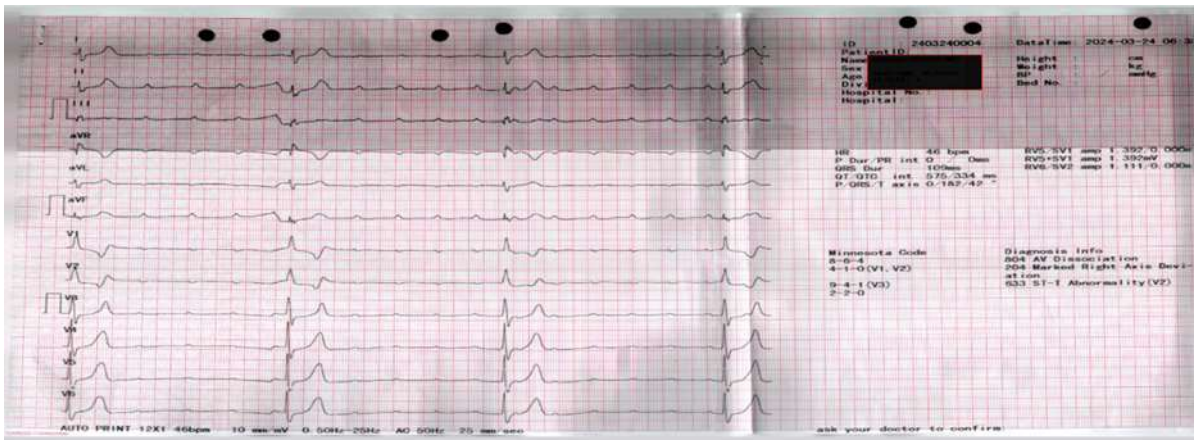

Figure 1. ECG on first day of admission, showing complete AV block with junctional escape rhythm.

The patient was given two injections of atropine sulfate to increase his heart rate. However, after giving atropine, his heart rate actually decreased to 31 times per minute after the first injection and 21 times per minute after the second injection. This condition indicates resistance to atropine, which can occur in complete AV block due to inflammation or fibrosis of the cardiac conduction system. Next, the patient was given a dopamine infusion at an initial dose of 5 mcg/kg/minute to increase his heart rate and blood pressure. However, his blood pressure actually decreased to 80/60 mmHg, so he was given 200cc of normal saline and the dopamine dose was increased to 10 mcg/kg/minute. Based on clinical symptoms, history of exposure to infection, and ECG findings, the doctor suspected the patient was suffering from ARF complicated by complete AV block. To treat ARF, the patient was given an intramuscular injection of Benzathine Penicillin G 1.2 million units and prednisone 20 mg orally. Apart from that, omeprazole

and ondansetron are also given to treat complaints of persistent nausea and vomiting. After six hours of observation in the emergency room, the patient's condition improved with a blood pressure of 100/60 mmHg and a heart rate of 57 beats per minute. The patient was then transferred to the ICU for further monitoring. On initial laboratory examination, the patient's white blood cell count was normal (5.90 x 10^3/uL), hemoglobin 12.9 g/dL, and platelet count 228 x 10^3/uL. Kidney function, electrolytes, and blood glucose levels were also within normal limits. However, hs-Troponin I levels increased to 0.18 ng/mL (normal <0.03 ng/mL), indicating heart muscle damage that may be caused by rheumatic carditis. Chest x-ray results showed normal heart and lung sizes, ruling out the possibility of heart enlargement or pulmonary edema due to heart failure. Antistreptolysin O (ASTO) examination on the following day showed a titer of 200 IU/mL (normal <200 IU/mL), which is the upper limit of normal values. Although not specifically confirming recent streptococcal infection, an elevated ASTO titer still supports the diagnosis of ARF because it indicates an immune response to a previous streptococcal infection. Transthoracic echocardiography is performed to assess heart structure and function. The results showed mild mitral regurgitation and mild tricuspid regurgitation, with a low probability of pulmonary hypertension. The left ventricular ejection fraction was normal (63.38%), without any left ventricular hypertrophy, and the right ventricular systolic function was also normal. These echocardiography findings show that although there are abnormalities in the heart valves, overall heart function is still good.

During treatment in the ICU, the patient's condition continues to be closely monitored. On the second day, the patient did not complain of any symptoms, his blood pressure was stable at 95/58 mmHg, and his heart rate was 45 beats per minute. The dopamine dose was reduced to 7.5 mcg/kg/minute, and prednisone continued to be given four times daily. The ECG still shows a complete AV block with a junctional discharge rhythm. On the fourth day of treatment, significant changes occurred in the patient's ECG. Complete AV block recovered to normal sinus rhythm with a heart rate of 86 beats per minute (Figure 2). This shows a positive response to the medical therapy administered, especially prednisone which has anti-inflammatory effects. After the patient's condition was stable and there were no more complaints, he was sent home with prednisone therapy 20 mg four times a day to continue ARF treatment. Patients are also scheduled for weekly and monthly control at the outpatient clinic for further monitoring and therapy adjustments.

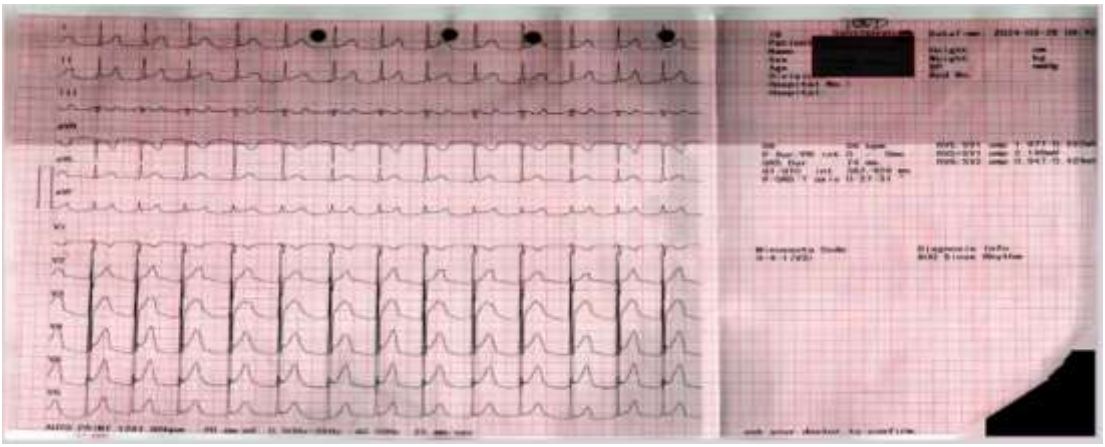

Figure 2. ECG on 4th day of admission, showing sinus rhythm with first-degree AV block with early repolarization.

3. Discussion

This case report provides an interesting overview of the unusual manifestations of acute rheumatic fever (ARF) in a young adult, with a focus on a rare cardiac complication, namely a complete atrioventricular (AV) block. This case provides an opportunity to delve deeper into the theoretical, pathophysiological, clinical, and pharmacological aspects underlying this condition. Acute rheumatic fever (ARF) is a systemic inflammatory disease post-group A streptococcus infection that can affect various organs, especially the heart, joints, skin, and central nervous system. The pathogenesis of ARF involves an abnormal immune response to streptococcal infection, in which antibodies produced to fight the bacteria mistakenly attack the body's tissues. The cardiac complication of ARF, known as rheumatic carditis, is the most serious manifestation and can cause significant morbidity and mortality. Rheumatic carditis can affect all layers of the heart, including the endocardium, myocardium, and pericardium. Inflammation of the heart valves can cause regurgitation or valve stenosis, while inflammation of the myocardium can cause ventricular dysfunction and heart rhythm disturbances. Complete AV block is a rare cardiac complication of ARF but has serious consequences. Complete AV block occurs when electrical impulses from the atria cannot reach the ventricles due to disturbances in the heart's conduction system. This can result in significant bradycardia and symptoms such as syncope, dizziness, and fatigue.[8,9]

Complete atrioventricular (AV) block, although rare, is a serious cardiac complication of acute rheumatic fever (ARF). This condition occurs when electrical impulses from the atria cannot reach the ventricles, disrupting the synchronization of heart contractions and potentially causing life-threatening symptoms. A thorough understanding of the pathophysiology of complete AV block in ARF is essential to develop effective prevention and treatment strategies. The cardiac conduction system is a specialized tissue that produces and conducts electrical impulses that regulate heart rate. The sinoatrial (SA) node, located in the right atrium, functions as the heart's natural pacemaker, producing electrical impulses that trigger atrial contractions. These electrical impulses then travel through the AV node, which is located on the border between the atria and ventricles. The AV node has an important role in regulating the flow of electrical impulses from the atria to the ventricles. The AV node slows the conduction of electrical impulses, allowing the atria to contract completely before the ventricles contract. After passing through the AV node, electrical impulses travel through the bundle of His, which branches into the right and left bundle branches. These branches then conduct electrical impulses to the Purkinje fibers, which trigger ventricular contraction. In acute rheumatic fever (ARF), group A streptococcal infection triggers a complex immune response. The body produces antibodies to fight streptococcal bacteria, but these antibodies can also attack the body's own tissue because of the structural similarities between streptococcal proteins and heart proteins. This phenomenon is known as cross-reaction or molecular mimicry. This cross-reaction triggers an inflammatory response in the heart, especially in the AV node and bundle of His. Inflammatory cells such as lymphocytes and macrophages infiltrate cardiac tissue, releasing various inflammatory mediators such as cytokines and chemokines. These inflammatory mediators cause direct damage to heart cells and disrupt the function of the AV node and bundle of His. In addition, the inflammatory response can also activate the complement system, which is part of the innate immune system. Activation of the complement system results in the formation of a membrane attack complex (MAC) that can damage cardiac cell membranes and cause cell death. Chronic inflammation of the AV node and bundle of His can trigger the process of fibrosis, which is the formation of scar tissue. Fibrosis occurs when fibroblast cells produce excess collagen,

replacing healthy heart tissue with scar tissue that is inelastic and cannot conduct electrical impulses well. Fibrosis of the AV node and bundle of His can disrupt the electrical conduction of the heart and cause varying degrees of AV block, including complete AV block. In complete AV block, electrical impulses from the atria cannot reach the ventricles at all, so the ventricles must rely on slower backup pacemakers, such as the AV node or distal bundle of His. This results in significant bradycardia and can be life-threatening.[10-12]

Complete atrioventricular (AV) block, although rare in acute rheumatic fever (ARF), is a serious complication and can be life-threatening. This condition can occur in all age groups but is more common in children and adolescents. Symptoms of complete AV block in ARF can vary, depending on the severity of the block and the presence of other complications. In mild cases, patients may not experience any symptoms or only experience mild symptoms such as fatigue and dizziness. A significant decrease in heart rate is the main symptom of complete AV block. Bradycardia can cause a variety of symptoms, depending on its severity. In mild cases, patients may only experience fatigue and dizziness. However, in more severe cases, bradycardia can cause syncope (fainting), shortness of breath, chest pain, and even cardiac arrest. Syncope is a sudden and temporary loss of consciousness due to decreased blood flow to the brain. Syncope is one of the most common and concerning symptoms of complete AV block. Syncope can occur spontaneously or be triggered by physical activity or changes in body position. Dizziness and fatigue are other common symptoms of complete AV block. This symptom is caused by a decrease in cardiac output due to bradycardia. Patients may feel dizzy when standing or doing physical activity and often feel tired even after getting enough rest. Shortness of breath may occur with complete AV block if bradycardia causes a significant reduction in cardiac output. Decreased cardiac output can cause fluid to build up in the lungs, resulting in shortness of breath. In the most severe cases, complete AV block can cause cardiac arrest. Cardiac arrest is a medical emergency in which the heart stops beating effectively. Cardiac arrest requires immediate cardiopulmonary resuscitation (CPR) to save the patient's life. The diagnosis of complete AV block in ARF is made based on a combination of history, physical examination, and supporting examinations. A careful history is essential to identify the typical symptoms of complete AV block, such as syncope, dizziness, and fatigue. In addition, a history of fever, joint pain, and previous streptococcal infections also needs to be explored to direct the diagnosis towards ARF. Physical examination can reveal signs of heart failure due to complete AV block, such as edema, hepatomegaly (enlarged liver), and rales (abnormal breath sounds) on lung auscultation. In addition, a physical examination can also identify signs of rheumatic carditis, such as a heart murmur. ECG is the most important examination to confirm the diagnosis of a complete AV block. On an ECG, complete AV block is characterized by the absence of a connection between the P wave (which represents atrial electrical activity) and the QRS complex (which represents ventricular electrical activity). In addition, an ECG can show the presence of a junctional or ventricular discharge rhythm, which is an abnormal heart rhythm produced by the pacemaker cells in the AV node or ventricle. Echocardiography can provide additional information that is useful in the diagnosis and management of complete AV block in ARF. Echocardiography can assess heart function, the presence of structural abnormalities such as valve regurgitation, and the presence of signs of inflammation in the heart. In addition, echocardiography can help determine the etiology of complete AV block, whether caused by ARF or another condition.[13-15]

Complete AV block in ARF has significant implications for the patient. Bradycardia caused by

complete AV block can cause symptoms that interfere with daily activities and reduce the patient's quality of life. In addition, complete AV block can also increase the risk of serious complications such as heart failure and cardiac arrest. Therefore, rapid and appropriate diagnosis and treatment are very important to prevent complications and improve the quality of life of patients with complete AV block in ARF. Adequate medical therapy, including antibiotics to eradicate streptococcal infection and anti-inflammatory drugs to reduce inflammation, can help reverse complete AV block and prevent further complications. In cases unresponsive to medical therapy, placement of a temporary or permanent pacemaker may be necessary to maintain an adequate heart rate and prevent life-threatening complications.[15,16]

Management of complete atrioventricular (AV) block in acute rheumatic fever (ARF) requires a holistic approach that includes medical therapy, non-pharmacological interventions, and long-term monitoring. The main goals of management are to treat the underlying cause, improve symptoms, prevent complications, and improve the patient's quality of life. Medical therapy for complete AV block in ARF includes medications to treat streptococcal infection, reduce inflammation, and improve AV conduction. Giving antibiotics is an important first step in the management of ARF. Penicillin antibiotics, such as benzathine penicillin G, are the main choice for eradication of group A streptococcal infections. Adequate and timely administration of antibiotics can prevent further cardiac complications and improve the patient's prognosis. Anti-inflammatory drugs, such as corticosteroids (eg, prednisone) or aspirin, are used to reduce inflammation in the heart and other tissues. Anti-inflammatory drugs can help improve AV conduction and reverse complete AV block. In severe cases, immunosuppressive therapy such as methotrexate or azathioprine may be considered. Chronotropic drugs, such as atropine or isoproterenol, may be used to temporarily increase heart rate in patients with significant bradycardia. However, the effects of these drugs are usually temporary and cannot be relied upon in the long term. In cases of persistent or life-threatening complete AV block, placement of a temporary or permanent pacemaker may be necessary to maintain an adequate heart rate and prevent complications such as heart failure and cardiac arrest. The decision to implant a pacemaker must consider various factors, including the patient's age, the severity of the AV block, the presence of other cardiac complications, and the response to medical therapy. In addition to medical therapy, non-pharmacological interventions are also important in the management of complete AV block in ARF. Psychological support and patient and family education about the disease, treatment, and prognosis can help reduce anxiety, increase adherence to therapy, and improve the patient's quality of life. Long-term monitoring is essential for patients with complete AV block in ARF. Routine monitoring with ECG and echocardiography can help detect ARF recurrence or other cardiac complications early. In addition, patients need to undergo long-term antibiotic prophylaxis to prevent recurrent streptococcal infections and further cardiac complications. Complete AV block in ARF is a serious heart complication but can be treated well if diagnosed and treated quickly and appropriately. Comprehensive management, including medical therapy, non-pharmacological interventions, and long-term monitoring, can improve the patient's prognosis and quality of life.[17,18]

This case highlights some of the challenges in the management of complete AV block in ARF. First, the diagnosis of complete AV block in ARF may be delayed or missed due to nonspecific symptoms and lack of clinician awareness of this cardiac complication. Therefore, it is important to increase clinician awareness of the possibility of complete AV block in ARF, especially in patients with unusual symptoms or a history of exposure to streptococcal infection. Second, treating complete AV block in ARF requires a

comprehensive and individual approach. Administration of drugs such as atropine and dopamine can help increase heart rate temporarily, but placement of a temporary or permanent pacemaker may be necessary if complete AV block persists or is life-threatening. The decision to implant a pacemaker must consider various factors, including the patient's age, the severity of the AV block, the presence of other cardiac complications, and the response to medical therapy. Third, further research is needed to better understand the pathophysiology of complete AV block in ARF and develop more effective prevention and treatment strategies. Research on biomarkers of inflammation and fibrosis may help in identifying patients at high risk for complete AV block and monitoring response to therapy. In addition, research on new therapies, such as immunomodulatory therapy or regenerative therapy, may open new opportunities in treating complete AV block in ARF.[19,20]

4. Conclusion

This case report makes an important contribution to our understanding of the manifestation and management of complete AV block in ARF, especially in young adult patients. This case highlights the importance of clinician awareness of the rare cardiac complications of ARF and emphasizes the importance of prompt and appropriate diagnosis and treatment.

5. References

1. Gewitz MH, Baltimore RS, Tani LY. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. 2015; 131(20): 1806-18.
2. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet. 2012; 379(9819): 953-64.
3. Watkins DA, Johnson CO, Colquhoun SM. Global, regional, and national burden of rheumatic heart disease, 1990–2015. N Engl J Med. 2017; 377(8): 713-22.
4. Zühlke L, Mirabel M, Marijon E. Update on rheumatic fever and rheumatic heart disease. Curr Opin Rheumatol. 2018; 30(4): 412-8.
5. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005; 5(11): 685-94.
6. Remenyi B, Wilson N, Steer A. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. Nat Rev Cardiol. 2012; 9(5): 297-309.
7. Beaton A, Okello E, Lwabi P. Echocardiographic screening for rheumatic heart disease in Ugandan schoolchildren. N Engl J Med. 2018; 379(8): 701-12.
8. Karthikeyan G, Mayosi BM. Is primary prevention of rheumatic fever a realistic goal in developing countries? Curr Opin Cardiol. 2018; 33(4): 343-50.
9. Steer AC, Batzloff MR, Carapetis JR. Group A streptococcal vaccines: facts versus fantasy. Curr Opin Infect Dis. 2018; 31(3): 254-62.
10. Engel ME, Frenck R, Moorthy V. Prevention of rheumatic fever: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2009; 120(11): 1024-32.
11. Liu L, Johnson C, Cousens S. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012; 379(9832): 2151-61.
12. Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute

rheumatic fever: a meta-analysis. BMC Cardiovasc Disord. 2004; 4: 11.

13. Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. Cochrane Database Syst Rev. 2012; (9): CD002227.
14. RHD Action. The global status of rheumatic heart disease control and prevention: a first step towards evidence-based global advocacy. Geneva: RHD Action. 2018.
15. World Health Organization. Rheumatic fever and rheumatic heart disease. Geneva: World Health Organization. 2018.
16. Narula J, Narula N, Reddy KS. Rheumatic fever. Lancet. 2013; 381(9880): 1947-58.
17. Tibazarwa KB, Volmink J, Mayosi BM. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. Heart. 2008; 94(12): 1534-40.
18. Haidan A, Gewitz MH, Cilliers AM. International consensus statement on the management of acute rheumatic fever. Nat Rev Cardiol. 2015; 12(7): 414-26.
19. Oliveira Filha AG, Dantas LN, Hilário MO. Clinical presentation and outcome of rheumatic fever in the modern era: a systematic review and meta-analysis. Heart. 2018; 104(17): 1363-70.
20. Spagnolo P, Oliveira Filha AG, Dantas LN. Clinical presentation and outcome of rheumatic fever in the modern era: a systematic review and meta-analysis. Heart. 2018; 104(17): 1363-70.