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INTRODUCTION

Group A Streptococcus causes a diverse spectrum of disease, ranging from benign and self-limited infection of the throat or skin, to lethal soft tissue infections accompanied by multi-organ failure. Until the advent of the antibiotic era, Group A Streptococcus was a major cause of death in industrialized countries as a result of sepsis, rheumatic heart disease and fatal epidemics of scarlet fever [1, 2]. The 1980s saw an increase in rheumatic fever cases in the Rocky Mountain states of the USA, along with an apparent resurgence in severe Group A Streptococcus disease in industrialized countries. The resultant increased attention paid to Group A Streptococcus disease in recent years has also brought to focus the continuing high burden of Group A Streptococcus disease in developing countries, particularly those in tropical regions [3].

EPIDEMIOLOGY

The burden of all Group A Streptococcus infections is highest in resource-limited settings, most of which are in tropical regions. It is assumed that the major reasons for this relate to poverty, overcrowded living conditions and limited access to medical care, although geography and climate may also play a role. The estimated number of cases and deaths of Group A Streptococcus diseases is shown in Table 36-1. Of the more severe diseases, 79% of rheumatic heart disease cases, 95% of acute rheumatic fever cases, 97% of acute post-streptococcal glomerulonephritis cases and 97% of invasive Group A Streptococcus cases come from less developed countries [3].

Pharyngitis is the most common manifestation of Group A Streptococcus disease—its incidence is highest in school-aged children. One episode occurs every 1–2 child years in some resource-limited settings, while only 1 episode every 7–8 child years has been observed in developed urban settings. Limited data on the incidence of Group A Streptococcus pharyngitis in tropical areas suggest significant variability, with rates comparable to temperate climates in some settings but, in others, the documented rate is considerably lower. Transmission is higher in winter months. Impetigo is common in childhood; transmission occurs readily in school and preschool care settings, especially in the summer months. In tropical settings where the burden is particularly high, the majority of children in some communities have impetigo at any one time.

Cellulitis and erysipelas are the most frequent manifestations of invasive Group A Streptococcus infection and, in contrast to pharyngitis and impetigo, incidence increases with age. In the mid-1980s, reports emerged from industrialized countries of both increasing numbers of severe necrotizing Group A Streptococcus infections and of streptococcal toxic shock syndrome [4]. Group A Streptococcus strains belonging to emm types 1 and 3, in particular, have been implicated in this rise. Most cases of severe invasive Group A Streptococcus disease are sporadic, but secondary cases and case clusters have been reported. Limited data suggest that both the incidence and case-fatality of invasive Group A Streptococcus disease in resource-limited countries is several-fold higher than in industrialized countries.

Acute rheumatic fever and rheumatic heart disease continue to result in a substantial component of Group A Streptococcus-related morbidity and mortality in resource-limited settings. Of the 517,000 Group A Streptococcus-related deaths each year, it is estimated that two thirds are caused by rheumatic heart disease or its complications [3]. The true prevalence of rheumatic heart disease remains uncertain, with estimates of at least 1.3 per 1000 school-aged children in developing countries based on auscultatory screening, while estimates based on echocardiography suggest the true prevalence may be more than 10 times higher [5]. Acute rheumatic fever has become uncommon in industrialized settings, although the incidence remains high among indigenous populations in Australia and New Zealand.

The incidence of acute post-streptococcal glomerulonephritis appears to be declining in industrialized settings, but sporadic cases still occur. Acute post-streptococcal glomerulonephritis continues to occur both sporadically and in epidemics in tropical climates (where Group A Streptococcus pyoderma is also common); limited data suggest that acute mortality and chronic morbidity from acute post-streptococcal glomerulonephritis may be higher in developing settings.

NATURAL HISTORY, PATHOGENESIS AND PATHOLOGY

The oropharynx and the skin of humans are the only recognized ecologic niches for Group A Streptococcus and they represent the major entry sites for both local and invasive infection [6] (see Fig. 36.1). Up to 20% of school-aged children may be colonized in the oropharynx in temperate and some tropical regions, although in many tropical settings, less than 5% of children carry Group A Streptococcus (with groups C and G streptococci being more common). Surface proteins facilitate specific adhesion of Group A Streptococcus to either the mucosal epithelium of the throat or to the skin (or both).
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, becoming established only days before inoculation (e.g. by insect bite) and subsequent pyoderma. Local infection of the oropharynx (pharyngitis) or skin (pyoderma) is mostly benign with spontaneous resolution usually within days. Invasion of Group A *Streptococcus* into normally sterile sites occurs less commonly, but is often severe with clinical manifestations arising from complex host-pathogen interactions. Preceding viral infection, in particular with varicella or influenza A, has been implicated as a frequent antecedent to invasive infection. The skin and throat are frequent antecedent to invasive infection. The skin and throat are the major portals for entry, after which Group A *Streptococcus* evades host defenses by elaborating a number of virulence factors, chief of which is M protein that extends as hair-like filaments from the cell surface. M protein (together with the hyaluronic acid capsule and other surface proteins) enables Group A *Streptococcus* to evade phagocytosis by multiple mechanisms, including preventing opsonization by blocking complement fixation to the bacterial cell wall.

A number of additional cellular products appear to facilitate direct spread of the invading organism through tissue planes and bacteria can result in hematogenous dissemination. Some strains have the capacity to elaborate pyrogenic exotoxins that may act as "superantigens", leading to polyclonal proliferation of subsets of T lymphocytes, massive cytokine production and shock [7].

Antibodies against Group A *Streptococcus* proteins (in particular antibodies against serotype-specific epitopes on the M protein) are important in providing protection against subsequent infection. However, aberrant immune responses to otherwise benign Group A *Streptococcus* pharyngitis or impetigo can result in the immune-mediated manifestations, acute rheumatic fever and acute post-streptococcal glomerulonephritis. In acute rheumatic fever, cross-reactive antibodies are thought to arise in genetically predisposed individuals infected with rheumatogenic Group A *Streptococcus* strains. These strains elicit immune responses to antigens with a similarity between epitopes on the M protein and certain host proteins contained within endocardial, synovium and neural tissues.

### CLINICAL FEATURES

Group A *Streptococcus* 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 3–5 days, although suppurrative complications (which are now uncommon in industrialized settings) include peritonsillar and retropharyngeal abscess, suppurative lymphadenitis, otitis media, mastoiditis and meningitis. Non-suppurative complications include scarlet fever, acute rheumatic fever or acute post-streptococcal glomerulonephritis. 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). While most cases are benign, scarlet fever was often lethal in the pre-antibiotic era. Many cases likely represented what would be regarded today as streptococcal toxic shock syndrome (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. In tropical and impoverished settings "pyodermatous" lesions may be pustular and ulcerative. 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 often formation of superficial bullae. Cellulitis involves the deeper subcutaneous tissues causing a more diffuse and less clearly demarcated area of inflammation. Infection of the draining lymphatic tracts (lymphangitis) results in tender linear streaks extending from the site of infection. Unlike impetigo, cellulitis and erysipelas are usually 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 and bullae may form and then slough. STSS is characteristically associated with Group A Streptococcus necrotizing fasciitis, although it may arise in the setting of other invasive Group A Streptococcus infections. The case definition of STSS requires the confirmation of Group A Streptococcus infection, along with hypotension and two or more features of multi-organ involvement: rash, coagulopathy, respiratory distress syndrome, renal failure or hepatic impairment [8].

Otitis media, retropharyngeal and peritonsillar abscess, sinusitis, meningitis, pneumonia, bacteremia and endocarditis may arise either as a complication of tonsillopharyngitis, following surgery or trauma (including burns), following varicella infection, or without apparent antecedent. Historically, outbreaks of Group A Streptococcus pneumonia were reported among previously healthy adults, although more recent reports have described the highest risk amongst the elderly and those with underlying medical conditions; infection in these individuals is often associated with high case fatality [9]. A viral prodrome is often reported, although the onset of fever, chest pain and dyspnea is characteristically rapid. Group A Streptococcus pneumonia may be necrotizing with pleural effusions frequently present early and early complications include lung abscess formation, mediastinitis and pericarditis. Group A Streptococcus is an uncommon cause of meningitis in children and adults, with most reports arising in individuals with a pre-existing focus of Group A Streptococcus infection (e.g. pharyngitis, otitis media) or with other risk factors (e.g. skull defect or post-cranial surgery) [10]. Puerperal sepsis caused by Group A Streptococcus was a frequent cause of death in the pre-antibiotic era with outbreaks resulting from nosocomial transmission. A study in four tropical developing countries (Papua New Guinea, Ethiopia, The Gambia and The Philippines) during the 1990s found that Group A Streptococcus was one of the three leading causes of bacteremia in children aged <90 days, suggesting that Group A Streptococcus puerperal sepsis and septic abortion remain common in less developed, tropical countries [11]. Unlike Group B Streptococcus, Group A Streptococcus more commonly affects the mother than the infant, manifesting as post-partum endometritis, peritonitis, septic thrombophlebitis or bacteremia without focus [12]. However, chorioamnionitis and neonatal sepsis are also reported.

Acute rheumatic fever is characterized by various combinations of fever, polyarthritides or arthralgias, carditis, characteristic rash (erythema marginatum), chorea and subcutaneous nodules [13] (Table 36-3). Chorea and insidious carditis can occur as a manifestation of acute rheumatic fever in the absence of other features. Severe or recurrent episodes of acute rheumatic fever may result in progressive damage to the mitral valve (and sometimes the aortic valve) resulting in incompetence and progressive heart failure (rheumatic heart disease). Over several years, the valve may eventually become stenotic. Acute post-streptococcal glomerulonephritis can occur 1–2 weeks after

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**FIGURE 36.1** The inter-related manifestations of Group A Streptococcus colonization and local and invasive infection, including immune-mediated and toxin-mediated syndromes. ARF, acute rheumatic fever; RHD, rheumatic heart disease.
throat infection or a few weeks after Group A Streptococcus skin infection. The features are hematuria (microscopic or gross), edema (which may be most evident peri-orbitally) and hypertension. Severe cases can also be complicated by encephalopathy. 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 following Group A Streptococcus infection. The existence of PANDAS is controversial [14]. Post-streptococcal reactive arthritis describes a syndrome of polyarthritis that differs from acute rheumatic fever by affecting a range of smaller joints, being relatively resistant to anti-inflammatory treatment and not being associated with carditis, although cases of acute rheumatic fever have been misdiagnosed as post-streptococcal reactive arthritis [15, 16].

PATIENT EVALUATION, DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Viruses account for most episodes of acute pharyngitis in all age groups. Group A Streptococcus is isolated in only 20–40% 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 not represent infection, but colonization. The distinguishing features of Group A Streptococcus pharyngitis and scarlet fever, and differential diagnoses, are detailed in Table 36-2.

Streptococcus aureus is a major cause of community-acquired pyogenic infection and an important differential diagnosis for invasive Group A Streptococcus infection, especially for skin and osteoarticular infections and necrotizing pneumonia. The features which may help to distinguish Group A Streptococcus from S. aureus and other skin infections are listed in Table 36-2. In addition, a form of toxic shock syndrome (TSS) may complicate S. aureus infection, and shares many features with STSS with the exception that it is more frequently associated with colonization rather than bacteremia or severe underlying 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 more expanded array of pathogens and therefore require broader empirical therapy and heightened efforts to obtain a microbiologic diagnosis [17].

The arthritis of acute rheumatic fever may be mistaken for septic arthritis (e.g., the polyarthritides of disseminated gonococcosis or multifocal S. aureus infection), rheumatologic causes of polyarthritis, including juvenile rheumatoid arthritis, and post-streptococcal reactive arthritis (see Table 36-2). Acute rheumatic fever is the most common cause of chorea in most populations with a high incidence of acute rheumatic fever—particularly those in tropical, less-developed countries—and can occur in the absence of other features of acute rheumatic fever or serologic evidence of Group A Streptococcus infection. However, chorea may also be a manifestation of systemic lupus erythematosus, neurovascular disease, drugs, thyrotoxicosis, Wilson’s disease and a number of genetic neurodegenerative diseases that must be considered, especially where acute rheumatic fever is uncommon.

Group A Streptococcus pharyngitis may be diagnosed presumptively by culturing colonies of Gram-positive cocci displaying surrounding hyaline zones and susceptibility to the group A carbohydrate.

### Table 36-2: Differential Diagnosis for Selected Group A Streptococcus Infections and Group A Streptococcus-Related Syndromes

| Group A Streptococcus pharyngitis | 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
| CMV and HIV may both cause a “mononucleosis-like” illness
| HIV seroconversion illness may occur in the window period before ELISA tests become positive
| Enterovirus “herpangina” is associated with discrete ulcerative lesions of the posterior pharynx
| Group C and G streptococci are not thought to cause acute rheumatic fever or acute post-streptococcal glomerulonephritis
| Arcanobacterium haemolyticum is more common in adolescence and associated with a pleomorphic rash affecting the extensor surfaces and spreading to the neck and trunk
| Neisseria gonorrhoeae throat infection is more frequently asymptomatic, but should be considered in sexually active individuals
| Mycoplasma 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 programmes are poorly established or have been interrupted
| 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

| Primary Rhinoviruses
| Coronavirus
| Adenoviruses
| Epstein-Barr virus (EBV)
| Enteroviruses

| Secondary Group C and G streptococci
| Cytomegalovirus (CMV)
| Human immunodeficiency virus (HIV)

| Other Arcanobacterium haemolyticum
| Neisseria gonorrhoeae
| Mycoplasma pneumoniae
| Chlamydia pneumoniae
| Corynebacterium diphtheriae
| Herpes Simplex Virus (HSV)
| Yersinia enterocolitica
| Francisella tularensis
| Mixed anaerobes and spirochetes
### Scarlet fever

**Primary**
- Measles
- Rubella
- Roseola
- EBV
- Parvovirus B19

**Secondary**
- Kawasaki disease
- Still's disease
- Enteroviruses
- Drug eruption
- Anticonvulsant hypersensitivity syndrome

- 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 spots. Rubella is associated with post-auricular lymphadenopathy
- 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
- Kawasaki disease (KD) and Still's disease (SD; systemic-onset juvenile rheumatoid arthritis) 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

**Secondary**
- Kawasaki disease
- Still's disease
- Enteroviruses
- Drug eruption
- Anticonvulsant hypersensitivity syndrome

**Other**
- *Staphylococcus aureus* impetigo is more commonly (but not always) bullous and may co-infect with Group A *Streptococcus* in pyodermatous impetigo
- Non-group A beta-hemolytic streptococci may cause clinically indistinguishable lesions to Group A Streptococci, but are not associated with acute rheumatic fever or acute post-streptococcal glomerulonephritis
- Scabies may result in crusted lesions and burrows that are itchy and involve the interdigital spaces or diffusely involving the trunk. Infestation may predispose to pyoderma
- Tinea causes superficial scaly non-exudative lesions frequently with central sparing

### Cellulitis and erysipelas

**Primary**
- *S. aureus*
- Group B, C and G *Streptococcus*

**Secondary**
- Enterobacteriacae
- *Pseudomonas aeruginosa*
- HSV
- Anaerobes

**Other**
- *Aeromonas* species
- *Pasteurella multocida*
- *Eikenella corrodens*
- *Erysipelothrix rhusiopathiae*
- *Contact dermatitis*

**Other**
- *Staphylococcus aureus* usually associated with clear portal of entry, e.g. wound
- Enterobacteriacae, pseudomonas and anaerobes more common in immunocompromised hosts, e.g. diabetic foot infections, neutropenic hosts
- HSV associated with vesicular lesions
- *Pasteurella multocida*, *E. corrodens* and anaerobes following human or animal bites
- *Aeromonas* species may be rapidly progressive and associated with water exposure
- *Erysipelothrix 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
- Clostridium perfringens

**Secondary**
- *Vibrio vulnificus*

**Other**
- *Clostridium septicum*

**Other**
- Unlike other forms of necrotizing fasciitis, Group A *Streptococcus* necrotizing fasciitis is rarely associated with gas formation
- 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
- Clostridial "gas gangrene": usually secondary to traumatic interruption of vascular supply to affected limb or a colonic pathology in case of *C. septicum*
- *Vibrio vulnificus* associated with underlying illnesses and water exposure
zones of beta-hemolysis on blood agar. Other beta-hemolytic streptococci may colonize the oropharynx (e.g. Group C and G streptococci), and differentiation requires the demonstration of growth inhibition by bacitracin or the use of commercially available, group-specific antigen detection kits. Rapid diagnostic tests have been developed to allow clinicians to reliably distinguish Group A *Streptococcus* from viral pharyngitis at the point of care. Evaluations of these tests suggested variable sensitivity of earlier generation kits (~85%), but improved sensitivity of later-generation optical immunoassay-based kits and good specificity.

Group A *Streptococcus* cellulitis and erysipelas are clinical diagnoses that 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 nonviable tissue at surgery. Imaging results are frequently nondefinitive and may inadvertently delay the diagnosis and institution of appropriate treatment. Group A *Streptococcus* can usually be cultured from operative specimens, if not from blood in patients with necrotizing fasciitis.

The diagnosis of a primary episode of acute rheumatic fever is based on the most recent version of the Jones’ criteria—currently the 1992 version (Table 36-3). These clinical and investigational criteria have been repeatedly revised since the original 1944 version to maintain their sensitivity and negative predictive value but decreasing their positive predictive value in settings where incidence is decreasing. As a result, some high-burden settings have chosen to modify the revised criteria to retain their sensitivity and negative predictive value [18].

In acute post-streptococcal glomerulonephritis, activation of the alternative complement pathway results in a depressed C3 level (usually <0.7 mg/dL) and moderate-to-severe toxicity if multifocal. Effusions are purulent and usually (but not always) culture-positive. 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. *Neisseria gonorrhoeae* may be multifocal and migratory, and must be considered if sexually active. Also associated with cutaneous lesions in disseminated disease. Culture of joint fluid is frequently negative. *Streptococcus* and serositis, may be present.

| TABLE 36-2 | Differential Diagnosis for Selected Group A *Streptococcus* Infections and Group A *Streptococcus*-Related Syndromes—cont’d |
|---|---|
| **Acute rheumatic fever** |  |
| **Primary** | *S. aureus*  
Post-streptococcal reactive arthritis (PSRA)  
*Staphylococcus aureus* is usually monarticular. Associated with sepsis and moderate-to-severe toxicity if multifocal. Effusions are purulent and usually (but not always) culture-positive  
*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  
*Neisseria gonorrhoeae* may be multifocal and migratory, and must be considered if sexually active. Also associated with cutaneous lesions in disseminated disease. Culture of joint fluid is frequently negative  
Juvenile rheumatoid arthritis (JRA) arthritis is usually symmetrical, non-migratory and has a more gradual onset. Other features, e.g. iritis and serositis, may be present  
Transient synovitis more frequent 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 and dsDNA  
Reactive arthritis is associated with rash of palms and soles, conjunctivitis and urethritis |
| **Secondary** | *N. gonorrhoeae*  
Rheumatoid arthritis  
Transient synovitis  
*Post-streptococcal* glomerulonephritis distinguished by complement profile (low C3, normal C4) and raised streptococcal serology titers, although these may be coincidentally raised in non-post-streptococcal glomerulonephritis. Also anti-streptolysin O titer (ANA) may be normal if post-streptococcal glomerulonephritis secondary to impetigo  
*SLE*, MCGN and glomerulonephritides of chronic disease are also associated with low C3 which resolves only slowly if untreated (8 weeks or more)  
*SLE* is associated with depressed C4 and other manifestations, e.g. arthritis and/or iritis, positive antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) autoantibodies  
MCGN more frequently associated with heavy proteinuria and nephrotic syndrome  
Glomerulonephritides of chronic disease is associated with endocarditis, chronic hepatitis B or C, syphilis and malaria. Distinguished from post-streptococcal glomerulonephritides 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 (antineutrophil cytoplasmic antibody (ANCA) positive)  |
| **Other** | Systemic lupus erythematosus (SLE)  
Reactive arthritis  
*SLE* associated with depressed C4 and other manifestations, e.g. arthritis and/or iritis, positive antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) autoantibodies  
MCGN more frequently associated with heavy proteinuria and nephrotic syndrome  
Glomerulonephritides of chronic disease is associated with endocarditis, chronic hepatitis B or C, syphilis and malaria. Distinguished from post-streptococcal glomerulonephritides 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 (antineutrophil cytoplasmic antibody (ANCA) positive)  |
| **Acute post-streptococcal glomerulonephritis** |  |
| **Primary** | SLE  
IgA nephropathy  
Mesangiocapillary glomerulonephritis (MCGN)  
Rapidly progressive glomerulonephritis  
Post-streptococcal glomerulonephritis distinguished by complement profile (low C3, normal C4) and raised streptococcal serology titers, although these may be coincidentally raised in non-post-streptococcal glomerulonephritis. Also anti-streptolysin O titer (ANA) may be normal if post-streptococcal glomerulonephritis secondary to impetigo  
*SLE*, MCGN and glomerulonephritides of chronic disease are also associated with low C3 which resolves only slowly if untreated (8 weeks or more)  
*SLE* is associated with depressed C4 and other manifestations, e.g. arthritis and/or iritis, positive antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) autoantibodies  
MCGN more frequently associated with heavy proteinuria and nephrotic syndrome  
Glomerulonephritides of chronic disease is associated with endocarditis, chronic hepatitis B or C, syphilis and malaria. Distinguished from post-streptococcal glomerulonephritides 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 (antineutrophil cytoplasmic antibody (ANCA) positive)  |
| **Secondary** | Benign familial hematuria  
Henoch Schönlein purpura  
Sickle cell nephropathy  
Subacute endocarditis  
*Benign familial hematuria*  
*Henoch Schönlein purpura*  
*Sickle cell nephropathy*  
*Subacute endocarditis*  
*SLE* associated with depressed C4 and other manifestations, e.g. arthritis and/or iritis, positive antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) autoantibodies  
MCGN more frequently associated with heavy proteinuria and nephrotic syndrome  
Glomerulonephritides of chronic disease is associated with endocarditis, chronic hepatitis B or C, syphilis and malaria. Distinguished from post-streptococcal glomerulonephritides 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 (antineutrophil cytoplasmic antibody (ANCA) positive)  |
| **Other** | Hemolytic-uremic syndrome  
Trauma  
Congenital anomalies  
Tumor  
Hemolytic-uremic syndrome  
Trauma  
Congenital anomalies  
Tumor  
SLE is associated with depressed C4 and other manifestations, e.g. arthritis and/or iritis, positive antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) autoantibodies  
MCGN more frequently associated with heavy proteinuria and nephrotic syndrome  
Glomerulonephritides of chronic disease is associated with endocarditis, chronic hepatitis B or C, syphilis and malaria. Distinguished from post-streptococcal glomerulonephritides 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 (antineutrophil cytoplasmic antibody (ANCA) positive)  |
The use of antibiotics for the routine treatment of Group A Streptococcus pharyngitis is contentious because of the usually self-limiting nature of the illness. Studies suggest that treatment reduces the average duration of sore throat by 16 hours and decreases the risk of rheumatic fever and otitis media by around 70%, and the risk of peritonsillar abscess by around 85% [20]. In low-incidence settings, the numbers needed to treat to prevent complications is likely to be very large, so the main aim of antibiotic treatment, if chosen to be used, is alleviation of symptoms and shortening of the duration of illness. However, antibiotic treatment of Group A Streptococcus pharyngitis is essential in populations with a high incidence of acute rheumatic fever and, if diagnostic facilities are limited, empirical treatment of all sore throat cases may be justified. There is little evidence that antibiotics reduce the risk of subsequent acute post-streptococcal glomerulonephritis.

Treatment recommendations are detailed in Table 36-4. Ten days of twice-daily oral penicillin V or a single dose of intramuscular benzathine penicillin G are the preferred treatment for Group A Streptococcus pharyngitis, although once-daily oral amoxicillin appears to be effective for symptom resolution and Group A Streptococcus eradication [21]. Short courses (up to 5 days) of macrolides and some cephalosporins 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 in preventing acute rheumatic fever. Treatment of impetigo may be with oral or topical antibiotics—options are given in Table 36-4.

Penicillin is the treatment of choice for invasive infection where Group A Streptococcus is confirmed or highly likely (e.g. erysipelas or perianal cellulitis). Because of the narrow spectrum of penicillin, empirical treatment prior to microbiologic confirmation is generally with one or more alternative antimicrobials. For example, an anti-staphylococcal penicillin or a first-generation cephalosporin is required to cover both Group A Streptococcus and S. aureus in cellulitis (see Table 36-4). Where methicillin-resistant S. aureus (MRSA) is prevalent, clindamycin may be an acceptable alternative if prevailing MRSA strains are susceptible. Some complications or invasive diseases frequently seen as complications of Group A Streptococcus infection (e.g. peritonsillar abscess) may also be caused by organisms other than Group A Streptococcus.

As necrotizing soft tissue infections may be polymicrobial, broad-spectrum cover (e.g. with a carbapenem) is recommended until the microbiologic cause is confirmed.

Urgent and aggressive debridement of nonviable tissues has been the cornerstone of management of Group A Streptococcus necrotizing fasciitis, along with intensive supportive care and antibiotics. However, some authorities have suggested that a less aggressive approach may be acceptable if antibiotics and adjunctive therapy with intravenous immunoglobulin (IVIG) are instituted early [22]. Clindamycin is recommended as an adjunct to penicillin for the treatment of severe invasive Group A Streptococcus disease, including necrotizing infections, during the first few days of treatment—this is supported by the superior activity of clindamycin over penicillin in animal models [19]. However, penicillin should always be given unless there is a history of hypersensitivity. Although supportive data are limited, administration of 1 or 2 doses of IVIG early in the course of STSS is widely recommended. A multicenter, randomized, controlled trial revealed a trend toward a reduction in mortality among recipients, but the study was terminated early because of slow recruitment [23]. IVIG is also recommended by some as adjunctive treatment in severe invasive Group A Streptococcus infections, even in the absence of toxic shock.

**TABLE 36-3** World Health Organization 2002–2003 Criteria for the Diagnosis of Rheumatic Fever and Rheumatic Heart Disease

| Major manifestations | Carditis  
Polyarthritis  
Chorea  
Erythema marginatum  
Subcutaneous nodules |
|----------------------|--------------------------------------------------------|
| Minor manifestations | Clinical: Arthralgia Fever  
Laboratory: Elevated acute phase reactants (ESR, leukocyte count)  
ECG: Prolonged PR interval |
| Evidence of antecedent Group A Streptococcus infection | Elevated or rising streptococcal antibody titers (anti-streptolysin O or anti-DNase B titer)  
Positive throat culture or rapid streptococcal antigen test  
Recent scarlet fever |
| Diagnostic categories: | Primary episode of acute rheumatic fever  
Two major manifestations, or one major and two minor manifestations plus evidence of antecedent Group A Streptococcus infection |
| | Recurrent attack of acute rheumatic fever in a patient with established rheumatic heart disease  
Two major manifestations plus evidence of antecedent Group A Streptococcus infection |
| | Recurrent attack of acute rheumatic fever in a patient with established rheumatic heart disease  
Two major manifestations, or one major and two minor manifestations plus evidence of antecedent Group A Streptococcus infection |
| | Rheumatic chorea  
Insidious onset rheumatic carditis |
| | Chronic valve lesions of rheumatic heart disease (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve disease) |

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**TREATMENT**

Penicillin remains the antibiotic of choice for most Group A Streptococcus infections. Group A Streptococcus remains universally sensitive to penicillin and, while treatment failures occur, they invariably relate to lack of *in vivo* efficacy rather than *in vitro* non-susceptibility. As penicillins target cell wall synthesis, they may be less effective in the stationary phase of bacterial growth as they may occur in severe infections complicated by large bacterial loads [19]. However, even in instances where alternative antibiotics may be preferred because of differing mechanisms of action, they are generally used as an adjunct to—rather than in replacement of—penicillin therapy. Erythromycin and the newer macrolides have been used for Group A Streptococcus disease 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.
### TABLE 36-4  Antibiotic Treatment Guidelines for Selected Group A Streptococcus Infections

| Rationale                                                                 | Medication                  | Evidence* | Dose                                                                 | Comments                                                                                                                                                                                                 |
|--------------------------------------------------------------------------|-----------------------------|-----------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Group A Streptococcus pharyngitis**                                    |                             |           |                                                                     |                                                                                                                                            |
| Prevention of acute rheumatic fever in moderate-to-high endemic settings | Oral phenoxymethylpenicillin (penicillin V) | 1         | 10 mg/kg up to 500 mg BD for 10 days                                | Treatment may be primarily for symptom alleviation unless the risk of sequelae is high                                                                                                                  |
| Prevention of suppurative complications                                  | Oral amoxicillin            | 1         | ≤30 kg: 750 mg daily for 10 days >30 kg: 1500 mg daily for 10 days   | Not proven to prevent acute rheumatic fever                                                                                                                                                           |
| Alleviation of symptoms                                                  | IM benzathine penicillin    | 1         | 3–6kg: 225 mg 6–10kg: 337.5 mg 10–15kg: 450 mg 15–20kg: 675 mg 20+ kg: 900 mg as a single dose | Preferred where risk of rheumatic fever is high and adherence to oral therapy not assured                                                                                                             |
| Prevent secondary cases                                                  | Oral roxithromycin†         | 1         | 20 mg/kg up to 500 mg daily for 3 days                              | If hypersensitive to penicillin                                                                                                                                                                        |
| **Impetigo**                                                             |                             |           |                                                                     |                                                                                                                                            |
| Alleviate symptoms                                                       | Topical mupirocin 2%        | 1         | 8-hourly for 7 days                                                  | Preferred for mild disease, but not proven in high-endemic settings. Use saline, soap water or 0.1% potassium permanganate to remove crusts prior to applying. Strains of *Staphylococcus aureus* may be resistant or may acquire resistance to topical antibiotics |
| Possibly prevent invasive complications                                  | Oral di/flucloxacillin      | 1         | 12.5 mg/kg up to 500 mg q 6-hourly for 10 days                     | First-line treatment if multiple lesions and *S. aureus* is likely                                                                                                                                  |
|                                                                           | IM benzathine penicillin    | 1         | 3–6kg: 225 mg 6–10kg: 337.5 mg 10–15kg: 450 mg 15–20kg: 675 mg 20+ kg: 900 mg as a single dose | Preferred in endemic settings where risk of acute post-streptococcal glomerulonephritis is high and/or adherence to oral therapy not assured. Exclude *S. aureus* infection if refractory to treatment |
|                                                                           | Oral erythromycin           | 1         | 12.5 mg/kg up to 500 mg TDS for 10 days                            | If hypersensitive to penicillin                                                                                                                                                                        |
| **Erysipelas and cellulitis mild/early**                                |                             |           |                                                                     |                                                                                                                                            |
| Alleviate symptoms                                                       | Oral di/flucloxacillin      | 1         | 12.5 mg/kg up to 500 mg q 6-hourly for 7–10 days                   | Switch to IV therapy if failure to respond and consider resistant pathogens, e.g. methicillin-resistant *Staphylococcus aureus* (MRSA)                                                             |
| Prevent progression                                                      | Oral phenoxymethylpenicillin (penicillin V) | 2         | 10 mg/kg up to 500 mg BD for 10 days                               | If *S. aureus* is unlikely (e.g. early erysipelas or perianal cellulitis) or if Group A *Streptococcus* confirmed on culture. Exclude *S. aureus* infection if refractory to treatment                                      |
| Prevent complications                                                    | Oral cephalaxin             | 1         | 12.5 mg/kg up to 500 mg q 8-hourly for 7–10 days                   | If non-immediate type hypersensitivity to penicillins                                                                                                                                               |
|                                                                           | Oral clindamycin            | 1         | 10 mg/kg up to 450 mg q 8-hourly for 7–10 days                     | If immediate type hypersensitivity to penicillin or infection with clindamycin-sensitive MRSA likely                                                                                                 |
### TABLE 36-4 Antibiotic Treatment Guidelines for Selected Group A *Streptococcus* Infections—cont’d

| Rationale | Medication       | Evidence* | Dose                                      | Comments                                                                 |
|-----------|-----------------|-----------|-------------------------------------------|--------------------------------------------------------------------------|
| **Erysipelas and cellulitis moderate-to-severe** |                 |           |                                           |                                                                          |
| • Alleviate symptoms | IV di/flucloxacillin | 1         | 50 mg/kg up to 2 g q 6-hourly            | Preferred treatment unless MRSA is likely                                |
| • Prevent complications | IV cephalothin | 2         | 50 mg/kg up to 2 g q 6-hourly            | If non-immediate type hypersensitivity to penicillin                     |
| | IV/oral clindamycin | 1         | 10 mg/kg up to 450 mg q 8-hourly for 7–10 days | If immediate type hypersensitivity to penicillin or infection with clindamycin sensitive MRSA likely. Bioavailability of clindamycin is high so oral clindamycin can be considered except in infants |
| | IV vancomycin | 1         | 25 mg/kg (<12 yr use 30 mg/kg) up to 1g BD | If infection with clindamycin-resistant MRSA likely. Adjust dose on basis of trough blood levels |
| **Necrotizing fasciitis§** |                 |           |                                           |                                                                          |
| Prevent death | IV meropenem | 5         | 25 mg/kg up to 1 g q 8-hourly           | Broad-spectrum cover is recommended in addition to surgical debridement until Group A *Streptococcus* infection is confirmed, thereafter penicillin + clindamycin is recommended |
| Prevent complications | IV benzylpenicillin | 2         | 45 mg/kg up to 1.8 g q 4-hourly        | If Group A *Streptococcus* infection is confirmed. Use in addition to surgical debridement |
| Alleviate symptoms | IV cephalothin | 5         | 50 mg/kg up to 2 g q 6-hourly           | 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 |
| Minimize disfigurement | + IV clindamycin | 2         | 15 mg/kg up to 600 mg q 8-hourly        | Use as an adjunct to meropenem or penicillin if Group A *Streptococcus* infection is suspected or confirmed |
| **Streptococcal toxic shock syndrome (STSS)§** |                 |           |                                           |                                                                          |
| • Prevent death | Intravenous immunoglobulin (IVIG) | 4         | 2 g/kg as an immediate infusion, repeated once in 48–72 h if necessary | Use as an adjunct to penicillin and clindamycin therapy +/- debridement as recommended above for necrotizing fasciitis |
| • Minimize complications |                 |           |                                           |                                                                          |

*Continued*
**TABLE 36-4 Antibiotic Treatment Guidelines for Selected Group A Streptococcus Infections—cont’d**

| Rationale                     | Medication                      | Evidence* | Dose                                      | Comments                                                                                           |
|-------------------------------|---------------------------------|-----------|-------------------------------------------|---------------------------------------------------------------------------------------------------|
| **Acute rheumatic fever treatment** |                                 |           |                                           |                                                                                                    |
| • Alleviate symptoms          | Aspirin                         | 1         | 80–100mg/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 |
| • Prevent death from acute cardiac failure | IM benzathine penicillin G | 5         | ≤20 kg: 450 mg as a single dose >20 kg: 900 mg as a single dose | Preferred where adherence to oral therapy not assured. Treatment should focus on pain relief with salicylates and management of cardiac failure |
|                               | Oral phenoxymerhenpenicillin (penicillin V) | 5         | 250 mg BD for 10 days                     | An acceptable alternative to benzathine penicillin 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 |
|                               | 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 acute rheumatic fever | IM benzathine penicillin G | 1         | <20 kg: 450 mg >20 kg: 900 mg every 3–4 weeks | Preferred regimen. Should be continued for at least 10 years and at least until patient is 21 years old. Patients with established valve disease may require longer duration. Four-weekly injections satisfactory if a good control programme is in place |
| • Prevent progressive carditis | Oral phenoxymerhenpenicillin (penicillin V) | 1         | 250 mg BD                                | Associated with inferior adherence. Only where IM injections are refused or risk of progressive carditis very low |
|                               | Oral erythromycin               | 5         | 250 mg BD                                | If hypersensitive to penicillin. Dose for erythromycin ethyl succinate is 400 mg BD                  |

*Level of evidence: 1=randomized controlled trial, 2=comparison clinical study > 20 patients, 3=comparison clinical study < 20 patients, 4=case series, 5=expert opinion on basis of in vitro data or animal studies.

†Roxithromycin, semi-synthetic macrolide not commercially available in the USA.

§Intravenous immune globulin (IVIG) 2 g/kg as a single infusion, repeated if necessary 24–48 hours later is also recommended for necrotizing fasciitis or other severe invasive Group A Streptococcus infections (e.g. impending STSS), if indicated, IVIG should be administered as early as possible.

Management of acute rheumatic fever is primarily symptomatic. Penicillin is generally given to eradicate colonization, although acute infection has usually passed by the time symptoms of acute rheumatic fever develop. Salicylates are used to relieve fever and the pain from arthritis that 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 in rheumatic heart disease.

Management of acute post-streptococcal glomerulonephritis 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 occasionally required to manage severe hyperkalemia or symptomatic uremia.

Contacts of patients with Group A Streptococcus infection may be colonized with the same Group A Streptococcus strain, but primary prophylaxis of contacts is rarely indicated for simple Group A Streptococcus pharyngitis. Even for contacts of severe invasive infections, it is estimated that around 2000 contacts would need to receive prophylaxis in order to avoid a single, severe infection—opinion on the value of treating contacts is divided [24]. If prophylactic treatment of contacts is attempted, regimens combining rifampin with penicillin, or using alternative antibiotics such as cephalexin or azithromycin, are usually recommended as a result of the increasing failures of penicillin alone in eradicating carriage.
However, regular secondary prophylaxis is recommended for all children and adults with previous acute rheumatic fever or established rheumatic heart disease. Monthly intramuscular benzathine penicillin G is central to the management of children and adults with acute rheumatic fever and rheumatic heart disease (see Table 36-4).

During outbreaks of acute post-streptococcal glomerulonephritis secondary to Group A Streptococcus pyoderma, community-based treatment of infected individuals and their contacts with benzathine penicillin G appears to decrease the transmission of acute post-streptococcal glomerulonephritis-producing Group A Streptococcus stains. In addition to treating infected individuals, reducing the transmission of Group A Streptococcus pyoderma in resource-limited settings is likely to require skin hygiene measures, including the control of scabies.

After a century of research, the development of a vaccine against Group A Streptococcus disease is at last showing promise. The most advanced of the current candidates is a multivalent vaccine including 26 of the most common Group A Streptococcus emm types encountered in North America and Europe. Unfortunately, there is a limited match of these strains with prevalent emm types in Africa and the Pacific, where emm types are more variable [25]. Other candidate vaccines, containing antigens conserved among most, or all, Group A Streptococcus strains, are approaching clinical trials.

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