# Clinical Signs of Rheumatic Fever - Case Series

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ABSTRACT

Acute rheumatic fever is an autoimmune disease following group A β-hemolytic Streptococcal infection. The disease may present with variable symptoms and signs. **Cases:** The first case is an 8-year-old boy with arthritis and previous streptococcal infection. The treatment was glucocorticoids and antibiotics. The second case is a 17-year-old boy with prolonged fever and palpitations. Carditis was found on echocardiography. The treatment was aspirin and antibiotics. The third case is a 17-year-old girl with a congenital heart defect. The patient had severe carditis as well as arthritis. The treatment was diuretics, antibiotics, steroids, antiarrhythmics, and beta-blockers. Management differed in each case, but all had favorable outcomes. **Conclusion:** Clinicians should be aware of the various manifestations of rheumatic fever and come to a swift diagnosis to initiate prompt treatment, which thus can decrease disease burden and morbidity.

**Keywords:** Acute rheumatic fever, autoimmune disease, rheumatic heart disease, Streptococcal infection.

ABSTRAK

Demam rematik akut adalah penyakit autoimun yang didahului adanya infeksi *Streptococcus* grup A β-hemolitik, dapat mempunyai gejala yang bervariasi. **Kasus**: Pasien pertama anak laki-laki berusia 8 tahun dengan artritis dan riwayat infeksi *Streptococcus*. Terapinya adalah antibiotik dan *glucocorticoid*. Pasien kedua laki-laki berusia 17 tahun dengan demam berkepanjangan dan palpitasi. Pada ekokardiografi didapatkan karditis. Terapinya adalah antibiotik dan *aspirin*. Pasien ketiga perempuan berusia 17 tahun dengan kelainan jantung bawaan. Pasien mengalami karditis parah serta artritis. Terapinya adalah diuretik, antibiotik, *steroid*, anti-aritmia, dan *beta-blocker*. Tata laksana berbeda pada masing-masing kasus dengan hasil yang memuaskan. **Simpulan:** Klinisi hendaknya mengenali berbagai gejala demam rematik agar mampu mendiagnosis dan segera memulai pengobatan agar bisa mengurangi beban penyakit dan morbiditas. **Claudia Natasha Liman, Ferry Gozali, Putu Pradnyanita Mustika. Berbagai Presentasi Klinis Demam Rematik - Kasus Serial.**

**Kata Kunci:** Demam rematik akut, penyakit autoimun, penyakit jantung rematik, infeksi *Streptococcus*.



## BACKGROUND

Acute rheumatic fever (ARF) is an immune-mediated disease following group A Streptococcus pharyngitis. The incidence of ARF is estimated to be higher in developing countries, especially in susceptible hosts,[1] and may be attributed to other risk factors for ARF: low socio-economic status with overcrowding, poor nutrition, poor sanitation, and lack of access to healthcare.[2] Inadequate or delayed treatment may result in the development of rheumatic heart disease (RHD), which increases patient burden and may cause life-long debilitation.

## CASE 1

An 8-year-old boy with persistent fever for 6 days only mildly decreased with antipyretics. The patient also complained of a dry cough one day prior to the onset of fever. Three days later, a non-itchy rash was observed on his abdomen. There was also myalgia, fatigue, low intake, as well as nausea and vomiting. He has a history of recurrent upper respiratory tract infection. Immunization status was complete. On the second day, the patient complained of joint pain on all fingers and wrists of both hands. The pain was tolerable but caused a clear discomfort. Other symptoms such as palpitation, diarrhea, chest discomfort, nodules, uncontrollable movement, and red urine were not observed.

On examination, there was a desquamation of abdomen skin and a faint murmur on auscultation. ECG revealed a prolonged PR interval. Anti-streptolysin titer was elevated (400 IU), along with leukocytosis (15.500/mm$^3$), increased erythrocyte sedimentation rate (ESR 94 mm/hour), and C-reactive protein (CRP 70 mg/L). Plain chest radiology revealed increased bronchovascular markings. Fever was continued until day 10, albeit with continuous antipyretic administration. Rheumatoid arthritis was diagnosed with arthritis as the major criterium and prolonged fever of >38.5 °C, increased ESR, and CRP as minor Jones criteria.

Penicillin G Benzathine 600,000 IU intramuscular single dose and oral prednisone 50 mg divided into four doses of 15 mg, 15 mg, 10 mg, and 10 mg daily were administered for 2 weeks. The patient felt significantly less pain and joint swelling. His appetite was increasing, and his overall condition improved. The patient was discharged after six days with no seizures. At follow-up three days post-discharge, the patient presented well, with no heart murmur.

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## CASE 2

A 17-year-old boy with continuous fever for 10 days. Other symptoms such as cough, coryza, diarrhea, dysuria, myalgia, arthralgia, rash, nausea, vomiting, jaundice, chest pain, or weight loss were not found. He had recurrent upper respiratory tract infection. Physical examination was uneventful except for a temperature of 39-40 °C. The Widal test revealed *S. typhii O* 1/320, *S. typhii H* 1/150, and *S. para B-H* 1/160. The patient was initially diagnosed with typhoid fever. Intravenous ceftriaxone of one gram twice daily, oral paracetamol 3 dd 500 mg daily, and maintenance fluids were administered. Fever of 39-40°C and mild loss of appetite continued for three days, and the patient's condition did not improve significantly. The patient started to complain of a fluttery feeling in his chest without chest pain or dyspnea. Electrocardiogram and plain chest radiography were within normal limits. An echocardiography was done with an adult probe due to limited facilities and detected an elevated ejection fraction, mild mitral and pulmonal valve regurgitation, frequent ventricular extrasystole, and mild pericardial effusion. Complete blood counts were within normal limits. Anti-streptolysin titer was 400 IU/mL, ESR 71 mm/hour, and CRP 65 mg/L. The patient was diagnosed with acute rheumatic fever with pericarditis and typhoid fever. Carditis diagnosis was supported by the major Jones criterion of prolonged fever of >38.5C plus increased ESR and CRP as two minor criteria.

The treatment was penicillin G benzathine injection 1,200,000 IU intramuscular single dose, trimetazidine 2 dd 35 mg daily, and high-dose aspirin of 5200 mg daily for two weeks before tapering off. Hemostasis function tests were to be repeated every two weeks.

After nine days, the patient was afebrile for 2 x 24 hours and did not develop new complaints; the patient was discharged and treated with 5,200 mg aspirin (100 mg/kg/day) divided into daily doses of 16-16-16-17 tablets 80 mg each for two weeks, ranitidine 3 dd 150 mg, and trimetazidine 2 dd 35 mg. At follow-up three days post-discharge, palpitations were significantly less, and no murmur was heard on auscultation. The patient was advised to receive the second dose of penicillin G benzathine 21 days after the first dose. Aspirin was tapered off to a dose of 60 mg/kg/day after two weeks of 100 mg/kg/day as per protocol.

## CASE 3

A 17-year-old girl with worsening dyspnea was on exertion for four days. Patient felt more comfortable in upright sitting position. She had a non-productive cough, palpitations, and low intake due to nausea and vomiting for the past week and fever, joint morning pain, particularly on the lower extremities, and diaphoresis for two weeks. Weight loss, contact with a tuberculosis-positive patient, rash, and previous medical history were denied, but she had had poor weight gain since childhood. The patient admitted to having frequent sore throats and coughs but was self-medicated and has never seen a physician. Her nutritional status is moderate protein-energy malnutrition.

On examination, the patient was tachycardic, tachypneic, and needed oxygen supplementation. There was mild exophthalmos and ptosis, with elevated jugular venous pressure, visible heave, thrill, and murmur. Laboratory results revealed mild leukocytosis, elevated ESR, and partially compensated respiratory alkalosis. Cardiomegaly was found on chest radiology, and echocardiography revealed right atrium and ventricle dilation, moderate mitral regurgitation, severe tricuspid regurgitation, moderate pulmonic regurgitation, as well as an ostium secundum atrial septum defect with suspected pulmonary hypertension. The patient was diagnosed with acute heart failure due to rheumatic heart disease and atrial septal defect with mitral stenosis, pulmonary regurgitation, tricuspid regurgitation, and bronchopneumonia. This patient presented with arthritis and carditis as two major criteria and >38.5 °C fever and increased ESR of 93 mm/hour as minor Jones criteria. Complete blood counts were within normal limits. Anti-streptolysin titer was 800 IU/mL.

The patient was started on daily ceftriaxone 2 dd 1,5 grams IV, furosemide 10 mg IV, spironolactone 25 mg per oral, amiodarone 200 mg per oral, captopril 3 dd 6,25 mg per oral, prednisone 4 dd 10 mg per oral, and a nebulized bronchodilator with corticosteroid three times daily.

Benzathine penicillin G 1,200,000 IU intramuscular single dose was administered. Thyroid panel showed TSH 1.81 mU/L and FT4 1.67 pmol/L, showing subclinical hyperthyroid, explaining her exophthalmos and ptosis. Lab results on the fifth day showed hypocalcemia of 7.7 mg/dL; a calcium carbonate tablet of 3 dd 500 mg daily was started. Dyspnea was minimal in the following days; oxygen supplementation was tapered off, and the patient felt comfortable.

The patient was discharged after seven days and was otherwise stable with furosemide 20 mg once daily, digoxin 0,125 mg once daily, bisoprolol 2,5 mg once daily, spironolactone 25 mg once daily, captopril 6,25 mg three times daily, calcium carbonate 500 mg three times daily, N-acetylcysteine 200 mg three times daily, prednisone 10 mg four times daily, and recommendations for the second dose of Penicillin G Benzathine 1,200,000 IU injections 21 days after the first dose.

## DISCUSSION

Acute rheumatic fever (ARF) is an autoimmune disease following group A β-hemolytic streptococcal throat infection. ARF is not uncommon, particularly in developing countries, as the risk factors include poverty, overcrowding, and poor access to healthcare facilities.[1] The prevalence of rheumatic fever in Israel is around 7.5 cases per 100,000 population.[2] In 2015, it was estimated that the prevalence of rheumatic heart disease globally was around 33.4 million.[3] Untreated or inadequately treated ARF may develop into rheumatic heart disease (RHD). On a global scale, death by RHD decreased from 8.9 per 100,000 in 1990 to 3.9 per 100,000 in 2019. South Asia is the biggest contributor.[4]

The diagnosis of ARF is largely based on clinical evaluation using the modified Jones criteria.[5] Major criteria are arthritis, carditis (clinical or subclinical), subcutaneous nodules, erythema marginatum, and Sydenham's chorea. Minor criteria are fever >38.5°C, elevated ESR and/or CRP, prolonged PR interval (unless carditis is a major criterion), and polyarthralgia. Diagnosis of ARF is made upon presentation of two major or one major plus two minor criteria. Currently, there is no gold standard laboratory marker for the diagnosis of ARF.

Laboratory markers for ARF are elevated anti-streptolysin titers or positive culture from a throat swab.[6] Diagnosis of ARF should be reserved if there is no evidence of prior Streptococcus infection.[6] The American Heart Association strongly suggests the use

of echocardiography instead of relying on clinical auscultatory skills to diagnose cardiac manifestations of ARF, especially because carditis sequalae is the most concerning and requires long-term management.[7] Rheumatic valvulitis often presents as mitral or aortic valve regurgitation; however, emerging evidence has shown that cardiac manifestations can involve endocardium, myocardium, and pericardium.[7]

Joint involvement in ARF may be mono- or polyarthritic; multiple joint involvement is more common. Pain in different joints may occur separately or overlapping and should rapidly subside with aspirin or other nonsteroidal anti-inflammatory or glucocorticoid treatment. Chorea in ARF is described as Sydenham's chorea, characterized by involuntary, non-rhythmic, and purposeless movements of the trunk and limbs that disappear with sleep. If chorea is present, echocardiography must be done because chorea is strongly associated with carditis. Erythema marginatum is the least common major manifestation, found in less than 10% of ARF cases. Subcutaneous nodules are small, painless nodules that appear over bony prominences or tendons, are typically symmetrical, and last for one to two weeks.[6]

All three cases initially presented as prolonged fever. A history of self-medication is present in the third patient, while recurrent upper respiratory tract infection is found in all three cases. The first case presented with polyarthralgia, the second patient developed palpitations, and the third patient showed signs of heart failure. The cause of infection in all three cases was unclear; prolonged fever may be due to acute rheumatic fever.

The first case presents arthralgia as a major symptom along with high-grade fever and increased inflammatory markers. Electrocardiogram showed prolonged PR interval, and upon auscultation, an unclear murmur was heard; however, echocardiography did not show any abnormalities. It should be noted that an adult probe was used due to limited facility, meaning a lower frequency transducer, hence mild abnormalities might not be detected.

The second case presents as carditis detected through echocardiogram, high-grade fever, and increased inflammatory markers. The patient initially presented with prolonged fever of unknown origin, and cardiologic evaluation was done because of a palpitation complaint. Elevated ejection fraction, mild mitral and pulmonal valve regurgitation, frequent ventricular extrasystole, and mild pericardial effusion were found on echocardiography.

The third patient presented with symptoms of rheumatic heart disease and had developed heart failure. The patient complaint of dyspnea, non-productive cough, palpitations, joint pain, and diaphoresis also appeared to be moderately malnourished with a history of difficult weight gain since early childhood. The patient was tachycardic, tachypneic, had elevated jugular venous pressure, a visible heave and palpable thrill, as well as a grade 6 murmur. Subclinical hyperthyroidism is likely to be incidental and have no relation with the development suggestive of congenital heart disease, as found in chest radiology of rheumatic heart disease. Cardiomegaly suggestive of congenital heart disease was found in chest radiology. An echocardiography found right atrium and ventricle dilation, moderate mitral regurgitation, severe tricuspid regurgitation, moderate pulmonic regurgitation, as well as an ostium secundum atrial septum defect with suspected pulmonary hypertension. A history of poor weight gain despite adequate nutritional intake should increase suspicion of a congenital heart disease. Elevated ESR adds to fulfill two major as well as two minor criteria.

Co-existing congenital heart disease with rheumatic heart disease is an uncommon occurrence.[7] A study in India in 2002 found the prevalence of rheumatic heart disease was 8.8% in children with congenital heart disease, significantly higher compared to 0.3% among those without disease.[8] One of the five cases reported presented with ostium secundum type atrial septal defect. Management was pharmacological; carditis was treated with benzathine, penicillin prophylaxis, steroids, and aspirin.[8] Treatment of the third patient in this case series was varied. This can be due to the difference in carditis severity; the severity of carditis in the 2002 case report was not specified.

Another case of RHD complicating the existing congenital heart disease (CHD) was reported in India in 2008. This patient presented with a newly diagnosed tetralogy of Fallot alongside RHD; the existing CHD further complicated RHD symptoms, as well as increasing the risk of infective endocarditis.[9] In the case reported in India, the patient did well on steroids and aspirin as well as benzathine penicillin prophylaxis and did not need surgical intervention,[9] as in the third patient in this case report. It has been theorized that congenital heart disease predisposes the progression of acute rheumatic fever to rheumatic heart disease, though the exact mechanism is unclear.[8]

A differential diagnosis of juvenile idiopathic arthritis (JIA) may be considered in the first case. Juvenile idiopathic arthritis is diagnosed after symptoms have persisted for at least 6 weeks and occurs in children less than 16 years of age.[10] This patient fits the age criteria; however, joint pains only lasted several days. Also, the affected joints were not swollen, tender, or warm on palpation, as is often found in JIA. Systemic symptoms of JIA include fever commonly present in the afternoon, while in this patient the fever had no pattern.[11]

Appropriate and timely diagnosis of ARF is crucial and will determine disease outcome. Morbidity in ARF most notably occurs in cases with carditis. High suspicion of ARF is warranted in endemic areas, such as the Middle East, sub-Saharan Africa, the South Pacific, and Central and South Asia.[12] Patients with suspected ARF should be admitted,cular benzathine penicillin G 0.6 eradication unit is given upon confirmation of group A Streptococcus infection and is repeated every 28 days or 21 days in high-risk cases. and the mainstay of management is eradication of pathogen group A Streptococcus as well as secondary prophylaxis and symptoms management. Intramuscular benzathine penicillin G 0.6 to 1.2 million units is given upon confirmation of group A Streptococcus infection and is repeated every 28 days or 21 days in high-risk cases.[6] The dose for children weighing less than 27 kg is 600,000 IU and 1.2 million IU for children >27 kg. In rheumatic fever with carditis with or without residual heart disease, treatment is continued for 10 years or until the patient is 40 years old for adults or 21 years old for children. For rheumatic fever without carditis, the treatment is continued for 5 years or until the patient is 21 years of age.[13] Adherence to prophylactic benzathine penicillin G is crucial




to prevent recurrent infections.[14]

In mild to moderate carditis, the treatment should be started on aspirin 90-100 mg/kg/day in four to six divided doses for four to eight weeks, depending on the clinical response.[13] The dose is then gradually tapered off over a period of four to six weeks. In severe carditis, prednisone 2 mg/kg/day is given in four divided doses over a period of two to six weeks. Prednisone is then tapered off, and aspirin is to be given in the final week of tapering off. In cases of arthritis, aspirin is continued for two weeks and gradually withdrawn over two to three weeks. Rapid resolution of joint pain upon aspirin administration is indicative of ARF.[13] Bed rest is indicated in all ARF cases; its duration depends on severity. Additionally, the patient must remain rested until symptoms of heart failure have subsided.[13]

In moderate to severe mitral regurgitation, diuretics are used to reduce afterload, along with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARB).[15] The only proven effective treatment for mitral stenosis is catheterization or surgical intervention. In acute pulmonary edema, loop diuretics may be used with diuresis monitoring; β-blockers may be used to reduce heart rate.[15]

Benzathine and penicillin G were administered in all three patients based on laboratory evidence of Group A Streptococcus infection. In the first case, secondary prophylaxis injections were scheduled every 28 days, whereas in the second and third cases, every 21 days, following recommendations regarding more frequent doses in high-risk cases.[6] The second case presents as mild to moderate carditis; hence, the use of aspirin is justified. The third case presents as severe carditis with heart failure; hence, prednisone is used in place of aspirin plus diuretics as well as ACE inhibitors. Though murmur was heard on auscultation in the first case, carditis could not be established through echocardiography, hence aspirin was not initiated.

## CONCLUSION

Rheumatic fever is still prevalent in Indonesia. Poor hygiene, poor access to proper healthcare facilities, a crowded home environment, and an overall inadequate understanding of the disease are all risk factors commonly found in Indonesia. Pharyngitis is frequent and is often undermined, even in a medical facility.

Recurrent ARF can develop into rheumatic heart disease if inadequately treated. Consider anti-streptolysin titer evaluation in cases of prolonged fever. Early detection and treatment can prevent the risk of complications.

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