Acute Rheumatic Fever

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EDUCATION GAPS

1. Clinicians should be aware of current prevalence of acute rheumatic fever and rheumatic heart disease.
2. Clinicians should be able to diagnose acute rheumatic fever using the 2015 updated Jones criteria.
3. Clinicians should be aware of the role of echocardiography in diagnosis, risk stratification, and treatment of children with acute rheumatic fever and rheumatic heart disease.

OBJECTIVES *After completing this article, readers should be able to:*

1. Identify the population at risk for acute rheumatic fever (ARF).
2. Diagnose ARF based on the 2015 modified Jones criteria.
3. Understand the use of echocardiography to diagnose subclinical and early cases of rheumatic carditis.
4. Treat patients with ARF with and without carditis.
5. Learn primordial, primary, and secondary prophylaxis for ARF.

ABSTRACT

The incidence of acute rheumatic fever (ARF) is 8 to 51 per 100,000 people worldwide. It most commonly affects children 5 to 15 years of age after a group A streptococcal infection. Overcrowding and poor socioeconomic conditions are directly proportional to the incidence of ARF. Rheumatic carditis is a manifestation of ARF that may lead to rheumatic heart disease (RHD). Timely treatment of group A streptococcal infection can prevent ARF, and penicillin prophylaxis can prevent recurrence of ARF. Prevention of recurrent ARF is the most effective way to prevent RHD. ARF is diagnosed using the 2015 modified Jones criteria. There is no gold standard laboratory test. Therefore, clinicians need to be aware of the clinical signs and symptoms of ARF to include in their differential diagnosis when seeing such patients. Secondary prophylaxis with benzathine penicillin G has been shown to decrease the incidence of RHD and is key to RHD control. Clinicians need to understand the implications of secondary prophylaxis for ARF. There is also a need to improve ARF diagnosis, to find novel therapies to reduce the incidence of ARF, and to reduce the prevalence of RHD. RHD research is neglected and underfunded. Thus, there is also a need for RHD advocacy and public health awareness to increase research on RHD.

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ABBREVIATIONS

ARF acute rheumatic fever
GAS group A *Streptococcus*
HLA human leukocyte antigen
RHD rheumatic heart disease

EPIDEMIOLOGY

Once public health problems across the globe, acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are now considered public health problems only in low-resource settings in low- or middle-income countries and neglected or indigenous populations in developed countries. The incidence of ARF and RHD varies widely and is inversely proportional to socioeconomic development. The incidence of ARF ranges from 8 to 51 per 100,000 children and young adults worldwide. (1) This number can be as high as 200 per 100,000 in endemic areas. (2) There are at least 470,000 cases of ARF that occur every year worldwide. (3) However, the true incidence of ARF is difficult to assess because ARF occurs mostly in places such as Asia and Africa, where there may not be robust regional or centralized data. The incidence of ARF in 1935 and 1936 was reported to be 28.5 per 100,000 individuals aged 5 to 19 years in the United States and is now negligible. (4) Interestingly, the decline in the incidence of ARF and RHD in high-income countries started before the initiation of secondary penicillin prophylaxis. This is thought to be partly due to improved public health conditions and partly due to a change in streptococcal strain with decreased virulence. In the mid-1980s there was a focal resurgence of ARF in 24 states of the United States, which was postulated to be secondary to the resurgence of a new rheumatogenic strain of streptococcus. (5)

Children aged 5 to 15 years are most commonly affected by ARF. ARF is uncommon before 5 years of age and seldom occurs before 2 to 3 years of age. These age groups coincide with the age group that is mostly infected by group A *Streptococcus* (GAS). There is a 3% risk of ARF after an untreated GAS infection. (4) In children with previous ARF, however, the risk of recurrence rises to more than 50%. (6) Epidemiologic data suggest that the incidence of streptococcal infection has not changed over time. However, the incidence of ARF and RHD has declined, suggesting that host and environment play a significant part in the epidemiology of ARF. Overcrowding is thought to be a major contributor to the higher incidence of ARF and RHD in low- and middle-income countries and among indigenous populations in developed countries. This, along with other challenges, such as poor access to health care and delayed or missed diagnosis of GAS pharyngitis, has allowed ARF and RHD to persist.

According to the 2017 Global Burden of Disease Study, there are globally 39 million patients with RHD, which causes 9 million disability-adjusted life-years lost and 275,000 deaths yearly. (2)(7)(8)(9) RHD is the worldwide leading cause of acquired cardiac morbidity and mortality in the young, with 79% to 98% of the disease occurring in low- and middle-income settings. (10) Approximately, 30% to 60% of people with ARF in endemic communities subsequently develop RHD. (11)

HOW DOES GAS CAUSE ARF?

Dr. Wannamaker, in his Duckett Jones Memorial Lecture of 1973 called "The Chain that Links the Heart to the Throat," discussed the possibility of direct toxic effects of GAS on the cardiac tissue and the immunologic mechanism of ARF secondary to GAS pharyngitis. (12) ARF, a systemic inflammatory autoimmune reaction, typically occurs 2 to 4 weeks after a GAS throat infection, commonly referred to as "strep throat." (13) The development of ARF has been postulated to involve the combination of a genetically susceptible individual, a rheumatogenic GAS infection, and an abnormal host immune response. (14)

GAS, also known as *Streptococcus pyogenes,* is a gram-positive bacterium with an outer layer composed of hyaluronic acid. The cell wall comprises repeated units of *N*-acetyl-D-glucosamine carbohydrates. (15) When cultured, the bacterium forms heavily encapsulated hyaluronic acid mucoid colonies on blood agar. The classification of *Streptococcus* is based on the serology of its cell wall polysaccharides, giving Lancefield groups A, B, F, and G. (16) Only serotype B is associated with ARF. M protein along with lipoteichoic acid on the cell wall helps the bacteria adhere to the host epithelium. There have been more than 100 M serotypes identified. (17) M protein is related to bacterial virulence and shares structural homology with myosin, tropomyosin, laminin, vimentin, keratin, and laminin, which is the basis of noninfectious autoimmune diseases caused by GAS. (18) The M protein on the cell wall also evokes a strong type of specific immune response.

The pathogenesis of ARF is incompletely understood. A streptococcal infection can trigger autoimmunity. (19) Only true infection (not colonization) results in an immune response, which can lead to ARF. ARF follows GAS pharyngitis by 10 days to 5 weeks. Molecular mimicry is the most common hypothesis for the pathogenesis of ARF. GAS M proteins usually trigger humoral and cell-mediated immune pathways, which lead to the creation of antibodies that attack human cardiac myosin and laminin in the heart valves, causing valvulitis. The antiphagocytic properties of M protein and hyaluronate of *Streptococcus* promote the delivery of many antigens and toxins to the lymphoid tissues of the

pharynx, which essentially hypersensitizes the body to streptococcal antigens. Swallowing bacteria during infection increases exposure to streptococcal antigens through the gastrointestinal tract. First, autoantibodies activate the endothelium, triggering increased surface expression of VACM1. (20) This assists T-cell intrusion to the avascular valve matrix, leading to a TH1 response. This upregulates translocation of CD4 T cells and B lymphocytes in the extravascular space, leading to local tissue damage and the production of inflammatory cytokines. There are increased amounts of tumor necrosis factor α and interferon γ and decreased amounts of anti-inflammatory cytokines such as interleukin-4. Epitope spreading is another mechanism by which T cells recognize other intracardiac self-antigens such as vimentin and alpha-tropomyosin, thus damaging them. (21) This leads to the amplification of inflammation. Ongoing inflammation leads to neovascularization, which recruits more T cells, leading to granulomatous inflammation and classic changes of chronic RHD such as Aschoff bodies. Similarly, antibodies against GAS *N*-acetyl-D-glucosamine cross-react with basal ganglia cells, which can lead to excess release of dopamine. Increased dopamine can cause the clinical symptoms of Sydenham chorea. Accumulation of immune complexes in the joints can cause transient joint inflammation as found in ARF.

There is evidence of genetic susceptibility to produce the cross-reactive antibodies as well and cause valve damage by the antibodies. Studies have found an association between alleles of major histocompatibility complex and ARF. The human leukocyte antigen class II (HLA-II) molecules that are expressed on the surface of antigen-presenting cells trigger activation of T lymphocytes. (7) DR7 and DR4 alleles of HLA-II are shown to be associated with ARF. Some alleles of tumor necrosis factor α located in the major histocompatibility complex region have also been shown to be associated with ARF. There may be increased susceptibility to certain ethnicities, such as seen in studies from indigenous populations in New Zealand, Hawaii, and Australia. (9)(22) The high prevalence in this population in developed countries has also been found to be associated with poverty, overcrowding, and poor access to health care.

PATHOLOGY

There are 2 phases of evolution of carditis. The first is the exudative phase, which occurs in the first 2 to 3 weeks after disease onset. This phase is notable for interstitial edema, cellular infiltration, collagen fragmentation, and scattered fibrinoid deposition. The second phase, or the proliferative phase, lasts months to years. This is when Aschoff bodies are found in the myocardium secondary to the accumulation of lymphocytes and granulomatous inflammation. (23) On pathology examination, Aschoff bodies are pathognomonic of RHD. There is often cardiomegaly due to edema and nonspecific inflammation of the myocardium. The conduction system is rarely affected, except for a prolonged PR interval. Valves are edematous and vascularized secondary to endocarditis. Over time the inflammation becomes chronic and leads to fibrosis and damages the valves. Inflammation may lead to elongation and rupture of chordae of the mitral valve, leading to severe mitral regurgitation.

Progression of ARF to RHD depends mainly on the severity of initial carditis, ARF recurrences, and adherence to penicillin prophylaxis. Patients with severe mitral or aortic regurgitation or signs of heart failure at presentation will likely have persistent RHD versus patients with mild mitral regurgitation or aortic regurgitation. Therefore, early detection of carditis or detection of subclinical carditis by echocardiography and prompt treatment may improve the outcome of ARF. (24) Prophylactic penicillin to prevent recurrences also reduces the severity and incidence of RHD.

CLINICAL ASPECTS

Diagnosis of Streptococcal Infection

GAS pharyngitis rarely affects children younger than 3 years. Clinical features of GAS pharyngitis are acute sore throat, odynophagia, fever, and headache. Children may have nausea, vomiting, and abdominal pain. On physical examination they may have exudative or nonexudative tonsillopharyngeal erythema, anterior cervical lymphadenitis, petechiae on the soft palate, erythema and swelling of the uvula, and/or scarlatiniform rash. (22) History of recent sick contact with patients with GAS pharyngitis is also helpful to diagnose streptococcal infection. Throat culture and/or rapid antigen tests are performed to test for GAS pharyngitis. Evidence of a history of recent GAS infection can be obtained from an increase in anti–streptolysin O titers or other streptococcal antibodies, such as anti–deoxyribonuclease B. A rise in titers is a better marker of infection than is a single titer in streptococcal antibody production. (13) It is possible that a positive anti–streptococcal antibody may result from chronic colonization. Anti–streptolysin O titers start to rise 1 week after infection and peak at 3 to 6 weeks. Anti–deoxyribonuclease B titers start to rise 1 to 2 weeks after infection and peak at 6 to 8 weeks. Raised titers can persist for several months. (11)

Diagnosis of ARF

ARF is diagnosed using modified Jones criteria (Table 1). Jones criteria were first published in 1944 and underwent multiple modifications; the last update was in 2015. The 2015 revision accounted for differences in diagnostic criteria between high-

Table 1. Modified Jones Criteria for Diagnosis of ARF (2015) (22)

A. FOR ALL PATIENTS WITH EVIDENCE OF PRECEDING GAS INFECTION	
Diagnosis of initial ARF	2 Major manifestations or 1 major plus 2 minor manifestations
Diagnosis of recurrent ARF	2 Major criteria or 1 major and 2 minor criteria or 3 minor criteria
B. Major criteria	
Low-risk populations[a]	Moderate- or high-risk populations
Clinical or subclinical carditis[b]	Clinical or subclinical carditis
Arthritis	Arthritis
Polyarthritis only	a. Monoarthritis or
	b. Polyarthritis or
	c. Polyarthralgia[c]
Chorea	Chorea
Erythema marginatum	Erythema marginaturm
Subcutaneous nodules	Subcutaneous nodules
C. Minor criteria	
Low-risk populations	High-risk populations
Polyarthralgia	Monoarthralgia
Fever (>101.3°F [>38.5°C])	Fever (>100.4°F [>38°C])
ESR >60 mm/hr and/or CRP >3 mg/dL (>30 mg/L)[d]	ESR >30 mm/hr and/or CRP >3 mg/dL (>30 mg/L)[d]
Prolonged PR interval, after accounting for age variability (unless carditis is a major criteria)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criteria)

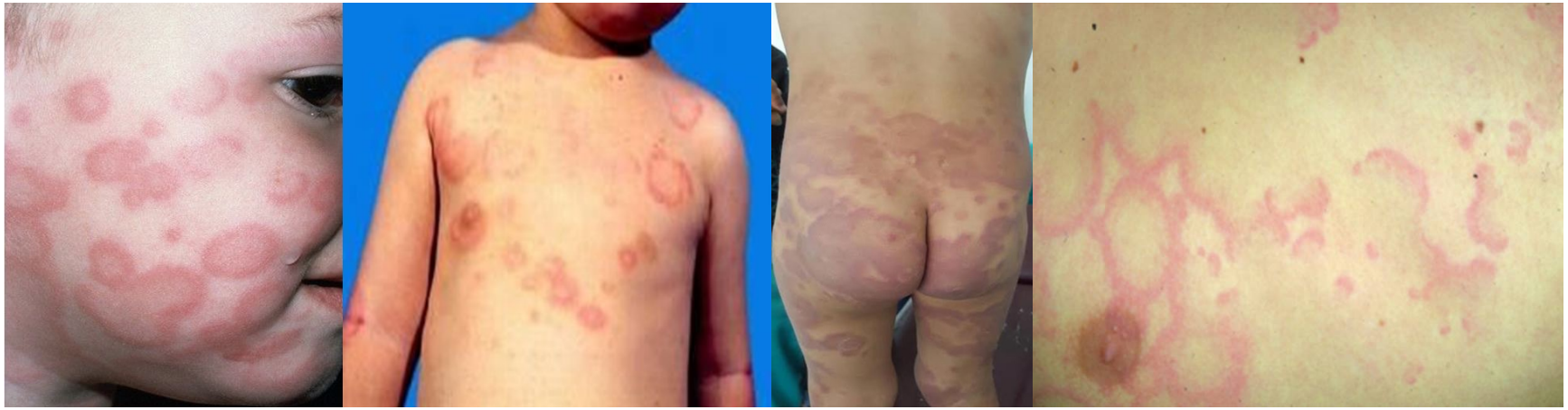
ARF=acute rheumatic fever; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; GAS=group A streptococcal infection.
[a]Low-risk populations are those with an ARF incidence of 2 or less per 100,000 school-age children or all-age rheumatic heart disease prevalence of 1 or less per 1,000 population per year.
[b]Subclinical carditis indicates echocardiographic valvulitis as defined by World Heart Federation criteria.
[c]See the section on polyarthralgia, which should be considered as a major manifestation only in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and subcutaneous nodules are rarely stand-alone major criteria. In addition, joint manifestations can be considered only in either the major or minor categories but not both in the same patient.
[d]The CRP value must be greater than the upper limit of normal for the laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.

and low-risk populations and included Doppler echocardiography as a tool to better assess valvar regurgitation to diagnose early cardiac involvement. (25)

The initial diagnosis of ARF is positive if there are 2 major criteria or 1 major and 2 minor criteria present along with evidence of persistent streptococcal infection. Presence of Sydenham chorea is by itself enough to diagnose ARF.

Carditis

Rheumatic carditis is classically described as pancarditis, that is, all layers of the heart are inflamed. Valvulitis clinically manifests as mitral and/or aortic regurgitation. The mitral valve is the most commonly affected valve, followed by the aortic valve. The tricuspid valve and pulmonary valves may be rarely affected. Presence of congenital anomaly in the pulmonary valve predisposes to valvar involvement. (26) Echocardiographic diagnosis of valvulitis is defined as mitral or aortic valve regurgitation. Subclinical carditis is defined as the circumstance when classic auscultatory findings of valvar dysfunction are absent or not recognized by the clinician but there is valvulitis by echocardiography (Fig 1). In the figure, the blue jet represents the mitral valve regurgitation from the left ventricle to the left atrium. Echocardiographic carditis is one of the major Jones criteria. Doppler echocardiography also better defines the presence and severity of carditis compared with clinical examination. Rheumatic carditis is usually not associated with severely depressed cardiac function. Carditis on physical examination manifests as tachycardia, displaced apex beat, friction rub, presence of third or fourth heart sound, and gallop, along with mitral regurgitation (seagull murmur) and, rarely, aortic regurgitation. In patients with severe mitral regurgitation, there can



L'érythème marginé discoïde (de BESNIER), est une éruption cutanée observée jusqu'à 10% des cas au cours du RAA (ARF =Acute Rhumatic Fever)

- Maculaire, arrondies, s'étendant de manière centrifuge avec bordure périphérique plus marquée et réalisant un aspect clinique d'érythème annulaire centrifuge.
- Non prurigineuse
- Fugace et migratrice

→ Ressemble à l'urticaire ou à la maladie sérique (mais ne gratte pas)

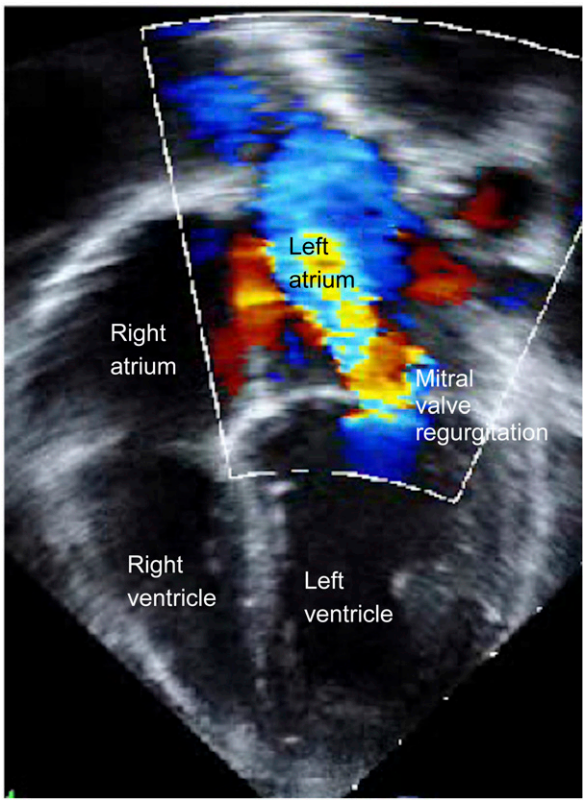


Figure 1. Echocardiogram with color Doppler showing severe mitral regurgitation.

be a low-pitched mid-diastolic murmur called Carey Coombs murmur. This is best heard at the apex of the heart using the bell of the stethoscope with the patient in the left lateral decubitus position. On chest radiography, carditis can manifest as cardiomegaly and left atrial enlargement. Left atrial enlargement on chest radiography shows as a double-density sign, flattening of the left border of the heart, and elevation of the left bronchus. By echocardiography, left ventricular dilation, left atrial dilation, effusion, and regurgitation can be seen. Other congenital mitral valve lesions need to be ruled out by echocardiography when diagnosing ARF. Because up to 90% of patients with ARF have echocardiographic carditis, it is recommended to obtain an echocardiogram in all cases of confirmed and suspected ARF. In patients with no carditis on ARF presentation, serial echocardiography is recommended to monitor for development of carditis.

Arthritis

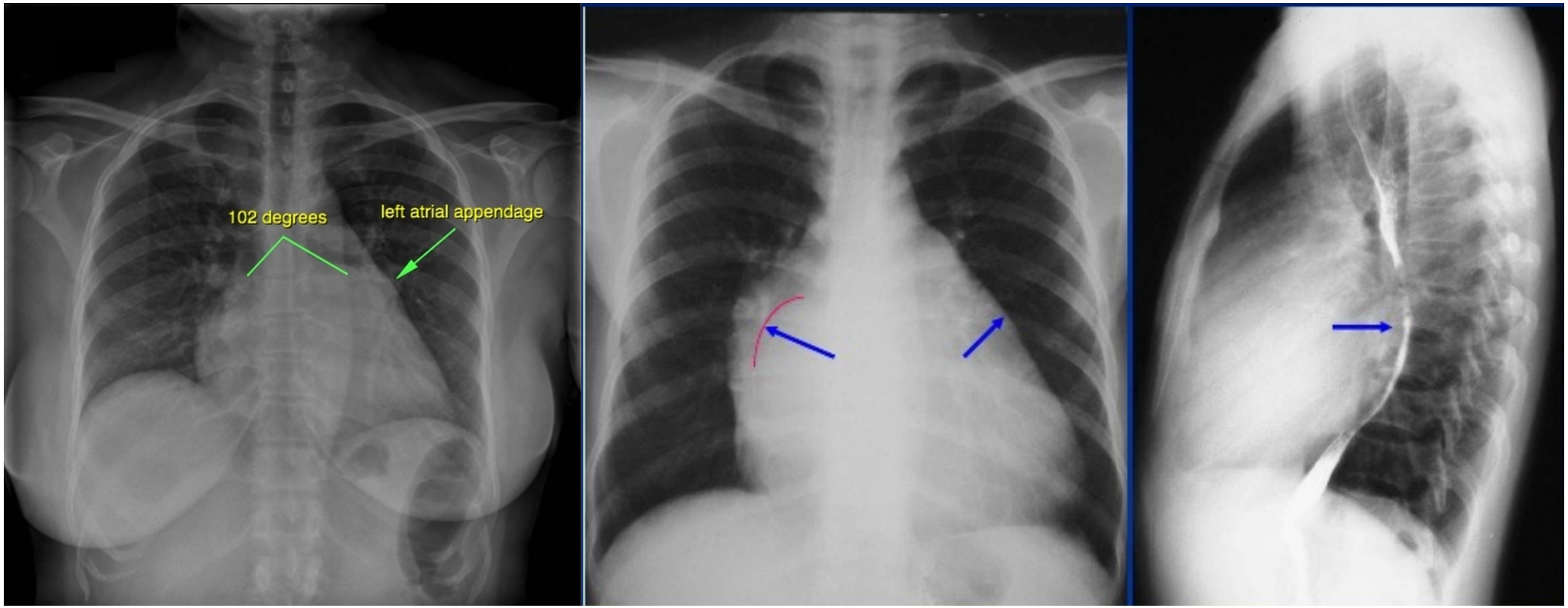
Patients with ARF present most frequently with arthritis. The joints are exquisitely tender and out of proportion to the physical signs. Other signs of inflammation, such as redness, heat, and swelling of the joint, are less compared with other forms of arthritis. Signs and symptoms of arthritis are greater in older patients compared with younger patients with ARF. Arthritis is typically nonsuppurative, migratory, and self-limiting. It generally affects large joints such as wrists, elbows, knees, and ankles. Arthritis responds very well to salicylates. There are no long-term sequelae of arthritis. Classically, ARF arthritis is described as migratory polyarthritis. Many patients, however, present with polyarthralgia or aseptic monoarthritis. Thus, polyarthralgia and monoarthritis have been incorporated in the modified Jones criteria as major manifestations in high-risk populations. Because the incidence of ARF is high in children in endemic areas with arthritis, it is suggested that children with fever, arthritis, and elevated inflammatory markers should undergo echocardiography to evaluate for ARF. (1) Arthritis lasts 1 to 5 days at each joint, with peak symptoms at 2 days. It completely resolves in 2 to 4 weeks. There is usually no sequelae to the arthritis except in Jaccoud arthritis, where there is permanent damage of the metacarpophalangeal joints. (27)

Sydenham Chorea

Chorea is a late manifestation of ARF occurring in 30% of the patients. (28) The latent period after GAS infection varies from 1 to 7 months before the onset of Sydenham chorea. The peak incidence is at age 8 to 9 years. (29) It can be an isolated finding of ARF or can occur with carditis. Simultaneous arthritis is rare due to the late manifestation. So, culture and serologic evidence of GAS infection may be absent at the time of presentation. Sydenham chorea usually manifests as purposeless, bilateral or unilateral involuntary movement that disappears during sleep. It can be only briefly suppressed voluntarily. Face and hands are most involved. Frequently patients have facial grimacing in addition to abrupt limb movements. Patients may present with deterioration of handwriting, slurred speech, and emotional lability. It is uncommon after puberty and is more common in females. The differential diagnosis of chorea includes Huntington chorea, systemic lupus erythematosus, tics, Wilson disease, and drug reactions.

Erythema Marginatum

Erythema marginatum is an evanescent, serpiginous rash that begins on the trunk, does not involve the face, blanches with pressure, is nonpruritic and nonindurated, and may be induced by application of heat (Fig 2). The rash is likely secondary to vasculitis and is an uncommon manifestation of ARF. It is frequently associated with subcutaneous nodules and carditis.


102 degrees
left atrial appendage

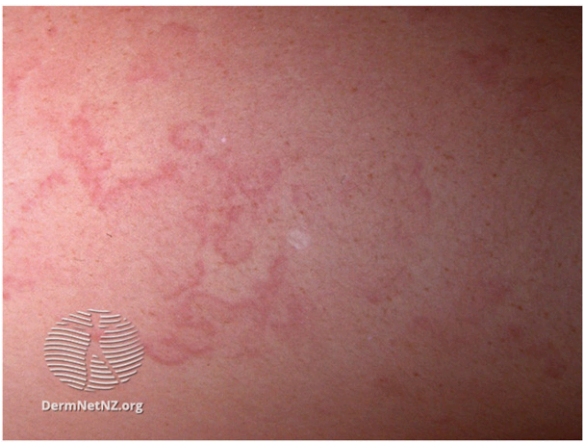


Figure 2. Erythema marginatum. (Reprinted with permission from DermNetNZ.org.)

Subcutaneous Nodules

Subcutaneous nodules are a rare manifestation of ARF. They are typically associated with carditis. (30) They are small (1–2 mm in diameter), firm, painless nodules where the overlying skin moves freely. They are located over the extensor surfaces of the elbows, knees, wrists, and occipital region.

Minor Manifestations

Temperature greater than 100.4°F (38°C) is considered a minor manifestation in high-risk populations, and greater than 101.3°F (>38.5°C) is a minor criterion in low-risk populations. Erythrocyte sedimentation rate (ESR) greater than 60 mm/hr in the first hour and C-reactive protein (CRP) level greater than 3 mg/dL (>30 mg/L) are considered typical for ARF. CRP level and ESR are rarely low in ARF, except in patients with Sydenham chorea. Other clinical features of ARF that are not a part of Jones criteria are abdominal pain, tachycardia at rest, disproportionate tachycardia with fever, malaise, anemia, leukocytosis, epistaxis, and chest pain. A family history of ARF is also an important part of history taking. (25)

DIFFERENTIAL DIAGNOSIS

The diseases that may mimic ARF are arthralgias with streptococcal pharyngitis, mesenteric adenitis, coccidioidomycosis ("desert rheumatism") and histoplasmosis. Poststreptococcal reactive arthritis does not respond as well to salicylates as ARF does and usually lasts for a longer duration.

RECURRENCE OF ARF

In patients with a history of ARF or RHD, recurrent ARF may be diagnosed if one has a GAS infection with 2 major manifestations or 1 major and 2 minor or 3 minor manifestations. In the presence of only minor manifestations, other causes need to be ruled out. Congestive heart failure is more common in patients with recurrent carditis. It may be challenging to diagnose carditis in recurrent ARF with existing valvular lesions.

Patients with ARF most commonly present with carditis (50%–70%) and arthritis (35%–66%), followed by chorea (10%–30%), subcutaneous nodules (0%–10%), and erythema marginatum (<6%). Erythema marginatum remains much less common but is a highly specific manifestation of ARF.

There is no single laboratory test to diagnose ARF. The host reacts to the inflammatory response with polyserositis, which may involve the pericardium, pleura, peritoneum, and synovia. The basal ganglia is also affected. Children with ARF before 5 years of age commonly present with arthritis and rarely present with chorea. They often progress to have severe RHD. Carditis is more common in younger patients, but it is more severe when it occurs in older patients. The susceptibility to ARF wanes with age.

MANAGEMENT

Management of ARF has not notably changed since the 1950s. Treatment is mostly supportive and not based on robust clinical trials. Anti-inflammatory treatments are usually prescribed for ARF for joint and cardiac inflammation with temporary relief of symptoms, but there is no evidence that it changes outcome (Fig 3). The natural history of ARF shows that it generally lasts for 3 months, with the spectrum from complete recovery to severe valvar disease leading to congestive cardiac failure.

Arthritis

Generally, ambulatory restriction is recommended for 6 weeks. Patients are recommended to take aspirin, 100 mg/kg per day divided into 4 doses, or naproxen, 10 to 20 mg/kg per day. Aspirin dose is titrated to keep serum salicylate levels at 200 to 300 μg/mL (1.4–2.2 mmol/L). As described earlier, patients generally have a dramatic response to salicylates, with resolution of symptoms in 1 to 3 days. Treatment is generally required for 1 to 4 weeks but has been reported to be given for up to 12 weeks. Aspirin can be given at a high dose of 100 mg/kg for 2 weeks and then reduced to 60 mg/kg per day for the remaining duration depending on clinical response. Corticosteroids can be used but they are associated with a rebound increase in ESR after cessation of therapy. Other differential diagnoses need to be considered if a patient does not respond to aspirin therapy.

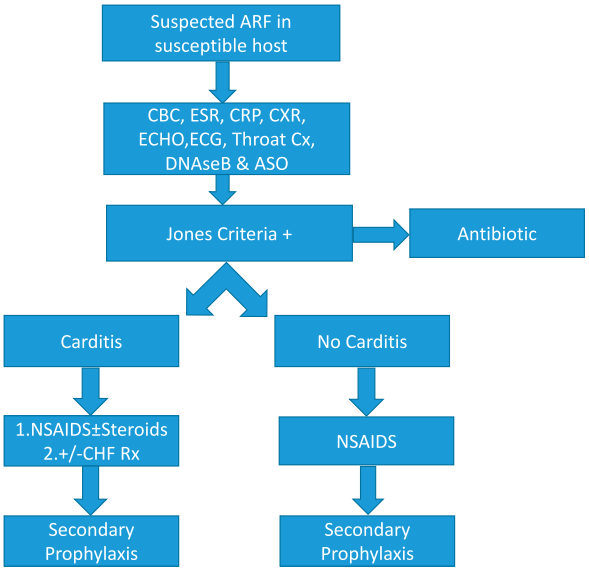


Figure 3. Approach to acute rheumatic fever. ASO=anti–streptolysin O, CBC=complete blood cell count, CHF Rx=congestive heart failure treatment, CRP=C-reactive protein, Cx=culture, CXR=chest radiography, DNaseB=deoxyribonuclease B, ECG=electrocardiography, ECHO=echocardiography, ESR=erythrocyte sedimentation rate.

Acute Carditis

Activity is generally restricted for 4 to 6 weeks. For mild to moderate carditis, aspirin is given: 80 to 100 mg/kg per day in children and 4 to 6 g/day in adults, with a goal salicylate level in blood of 200 to 300 µg/mL (1.4–2.2 mmol/L).

For moderate to severe carditis with heart failure, one may consider prednisone, 2 mg/kg per day for 2 weeks then taper off, although there is lack of evidence that corticosteroids are more efficacious than salicylates. Clinical status is followed up with CRP and ESR. In addition, diuretics and angiotensin-converting enzyme inhibitors may be used as appropriate for heart failure management along with salt restriction. The mechanism of heart failure and pulmonary edema in ARF is mostly mitral or aortic regurgitation and less commonly ventricular dysfunction. Intravenous immunoglobulin has not been shown to change the disease progression or outcome. (31) Patients with large effusions with tamponade may need pericardiocentesis. On Cochrane systematic analysis of all trials up until 2015, it was found that the use of corticosteroids or intravenous immunoglobulin to reduce the risk of heart valve lesions in patients with ARF is not supported by good-quality evidence. (19) Rarely, there is rupture of mitral valve chordae causing severe mitral valve prolapse and fulminant mitral regurgitation, which may require emergency surgery. (32) Valve repair is preferred over replacement because valve replacement entails the added burden of anticoagulation therapy. Complications associated with noncompliance with warfarin therapy include bleeding/valve thrombosis as well as the possible fetal complications of warfarin in pregnancy. Although bioprosthetic valves will require less rigorous anticoagulation therapy, their use is limited by their less durability in young patients. Studies have shown that mitral valve repair has similar or higher rates of repeated operation compared with valve replacement.

Chorea

Sydenham chorea resolves spontaneously in 1 to 6 months. Mild cases of chorea can resolve within 2 weeks. Because chorea is secondary to excess dopamine in basal ganglia, dopamine antagonists have been used with some success. Commonly, haloperidol, pimozide, and chlorpromazine have been used. However, they are limited by their extrapyramidal adverse effects. For prolonged use, carbamazepine and sodium valproate are preferred for better adverse effect profiles. A neurologic consultation would be helpful for patients with chorea along with close management with cardiology.

Treatment of GAS

Primary Treatment. Treatment for primary streptococcal infections is oral penicillin or phenoxymethylpenicillin for 10 days or 1 dose of intramuscular benzathine penicillin G. Oral amoxicillin (40 mg/kg per day for 10 days), oral cephalosporins, and high-dose azithromycin can be used (Table 2). Penicillin resistance of GAS is extremely rare. Resistance to macrolides has been reported. Patients who had angioedema, hypotension or anaphylaxis after penicillin injections should receive macrolide antibiotics. Repeated throat cultures and repeated treatment are not routinely practiced.

Prevention of repeated GAS infection is the most useful way to prevent progression of RHD. Recurrence of GAS infection may be symptomatic or asymptomatic. Therefore, continuous treatment of GAS is required in place of symptomatic treatment of pharyngitis. Thus, benzathine penicillin G should be given as soon as the patient is diagnosed as having ARF even if the throat culture is negative at that time. Also, if family members of patients with RHD have a GAS infection, they should be treated promptly. For secondary long-term prophylaxis, benzathine penicillin G intramuscularly every 3 to 4 weeks is recommended (Table 3). Alternative but less effective is oral penicillin twice a day or sulfadiazine or erythromycin daily for those allergic to penicillin. Duration of prophylaxis is shown in Table 4.

PREVENTION

Primordial Prevention

The decline in ARF in higher-income countries was likely a result of improved socioeconomic and public health conditions. This meant less overcrowding and likely reduced transmission of GAS. Another avenue for potential

Table 2. Primary Treatment of Streptococcal Pharyngitis

AGENT	DOSE	MODE	DURATION, D
Penicillin			
Penicillin V (phenoxymethylpenicillin)	Children ≤60 lb (≤27 kg): 250 mg 2–3 times daily; children >60 lb (>27 kg), adolescents, and adults: 500 mg 2–3 times daily	Oral	10
Amoxicillin	50 mg/kg once daily (maximum 1 g)	Oral	10
Benzathine penicillin G	600,000 U for patients ≤60 lb (≤27 kg); 1,200,000 U for patients >60 lb (>27 kg)	Intramuscular	Once
For individuals allergic to penicillin			
Narrow spectrum cephalosporin (cephalexin, cefadroxil)[a]	Variable	Oral	10
Clindamycin	20 mg/kg per day divided into 3 doses (maximum 1.8 g/d or 300 mg per dose)	Oral	10
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5
Clarithromycin	15 mg/kg per day divided into 2 doses (maximum 250 mg BID)	Oral	10

The following are not acceptable: sulfonamides, trimethoprim, tetracyclines, and fluoroquinolones. BID=twice per day.
[a]To be avoided in individuals with immediate (type I) hypersensitivity to a penicillin.

primordial prevention is vaccination against GAS. The M protein on the cell wall of the GAS is encoded by the *emm* gene. This is the primary target for GAS vaccine development. The N and C terminals of the M protein are both antigenic targets for vaccine development. However, one challenge in developing GAS vaccine is that the *emm* gene is diverse globally, and more than 200 types of the *emm* gene exist. (33) Vaccines are now in research trials and have the potential to reduce ARF and RHD significantly.

Primary Prevention

Prevention and timely treatment of GAS infection within 9 days of onset of sore throat has been shown to prevent ARF and RHD. There are multiple barriers to successful primary prevention of ARF in many low- and middle-income settings, including lack of health-seeking behavior, low awareness about the significance of prompt treatment of GAS, and scanty resources for bacteriologic confirmation of GAS. School-based sore throat identification and treatment programs have been shown to reduce the number of ARF cases by 21% in one study. (34) Echocardiographic screening of school-age children for RHD in high-risk areas has shown that subclinical RHD is 10 to 13 times higher than is clinically detected RHD in school-age children in endemic areas. (10)

Secondary Prevention

Prevention of long-term recurrence of GAS infection by secondary prophylaxis is proved to reduce the recurrence of ARF and progression to RHD (Fig 4). Challenges of

Table 3. Secondary Prophylaxis for Acute Rheumatic Fever (6)

AGENT	DOSE	ROUTE
Benzathine penicillin G	600,000 IU for children ≤60 lb (≤27 kg), 1,200,000 IU for those >60 lb (>27 kg) every 3–4 wk[a]	Intramuscular
Penicillin V	250 mg twice daily	Oral
Sulfadiazine	0.5 g once daily for patients ≤60 lb (≤27 kg), 1.0 g once daily for patients >60 lb (>27 kg)	Oral
For individuals allergic to penicillin		
Macrolide or azalide	Variable	Oral

[a]In high-risk situations, administration every 3 weeks is justified and recommended.

Table 4. Duration of Secondary Prophylaxis for Acute Rheumatic Fever (6)

CATEGORY	DURATION AFTER LAST ATTACK
Rheumatic fever with carditis and residual heart disease (persistent valvular disease[a])	10 y or until 40 y of age (whichever is longer), sometimes lifelong
Rheumatic fever with carditis but no residual heart disease (no valvular disease[a])	10 y or until 21 y of age, whichever is longer
Rheumatic fever with no carditis	5 y or until 21 y of age (whichever is longer)

[a]Clinical or echocardiographic evidence.

secondary prevention of ARF include poor patient compliance secondary to lack of awareness of RHD and pain of intramuscular injections, poor availability of intramuscular penicillin, inconsistent quality of penicillin, and fear of anaphylaxis to penicillin. (22)

CONCLUSION

ARF and RHD continue to be major public health problems in low-resource settings and certain indigenous populations in high-income countries. Development of ARF depends on factors related to GAS, genetic susceptibility of the host, and environment. The pathogenesis is likely related to molecular mimicry where antibodies against M protein of GAS react against valve tissues. The most common clinical features of ARF are arthritis, carditis, and chorea. Modified 2015 Jones criteria are used to diagnose ARF. Echocardiography should be performed in all suspected and confirmed cases of ARF. The most important risk factors for RHD are the severity of initial carditis and ARF recurrences. ARF can be best controlled by a combination of primordial prevention by socioeconomic and public health improvement, primary prevention by prompt treatment of GAS pharyngitis, and secondary prevention with penicillin to prevent recurrence of ARF.

EVIDENCE

- Based on consensus, it is reasonable to have a high suspicion of acute rheumatic fever (ARF) in children from endemic areas.
- Based on relatively strong evidence, it is recommended to obtain Doppler echocardiograms in all patients confirmed to have ARF and follow them up with serial echocardiograms even if carditis was absent in the first echocardiogram.
- There is strong evidence that increasing or rising anti–streptolysin O is better evidence of group A streptococcal (GAS) infection compared with single titers. Patients with positive rapid antigen tests or cultures and pharyngitis should also get treated for infection.
- There is consensus that to diagnose ARF, patients should have confirmation of GAS infection along with 2 major criteria or 1 major and 2 minor criteria. There is expert opinion to diagnose recurrence of ARF based on the above or on the presence of 3 minor criteria.

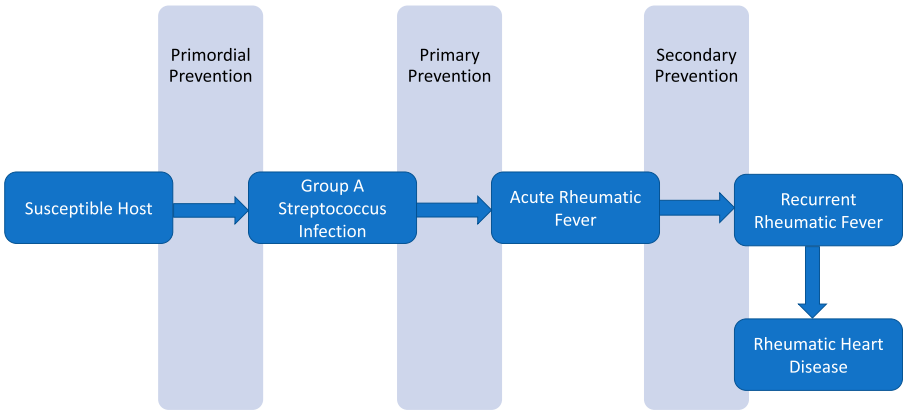


Figure 4. Prevention of acute rheumatic fever and rheumatic heart disease.

- For treatment of GAS, intramuscular benzathine penicillin G or oral penicillin V are strongly recommended, except when the patient is allergic to penicillin. There is strong evidence that tetracycline should not be used to treat GAS. For secondary prophylaxis, long-acting penicillin preparation every 4 weeks should be used to prevent ARF recurrence. If feasible, it should be given every 3 weeks in endemic areas or in high-risk populations in developed countries.
- There is expert consensus that patients with carditis and valvar regurgitation should receive antibiotic prophylaxis into adulthood and probably for life. For patients with carditis but no persistent valve disease, patients should continue prophylaxis for 10 years or until the patient is 21 years of age, whichever is longer. Patients with no carditis should receive penicillin prophylaxis until 21 years of age or for 5 years after diagnosis, whichever is longer.
- There is expert consensus to offer 12 months of secondary prophylaxis in uncertain cases of ARF and reevaluate later.
- There is strong evidence that intravenous immunoglobulin is not effective to treat ARF.

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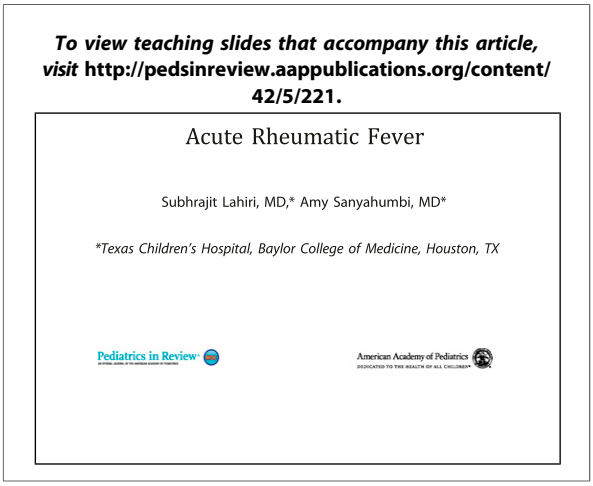

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1. You are evaluating a 9-year-old boy who is admitted to the hospital with fever and fatigue. On physical examination he is febrile to 102°F (38.9°C) and has tachycardia, a displaced apex beat, gallop rhythm, and high-frequency S1 coincident apical holosystolic murmur accompanied by a low-pitched mid-diastolic murmur. A chest radiograph shows cardiomegaly and left atrial enlargement. An echocardiogram reveals severe mitral regurgitation. A laboratory evaluation reveals a normal complete blood cell count and a significantly elevated erythrocyte sedimentation rate. Which of the following additional clinical or laboratory findings would fulfill the revised Jones criteria for acute rheumatic fever in this patient?

   A. Anemia.
   B. Elevated C-reactive protein level.
   C. Presence of erythema nodosum on physical examination.
   D. Prolonged PR interval on electrocardiogram.
   E. Rising anti–streptolysin O (ASO) titer.

2. A 7-year-old previously healthy girl initially had a swollen and painful right knee 6 days ago and then developed painful swelling in the left knee 3 days later. The right knee has improved now, but her left elbow began to hurt yesterday. Her parents state that she had a sore throat and fever 2 weeks ago, which resolved over 2 days without treatment. On physical examination she is afebrile, is generally well-appearing, and has normal vital signs. Her left knee is swollen, exquisitely tender, and mildly erythematous. Her left elbow is mildly swollen and tender. A complete blood cell count is normal. Which of the following is the most appropriate diagnostic study to obtain at this time in this patient?

   A. Antinuclear antigen titer.
   B. Aspiration of her knee joint.
   C. Blood culture.
   D. Echocardiogram.
   E. Magnetic resonance image of the left knee.

3. You are evaluating a 10-year-old girl who has had migratory polyarthritis during the past week and daily fever (up to 101.8°F [38.8°C]). She initially developed a tender and swollen left knee, which resolved over 3 days. She then developed swelling and tenderness of her right knee, which also has improved. Yesterday she developed marked tenderness and swelling of her right ankle. Three weeks ago she experienced a sore throat and low-grade fever that resolved spontaneously. On physical examination she has exquisite tenderness, swelling, and mild erythema of her right ankle joint. Her echocardiogram and electrocardiogram are normal. Her erythrocyte sedimentation rate is 120 mm/hr. Her ASO titer is markedly elevated at 1,800 IU. Which of the following is the most appropriate therapeutic intervention for her arthritis at this time?

   A. Aspiration of the ankle joint.
   B. Intravenous cefazolin.
   C. Intravenous immunoglobulin.
   D. Naproxen.
   E. Prednisone.

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4. A 6-year-old previously healthy boy presents with fever and fatigue and is found to have significant mitral valve regurgitation. After assessment he has been diagnosed by his pediatric cardiologist as having acute rheumatic carditis without evidence of heart failure. In addition to primary treatment of group A streptococcal infection with penicillin, which of the following is the most appropriate treatment at this time for this child?

   A. Aspirin.
   B. Intravenous immunoglobulin.
   C. Prednisone.
   D. Supportive care.
   E. Warfarin.

5. You are seeing an 8-year-old previously healthy girl who has developed purposeless involuntary movements of both hands and facial grimacing. During the past several weeks her parents have noted intermittent slurred speech, deterioration in her handwriting and schoolwork, and emotional lability. The movements seem to be exacerbated by stress and disappear with sleep. Family history is negative for movement disorders. She undergoes an evaluation by a pediatric neurologist, who confirms the clinical diagnosis of Sydenham chorea and prescribes haloperidol. Findings from laboratory evaluation, including throat culture for group A *Streptococcus* and an ASO titer, are negative. An echocardiogram is normal. Which of the following is the most appropriate management for this child?

   A. Intravenous immunoglobulin.
   B. Oral penicillin for 10 days.
   C. Oral penicillin for 10 days followed by intramuscular benzathine penicillin G every 3 to 4 weeks.
   D. Repeated throat culture.
   E. Supportive care without further testing or treatment at this time.

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