14 - 371 Acute Rheumatic Fever

371 Acute Rheumatic Fever

Fraenkel L et al: 2021 American College of Rheumatology guide

line for the treatment of rheumatoid arthritis. Arthritis Rheumatol 73:1108, 2021. Gravallese EM, Firestein GS: Rheumatoid arthritis: Common ori gins, divergent mechanisms. N Engl J Med 388:529, 2023. Karimi J et al: Genetic implications in the pathogenesis of rheumatoid PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders arthritis; an updated review. Gene 702:8, 2019. Moreland LW et al: A randomized comparative effectiveness study of oral triple therapy versus methotrexate plus etanercept in early aggressive rheumatoid arthritis: The Treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum 64:2824, 2012. VIDEO 370-1 Transverse view of 2nd MCP demonstrating synovial hypertrophy with abnormal power doppler signal (yellow) consistent with synovitis. Synovial proliferation is displacing the overlying extensor tendon of the digit above the joint space. This view demonstrates small erosions of the dorsal metacarpal head. (Courtesy of Dr. Philip Chu.) VIDEO 370-2 Longitudinal dorsal view of the 2nd MCP demonstrating synovial hypertrophy with abnormal power doppler signal (yellow) consistent with synovitis. (Courtesy of Dr. Philip Chu) VIDEO 370-3 Transverse view of 2nd MCP demonstrating synovial hypertrophy and intrasynovial effusion with abnormal power doppler signal (yellow) consistent with synovitis. Fluid and synovial proliferation is displacing the overlying extensor tendon of the digit above the joint space. (Courtesy of Dr. Philip Chu.) Joseph Kado, Jonathan Carapetis

Acute Rheumatic Fever Acute rheumatic fever (ARF) is a multisystem disease resulting from an autoimmune reaction to infection with group A Streptococcus. Although many parts of the body may be affected, almost all of the manifestations resolve completely. The major exception is cardiac valvular damage (rheumatic heart disease [RHD]), which may persist after the other features have disappeared. GLOBAL CONSIDERATIONS ARF and RHD are diseases of poverty. They were common in all coun tries until the early twentieth century, when their incidence began to decline in industrialized nations. This decline was largely attributable to improved living conditions—particularly less crowded housing and better hygiene—which resulted in reduced transmission of group A streptococci. The introduction of antibiotics and improved systems of medical care had a supplemental effect. The virtual disappearance of ARF and reduction in the incidence of RHD in high-income countries during the first half of the twentieth century unfortunately was not replicated in low- and middle-income countries (LMICs), where these diseases continue unabated. RHD is the most common cause of acquired heart disease in children

in LMICs and is a major cause of mortality and morbidity in adults as well. It is estimated that >40 million people worldwide are affected by RHD, with >300,000 deaths occurring each year. Some 95% of ARF cases and RHD deaths now occur in developing countries, with particularly high burdens in sub-Saharan Africa, Pacific nations, Australasia, China, and South and Central Asia. The pathogenetic pathway from exposure to group A Streptococcus followed by pharyngeal or superficial skin infection and subsequent development of ARF, ARF recurrences, and development of RHD and its complications is associated with a range of risk factors and, therefore, potential interventions at each point (Fig. 371-1). In affluent countries, many of these risk factors are well controlled, and where needed, interventions are in place. Unfortu nately, the greatest burden of disease is found in LMICs, most of which do not have the resources, capacity, and/or interest to tackle this multi faceted disease. In particular, few of these countries have coordinated,

register-based RHD control programs, which have been proven to be cost-effective in reducing the burden of RHD. Enhancing awareness of RHD and mobilizing resources for its control in LMICs are issues requiring international attention. In 2018, member states of the World Health Organization (WHO) unanimously adopted a Global Resolu tion on Rheumatic Fever and Rheumatic Heart Disease, calling on all states as well as international stakeholders and the WHO itself to take practical actions to control these diseases. EPIDEMIOLOGY ARF is mainly a disease of children aged 5–14 years. Initial episodes become less common in older adolescents and young adults and are rare in persons aged >30 years. By contrast, recurrent episodes of ARF remain relatively common in adolescents and young adults. This pattern con trasts with the prevalence of RHD, which peaks between 25 and 40 years. There is no clear gender association for ARF, but RHD more commonly affects females, sometimes up to twice as frequently as males. PATHOGENESIS ■ ■ORGANISM FACTORS Conventional teaching has it that ARF is exclusively caused by infection of the upper respiratory tract with group A streptococci (Chap. 153). Although classically, certain M-serotypes (particularly types 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29) were associated with ARF, recent evidence demonstrates that many more M-serotypes are rheumatogenic and that so-called “rheumatogenic motifs” are found in only a minority of serotypes associated with rheumatic fever. This epidemiologic evidence also points to a clear role of skin infection in the pathogenesis of ARF. The potential role of groups C and G streptococci is unclear at this time. ■ ■HOST FACTORS Based on epidemiologic evidence, ~3–6% of any population may be sus ceptible to ARF, and this proportion does not vary dramatically between populations. Findings of familial clustering of cases and concordance in monozygotic twins—particularly for chorea—confirm that suscep tibility to ARF is an inherited characteristic, with 44% concordance in monozygotic twins compared to 12% in dizygotic twins and heritability more recently estimated at 60%. Most evidence for host factors focuses on immunologic determinants. Initial studies found associations with human leukocyte antigen (HLA) class II alleles, some protective and some associated with increased susceptibility, as well as polymorphisms in tumor necrosis factor and mannose binding lectin. Recent genomewide association studies and genomic sequencing analyses have identi fied associations with a range of genes including the immunoglobulin heavy chain (IGH) locus (specifically the IGHV4-61*02 allele), comple ment factor H, and some HLA class II (a range of HLA-DQ A and B alleles) and III loci. The associations are often population dependent, although increasing consistency is being found across populations in meta-analyses of genomic studies. Over coming years, further genomic analyses are expected to provide additional insights into ARF and RHD pathogenesis, as well as host protective and susceptibility factors. ■ ■THE IMMUNE RESPONSE The most widely accepted theory of rheumatic fever pathogenesis is based on the concept of molecular mimicry, whereby an immune

response targeted at streptococcal antigens (mainly thought to be on the M protein) also recognizes human tissues. In this model, antigen processing cells of the innate immune system present streptococcal antigens after throat (and possibly skin) group A streptococcal infec tion to T cells, which then lead to activation of both humoral and cellu lar immunity. Cross-reactive antibodies bind to endothelial cells on the heart valve, leading to activation of the adhesion molecule VCAM-1, with resulting recruitment of activated lymphocytes and lysis of endo thelial cells in the presence of complement. The latter leads to release of peptides including laminin, keratin, and tropomyosin, which, in turn, activates cross-reactive T cells that invade the heart, amplifying the damage and causing epitope spreading. An alternative hypothesis proposes that the initial damage is due to streptococcal invasion of epithelial surfaces, with binding of M protein to type IV collagen

Asymptomatic infection Overcrowded living conditions Failure to seek health care for sore throat Risk factors Poverty Inadequate diagnosis and treatment of streptococcal pharyngitis Rural residence Urban slum residence Treatment failure Exposure to group A streptococcus Group A streptococcal upper respiratory tract infection* Better diagnosis and treatment of sore throat in primary care Better primary care Economic development Good evidence base Better living conditions Opportunities for Intervention Systematic sore throat screening and treatment programs Unproven/ Hypothesized/ Future (Vaccine) (Skin infection control programs) *Increasing evidence of the role of streptococcal skin infection FIGURE 371-1 Pathogenetic pathway for acute rheumatic fever and rheumatic heart disease (RHD), with associated risk factors and opportunities for intervention at each step. Interventions in parentheses are either unproven or currently unavailable. allowing it to become immunogenic, but not through the mechanism of molecular mimicry. CLINICAL FEATURES There is a latent period of ~3 weeks (1–5 weeks) between the precipitat ing group A streptococcal infection and the appearance of the clinical features of ARF. The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A strep tococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing. The most common clinical features are polyarthritis (present in 60–75% of cases) and car ditis (50–75%). The prevalence of chorea in ARF varies substantially between populations, ranging from <2 to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases. ■ ■HEART INVOLVEMENT Up to 75% of patients with ARF progress to RHD. The endocardium, pericardium, or myocardium may be affected. Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve involvement is rare. Damage to the pulmonary or tricuspid valves is usually secondary to increased pulmonary pressures resulting from left-sided valvular disease. Early valvular damage leads to regurgita tion. Over ensuing years, usually as a result of recurrent episodes, leaf let thickening, scarring, calcification, and valvular stenosis may develop (Fig. 371-2). See Videos 371-1 and 371-2. Therefore, the characteristic manifestation of carditis in previously unaffected individuals is mitral

Poor access to health care Poor access to health care Inherited susceptibility Lack of medication Poor delivery of secondary prophylaxis Female gender (chorea) CHAPTER 371 Lack of cardiac surgical facilities Poor access to health care Asymptomatic or undiagnosed acute rheumatic fever Acute Rheumatic Fever Recurrent acute rheumatic fever Heart failure Rheumatic heart disease (RHD) Surgery Disability Death Acute rheumatic fever Stroke Endocarditis Improved access to

health care Secondary prophylaxis Register-based programs Register-based control programs Integration of RHD control into primary care, childhealth, and noncommunicable disease programs Specialist services

• Cardiology

• Cardiac surgery Echocardiographic screening (Immunotherapies) regurgitation, sometimes accompanied by aortic regurgitation. Myo cardial inflammation may affect electrical conduction pathways, lead ing to P-R interval prolongation (first-degree atrioventricular block or rarely higher-level block) and softening of the first heart sound. People with RHD are often asymptomatic for many years before their valvular disease progresses to cause cardiac failure. Moreover, particularly in resource-poor settings, the diagnosis of ARF is often not made, so children, adolescents, and young adults may have RHD but not know it. These cases can be diagnosed using echocardiography; auscultation is poorly sensitive and specific for RHD diagnosis in asymptomatic patients. Echocardiographic screening of school-aged children in populations with high rates of RHD is becoming more widespread and has been facilitated by improving technologies in portable echocardiography and the avail ability of consensus guidelines for the diagnosis of RHD on echocardiog raphy (Table 371-1). These guidelines replace the previous “definite,” “borderline,” and “latent” diagnostic category terms with a classification based on the risk of progression to more advanced valvular heart disease and provide recommendations on secondary prophylaxis for each group. ■ ■JOINT INVOLVEMENT The most common form of joint involvement in ARF is arthritis, i.e., objective evidence of inflammation, with hot, swollen, red, and/or ten der joints, and involvement of more than one joint (i.e., polyarthritis). Polyarthritis is typically migratory, moving from one joint to another over a period of hours. ARF almost always affects the large joints— most commonly the knees, ankles, hips, and elbows—and is asymmet ric. The pain is severe and usually disabling until anti-inflammatory medication is commenced.

RV PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders LV AV MV LA FIGURE 371-2 Transthoracic echocardiographic image from a 5-year-old boy with chronic rheumatic heart disease. This diastolic image demonstrates leaflet thickening, restriction of the anterior mitral valve leaflet tip, and doming of the body of the leaflet toward the interventricular septum. This appearance (marked by the arrowhead) is commonly described as a “hockey stick” or an “elbow” deformity. AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (Courtesy of Dr. Bo Remenyi, Department of Paediatric and Congenital Cardiac Services, Starship Children’s Hospital, Auckland, New Zealand.) Less severe joint involvement is also relatively common and has been recognized as a potential major manifestation in high-risk populations in the most recent revision of the Jones criteria. Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis. In some populations, aseptic monoarthritis may be a presenting feature of ARF, which may, in turn, result from early commencement of anti-inflammatory medication before the typical migratory pattern is established. The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs). ■ ■CHOREA Sydenham’s chorea commonly occurs in the absence of other manifes tations, follows a prolonged latent period after group A streptococcal infection, and is found mainly in females. The choreiform movements affect particularly the head (causing characteristic darting movements of the tongue) and the upper limbs (Chap. 447). They may be gen eralized or restricted to one side of the body (hemi-chorea). In mild

cases, chorea may be evident only on careful examination, whereas in the most severe cases, the affected individuals are unable to perform activities of daily living. There is often associated emotional lability or obsessive-compulsive traits, which may last longer than the chorei form movements (which usually resolve within 6 weeks but sometimes may take up to 6 months). More than 50% of patients presenting with chorea will have carditis, for which reason echocardiography should be part of the workup. ■ ■SKIN MANIFESTATIONS The classic rash of ARF is erythema marginatum (Chap. 21), which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge. The rash is evanescent, appearing and disappearing before the examiner's eyes. It occurs usually on the trunk, sometimes on the limbs, but almost never on the face. Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae. They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

TABLE 371-1 Staging of Rheumatic Heart Disease Detected by Echocardiographya,b Stage A: Minimal Echocardiographic Criteria for RHD Applies only to individuals aged ≤20 years old • Clinical risk: might be at risk of valvular heart disease progression • Echocardiographic features: the presence of mildc MR or AR without morphologic features Stage B: Mild RHD Can apply to any age • Clinical risk: at moderate or high risk of progression and at risk of developing symptoms of valvular heart disease • Echocardiographic features: evidence of mildc valvular regurgitation plus at least one morphologic feature in individuals aged ≤20 years and at least two morphologic features in individuals aged >20 yearsd; or mild regurgitation in both mitral and aortic valves Stage C: Advanced RHD at Risk of Clinical Complications Can apply to any age • Clinical risk: at high risk of developing clinical complications that require medical or surgical intervention • Echocardiographic features: moderate or severe MR, moderate or severe AR, any MS or ASe, pulmonary hypertension, and decreased LV systolic function Stage D: Advanced RHD with Clinical Complications Can apply to any age • Clinical risk: established clinical complications include cardiac surgery, heart failure, arrhythmia, stroke, and infective endocarditis • Echocardiographic features: moderate or severe MR, moderate or severe AR, any MS or ASe, pulmonary hypertension, and decreased LV systolic function aTo be applied in high-risk settings and requires other causes of valvular heart disease to have been excluded. bAfter the application of the confirmatory echocardiographic criteria, diagnostic categories might include "normal" and "other," which encompasses other diseases such as congenital heart disease, cardiomyopathies, and pericardial effusion. cFulfilling the confirmatory criteria for pathologic regurgitation (see Source). dThis cutoff value is derived from expert consensus. eAortic stenosis is defined in accordance with international guidelines on valvular heart disease. A diagnosis of rheumatic aortic stenosis requires the exclusion of other causes, including bicuspid aortic valve and degenerative calcific AS. Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis, RHD, rheumatic heart disease. Source: Reproduced with permission from J Rwebembera et al: 2023 World Heart Federation guidelines for the echocardiographic diagnosis of rheumatic heart disease. Nat Rev Cardiol 21:250; 2023. ■ ■OTHER FEATURES Fever occurs in most cases of ARF, although rarely in cases of pure chorea. Although high-grade fever (≥39°C) is the rule, lower grade temperature elevations are not uncommon. Elevated acute-phase reac tants are also present in most cases. ■ ■EVIDENCE OF A PRECEDING GROUP A STREPTOCOCCAL INFECTION With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding group A streptococcal infection is essential in making the diagnosis

of ARF. Because most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed. The most com mon serologic tests are the anti-streptolysin O (ASO) and anti-DNase B (ADB) titers. Where possible, age-specific reference ranges should be determined in a local population of healthy people without a recent group A streptococcal infection. ■ ■CONFIRMING THE DIAGNOSIS Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating group A streptococcal infection, and the exclusion of other diagnoses. This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the Jones criteria) to aid in the diagnosis. The most recent revision of the Jones criteria (Table 371-2) requires the clinician to determine if the patient is from a setting or population known to experience low rates of ARF.

TABLE 371-2 Jones Criteria A. For All Patient Populations with Evidence of Preceding Group A Streptococcal Infection Diagnosis: initial ARF 2 major manifestations or 1 major plus 2 minor manifestations Diagnosis: recurrent ARF 2 major or 1 major and 2 minor or

3 minor B. Major Criteria Low-risk populationsa Moderate- and high-risk populations Carditisb Carditis • Clinical and/or subclinical • Clinical and/or subclinical Arthritis Arthritis • Polyarthritis only • Monoarthritis or polyarthritis • Polyarthralgiac Chorea Chorea Erythema marginatum Erythema marginatum SC nodules SC nodules C. Minor Criteria Low-risk populationsa Moderate- and high-risk populations Polyarthralgia Monoarthralgia Fever (≥38.5°C) Fever (≥38°C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dLd ESR ≥30 mm/h and/or CRP ≥3.0 mg/dLd Prolonged PR intervale, after Prolonged PR intervale, after accounting for age variability (unless carditis is a major criterion) accounting for age variability (unless carditis is a major criterion) aLow-risk populations are those with ARF incidence ≤2 per 100,000 school-age children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year. bSubclinical carditis indicates echocardiographic valvulitis. (See source document.) cPolyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and SC nodules are rarely “standalone” major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient. (See source document for more information.) dCRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used. eProlonged PR interval can only be considered in the absence of carditis as a major criterion. Abbreviations: ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SC, subcutaneous. Source: Reproduced with permission from MH Gewitz et al: 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 131(20):1806, 2015. https://www.ahajournals.org/doi/full/10.1161/ CIR.0000000000000205. For this group, there is a set of “low-risk” criteria; for all others, there is a set of more sensitive criteria. TREATMENT Acute Rheumatic Fever Patients with possible ARF should be followed closely to ensure that the diagnosis is confirmed, treatment of heart failure and other symptoms is undertaken, and preventive measures including com mencement of secondary prophylaxis, inclusion on an ARF registry, and health education are commenced. Echocardiography should be performed on all possible cases to aid in making the diagnosis and to determine the severity at baseline of any carditis. Other tests that should be performed are listed in Table 371-3. There is no treatment for ARF that has been

proven to alter the likelihood of developing, or the severity of, RHD. With the excep tion of treatment of heart failure, which may be lifesaving in cases of severe carditis, the treatment of ARF is symptomatic. ANTIBIOTICS All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection (Chap. 153). Penicil lin is the drug of choice and can be given orally (as phenoxymethyl

TABLE 371-3 Testing and Monitoring of ARF in the Acute Setting Investigations Always request: • Electrocardiogram (ECG) • Echocardiogram • Complete blood count (CBC) • C-reactive protein (CRP) • Streptococcal serology (antistreptolysin and anti-DNase B) In relevant situations: • Throat swab • Skin sore swab • Blood cultures • Synovial fluid aspirate CHAPTER 371 Acute Rheumatic Fever • Ensure sample does not clot by using correct tubes that have been well mixed and transported promptly to the laboratory • Include request for cell count, microscopy, culture, and gonococcal polymerase chain reaction (PCR) • Pregnancy test • Creatinine test (UEC [urea, electrolytes, creatinine]) since nonsteroidal

anti-inflammatory drugs can affect renal function Tests to exclude alternative diagnoses, depending on clinical presentation

and locally endemic infections: • Autoantibodies, double-stranded DNA, anti–cyclic citrullinated peptide

(anti-CCP) antibodies • Urine for Neisseria gonorrhoeae molecular test • Urine for Chlamydia trachomatis molecular test • Serologic or other testing for viral hepatitis, Yersinia spp., cytomegalovirus (CMV), parvovirus B19, respiratory viruses, Ross River virus, Barmah Forest virus Source: Reproduced with permission from RDHAustralia, Menzies School of Health Research. RHDAustralia (ARF/RHD writing group). The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (3rd edition); 2020. Available at https://www.rhdaustralia.org.au/ arf-rhd-guideline. penicillin, 500 mg [250 mg for children ≤27 kg] PO twice daily, or amoxicillin, 50 mg/kg [maximum, 1 g] daily, for 10 days) or as a single dose of 1.2 million units (600,000 units for children ≤27 kg) IM benzathine penicillin G. SALICYLATES AND NSAIDS These may be used for the treatment of arthritis, arthralgia, and fever once the diagnosis is confirmed. They are of no proven value in the treatment of carditis or chorea. Aspirin has traditionally been the first-line choice, delivered at a dose of 50–60 mg/kg per day, up to a maximum of 80–100 mg/kg per day (4–8 g/d in adults) in 4–5 divided doses. At higher doses, the patient should be monitored for symptoms of salicylate toxicity such as nausea, vomiting, or tinnitus; if symptoms appear, lower doses should be used. Owing to the frequency of gastrointestinal side effects and the potential of more severe adverse effects of aspirin, many clini cians now prefer to use naproxen at a dose of 10–20 mg/kg per day because it may be safer than aspirin and has the advantage of twicedaily dosing. When the acute symptoms are substantially resolved, usually within the first 2 weeks, patients on higher doses of antiinflammatory medications can have the dose reduced for a further 2–4 weeks. Fever, joint manifestations, and elevated acute-phase reactants sometimes recur up to 3 weeks after the medication is discontinued. This does not indicate a recurrence and can be man aged by recommencing anti-inflammatory agents for a brief period. CONGESTIVE HEART FAILURE Glucocorticoids The use of glucocorticoids in ARF remains con troversial. Two meta-analyses have failed to demonstrate a benefit of glucocorticoids compared to placebo or salicylates in improving the short- or longer-term outcome of carditis.

However, the studies included in these meta-analyses all took place >40 years ago and did not use medications in common usage today. There are some recent data that suggest corticosteroids improve laboratory, radiologic,

and echocardiographic parameters in carditis. Many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure. However, the potential benefits of this treatment should be balanced against the possible adverse effects. If used, prednisone or prednisolone is recommended at a dose of 1–2 mg/kg per day (maximum, 80 mg), usually for a few days or up to a maximum of 3 weeks. MANAGEMENT OF HEART FAILURE See Chap. 265. BED REST Traditional recommendations for long-term bed rest, once the cor nerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthral gia are present and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated. CHOREA Medications to control the abnormal movements do not alter the duration or outcome of chorea. Milder cases can usually be man aged by providing a calm environment. In patients with severe cho rea, carbamazepine or sodium valproate is preferred to haloperidol. A response may not be seen for 1–2 weeks, and medication should be continued for 1–2 weeks after symptoms subside. There is recent evidence that corticosteroids are effective and lead to more rapid symptom reduction in chorea. They should be considered in severe or refractory cases. Prednisone or prednisolone may be commenced at 0.5 mg/kg daily, with weaning as early as possible, preferably after 1 week if symptoms are reduced, although slower weaning or temporary dose escalation may be required if symptoms worsen. INTRAVENOUS IMMUNOGLOBULIN (IVIG) Small studies have suggested that IVIg may lead to more rapid reso lution of chorea but have shown no benefit on the short- or longterm outcome of carditis in ARF without chorea. In the absence of better data, IVIg is not recommended except in cases of severe chorea refractory to other treatments.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders PROGNOSIS Untreated, ARF lasts on average 12 weeks. With treatment, patients are usually discharged from hospital within 1–2 weeks. Inflammatory markers should be monitored every 1–2 weeks until they have normal ized (usually within 4–6 weeks), and an echocardiogram should be performed after 1 month to determine if there has been progression of carditis. Cases with more severe carditis need close clinical and echo cardiographic monitoring in the longer term. Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis. Patients should be entered onto the local ARF registry (if present) and contact made with primary care practitioners to ensure a plan for follow-up and administration of secondary prophy laxis before the patient is discharged. Patients and their families should also be educated about their disease, emphasizing the importance of adherence to secondary prophylaxis. PREVENTION ■ ■PRIMARY PREVENTION Ideally, primary prevention would entail elimination of the major risk factors for streptococcal infection, particularly overcrowded housing. This is difficult to achieve in most places where ARF is common but must remain a priority in ongoing efforts to achieve global control of ARF and RHD. Concerted international efforts are underway to develop a vaccine against group A Streptococcus that would prevent infection of the throat or skin and consequently prevent ARF in the absence of a suitable vac cine; however, the mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group

A streptococcal sore throat with antibiotics). If commenced within 9 days of sore throat onset, a course of penicillin (as outlined above for treatment of ARF) will prevent almost all cases of ARF that would oth erwise have developed. In settings where ARF and RHD are common but microbiologic diagnosis of group A streptococcal pharyngitis is not available, such as in resource-poor countries, primary care guidelines sometimes recommend that all patients with sore throat be treated with penicillin (an approach that has the potential drawbacks that come from antibiotic overuse, including side effects and increasing pres sure on antimicrobial resistance in group A Streptococcus or bystander pathogens) or, alternatively, that a clinical algorithm be used to identify patients with a higher likelihood of group A streptococcal pharyngitis. Although imperfect, such approaches recognize the importance of ARF prevention at the expense of overtreating many cases of sore throat that are not caused by group A Streptococcus. Although there is no proof that antibiotic treatment of group A streptococcal skin infections can prevent ARF, the increasing evidence that impetigo is strongly associ ated with ARF in some populations argues for a focus on treatment and prevention of group A streptococcal skin infections as part of a comprehensive ARF control strategy in regions with endemic impetigo. ■ ■SECONDARY PREVENTION The mainstay of controlling ARF and RHD is secondary prevention. Because patients with ARF are at dramatically higher risk than the gen eral population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences. The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if ≤27 kg) delivered intramuscularly every 4 weeks. It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk, although in settings where good compliance with an every-4-week dosing schedule can be achieved, more frequent dosing is rarely needed. Evidence has emerged recently that subcutane ous delivery of benzathine penicillin G provides more optimal pharma cokinetics than intramuscular delivery and may have added advantages of reducing pain and allowing for larger doses to be delivered less frequently, although this approach is yet to be recommended in clinical guidelines. Oral penicillin V (250 mg) can be given twice daily instead but is less effective than benzathine penicillin G. Penicillin-allergic patients can receive erythromycin (250 mg) twice daily. The duration of secondary prophylaxis is determined by many fac tors, in particular the duration since the last episode of ARF (recur rences become less likely with increasing time), age (recurrences are less likely with increasing age), and the severity of RHD (if severe, it may be prudent to avoid even a very small risk of recurrence because of the potentially serious consequences) (Table 371-4). Secondary prophylaxis is best delivered as part of a coordinated RHD control pro gram, based around a registry of patients. Registries improve the ability to follow patients and identify those who default from prophylaxis and to institute strategies to improve adherence. TABLE 371-4 American Heart Association Recommendations for Duration of Secondary Prophylaxisa CATEGORY OF PATIENT DURATION OF PROPHYLAXIS Rheumatic fever without carditis For 5 years after the last attack or 21 years of age (whichever is longer) Rheumatic fever with carditis but no residual valvular disease For 10 years after the last attack, or 21 years of age (whichever is longer) Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes lifelong prophylaxis aThese are only recommendations and must be modified by individual circumstances as warranted. Note that some organizations recommend a minimum of 10 years of prophylaxis after the most recent episode, or until 21 years of age (whichever is longer), regardless of the presence of carditis with the initial episode. Source: Reproduced with permission from MA Gerber et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. Circulation 119:1541, 2009. https://www.ahajournals.org/doi/10.1161/ CIRCULATIONAHA.109.191959?url_ver=Z39.88-

2003&rfr_id=ori:rid:crossref. org&rfr_dat=cr_pub%20%200pubmed.

Revision #1
Created 2026-01-06 16:34:54 UTC by Omar Ayman
Updated 2026-01-06 16:34:54 UTC by Omar Ayman