disease 3509 16.9.1 Acute rheumatic fever 3509 Jon

disease 3509 16.9.1 Acute rheumatic fever 3509 Jonathan R. Carapetis

16.9 Cardiac involvement in infectious disease CONTENTS 16.9.1 Acute rheumatic fever 3509 Jonathan R. Carapetis 16.9.2 Endocarditis 3519 James L. Harrison, John L. Klein, William A. Littler, and Bernard D. Prendergast 16.9.3 Cardiac disease in HIV infection 3534 Peter F. Currie 16.9.4 Cardiovascular syphilis 3539 Krishna Somers 16.9.1 Acute rheumatic fever Jonathan R. Carapetis ESSENTIALS Acute rheumatic fever is an immunologically mediated multisystem disease induced by recent infection with group A streptococcus. About 5% of people have the potential to develop acute rheum- atic fever after infection by a strain of streptococcus with propen- sity to cause the condition. Most cases (97%) occur in low-income and some middle-income countries, with indigenous populations in some affluent countries also affected. Children aged 5–15 years are most commonly affected, and rheumatic heart disease remains the most common acquired heart disease of childhood in the world. Presentation—after a latent period (1–5 weeks in most cases, but up to 6 months for presentation with chorea) the disease presents with one or more of the following major criteria: (1) carditis—most typ- ically manifest as an apical pansystolic murmur of mitral regurgita- tion, but subclinical disease (evident only on echocardiogram) is also now recognized; (2) polyarthritis—severe, large-joint, and migratory; (3) chorea; (4) subcutaneous nodules; (5) erythema marginatum. Other minor criteria that can support the diagnosis include fever, polyarthralgia, or monoarthritis, elevated C-reactive protein or erythrocyte sedimentation rate, prolongation of the PR interval on the ECG. Diagnosis—in addition to the criteria just described, evidence of preceding group A streptococcal infection is required: (1) positive throat culture, or (2) elevated or rising antistreptolysin O or other streptococcal antibody, or (3) rapid antigen test for group A strepto- coccus. The most recent revision of the Jones criteria for diagnosis of acute rheumatic fever allows subclinical carditis as a major mani- festation and more sensitive criteria in populations at moderate or high risk of disease, with monoarthritis and polyarthralgia acceptable as major manifestations and lower grade fever (≥38°C compared to ≥38.5°C) and less-

elevated ESR (≥30 mm/h compared to ≥60 mm/h) as minor manifestations in those groups. Prognosis and management—untreated acute rheumatic fever lasts for about 3 months. All patients with acute disease should be given penicillin to eradicate the group A streptococcus that precipi- tated the attack. Children with arthritis or severe arthralgia should be treated with nonsteroidal anti-inflammatory medication (usually salicylates). For severe carditis, many clinicians use oral prednisone or prednisolone at a dose of 40–60 mg/day (1–2 mg/kg per day in children), tapering after 2 or 3 weeks, but benefit is not proven. Important prognostic factors are the severity of the acute carditis and the number of recurrences: 30–60% of patients with a first episode of acute rheumatic fever will develop chronic rheumatic heart disease, but more than 70% of those with severe carditis at the first episode, or with recurrent episodes. Recent evidence suggests a benefit of cor- ticosteroids for severe or refractory chorea. Secondary prophylaxis—every patient with acute rheumatic fever
should immediately commence intramuscular benzathine benzy lpenicillin every 3 or 4 weeks (preferable), or twice daily oral phenoxymethylpenicillin. In patients without carditis, this should continue for 5 years or until age 21, whichever comes later (al- though some organizations recommend a minimum of 10 years from last episode); with mild or healed carditis, for 10 years or until age 21, whichever is longer; those with more severe valvular disease or after valve surgery should have secondary prophylaxis until age 40 or sometimes for life. Primary prophylaxis—a full course of penicillin treatment com- mencing within 9 days of the onset of symptomatic group A strepto- coccal pharyngitis will prevent the subsequent development of acute rheumatic fever in most cases and should be advocated.

section 16 Cardiovascular disorders 3510 Introduction Acute rheumatic fever is an immunologically mediated multisystem disease induced by recent infection with group A streptococcus. Most medical practitioners in industrialized countries will rarely, if ever, see a case. However, the dramatic decline in incidence of acute rheumatic fever in industrialized countries during the second half of the 20th century was not replicated in many developing countries, or among some indigenous and other populations living in poverty in industrialized countries. Acute rheumatic fever continues largely unabated in many low-income countries, and rheumatic heart dis- ease remains the most common acquired heart disease of childhood in the world. Epidemiology It is estimated that 33.4 million people are affected by rheumatic heart disease, with more than 10.5 million disability adjusted life years lost and 319 000 deaths occurring each year as a result. Ninety- seven per cent of acute rheumatic fever cases and deaths occur in developing countries. Although acute rheumatic fever and rheum- atic heart disease are relatively common in all developing countries, they occur at particularly high rates in sub-Saharan Africa, Pacific nations, Australasia, the Indian subcontinent, and Central Asia. There have been dramatic declines in incidence in recent decades in many Latin American and Asian countries with improving eco- nomic and living conditions, although many of these countries have subpopulations living in poverty that continue to suffer high rates. In most populations with high incidence, the predisposing condi- tions are those that promote endemicity and high levels of transmis- sion of group A streptococci: these include overcrowded housing, poor personal and community hygiene, poor access to medical services, and, in some circumstances, widespread skin infection, and scabies infestation. Outbreaks of acute rheumatic fever occurred in middle-class areas of the United States during the 1980s and 1990s. These out- breaks arose because of the emergence of virulent strains of group A streptococci, particularly belonging to M serotypes 1, 3, and 18. By contrast, outbreaks of acute rheumatic fever have rarely, if ever, been described from developing countries; most cases appear

to arise from the ongoing circulation of pathogenic group A streptococcal strains in the population. Recurrent episodes are almost as common as primary episodes in many populations with high incidence rates of acute rheumatic fever. These may lead to accumulated cardiac valvular damage and are therefore responsible for many cases of rheumatic heart disease, yet they are almost entirely preventable using secondary prophylaxis. In many developing countries, females are affected more than males, although this gender association is stronger for rheumatic heart disease (especially mitral stenosis) than for acute rheumatic fever; this may reflect a greater tendency to recurrences among fe- males. Any female preponderance may relate to inherited charac- teristics, to greater exposure to group A streptococci because of the increased involvement of girls and young women in child-rearing in most cultures, or to reduced access by females to primary and sec- ondary prophylaxis. The maximum incidence of acute rheumatic fever is between the ages of 5 and 15 years in all populations. Approximately 5% of cases occur in children younger than 5 years, but very rarely are children younger than 3 years affected. This age distribution par- allels that of group A streptococcal pharyngitis, and supports the hypothesis that all cases of acute rheumatic fever follow this condi- tion. However, it may be that cases do not occur in infants or very young children because of the need for maturity of the immune system (particularly of cellular immunity), or sensitization of the immune response by prior streptococcal infections. New cases occur occasionally up to age 30, but rarely beyond. Hypotheses to explain the reduced incidence in adulthood include development of non-type-specific immunity to primary group A streptococcal infections, further maturation of immune responses, or reduced sensitization by recurrent streptococcal infections. Pathogenesis Despite a century of research, the pathogenesis of acute rheumatic fever remains incompletely understood. The presumed pathogenetic pathway relies on development of cross-reactive immune responses between epitopes of group A streptococcus and human tissue, sum- marized in Fig. 16.9.1.1. Host factors Epidemiological evidence suggests that less than 5–6% of people have the potential to develop acute rheumatic fever after relevant streptococcal exposure, and that this proportion does not vary substantially between populations. Attack rates of acute rheum- atic fever after untreated group A streptococcal pharyngitis vary from less than 1% to 3%. Genetic susceptibility to acute rheum- atic fever is suggested by a 44% concordance in monozygotic twins compared to 12% in dizygotic twins, and heritability more recently estimated at 60%. Older studies have associated genetic susceptibility with human leukocyte antigen (HLA) class II alleles, particularly HLA-DR7 and DR4, polymorphisms at the tumour necrosis factor-α locus (TNFα-308 and TNFα-238), high levels of circulating mannose binding lectin, and Toll-like receptors. Recent genome-wide asso- ciation studies are providing further insights: in New Caledonian and Fijian populations an association with the Immunoglobulin Heavy Chain locus on chromosome 14 was reported, and a study in Aboriginal Australians found an association at the HLA DQA1 locus on chromosome 6, both of which support the hypothesis of molecular mimicry leading to the aberrant immune response of acute rheumatic fever. Organism factors The observation that outbreaks of pharyngitis due to certain sero- types of group A streptococcus resulted in high attack rates of acute rheumatic fever, whereas no cases occurred after infection with other serotypes, led to the concept of ‘rheumatogenicity’—that only some strains of group A streptococcus have the potential to cause acute rheumatic fever. M serotypes 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29 were most frequently implicated in studies predominantly from the United States of America. However, recent studies from regions

 with high endemicity of group A streptococcal infections have not found consistent M serotype, or emm genotype, associations with acute rheumatic fever. There

may be substantial genetic diversity among strains belonging to a particular emm type, and not all strains of ‘rheumatogenic serotypes’ appear to cause acute rheumatic fever. Therefore, rheumatogenicity may be strain specific rather than sero- type specific (i.e. any group A streptococcus may acquire the poten- tial to cause acute rheumatic fever). The pathogenic factor(s) are not known. Parts of the organism have immunological cross-reactivity with human tissue; there is close homology between regions of the M protein and human myosin, tropomyosin, keratin, actin, laminin, vimentin, and N- acetylglucosamine. Other components of group A streptococci, including the hyaluronic acid capsule, the cell-wall associated group-specific carbohydrate, and the cell membrane, cross-react with a variety of human tissues damaged in acute rheumatic fever, including components of heart muscle and valves, joints, and brain. Acute rheumatic fever-associated strains of group A streptococcus also tend to be heavily encapsulated with hyaluronic acid, and not to express opacity factor. Group A streptococci possess compo- nents which act as superantigens, selectively stimulating subsets of T cells without the need for antigen presentation. Their role in acute rheumatic fever pathogenesis is not yet clear. Site of infection Although it is widely accepted that acute rheumatic fever may result from group A streptococcal infection of the upper respira- tory tract, but not of the skin, there is increasing evidence that this may not always be the case. Upper respiratory tract infection certainly accounts for most, if not all, episodes of acute rheumatic fever in populations with low rates of streptococcal skin infections. However, in populations where streptococcal impetigo is highly endemic, it may be that skin infection accounts for many cases of acute rheumatic fever, either de novo or after subsequent throat in- fection. Determining whether group A streptococcal skin infection may have a role in pathogenesis of acute rheumatic fever would have enormous public health implications, as it may redirect pre- sent approaches to primary prevention. The immune response Molecular mimicry between group A streptococcal epitopes and human tissue is thought to be the basis for the autoimmune re- sponse that leads to rheumatic fever. Some models suggest that binding of cross-reactive antibodies to heart valve endothelium leads to activation of the adhesion molecule VCAM-1 and sub- sequent recruitment of inflammatory cells. The ensuing tissue damage results in the release of peptides such as laminin, keratin, and tropomyosin, which lead to further damage from activation of cross-reactive T cells. Recently, an alternative hypothesis has been suggested proposing that streptococcal invasion of epithe- lial surfaces leads to binding of streptococcal M protein to type IV collagen through a mechanism not involving molecular mimicry. Overall, it is not entirely clear if the initial damage in rheumatic fever is primarily due to cellular or humoral immunity, but it does appear that ongoing damage is mainly due to T-cell and macro- phage infiltration. GAS adhesion and invasion GAS antigen processing and presentation to B and T cells BCR B cell Macrophage TCR T cell MHC class II Activated cross- reactive T cell Activated cross-reactive B cell Generarion of cross-reactive B and T cells Tissue and organ- specific manifestations Heart Brain (chorea) Joints (arthritis) Skin (erythema marginatum and subcutaneous nodules) Cross-reactive antibody GAS Pharyngeal epithelium Fig. 16.9.1.1 Generation of cross-reactive immune response in acute rheumatic fever. GAS, group A streptococcus. Reprinted from Carapetis JR, et al. (2016). Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers, 14(2), 15084.

 Clinical manifestations There is always a latent period between group A streptococcal infec- tion and the development of acute rheumatic fever. This varies from 1 to 5 weeks in most cases (usually c.3 weeks), but may be shorter in recurrences. Chorea may occur up to 6 months after the precipitating streptococcal infection. The preceding

infection is asymptomatic in about two-thirds of cases. The tissues most commonly affected are the heart, joints, and brain. Although the symptoms due to each can be disabling in the short term, only cardiac damage may be permanent and progressive. Therefore, the focus in controlling or treating acute rheumatic fever is always to prevent the development of rheumatic heart disease. The frequency with which the various clinical manifestations have occurred in recent descriptions of acute rheumatic fever is listed in Table 16.9.1.1. Carditis Although inflammation in acute rheumatic fever may affect the pericardium (causing pericardial rubs and occasionally pleuritic chest pain) or the myocardium (sometimes causing cardiac failure, and evident on biopsy with pathognomonic Aschoff bodies), endo- cardial inflammation is the most important cause of cardiac damage. If either acute cardiac failure or chronic cardiac disease occurs, it is almost always due to damage to the cardiac valves. A murmur is the most common evidence of acute valvular dis- ease, usually the apical pansystolic murmur of mitral regurgita- tion, with or without a low-pitched mid-diastolic (Carey–Coombs) murmur. Occasionally an aortic regurgitant murmur may be heard, mainly in older adolescents or young adults. Murmurs of tricuspid or pulmonary regurgitation are rare and are usually secondary to increased pulmonary venous pressures resulting from mitral regur- gitation or stenosis. Sinus tachycardia or gallop rhythms may also be present in acute carditis. Valves affected by rheumatic carditis may have a characteristic appearance or pattern of regurgitation on Doppler echocardiog- raphy (when interpreted by experienced technicians), which may be found even in the absence of a cardiac murmur (subclinical dis- ease). Recent efforts to standardize the echocardiographic diagnosis of rheumatic heart disease have led to publication of an evidence- based guideline by the World Heart Federation, which focuses on features of mitral and aortic regurgitation and valvular morphology that can be considered pathological, and combines these features into criteria for ‘definite’ and ‘borderline’ rheumatic heart disease. Although these criteria were devised for rheumatic heart disease ra- ther than acute rheumatic fever, there is accumulating evidence that many similar features are useful in diagnosing acute rheumatic card- itis on echocardiography. The recent revision of the Jones criteria identifies the features of regurgitant jets and valvular morphology that can be used to make a diagnosis of acute rheumatic carditis, even in the absence of a significant cardiac murmur (Table 16.9.1.2). Mitral or aortic stenosis may develop as later complications of se- vere and/or recurrent acute carditis due to scarring and contraction following the acute inflammatory process. Rarely, mitral stenosis may occur in young children with acute rheumatic fever—so-called ‘juvenile mitral stenosis’—the reasons for the development of this condition are not clear. Damage to the electrical conduction pathways may result in prolongation of the PR interval on electrocardiography (ECG). Although a subset of healthy people may have this finding, the pres- ence of a prolonged PR interval that resolves over the ensuing few days to weeks may be a useful diagnostic feature in cases where the clinical manifestations are not clear. Occasionally, in the acute phase, second-or third-degree heart block or a nodal rhythm may be present (Fig. 16.9.1.2). Arthritis The characteristic joint manifestation of acute rheumatic fever is severe, large-joint, migratory polyarthritis. The knees, ankles, wrists, and elbows are most commonly involved; only rarely, and usually only when the patient is untreated for several days, are the hips or small joints of the hands or feet inflamed. One joint char- acteristically becomes exquisitely painful and inflamed as another is waning. Most patients have only one or two joints affected at any one time, and each joint may be involved for just a few hours or up to 1 or 2 days. The arthritis is so responsive to nonsteroidal anti-inflammatory medication (NSAIDs) that its persistence more than 1 or 2 days after commencing high-dose aspirin should lead one to consider alternative diagnoses. Arthritis of a single large joint, and polyarthralgia in the absence of clear arthritis, are increasingly described in acute rheumatic

fever from regions with high rates of disease. This is sometimes, but not always, due to early administration of anti-inflammatory medica- tion, before the typical migratory pattern has emerged. Other causes of monoarthritis, including septic arthritis, should first be excluded before a diagnosis of acute rheumatic fever is entertained. Arthralgia (joint pain without objective evidence of inflammation) is usually migratory and affects large joints, and like the arthritis of acute rheumatic fever is very responsive to NSAIDs. Sydenham's chorea In 1686 the English physician Thomas Sydenham described rheum- atic chorea, initially naming it 'St Vitus' dance'. It is the most intriguing manifestation of acute rheumatic fever, particularly as it commonly occurs in the absence of other manifestations, usually follows a pro- longed latent period (up to 6 months) after the precipitating group A streptococcal infection, and occurs most commonly in females
Table 16.9.1.1 Frequency of clinical manifestations in acute rheumatic fever Manifestation Proportion of patients with manifestation (%) Choreaa absent Choreaa present Carditis 40–60 20–30 Polyarthritis 50–75 <10 Erythema marginatum 1–10 0–1 Subcutaneous nodules 1–10 0–1 Fever >37.5°C

> 90 10–25 Arthralgia <10–20 <5 Elevated acute-phase reactants 90 10–25 Prolonged PR interval 30–50 5–10 a Chorea is present in <10% to >30% of patients with acute rheumatic fever, depending on the population.

 (and almost never in postpubertal males). The rapid, jerky, invol- untary movements affect predominantly the upper limbs and face, may be asymmetrical, and may be sufficiently severe to render the patient unable to eat, drink, walk, or perform other activities of daily living. Mild chorea can sometimes be detected by having the patient join palms above the head to reveal occasional twitches of the arms or the head. Typical signs include the 'milkmaid's grip' (rhythmic squeezing when the patient grasps the examiner's fingers), spooning of extended hands (caused by flexion of the wrists and extension of the fingers), darting of the protruded tongue, and the 'pronator sign' (the arms and palms turn outwards when held above the head). As with other forms of chorea, the disorder usually becomes more evident with anxiety or purposeful movements (such as drinking or writing). Movements may appear semi-purposeful, and symptoms subside during sleep. Sydenham's chorea is often associated with ex- cessive emotional lability or personality changes, which may pre- cede the abnormal movements. Most patients can be reassured that Sydenham's chorea will re- solve completely and leave no long-lasting effects, usually within 6 weeks and almost always within 6 months, but rarely lasting up to 3 years.
Subcutaneous nodules and erythema marginatum Both of these manifestations are found in less than 2% of patients with acute rheumatic fever, although they were described in up to 10–20% of patients in earlier studies from the United States of America and the United Kingdom.
Subcutaneous nodules are firm, painless lumps, usually between 0.5 and 2 cm in diameter, commonly found in crops of three or more, and usually appear 2 to 3 weeks after the onset of acute rheumatic fever. They occur mainly over extensor surfaces or bony protuberances, particularly the hands, feet, occiput, and back. The nodules are similar to those found in rheumatoid arthritis, though often smaller, and are most likely to be associated with severe carditis. Nodules usually last from a few days to 2 or 3 weeks. The characteristic rash, erythema marginatum, appears as a light pink macule that spreads outwards with a serpiginous, well-demarcated edge, while the central portion clears. It appears, disap- pears, or moves before the

observer’s eyes. Multiple areas are often involved, usually over the trunk, occasionally over the proximal por- tions of the limbs, but rarely, if ever, the face. It usually appears to- gether with the other initial symptoms of acute rheumatic fever but may recur intermittently for weeks or even months. This does not indicate ongoing rheumatic inflammation, and patients can be re- assured that the rash will eventually disappear without complications. Fever With the exception of those with pure chorea, 90% of patients will have a temperature at presentation higher than 37.5°C. Although it has been reported that the temperature usually exceeds 39°C, others have found only 25% of confirmed cases with fever to that level. The recent revision of the Jones criteria specifies that a temperature of 38.5°C or more is sufficient to be a minor manifestation in low-risk populations while a temperature of 38.0°C or more is sufficient in moderate-to high-risk populations. As with arthritis, fever is very sensitive to NSAIDs, usually resolving completely within 1 or 2 days of commencing high-dose salicylates. Table 16.9.1.2 Findings on echocardiography in rheumatic valvulitis Valve Doppler findings Morphological findings Mitral valve Pathological mitral regurgitation (all 4 met) Acute mitral valve changes Seen in at least 2 views Annular dilation Jet length ≥2 cm in at least one view Chordal elongation Peak velocity >3 m/s Chordal rupture resulting in flail leaflet with severe mitral regurgitation Pansystolic jet in at least one envelope Anterior (or less commonly posterior) leaflet tip prolapse Beading/nodularity of leaflet tips Chronic mitral valve changes: not seen in acute carditis Leaflet thickening Chordal thickening and fusion Restricted leaflet motion Calcification Aortic valve Pathological aortic regurgitation (all 4 met) Aortic valve changes in either acute or chronic carditis Seen in at least 2 views Irregular or focal leaflet thickening Jet length ≥1 cm in at least one view Coaptation defect Peak velocity >3 m/s Restricted leaflet motion Pan diastolic jet in at least one envelope Leaflet prolapse Reproduced with permission from Gewitz MH, et al. (2015). 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 Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council of Cardiovascular Disease in the Young Endorsed by the World Heart Federation. Circulation, 131, 1806–18.

 Elevated acute-phase reactants Almost all patients, except those with pure chorea, have a dra- matically elevated erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP). There appears little difference between these measurements in their diagnostic usefulness. The CRP may return to normal more rapidly than the ESR when rheumatic activity subsides. Mild to moderate peripheral leucocytosis is common, al- though this is a less sensitive marker of rheumatic inflammation and has therefore been removed as a minor manifestation from the most recent revision of the Jones criteria. Other features Severe central abdominal pain is found at presentation in a small proportion of patients. It may be associated with other features of acute rheumatic fever; if not, these features usually appear within 1 or 2 days. The pain responds quickly to NSAIDs. Epistaxis was reported frequently in historical accounts of acute rheumatic fever, but does not feature prominently in recent descriptions. Pulmonary infiltrates may be found in patients with acute carditis; this has been labelled ‘rheumatic pneumonia’ although it is not clear whether the infiltrates represent rheumatic inflammation or another process. There may be microscopic haematuria, pyuria, or proteinuria; also mild elevations of liver transaminases—these are nonspecific and not usually severe. Associated poststreptococcal syndromes Poststreptococcal reactive arthritis has been differentiated from rheumatic fever by some authors because it has a shorter incubation period after streptococcal infection, sometimes follows nongroup- A β-haemolytic streptococcal infection,

may have a different pattern of arthritis (including small joint involvement), and is less responsive to NSAIDs. Because of the lack of cardiac involvement, these patients are said not to require secondary prophylaxis. However, descriptions of patients who have subsequently developed carditis have led other authors to question the distinction between poststreptococcal re- active arthritis and rheumatic fever. If poststreptococcal reactive arthritis is diagnosed, secondary prophylaxis should be prescribed for at least 1 year and discontinued if there is no evidence of carditis. In populations with high incidence rates of acute rheumatic fever, it may be prudent to treat all cases of possible poststreptococcal re- active arthritis as acute rheumatic fever. The frequent finding of emotional lability, motor hyperactivity, and occasional obsessive–compulsive symptoms in patients with Sydenham's chorea led to the observation that group A strepto- coccal infections may precipitate or exacerbate other disorders of the basal ganglia. These include tic disorders, Tourette's syndrome, and obsessive–compulsive disorder, and the term PANDAS (paedi- atric autoimmune neuropsychiatric disorders associated with streptococcal infections) has been coined. A recent follow-up study that failed to find any exacerbations of symptoms associated with streptococcal infections in PANDAS patients has raised questions about the existence of PANDAS as a distinct disease entity. Diagnosis Because of the diversity of symptoms and signs, and the nonspecific nature of most of them, in 1944 Dr T. Duckett Jones developed a set of criteria to aid in the diagnosis of acute rheumatic fever. The Jones criteria have subsequently been revised and updated several times to improve their specificity in an era of declining acute rheumatic fever incidence in high-income countries. Because the Jones cri- teria were perceived to be overly specific for populations with high incidence of disease, other bodies have recently published their own diagnostic criteria, including the World Health Organization (WHO) and expert groups in Australia and New Zealand. The American Heart Association has responded to these concerns in its latest revision of the Jones criteria, presenting more sensitive cri- teria for populations at moderate or high risk of acute rheumatic fever (Table 16.9.1.3). The manifestations are divided into major, those which are most predictive of acute rheumatic fever, and minor, those which are commonly found in acute rheumatic fever but are less specific. The diagnosis of an initial episode requires the presence of either two major, or one major and two minor criteria, plus the demonstration of a current or recent group A streptococcal infection. Evidence of group A streptococcal infection is not required for chorea, where the Day 1 Complete heart block Day 3 Second-degree heart block Day 4 First-degree heart block Day 18 Normal sinus rhythm Fig. 16.9.1.2 ECG changes in a young adult with acute rheumatic fever, showing evolution over 18 days from complete heart block, to second-degree (Wenckebach) block, to first-degree block, and then to normal sinus rhythm. Reprinted from Bishop W, et al. (1996). A subtle presentation of acute rheumatic fever in remote Northern Australia. Australian and New Zealand Journal of Medicine, Vol 26, Issue 2, © 1996 John Wiley & Sons Inc.

 onset may be delayed up to 6 months after streptococcal infection, and late-onset carditis, when low-grade inflammation may persist for prolonged periods after the precipitating infection. Recurrences can be diagnosed with less stringent criteria. Proof of a recent group A streptococcal infection can include demonstrating the organism in the upper respiratory tract, either by culture or rapid antigen techniques. However, most children with acute rheumatic fever no longer have a group A streptococcus Table 16.9.1.3 Revised Jones criteria (2015 revision) 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/high-risk populations Carditisb Carditis Clinical and/or subclinical Clinical and/or subclinical Arthritis Arthritis Polyarthritis only Monoarthritis or polyarthritis Polyarthralgia Chorea Chorea Erythema marginatum Erythema marginatum Subcutaneous nodules Subcutaneous nodules C. Minor criteria Low-risk populationsa Moderate/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/dlc ESR ≥ 30 mm/Hr and/or CRP ≥3.0 mg/dlc Prolonged PR interval (unless carditis is a major criterion) Prolonged PR interval (unless carditis is a major criterion) ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RHD, rheumatic heart disease. a Low-risk populations = ARF incidence ≤2 per 100 000 school-aged children or all age RHD prevalence of ≤1 per 1000 population per year. b Subclinical carditis = echocardiographic valvulitis as defined in Table 16.9.1.2. Erythema marginatum and subcutaneous 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. c CRP value must be greater than upper limit of normal for laboratory. Reproduced with permission from Gewitz MH, et al. (2015) 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 Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council of Cardiovascular Disease in the Young Endorsed by the World Heart Federation. Circulation, 131, 1806–18. Table 16.9.1.4 Differential diagnoses of common major presentations of acute rheumatic fever Presentation Polyarthritis and fever Carditis Chorea Differential diagnoses Septic arthritis (including gonococcal) Innocent murmur SLE Connective tissue and other autoimmune diseasea Mitral valve prolapse Drug intoxication Viral arthropathyb Congenital heart disease Wilson’s disease Reactive arthropathyb Infective endocarditis Tic disorderc Lyme disease Hypertrophic cardiomyopathy Choreoathetoid cerebral palsy Sickle cell anaemia Myocarditis—viral or idiopathic Encephalitis Infective endocarditis Pericarditis—viral or idiopathic Familial chorea (including Huntington’s) Leukaemia or lymphoma Intracranial tumour Gout and pseudogout Lyme disease Hormonald SLE, systemic lupus erythematosus. a Includes rheumatoid arthritis, juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis, sarcoidosis, among others. b Mycoplasma, cytomegalovirus, Epstein–Barr virus, parvovirus, hepatitis, rubella vaccination, Yersinia, and other gastrointestinal pathogens. c Possibly including PANDAS. d Includes oral contraceptives, pregnancy (chorea gravidarum), hyperthyroidism, hypoparathyroidism. Reprinted from The Lancet, Vol. 366, Carapetis JR, McDonald M, Wilson NJ, Acute rheumatic fever, pp. 155–68. Copyright (2005), with permission from Elsevier.

section 16 Cardiovascular disorders 3516 detectable by these methods, and up to 15–25% of normal children in temperate climate countries may carry the organism in their throat. Serological techniques are therefore most commonly used, par- ticularly the antistreptolysin O, anti-DNase B, or antihyaluronidase titres. One of any two of these tests will be positive in well over 90% of recent streptococcal infections. Their usefulness is increased by per- forming more than one serological test, or by demonstrating rising titres in paired sera. Serology is of limited value in regions with high prevalence rates of streptococcal impetigo, where children may have positive antistreptococcal titres most of the time. There is therefore a need for a better diagnostic test of recent streptococcal infection, or an objective diagnostic test for acute rheumatic fever itself. The most common clinical presentation, that of a child with fever and polyarthritis, raises multiple differential diagnoses that will vary by region. Table 16.9.1.4 lists some alternative diagnostic possibil- ities for the three most common major manifestations. Treatment If untreated, acute

rheumatic fever lasts on average for 3 months. Except in the case of life-threatening acute carditis, there is no evi- dence that presently available treatments alter the outcome. Most treatments are designed to provide symptomatic relief or are based on theoretical (but unproven) approaches to attenuating the long- term damage. If practical, all patients with acute rheumatic fever should be ad- mitted to hospital to confirm the diagnosis, perform baseline in- vestigations to ascertain the status of the heart, provide adequate treatment for the acute phase, commence secondary prophylaxis, allow communication of details to personnel responsible for long- term follow-up of the patient, and begin education of the patient and family. The mainstays of treatment are bed rest, penicillin, and salicylates. Bed rest Previous recommendations that children with acute rheumatic fever be rested in bed until all signs of active inflammation abated were probably more extreme than is necessary. Once symptoms of arth- ritis have subsided and any cardiac failure is controlled, the child may begin gentle mobilization, which may be increased as tolerated. There is no evidence that bed rest beyond the period where mobil- ization leads to exacerbation of pain or cardiac failure has any long- term benefit. Penicillin All patients with acute rheumatic fever should be given penicillin to eradicate the group A streptococcus that precipitated the attack. This is based on an early finding that, in some cases, prolonged group A streptococcal infection led to more severe acute rheumatic fever. Although in most cases the precipitating organism cannot be cul- tured, a treatment course of penicillin is prudent in case the strain remains present in low numbers, and to prevent its transmission to other contacts. As the aim is eradication of group A streptococcal in- fection, penicillin may be administered either as a single intramus- cular injection of benzathine benzylpenicillin at a dose of 1.2 million units (600 000 U for patients <27 kg) into the gluteal or quadriceps muscles, or as a 10-day course of oral phenoxymethylpenicillin (V) at a dose of 500 mg (adolescents and adults) or 250 mg (children) given two times daily or amoxicillin 50 mg/kg (max 1 g) daily. In the case of penicillin allergy, the present recommendation is to use oral erythromycin at 20–40 mg/kg per day given two to four times daily for 10 days, although in some regions levels of erythromycin resist- ance among group A streptococci are increasing. Anti-inflammatory treatment Children with arthritis or severe arthralgia should be treated with NSAIDs; salicylates have been most widely used, although the increasing experience with other non-steroidal anti-inflammatory medications and the relatively narrow safety profile of salicylates mean that naproxen or ibuprofen are preferred agents. If aspirin is to be used, it should be administered at a dose of 50–60 mg/kg per day up to a maximum of 80–100 mg/kg per day (4–8 g/day in adults), given in 4–5 divided doses, usually results in defervescence and resolution of arthritis and arthralgia within 1–2 days. Sometimes higher doses lead to nausea or vomiting, which can be minimized by increasing from lower starting doses. After a few days or up to 2 weeks, when the initial symptoms are abating, patients on higher doses can have the dose re- duced to 50–60 mg/kg per day for the remaining 2–4 weeks. Arthritis or arthralgia may return up to 2 to 3 weeks after discontinuation of therapy; this is usually a brief and mild recrudescence, often associ- ated with increased ESR or CRP, and can be managed either with rest and reassurance or a short course of lower-dose NSAIDs. When the diagnosis is uncertain, NSAIDs should be withheld for a day or two to look for the development of characteristic migratory polyarthritis. In such cases, paracetamol or codeine can be used to control pain until the diagnosis is confirmed. There is no evidence that salicylates reduce the severity of acute carditis or the risk of chronic cardiac valve damage. Corticosteroids For many years, corticosteroids have been used in acute rheumatic fever, particularly for patients with severe carditis. Two meta-analyses have found no evidence that they reduce the risk of long-term valve damage. However, the studies included in these meta-analyses were all conducted more than 40 years ago and used corticosteroid medi- cations not in common usage today. Many

clinicians continue to use oral prednisone or prednisolone at a dose of 40–60 mg/day (1–2 mg/ kg per day in children), tapering after 2 or 3 weeks, in the belief that this might reduce the severity of acute carditis. The role of cortico- steroids in chorea is discussed separately. Treatment of cardiac failure There is no doubting the need to treat cardiac failure. Diuretics, angiotensin-converting enzyme (ACE) inhibitors (especially in aortic regurgitation), and fluid restriction are most commonly em- ployed. Digoxin is usually restricted to cases where atrial fibrillation coexists with cardiac failure, often found in older patients with es- tablished mitral stenosis. If medical therapy fails, cardiac surgery should be considered, even during the acute phase. In populations where fulminant acute carditis is relatively common (e.g. South Africa), mitral valve repair or replacement can be life-saving and surgeons have developed tech- niques for undertaking these procedures despite friable, acutely in- flamed valvular and perivalvular tissues. In recent years, there has been a greater tendency to undertake valve repair rather than re- placement, or to use homografts or xenografts rather than mech- anical prostheses. This is to avoid high rates of thromboembolic

 complications associated with mechanical prostheses, particularly in populations where compliance with anticoagulation chemo- therapy is suboptimal and there are difficulties in monitoring co- agulation indices. Treatment of chorea Sydenham’s chorea always resolves, and in most cases there is no need for medical treatment. However, medications may reduce ab- normal movements in moderate or severe chorea. Carbamazepine or sodium valproate are recommended as first line treatment, halo- peridol less commonly because of its side effect profile. Other medi- cations sometimes employed include pimozide, chlorpromazine, or benzodiazepines. All of these medications should be used sparingly and only for limited periods, and the tendency to try multiple medi- cations should be avoided. Recent evidence suggests that corticosteroids lead to more rapid symptom reduction in chorea, so oral prednisone or prednisolone may be considered for severe or refractory cases (0.5 mg/kg daily, weaning as early as possible, preferably after 1 week if symptoms reduce). Psychotherapeutic interventions have little role in the short to medium term, and may increase the stigma of this self-limited or- ganic disease. However, behavioural therapy should be considered if longer-term behavioural abnormalities persist (e.g. emotional la- bility, obsessive–compulsive traits). Newer therapies Because of the autoimmune nature of acute rheumatic fever, immunomodulatory therapies have been tried. Intravenous im- mune globulin (IVIG) has been given in some small trials. One study showed no apparent benefit on rate of improvement of clin- ical, laboratory, or echocardiographic parameters of acute carditis, but another suggested that it may accelerate recovery from chorea. Other therapies have yet to be formally assessed. Prognosis and follow-up The most important prognostic factors are the severity of the acute carditis and the number of recurrences. Overall, approximately 30– 50% of patients with a first episode of acute rheumatic fever will de- velop chronic rheumatic heart disease. This increases to more than 70% in patients with severe carditis at the first episode, or in those who have had at least one recurrence. Any patient with acute rheumatic fever requires long-term follow- up. Follow-up assessments should focus on cardiac status, adherence to secondary prophylaxis, early treatment of group A streptococcal pharyngitis, and prevention of streptococcal pyoderma (including hygiene and treatment or prevention of scabies infestation). Patients with evidence of cardiac valve damage should be assessed regularly by specialist physicians and considered for cardiac surgery before substantial left ventricular dysfunction occurs. Vasoactive drugs, particularly ACE inhibitors, may delay the need for operation in asymptomatic patients with chronic aortic regurgitation. Regular echocardiography may be useful to follow the progress of rheum- atic heart disease, especially in populations where follow-up may be irregular or in whom

communication or cultural differences make clinical assessment difficult. For reasons that are not clear, presentations of acute rheumatic fever are uncommon in many low-income countries where rheumatic heart disease is highly prevalent. In these settings, rheumatic heart disease often presents at an advanced stage, and the prognosis is poor; the recent REMEDY study followed nearly 3000 individuals with rheumatic heart disease and found that 21% of those in low- income countries had died within the first two years of presentation. Recurrences About 75% of all recurrences occur within 2 years of an episode of acute rheumatic fever. The reasons for this are not known, but are thought to relate to a time-dependent sensitization of the im- mune response. The clinical features of recurrences tend to mimic those present at the initial episode, particularly in the case of chorea. However, this rule is not absolute, and the risk of developing other manifestations, particularly carditis, increases with each recurrence. The practical implication of this is that the absence of carditis at the first episode does not help to identify patients who may not need secondary prophylaxis. Prevention of acute rheumatic fever Secondary prophylaxis Every patient with acute rheumatic fever should immediately com- mence secondary prophylaxis: long-term, regular antibiotics to prevent primary group A streptococcal infections. This strategy is proven to reduce the incidence of recurrences and the risk of developing chronic rheumatic heart disease. The optimal regimen is 1.2 million units (900 mg) of intramus- cular benzathine benzylpenicillin every 3 or 4 weeks, and this is com- monly given in populations with high incidences of acute rheumatic fever and programmes in place to support the regimen. An alterna- tive strategy is to use oral phenoxymethylpenicillin at a dose of 250 mg twice daily; this is less effective than benzathine benzylpenicillin, and adherence is usually less reliable. For patients proven to be allergic to penicillin, the present rec- ommendation is to use oral erythromycin at a dose of 250 mg twice daily. Recent trials have shown newer oral cephalosporins to be effective at eliminating upper respiratory tract carriage of group A streptococci. However, none of these antibiotics has been evalu- ated for the ability to prevent acute rheumatic fever. The duration of secondary prophylaxis is dictated by the redu- cing risk of recurrence with increasing age, with time since the last episode, and the possible consequences of recurrences. In pa- tients without carditis, secondary prophylaxis should continue for 5 years following the most recent episode or until age 21 years, whichever comes later. In patients with mild or healed carditis, prophylaxis should be continued for 10 years following the most recent episode or until age 21 years, whichever is longer. Patients with more severe valvular disease or those who have undergone valve surgery should have secondary prophylaxis until age 40 or sometimes for life. Primary prophylaxis A full course of penicillin treatment commencing within 9 days of the onset of symptomatic group A streptococcal pharyngitis will prevent the subsequent development of acute rheumatic fever in most cases. After the diagnosis has been confirmed by a throat culture or rapid antigen diagnostic test, the treatment of choice is penicillin, administered either as a single intramuscular injection

section 16 Cardiovascular disorders 3518 of benzathine benzylpenicillin (600 000 U for children who weigh <27 kg, or 1.2 million U for larger children and adults) or as a full 10 days of oral phenoxymethylpenicillin (250 mg for children or 500 mg for adults given two times daily) or amoxicillin (50 mg/kg to a maximum of 1 g as a daily dose). The importance completing the 10-day course, even if symptoms abate quickly, should be stressed to patients and parents. Shorter courses of oral penicillin treatment are associated with higher risks of acute rheumatic fever. There has never been a clinical isolate of group A streptococcus that is re- sistant to penicillin; therefore, the use of other antibiotics for pri- mary prophylaxis should be restricted to patients who are allergic to penicillin. In the case of penicillin allergy, a 10-day course of erythro- mycin or

clarithromycin is recommended. First-generation oral cephalosporins may also be considered, as may a 5-day course of azithromycin. However, these agents have not been evaluated in populations with high incidences of acute rheumatic fever. It is not possible to predict which episodes of group A strepto- coccal pharyngitis will precipitate acute rheumatic fever, so this treat- ment must be offered in all cases to be effective. Unlike prevention of recurrent episodes, which is virtually complete using secondary prophylaxis, penicillin treatment of streptococcal pharyngitis will at best prevent only the one-third or so of cases of acute rheumatic fever that follow a sore throat. However, this important intervention may also arrest the spread of pathogenic group A streptococci in the community. Penicillin treatment of group A streptococcal pharyn- gitis should begin as early as possible in patients with a history of acute rheumatic fever, should they not be taking secondary prophy- laxis, but even then may not prevent a recurrence, hence the need for secondary prophylaxis. In recent years, the use of primary prophylaxis has been ques- tioned in some industrialized countries where acute rheumatic fever is now rare. It is argued that the strategy prevents few cases of acute rheumatic fever but contributes to overuse of antibiotics. Similar arguments were raised in the United States of America during the 1970s, but faded somewhat with the resurgence of acute rheumatic fever in that country during the 1980s. Any country considering abandoning primary prophylaxis should first have in place effective surveillance to detect changes in the epidemiology of primary group A streptococcal infections and the appearance of cases of acute rheumatic fever. Primary prophylaxis is unsuccessful in most developing coun- tries. It requires trained health workers, microbiology laboratories, transportation, and communication infrastructure, the availability of penicillin, and a population likely to seek and adhere to treat- ment for sore throats. Approaches based on diagnosis using clinical algorithms, or an approach of treating all sore throats with intra- muscular benzathine benzylpenicillin without further attempts at diagnosis, are being increasingly recommended in resource-poor settings. If primary prophylaxis were to be instituted effectively in developing countries, there would be a substantial impact on acute rheumatic fever incidence, but it would not disappear because most cases do not follow a sore throat. Other methods of primary prevention are clearly needed in developing countries. Improved living standards, particularly less-crowded housing, and access to primary healthcare, are pri- orities. Although streptococcal skin infections may be linked to acute rheumatic fever pathogenesis, there are no trials of impetigo control programmes to prevent acute rheumatic fever. There is a current focus on attempts to develop a group A streptococcal vac- cine. Clinical trials of prospective vaccines have begun, but the pro- cess will take many years, and recent experience suggests that new vaccines are often beyond the financial reach of most developing countries. For the foreseeable future at least, acute rheumatic fever prevention in many developing countries will depend on improving adherence to secondary prophylaxis and developing new strategies for primary prevention. FURTHER READING Anonymous (1995). Strategy for controlling rheumatic fever/rheum- atic heart disease, with emphasis on primary prevention: memo- randum from a joint WHO/ISFC meeting. Bull World Health Org, 73, 583–7. Bisno AL (1991). Group A streptococcal infections and acute rheum- atic fever. N Engl J Med, 325, 783–93. Bryant P, et al. (2014). Susceptibility to acute rheumatic fever based on differential expression of genes involved in cytotoxicity, chemotaxis, and apoptosis. Infect Immun, 82, 753–61. Carapetis JR, et al. (2005). The global burden of group A streptococcal diseases. Lancet Infect Dis, 5, 685–94. Carapetis JR, et al. (2016). Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers, 14(2), 15084. Carapetis JR, McDonald M, Wilson NJ (2005). Acute rheumatic fever. Lancet, 366, 155–68. Cilliers AM (2006). Rheumatic fever and its management. BMJ, 333, 1153–6. Cilliers AM, Manyemba J, Saloojee H (2003). Anti-inflammatory treatment for carditis in acute rheumatic fever. Cochrane Database Syst Rev, CD003176. Cunningham MW (2004). T cell mimicry

in inflammatory heart dis- ease. Mol Immunol, 40, 1121–7. Dale JB, et al. (2013). Group A streptococcal vaccines: paving a path for accelerated development. Vaccine, 31 Suppl 2, B216–22. Gewitz MH, et al. (2015). Revision of the Jones criteria for the diag- nosis of acute rheumatic fever in the era of Doppler echocardiog- raphy: a scientific statement from the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council of Cardiovascular Disease in the Young Endorsed by the World Heart Federation. Circulation, 131, 1806–18. Hu MC, et al. (2002). Immunogenicity of a 26-valent group A strepto- coccal vaccine. Infect Immun, 70, 2171–7. Irlam J, et al. (2013). Primary prevention of acute rheumatic fever and rheumatic heart disease with penicillin in South African children with pharyngitis: a cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes, 6, 343–51. Kaplan EL (1993). T. Duckett Jones Memorial Lecture. Global assess- ment of rheumatic fever and rheumatic heart disease at the close of the century. Influences and dynamics of populations and patho- gens: a failure to realize prevention? Circulation, 88, 1964–72. Karthikeyan G, Mayosi BM (2009). Is primary prevention of rheum- atic fever the missing link in the control of rheumatic heart disease in Africa? Circulation, 120, 709–13. McDonald M, Currie BJ, Carapetis JR (2004). Acute rheumatic fever: a chink in the chain that links the heart to the throat? Lancet Infect Dis, 4, 240–5. McDonald M, et al. (2005). Preventing recurrent rheumatic fever: the role of register-based programs. Heart, 91, 1131–3.

Revision #1
Created 2026-01-22 16:39:45 UTC by Omar Ayman
Updated 2026-01-22 16:39:45 UTC by Omar Ayman