40 Group A *Streptococcus*

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KEY FEATURES

- Group A *Streptococcus* or *Streptococcus pyogenes* is the predominant cause of bacterial pharyngitis, and skin infection globally.
- Group A *Streptococcus* is also a cause of severe invasive, necrotizing, and toxin-mediated syndromes and debilitating non-suppurative sequelae, including rheumatic fever and acute post-streptococcal glomerulonephritis.
- Group A streptococcal infection is estimated to result in over 639,000 deaths annually, the majority in developing countries, caused by invasive infection or from rheumatic heart disease and its complications.
- Group A *Streptococcus* is universally sensitive to penicillin, which remains the mainstay of treatment and for the prevention of rheumatic heart disease.

INTRODUCTION

Group A *Streptococcus* (GAS) causes a diverse spectrum of disease, ranging from benign and self-limited infections of the throat or skin, to lethal soft tissue infections accompanied by multi-organ failure. Until the advent of the antibiotic era, GAS was a major cause of death in industrialized countries due to fatal epidemics of scarlet fever, sepsis, and rheumatic heart disease (RHD). The 1980s saw an increase in rheumatic fever cases in the Rocky Mountain states of the United States, along with an apparent resurgence in severe GAS disease in industrialized countries.[1] The subsequent awareness of GAS disease in recent years has also brought to focus its disproportionately high burden in resource-limited settings, especially in tropical regions. The severe implications of advanced RHD and the existence of effective strategies for prevention and treatment highlight the need for better data to accurately determine worldwide burden.[2,3]

EPIDEMIOLOGY

As expected, the burden of all GAS infections is highest in resource-limited settings. This is likely related to poverty, overcrowded living conditions, and reduced access to medical care, although geography and climate may also play a role. The estimated number of cases and deaths from GAS diseases are summarized in Table 40.1. Of these, 79% of RHD cases, 95% of acute rheumatic fever (ARF) cases, 97% of acute post-streptococcal glomerulonephritis (APSGN) cases, and 97% of invasive GAS cases come from less developed countries.[2]

Pharyngitis is the most common manifestation of GAS disease; the peak incidence is in school-aged children. Compared with the incidence in developed urban settings, which may be as low as one episode per 8 child years, the incidence in resource-limited settings may be four to eight times higher.[2] GAS colonization has been detected in the oropharynx of approximately one in eight school-aged children; lower rates occur below the age of 5 years (≈5%), with groups C and G streptococci being more common.

Approximately one-third of school-aged children who present with a sore throat will have GAS as the causative organism; this declines to <15% in adulthood. In temperate climates, there is significant seasonal variation in the rates of GAS pharyngitis, peaking during winter/early spring. In tropical climates, the seasonal variation appears to be less marked, although robust data are lacking.[4] It is unclear as to whether other factors affect this (e.g., increased viral transmission or crowding).[5] Impetigo is common in childhood; transmission occurs readily in school and pre-school care settings, especially during summer in humid locations. In tropical settings where the burden is particularly high, almost half of children can have impetigo at any one time.[6]

Outbreaks of scarlet fever occur sporadically even in the industrialized world, although they are much less common since the advent of antibiotics. In 2011 Hong Kong had an incidence 10 times the baseline rate; similarly, an epidemic in northwest London occurred in 2014 with an incidence three to six times higher than average.[7]

Cellulitis and erysipelas are the most common manifestations of invasive GAS infection. Cellulitis is associated with increasing temperatures in temperate climates. The increased humidity of the tropics also contributes to an increased rate of cellulitis in these areas. Unlike pharyngitis and impetigo, incidence of cellulitis increases with age. Erysipelas does not appear to have a predilection to changes in climate and has a bi-modal incidence affecting the young and the elderly. In the mid-1980s, reports emerged from industrialized countries of both increasing numbers of severe necrotizing GAS infections and of streptococcal toxic shock syndrome (STSS) affecting otherwise healthy individuals. GAS strains belonging to *emm* types—1, 3, 12, and 18 in particular—have been implicated.[1] Severe invasive GAS infections mostly occur sporadically, but secondary cases and case clusters have been reported.[8] In industrialized countries, the case mortality for severe GAS infection ranges from 10% in younger patients to 20% in the elderly. Limited data suggest a higher mortality in resource-limited settings.

ARF is uncommon in industrialized settings, although the incidence remains high among Indigenous populations in Australia, New Zealand, and the Pacific. The largest burden of disease is thought to exist in India, China, Pakistan, Indonesia, and the Democratic Republic of Congo; together these five countries are estimated to account for 73% of the global burden.[9] Seasonal variation in the incidence of ARF mimics the variation seen with GAS pharyngitis. Estimates of global burden are given in Table 40.1, although the true prevalence of ARF/RHD remains uncertain, due to the accuracy of diagnosis and lack of widespread screening programs.

ARF and RHD continue to result in the major component of GAS-related morbidity and mortality in resource-limited settings. RHD is estimated to affect more than 33 million people worldwide.[9] RHD and its associated complications (e.g., infective endocarditis, stroke) are thought to be responsible for two-thirds of the estimated 639,000 GAS-related deaths each year. The ability to identify clinically silent (subclinical) carditis with echocardiography in ARF has resulted in significant increase in detection in some areas, rates up to 10 times higher than those using auscultation alone.[10]

The incidence of APSGN appears to be declining in industrialized settings. APSGN continues to occur both sporadically and in epidemics in tropical climates where pyoderma rates are also high. Seasonal variation is similar to pyoderma, peaking in hot,

TABLE 40.1 Summary of Estimated Global Burden of GAS Diseases

Disease	Year of Publication	Number of Existing Cases	Number of New Cases Each Year	Number of Deaths Each Year
Rheumatic heart disease (RHD)	2017	33.4 million[9]		319,000[9]
	2005		282,000[2]	
History of acute rheumatic fever without carditis, requiring secondary prophylaxis[2]	2005	1.88 million	188,000*	
RHD-related infective endocarditis[29]	2016		78,000[Ω]	14,000
RHD-related stroke	2016	640,000[2]	345,000[11]	134,000[11]
	2005			
Acute post-streptococcal glomerulonephritis[2]	2005	§	472,000	9,000
Invasive group A streptococcal diseases[2]	2005		663,000	163,000
Pyoderma[6]	2015	162 million		
Pharyngitis[2]	2005		616 million	

All estimates rounded down.
*New RHD cases were calculated based on the proportion of incident acute rheumatic fever cases expected to develop RHD. The remainder of incident acute rheumatic fever cases are included in the "History of acute rheumatic fever without carditis" row. Therefore the total number of new acute rheumatic fever cases each year is 188,000 + 282,000 = 470,000
§No satisfactory data available to identify glomerulonephritis-induced chronic renal impairment or end-stage renal failure on the global scale.
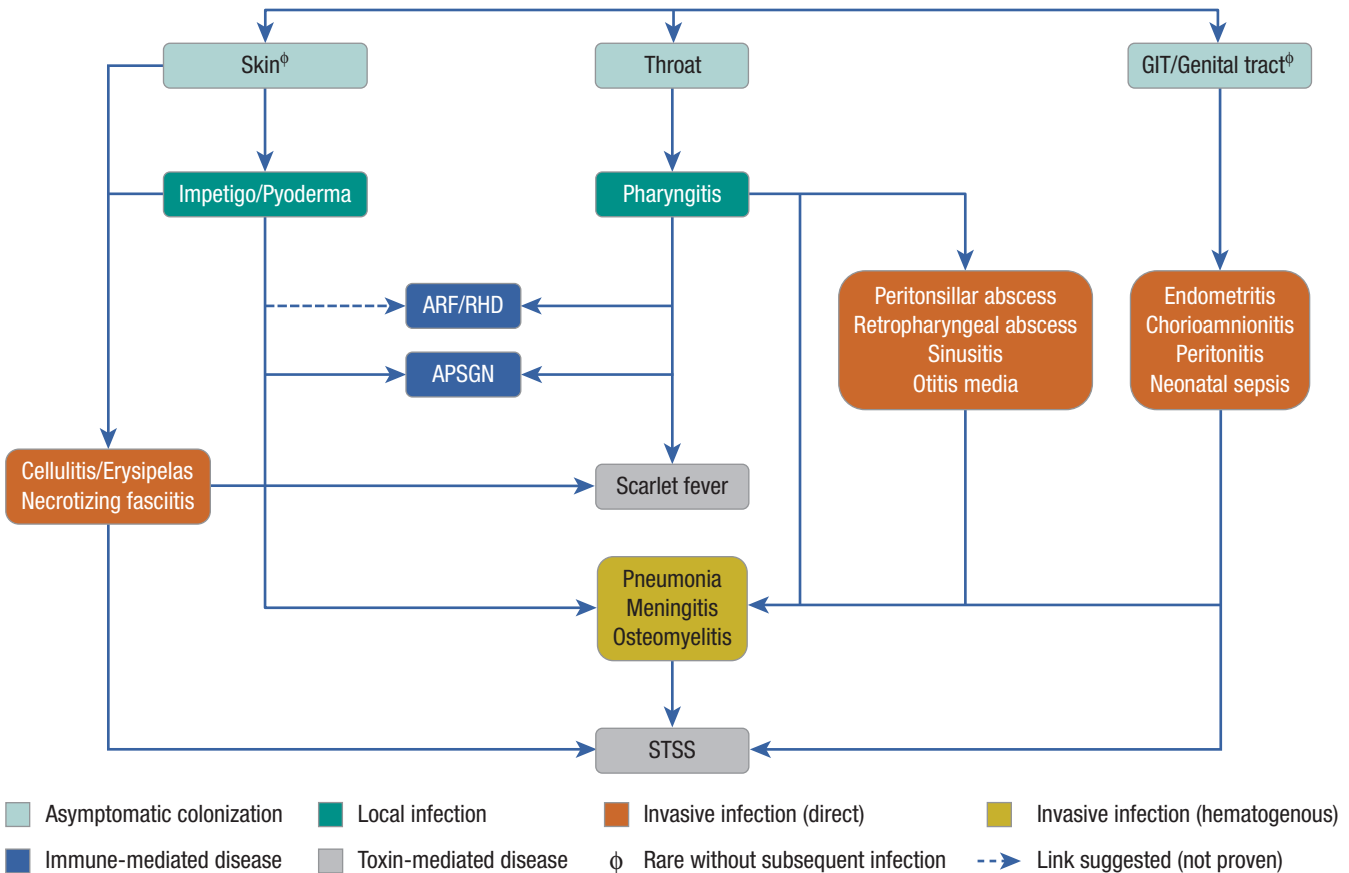Ω Inferred from relevant reference.

Fig. 40.1 The interrelated manifestations of GAS colonization and local and invasive infection, including immune-mediated and toxin-mediated syndromes. *APSGN,* Acute post-streptococcal glomerulonephritis; *ARF,* acute rheumatic fever; *GIT,* gastrointestinal system; *RHD,* rheumatic heart disease; *STSS,* streptococcal toxic shock syndrome.

humid seasons. The incidence varies considerably over time, at 6 to 239 cases per 100,000 in low-resource settings and <1 case per 100,000 in developed countries. Increasingly, studies have shown evidence that APSGN is associated with an increased albumin:creatinine ratio and a threefold increased risk of developing chronic kidney disease.[11] Mortality is approximately 1.7%.[3]

NATURAL HISTORY, PATHOGENESIS, AND PATHOLOGY

The oropharynx and the skin of humans are the only recognized ecologic niches for GAS, and they represent the major entry sites for both local and invasive infection (Fig. 40.1).[12] Surface proteins

facilitate specific adhesion of GAS to either the mucosal epithelium of the throat or skin. Asymptomatic colonization of the oropharynx may persist at low levels for weeks without eliciting a host immune response. Colonization of the skin is more transient, usually becoming established only days before inoculation (e.g., by insect bite) and subsequent pyoderma. Poor food hygiene has been responsible for several outbreaks of GAS pharyngitis in both low-resource settings and industrialized areas.[12]

Pharyngitis and pyoderma are mostly benign with spontaneous resolution usually within days. Invasion by GAS into normally sterile sites occurs less commonly, but when this occurs it may result in severe clinical manifestations arising from complex host–pathogen interactions. Viral infection, notably with measles, varicella, or influenza, is occasionally antecedent to invasive infection. The skin and throat are the main portals for entry, after which GAS evades host defenses by expressing a number of virulence factors, chief of which is M protein, which extends as hairlike filaments from the cell surface. Together with the hyaluronic acid capsule and other surface proteins, M protein enables GAS to evade phagocytosis by multiple mechanisms, including preventing opsonization by blocking complement fixation to the bacterial cell wall.[12]

Several additional cellular products appear to facilitate direct spread of the invading organism through tissue planes, potentially leading to bacteremia and hematogenous dissemination. Certain high-virulence strains of GAS secrete "super-antigens" which are able to stimulate T lymphocytes and antigen-presenting cells simultaneously, leading to overwhelming cytokine production and resultant shock seen in STSS.[12,13]

Antibodies against GAS proteins are important in providing protection against subsequent infection, in particular, those targeting serotype-specific epitopes on the M protein. However, aberrant immune responses to otherwise benign GAS infection of the throat or skin can result in the immune-mediated manifestations: ARF, RHD, and APSGN. In ARF, cross-reactive antibodies are thought to arise in genetically predisposed individuals infected with rheumatogenic GAS strains. These immune-mediated responses affect the endocardial, synovial, and neural tissue resulting in the syndrome of ARF.[12] Recent genome-wide association studies have identified an association between RHD and polymorphisms of the gene encoding the immunoglobulin heavy chain, specifically the IGHV4-61 segment in certain populations.[14] Impetigo is suspected to cause ARF, although this has not been proven. Case reports exist to support the possible link between a patient with GAS impetigo and concurrent group C *Streptococcus* (GCS) pharyngitis suffering from ARF.[15] Further work is required to clarify a definitive link between impetigo and ARF, as well as the association between group C/G *Streptococcus* and ARF, as has been noted for APSGN.

CLINICAL FEATURES

GAS pharyngitis may be mild or associated with high fever, tender anterior cervical lymphadenopathy, tonsillar exudates, and raised peripheral white cell count. Symptoms usually resolve after 3 to 5 days, although suppurative complications include peritonsillar and retropharyngeal abscess (which are now less common in industrialized settings), suppurative lymphadenitis, otitis media, mastoiditis, and meningitis. Non-suppurative complications include scarlet fever, ARF, or APSGN. Scarlet fever is characterized by a diffuse blanching rash that spreads from the chest to the abdomen and extremities, leaving a sandpaper-like texture to the skin. Desquamation of the fingers, toes, groin, and axilla occurs one or more weeks later. The tongue is frequently coated in a white film (white strawberry tongue) that eventually gives way to a beefy red appearance (red strawberry tongue). Although most cases are benign, scarlet fever was often lethal in the pre-antibiotic era. Many cases likely represented what would be regarded today as STSS.

In simple impetigo, infection is confined to the epidermis with the formation of superficial crusted lesions on the face or other exposed body parts. Especially in tropical and impoverished settings, "pyodermatous" lesions may be pustular and ulcerative, with deeper ulceration leading to ecthyma. Children are usually afebrile and otherwise well, although resolution of pyoderma may take many days and result in scarring. Erysipelas, which typically affects the face or an extremity, is a painful infection of the dermis resulting in a clearly demarcated red and raised area of inflammation and sometimes superficial bullae formation. Cellulitis involves the deeper subcutaneous tissues, causing a more diffuse and less clearly demarcated area of inflammation. Lymphangitis, infection of the draining lymphatic ducts, results in tender linear streaks extending proximally from the site of infection. Unlike impetigo, GAS cellulitis and erysipelas are often associated with fever and systemic toxicity.

Necrotizing fasciitis is a rapidly progressing infection of the subcutaneous fat, the superficial fascia, and deeper structures, including muscle. Shock, multi-organ failure, and death may ensue within hours or days of onset. Initially, the overlying skin is relatively spared, and severe escalating pain may be disproportionate to clinical findings. The skin subsequently becomes violaceous, there may be bullae formation and associated sloughing. STSS is characteristically associated with GAS necrotizing fasciitis, although it may arise in the setting of other invasive GAS infections. The case definition of STSS requires the confirmation of GAS infection, along with hypotension and two or more features of multi-organ involvement: rash, coagulopathy, acute respiratory distress syndrome, renal failure, or hepatic impairment.[16]

Otitis media, retropharyngeal and peritonsillar abscess, sinusitis, meningitis, pneumonia, bacteremia, necrotizing fasciitis, and endocarditis may arise without apparent antecedent or as a complication of tonsillopharyngitis, surgery or trauma (including burns), or varicella infection. Historically, outbreaks of GAS pneumonia were reported among previously healthy adults, although more recent reports have described the highest risk among the elderly and those with underlying medical conditions; infection in these individuals is often associated with high case fatality. A viral prodrome is often reported, although the onset of fever, chest pain, and dyspnea is characteristically rapid. GAS pneumonia may be necrotizing with pleural effusions frequently present early. Other complications include lung abscess formation, mediastinitis, and pericarditis. GAS uncommonly causes meningitis; most reports involve individuals with a pre-existing focus of GAS infection (e.g., pharyngitis, otitis media) or with other risk factors (e.g., skull defect or post-cranial surgery).[17] Puerperal sepsis caused by GAS was a frequent cause of death in the pre-antibiotic era with outbreaks resulting from nosocomial transmission. Unlike group B *Streptococcus*, GAS more commonly affects the mother than the infant, manifesting as post-partum endometritis, peritonitis, septic thrombophlebitis, or bacteremia without focus.[18] Chorioamnionitis, septic abortion, and neonatal sepsis have also been reported. A study in four tropical developing countries (Papua New Guinea, Ethiopia, the Gambia, and the Philippines) during the 1990s found that GAS was one of the three leading causes of bacteremia in newborns <90 days old, suggesting that peripartum infections remain common.[19] Similarly, GAS was the third most common cause of bacteremia in neonates (behind *Escherichia coli* and group B *Streptococcus*) in a large prospective, population-based study in Kilifi, Kenya.[20]

ARF is characterized by various combinations of fever, mono/poly arthritis or arthralgias, carditis (both clinical and sub-clinical), erythema marginatum, chorea, and subcutaneous nodules.[21] Chorea and insidious carditis can occur as a manifestation of ARF in the absence of other features. The 2015 revision of the Jones criteria now includes assessment by echocardiography to ensure that subclinical carditis is identified, as it is often not clinically evident. Severe or recurrent episodes of ARF may result in progressive

damage to the mitral valve (most commonly) and/or the aortic valve, resulting in RHD. Over several years, the valve may eventually become stenotic, resulting in subsequent atrial fibrillation and right ventricular failure. Post-streptococcal reactive arthritis describes a syndrome of polyarthritis that differs from ARF by affecting a range of smaller joints, being relatively resistant to anti-inflammatory treatment, and not being associated with carditis, although cases of ARF have been misdiagnosed as post-streptococcal reactive arthritis.[21]

APSGN can occur 1 to 2 weeks after throat infection or a few weeks after GAS skin infection. The features are hematuria (usually gross), edema, and hypertension. Severe cases can also be complicated by hypertensive encephalopathy (posterior reversible encephalopathy syndrome). The illness is generally benign in childhood, but there may be an appreciable mortality among adults as a result of renal and congestive cardiac failure.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a term used to describe some children with tic or obsessive compulsive disorders in whom symptoms appear to develop or worsen after GAS infection. The existence of PANDAS remains controversial, and studies have found no definitive link with GAS infection.[22]

PATIENT EVALUATION, DIAGNOSIS, AND DIFFERENTIAL DIAGNOSIS

Viruses account for most episodes of acute pharyngitis in all age groups. GAS is isolated in only 20% to 40% of cases of exudative pharyngitis in school-aged children and an even lower proportion of cases in younger children and adults. Recovery of the organism may represent colonization rather than infection. The distinguishing features of GAS pharyngitis and scarlet fever, and differential diagnoses, are detailed in Table 40.2.

GAS pharyngitis may be diagnosed presumptively by culturing colonies of gram-positive cocci displaying surrounding zones of beta-hemolysis on blood agar. Other beta-hemolytic streptococci may colonize the oropharynx (e.g., group C and G streptococci), and differentiation is by demonstration of growth inhibition by bacitracin or the use of commercially available group-specific antigen detection kits. Rapid antigen detection tests have been developed to allow clinicians to reliably distinguish GAS from viral pharyngitis at the point of care with good sensitivity and specificity, although this varies by test.

Staphylococcus aureus is a major cause of community-acquired pyogenic infection and an important differential diagnosis for invasive GAS infection, especially for skin, osteo-articular infections, and necrotizing pneumonia. The features that may help to distinguish GAS from *S. aureus* and other skin infections are listed in Table 40.2. In addition, a form of toxic shock syndrome may complicate *S. aureus* infection and shares many features with STSS, with the exception that it is more frequently associated with colonization by *S. aureus* rather than with invasive infection.

Invasive infections resulting from trauma or bites, exposure to water or soil, or involving immunocompromised hosts (including diabetic foot infections) may be caused by a variety of pathogens and therefore require broader empirical therapy and heightened efforts to obtain a microbiologic diagnosis to target therapy.[23]

GAS cellulitis and erysipelas are clinical diagnoses and are only occasionally confirmed by positive blood cultures. Culture of percutaneous aspirates is helpful if positive, but is usually negative. The clinical suspicion of necrotizing fasciitis or myonecrosis must be confirmed promptly by the demonstration of non-viable tissue at surgery. Imaging results are frequently non-definitive and may inadvertently delay the diagnosis and institution of appropriate treatment. GAS can usually be cultured from operative specimens, if not from blood, in patients with necrotizing fasciitis.

The arthritis of ARF may be mistaken for septic arthritis (e.g., the polyarthritis of disseminated gonococcosis or multi-focal *S. aureus* infection), rheumatologic causes of polyarthritis, and post-streptococcal reactive arthritis (see Table 40.2). ARF is the most common cause of chorea in most populations with a high incidence of ARF—particularly those in tropical, less developed

TABLE 40.2 Differential Diagnosis for Selected GAS Infections and GAS-Related Syndromes

GROUP A STREPTOCOCCUS		
Primary	Rhinoviruses Coronaviruses Adenoviruses Epstein–Barr virus (EBV) Enteroviruses Influenza A and B	• Coryza, rhinorrhea, and hoarseness are prominent features of rhinovirus and coronavirus-associated pharyngitis, which is usually non-exudative. • Adenovirus may be exudative and associated with conjunctivitis (i.e., "pharyngoconjunctival fever"). • EBV-associated pharyngitis is often part of "infectious mononucleosis" and is associated with prominent lymphadenopathy and systemic features (e.g., myalgias and atypical lymphocytosis ± elevated transaminases).
Secondary	Group C and G streptococci Cytomegalovirus (CMV) Human immunodeficiency virus (HIV) Cocksackie virus	• CMV and HIV may both cause a "mononucleosis-like" illness. • Enterovirus "herpangina" is associated with discrete ulcerative lesions of the posterior pharynx.
Other	*Arcanobacterium haemolyticus* *Neisseria gonorrhoeae* *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Corynebacterium diphtheriae* *Fusobacterium necrophorum* Herpes simplex virus (HSV) *Yersinia enterocolitica* *Francisella tularensis* Mixed anaerobes and spirochetes	• *A. haemolyticus* is more common in adolescence and associated with a pleomorphic rash affecting the extensor surfaces and spreading to the neck and trunk. • *N. gonorrhoeae* throat infection is often asymptomatic, but should be considered in sexually active individuals. • *M. pneumoniae* and *C. pneumoniae* produce pharyngitis accompanied by lower respiratory symptoms. • Diphtheria is marked by extreme toxicity and the development of a thick pharyngeal exudate. Death is commonly caused by toxin-mediated cardiac suppression or direct invasion of local structures and asphyxiation. Remains a risk in settings where vaccination programs are lacking. • Primary HSV gingivostomatitis results in ulcerative lesions of the lips, tongue, and buccal mucosa associated with fever, pain, and drooling. • Acute necrotizing ulcerative gingivitis is caused by infection with mixed anaerobes and oral spirochetes, results in painful inflammation and sloughing of the gums. Associated with limited nutrition and dental hygiene. • *F. necrophorum* is implicated in the development of Lemierre's syndrome in otherwise healthy individuals (oropharyngeal infection, sepsis, jugular vein thrombosis, septic emboli). Associated with poor response to standard therapy/deterioration. • Cocksackie virus is associated with hand-foot-and-mouth disease

TABLE 40.2 Differential Diagnosis for Selected GAS Infections and GAS-Related Syndromes—cont'd

SCARLET FEVER

Primary	Measles Rubella Roseola EBV Parvovirus B19	• Measles and rubella should be considered, especially if unvaccinated or history of recent contact. Measles is associated with prodromal conjunctivitis and coryzal symptoms and Koplik's spots. Rubella is associated with post-auricular lymphadenopathy.
Secondary	Kawasaki's disease (KD) Still's disease (SD) Enteroviruses Drug eruption Anti-convulsant hypersensitivity syndrome	• Parvovirus "fifth disease or erythema infectiosum" associated with distinctive "slapped cheek" rash of face and reticular rash of limbs appearing after fever resolution. • Roseola rash associated with defervescence and affects younger children (infants) more than scarlet fever. • KD and SD associated with multiple symptoms and prolonged fever (>5 days). KD is also associated with conjunctivitis, edema of the hands and feet, and stomatitis. SD is associated with transient or "evanescent" rash, lymphadenopathy, hepatosplenomegaly, uveitis, ± arthritis.

IMPETIGO

Primary	*Staphylococcus aureus* Group C and G beta-hemolytic streptococci Scabies Tinea	• *S. aureus* impetigo is more commonly (but not always) bullous and may co-infect with GAS in pyodermatous impetigo. • Scabies may result in crusted lesions and burrows that are itchy and involve the interdigital spaces or diffusely involve the trunk. Infestation may predispose to pyoderma. Co-infection requires concurrent treatment with scabicidal agents.
Secondary	Eczema HSV	• Tinea causes superficial, scaly, non-exudative lesions frequently with central sparing. • Eczema is itchy, often in limb flexures. • HSV presents with localized vesicles and sometimes pain, ± local lymph gland enlargement.

CELLULITIS AND ERYSIPELAS

Primary	*S. aureus* Group A/B/C/G *Streptococcus*	• *S. aureus* usually associated with clear portal of entry (e.g., wound). • Enterobacteriaceae, *Pseudomonas,* and anaerobes are more common in immunocompromised hosts (e.g., diabetic foot infections) neutropenic hosts.
Secondary	Enterobacteriaceae *Pseudomonas aeruginosa* HSV Anaerobes	• HSV associated with vesicular lesions. • *P. multocida, E. corrodens*, and anaerobes after human or animal bites • *Aeromonas* species may be rapidly progressive and associated with water exposure.
Other	*Aeromonas* species *Pasteurella multocida* *Eikenella corrodens* *Erysipelothrix rhusiopathiae* Contact dermatitis	• *E. rhusiopathiae* and contact dermatitis are not associated with toxicity and may be suspected because of distribution (e.g., on hands) and exposure history (e.g., meat worker).

NECROTIZING FASCIITIS

Primary	Polymicrobial	• Unlike other forms of necrotizing fasciitis, group A *Streptococcus* necrotizing fasciitis is rarely associated with gas formation.
Secondary	*Clostridium* spp. *S. aureus* *Vibrio vulnificus* Enterobacteriaceae spp.	• Polymicrobial infection may be associated with abdominal surgery or an occult colonic source, typically involving the perineum and abdominal wall (Fournier's gangrene) and in patients with diabetes or peripheral vascular disease. • *S. aureus* is typically associated with skin breakage. MRSA causes 10%–30% of *S. aureus* necrotizing fasciitis.
Other	*Aeromonas hydrophila* *Candida* spp. Mucormycetes	• Clostridial "gas gangrene": usually secondary to traumatic interruption of vascular supply to affected limb, colonic or obstetric origin. More frequent in drug users. • *V. vulnificus* associated with underlying illnesses and water exposure. • *Aeromonas* is associated with water. • *Candida* spp. and mucormycetes associated with immunosuppression/trauma.

ACUTE RHEUMATIC FEVER

Primary	*S. aureus* Post-streptococcal reactive arthritis (PSRA)	• *S. aureus* is usually monoarticular. Associated with sepsis and moderate-to-severe toxicity if multifocal. Effusions are purulent and usually (but not always) culture-positive.
Secondary	*N. gonorrhoeae* Juvenile idiopathic arthritis (JIA) Transient synovitis Infective endocarditis	• PSRA associated with small joints and absence of other clinical features of acute rheumatic fever or a propensity to rheumatic heart disease. A diagnosis of PSRA should rarely be made in populations with a high incidence of acute rheumatic fever, and all cases should be given at least 12 months of penicillin prophylaxis before re-evaluation.
Other	Systemic lupus erythematosus (SLE) Reactive arthritis	• *N. gonorrhoeae* may be multi-focal and migratory and must be considered if sexually active. Associated with cutaneous lesions in disseminated disease. Culture of joint fluid is frequently negative. • JIA, previously juvenile rheumatoid arthritis, is usually symmetric, non-migratory, and has a more gradual onset. Other features (e.g., iritis and serositis) may be present. • Transient synovitis more frequently occurs in younger children, affects the hips, is self-resolving, and less associated with raised inflammatory markers and fever. • SLE associated with raised antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) autoantibodies. • Reactive arthritis is associated with rash of palms and soles, conjunctivitis, and urethritis. • Infective endocarditis is diagnosed based on the modified Duke criteria.

Continued

TABLE 40.2 Differential Diagnosis for Selected GAS Infections and GAS-Related Syndromes—cont'd

ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS		

Primary	SLE
	IgA nephropathy
	Membranoproliferative
	  glomerulonephritis (MPGN)
	Rapidly progressive
	  glomerulonephritis
		• Post-streptococcal glomerulonephritis distinguished by complement profile (low C3, low CH50, normal C4) and raised streptococcal serology titers, although these may be coincidentally raised in non–post-streptococcal glomerulonephritis. Anti-streptolysin O titer (ASOT) may be normal if post-streptococcal glomerulonephritis secondary to impetigo.
		• SLE, MPGN, and glomerulonephritis of chronic disease are also associated with low C3, which resolves slowly if untreated over 8 weeks or more.

Secondary	Benign familial hematuria Henoch–Schönlein purpura Sickle cell nephropathy Subacute endocarditis	• SLE is associated with depressed C4 and other manifestations (e.g., arthritis and/or iritis), positive ANA and dsDNA autoantibodies. • MPGN presents with proteinuria, hematuria, and pyuria. Patients also have increased risk of chronic kidney disease (CKD).
Other	Hemolytic-uremic syndrome Trauma Congenital anomalies Tumor	• Glomerulonephritis of chronic disease is associated with endocarditis, chronic hepatitis B or C, syphilis, and malaria. Distinguished from post-streptococcal glomerulonephritis by other features (e.g., fever, positive blood cultures, hepatitis, etc.). • Rapidly progressive glomerulonephritis is associated with progression to end-stage renal failure. Occasionally secondary to post-streptococcal glomerulonephritis but may be secondary to SLE (ANA positive) or Wegener's granulomatosis (anti–neutrophil cytoplasmic antibody [ANCA] positive).

countries—and can occur in the absence of other features of ARF or serologic evidence of GAS infection. However, chorea may also be a manifestation of systemic lupus erythematosus, neuro-vascular disease, drugs, thyrotoxicosis, Wilson's disease, and a number of genetic neurodegenerative diseases that must also be considered, especially where ARF is uncommon.[21,24]

The diagnosis of a primary episode of ARF is based on the most recent 2015 revision of the Jones criteria (Table 40.3), which includes the use of echocardiography to evaluate for clinically silent carditis. These clinical and investigational criteria have been repeatedly revised since the original 1944 version. The criteria now require the risk stratification of an individual to either low risk (ARF incidence ≤2 per 100,000 school aged children [5–14 years old] per year, or all-age RHD prevalence of ≤1 per 1000 population per year) or moderate/high risk (ARF incidence >2 per 100,000 school aged children [5–14 years old] per year, or all-age RHD prevalence >1 per 1000 population per year). Although not essential for diagnosis, echocardiography is recommended where available, due to the rates of sub-clinical carditis.[21] The RHD diagnostic criteria with echocardiography are highly specific and beyond the scope of this chapter.

In APSGN, activation of the alternative complement pathway results in depressed serum C3 and CH50 levels (usually with a normal C4) that resolve after several weeks. Diagnosis requires the clinical picture of acute nephritis (hematuria, proteinuria, hypertension, and edema), together with evidence of recent GAS infection (culture or serology) and a compatible complement profile. Renal biopsy is reserved for atypical features, such as anuria or prolonged reduced renal function, and depressed complement that does not improve after several weeks.[25] See Table 40.2 for differential diagnoses.

TREATMENT

GAS remains universally sensitive to penicillin, which is the treatment of choice.[5,23] Although treatment failures occur, they never occur due to in vitro non-susceptibility. As penicillins target cell wall synthesis, they may be less effective in the stationary phase of bacterial growth when penicillin-binding proteins are not expressed. This is thought to occur in severe infections complicated by large bacterial loads, the Eagle effect.[12] However, in instances where alternative antibiotics may be used because of differing mechanisms of action, they are generally given as an adjunct to—rather than in replacement of—penicillin therapy. Erythromycin and the newer macrolides have been used for GAS

infection where individuals have immediate hypersensitivity to penicillin. Macrolide resistance is common in some settings and can arise abruptly, apparently related to the population level of macrolide consumption. Some mutations confer resistance to both macrolides and clindamycin, but these remain uncommon.[5]

In populations in whom ARF is now rare, antibiotics for the routine treatment of GAS pharyngitis is contentious because of the usually self-limiting nature of the illness. A Cochrane systematic review suggested that treatment of a sore throat with antibiotics reduces symptoms by 32% on day 3 and 51% on day 7, although it was noted that 82% of controls have self-resolved by day 7. It was noted that treatment decreased the risk of rheumatic fever by 73% and the risk of peritonsillar abscess by 85%; however, in low-incidence settings, the numbers needed to treat to prevent complications are likely to be very large. Therefore the aim of antibiotic treatment, if used, is alleviation of symptoms and shortening the duration of illness. Treatment of GAS pharyngitis is essential in populations with a high incidence of ARF and, if diagnostic facilities are limited, empiric treatment of all sore throat cases may be justified. The use of antibiotics to reduce the risk of subsequent APSGN is limited due to insufficient studies.[26] Treatment recommendations are detailed in Table 40.4. Ten days of twice-daily oral penicillin V or a single dose of intramuscular benzathine penicillin G (BPG) is the preferred treatment for GAS, although once-daily oral amoxicillin appears to be effective for symptom resolution and GAS eradication.[5] Short courses (up to 5 days) of macrolides have been shown to have equivalent clinical and short-term microbiologic cure rates, but the risk of late microbiologic failure may be higher. There are insufficient data regarding the efficacy of short-course or non-penicillin regimens for preventing ARF. Treatment of impetigo may be with oral, intra-muscular, or topical antibiotics, although topical treatment is discouraged in high-prevalence settings because of the rapid emergence of antimicrobial resistance. A randomized controlled trial in north Australia showed non-inferiority of short-course oral trimethoprim/sulfamethoxazole (co-trimoxazole) compared with the single-dose BPG. The co-trimoxazole group had improved clearance of staphylococci, including methicillin-resistant *S. aureus* (MRSA).[27] Options for treatment are given in Table 40.4.

Penicillin is the treatment of choice for invasive infection where GAS is confirmed or highly likely (e.g., erysipelas or perianal cellulitis). Because of the narrow spectrum of penicillin, empirical treatment before microbiologic confirmation is generally with one or more alternative antimicrobials. For example, an

TABLE 40.3 American Heart Association—2015 Revised Jones Criteria for the Diagnosis of Acute Rheumatic Fever in the Era of Doppler Echocardiography

MAJOR MANIFESTATIONS[α]	
Low Risk[β]	**Moderate/High Risk[β]**
Carditis—Clinical and/or subclinical[Ω]	Carditis—Clinical and/or subclinical[Ω]
Arthritis—Polyarthritis only	Arthritis—Monoarthritis or polyarthritis
	Polyarthralgia[‡]
Chorea[#]	Chorea[#]
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
MINOR MANIFESTATIONS[α]	
Low Risk[β]	**Moderate/High Risk[β]**
Polyarthralgia	Monoarthralgia
Fever >38.5°C	Fever >38.0°C
ESR ≥60 mm/h and/or CRP >3.0 mg/dL[Y]	ESR ≥30 mm/h and/or CRP 3.0 mg/dL[Y]
Prolonged PR interval[∞]	Prolonged PR interval[∞]
DIAGNOSIS	
Primary episode of acute rheumatic fever	Evidence of antecedent GAS infection[*] and: • Two major manifestations or • One major and two minor manifestations
Recurrent attack of acute rheumatic fever with or without evidence of RHD	Evidence of antecedent GAS infection[*] and: • Two major manifestations or • One major and two minor manifestations or • Three minor manifestations
Possible ARF	High clinical suspicion in high-risk groups, although does not fulfill strict Jones criteria; refer to guidelines

CRP, C reactive protein; *ESR,* erythrocyte sedimentation rate; *GAS,* group A *Streptococcus.*

[α]Consider differential diagnosis for all signs/symptoms.

[β]Low risk equals incidence of ≤2/100,000 school-aged children, or all-age prevalence of ≤1 per 1000 population per year. Children not clearly low risk should be classified as moderate/high risk, depending on their reference population.

[Ω]Detection of subclinical carditis requires echocardiography with strict criteria; refer to guidelines. Repeat echocardiography if initially negative and high clinical suspicion.

[‡]See guidelines regarding polyarthralgia, which 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 subcutaneous nodules are rarely "stand-alone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories, but not both in the same patient.

[#]If Sydenham (rheumatic) chorea is present, evidence of GAS infection or other criteria is not required for the diagnosis of ARF, refer to guidelines.

[Y]CRP must be elevated by local laboratory reference values. Peak ESR values should be used, as they often fluctuate.

[∞]Unless carditis is a major criteria. Correct PR interval for age.

[*]Evidence of GAS infection includes positive throat culture for GAS, RADT, increased or rising ASOT, or anti-DNAse B.

From Gewitz MH, Baltimore RS, Tani LY, et al; on behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation 2015;131:1806–1818.

anti-staphylococcal penicillin or a first-generation cephalosporin is required to cover both GAS and *S. aureus* in cellulitis (see Table 40.4). Where MRSA is prevalent, clindamycin may be acceptable, providing local MRSA strains are susceptible. Suppurative diseases frequently seen as complications of GAS infection (e.g., peritonsillar abscess) may also be caused by organisms other than GAS.[5]

As necrotizing soft tissue infections may be polymicrobial, broad-spectrum cover (e.g., with a carbapenem + clindamycin ± vancomycin) is recommended until the microbiologic cause is confirmed. Urgent and aggressive debridement of non-viable tissues has been the cornerstone of management of GAS necrotizing fasciitis, along with intensive supportive care and antibiotics.[23] Clindamycin is recommended as an adjunct to penicillin for the treatment of severe invasive GAS disease, including necrotizing infections, during the first few days of treatment. Clindamycin has multiple mechanisms of action, targeting protein synthesis as opposed to penicillin-binding proteins and exhibiting an inhibitory effect against super-antigens, thereby reducing the inflammatory response. Observational studies have demonstrated a benefit of clindamycin in reducing mortality in patients with necrotizing fasciitis.[8] In instances where clindamycin is used, penicillin should always be given unless there is a history of hypersensitivity. Although

supportive data are limited, administration of one or two doses of intravenous immunoglobulin (IVIG) early in the course of STSS is recommended. Although some studies have shown benefit of early IVIG for preventing the need for surgery in STSS, this should not delay early exploration and aggressive debridement, which remain the current recommended treatment in necrotizing fasciitis.[23] IVIG is also recommended by some as adjunctive treatment in severe invasive GAS infections, even in the absence of toxic shock.

Management of ARF is primarily symptomatic. Penicillin is generally given to eradicate colonization, although acute infection has usually passed by the time symptoms of ARF develop. Salicylates or non-steroidal anti-inflammatories are used to relieve fever and pain from arthritis, which is often severe. Where necessary, cardiac failure is managed with diuretics and angiotensin-converting enzyme (ACE) inhibitors. Steroids are sometimes used in cases of severe carditis, although there is no evidence that they improve the long-term outcome in RHD. Mitral valve repair, balloon valvuloplasty, or valve replacement may be required to manage patients with severe valve disease.[24]

Management of APSGN is based on control of hypertension with fluid restriction and use of a loop diuretic such as furosemide. ACE inhibitors may also be needed as an adjunct. Dialysis is

(n)

rarely required to manage severe hyperkalemia or symptomatic uremia.

Contacts of patients with GAS infection may be colonized with the same GAS strain, but primary prophylaxis of contacts is rarely indicated for simple GAS pharyngitis. For contacts of severe invasive GAS infection, approximately 250 people would need to be treated to prevent one severe infection, and many experts now recommend routine treatment of close contacts.[5,8] If prophylactic treatment of contacts is attempted, regimens combining rifampin with penicillin, or using alternative antibiotics such as cephalosporins or azithromycin, are usually recommended as a result of the increasing failures of penicillin alone in eradicating carriage.[5]

Regular secondary prophylaxis *is* recommended for all children and adults with previous ARF or established RHD to prevent recurrence. Current guidelines recommend intramuscular BPG four times a week for 10 years. Secondary prophylaxis is central to the management of children and adults with ARF/RHD (see Table 40.4).

During outbreaks of APSGN secondary to GAS pyoderma, community-based treatment of infected individuals and their contacts with BPG appears to decrease the transmission of nephritogenic GAS strains. In addition to treating infected individuals, reducing the transmission of GAS pyoderma in resource-limited settings is likely to require skin hygiene measures, including the control of scabies.

TABLE 40.4 Antibiotic Treatment Guidelines for Selected GAS Infections[∞]

Rationale	Medication	Evidence*	Dose	Comments
GROUP A *STREPTOCOCCUS* PHARYNGITIS				
• Prevention of ARF in moderate- to high-risk patients • Prevention of suppurative complications • Alleviation of symptoms • Prevent secondary cases	Oral phenoxymethyl penicillin (penicillin V)	1	15 mg/kg up to 500 mg q12h for 10 days	Treatment may be primarily for symptom relief unless high risk of sequelae
	IM benzathine penicillin G	1	<27 kg: 0.6 MIU once >27 kg: 1.2 MIU once	Preferred where risk of rheumatic fever is moderate/high and adherence to oral therapy not assured
	Cephalexin	1	20 mg/kg up to 500 mg q12h for 10 days	Hypersensitivity to penicillin (excluding immediate hypersensitivity)
	Oral azithromycin†	1	12 mg/kg up to 500 mg daily for 5 days	If immediate hypersensitivity to penicillin
IMPETIGO				
• Alleviate symptoms • Prevent secondary cases • Possibly prevent invasive complications • Treat scabies co-infection if present	Trimethoprim + sulfamethoxazole	1	4 + 20 mg/kg up to 160 mg + 800 mg q12h for 5 days	Alternative to BPG, also active against MRSA; use if allergy to penicillin
	IM benzathine penicillin G	1	3–6 kg: 0.3 MIU once 6–10 kg: 0.45 MIU once 10–15 kg: 0.6 MIU once 15–20 kg: 0.9 MIU once >20 kg: 1.2 MIU once[Ω]	Preferred in endemic settings where risk of APSGN is high and/or adherence to oral therapy not assured; exclude *S. aureus* infection if refractory to treatment
	Oral di/flucloxacillin	1	12.5 mg/kg up to 500 mg q6h for 10 days	First-line treatment if multiple lesions and *S. aureus* is likely
	Topical mupirocin 2% ointment	1	q8h for 7 days	For mild disease, not proven in high-endemic settings. Use saline, soap and water, or 0.1% potassium permanganate to remove crusts before applying. *S. aureus* may be or readily acquire resistance to topical antibiotics.
ERYSIPELAS AND CELLULITIS: MILD/EARLY				
• Alleviate symptoms • Prevent progression • Prevent complications	Oral di/flucloxacillin	1	12.5 mg/kg up to 500 mg q6h for 5–10 days	Switch to IV therapy if failure to respond and consider resistant pathogens (e.g., MRSA)
	Oral phenoxymethylpenicillin (penicillin V)	2	12.5 mg/kg up to 500 mg q6h for 5–10 days	If *S. aureus* is unlikely (e.g., early erysipelas or perianal cellulitis) or if GAS confirmed on culture; exclude *S. aureus* infection if refractory to treatment
	Oral cephalexin	1	12.5 mg/kg up to 500 mg q6h for 5–10 days	If non-immediate type hypersensitivity to penicillin
	Oral clindamycin	1	10 mg/kg up to 450 mg q8h for 5–10 days	If immediate type hypersensitivity to penicillin or infection with clindamycin-sensitive MRSA likely
ERYSIPELAS AND CELLULITIS: MODERATE TO SEVERE (POOR RESPONSE TO ORAL THERAPY OR SYSTEMIC FEATURES)				
• Alleviate symptoms • Prevent complications	IV di/flucloxacillin	1	50 mg/kg up to 2 g q6h	Preferred treatment unless MRSA is likely
	IV cephazolin	2	50 mg/kg up to 2 g q8h	If non-immediate type hypersensitivity to penicillin
	IV/oral clindamycin	1	15 mg/kg up to 600 mg q8h	If immediate type hypersensitivity to penicillin or infection with clindamycin-sensitive MRSA likely; oral bioavailability of clindamycin is high except in infants
	IV vancomycin	1	25 mg/kg (<2 yr use 30 mg/kg) up to 1.5 g q12h	If infection with clindamycin-resistant MRSA likely; adjust dose on basis of trough blood levels

TABLE 40.4 Antibiotic Treatment Guidelines for Selected GAS Infections—cont'd

Rationale	Medication	Evidence*	Dose	Comments
NECROTIZING FASCIITIS/STREPTOCOCCAL TOXIC SHOCK SYNDROME§				
• Prevent death • Prevent complications • Alleviate symptoms • Minimize disfigurement	IV meropenem	2	25 mg/kg up to 1 g q8h	Broad-spectrum cover is recommended in addition to surgical debridement until group A *Streptococcus* infection is confirmed; thereafter penicillin + clindamycin is recommended
	+ IV clindamycin until stabilized	1	15 mg/kg up to 600 mg q8h	Use as an adjunct to meropenem or penicillin if GAS infection is suspected or confirmed
	+ IV vancomycin	2	25 mg/kg (<12 yr use 30 mg/kg) up to 1.5 g q12h	If infection with MRSA is suspected; adjust dose on basis of trough blood levels
	+ intravenous immunoglobulin (IVIG)	2	1 g/kg as an immediate infusion, repeat on days 2 + 3 at 0.5 g/kg or 2 g/kg as a single dose	Adjunct to penicillin and clindamycin therapy ± debridement as recommended earlier for necrotizing fasciitis; dosage recommendations vary; see expert advice
	IV benzylpenicillin	2	50 mg/kg up to 1.8 g q4h^	If GAS infection is confirmed
	IV cephazolin	5	50 mg/kg up to 2 g q8h	If GAS confirmed and non-immediate type hypersensitivity to penicillin; if there is a history of immediate-type hypersensitivity to β-lactams, seek expert advice
ACUTE RHEUMATIC FEVER: TREATMENT				
• Alleviate symptoms • Prevent death from acute cardiac failure	Aspirin	1	50–100 mg/kg/day (up to 4–8 g/day) in 4–5 divided doses	For the control of pain of acute rheumatic fever arthritis; duration dependent on clinical response
	Naproxen	1	10–20 mg/kg/day in 2 divided doses (max 1250 mg/day)	For the control of pain of acute rheumatic fever arthritis; duration dependent on clinical response
	IM benzathine penicillin G (BPG)	5	<20 kg: 0.6 MIU as a single dose ≥20 kg: 1.2 MIU as a single dose^Ω	Preferred where adherence to oral therapy not assured; treatment should focus on pain relief with salicylates and management of cardiac failure
	Oral phenoxymethylpenicillin (penicillin V)	5	250 mg q12h for 10 days	An acceptable alternative to BPG if adherence can be assured (e.g., in hospital)
	Oral prednisolone	5	1–2 mg/kg/day (up to 80 mg/day)	Not routinely recommended for carditis, but may be considered for severe carditis if surgery is not an option; some evidence of benefit in refractory chorea
	Carbamazepine	3	7–10 mg/kg/day in 3 divided doses	Not routinely recommended for management of chorea, but may be considered in severe cases
ACUTE RHEUMATIC FEVER: PROPHYLAXIS				
• Prevent further episodes of ARF • Prevent progressive carditis	IM benzathine penicillin G	1	<20 kg: 0.6 MIU ≥20 kg: 1.2 MIU every 3–4 weekly^Ω	Preferred regimen; Four-weekly injections should be continued for at least 10 yr and patient at least 21 years old; established valve disease may necessitate longer duration. Refer to local guidelines
	Oral phenoxymethyl penicillin (penicillin V)	1	250 mg q12h	Associated with inferior adherence; only where IM injections are refused or risk of progressive carditis very low
	Oral erythromycin†	5	250 mg q12h	If hypersensitive to penicillin; dose for erythromycin ethyl succinate is 400 mg q12h

*Level of evidence: 1 = randomized controlled trial, 2 = comparative clinical study >20 patients, 3 = comparative clinical study <20 patients, 4 = case series, 5 = expert opinion on basis of in vitro data or animal studies.
†Variable rates of streptococcal resistance are reported.
§If indicated, IVIG should be administered as early as possible.
^In all cases, consult local guidelines for specific advice.
Ω Australian Guidelines.
^600mg = 1 MIU.
MIU, Million international units.

Work continues on the development of a vaccine targeted against GAS, the most advanced of the current candidates is a multi-valent vaccine containing 30 of the most common GAS *emm* types encountered in North America and Europe, which is currently undergoing clinical trials. There is a limited match between these strains and prevalent *emm* types in Africa and the Pacific, where *emm* types are more variable, but potential serotype cross-reactivity may provide broader strain protection. Other candidate vaccines, containing antigens conserved among most, or all, GAS strains, are approaching clinical trial phase.[28]

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