area. Rhinorrhea, suppurative complications, low-grade fever, and a more protracted course tend to characterize infections at this age. Exudative pharyngitis in children younger than 3 years is rarely streptococcal in cause.

In the absence of suppurative complications the disease is self-limited. Fever abates within 3 to 5 days. Almost all acute signs and symptoms subside within 1 week, although several additional weeks may be required for tonsils and lymph nodes to return to their usual size. Penicillin shortens the period of fever, toxicity, and infectivity.[77–79] Given the rather brief time course of untreated disease, however, such shortening of the clinical syndrome may not be striking unless therapy is initiated within the first 24 hours of illness. Antibiotic treatment shortens the clinical symptoms by 24 hours, and the main reason for treatment is the prevention of rheumatic fever.[80]

Scarlet Fever

Scarlet fever results from infection with a streptococcal strain that elaborates streptococcal pyrogenic exotoxins (erythrogenic toxins). Although this disease is usually associated with pharyngeal infections, it may follow streptococcal infections at other sites, such as wound infections or puerperal sepsis. The clinical syndrome is similar in most respects to that associated with nontoxigenic strains, save for the scarlatinal rash. The latter must be differentiated from those of viral exanthems, drug eruptions, staphylococcal TSS, and Kawasaki disease.

The rash usually appears on the second day of clinical illness as a diffuse red blush, with many points of deeper red that blanch on pressure. It is often first noted over the upper part of the chest and then spreads to the remainder of the trunk, neck, and extremities. The palms, soles, and usually the face are spared. Skin folds in the neck, axillae, groin, elbows, and knees appear as lines of deeper red (Pastia lines). There are scattered petechiae, and the Rumpel-Leeds test of capillary fragility is positive. Occlusion of sweat glands imparts a sandpaper texture to the skin, which is a particularly helpful finding in dark-skinned patients.

The face appears flushed, except for marked circumoral pallor. In addition to findings of exudative pharyngitis and tonsillitis, patients display an enanthem characterized by small, red, hemorrhagic spots on the hard and soft palates. The tongue is initially covered with a yellowish white coat through which may be seen the red papillae (white strawberry tongue). Later, the coating disappears, and the tongue is beefy red in appearance (red strawberry tongue). The skin rash fades over the course of 1 week and is followed by extensive desquamation lasting for several weeks. A modest eosinophilia may be present early in the course of the illness.

Severe forms of scarlet fever, either associated with local and hematogenous spread of the organism (septic scarlet fever) or with profound toxemia (toxic scarlet fever), are characterized by high fever and marked systemic toxicity. The course may be complicated by arthritis, jaundice, and, very rarely, hydrops of the gallbladder. Such severe forms of the disease are infrequent in the antibiotic era. In the late 1800s scarlet fever was associated with mortalities of 20% in Chicago, New York, and Scandinavia. Recently, an epidemic of 900 cases of scarlet fever occurred in Hong Kong between January and July 2011 associated with *emm12 S. pyogenes* strains.[81] Similarly, in Great Britain, the scarlet fever incidence increased from 8.2 per 100,000 population in 2013 to 33.1 per 100,000 in 2016, and 1 in 40 cases required hospitalization, suggesting increased virulence among prevalent strains.[74] In both studies the *emm12* type was predominant, and those from China were 100% resistant to erythromycin and clindamycin[82] and harbored the genes for superantigens SSA and SpeC.[63]

Suppurative Complications

Inflammation in the facial area induced by acute streptococcal infection may affect structures that are directly contiguous to the pharynx or that drain that site. Such relatively rare complications include peritonsillar cellulitis, peritonsillar abscess, retropharyngeal abscess, suppurative cervical lymphadenitis, mastoiditis, acute sinusitis, and otitis media.[83] Peritonsillar or retropharyngeal abscesses, however, frequently contain a variety of other oral flora, including anaerobes, with or without GAS.[84] GAS are responsible for only a small minority of cases of otitis media or sinusitis.

Extension up the cribriform plate of the ethmoid or via the mastoid bone may cause meningitis, brain abscess, or thrombosis of the intracranial venous sinuses. Streptococcal pneumonia, another potential suppurative complication, is discussed later. Finally, bacteremic spread of the streptococci may result in a variety of metastatic foci of infection, such as suppurative arthritis, endocarditis, meningitis, brain abscess, osteomyelitis, or liver abscess. Such complications of streptococcal pharyngitis are extremely rare since the advent of effective chemotherapy.

Nonsuppurative Complications

The nonsuppurative complications of streptococcal pharyngitis, acute rheumatic fever and acute poststreptococcal glomerulonephritis, are discussed in Chapter 198. The role of streptococci vis-à-vis other infectious and noninfectious agents in initiating certain other acute inflammatory disorders, such as erythema nodosum and anaphylactoid purpura, remains unresolved.

Diagnosis

Pharyngitis and tonsillitis may be caused by infectious agents other than *S. pyogenes.*[75,85] Among these are streptococci of groups C[86,87] and G.[88–90] *Corynebacterium diphtheriae,* the other major bacterial pathogen associated with exudative pharyngitis, is now extremely rare in the United States[91] and, when it occurs in the classic form, is differentiated by the appearance of the diphtheritic membrane, respiratory embarrassment, severe systemic toxicity, and myocardial and neurologic manifestations. Other bacterial agents such as *Neisseria gonorrhoeae* and perhaps *Neisseria meningitidis* occasionally cause pharyngitis, as does *Mycoplasma pneumoniae.*

Pharyngitis due to *Arcanobacterium* (formerly *Corynebacterium*) *hemolyticum,* although rare, may closely mimic that caused by *S. pyogenes.*[92,93] *A. hemolyticum* affects primarily teenagers and young adults, and the patients may exhibit both an exudative pharyngitis and a scarlatiniform rash. The organism is more readily identified on rabbit or human blood agar than on sheep blood agar. Another rare cause of acute pharyngitis is *Yersinia enterocolitica.*[94] Patients infected with this organism may appear quite ill and may or may not have associated enteric symptoms. When *Y. enterocolitica* pharyngitis is associated with disseminated yersiniosis, the mortality rate may be appreciable. Diagnosis depends on clinical clues because the organism is unlikely to be detected on routine throat cultures and antistreptococcal therapy is unavailing (see Chapter 229B). The oropharyngeal form of tularemia is characterized by severe sore throat, exudative and ulcerative tonsillopharyngitis, and cervical adenopathy (see Chapter 227).

Acute pharyngitis is more frequently caused by viruses than by bacteria. Infectious mononucleosis and adenovirus infections frequently give rise to exudative pharyngitis and thus may closely mimic streptococcal sore throat. Herpes simplex viruses 1 and 2,[95–97] influenza,[98] and parainfluenza viruses may also simulate streptococcal pharyngitis, as may initially the acute retroviral syndrome in human immunodeficiency virus (HIV) infection. Pharyngitis associated with the acute retroviral syndrome is, however, not exudative.[99] Even when careful microbiologic techniques are used to detect bacteria, mycoplasmas, and viruses, no causative agent can be detected in a substantial proportion of all cases of acute sore throat.[100] A more complete discussion of the differential diagnosis of acute pharyngitis may be found in Chapter 59.

Approximately one-fourth to one-third of all children complaining of sore throat have a positive throat culture for GAS. Of these, about half can be demonstrated to have immunologically significant infection, as judged by a significant rise in serum titer of one or more antistreptococcal antibodies. Many of the remainder are likely to be asymptomatic carriers because the average carriage rate among school-age children in temperate climates during the winter months may approximate 15% to 20%. Such asymptomatic carriers are at no risk for developing suppurative and nonsuppurative complications and do not require antibiotic therapy. Although acutely infected individuals tend to have more strongly positive throat cultures, this distinction cannot be made with confidence in patients whose signs and symptoms are compatible with those of streptococcal pharyngitis.

Numerous studies have tested the precision with which physicians may differentiate between streptococcal and nonstreptococcal sore throat

by clinical criteria alone. In the presence of a classic scarlatinal rash or during a documented epidemic of streptococcal infections, such differentiation is usually easy. On the other hand, in the case of endemically occurring infections, the problem is much more complex. Certain clinical findings, particularly fever, sore throat, tonsillopharyngeal exudate, and tender, enlarged lymph nodes at the angles of the jaws, have a statistically significant correlation (≈85%) with the presence of positive throat cultures for GAS.[101] Such findings are not diagnostic, however. Although only approximately 50% of patients with immunologically proven streptococcal sore throat have tonsillar exudate, a substantial proportion of cases of exudative pharyngitis are nonstreptococcal in cause.

It is possible to identify individual patients in which "strep throat" can be effectively excluded on a combination of epidemiologic (see earlier) and clinical grounds. For example, symptoms of the common cold are not caused by *S. pyogenes*. Similarly, the presence of hoarseness and conjunctivitis and the absence of fever or pharyngeal erythema make streptococcal pharyngitis very unlikely. A number of investigators have developed clinical algorithms in children and adults to assist in determining the likelihood that a particular patient has group A streptococcal pharyngitis.[101–107] These algorithms are useful and accurate in identifying patients whose risk for streptococcal infection is so low as to obviate the need for further microbiologic testing. Otherwise, such testing should be performed.

One published practice guideline[108,109] has suggested that in adults with features strongly suggestive of streptococcal pharyngitis, empirical antimicrobial therapy without microbiologic confirmation is an acceptable alternative. That guideline uses an algorithm, developed by Centor and coworkers,[107] using four clinical criteria—presence of tonsillar exudates, presence of swollen tender anterior cervical nodes (i.e., cervical lymphadenitis), lack of cough, and history of fever—that have been reported to be independently associated with the likelihood of a positive throat culture for GAS.[110] A subsequent cost-effectiveness analysis[111] and two prospective clinical studies[112,113] have concluded that such empirical therapy is neither the most effective nor least expensive strategy for diagnosis of strep throat in adults. Furthermore, empirical therapy in adults leads to considerable overuse of antibiotics.[114] It is important to realize that the most common age group of streptococcal pharyngitis is in the 5- to 15-year-old group. This is of particular concern because annually 73% of the 6.7 million adults who visit primary care providers in the United Sates with the complaint of sore throat receive a prescription for antibiotics.[115]

Thus, for adults and children, expert panels of the Infectious Diseases Society of America,[80] American Heart Association (AHA),[116] and American Academy of Pediatrics (AAP)[117] recommend that the presence of GAS in the pharynx should be documented by a throat culture or rapid antigen detection test (RADT).[79,116,117] It should be noted that a positive test does not discriminate between active streptococcal infection versus colonization and a concomitant viral infection. Clinical criteria for streptococcal pharyngitis should be present before antibiotic treatment is considered.

Throat Culture

Throat culture remains the gold standard for diagnosing streptococcal pharyngitis. Failure to isolate β-hemolytic streptococci in a carefully obtained and accurately interpreted throat culture rules out the diagnosis of streptococcal sore throat for practical purposes. In cases in which doubt exists as to the validity of a negative culture, it may be preferable to repeat the culture rather than to treat empirically with antimicrobial agents.

Although a negative culture eliminates the necessity for therapy, a positive culture does not differentiate between acute infection and asymptomatic carriage. Serum antibody titers do not rise until convalescence and thus are of no help in short-term management. Although the degree of positivity of the throat culture may assist in making this differentiation, it is best to assume that all positive cultures in patients with acute pharyngitis are significant and to treat accordingly while recognizing that, even with the use of the throat culture, some degree of overtreatment is inevitable.

Detailed instructions for obtaining and processing a throat culture have been published by the AHA.[118] Sheep blood agar is preferred because clear-cut patterns of hemolysis are obtained using this medium. In regard to isolation of GAS, there is controversy in the literature as to the relative merits of plain sheep blood agar plates versus plates to which trimethoprim-sulfamethoxazole has been added to suppress competing normal pharyngeal flora. Similar controversy exists about the optimal atmosphere for incubation—aerobic, aerobic in the presence of 5% to 10% carbon dioxide, or anaerobic. Detailed analyses of these issues have been published.[119,120] If blood agar plates are not immediately available, the swab may be placed in a dry sterile tube for transportation to the laboratory. After overnight incubation at 35°C to 37°C, culture plates from patients with streptococcal pharyngitis show colonies surrounded by clear zones of hemolysis and β-hemolysis around the agar stab. Plates that are negative on first reading should be reexamined after an additional 24 hours of incubation. Serologic grouping of β-hemolytic streptococcal isolates may now be readily performed by using commercially available kits. Fluorescent antibody techniques provide excellent results and specifically identify group A organisms. No quantitative information is gained about the degree of positivity of the culture. A less expensive screening procedure, the bacitracin sensitivity test, is best performed once the organism has been isolated in pure culture. This susceptibility procedure is based on the observation that greater than 95% of all group A streptococcal strains are inhibited by low-potency (0.04 unit) bacitracin disks, whereas 80% to 90% of non–group A strains are resistant.

Because no GAS resistant to penicillin or cephalosporins have yet been detected, antibiotic testing is unnecessary if these drugs are to be used. The same holds true in general for macrolides because GAS resistant to this drug are rare in the United States at this time[121] (see later section "Treatment" for caveats).

Rapid Antigen Detection Tests

RADTs allow detection of the presence of the group A carbohydrate antigen directly from throat swabs. Unlike the throat culture, which requires overnight or longer to yield a definitive result, RADTs can be completed in a matter of minutes. By facilitating early diagnosis and therapy, a RADT may possibly shorten the duration of illness, decrease secondary spread of the organism, and allow earlier return of patients and parents to school and work. Earlier tests based on latex agglutination methodology have been largely replaced by enzyme immunoassays that are easier to interpret and more sensitive. More recently, tests using optical immunoassay (OIA) and chemiluminescent DNA probes have become available.

Most currently commercially available RADTs are highly specific (95% or higher), so a positive result obviates the need for a throat culture. Unfortunately, the sensitivity of these tests is lower than that of the conventional throat culture, and therefore they may be negative in patients in whom conventional culture proves to be positive. Some investigators[122,123] have found newer tests such as OIA to have a sensitivity equivalent to that of culture, but others have reached opposite conclusions.[124–126] At present the AAP recommends that a negative RADT be confirmed with a throat culture. In view of conflicting data about sensitivity of commercially available RADTs, as well as the paucity of studies directly comparing the various tests with each other, physicians who elect to use any RADT in children and adolescents without culture backup of negative results should do so only after confirming in their own practice that the rapid test is comparable in sensitivity to the throat culture.[117]

In considering appropriate laboratory diagnostic testing for adults, certain epidemiologic distinctions from pediatric disease deserve consideration. The GAS cause 15% to 30% of cases of acute pharyngitis in pediatric patients but only approximately 10% of such illnesses in adults.[106,127,128] However, the risk for streptococcal pharyngitis may be higher in parents of school-age children and adults whose occupation brings them into close association with children. Moreover, the risk for a first attack of acute rheumatic fever is extremely low in adults in the United States and most other developed countries, even if they experience an undiagnosed and untreated episode of streptococcal pharyngitis. These facts make performance of RADT without culture backup of negative results an acceptable alternative to throat culture.[79,116] The generally high specificity of RADTs should minimize overprescribing

of antimicrobial agents for adults. This latter point is of particular importance in view of national data, indicating that antibiotics are prescribed for approximately 75% of adults consulting community primary care physicians for the complaint of sore throat and that the prescription of more expensive, broader-spectrum antibiotics is frequent.[115] Physicians who wish to ensure they are achieving maximal sensitivity in diagnosis may continue to use the conventional throat culture or to back up a negative RADT with a culture. It should be clear that demonstration of GAS in the throat is not sufficient to initiate treatment, the exception being in those with a history of acute rheumatic fever. However, in one recent adult study,[113] OIA without culture backup was performed in adults exhibiting two or more of Centor and coworkers' criteria.[107] When compared with throat culture, this strategy led to nearly optimal treatment (94%) and antibiotic prescription (37%), with minimal antibiotic overuse (3%) and underuse (3%).

Therapy

Antimicrobial therapy is indicated for children and adults with symptomatic pharyngitis (see Centor criteria earlier) after the presence of the organism in the throat is confirmed by culture or RADT. The goals of antimicrobial therapy are (1) prevention of acute rheumatic fever, (2) prevention of suppurative complications, (3) improvement in clinical symptoms and signs, and (4) rapid decrease in infectivity so as to reduce transmission of group A β-hemolytic streptococci to family members, classmates, and other close contacts and to allow the rapid resumption of usual activities. There is no firm evidence that poststreptococcal acute glomerulonephritis is preventable by treatment of the antecedent streptococcal infection.[129]

Treatment of group A streptococcal sore throat as long as 9 days after onset is still effective for the prevention of rheumatic fever.[130] Thus, if the patient is seen early in the course of the illness, the delay in initiation of therapy occasioned by obtaining a positive throat culture is not ordinarily a matter of concern in this regard. As noted, patients with signs and symptoms of acute pharyngitis and a positive rapid test (properly performed and interpreted) for group A carbohydrate antigen should receive appropriate antimicrobial therapy.

In the minority of patients who are severely ill or toxic at presentation and in whom there is clinical and epidemiologic evidence resulting in a high index of suspicion, oral antimicrobial therapy can be initiated while awaiting the results of the throat culture (either as a primary diagnostic tool or in confirmation of a negative RADT). If oral therapy is prescribed, a positive throat culture serves as a guide to the necessity of completion of a full antimicrobial course or, alternatively, of recalling the patient for an injection of penicillin G benzathine. Early initiation of antimicrobial therapy may result in faster resolution of the signs and symptoms in children and adults,[77–79] but group A streptococcal pharyngitis is usually a self-limited disease; fever and constitutional symptoms are markedly diminished within 3 or 4 days of onset, even without antimicrobial therapy.[131] Thus antimicrobial therapy initiated within the first 48 hours of onset hastens symptomatic improvement by only 1 to 2 days.

The drug of choice in the treatment of streptococcal infection is penicillin because of its efficacy in the prevention of rheumatic fever, safety, narrow spectrum, and low cost (Table 197.1).[79,116,117] Prevention of acute rheumatic fever is believed to require eradication of the infecting streptococcus from the pharynx, an effect that depends on prolonged rather than high-dose penicillin therapy. This objective may be accomplished by the administration of a single injection of 1.2 million units of penicillin G benzathine. For children weighing 60 pounds (27 kg) or less, the dose is reduced to 600,000 units. Most physicians in the United States, however, elect to administer oral therapy. In this case penicillin V, in one of the regimens listed in Table 197.1, must be continued for a full 10 days. Amoxicillin is often prescribed in preference to penicillin V in children requiring liquid medication because of poor palatability of oral suspensions of penicillin V. Once-daily amoxicillin therapy is effective for the treatment of group A streptococcal pharyngitis[132–134] in children. An oral time-release formulation of amoxicillin has recently been approved by the US Food and Drug Administration (FDA) for once-daily treatment of group A streptococcal pharyngitis in adolescents and adults. Because of its convenience, low cost, and relatively narrow spectrum, once-daily amoxicillin is an acceptable alternative regimen for the treatment of group A β-hemolytic streptococcal pharyngitis.[116]

TABLE 197.1 Primary Prevention of Rheumatic Fever (Treatment of Streptococcal Tonsillopharyngitis)

AGENT	DOSAGE	ROUTE	DURATION (DAYS)
Penicillins			
Penicillin V (phenoxymethyl penicillin)	Children ≤27 kg (60 lb): 250 mg two to three times daily Children >27 kg, adolescents, and adults: 500 mg two to three times daily	Oral	10
or			
Amoxicillin	50 mg/kg once daily (maximum, 1 g)	Oral	10
or			
Benzathine penicillin G	600,000 U for patients ≤27 kg; 1.2 million U for patients >27 kg	Intramuscular	Once
For Individuals Allergic to Penicillin			
Narrow-spectrum cephalosporin[b] (cephalexin, cefadroxil)	Variable	Oral	10
or			
Clindamycin	20 mg/kg/d divided in three doses (maximum, 1.8 g/d)	Oral	10
or			
Azithromycin	12 mg/kg once daily (maximum, 500 mg)	Oral	5
or			
Clarithromycin	15 mg/kg/d divided twice daily (maximum, 250 mg twice daily)	Oral	10

[a]The following are not acceptable: sulfonamides, trimethoprim, tetracyclines, and fluoroquinolones.
[b]To be avoided in those with immediate (type I) hypersensitivity to a penicillin.
From Gerber M, Baltimore R, Eaton C, et al. Prevention of rheumatic fever and diagnosis of acute streptococcal pharyngitis. A scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. *2009;119:1541–1551.*

A variable percentage of patients continue to harbor GAS of the originating serotype in their pharynx after completion of a course of oral penicillin.[135] Such bacteriologic treatment failures are sometimes associated with symptomatic relapse. Unless such children have symptomatic sore throat as clinically defined earlier, they should not be re-treated unless there is a history of rheumatic fever. Because penicillin is ineffective in eradicating asymptomatic streptococcal pharyngeal carriage, apparent treatment failures may actually represent persistence of such carriage in patients with superimposed viral pharyngitis.[136]

Oral cephalosporins are highly effective in the treatment of streptococcal pharyngitis, and meta-analyses have suggested that streptococcal eradication rates and clinical cure rates attained with these agents are slightly higher in children and adults than those achieved with penicillin.[135,137,138] However, these analyses have been strongly challenged on methodologic grounds.[139] This is related to high efficacy in treatment in patients with no prior antibiotic treatment and in vitro data that has never identified penicillin resistance in GAS. In penicillin-allergic patients, macrolide (erythromycin or clarithromycin) or azalide (azithromycin)

antimicrobial agents, clindamycin, or first-generation cephalosporins are the agents of choice.[79] The latter should be avoided in those with immediate (type I) penicillin hypersensitivity (see Table 197.1). Cephalosporins should not be administered to patients with a history of immediate (anaphylactic-type) hypersensitivity to penicillin. The physician should bear in mind the possibility of an increased risk for allergic reactions to cephalosporins when treating penicillin-allergic patients.

Erythromycin is less expensive than clarithromycin or azithromycin but may be associated with more gastrointestinal side effects. Although there have been reports of relatively high levels of resistance to macrolide antimicrobial agents from several countries[140–142] (see section on invasive infection later, where resistance to these agents is high in China) and reports of increased rates of macrolide resistance in certain localized areas of the United States,[143,144] three multistate surveillance studies conducted during 2002 and 2003 detected overall macrolide resistance rates of 3.8%,[145] 5.2%,[146] and 6.8%, respectively.[147] However, given the increasing use of azalides for upper and lower respiratory tract infections, the situation may change. Physicians should therefore be cognizant of local patterns of antimicrobial resistance. In areas in which macrolide resistance is known to be prevalent, antimicrobial susceptibility testing should be performed if these agents are used to treat group A streptococcal infections. Furthermore, continued surveillance of national trends in macrolide susceptibility is warranted.

There has been considerable recent interest in abbreviated courses of antimicrobial therapy. It has been reported that second- and third-generation cephalosporins, such as cefuroxime,[148,149] cefixime,[150] ceftibuten,[151] cefdinir,[152] cefpodoxime,[153] and cefditoren,[154] are effective in eradication of GAS from the pharynx when administered for 5 days, although not all of these are approved by the FDA for a 5-day course of therapy for acute streptococcal pharyngitis at the time of this writing. Although such shortened courses might theoretically enhance patient compliance, the potential ecologic effects of using these broad-spectrum agents to treat such a common bacterial infection are of great concern. This is particularly true should these agents be used as first-line therapy for strep throat. Moreover, even when administered for short courses, they are considerably more expensive than penicillin. Clearly, penicillin treatment is also associated with potential adverse effects.

Similar favorable results of short-course therapy have also been reported for the newer macrolides or azalides, clarithromycin,[155] and azithromycin.[156–159] Because of its long intracellular half-life and slow release from tissue sites, a 5-day course of azithromycin is approved by the AHA [116] for use in penicillin-allergic patients. As noted, promiscuous use of macrolides has been associated with development of resistance by GAS.[140,141]

Because tetracycline-resistant GAS are prevalent in many areas, this drug is not recommended. Sulfonamides, which are effective for the secondary prophylaxis of rheumatic fever (see Chapter 198), are ineffective for the eradication of pharyngeal organisms or the prevention of rheumatic fever when used as therapy for acute pharyngeal infections.

Patients with more severe suppurative infections, such as those involving the mastoid or ethmoid, may require higher doses of penicillin or other β-lactam antibiotics administered parenterally. When streptococcal upper respiratory tract infection is complicated by the development of abscesses associated with suppurative cervical adenitis or in the peritonsillar or retropharyngeal soft tissues, aspiration or incision and drainage is usually required.

Because prevention of rheumatic fever appears to require eradication of the streptococcal organism from the pharynx, treatment failures are of concern. In addition to true treatment failure (i.e., reisolation of the original infecting streptococcal serotype shortly after completion of a full course of antibiotic therapy), causes of posttreatment culture positivity include failure of compliance with oral medication schedules and reinfection with the same or different streptococcal types in the home or school environment. Apparent failure may also occur when the patient is in reality an asymptomatic postconvalescent streptococcal carrier suffering from an acute viral pharyngitis. In everyday practice it is often impossible to differentiate among these alternatives.

Nevertheless, routine reculture of the throat after a course of antistreptococcal therapy in an asymptomatic patient is not advised[79] because the cost-benefit ratio of such cultures continues to decline in parallel with the incidence of acute rheumatic fever in developed countries. Such cultures should be undertaken in high-risk circumstances (e.g., if the patient or a family member has a history of rheumatic fever) or when symptoms compatible with streptococcal infection persist or recur. When an increased incidence of acute rheumatic fever is detected in a community, as happened in a number of US cities during the 1980s, the approach to streptococcal infection must be particularly rigorous, and serious consideration should be given to routine performance of posttreatment cultures. If reculture is undertaken in patients with a history of rheumatic fever, re-treatment with an oral cephalosporin might be considered in view of the slightly increased eradication rates observed with these agents; this may be due to β-lactamase production by the oral microbiota.

The presence of persistently but weakly positive throat cultures after repeated courses of antibiotic therapy in an otherwise asymptomatic patient is not a cause for alarm. Such persons are asymptomatic postconvalescent streptococcal carriers[136] who are neither at risk for developing rheumatic fever nor likely to spread their infection to others. Their most frequent problem is anxiety produced by multiple medical consultations associated with the streptococcal colonization. In the event in which, for medical or psychological reasons, eradication of chronic streptococcal carriage becomes highly desirable, clindamycin,[160] amoxicillin-clavulanate,[161] or azithromycin may be efficacious.[79,162] Any of these antibiotic treatments can have adverse events, such as *Clostridioides difficile* (formerly *Clostridium difficile*) colitis.

Streptococcal acquisition rates of 25% or higher have been recorded in family contacts. Certainly, family contacts with symptoms of upper respiratory tract infection should be cultured and treated appropriately if positive. Asymptomatic family contacts should also be cultured in high-risk circumstances, such as a family member who has had rheumatic fever or known cases of rheumatic fever or poststreptococcal glomerulonephritis occurring in the general area. In situations of lesser risk, routine culture of asymptomatic family contacts is not recommended.[79,116] The advisability of culture and/or prophylaxis of household contacts of patients with invasive group A streptococcal infection is discussed later.[162]

There is no firm evidence to suggest that tonsillectomy reduces the incidence of rheumatic fever, either in healthy persons or in persons who have had rheumatic fever and faithfully maintained continuous antibiotic prophylaxis. In certain patients with recurrent bouts of tonsillopharyngitis, however, tonsillectomy may decrease the frequency of incapacitating acute infections.[163,164] Tonsillectomy should be considered only for the most severely affected patients.[165]

STREPTOCOCCAL PYODERMA

Pyoderma, impetigo, and *impetigo contagiosa* are terms used synonymously to describe discrete purulent lesions that are primary infections of the skin and that are extremely prevalent in many parts of the world. In the great majority of cases pyoderma is caused by β-hemolytic streptococci and/or *S. aureus.*

Epidemiology

Pyoderma occurs most frequently in economically disadvantaged children dwelling in tropical or subtropical climates. It is also prevalent in northern climates during the summer.[166] The peak incidence of impetigo is in children age 2 to 5 years. This disorder also occurs among older children and adults whose recreational activities or occupation results in cutaneous cuts or abrasions.[167–169] There is no gender predilection, and all races appear to be susceptible. The prevalence of streptococcal pyoderma is markedly influenced by several factors, the most important of which appear to be climate and level of hygiene.

Meticulous prospective studies of streptococcal impetigo have demonstrated that the responsible microorganisms initially colonize the unbroken skin,[166] an observation that probably explains the influence of personal hygiene on disease incidence. Development of skin colonization with a given streptococcal strain precedes the development of impetiginous lesions by an average interval of 10 days. The mechanism of production of skin lesions is unproved, but it is most likely caused by intradermal inoculation of surface organisms by abrasions, minor trauma, or insect bites. Frequently, there is a transfer of the streptococcal strains from the skin and/or pyoderma lesions to the upper respiratory

tract. The interval between colonization of the skin and colonization of nose or throat or both averages 2 to 3 weeks.

Bacteriology and Immunology

Streptococci isolated from pyodermal lesions are primarily group A, but on occasion, representatives of other serogroups, such as C and G, are responsible. GAS that cause impetigo differ in several respects from those usually associated with tonsillitis and pharyngitis. Skin strains belong to different M serotypes or genotypes from the classic throat strains; because most have been identified more recently, they tend to comprise the higher-numbered M types. Throat and skin strains can also be differentiated by genetic markers.[170] A relatively small number of serotypes seem capable of regularly initiating both pharyngitis and pyoderma.[171]

Assays of streptococcal antibodies are of no value in the diagnosis and management of impetigo, but they provide helpful supporting evidence of recent streptococcal infection in patients suspected of having poststreptococcal glomerulonephritis. The ASO response is weak in patients with streptococcal impetigo,[172,173] presumably because the activity of SLO response is inhibited by skin lipids (cholesterol),[174] whereas anti–DNase B levels are elevated.[172,173]

Clinical Manifestations

The lesion of streptococcal pyoderma begins as a papule that rapidly evolves into a vesicle surrounded by an area of erythema. The vesicular lesions are evanescent and rarely recognized clinically; they give rise to pustules that gradually enlarge and then break down over a period of 4 to 6 days to form characteristic thick crusts (Fig. 197.4). The lesions heal slowly and leave depigmented areas. A deeply ulcerated form of impetigo is known as *ecthyma*.

Streptococcal impetigo occurs on exposed areas of the body, most frequently on the lower extremities or face. The lesions remain well localized but are frequently multiple. Although regional lymphadenitis may occur, systemic symptoms are not ordinarily present.

In the past the lesions just described could be rather confidently diagnosed as streptococcal. This was the predominant form of impetigo and could be distinguished from bullous impetigo caused by phage group II *S. aureus*. Although bullous impetigo remains almost exclusively staphylococcal in cause, the bacteriology of nonbullous impetigo has changed.[175] *S. aureus,* either alone or in combination with *S. pyogenes,* is now the predominant causative agent.[176–178] Almost all such staphylococci are penicillinase producers. Therefore treatment with penicillin, which in the past had been highly effective against nonbullous impetigo, even when both streptococci and staphylococci were isolated from the lesions, now frequently fails.[177]

Therapy and Prevention

Because of the current frequency of isolation of *S. aureus* from nonbullous impetigo lesions and concomitant reports of penicillin failures,[177,179,180] penicillinase-resistant penicillins or first-generation cephalosporins are preferred.[177] Erythromycin has long been a mainstay of pyoderma therapy, but its use may be lessened in areas in which erythromycin-resistant strains of *S. aureus* or, more recently, *S. pyogenes* are prevalent. Topical therapy with mupirocin is equivalent to oral systemic antimicrobial therapy[181,182] and may be used when lesions are limited in number. It is expensive, however, and some strains of staphylococci may be resistant.[183] Retapamulin, a novel pleuromutilin antibacterial agent, has recently been approved by the FDA for treatment of bullous and nonbullous impetigo caused by GAS and methicillin-susceptible strains of *S. aureus* in children 9 months of age or older.[184–186] In vitro data have suggested that it may be more effective than mupirocin against methicillin-resistant *S. aureus*.

Adherence to good regimens of personal hygiene is the most effective measure currently available for prevention of impetigo.

FIG. 197.4 Multiple pyoderma lesions on the lower extremities of a child in rural Mississippi. *(Courtesy Dr. K. Nelson, Baltimore.)*

Complications

Suppurative complications are uncommon. For as yet unexplained reasons, rheumatic fever has never been shown to occur after streptococcal pyoderma. On the other hand, cutaneous infections with nephritogenic strains of GAS are the major antecedent of poststreptococcal glomerulonephritis in many areas of the world. There are as yet no conclusive data to indicate that treatment of an individual case of pyoderma prevents the subsequent occurrence of nephritis in these patients. Such therapy is nevertheless important as an epidemiologic measure in eradicating nephritogenic strains from the environment.

INVASIVE STREPTOCOCCAL INFECTIONS OF SKIN AND SOFT TISSUES

In the mid-1980s outbreaks of acute rheumatic fever began to occur throughout the United States, concomitant with the reappearance of certain streptococcal strains exhibiting characteristics known to be associated with rheumatogenicity (see Chapter 198). Shortly thereafter, invasive streptococcal infections, of a frequency and severity not seen in the preceding decades, began to be reported both in the United States and abroad.[187–190] Although strains of a number of group A streptococcal M types have been isolated from invasive infections, there has been a definite and consistent tendency for M types 1 and 3 to be associated with life-threatening infections.[8,188–191] A high proportion of these cases has occurred in adults, and the portal of entry is frequently the skin or soft tissues. In some cases the infections give rise to shock and multiorgan failure, features that simulate, in certain respects, staphylococcal TSS.[192] Thus these life-threatening group A streptococcal infections have been termed strep TSS. Clinical features of serious streptococcal skin and soft tissue infections and TSS are described later.

Erysipelas

Erysipelas is a superficial cutaneous process, usually restricted to the dermis but with prominent lymphatic involvement. It is distinguished clinically from other forms of cutaneous infection by three features: The lesions are raised above the level of the surrounding skin; there is a clear line of demarcation between involved and uninvolved tissue; and the lesions are a brilliant salmon red. This disorder is more common in infants, young children, and older adults. It is almost always caused by β-hemolytic streptococci. Using immunofluorescence techniques combined with conventional culture on skin biopsies from patients with lower limb infections, GAS were found responsible for 26 of 27 cases of erysipelas and 11 of 15 cases of acute cellulitis.[193] Uncommonly, group B streptococci or *S. aureus* may be the culprit. In older reports erysipelas was described as characteristically involving the butterfly area of the face (Fig. 197.5), but at present the lower extremities are more frequently involved (Fig. 197.6). In patients with facial erysipelas there is frequently a history of preceding streptococcal sore throat, although the exact mode of spread to the skin is unknown. When erysipelas involves the extremities, breaks in the cutaneous barrier serve as portals of entry; these include surgical incisions, trauma or abrasions, dermatologic diseases such as psoriasis, or local fungal infections.

The cutaneous lesion begins as a localized area of erythema and swelling and then spreads rapidly with advancing red margins, which

FIG. 197.5 Facial erysipelas. The lesion is well demarcated from surrounding skin and illustrates the typical butterfly distribution. *(From Bisno AL. Cutaneous infections: microbiologic and epidemiologic considerations.* Am J Med. *1984;76:172–179.)*

FIG. 197.6 Erysipelas in saphenous venectomy limb. This patient had undergone coronary artery bypass grafting.

are raised and well demarcated from adjacent normal tissue. There is marked edema, often with bleb formation, and in facial erysipelas the eyes are frequently swollen shut. The lesion may demonstrate central resolution while continuing to extend on the periphery. The cutaneous inflammation is accompanied by chills, fever, and toxicity.

The differential diagnosis is limited. Early on the lesions of facial herpes zoster, contact dermatitis, or giant urticaria may be confused with erysipelas. Lesions resembling erysipelas may occur in patients with familial Mediterranean fever. Cutaneous lesions similar in appearance to those of erysipelas may occur on the hands of patients who sustain cuts or abrasions while handling fish or meats. This entity, known as erysipeloid of Rosenbach and caused by *Erysipelothrix rhusiopathiae,* is usually unaccompanied by fever or systemic symptoms.

With early diagnosis and treatment, the prognosis is excellent. Rarely, however, the process may spread to deeper levels of the skin and soft tissues. Blood cultures are positive for β-hemolytic streptococci in 4.6% to 9% of patients.[194] Penicillin, either parenterally or orally, depending on clinical severity, is the treatment of choice. If staphylococcal infection is suspected, a penicillinase-resistant semisynthetic penicillin or cephalosporin should be selected. In a randomized, prospective multicenter trial,[195] roxithromycin, a macrolide antimicrobial agent, was equivalent to penicillin. Increased levels of macrolide resistance among GAS, however, have been detected in certain areas of the United States.[143,144]

Streptococcal Cellulitis

Streptococcal cellulitis, an acute spreading inflammation of the skin and subcutaneous tissues, results from infection of burns, wounds, or surgical incisions but may also follow mild trauma. Clinical findings include local pain, tenderness, swelling, and erythema. The process may extend rapidly to involve large areas of skin. Systemic manifestations include fever, chills, and malaise, and there may be associated lymphangitis, bacteremia, or both. In contrast to erysipelas, the lesion is not raised, the demarcation between involved and uninvolved skin is indistinct, and lesions are more pink than salmon red. Often, however, the clinical differentiation between these entities is not clear cut.

Two predisposing causes of streptococcal cellulitis deserve special mention. One is the parenteral injection of illicit drugs.[196–198] These cases are often associated with bacteremia and deep tissue infections, such as septic thrombophlebitis, suppurative arthritis, osteomyelitis, and, occasionally, infective endocarditis. Second, patients who have impaired lymphatic drainage from upper or lower extremities are prone to recurrent episodes of streptococcal cellulitis. Examples include individuals with filariasis and women who have undergone radical mastectomy with axillary node dissection.[199] It is speculated that repetitive infection further damages local lymphatics and worsens lymphatic stasis.[200]

Recurrent episodes of severe cellulitis have also been reported in certain patients who have undergone coronary artery bypass grafting.[201] The lesion invariably occurs in the extremity from which the saphenous vein was removed, and at times it may exhibit features of erysipelas (see Fig. 197.6). Patients with tinea pedis of the venectomy limb appear to be particularly at risk.[202–204] As with other forms of cellulitis, pathogenic bacteria are difficult to recover during these episodes. The appearance of the lesions and the response to penicillin therapy suggest, however, a streptococcal cause. The few β-hemolytic streptococci that have been recovered and characterized often belong to serogroups other than A.[205]

Disruption of the cutaneous barrier (leg ulcers, wounds, dermatophytosis) is a risk factor for the development of cutaneous streptococcal infection.[206] There is suggestive evidence that local dermatophyte infection (i.e., athlete's foot) may serve as a reservoir for β-hemolytic streptococci that initiate episodes of erysipelas or cellulitis of the lower extremities.[202,207] Thus care should be taken to eradicate such fungal infections in patients who experience recurrent bouts of erysipelas or cellulitis. Another potential reservoir is intestinal streptococcal colonization.[208] Other risk factors include venous insufficiency, edema, and obesity.[206] Not surprising, an increased risk for recurrent cellulitis has also been reported in homeless persons.[209]

Cellulitis may be caused by infection with a variety of bacterial pathogens (see Chapter 93), but most cases are caused by *S. pyogenes* (or, on occasion, streptococci of groups B, C, or G) or by *S. aureus. S. aureus* infection of the skin is usually associated with a pyogenic, fluctuant

focus with surrounding erythema and is referred to as "purulent cellulitis." In the absence of positive blood cultures, which are present in only 5% of cases of nonpurulent cellulitis, a specific microbiologic diagnosis is often not possible. Aspirate or biopsy samples from sites of active cellulitis are helpful when positive on smear or culture, but unfortunately such specimens are usually negative in adult patients.[210–212]

It is often impossible to differentiate streptococcal from staphylococcal cellulitis on initial presentation confidently. In this case a semisynthetic penicillinase-resistant penicillin should be used. In penicillin-allergic patients a first-generation cephalosporin may be used if the hypersensitivity is not of the immediate type. Clindamycin or vancomycin may be used in patients who manifest anaphylactic hypersensitivity to β-lactam antibiotics, and the latter should be administered if there is reason to suspect infection with methicillin-resistant *S. aureus*. Patients with milder cases of streptococcal cellulitis may be switched to oral medications after an initial favorable response to parenteral therapy.

The role of continuous antimicrobial prophylaxis[213–215] in patients prone to frequent recurrences remains unsettled. At present such prophylaxis seems justified only for patients with very frequent or severe episodes, and the optimal regimen has not been established.

Elevation of the affected extremity and evaluation of blood flow are important adjunctive measures to improve circulation and to detect potential compartment syndrome, which reduces distal blood flow.

Necrotizing Fasciitis (Streptococcal Gangrene)

Necrotizing fasciitis is an infection of the deeper subcutaneous tissues and fascia, characterized by extensive and rapidly spreading necrosis and by gangrene of the skin and underlying structures. As detailed in Chapter 198, this entity may arise in several distinct epidemiologic settings, may be caused by multiple aerobic and anaerobic microorganisms, and may vary in clinical manifestations. The present discussion is limited to necrotizing fasciitis caused by GAS[216] and described by Meleney[217] in 1924 as hemolytic streptococcal gangrene. Characteristically, streptococcal gangrene begins at a site of trivial or even inapparent trauma or in an operative incision. The initial lesion may appear only as an area of mild erythema but over the next 24 to 72 hours undergoes a rapid evolution. The inflammation becomes more pronounced and extensive, the skin becomes dusky and then purplish, and bullae containing yellow or hemorrhagic fluid appear. Bacteremia is frequently present, and metastatic abscesses may occur. By the fourth to fifth day, frank gangrenous changes are evident in the affected skin,[218] followed by extensive sloughing. The process may march inexorably over large areas of the body unless measures are taken to contain it. The patient with streptococcal gangrene appears perilously ill, with high fever and extreme prostration. Mortality rates are high, even with appropriate treatment.[218] Fournier gangrene, a form of necrotizing fasciitis involving the male genital area, may rarely be caused by GAS.

The course of necrotizing fasciitis today appears to be much more fulminant than that described by Meleney.[217] Specifically, ecchymoses and bullae may appear within 2 to 3 days, and associated myonecrosis is more common. In addition, the mortality rate in 1924 was 20%, whereas mortality rates of 20% to 70% have been reported in the current era. This difference is even more remarkable because antibiotics, intravenous (IV) fluids, ventilators, and dialysis were not available in 1924.

Diagnosis and Differential Diagnosis

Successful management of necrotizing fasciitis is dependent on early recognition, yet early in their course, patients may present with fever and toxicity when the cutaneous lesion may appear relatively benign.[219] Fever and severe pain are the first manifestations of disease. In those with a defined portal of entry, such as a surgical incision, burn, insect bite, or varicella lesion, there is redness of the skin, pain, and swelling. In the 50% of patients who develop necrotizing fasciitis without a defined portal of entry, the infection begins deep to the skin, frequently at the site of a hematoma, muscle strain, or traumatic joint injury. In these patients crescendo pain is the most reliable clinical clue and is likely related to tissue ischemia arising from toxin-induced vascular occlusion.[220]

Routine radiographs, computed tomography (CT), and magnetic resonance imaging (MRI) may show localized swelling of the deep structures but characteristically do not show frank abscess formation or gas in the tissue and *thus are not definitive procedures*. This is particularly problematic in those patients without a portal of entry who have deep infection at the site of recent trauma, such as muscle tear, hematoma, or prior surgery, in whom the clinician cannot distinguish the cause of the deep swelling. Unfortunately, imaging studies often serve to delay rather than facilitate a diagnosis. Clinical judgment is crucial, and initiation of aggressive medical and surgical treatment may be caused by the time it takes for imaging studies. Fever and increasingly severe pain are the best and earliest signs of infection. Some patients do not present with fever,[219] and others may have taken nonsteroidal antiinflammatory drugs (NSAIDs) that mask fever and reduce pain. Unexplained tachycardia, marked left-sided shift, and an elevated creatine phosphokinase level are also important clues to the diagnosis of necrotizing fasciitis, and their presence should prompt surgical inspection of the deep tissues. Gram stains of aspirated fluid reveal chains of gram-positive cocci that contain few, if any, WBCs. Similarly, a biopsy with frozen section may aid in the diagnosis of necrotizing fasciitis.[221,222]

Myositis and Myonecrosis

Most cases of purulent muscle infection occur in the tropics, and *S. aureus* is the predominant causative agent. Myositis caused by GAS has been rare but occurs in many patients with necrotizing fasciitis and strep TSS. Most of these cases occur after blunt nonpenetrating trauma or occur spontaneously. Most likely, bacteria are translocated to the deep tissue hematogenously from the throat. Systemic toxicity is common, and mortality as high as 80% has been reported.[223] Destruction of tissue is poorly understood, but infection and inflammation within the confined muscle compartment space may result in pressures exceeding arterial pressure, necessitating emergent fasciotomy and débridement (Fig. 197.7). There is much overlap in the clinical features of necrotizing fasciitis and myonecrosis,[218,223] and the differentiation must be made by surgical inspection or biopsy.

Streptococcal Toxic Shock Syndrome

Strep TSS is defined as described in Table 197.2 but, simply put, it is any streptococcal infection associated with the sudden onset of shock and organ failure. Such cases were first described in the mid to late 1980s, and reports of strep TSS have subsequently emanated from North America, Europe, Australia, and Asia.[188,192,195,224–232] Most cases have occurred sporadically. The highest incidence of invasive streptococcal disease occurred in a small Minnesota community, where 26 cases per 100,000 population were recorded.[231] In addition, outbreaks of invasive group A streptococcal infections have occurred in closed environments, such as nursing homes[233–237] and hospitals.[238] Secondary cases of strep TSS are unusual, but transmission to family members[238,239] or health

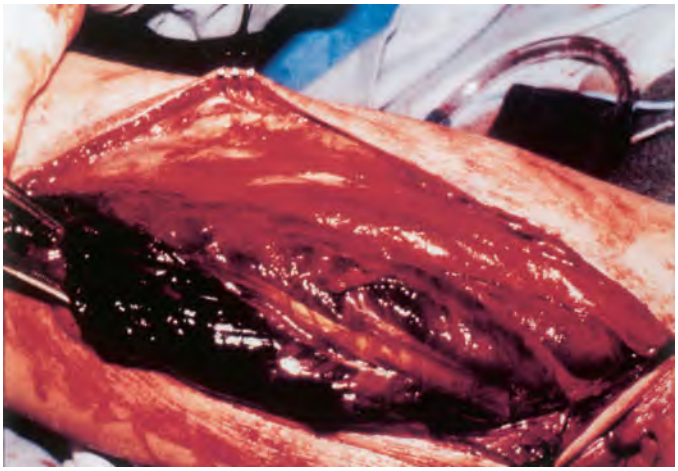

FIG. 197.7 Surgical exploration of patient with streptococcal toxic shock syndrome. This patient had necrotizing fasciitis and myositis that occurred spontaneously, with no prior injury to the site. *(From Stevens D. Streptococcal toxic shock syndrome.* Infect Med. *1992;9:33–39.)*

TABLE 197.2 Case Definition for the Streptococcal Toxic Shock Syndrome

I. Isolation of group A streptococci *(Streptococcus pyogenes)*
   A. From a normally sterile site (e.g., blood, cerebrospinal, pleural, or peritoneal fluid, tissue biopsy, surgical wound)
   B. From a nonsterile site (e.g., throat, sputum, vagina, superficial skin lesion)

II. Clinical signs of severity
   A. Hypotension: systolic blood pressure ≤90 mm Hg in adults or below fifth percentile for age in children
   and
   B. Two or more of the following signs:
      1. Renal impairment: creatinine ≥177 μmol/L (≥2 mg/dL) for adults or ≥2 times the upper limit of normal (ULN) for age; in patients with preexisting renal disease, a twofold or greater elevation over the baseline level
      2. Coagulopathy: platelets ≤100 × 10^{11}/L (≤100,000/mm^3) or disseminated intravascular coagulation defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
      3. Liver involvement: serum aspartate aminotransferase, alanine aminotransferase, or total bilirubin levels greater than or equal to two times the ULN for age; in patients with preexisting liver disease, a twofold or greater elevation over the baseline level
      4. Adult respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure, evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
      5. A generalized erythematous macular rash that may desquamate
      6. Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

[a]An illness fulfilling criteria IA and II (A and B) can be defined as a definite case. An illness fulfilling criteria IB and II (A and B) can be defined as a probable case if no other cause for the illness is identified.
From Defining the group A streptococcal toxic shock syndrome: rationale and consensus definition. The Working Group on Severe Streptococcal Infections. JAMA. *1993;269:390–391.*

TABLE 197.3 Factors That Increase the Likelihood of Developing Streptococcal Toxic Shock Syndrome

Age (neonates and older adults)
Diabetes
Alcoholism
Surgical procedures
Trauma
  Penetrating (insect bites, lacerations, slivers, abrasions, burns)
  Nonpenetrating (hematoma, bruise, muscle strain, hemarthrosis)
Varicella
  Contact with a case
  High prevalence of invasive strains in the community
Nonsteroidal antiinflammatory drugs[a]

[a]Based on limited evidence.

care workers[238,240] has been well documented by demonstrating identical pulsed-field gel electrophoresis patterns from cross-infecting strains. Although many of the studies cited earlier described strep TSS in adults, several reports have documented that this disorder also occurs in children.[225,230,231,241,242] Thus persons of all ages can be afflicted and, although some have underlying medical conditions such as diabetes and alcoholism,[225,227,243–247] many have no predisposing medical condition and are not immunocompromised. This contrasts sharply to reviews of group A streptococcal bacteremia from several decades ago[243–245] that found the disease to occur primarily among the very young, the very old, or patients with predisposing conditions, such as cancer, renal failure, leukemia, severe burns, or iatrogenic immunosuppression.

The portals of entry for streptococci are the vagina, pharynx, mucosa, and skin in 50% of cases.[8] Surgical procedures such as suction lipectomy, hysterectomy, vaginal delivery, bunionectomy, reduction mammoplasty, hernia repair, bone pinning, and vasectomy have provided portals in other cases (Table 197.3). Rarely, infection occurs secondary to streptococcal pharyngitis.[248–250] Virus infections such as varicella and influenza have provided portals of entry in other cases.[8,230,248]

Additional factors that increase the risk for invasive group A streptococcal infection, including bacteremia, strep TSS, and necrotizing fasciitis, are listed in Table 197.3. Three studies have demonstrated that a high or increasing prevalence of M-1 or M-3 strains among throat isolates may signal an increased incidence of strep TSS in a community.[230,246,251] NSAIDs taken for problems such as muscle strain, trauma, or postpartum pain may mask the early signs and symptoms of streptococcal infection or possibly predispose to more severe infection, such as necrotizing fasciitis or strep TSS.[8,252,253]

Pathogenesis

Entry of GAS into the deeper tissues and bloodstream may occur as a result of breach of a barrier, or the organism itself may penetrate intact mucous membranes, such as the pharyngeal mucosa. Although bacteremia is a very uncommon phenomenon in streptococcal pharyngitis, transient bacteremia must occur in those 50% of patients who develop invasive infections without a portal of entry. In either case, GAS avoid phagocytosis largely because of the antiphagocytic properties of M protein.[12] Adherence of GAS to pharyngeal mucosal cells is a prerequisite to colonization or infection and has been related to surface structures, such as lipoteichoic acid and fibronectin-binding proteins. Penetration or translocation of GAS through respiratory epithelial cells has been demonstrated for M-1 types of GAS. Some have suggested that those M-1 strains possessing an invasin *(inv+)* gene penetrate more efficiently.[254] If penetration of mucosal barriers occurs commonly, it does not result in clinically detectable bacteremia in the vast majority of patients because the incidence of invasive infection is very low, that is, 3.5 cases per 100,000 population.[255] Thus clearance of GAS must be highly efficient in the vast majority of humans either because of preexisting type-specific immunity or nonspecific clearance mechanisms in the reticuloendothelial system. Recent studies have suggested that after colonization of mucosa or skin, SpeB may play a role in attenuation of the local host response because of its proteolytic activity. Later in the growth cycle, group A streptococcal production of SpeB is curtailed through alteration of the control of virulence regulator (CovR), allowing these particular strains to bind plasminogen, evade the immune system, and switch to an invasive phenotype.[256]

How and why GAS cause deep infection of traumatized muscle and fascia in the absence of penetrating injury remains an enigma. Recent studies have demonstrated that injured muscle cells express vimentin on their surface during the healing and repair process and that GAS bind vimentin.[257] In addition, intravenously injected GAS traffic to the site of muscle injury, and this process is augmented in the presence of NSAIDs.[258] Although controversy remains regarding a link between NSAID use and increased risk and severity of group A streptococcal infections (for review see reference 259), experimental evidence from three independent laboratories supports this notion.[258,260,261]

Mechanisms of Shock and Organ Failure

Within the deeper tissues and bloodstream, the induction of cytokine synthesis plays a critically important role in the production of shock and organ failure. Pyrogenic exotoxins (scarlatina toxins, erythrotoxins) have the ability to cause fever, enhance susceptibility to endotoxin, suppress IgM antibody synthesis, and act as superantigens. These toxins, such as the staphylococcal enterotoxins (A, B, C) and TSST-1, can stimulate T-cell responses through their ability to bind to both the class II MHC antigen-presenting cells and the V-β region of the T-cell receptor.[262] The net effect is the induction of monocyte cytokines (tumor necrosis factor-α [TNF-α], interleukin [IL]-1β, and IL-6) as well as the lymphokines (TNF-β, IL-2, and interferon-γ).[263–269] There is evidence that M-protein fragments may also act as superantigens.[267] Pyrogenic exotoxins C and MF, as well as SSA and several new streptococcal pyrogenic exotoxins, are also capable of inducing massive quantities of proinflammatory cytokines and lymphokines,[268] which contribute to shock and organ failure. Some clinical studies have suggested that variation in human leukocyte antigen haplotype may predispose worse outcomes in some patients with strep TSS.[269]

Other streptococcal virulence factors are also capable of inducing proinflammatory cytokines, such as TNF-α and IL-1β. Specifically,

SpeB, a potent cysteine protease, causes release of IL-1β from preformed intracellular pools.[270] SLO also stimulates mononuclear cells to produce TNF-α and IL-1β and, in the presence of SpeA, has synergistic effects on IL-1β production.[271] Heat-killed GAS, as well as peptidoglycan and lipoteichoic acid, are also potent inducers of TNF-α and IL-1β.[272,273] Noncytokine mechanisms of shock may also play a role. A cysteine protease produced by GAS was shown to release bradykinin from a high-molecular-weight kininogen.[274] Bradykinin is a potent vasodilator of systemic and pulmonary vasculature and could be responsible, at least in part, for the early hypotension observed in strep TSS.[274] Recent studies demonstrated that SLO causes early, direct cardiomyocyte contractile dysfunction.[53] These effects were mediated by an influx of calcium through SLO-induced membrane pores. Upon removal of SLO, normal electrical pacing resumed, suggesting that membrane lesions were repaired and normal intracellular calcium levels were restored. These observations are consistent with the clinical observation that cardiomyopathy is a reversible condition in patients who survive strep TSS.[275]

Thus there are likely many streptococcal and host factors that contribute to the shock and organ failure characteristic of strep TSS. That TNF plays a central role is supported by two observations. First, high levels of TNF were observed in a baboon model of group A streptococcal bacteremia at a point in time when profound hypotension was manifest.[276] Second, in that model a neutralizing monoclonal antibody against TNF restored normal blood pressure and reduced mortality by 50%.[276] Diffuse capillary leak contributes to volume depletion and hypotension and is likely related to cytokine release but may also be related to circulating M-protein–fibrinogen complexes.[277] Recent evidence suggests that cardiomyocyte-derived cytokines are produced after direct *S. pyogenes* stimulation and after exposure to *S. pyogenes*–activated inflammatory cells.[278] In addition, viable *S. pyogenes* induced production of cardiomyocyte-derived stimulator(s) that boost(s) macrophage production of matrix metalloproteinase-9, proinflammatory cytokines (IL-1β, IL-6), and cardiodepressant factors (inducible nitric oxide synthase).[279] These locally produced, cardiomyocyte-derived cytokines, termed *cardiokines,* may further mediate cardiac contractile dysfunction in some patients with strep TSS.[275]

Clinical Manifestations

The first phase of strep TSS begins with an influenza-like prodrome characterized by fever, chills, myalgias, nausea, vomiting, and diarrhea that precedes hypotension by 24 to 48 hours.[8] Confusion and/or combativeness is present in 55% of patients. Where there is a defined or superficial portal of entry such as a laceration, suspicion of streptococcal infection or frank evidence of infection may be present at this phase of infection. In contrast, in patients without a portal of entry (50% of cases) and who subsequently develop necrotizing fasciitis or frank myonecrosis, postpartum infection, peritonitis, or joint space infection, pain that progressively increases in severity is the most common initial symptom that prompts patients to seek medical care and, of interest, precedes clinical evidence of localized infection by 12 to 24 hours.[8] In both children[230] and adults[8] the soft tissues are the most common primary site of infection. In the remaining cases, pneumonia, meningitis, endophthalmitis, peritonitis, myocarditis, joint infection, and intrauterine infection have been described.[8,230]

The second phase of strep TSS is characterized by tachycardia, tachypnea, persistent fever, and, in patients who subsequently have necrotizing fasciitis or myonecrosis, increasingly severe pain at the site of infection. In others, fever and severe pain are the best early clinical clues.[280] In children, toxicity during varicella or persistence of fever longer than 4 days should also prompt careful evaluation. Many patients are seen in emergency departments at this stage and frequently sent home, on one or two occasions with mistaken diagnoses, such as deep vein thrombophlebitis, muscle strain, viral gastroenteritis, dehydration, and sprained ankle.[219] High fever and excruciating pain, particularly in individuals with no risk factors for deep vein thrombosis, should arouse suspicion of a deep-seated infection. The laboratory tests described later are helpful, and CT and MRI may be useful to define the level of tissue injury but are not specific (see earlier discussion of necrotizing fasciitis).

The third phase of strep TSS is characterized by the symptoms and signs mentioned but with the sudden onset of shock and organ failure. Many patients are in florid shock at the time of admission, but in almost 50% of patients, hypotension is apparent during the first 4 to 8 hours after admission. Clinical evidence of necrotizing fasciitis is frequently a late finding, often occurring after hypotension is present. The appearance of purple bullae and dusky-appearing skin is a bad prognostic sign and should prompt emergent surgical exploration (see earlier discussion of necrotizing fasciitis). It should be noted that currently the progression of necrotizing fasciitis from red skin to purple bullae may take place within a 24-hour period, whereas that described by Meleney[217] in 1924 took 7 to 10 days. In addition, the rapidity with which shock and multiorgan failure can progress is impressive, and many patients die within 24 to 48 hours of hospitalization.[8]

Laboratory tests should be performed in patients with aggressive soft tissue infections or in patients with severe pain and fever who appear toxic. The serum creatinine measurement is particularly useful because renal impairment (creatinine level more than twice normal) is apparent even during the second phase, before hypotension is apparent. In addition, creatine phosphokinase levels in serum are markedly elevated in those with necrotizing fasciitis and myonecrosis. The WBC count is usually normal or elevated at admission but with a profound left shift that includes myelocytes and metamyelocytes. Finally, serum albumin and calcium levels are usually low on admission and drop precipitously as a diffuse capillary leak syndrome develops. Thrombocytopenia does not develop until later in the course but is the earliest sign of disseminated coagulopathy.[8] Profound metabolic acidosis develops early in the third phase, and serum bicarbonate, lactate, and blood gas pH determinations are crucial tests to follow therapeutic progress. Because the acute respiratory distress syndrome develops in 55% of patients with strep TSS, pulse oximetry and, later, blood gas levels are necessary to evaluate the need for intubation and ventilation.

Management

Source Control

Prompt and aggressive surgical exploration and débridement of suspected deep-seated streptococcal infection are mandatory. It is as important to establish the cause of the infection as it is to determine the extent of necrosis. CT and MRI are helpful to locate the primary site of infection, but because the GAS do not form gas or frank abscess, radiologic interpretations are frequently not definitive. Such findings in a patient with extreme pain and fever or who is toxic should prompt surgical consultation. Once necrosis is established, extensive débridement is necessary because shock and organ failure continue to progress if devitalized tissue remains. Although necrosis of the fascia may be present, it is important to know that necrosis of muscle, skin, and subcutaneous tissue also is commonly present.

Fluid Resuscitation

If several liters of crystalloid IV fluid challenge do not rapidly improve blood pressure (mean arterial pressure > 60 mm Hg) or tissue perfusion, then invasive monitoring is indicated. The goal should be to maintain a pulmonary artery occlusion pressure of 12 to 16 mm Hg.[281] If this goal is reached but hypotension persists, the serum albumin concentration and hematocrit should be checked because profoundly low albumin levels are common and because hemolysins produced by GAS can cause dramatic drops in circulating red cell mass. Thus transfusion with packed red blood cells, with or without albumin, may be useful to improve blood pressure and preserve tissue perfusion.

Because of intractable hypotension and diffuse capillary leak, massive amounts of IV fluids (10–20 L/day) may be required in an adult. Albumin replacement may be necessary because many patients' serum albumin levels decrease to lower than 2.0 g/dL.

Antimicrobial Therapy

Prompt antimicrobial therapy is mandatory, and empirical broad-spectrum coverage for septic shock should be instituted initially. Once the streptococcal cause is confirmed, high-dose penicillin and clindamycin should be given.[282] This recommendation is based on the following information: (1) all strains of GAS remain sensitive to penicillin; (2)

resistance to erythromycin is currently found in less than 5% of GAS in the United States, but the rate is higher in certain locales, and there have been rare reports of resistance to clindamycin; (3) clindamycin and erythromycin are more active in experimental models of necrotizing fasciitis and myonecrosis; (4) penicillin-binding proteins are not expressed during stationary-phase growth of GAS, and thus penicillin is ineffective in severe deep infections in which large numbers of bacteria are present; (5) clindamycin suppresses exotoxin and M-protein production by GAS; (6) clindamycin has a much longer half-life; (7) combinations of penicillin and clindamycin have indifferent interaction against GAS in vitro at clinically relevant concentrations of antibiotics (no antagonistic effects were found)[283]; and (8) clindamycin and azithromycin suppress cytokine production by human mononuclear cells.[284,285] Recent reports from China concerning scarlet fever after strep throat have documented azithromycin and clindamycin resistance in 100% of strains[63,82] suggesting that susceptibility testing should be performed in such patients, particularly those with severe symptoms and signs of pharyngeal or invasive infection.

Management in the Intensive Care Unit

In patients with persistent hypotension, monitoring of cardiac outputs, pulmonary artery occlusion pressure, and mean arterial pressure is important. Intubation and ventilator support are usually required because of the high incidence of acute respiratory distress syndrome (55%) in patients with strep TSS. Pressors such as dopamine are used frequently, although no controlled trials have been performed in strep TSS. In patients with intractable hypotension, high doses of dopamine, epinephrine, or phenylephrine have been used, but caution should be exercised in those with evidence of disseminated intravascular coagulation and in particular in those with cold, cyanotic digits. Symmetrical gangrene involving all 20 digits, the tip of the nose, ear lobes, and the breast areola have been described. In addition, we have observed amputation of one, two, three, and even four extremities. In these cases, both excessive pressors and disseminated intravascular coagulation likely contributed to symmetrical gangrene.

Dialysis and Hemoperfusion

Either of these methodologies may be necessary because greater than 50% of patients develop acute renal failure. Both dialysis and hemoperfusion may also nonspecifically reduce the concentrations of circulating toxins. It is interesting that a study from Sweden that used hemofiltration achieved the lowest mortality rate ever recorded in patients with strep TSS.[247] Finally, a polystyrene superantigen absorbing device was developed in Japan and shown to be highly efficacious in absorbing pyrogenic exotoxin A or TSST-1 from plasma and, when used extracorporeally in animals infused with TSST-1 and lipopolysaccharide, mortality improved from 100% to 50%.[286]

Intravenous Immune Globulin

The rationale for the use of intravenous immune globulin (IVIG) in the treatment of strep TSS is based on the data implicating extracellular exotoxins as mediators of shock and organ failure. George and Gladys Dick, in 1924, demonstrated that convalescent sera from patients with scarlet fever neutralized scarlatina toxins and, when passively administered, attenuated the course of severe scarlet fever.[287] Just as penicillin was becoming available, anti–scarlatina toxin horse serum became commercially available in the United States; however, because of the availability of penicillin and the decline in the severity of scarlet fever, it was never used. Several reports have described the successful use of IVIG in patients with strep TSS.[288–290] One large treatment group (15 patients) showed a significant reduction in mortality compared with matched historical controls.[291] The mortality rate of 70% in the control group was among the highest ever reported, whereas the rate was 30% in the IVIG group. This rate is similar to that of some series that did not use IVIG.[8] A recent comparative observational (retrospective) study in Sweden analyzed the outcomes of 67 patients with streptococcal TSS. Twenty-three patients were treated with IVIG and had a 28-day survival of 87%, whereas the non–IVIG-treated group had a 28-day survival of 50%.[292] A double-blind clinical trial was undertaken in northern Europe comparing IVIG with albumin in patients with strep TSS. All patients received clindamycin. The mortality rate in the IVIG group was 16%, whereas that in the albumin group was 32%.[293] Unfortunately, the study was stopped because of low enrollment, and only 7 or 8 patients with proven group A streptococcal infections were in each group. Thus the differences were not significant. A retrospective study in patients with strep TSS has also shown no benefit of IVIG on mortality.[294] It is hoped that further double-blind studies with sufficient numbers of cases will resolve the continuing dilemma regarding the potential efficacy of IVIG.[295] Until then, IVIG could be given early, and more than one dose should be used because batches of IVIG have variable neutralizing activity against streptococcal exotoxins.[268,296]

There have been no comparative trials describing the efficacy of hyperbaric oxygen treatment in strep TSS, although some state that such treatment reduces mortality and the need for further débridements.[297] Certainly, use of this modality should not delay or be used in preference to surgical débridement when the latter is indicated.

BACTEREMIA

Group A streptococcal bacteremia has been relatively uncommon in the antibiotic era.[298] Before the mid-1980s, bacteremia occurred predominantly at the extremes of life and was usually community acquired. Occasional cases were seen in young and middle-age adults associated with surgical wound infections and endometritis.

During the past decade, however, there has been an increase in the number of reported cases of group A streptococcal bacteremia, reflecting the changing epidemiology and clinical patterns of invasive streptococcal infection as noted earlier. Many of the patients were previously healthy adults between the ages of 20 and 50 years. There has been an apparent increase in cases associated with parenteral injection of illicit drugs,[8,98,245] as well as nosocomial outbreaks in nursing homes.[233–237]

Bacteremia in children may emanate from an upper respiratory tract infection, but it is more commonly associated with cutaneous foci, including burns and varicella.[240] Older patients with streptococcal bacteremia present with a variety of chronic illnesses; their relation to the bacteremia is often unclear. However, diabetes mellitus, cirrhosis, and peripheral vascular disease, and possibly fatty liver, appear to be predisposing factors in older adults,[299] and, as in children, the portal of entry is usually the skin. Malignancy and immunosuppression are risk factors in both age groups.[218,300] Although group A streptococcal bacteremia may at times be transient and relatively benign,[301] it is more often fulminant. The onset is abrupt, with chills, high fever, and prostration. Rarely, patients may present with acute abdominal pain.[301,302] Mortality in five modern series[243,301–304] has ranged from 27% to 38%.

OTHER STREPTOCOCCAL INFECTIONS

Lymphangitis may accompany cellulitis or may occur after clinically minor or inapparent skin infection. Lymphangitis is readily recognized by the presence of red, tender, linear streaks directed toward enlarged, tender, regional lymph nodes. It is accompanied by systemic symptoms, such as chills, fever, malaise, and headache. Puerperal sepsis follows abortion or delivery when streptococci colonizing the patient herself or transmitted from medical personnel invade the endometrium and surrounding structures, lymphatics, and bloodstream. The resulting endometritis and septicemia may be complicated by pelvic cellulitis, septic pelvic thrombophlebitis, peritonitis, or pelvic abscess. This disease was associated with high mortality in the preantibiotic era. Although endocarditis caused by *S. pyogenes* was relatively common in the preantibiotic era, it is now rarely reported.[305,306] Meningitis caused by *S. pyogenes* usually follows upper respiratory tract infection, including sinusitis or otitis,[307] or neurosurgical conditions.[308] It is indistinguishable clinically from other forms of acute pyogenic meningeal infection.[309]

Pneumonia caused by *S. pyogenes* is frequently associated with preceding viral infections such as influenza, measles, or varicella or with chronic pulmonary disease. Numerous epidemics have been described in military recruit populations.[310,311] An increased number of cases has been reported over the past few years in association with the resurgence of invasive streptococcal infections. In one-third or fewer of the cases, there was a history of preceding streptococcal upper respiratory tract infection. The onset is typically abrupt, and the disease

is characterized by chills, fever, dyspnea, cough productive of blood-streaked sputum, pleuritic chest pain, and, in more severe cases, cyanosis. The pulmonary picture is that of bronchopneumonia, with consolidation being uncommon. Empyema develops in 30% to 40% of cases, tends to appear early in the disease, and typically consists of copious amounts of thin serosanguineous fluid. Bacteremia occurs in 10% to 15% of cases. Complications include mediastinitis, pericarditis, pneumothorax, and bronchiectasis; and the clinical course of the disease is often prolonged. Recent case reports describe a rapidly fulminant hemorrhagic pneumonia associated with hypervirulent serotype M1 strains.[312] Outside of these cases, mortality has generally been low with penicillin therapy and adequate drainage of empyema, perhaps reflecting its occurrence in healthy military recruits. However, in a recent Canadian report of 222 cases of community-acquired pneumonia among adults (median age, 56 years), the case-fatality rate was 38%.[313] Of interest, a recent review of deaths in the 1918 pandemic of influenza has demonstrated that the major cause of death was secondary bacterial pneumonia.[314] Whereas *S. pneumoniae* was the most common cause, GAS was the second, and *S. aureus* was the third. Among patients with empyema complicating pneumonia, GAS was the most common cause. Investigators have demonstrated in a mouse model that a nonlethal influenza infection greatly enhanced the severity and mortality of secondary respiratory tract infection after challenge with GAS.[315]

Group A streptococcal perianal cellulitis and vulvovaginitis are symptomatic but benign disorders primarily affecting children.[316,317] Asymptomatic carriage of GAS in the vagina, anus, scalp, or, rarely, upper respiratory tract of adults has, however, been the source of outbreaks of nosocomial streptococcal infection.[318]

Prophylaxis and Risk for Secondary Cases of Streptococcal Toxic Shock Syndrome

Strep TSS is most commonly community acquired and sporadic, yet clusters of invasive cases have been described in nursing homes,[233–237] families,[238,239] and hospital workers.[240,319] In San Francisco 23 hospital workers became colonized or infected with GAS as a result of contact from a single case of strep TSS.[319] This example, as well as many historical studies in schools, military posts, and nursing homes, shows that GAS are highly contagious. Luckily, mere contact or colonization is usually not sufficient to cause a secondary case of invasive group A streptococcal infection. Epidemiologic studies by the Centers for Disease Control and Prevention found one secondary case of invasive infection among more than 1500 contacts.[162] This would extrapolate to 66 per 100,000 population per year for secondary cases.[320] As noted, the current incidence of primary cases of invasive group A streptococcal infections in the United States is 3.5 per 100,000 population per year. Thus the risk to contacts is roughly 20 times greater than that for the general population but is still very low. Given the relative infrequency of these infections and the lack of a clearly effective chemoprophylactic regimen, routine screening for and prophylaxis against streptococcal infection are not recommended for household contacts of index patients. In deciding who should receive prophylaxis, the clinician needs to factor in the duration of contact, intimacy of contact, and underlying host factors of individual contacts. Specifically, contacts with open wounds, recent surgery, recent childbirth, concurrent viral infections such as varicella or influenza, or immunodeficiency diseases should receive prophylaxis. In a multicenter study of adults age 18 to 45 years, HIV infection and injecting drug use were independently associated with an increased risk for invasive group A streptococcal disease. In those 45 years of age or older, diabetes, cardiac disease, cancer, and corticosteroid use were significant risk factors.[299] Moreover, adults 65 years or older are at increased risk for mortality should they contract invasive disease. Thus it may be prudent to initiate prophylaxis in households with older adults or those with the just-mentioned risk factors.

Lacking firm data on which to base antimicrobial prophylaxis, it seems reasonable to choose those agents that have achieved highest rates of pharyngeal eradication in asymptomatic individuals; among these are clindamycin and azithromycin. Specific regimens have been published elsewhere.[162]

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The complete reference list is available online at Expert Consult.

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198 Nonsuppurative Poststreptococcal Sequelae: Rheumatic Fever and Glomerulonephritis

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SHORT VIEW SUMMARY

Definitions
- Acute rheumatic fever (ARF) and acute poststreptococcal glomerulonephritis (APSGN) are immune-mediated illnesses that develop after some group A streptococcal infections.
- ARF predominantly affects the heart and joints and can lead to chronic rheumatic heart disease, whereas APSGN is an immune complex nephritis.

Epidemiology
- ARF can follow an untreated group A streptococcal infection of the pharynx in individuals who appear to be genetically susceptible.
- ARF is most frequent in children 5 to 15 years of age and occurs most commonly in winter or spring.
- ARF now is much less common in developed areas of the world, compared with several decades ago. Most cases now occur in developing countries or in minority populations within Australia and New Zealand. In North America, there appears to be increased incidence in Mormon populations and Orthodox Jews in New York, perhaps related to large family size.
- APSGN can follow group A streptococcal infections of the skin or throat.
- Postpharyngeal APSGN occurs mainly in school-age children in winter or spring, whereas postpyoderma APSGN is most common in pre–school-age children in late summer or fall.

Microbiology
- Certain M types of group A streptococci (GAS; M-1, M-3, M-5, M-6, M-14, M-18, M-19) are considered rheumatogenic, that is, they have much greater ability to trigger the immune events that result in ARF when compared to nonrheumatogenic types. The molecular basis of rheumatogenicity is unknown.
- Nephritogenic M types of GAS are those with great propensity to lead to APSGN, specifically M-1, M-4, M-12, and M-25 after pharyngitis and M-2, M-9, M-55, M-57, M-59, M-60, and M-61 after pyoderma. The specific antigen(s) involved in this immune complex nephritis is still somewhat unclear.

Diagnosis
- Diagnosis of ARF is based upon the Jones criteria, comprising five major criteria, four minor criteria, and a requirement for evidence of antecedent group A streptococcal infection. The Jones criteria revision of 2015 expanded the definition of carditis to include echocardiographic evidence without a murmur and established slightly different minor criteria for patients from low-risk geographic areas and moderately high-risk areas.
- The five major Jones criteria are carditis, arthritis, chorea, erythema marginatum, and subcutaneous nodules. The four minor criteria are fever, arthralgia, elevated acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein), and prolonged PR interval. Diagnosis of ARF requires one major plus at least two minor criteria or two major criteria plus evidence of antecedent group A streptococcal infection.
- The diagnosis of APSGN is generally based upon acute onset of hematuria with hypertension, azotemia, and hypocomplementemia, and with evidence of recent streptococcal pharyngitis or pyoderma.

Therapy
- Treatment of ARF includes an antiinflammatory agent (aspirin for those with arthritis, mild carditis, or both; corticosteroids for those with moderate or severe carditis [see Table 198.3]); an agent such as phenobarbital, diazepam, haloperidol, valproate, or risperidone for those with chorea; and a prophylactic antibiotic (see "Prevention" later). A single dose of intramuscular (IM) benzathine penicillin (or an alternative agent for penicillin-allergic individuals) is indicated.
- Treatment of APSGN includes correction of circulatory overload and hypertension by salt and fluid restriction, diuretics as needed, and antihypertensives only if severe hypertension or hypertensive encephalopathy is present. Immunosuppressives are not beneficial.

Prevention
- Because ARF frequently recurs with subsequent group A streptococcal pharyngitis episodes, long-term prophylaxis is indicated with IM benzathine penicillin every 4 weeks or oral penicillin V twice daily, or with a daily sulfadiazine, macrolide, or azalide for penicillin-allergic individuals (see Table 198.4), usually at least until age 21.
- Because APSGN only very rarely recurs, no preventative antibiotic therapy is indicated.

RHEUMATIC FEVER

Acute rheumatic fever (ARF) is a disease characterized by nonsuppurative inflammatory lesions involving primarily the heart, joints, subcutaneous tissues, and central nervous system. In its classic form, ARF is acute, febrile, and largely self-limited. However, damage to heart valves may occur, and such damage may be chronic and progressive and lead to severe cardiac failure, total disability, and death many years after the acute attack. The manifestations of ARF are extremely variable; the disorder remains for the most part a clinical syndrome for which no specific diagnostic test exists. All cases of ARF follow group A streptococcal upper respiratory tract infection, although the exact mechanisms mediating development of the disease remain speculative. Persons who have suffered an attack of ARF are predisposed to recurrent episodes after subsequent group A streptococcal infections.

History

Guillaume de Baillou (1538–1616), also known as Ballonius, first clearly distinguished acute arthritis from gout. Thomas Sydenham (1624–1689) described chorea but failed to associate this entity with other manifestations of ARF. Raymond Vieussens (1641–1715) published pathologic descriptions of mitral stenosis and aortic insufficiency. It remained, however, for William Charles Wells, in 1812, to emphasize the association of rheumatism and carditis and to provide the first clear description of subcutaneous nodules. Jean-Baptiste Bouillard, in 1836, and Walter B. Cheadle, in 1889, published extensive studies of rheumatic arthritis and carditis that synthesized the syndrome of rheumatic fever and have come to be regarded as classic works in this field and that form the basis for modern clinical concepts of ARF. In 1904, Ludwig Aschoff described the specific rheumatic lesion in the myocardium.[1]

In 1880, J. K. Fowler pointed out the association between sore throat and rheumatic fever from his personal experience and, shortly after the dawn of the 20th century, Bela Schick identified ARF as one of the "nachkrankheiten" (sequelae) of scarlet fever. The introduction of Rebecca Lancefield's grouping system for β-hemolytic streptococci allowed clarification of the epidemiology of the disease by a number of investigators in the United States and the United Kingdom, including Coburn, Collis, Rammelkamp, Denny, Wannamaker, Massell, and Stollerman. Finally, the widespread introduction of antibiotic agents after World War II resulted in the development of strategies for primary and secondary prevention of rheumatic fever.[1]

Etiology and Pathogenesis

ARF is a delayed nonsuppurative sequela of upper respiratory infection caused by group A streptococci (GAS), a conclusion firmly supported by several lines of evidence. There is a close temporal relationship between epidemics of streptococcal sore throat and scarlet fever and epidemics of ARF. About two-thirds of patients with ARF relate a history of preceding pharyngitis; even in the absence of such clear-cut evidence, elevated serum levels of antistreptococcal antibodies almost always document recent streptococcal infection. Prospective studies of primary and recurrent ARF have shown that this disease occurs only after an immunologically significant streptococcal infection. Finally, continuous antimicrobial prophylaxis, when successful in preventing intercurrent group A streptococcal infections, also effectively prevents ARF recurrences in rheumatic persons.

An intriguing and as-yet unexplained aspect of the host-parasite relationship is the fact that, as far as is known, cutaneous streptococcal infections do not initiate ARF. This may indicate a requirement for the pharyngeal site, with its rich endowment of lymphoid tissue, for initiation of the disease process, or it may result from a lack of rheumatogenicity among the so-called pyoderma strains of GAS. However, some suggest that cutaneous infections might play a role in the etiology of ARF, based on epidemiologic observations and circulating GAS strains in hyperendemic areas, but this remains unclear.[2,3]

Host genetic factors appear to influence the susceptibility to ARF. Observational studies in the 19th century recognized familial tendencies to develop ARF, and in the early 1940s, studies showed familial tendencies to develop the disease, with greater risk occurring in children if both parents had rheumatic heart disease.[4] Considerable efforts examining human leukocyte antigen type predisposition to ARF have been undertaken, and more recently, an allele in an immunoglobulin heavy-chain locus was shown to be associated with rheumatic heart disease in Micronesian populations.[5] Alternatively, clustering by family also might reflect differences in the microbiome.

A substantial body of evidence indicates that GAS do vary in their rheumatogenic potential. Studies of outbreaks of streptococcal pharyngitis show that strains of certain M serotypes or genotypes are strongly and repeatedly associated with ARF (Table 198.1),[6] whereas strains of other equally prevalent types fail to initiate the disease or even to reactivate it in exquisitely susceptible hosts.[7] Investigations of endemic ARF cases in Trinidad[8] and Chile[9] indicated that streptococci causing ARF belong to different serotypes than those causing acute glomerulonephritis (AGN) when the conditions occur simultaneously in the same population. Strains of GAS isolated from ARF patients may, however, differ widely in different geographic locales.[10] Although the association of pyoderma strains of GAS (see Chapter 197) with ARF has been postulated by Australian investigators,[10,11] such strains have never been definitively associated with ARF[12,13] even when, as sometimes occurs, they colonize the throat. A study comparing group A streptococcal pharyngitis serotypes in Chicago in the 1960s, when ARF was common, to serotypes causing pharyngitis from 2001 to 2007, when ARF was very uncommon, showed marked reduction in circulating rheumatogenic types in the latter period.[14]

Rheumatogenic streptococcal strains exhibit distinct biologic characteristics. Their M protein molecules share a particular surface-exposed antigenic domain against which ARF patients mount a strong immunoglobulin G (IgG) response.[15] These strains fail to elaborate α(l)-lipoproteinase (so-called streptococcal opacity factor), and they are frequently heavily encapsulated.[16,17] The latter feature is manifested by the formation of mucoid colonies on blood-agar plates. Whether such strains express a unique rheumatogenic antigen, however, remains unknown.

TABLE 198.1 M Serotypes of Group A Streptococci Associated with Nonsuppurative Sequelae in the Western Hemisphere

ACUTE RHEUMATIC FEVER	PHARYNGITIS-ASSOCIATED AGN	PYODERMA-ASSOCIATED AGN
1	1	2
3	4	49[b]
5	12	55[b]
6	25	57
14		59
18		60
19		61
24		

[a]This list represents the major serotypes known to be associated with acute rheumatic fever and AGN in the Western Hemisphere, but it is not all-inclusive. M types of streptococcal strains isolated from various geographic areas vary widely.[10,184]
[b]M types 49 and 55 have also been reported on occasion to cause pharyngitis-associated AGN.
AGN, Acute glomerulonephritis.

It is probable that not all strains of rheumatogenic serotypes are equally dangerous. The propensity of a given strain to cause ARF likely depends on its degree of virulence, a reflection of quantitative factors such as expression of M protein, hyaluronate, or other less well-defined biologic properties. Virulence is likely to be enhanced in epidemiologic settings that favor rapid person-to-person transmission.

Although GAS is the causative agent of rheumatic fever, the exact mechanism whereby this microorganism induces the disease remains unexplained. Several theories have been advanced. These include the following: (1) toxic effects of streptococcal products, particularly streptolysins S or O, which are known to be capable of inducing tissue injury; (2) serum sickness–like reaction mediated by antigen-antibody complexes, perhaps localized to sites of tissue injury; (3) autoimmune phenomena induced by similarity or identity of certain streptococcal antigens to a wide variety of human tissue antigens[18]; and (4) binding of streptococcal M protein to the CB3 region of collagen type IV, which may trigger antibody to collagen, leading to ground substance inflammation in the subendothelial matrix of endothelium and perivascular connective tissue.[19]

Although none of these theories has been unequivocally proved or refuted, most attention has been focused on the concept of autoimmunity related to molecular mimicry.[20] Interest in this mechanism has been spurred by the identification of antibodies in the sera of patients with ARF or rheumatic heart disease (RHD) that react with the human heart in a variety of test systems. These so-called heart-reactive antibodies (HRAs) are also present at a much lower titer in sera of patients with uncomplicated streptococcal pharyngitis. The presence of bound immunoglobulin and complement in the myocardia of children dying of rheumatic carditis suggests that circulating HRAs may have pathogenetic significance.

Molecular techniques have been used to study the relationship between specific peptides of the M protein molecule and human tissues. Epitopes of streptococcal M proteins have been identified that share antigenic determinants with cardiac myosin,[21,22] sarcolemmal membrane proteins,[23] synovium, and articular cartilage.[24]

Goldstein and colleagues[25] described a cross-reaction between group A streptococcal polysaccharide and a structural glycoprotein of human and bovine heart valves. Such a cross-reaction might explain the observation that serum levels of antibody to group A streptococcal carbohydrate appear to remain elevated for many years in patients with rheumatic valvulitis but not in rheumatic patients without valvulitis,[26] and the levels decline remarkably after valve resection.

There is evidence that antibody to cardiac myosin in rheumatic carditis targets the S2 region and is similar among diverse populations worldwide.[27] Many children with Sydenham chorea have circulating antibodies that react both with neurons of the caudate and subthalamic nuclei and with group A streptococcal cell wall carbohydrate.[28] Taken together, these cross-reactive and toxic phenomena could explain most of the individual manifestations of ARF. On the other hand, it should be emphasized that no direct proof exists that these systems play any role in the pathogenesis of rheumatic fever.

Much of the work reviewed in the preceding paragraphs, particularly that related to HRAs and group A streptococcal carbohydrate, focused on humoral immune responses to streptococci. Indeed, serum antibody responses to streptolysin O, non–type-specific M-related antigens, and almost every other streptococcal antigen are, on average, more vigorous in patients with ARF than in those with uncomplicated streptococcal infections. However, it is likely that cellular immune responses to streptococcal antigens also play a critical role in the etiology of ARF.[29,30] Preparations of streptolysin S contain a nonspecific mitogen that is closely related but separable from the hemolytic activity. In rheumatic persons, lymphocyte reactivity to streptococcal cell walls and membranes is heightened, but the reactivity to membranes is more striking and persists for several years after an acute attack.[31] During active rheumatic carditis, both the number of helper (CD4) lymphocytes and the ratio of CD4 to CD8 cells are increased in heart valves as well as in peripheral blood.[32,33] Production of interleukin-1[34] and interleukin-2[34,35] is enhanced. That both M protein[36] and streptococcal pyrogenic exotoxins[37] function as superantigens suggests a potential mechanism mediating the unrestrained immunologic assault postulated to cause ARF.

Pathologic Findings

Rheumatic fever is characterized pathologically by the presence of exudative and proliferative inflammatory lesions of connective tissue, most notably in the heart, joints, blood vessels, and subcutaneous tissue.[38] In the early stages of the disease, there is fragmentation of collagen fibers, cellular infiltration that is predominantly lymphocytic, and fibrinoid deposition. This is followed shortly by the appearance of the myocardial Aschoff nodule (Fig. 198.1). The Aschoff nodule is a perivascular focus of inflammation that consists of an area of central necrosis surrounded by a rosette of large mononuclear and giant multinuclear cells. The nuclei of these cells may contain a clear area just within the nuclear membrane (owl-eyed nucleus) or present a serrated (caterpillar) appearance, depending on their orientation in microscopic cross section. Such cells are known as Anichkov myocytes, although immunohistochemical studies demonstrated that they are of macrophage-histiocyte origin.[39,40] Cardiac findings may include pericarditis, myocarditis, endocarditis, or combinations of these. Endocarditis involves the left side of the heart in almost all instances. A thickened and roughened area is frequently seen in the left atrium above the base of the posterior leaflet of the mitral valve (MacCallum patch). Valvular lesions begin as edema and cellular infiltration of the leaflets and chordae, with small verrucae along the line of closure. As healing progresses, the valves may become thickened and deformed, the chordae shortened, and the valve commissures fused, thereby resulting in valvular insufficiency with stenosis manifesting years later.

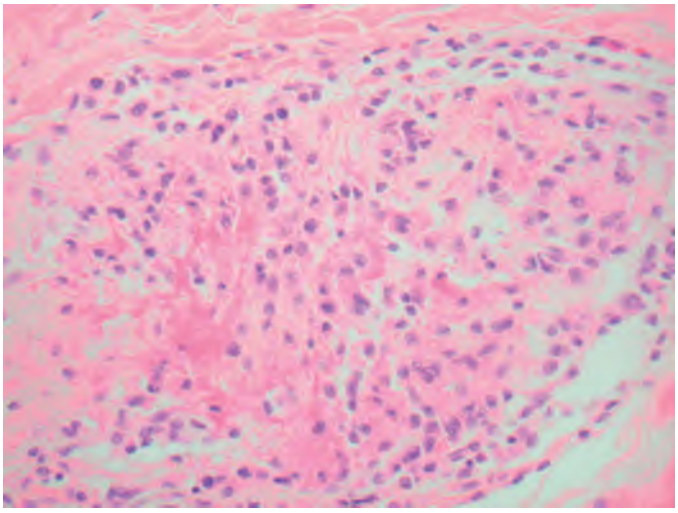

FIG. 198.1 Aschoff nodule.

The joint lesions are characterized by fibrinous exudate over the synovial membrane and serous effusion without joint destruction. Histologic findings include cellular infiltration and fibrinoid degeneration. Subcutaneous nodules resemble Aschoff bodies in many features. They consist of a central zone of fibrinoid necrosis surrounded by histiocytes and fibroblasts; perivascular accumulations of lymphocytes and polymorphonuclear leukocytes are also apparent. Although scattered areas of arteritis and petechial hemorrhages have been found in the brain, their relationship to Sydenham chorea remains uncertain.

Epidemiology

ARF is most frequent in children ages 5 to 15 years. Only approximately 5% of cases occur in children younger than 5 years.[41] Indeed, its relative rarity in infants and pre–school-aged children has led to the idea that repeated "primary" infections might be a precondition for the development of this disease. Both initial and recurrent episodes also occur in adults uncommonly.[42–44] There is no clear-cut gender predilection, although a female preponderance exists in certain clinical manifestations, notably mitral stenosis and Sydenham chorea when the latter occurs after puberty. In temperate climates, rheumatic fever tends to occur more during winter or spring and less frequently during the summer.

It is difficult for North American physicians to comprehend the magnitude of the problem of ARF in developing countries. The disease is highly endemic in the Middle East, the Indian subcontinent, and selected areas of Africa and South America.[45,46] The World Health Organization has estimated that approximately a half-million individuals worldwide acquire rheumatic fever annually, of whom 300,000 develop RHD. More than 15 million persons have been estimated to be living with this disease, and 319,000 die each year from RHD or its complications.[47,48] Extraordinarily high rates of ARF and RHD are seen in Aboriginal populations, such as those in New Zealand and Australia, and in Pacific Islanders. The annual incidence of ARF in Aboriginal children ages 5 to 14 years in Australia's Northern Territory was 150 to 380 per 100,000, and the point prevalence of RHD among the Aboriginal population has approached 2%.[2] In addition, the recognition that silent mitral regurgitation is common in school-age populations in many parts of the developing world may lead to a large increase in the estimated number of individuals affected by ARF/RHD.[49–52]

The overall incidence of ARF in the United States cannot be ascertained precisely because of inherent difficulties in diagnosing the disease and because most states no longer maintain rheumatic fever registries. There is general agreement, however, that the incidence of ARF and RHD declined markedly during the 20th century in the United States and Western Europe. The rate of decline appears to have been particularly steep during the 1960s and 1970s. A survey in Memphis, Tennessee,[53] indicated that during 1977 through 1981, the incidence of ARF in white suburban schoolchildren was only 0.5 per 100,000 annually. Similar rates were reported from many geographic areas of the United States. Traditionally, ARF in the United States was largely a disease of lower socioeconomic groups. The incidence was much higher in blacks than whites,[53,54] a fact that appears to relate to basic environmental conditions rather than to any genetic predisposition of blacks for the development of ARF. The major identified predisposing environmental condition is household crowding. The degree of crowding markedly influences the acquisition rate of GAS (see Chapter 197) and hence the risk of development of ARF.[55]

In the mid-1980s, a resurgence of ARF occurred in many communities in the United States.[56] Beginning in early 1985, an epidemic occurred in Salt Lake City, Utah, and the surrounding intermountain area.[55] By 2000, more than 500 cases had been diagnosed at the Primary Children's Medical Center in Salt Lake City. Smaller clusters of ARF, ranging from 15 to 40 cases, were reported during approximately the same time period from the following regions: Columbus and Akron, Ohio; Pittsburgh,

Pennsylvania; Nashville and Memphis, Tennessee; Kansas City, Missouri; Morgantown and Charleston, West Virginia; Dallas, Texas; and New York City, New York. Moreover, for the first time in many years, outbreaks occurred in army and navy training camps.[56–59]

Quite surprisingly, several of the 1980s civilian outbreaks[55,60] involved children of middle-class families residing in suburban or rural settings. The group A streptococcal strains most strongly associated epidemiologically with these ARF outbreaks belong to the well-recognized rheumatogenic serotypes (e.g., types M-1, M-3, M-5, M-6, and M-18); particularly prominent in this regard were highly mucoid strains of M-18.[17,61] Since the 1980s ARF has been very uncommon in most areas of the mainland United States, though outbreaks of rheumatic fever have been reported in the United States, such as that which occurred in Utah in the 1980s.[62]

Persons who have suffered an initial attack of ARF have a marked predilection to develop recurrences after subsequent episodes of streptococcal pharyngitis. The risk of recurrence after streptococcal infection is highest within the first few years after the initial attack and then declines. It is unclear whether the reason for this decline is the length of time since the preceding attack or the older age of the patient. Nevertheless, rheumatic patients remain at an increased risk of recurrence well into adult life. Two other factors that positively correlated with a risk of rheumatic recurrences after streptococcal infection are the magnitude of the anti–streptolysin O (ASO) response and the presence of preexisting heart disease. In the classic studies conducted at Irvington House, New York,[63] for example, 56% of streptococcal infections occurring in persons with RHD and accompanied by fourfold or higher ASO titer rises induced an ARF recurrence.

Clinical Manifestations

Rheumatic fever manifests itself as a variety of signs and symptoms that may occur singly or in combination. The most important of these, in terms of diagnosis, have been termed the *major manifestations* and include carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum. Certain additional findings frequently present in ARF, but those nonspecific in nature constitute the so-called *minor manifestations:* fever, arthralgia, first-degree heart block, and acute-phase reactants in the blood (C-reactive protein [CRP], leukocytosis, and erythrocyte sedimentation rate [ESR]).

The latent period between the onset of preceding streptococcal sore throat and the onset of ARF averages 19 days.[64] The range is 10 days to 5 weeks. The average latent period is the same for recurrent attacks as for initial episodes.

The mode of onset is variable. If acute polyarthritis is the initial complaint, the disease may have a rather abrupt onset and may be marked by fever and toxicity. On the other hand, when isolated mild carditis is the initial manifestation, the onset of ARF may be insidious or even subclinical.

Most attacks begin with polyarthritis. Carditis, if it appears, usually does so early in the course of the disease. Overall, arthritis occurs in approximately 75% of first attacks of ARF, clinically evident carditis in 40% to 50%, chorea in 15%, and subcutaneous nodules and erythema marginatum in less than 2%.[65,66] These incidences vary with age; carditis occurs most frequently when ARF strikes younger children, whereas the proportion of cases with arthritis increases with the age of the patient.

Carditis is the only manifestation of ARF that has the potential to cause long-term disability or death. Heart involvement in ARF may be pancarditis involving the endocardium, myocardium, and pericardium. While myocarditis and pericarditis may occur in ARF, the predominant manifestation of carditis is involvement of the endocardium presenting as valvulitis. Thus myocarditis or pericarditis without evidence of valvulitis is inconsistent with ARF. Nevertheless, in the absence of high fever or symptoms of acute pericarditis or congestive heart failure, it may be asymptomatic. Carditis almost always manifests itself within the first 3 weeks of an attack of ARF, if it appears at all. The clinical signs of carditis include the development of organic heart murmur(s) not previously present, cardiac enlargement, congestive heart failure, pericardial friction rubs, or signs of effusion. Because echocardiography is superior to auscultation for detection of valvular pathology,[67] the 2015 Jones criteria were revised to include mitral regurgitation demonstrated using

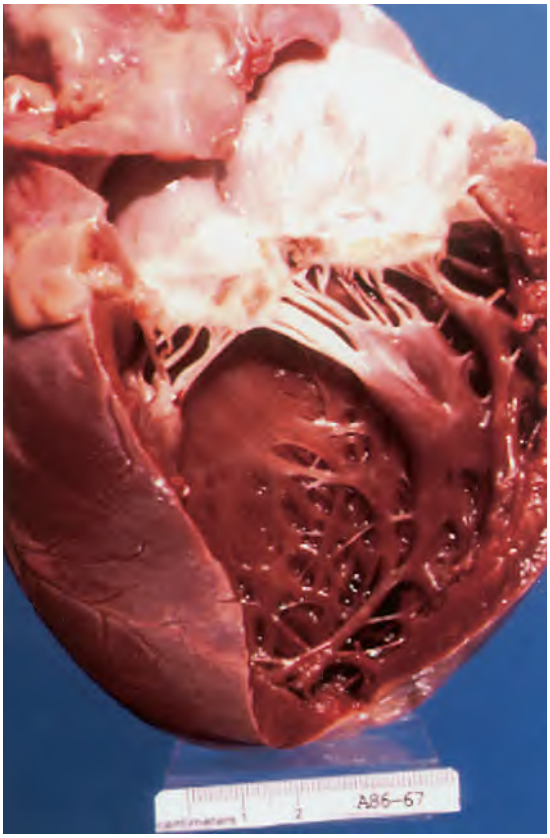

FIG. 198.2 Chronic rheumatic valvular heart disease. The mitral valve leaflets and chordae are thickened, fibrotic, and distorted; intercommissural adhesions are present. *(Courtesy Dr. L. Alvarez, Veterans Administration Medical Center, Miami, FL.)*

echocardiography. Thus now both pathologic and physiologic criteria that meet World Heart Federation criteria (rather than only pathologic) valvular involvement fulfills the criterion for carditis.[68] Intractable heart failure with pancarditis may cause death in the acute phase of ARF, but this is rare. Echocardiographic studies show that patients with ARF and congestive heart failure have preserved left ventricular systolic function and severe mitral or aortic regurgitation or both.[69–72] Serum levels of cardiac troponin I are not elevated in ARF patients with congestive heart failure.[69–73] Thus the cause of heart failure appears to be acute valvular dilatation rather than myocarditis.[74]

Chronic inflammatory changes involving the myocardium and endocardium may lead to the delayed development of chronic RHD (Fig. 198.2). Endocarditis involves the mitral valve more frequently than the aortic valve. There are three characteristic murmurs of acute rheumatic carditis: a high-pitched blowing holosystolic apical murmur of mitral regurgitation, a low-pitched apical mid-diastolic flow murmur (Carey Coombs murmur), and a high-pitched decrescendo diastolic murmur of aortic regurgitation at the secondary and primary aortic areas. Murmurs of mitral and aortic stenosis are associated with chronic but not with acute rheumatic valvular disease. The tricuspid valve is involved much less frequently and the pulmonic valve very rarely. Delayed atrioventricular conduction, as manifested by first-degree or greater degrees of heart block,[75] is a toxic phenomenon associated with ARF but is not in itself diagnostic of rheumatic carditis.

Joint involvement in ARF ranges from arthralgia without objective findings to frank arthritis characterized by heat, swelling, redness, and exquisite tenderness. There is an inverse relationship between the severity of joint involvement and the risk of development of carditis.[76] The most frequently involved joints are the knees, ankles, elbows, and wrists. The small joints of the hands are less frequently affected, and the spine is only rarely involved. When the course of the illness has not been suppressed by antiinflammatory drugs, classically, multiple joints are usually involved; approximately 50% of patients develop arthritis in more than

six joints. Arthritis in ARF is typically migratory in nature, that is, the inflammation travels from joint to joint. Once a joint becomes involved, inflammation begins to subside within a few days to a week. The evolution of arthritis in individual joints tends to overlap, so multiple joints may be inflamed at the same time. The typical migratory polyarthritis pattern may not be present, however, if effective antiinflammatory therapy is administered early in the course of the disease. In ARF, arthritis responds dramatically to salicylates or nonsteroidal antiinflammatory drugs (NSAIDs), and the absence of such a response should call the diagnosis into question. Moreover, the classic migratory pattern is not invariable. In some cases, the pattern may initially be additive, persisting in several joints simultaneously or even, rarely, monoarthritic.[77] It should be noted that the 2015 revision of the Jones criteria introduces less stringent arthritis/arthralgia criteria only for those individuals in moderate- and high-risk populations[78] (Table 198.2).

In most cases, the entire bout of polyarthritis subsides within 4 weeks, leaving no residual articular damage or deformity. One possible exception to this is the very rare occurrence of the so-called Jaccoud form of periarticular fibrosis after rheumatic arthritis.

The existence of poststreptococcal reactive arthritis distinct from ARF has been postulated to occur in some patients whose arthritis is atypical in time of onset or duration,[44] is nonmigratory, is unaccompanied by other major manifestations of rheumatic fever, and fails to respond promptly to salicylate therapy.[79–81] The ultimate prognosis of such cases is unknown, but, in a very few cases, mitral valve disease has apparently ensued.[82–84] Although the issue remains controversial,[85] it seems prudent to consider all cases of poststreptococcal polyarthritis that fulfill the Jones criteria as representing ARF,[79] provided that other common causes of polyarthritis have been excluded.[86–88]

Subcutaneous nodules are rare but are almost always associated with severe carditis and tend to occur several weeks after its onset. They are firm and painless and vary in size from a few millimeters to 2.0 cm. Such nodules are usually found over extensor surfaces or prominences and over tendons. Common sites are adjacent to elbows, knees, wrists, or ankles and over Achilles tendons, the occiput, or spinous processes of the vertebrae. Their number varies from one, requiring a thorough physical examination to detect, to a few dozen, which can be quite prominent as described in 1889 by Cheadle (Fig. 198.3). They usually persist for a few weeks. Somewhat similar but more persistent lesions are seen in rheumatoid arthritis. Pathology of the lesions is variable depending on the time since onset, but usually includes fibrous tissue (increasing in older lesions) and polymorphonuclear cells, as described by Jones in 1937 (Fig. 198.4).

Erythema marginatum is a rare nonpruritic, nonpainful erythematous eruption usually seen on the trunk or proximal aspects of the extremities but rarely, if ever, on the face. The individual lesions are evanescent, moving over the skin in serpiginous patterns that can change before the observer's eyes and are often likened to smoke rings, with a tendency

TABLE 198.2 2015 Revision of the Jones Criteria for the Diagnosis of Acute Rheumatic Fever in the Era of Doppler Echocardiography

CRITERIA	LOW-RISK POPULATIONS[a]	MODERATE-HIGH-RISK POPULATIONS
Criteria required	Initial diagnosis: 2 major manifestations or 1 major plus 2 minor manifestations Recurrent ARF: 2 major or 1 major and 2 minor or 3 minor	
Major Criteria		
Carditis	Carditis: clinical and/or subclinical[b]	
Arthritis	Polyarthritis only	Monoarthritis or polyarthritis OR polyarthralgia[c]
Erythema marginatum Subcutaneous nodules Chorea		
Minor Criteria		
Arthralgia[d]	Polyarthralgia	Monoarthralgia
Fever	≥38.5°C	≥38.0°C
Inflammatory markers	ESR[e] ≥60 or CRP[e] ≥3.0 mg/dL	ESR[e] ≥30 or CRP[e] ≥3.0 mg/dL
Prolonged PR interval	After accounting for age variability (unless carditis is a major criterion)	

[a]Low risk is defined as ≤2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of ≤1 per 1000; moderate-high risk is defined as >2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of >1 per 1000.
[b]Subclinical carditis indicates echocardiographic valvulitis.
[c]See section in Gewitz and colleagues[78] on 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. In addition, joint manifestations can only be considered in either the major or minor categories but not both in the same patient.
[d]Joint manifestations can only be considered in either the major or minor categories but not both in the same patient.
[e]CRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.
ARF, Acute rheumatic fever; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate.
From Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. *2015;131:1806-1818.*

FIG. 198.3 Subcutaneous nodules.

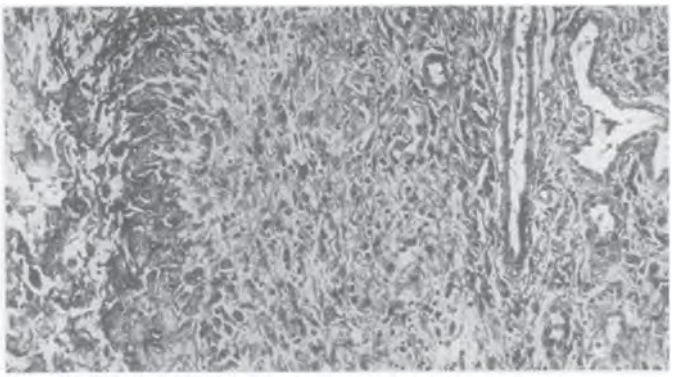

FIG. 198.4 Pathology of subcutaneous nodules. *Right,* Perivascular edema with lymphocytic infiltration from a subcutaneous nodule resected 7 days after detection. *Left,* Necrotic edematous collagen.

FIG. 198.5 Erythema marginatum: annular plaques (complete rings) of varying sizes, with macular centers and erythematous raised margins. Note the serpiginous borders formed by coalescence of several partial rings. *(Courtesy Dr. M. Tyrell, Saskatoon, Saskatchewan, Canada; and from Bisno AL. Noncardiac manifestations of rheumatic fever. In: Narula J, Virmani R, Reddy KS, et al, eds.* Rheumatic Fever. *Washington, DC: Armed Forces Institute of Pathology; 1999;245-256.)*

to advance at the margins while clearing in the center (Fig. 198.5). The lesions are usually macular with slightly raised margins and appear to be more a vasomotor phenomenon than a manifestation of cutaneous pathologic changes. Individual lesions may come and go in minutes to hours, but the process may go on intermittently for weeks to months and can be exacerbated by a warm cloth. Histopathologic examination may show perivascular infiltration of lymphocytes and neutrophils in the dermis.[89]

Sydenham chorea (St. Vitus dance) is a neurologic disorder characterized by emotional lability, muscular weakness, and rapid, uncoordinated, involuntary purposeless movements. The choreiform movements disappear during sleep and may be partially suppressed by sedation. The nonrhythmic movements are most notable in the face, hands, and feet. Sensation remains intact. Detailed descriptions of the nature of the choreiform movements can be found elsewhere.[1,90] Individual attacks in hospitalized patients usually last 2 to 4 months.

Chorea may occur in close temporal association with other major rheumatic manifestations or in isolated form (pure chorea). In cases of pure chorea, laboratory evidence of acute inflammation (elevated CRP, elevated ESR) or recent streptococcal infection (elevated levels of antistreptococcal antibodies) may be lacking. This observation, which led investigators in the past to question the relationship of ARF to pure chorea, is now known to result from the fact that Sydenham chorea often occurs with a substantially longer latent period than the other manifestations of ARF. Relapses of pure chorea may occur in some patients despite faithful adherence to prophylaxis with intramuscular benzathine penicillin.[91] Some patients with pure chorea are found on follow-up to have RHD manifested by mitral regurgitation or even mitral stenosis.[92]

Interest has focused on the possibility that certain other neurobehavioral conditions, including tics, obsessive-compulsive disorder, and Tourette syndrome, may be poststreptococcal sequelae.[93,94] This hypothesized entity has been termed *p*oststreptococcal *a*utoimmune *n*europsychiatric *d*isorders *a*ssociated with *s*treptococci (PANDAS). A prospective blinded cohort study of patients meeting suggested diagnostic criteria for PANDAS found that, after group A streptococcal infection, exacerbations of childhood tics and obsessive-compulsive disorders were more frequent in such patients than in control subjects. However, there has been no consistent relationship demonstrated between exacerbations and GAS infections. Streptococcal infection was not the only or even the most common antecedent of such exacerbations.[95] The relationship of streptococci to this proposed entity is unproven at this time.[93]

Several clinical manifestations of ARF occur with some frequency but are not in themselves specific enough to be considered major criteria. These minor criteria include fever, which accompanies almost all ARF attacks at their onset, and arthralgia. Slight differences in these minor criteria have been incorporated into the revised Jones criteria between low- and moderate- to high-risk populations. The pulmonary parenchyma in ARF rarely may be involved by a variety of pathologic processes, including pulmonary edema, atelectasis, pulmonary embolism, or thromboses.[96] Some believe that, in addition, a specific rheumatic pneumonia may occur in rare cases. Abdominal pain or epistaxis can occur.

The average duration of an attack, in the absence of antiinflammatory therapy, is approximately 3 months. Less than 5% of cases persist for longer than 6 months, justifying the designation of "chronic" rheumatic fever. Stollerman[1] listed the criteria for continuing clinical activity as follows: joint symptoms, new organic murmurs, changing heart size, congestive heart failure in the absence of long-standing valvular disease, subcutaneous nodules, sleeping pulse rate higher than 100 beats/min, erythema marginatum, chorea, elevated CRP levels, and a rectal temperature of 100.4°F or higher for 3 or more consecutive days.

Diagnosis

Because ARF can have such diverse manifestations (acute polyarthritis, congestive heart failure, chorea, or combinations of these) and because there is no specific diagnostic test for the disease, the differential diagnostic possibilities in an individual case may be extensive. Among the diseases that most frequently need to be differentiated are rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, serum sickness, sickle cell crisis or cardiopathy, septic arthritis (especially gonococcal arthritis in adolescent patients), Lyme disease,[97] infective endocarditis, viral myocarditis, and Henoch-Schönlein purpura. Choreiform movements have been described in patients with systemic lupus erythematosus,[98] neoplasms involving the basal ganglia,[99] legionnaires' disease,[100] hypoparathyroidism,[101] antiphospholipid syndrome,[102] Wilson disease, and Huntington disease. Chorea is also seen occasionally in women taking oral contraceptives[103] and during pregnancy (chorea gravidarum).[104]

Arriving at the correct diagnosis is particularly important in ARF, not only in terms of treatment for the acute attack and formulating an accurate prognosis but also because of the necessity for prescribing continuous antistreptococcal prophylaxis. To minimize overdiagnosis and underdiagnosis, the criteria originally formulated in 1944 by Jones[105] and updated and modified by a committee of the American Heart Association in 1992[87] and again in 2015[78] are generally accepted as the basis for reaching a diagnosis of ARF (see Table 198.2). The criteria are to be applied most stringently to the diagnosis of an initial ARF attack. Although most patients with recurrences fulfill the criteria, the diagnosis of recurrent ARF may be less apparent. In a patient with established RHD, for example, it may be difficult to diagnose recurrent carditis confidently, unless a previously normal valve is affected. The criteria therefore allow a presumptive diagnosis of recurrent ARF to be made if clinical findings are suggestive and there is supporting evidence of recent streptococcal infection.

Patients with ARF may have echocardiographic evidence of valvular regurgitation in the absence of an audible murmur. Although valvular regurgitation can also be detected in normal individuals by two-dimensional Doppler echocardiography and color flow Doppler imaging techniques, criteria for discriminating physiologic from pathologic regurgitation have been proposed by experienced investigators and endorsed by the World Heart Federation.[68,106–108] In a recent study from India, 333 patients suspected of having ARF were investigated using stringent echocardiographic criteria, and 15% were judged to have evidence of subclinical carditis.[68] A number of echocardiographic surveys of schoolchildren in several developing countries have identified up to 5% or more with subclinical (silent) mitral regurgitation.[49–52] The 2015 revision to the Jones criteria added so-called echocarditis (silent

regurgitation) as part of the major criteria.[78] The issue had been controversial,[74,109] but in some areas of the world with a high incidence of ARF (Australia, New Zealand), positive echocardiographic evidence had already been used to establish the diagnosis of carditis.[110,111] Handheld echocardiography has been utilized as an inexpensive tool in resource-limited settings to screen for RHD,[112] even when used by nonexperts. Using echocardiography, pathologic mitral regurgitation to fulfill the carditis criterion requires visualization in at least two views, a jet length ≥2 cm in at least one view, a peak velocity of >3 m/s, and a pansystolic jet in ≥1 envelope. Pathologic aortic regurgitation requires visualization in at least two views, a jet length ≥1 cm in at least one view, a peak velocity of >3 m/s, and a pandiastolic jet in ≥1 envelope.[78]

The Jones criteria are not infallible, particularly when the diagnosis rests on acute polyarthritis as the sole major criterion, with supporting evidence of fever plus an elevated ESR or CRP level. For this reason, evidence of recent streptococcal infection must be obtained to satisfy the Jones criteria. Such evidence might include a recent microbiologically documented episode of streptococcal pharyngitis; a positive throat culture or rapid streptococcal antigen test for GAS, although differentiation of infection from colonization presents a problem; or an elevated serum titer of antistreptococcal antibodies. In most cases, physicians rely on the latter criterion.

If a serum sample is obtained within 2 months of onset, approximately 80% of patients with ARF have an elevated ASO titer. If a second streptococcal antibody test is performed on the same serum specimen, the proportion of patients with ARF with at least one elevated titer will rise to 90%.[113] Although an elevated antistreptococcal antibody titer is certainly not diagnostic of ARF, failure to demonstrate evidence of recent immunologically significant streptococcal infection using ASO and anti–DNase B tests makes the diagnosis of ARF doubtful. An exception to this statement is the patient with pure chorea whose antibody titers may have declined to the normal range because of the long latent period between the antecedent streptococcal infection and the onset of this manifestation. Similarly, the onset of isolated carditis may be difficult to date; if recognition of isolated carditis is delayed, immunologic evidence of recent streptococcal infection may have disappeared.

Therapy and Prognosis

The objectives of therapy in ARF are to relieve inflammation, decrease fever and toxicity, and control cardiac failure. The mainstays of treatment are salicylates and corticosteroids. Neither of these agents prevents or modifies the development of chronic RHD.[114] A suggested treatment schedule is outlined in Table 198.3. Analgesics without antiinflammatory properties are recommended for patients with mild disease. This allows complete expression of the clinical manifestations to aid in diagnosis and also avoids posttherapeutic rebounds. Most patients require salicylates (50–70 mg/kg/day). If the high doses of salicylates required cannot be tolerated because of gastric irritation or if symptoms of salicylism develop, a reduction in the aspirin dosage or a change to corticosteroids is necessary. The more potent antiinflammatory action of corticosteroids should be used whenever salicylates fail to control the inflammatory process or whenever carditis with congestive heart failure is present. Although NSAIDs appear a reasonable alternative for patients who do not tolerate salicylates but do not require corticosteroids, there is a paucity of data on the use of these agents in ARF. Studies using either naproxen[115,116] or tolmetin[117] reported NSAIDs to be equivalent to aspirin in efficacy, with fewer side effects, though the numbers of patients in these studies was limited.

TABLE 198.3 Suggested Schedule of Antiinflammatory Therapy in Rheumatic Fever

CLINICAL SEVERITY	TREATMENT
Arthralgia or mild arthritis; no carditis	Analgesics only, such as codeine or acetaminophen
Moderate or severe arthritis; no carditis, or carditis *with or without* cardiomegaly, but without failure	Aspirin, 50–70 mg/kg/d for 3 weeks, increased if necessary; 25–35 mg/kg/d for the subsequent 6 weeks
Carditis with congestive failure, with or without joint manifestations	Prednisone, 2 mg/kg, max 60 mg/d; methylprednisolone sodium succinate intravenous in fulminating cases; after 2–3 weeks, slow withdrawal to be completed in 3 more weeks. Aspirin started when steroid withdrawal begins and continued for 1 month after discontinuation of prednisone.

Modified from Stollerman GH. Rheumatic Fever and Streptococcal Infection. *New York: Grune & Stratton; 1975.*

Reactivation of clinical or laboratory manifestations of rheumatic inflammation, or both, may occur after cessation of antiinflammatory therapy. This "rebound" phenomenon is more frequent after corticosteroids than aspirin. For this reason, therapy should be tapered rather than discontinued abruptly. Aspirin should be instituted as the steroid is being tapered and then should be continued for 1 month after treatment with corticosteroids is discontinued.

Heart failure should be treated by conventional measures. The potential risk of digitalis-induced arrhythmias in the patient with active myocarditis must be kept in mind. As noted, in the absence of preexisting valvular disease, congestive heart failure in ARF patients is usually attributable primarily to valvular dilatation and not to myocardial failure. Patients with chorea require a quiet, nonstimulatory environment and sedation. An agent such as phenobarbital or diazepam may be used. In patients with severe and debilitating hyperkinesis, haloperidol has been used. A review has suggested valproic acid as first-line treatment and risperidone for nonresponders.[118] Evidence suggests that corticosteroids may be beneficial in decreasing both the intensity and duration of chorea.[119] A prospective randomized trial of intravenous immunoglobulin in ARF in New Zealand failed to show that it altered the natural history of the disease.[120]

The only long-term sequela of ARF is RHD. The prognosis in rheumatic fever patients is greatly improved by prevention of recurrent attacks, with their concomitant threat of additional valvular damage. The ultimate prognosis of an individual attack is related to the severity of cardiac involvement during the acute phase. This was best studied in a joint UK-US study.[121] In that study, only 6% of patients with no carditis or with only questionable carditis during their attack of ARF had heart murmurs when reexamined 10 years later. Heart disease was present at follow-up in 30% of the patients initially found to have only apical systolic murmurs, in 40% of those with basal diastolic murmurs during the acute phase, and in 68% of those who initially suffered from congestive heart failure, pericarditis, or both. Patients with pure chorea appear to have a relatively high incidence of late development of RHD, even if carditis is not recognized at the time of the initial attack. These findings need to be reevaluated in the echocardiographic era.

RHD can be detected in asymptomatic individuals by auscultation of a murmur characteristic for mitral stenosis, as documented by Paul Dudley White in the 1950s.[122] Our concepts of the prevalence of RHD in developing countries requires revision in view of the results of echocardiographic screening of some 5800 randomly selected school-children in Colombia and Mozambique and other studies in underdeveloped areas.[49–52] These studies found the prevalence of RHD to be approximately 10-fold greater than recognized by conventional clinical auscultation by ordinary observers alone. Prospective follow-up of these children is required to determine the functional implications of these imaging studies.

Prevention

Prevention of ARF in persons without a prior history of this disease depends on accurate diagnosis and appropriate treatment of the antecedent streptococcal infection. This approach (primary prevention) is outlined in Chapter 197. It is effective[123] but suffers from the limitation that one-third or more of ARF cases follow streptococcal infections that are entirely subclinical or too mild to bring them to medical attention. Guidelines for treatment of streptococcal pharyngitis were published in 2012 by the Infectious Diseases Society of America.[124]

Rheumatic patients are at high risk of developing recurrent ARF after immunologically significant streptococcal upper respiratory infections and require continuous prophylaxis to prevent intercurrent streptococcal

TABLE 198.4 Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

AGENT	DOSE	MODE
Benzathine penicillin G	600,000 U for children ≤27 kg (60 lb), 1.2 million U for those >27 kg (60 lb) every 4 weeks[a]	Intramuscular
Penicillin V	250 mg twice daily	Oral
Sulfadiazine	0.5 g once daily for patients ≤27 kg (60 lb) 1.0 g once daily for patients >27 kg (60 lb)	Oral
For Individuals Allergic to Penicillin and Sulfadiazine		
Macrolide or azalide	Variable	Oral

[a]In high-risk situations, administration every 3 weeks is justified and recommended.
From Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. Circulation. *2009;191:1541-1551.*

TABLE 198.5 Duration of Secondary Rheumatic Fever Prophylaxis

CATEGORY	DURATION AFTER LAST ATTACK
Rheumatic fever with carditis and residual heart disease (persistent valvular disease[a])	10 yr or until age 40 yr, whichever is longer; sometimes lifelong prophylaxis (see text)
Rheumatic fever with carditis but no residual heart disease (no valvular disease[a])	10 yr or until age 21 yr, whichever is longer
Rheumatic fever without carditis	5 yr or until age 21 yr, whichever is longer

[a]Clinical or echocardiographic evidence.
From Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. Circulation. *2009;191:1541-1551.*

infections. The recommended regimen[125] for most patients in the United States and other countries in which ARF incidence is low consists of a single injection of penicillin G benzathine administered every 4 weeks (Table 198.4). In the most comprehensive study reported,[126] children following this regimen experienced a rheumatic fever recurrence rate of only 0.4 per 100 patient-years of observation. In areas of the world in which ARF and RHD remain very highly prevalent, ARF recurrence rates have been found to be even lower when injections of penicillin G benzathine are administered every 3 weeks rather than every 4 weeks.[127]

Oral sulfadiazine and penicillin V are also acceptable prophylactic agents but are less effective than penicillin G benzathine (see Table 198.4). The lesser efficacy of oral regimens is at least in part the result of the extreme difficulty of enforcing adherence. Patients allergic to penicillin and sulfadiazine may be given a macrolide or an azalide. Patients requiring protection for many years are often begun on a regimen of penicillin G benzathine, which is changed to oral prophylaxis later when the risk of recurrence is deemed to be lower.

The optimal duration of continuous antimicrobial prophylaxis remains controversial. The risk of ARF recurrence is neither continuous nor uniform. It declines with the age of the patient and the number of years since the most recent attack. It is positively correlated with the number of previous attacks and with the presence and severity of RHD. Thus the risk of recurrence becomes low in older adults without heart disease who are not in intimate contact with school-age children. The physician must decide whether and when to discontinue prophylaxis after careful assessment of the patient's risk of acquiring a streptococcal infection, the anticipated recurrence rate per infection, and the likely consequences of such recurrence. Even when all these factors are favorable, prophylaxis should not be discontinued generally until the patient has reached his or her early 20s and at least 5 years have elapsed since the most recent rheumatic attack.[128] Recommendations of the American Heart Association are given in Table 198.5.

Investigative efforts are currently being directed toward the development of a safe, effective vaccine for the prevention of streptococcal infection and ARF. Such a vaccine would have to provide protection against the major serotypes associated with ARF and highly invasive infections.[129,130] Finally, a school-based intervention to screen and treat cases of GAS sore throat in New Zealand was shown to decrease rates of ARF in a hyperendemic area.[131] The recent observation that 65% of new GAS acquisitions caused no symptoms yet were associated with an antibody response in children may suggest that primary prevention in high-prevalence areas of ARF/RHD may need to focus on both symptomatic and asymptomatic children,[132] but this requires further study.

GLOMERULONEPHRITIS

Poststreptococcal AGN is an acute inflammatory disorder of the renal glomerulus, characterized pathologically by diffuse proliferative glomerular lesions and clinically by edema, hypertension, hematuria, and proteinuria. The disease is a delayed nonsuppurative sequela of pharyngeal or cutaneous infection with certain nephritogenic group A streptococcal strains belonging to a limited number of serotypes.

History

Richard Bright (1789–1858) clearly differentiated cardiac from renal dropsy in 1836.[133] He also noted the association between acute scarlet fever and AGN.[133] Subsequently, many investigators confirmed the relationship between β-hemolytic streptococcal infections and subsequent AGN. Schick,[134] in 1907, commented on the similarity of the latent period in serum sickness to that in AGN, thus suggesting the possibility of an immunologic basis for the latter disease. Longcope[135] noted the association of streptococcal infections and AGN. Rammelkamp and Weaver[136] explained the puzzling variations in attack rate of AGN after group A streptococcal infection by proposing that only certain serotypes of *Streptococcus pyogenes* were nephritogenic. Classic detailed prospective studies of the epidemiology, bacteriology, immunology, and natural history of pyoderma-associated nephritis by Wannamaker[137] in Minnesota, Potter and colleagues[138] in southern Trinidad, and Dillon and coworkers[139] in Alabama have added greatly to our understanding of this disease.

Etiology and Pathogenesis

Poststreptococcal AGN follows infection with a limited number of group A streptococcal serotypes (see Table 198.1). Type 12 is the most frequent M serotype causing AGN after pharyngitis or tonsillitis, whereas M-49 is the type most frequently related to pyoderma-associated nephritis. Not all streptococcal strains belonging to these serotypes are nephritogenic, however. As yet, there are no reliable biologic markers to differentiate nephritogenic from nonnephritogenic streptococci. Poststreptococcal AGN is almost always caused by strains of serogroup A. Well-documented outbreaks caused by group C organisms (*Streptococcus equi* subsp. *zooepidemicus*) have been reported, however.[140,141]

The precise mechanism whereby streptococcal infection gives rise to AGN has not been delineated, although evidence strongly favors the view that the renal injury is immunologically mediated. This includes the approximately 7-day latent period between infection and the development of AGN, the associated hypocomplementemia, and the fact that IgG, complement components, and antigens that react with streptococcal antisera are present in the renal glomerulus early in the course of the disease.[142,143] It is possible that antibodies elicited by nephritogenic streptococci react with renal tissues in such a way as to produce glomerular injury, because antigenic similarities between constituents of the streptococcus and human kidney are described.[144,145] However, the electron microscopic finding of nodular subepithelial "humps" in renal biopsy specimens in AGN is compatible with renal injury caused by deposition of preformed complexes consisting of streptococcal antigen and host antibody within the glomerulus. These deposits are characteristic of experimentally induced disease caused by circulating immune complexes and of other immune complex–mediated

disorders. Several groups have detected circulating immune complexes in AGN.[146]

The identity of the streptococcal constituent(s) involved in the pathogenesis of AGN remains unknown. M protein is an obvious candidate because of the close association of nephritogenicity and certain M serotypes. Monoclonal antibodies raised against human glomeruli have been found to cross react with streptococcal M protein.[145] Moreover, in an animal model of nephritis induced by nephritogenic type 12 streptococci, eluted bound glomerular antibodies were found to be directed against type 12 M protein but not against other streptococcal and renal antigens. Others, however, have described cross-reactions between fragments of streptococcal cell membrane and human glomerular basement membrane.[142]

Several antigens isolated from nephritogenic streptococci have been investigated regarding their role in the pathogenesis of AGN, including streptococcal pyrogenic exotoxin B (SpeB)[147,148] and a nephritis-associated plasmin receptor (NAPlr) and nephritis-strain–associated protein (NSAP).[149–151] Streptokinase production has been postulated to play a role in the pathogenesis of AGN and has been found to be essential for development of the disease in a mouse model.[151] However, there is no unique reactivity to group A streptococcal streptokinase in sera of AGN patients, nor has streptokinase deposition been demonstrated in biopsy specimens obtained early in the disease.[152]

Pathologic Characteristics

In the acute phase of AGN, light microscopic examination of renal biopsy specimens demonstrates a marked increase in glomerular intracapillary cellularity caused by endothelial and mesangial cell proliferation. These changes involve almost all the glomeruli, which appear enlarged and bloodless, tending to fill the Bowman space.[153] In addition to this diffuse proliferative endocapillary process, a variable degree of polymorphonuclear leukocytic exudation is observed. Proliferation of parietal and visceral epithelial cells occurs only to a modest degree and is rarely extensive enough to give rise to well-developed crescent formation. Thin sectioning and special strains may reveal discrete deposits on the epithelial side of the basement membrane that correspond to the humps visible on electron microscopy. Focal degeneration, interstitial edema, and cellular infiltration also occur in the renal tubular cells, but these tubular changes are far less prominent than is the glomerulitis. Arterioles are normal or almost normal in most cases of AGN.

Immunofluorescence studies demonstrate considerable variability in the pattern of deposition of immunoglobulin and complement components. C3 is almost always present in the glomeruli, and granular deposits of IgG are also frequently demonstrable as discrete deposits similar in size and location to the subepithelial humps visualized by electron microscope,[143,154] although deposits of C3 may also occur in an interrupted linear pattern along the basement membrane or in the mesangium. Deposits of immunoglobulin M, C1q, C4, and fibrin are found less commonly. The rather weak and inconsistent deposition of early complement components suggests that activation of the alternate complement pathway plays a role in the immunopathology of AGN.

Epidemiology

It has been estimated that more than 470,000 cases of AGN occur annually worldwide, with approximately 5000 deaths.[155] The great majority of these occur in less-developed countries. The epidemiologic characteristics of AGN largely reflect those of the antecedent group A streptococcal infection, that is, pharyngitis or pyoderma (Table 198.6). Thus the classic streptococcal sore throat occurs primarily among school-age children during the cooler months of the year. Pyoderma is largely a disease of children ages 2 to 6 years and, in temperate climates, occurs during the summer and early fall. Given a skin infection with a nephritogenic strain, the attack rate of AGN is higher in children 6 years of age or younger than in older children.[156] AGN can also follow cutaneous infections other than pyoderma.[157,158] The latent period of AGN is variable but averaged 10 days after pharyngeal infection in the studies of Stetson and colleagues[159]; prospective studies at the Red Lake Indian Reservation in Minnesota have indicated the usual latent period of pyoderma-associated AGN to be 3 weeks or longer.[156]

TABLE 198.6 Epidemiologic Characteristics of Pharyngitis-Associated and Pyoderma-Associated Acute Glomerulonephritis (AGN)

FEATURE	PHARYNGITIS-ASSOCIATED AGN	PYODERMA-ASSOCIATED AGN
Age	Early school age	Pre–school-age
Gender	Male-to-female ratio ≅2:1	Equally distributed
Season	Winter and spring	Late summer and early fall
Geographic distribution	North and south	Predominantly south
Familial occurrence	Variable	Variable
Latent period	10 d	3 wk
Attack rate[a]	10%–15%	10%–15%
Serologic types	Limited types	Also limited but different types
Recurrences	Rare	Rare

[a]After infection with known nephritogenic strain.
Modified from Wannamaker LW. Differences between streptococcal infections of the throat and of the skin. N Engl J Med. *1970;282:23-31.*

Although the attack rate of AGN after throat or skin infection with a nephritogenic strain is substantial (i.e., 10%–15%),[156] the disease differs dramatically from ARF in that recurrences are rare. This is attributable at least in part to the relatively limited number of streptococcal strains that are nephritogenic and presumably also to the acquisition of type-specific protective immunity to the serotype that elicited the initial attack. When second attacks of AGN occur, they are clinically and histologically indistinguishable from the initial attack.[160] More common than recurrent AGN attacks is the propensity for streptococcal infections to precipitate exacerbations of chronic glomerulonephritis.[161] Such exacerbations often occur after a relatively brief latent period of 1 to 4 days. The coexistence of ARF and AGN in the same patient after pharyngeal infection is rare, but a few such cases have been reported.[162]

The introduction of a highly nephritogenic strain into a family unit may result in multiple cases. When systematic screening of sibling contacts for hypertension, urinary abnormalities, and serum complement levels has been performed, the incidence of proven and suspected cases of AGN in sibling contacts has been extremely variable,[163–165] with estimates ranging as high as 20%.

Clinical and Laboratory Features

The typical clinical features of AGN in children include edema, hypertension, and smoke- or rust-colored urine. Patients also exhibit pallor and may complain of lethargy, malaise, weakness, anorexia, headache, and dull back pain. Fever is not a prominent finding.

Facial and periorbital edema are usually present, especially in the morning, but edema also involves dependent areas, such as the feet and legs, scrotum, and sacrum. In severe cases, ascites or pleural effusions may occur. Another manifestation of fluid overload is circulatory congestion, which may give rise to dyspnea, orthopnea, rales at the lung bases, distended neck veins, and even frank pulmonary edema. Manifestations of circulatory overload tend to be particularly prominent in the occasional cases of AGN occurring in older adults and, in these patients, may obscure the correct diagnosis if urinary findings are not properly interpreted.

Hypertension occurs in most patients but is usually of modest degree. Hypertensive retinopathy or heart failure does not ordinarily complicate the clinical picture. On the other hand, up to 5% to 10% of AGN patients develop severe hypertension complicated by signs and symptoms of encephalopathy. These range from headache and vomiting to confusion, somnolence, and convulsions.

Although these clinical features are typical of hospitalized patients, many cases of AGN are so mild as to escape detection unless those at risk are tested for urinary sediment abnormalities and serum complement levels. Two studies that included renal biopsy data concluded

that in epidemic situations, as many as 50% of cases of AGN may be subclinical.[165,166]

Laboratory findings include a mild normocytic normochromic anemia, elevated ESR, slight hypoproteinemia, and elevations of the blood urea nitrogen and serum creatinine concentrations. Hypercholesterolemia and hyperlipemia may also be present. Serum levels of total hemolytic complement and C3 complement are markedly reduced in the great majority of patients with clinically apparent AGN. Urine volume may be significantly diminished, and the urine itself is smoky, rusty, or brownish, with a high specific gravity and positive test findings for protein and hemoglobin. Total urinary protein excretion is usually less than 3 g/day.[167] Microscopic examination of the urine reveals erythrocytes, leukocytes, and hyaline, granular, and red blood cell casts.

The urinary abnormalities in AGN must be distinguished from the transient mild hematuria and proteinuria that may be seen during the acute phase of acute streptococcal infection and other febrile illnesses. The relationship, if any, of these early urinary findings to the development of AGN is unknown.[167] Finally, diagnostic confusion is almost inevitable in the rare cases in which pronounced clinical manifestations of AGN occur in patients with minimal or no urinary sediment abnormalities.[168]

Diagnosis

The diagnosis of AGN is based on the clinical history, physical findings, and confirmatory evidence of antecedent streptococcal infection. The latter may include a recent history of scarlet fever, isolation of group A streptococci from throat or skin lesions, or demonstration of elevated serum titers of streptococcal antibodies. Even in the absence of bacteriologic isolation of streptococci, the presence of skin lesions compatible with streptococcal impetigo is highly suggestive.

It is almost always possible to demonstrate an elevated level of streptococcal antibodies in AGN, although, in cases with relatively short latent periods, serial bleedings may be necessary. In pyoderma-associated nephritis ASO responses are weak, and it is frequently necessary to assess levels of anti–DNase B. Although antistreptozyme titers rise in pyoderma nephritis, technical problems limit the reliability of the test. Finally, if renal biopsy is performed, the demonstration of diffuse proliferative glomerulonephritis with subepithelial electron-dense deposits is a very helpful confirmatory finding.

Poststreptococcal acute glomerulonephritis must be differentiated from other infectious processes involving the kidney and from other primary renal diseases. For example, often it may be extremely difficult to differentiate an acute exacerbation of chronic glomerulonephritis, such as may be precipitated by streptococci or by other intercurrent infections, from a true attack of AGN. A short latent period of 1 to 4 days suggests that the episode is an exacerbation of preexisting renal disease. Patients with infective endocarditis tend to develop high serum levels of circulating immune complexes and may develop diffuse proliferative or focal glomerulonephritis, which may be confused clinically with poststreptococcal nephritis. Other bacterial and protozoan illnesses, such as pneumococcal pneumonia, typhoid fever, leptospirosis, syphilis, toxoplasmosis, and *Plasmodium falciparum* malaria, on occasion are associated with nephritis. Viral infections, such as hepatitis B and C, infectious mononucleosis, measles, mumps, and enteroviral disease, have similarly been implicated as causes of viruria, transient renal dysfunction, or actual glomerulonephritis.[169] In addition to the development of focal and segmental glomerulosclerosis, patients infected with human immunodeficiency virus may rarely develop an immune complex glomerulonephritis.[170] Other entities that may at times mimic AGN are Henoch-Schönlein purpura, systemic lupus erythematosus, polyarteritis nodosa, acute tubular necrosis, focal glomerulonephritis with hematuria, hereditary nephritis, rapidly progressive glomerulonephritis, idiopathic nephrotic syndrome, and malignant hypertension.

Therapy

Because no form of treatment is known to alter the long-term prognosis of AGN, therapy is directed toward management of the acute issues. Attention is directed to the most immediate problem—circulatory overload—and to hypertension. In most cases, this is handled adequately by salt and fluid restriction alone, but diuretics may be required. Digitalis is not indicated because the risk of toxicity is substantial, and usually myocardial function is intact.[171] Specific antihypertensive therapy is usually unnecessary, except in cases of severe hypertension and hypertensive encephalopathy. Patients developing acute pulmonary edema or severe and prolonged oliguria require measures conventionally used for these conditions. Immunosuppressive therapy is not of benefit.

All nonallergic patients should receive penicillin, preferably intramuscular penicillin G benzathine (see Chapter 197 for dosage schedule), to eradicate the nephritogenic streptococcal strain. Penicillin-allergic patients should receive one of the alternative regimens listed in Chapter 196.

With skillful use of the supportive measures outlined here, mortality during the acute phase of AGN is now rare. Perhaps 1% or less of patients develop severe and irreversible renal failure. In the remainder, signs and symptoms often begin to abate within a few days after admission. Serum complement levels return to normal within a month, but microscopic hematuria and cylindruria frequently persist for months, despite the patient's general feeling of well-being.

Prevention

Although penicillin treatment of the antecedent streptococcal infection is highly efficacious in preventing ARF, the same does not appear to be the case in AGN. Stetson and colleagues,[159] in a controlled study of an epidemic of pharyngitis-associated (serotype M-12) AGN in a military population, found a small but not statistically significant preventive effect of penicillin. Uncontrolled observations during an epidemic of nephritis in Israel (both throat and skin infections caused by serotype M-55) documented the occurrence of AGN in a number of subjects who had received prior antibiotic therapy according to various dosage regimens.[172] Moreover, there was no difference in the clinical severity of AGN between subjects who had and those who had not received antibiotic therapy.

As noted, penicillin is nevertheless effective in epidemiologic attempts to eradicate nephritogenic strains by treatment of AGN patients and their colonized family contacts. In appropriate high-risk settings during epidemics of AGN, universal penicillin prophylaxis of selected populations might be considered in a manner somewhat analogous to that used in US military recruit camps for rheumatic fever control. Such universal prophylaxis is rarely indicated and should be used only after careful consideration of the specific epidemiologic parameters involved. Because recurrent episodes of AGN are so rare, continuous antistreptococcal prophylaxis, such as that used in the secondary prevention of rheumatic fever, is unnecessary.

Prognosis

One of the most important issues relating to poststreptococcal glomerulonephritis is the frequency with which patients afflicted with the disease eventually develop chronic glomerulonephritis. In a very small percentage of AGN patients, the acute attack is never resolved and the disease enters a subacute phase, leading to an almost complete loss of renal function within 6 months to 2 years. It is the ultimate fate of the remainder of the patients in whom the illness appears to have resolved clinically that remains controversial. Most observers agree that the long-term prognosis in children is excellent. A 10-year follow-up of 61 patients involved in an epidemic at Red Lake, Minnesota,[173] revealed no cases of chronic glomerulonephritis. Moreover, in a 12- to 17-year follow-up of 534 Trinidadians convalescent from AGN,[174] only 3.5% of the subjects had persistent urine abnormalities, 3.7% were hypertensive, and none had serum creatinine values higher than 1.25 mg/dL. These figures are not in excess of what would be expected in surveys of normal populations. Almost all the Trinidadian patients had been children at the time of their attack of AGN. There was no difference in outcome of sporadic AGN cases as opposed to those associated with epidemics. A report from Australia, however, noted increased prevalences of albuminuria and hematuria in Aboriginal children several years convalescent from two epidemics of AGN. There were no significant differences between patients and control subjects in blood pressure, serum creatinine level, or calculated glomerular filtration rate.[175] However, a recent report indicated that in the aboriginal Australians, chronic nephritis occurred later in life in many who had poststreptococcal AGN in childhood.[176]

Similarly, Baldwin[177] followed 168 subjects for periods up to 18 years and concluded that irreversible renal damage ensued in 50% of these patients, as evidenced by the presence of proteinuria, hypertension, or both, although clinical uremia occurred in only 6 patients. Renal biopsy specimens from the subjects in this series showed that proliferative changes had decreased, whereas glomerulosclerosis of marked degree was present in more than half of the specimens. Their study population contained a high proportion of adults, who are generally agreed to have a worse prognosis than children.[178] Moreover, the results presented have been challenged because of the difficulty of sorting out exacerbations of chronic nephritis from true de novo attacks of AGN in studies of sporadically occurring disease[179] and because of the paucity of published data documenting the poststreptococcal cause of the cases studied. More recently, however, a follow-up of Brazilian adults who contracted AGN from consumption of cheese contaminated with *S. equi* subsp. *zooepidemicus* revealed a high rate of hypertension and renal abnormalities, with some patients having reached end-stage renal disease at 5-year follow-up, though some improvement in glomerular filtration rate was noted by 10 years after the outbreak.[141,180,181]

Based on the bulk of currently available data, it seems likely that greater than 90% of children with AGN make an uneventful recovery and that this disease in children is not an important precursor of chronic glomerulonephritis or hypertension. The prognosis appears more guarded in adult patients,[141,182,183] but the proportion who might be left with residual renal function impairment is at present unknown.

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The complete reference list is available online at Expert Consult.

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199 Streptococcus pneumoniae

Edward N. Janoff and Daniel M. Musher

SHORT VIEW SUMMARY

Epidemiology

- *Streptococcus pneumoniae* is the leading bacterial cause of pneumonia and meningitis in children younger than 5 years and older adults worldwide.
- The incidence is highest in children younger than 2 years and adults older than 65 years; mortality is highest in older adults.
- Asymptomatic colonization is common and precedes almost all symptomatic clinical infections.
- Large outbreaks are uncommon, but smaller outbreaks occur under crowded conditions (prisons, nursing homes, military training).
- Groups at increased risk for serious pneumococcal disease include individuals at the extremes of age (particularly <2 years and >65 years of age), those with underlying organ dysfunction (asplenia and splenic dysfunction; chronic heart, lung, liver, and kidney disease), and immunocompromising conditions (particularly antibody defects, complement deficiencies, neutropenia, and malignancies).

Microbiology

- *S. pneumoniae* is a gram-positive, α-hemolytic, lancet-shaped diplococcus. Growth is inhibited by optochin, and colonies are soluble in bile.
- The 97 or more distinct capsular polysaccharides are identifiable by serotyping. The capsules are the principal source of resistance to phagocytosis.
- Effective phagocytosis and killing in vivo typically require antibodies (most often to capsular polysaccharide), complement, and phagocytes (neutrophils and macrophages).
- Pneumolysin is the cholesterol-binding, pore-forming primary toxin that causes both epithelial and endothelial damage and perturbs complement activity.

Diagnosis

- Gram stain and culture of good-quality sputum (>10 neutrophils/epithelial cell) from patients with pneumonia support a presumptive diagnosis of pneumococcal pneumonia. Blood cultures are positive in about 20% of patients with pneumococcal pneumonia, establishing a diagnosis of proven pneumococcal pneumonia.
- Detection of pneumococci by Gram stain and culture of cerebrospinal fluid establishes the diagnosis of pneumococcal meningitis.
- Detection of pneumococcal cell wall polysaccharide in urine (approximately 70% sensitive in adults with bacteremia; not specific in children) or of capsular polysaccharide in urine (sensitive, but limited to a small number of serotypes) is diagnostic of pneumococcal infection.

Clinical Manifestations

- The spectrum of pneumococcal infection ranges from asymptomatic pharyngeal colonization to mucosal disease (otitis media, sinusitis, pneumonia) to invasive disease (bacteria in a normally sterile site: bacteremia, meningitis, empyema, endocarditis, arthritis).
- Otitis media is the most common clinical syndrome in children; acute purulent sinusitis is the most common syndrome in adults, followed by pneumonia.
- Most invasive disease results from bacteremic seeding, but meningitis and empyema may also result from extension of local infection.

Therapy

- β-Lactam antibiotics are the mainstay of therapy for pneumococcal infection. Decreased susceptibility to penicillin, derived from evolved modifications of penicillin-binding proteins, compromises the efficacy of β-lactams in treatment of meningitis, but typically not pneumonia.
- Intravenous therapy, particularly ceftriaxone, is recommended for the initial treatment of serious pneumococcal infection; vancomycin is added initially with meningitis.
- Combined therapy with a β-lactam and macrolide (and addition of corticosteroids) may improve outcomes in severe pneumococcal pneumonia.
- Carbapenems, quinolones, linezolid, and vancomycin also show clinical activity against *S. pneumoniae*.

Prevention

- Two vaccines provide protection against invasive pneumococcal disease. The 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13), recommended for all children, provides them with >90% protection against bacteremia, up to 30% against pneumonia, and some protection against otitis media and meningitis. It also provides adults with 75% protection against bacteremia and 45% against pneumonia caused by vaccine-specific serotypes.
- The 23-valent pneumococcal polysaccharide vaccine for adults (PPSV23) provides 54% to 81% protection against bacteremia, but efficacy is limited for pneumonia. PPSV23 alone is recommended for persons under 65 years with underlying disease. Serial immunization with PCV13, then PPSV23, is approved for adults ≥65 years (given 1 year apart) and immunocompromised adults (given ≥8 weeks apart).
- Widespread pneumococcal vaccination of children has reduced the incidence of invasive disease and hospitalization for pneumonia in all age groups in the United States.

Long recognized for causing asymptomatic colonization and as a prominent cause of pneumonia, bacteremia, meningitis, sinusitis, and otitis media, *Streptococcus pneumoniae* is likely the most common cause of serious bacterial respiratory infection in both children and adults worldwide. Antimicrobials and vaccines have substantially reduced the incidence of, and morbid outcomes from, pneumococcal infection. However, acquisition of antibiotic resistance, the more limited impact of vaccines on mucosal disease (e.g., pneumonia, otitis media), the emergence of nonvaccine serotypes, and a growing immunocompromised population provide challenges for ongoing control of this prevalent and invasive pathogen.

HISTORY

S. pneumoniae has played a prominent role in the history of microbiology. Identified concurrently in 1881 in France by Pasteur and in the United States by Sternberg, this bacterium was soon recognized as the most common cause of lobar pneumonia and became known as the pneumococcus. Based on its appearance in Gram-stained sputum, the name *Diplococcus pneumoniae* was assigned in 1926 and changed to *Streptococcus pneumoniae* in 1974, based on its morphology during growth in liquid medium.

S. pneumoniae was the first organism to be recognized as showing characteristics of a prototypic extracellular bacterial pathogen by replicating extracellularly in mammalian tissues. Resistance to uptake by

phagocytic cells is largely related to the polysaccharide capsule. In the early 1890s, Felix and Georg Klemperer showed that immunization with killed pneumococci protected rabbits against subsequent pneumococcal challenge and that protection could be transferred by infusing serum ("humoral" substance) from immunized rabbits into naïve recipients. The basis for this immunity was shown by Neufeld and Rimpau to be the presence of factor(s) in serum that facilitate ingestion by white blood cells (WBCs), a process they called *opsonization,* derived from the Greek word for buying provisions.[1] These observations provided the basis for what we now call humoral immunity. Individual capsular serotypes were recognized when injection of killed organisms into a rabbit stimulated the production of serum antibody that agglutinated and caused capsular swelling ("Quellung") of the immunizing strain, as well as some, but not all, other pneumococcal isolates. Early in the 20th century, serotypes 1, 2, and 3 were distinguished, and all other pneumococci were called group 4.

In the first decade of the 20th century, the concept of humoral immunity was used to address the problem of epidemic lobar pneumonia that each year affected as many as 1 in 10 African miners.[1,2] A program of immunization with whole killed pneumococci substantially reduced the incidence of pneumonia. In the 1920s, Heidelberger and Avery[3] demonstrated that the protective antibody reacted with surface capsular polysaccharides, the first nonprotein antigen identified. Felton[4] prepared the first purified pneumococcal capsular polysaccharides (PPSs) for immunization of human subjects, and mass vaccination with Felton's type 1 polysaccharide aborted an epidemic of pneumonia at a state hospital in Massachusetts in the winter of 1937 to 1938.[5] Thus specific bacterial polysaccharide antigens could be used to stimulate antibodies that conferred protection against epidemic human infection. These observations were confirmed during World War II when MacLeod and coworkers[6] showed that vaccinating military recruits with capsular material from four serotypes of *S. pneumoniae* greatly reduced the incidence of pneumonia caused by serotypes in the vaccine but not by other serotypes.

S. pneumoniae also played a central role in the discovery of DNA. Experiments by Griffith[7] in the 1920s revealed that intraperitoneal injection into mice of live, unencapsulated (and therefore avirulent) pneumococci, together with heat-killed encapsulated pneumococci, led to the emergence of encapsulated virulent bacteria, a process he called *transformation.* This observation remained unexplained until the 1940s, when Avery and coworkers[8] provided conclusive evidence that these mutants had recovered the capacity to produce a capsule by taking up nucleic acids from killed, virulent organisms. Therefore this discovery was the first to identify a functional transferable material (DNA) that encoded for phenotype.

Finally, pneumococcal infections were among the first to be treated with an antimicrobial agent, in this case optochin (ethylhydrocupreine), a quinine derivative. The organism was also among the first to develop resistance to such therapy, resulting in failure of treatment both in experimental animals and in humans.

MICROBIOLOGY

S. pneumoniae is a gram-positive coccus that replicates in chains in liquid medium but appears as lancet-shaped diplococci in clinical specimens. The organism is catalase negative, but generates hydrogen peroxide (H_2O_2) via a flavoenzyme system and therefore grows better in the presence of a source of catalase, such as red blood cells. Pneumococci produce pneumolysin (formerly called α-hemolysin), which breaks down hemoglobin into a green pigment that surrounds the colonies during growth on blood and chocolate agar plates, a phenomenon still termed *α-hemolysis.* Pneumococci may be identified in the microbiology laboratory by three reactions: (1) α-hemolysis of blood agar, (2) susceptibility to optochin, and (3) solubility of colonies in bile salts (sodium deoxycholate). Some pneumococci are optochin resistant. A related species, *Streptococcus pseudopneumoniae,* which is associated with exacerbation of chronic obstructive pulmonary disease or pneumonia, is optochin-susceptible during growth in room air at 37°C but optochin-resistant when grown in the presence of increased carbon dioxide. These factors have led to greater reliance on the use of bile solubility and commercial DNA probes for the ribosomal RNA (rRNA) gene for definitive identification.

Peptidoglycan and teichoic acid are the principal constituents of the pneumococcal cell wall[9] (Fig. 199.1). Peptidoglycan consists of long chains of alternating *N*-acetyl-D-glucosamine and *N*-acetylmuramic acid, from which extend chains of four to six amino acids called stem peptides. Stem peptides are cross-linked by pentaglycine bridges, which provide substantial strength to the cell wall. Teichoic acid, a carbohydrate polymer that contains phosphorylcholine, is covalently linked to the peptidoglycan on the outer surface of the bacterial wall and protrudes into the capsule. Teichoic acid and tightly adherent fragments of peptidoglycan make up C-polysaccharide, a substance present in all pneumococci but only in a few species of viridans-group streptococci. C-polysaccharide reacts with acute-phase reactants in the blood during inflammation, including C-reactive proteins. Many proteins are expressed on the pneumococcal cell surface. Of particular importance in the pathogenesis of pneumococcal disease are those that bind to choline, including pneumococcal surface proteins A and C (PspA, PspC); surface adhesins choline-binding protein A (CbpA) and choline-binding protein C; and proteins involved in receptivity to DNA acquisition (or natural competence) (Table 199.1).

Nearly every clinical isolate of *S. pneumoniae* contains an external polysaccharide capsule, but unencapsulated isolates have been implicated in outbreaks of conjunctivitis.[10] Capsules (see Fig. 199.1) of repeating oligosaccharides are synthesized in the cytoplasm, polymerized, and transported to the bacterial surface by cell membrane transferases.[11] These polysaccharides are covalently bound to peptidoglycan and C-polysaccharide, which explains the difficulty of separating capsular from cell wall polysaccharide in vaccine preparations. Genetic control of this complex set of events has been elucidated for some serotypes; for example, a cassette of 15 genes that function as a single transcriptional unit is responsible for encapsulation in serogroup 19.[12] At least 97 serotypes of *S. pneumoniae* have been identified on the basis of antigenic differences in their capsular polysaccharides. Among the multiple genes that encode production of individual capsules, some are specific for individual polysaccharides, whereas others are conserved among nearly all pneumococci and even some other streptococci.[13]

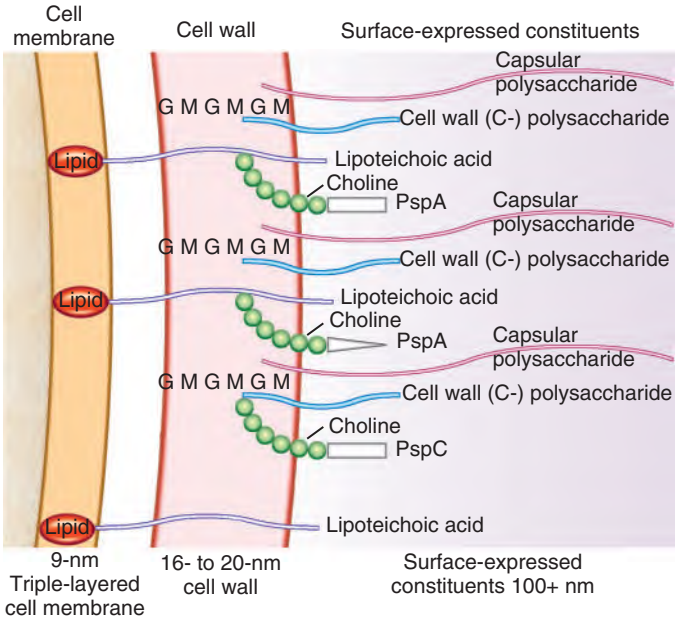


FIG. 199.1 Anatomy of the pneumococcus. A representation of the cell membrane, cell wall, and capsule of *Streptococcus pneumoniae.* Within the cell wall, M = *N*-acetylmuramic acid and G = *N*-acetyl-D-glucosamine. The stem peptides and the cross-linked pentaglycine bridges that extend from the long M-G-M-G chains are not shown. Cell wall (C-) polysaccharide consists of teichoic acid with peptidoglycan and phosphorylcholine (not shown). F antigen is the lipid/teichoic acid moiety in the cell membrane that extends into the cell wall. *PspA,* Pneumococcal surface protein A; *PspC,* pneumococcal surface protein C.

TABLE 199.1 Role of Pneumococcal Constituents as Virulence Factors

PNEUMOCOCCAL CONSTITUENT	MECHANISM	STRENGTH OF EVIDENCE AS A VIRULENCE FACTOR	
		Antibody Prevents Disease[b]	Mutants Lack Virulence
Capsular polysaccharide	Prevents phagocytosis; activates complement	4+	4+
Cell wall polysaccharide	Stimulates inflammation by strongly activating complement and stimulating release of cytokines	0	ND
Pneumolysin	Cytotoxic; activates complement, cytokines	2–3+	2–3+
PspA	Inhibits phagocytosis by blocking activation and deposition of complement on bacterial surface	2+	2+
PspC	Inhibits phagocytosis by binding complement factor H	1–2+	1–2+
PsaA	Mediates adherence	1–2+	1–2+
Autolysin	Causes bacterial disintegration, releases components	1+	2+
Neuraminidase	Possibly supports adherence	0–1+	0–1+

[a]The grading system is subjective and indicates (on a scale of 1+ to 4+) the stringency and importance of the demonstrated effect. For discussion and references, see the text and Weiser et al.[69]
[b]Animal models only, except capsular polysaccharides.
ND, Not done; *Psa,* pneumococcal surface adhesin; *Psp,* pneumococcal surface protein.

Antibodies induced in rabbits immunized with specific capsular types cause agglutination and create a hydrophobic border around the capsule. This latter reaction, called the Quellung reaction, renders the capsule refractile and therefore more readily visible under the microscope. Because serum antibody is the basis for identifying these types of pneumococcus, they are called serotypes. The American system numbers the serotypes sequentially in the order in which they were identified historically. The more widely accepted Danish numbering system distinguishes 46 serogroups, with groups containing antigenically related serotypes. For example, Danish serogroup 19 includes serotypes 19F, 19A, 19B, and 19C (the letter F indicates the first member of the group to be identified, followed by A, B, C, etc.), which in the American system would be serotypes 19, 57, 58, and 59, respectively. The serotypes that most frequently caused human disease were the earliest to be identified and the first to be assigned numbers, which explains why the lower-numbered serotypes are generally more likely to be implicated in human infection. In the 1930s, serotyping was used to direct therapy with capsule-specific horse antisera. Today, serotypes are important to define epidemiologic and public health surveillance, as targets for vaccines, and for understanding pathogenesis, but not for therapy.

Pneumococci express a competence-sensing protein and internalize DNA from other pneumococci or from other bacterial species.[14] This horizontal transfer of genetic information to pneumococci, called transformation, enables pneumococci to acquire new traits. Of note, a pneumococcus of one serotype can acquire DNA that encodes a different capsular polysaccharide, thereby changing its serotype. This exchange of genetic information occurs under experimental conditions as well as in nature.[15] Thus in addition to a highly conserved genetic core, *S. pneumoniae* supports a large number of noncore genes that provide remarkable diversity of genetic loci between isolates, particularly related to antimicrobial targets and targets of immune recognition (capsular polysaccharides and adhesins).[11,16,17]

EPIDEMIOLOGY

The spectrum of pneumococcal infections can range from asymptomatic colonization to mucosal disease (otitis media, sinusitis, pneumonia) to invasive infections (infection of previously sterile sites). Although otitis media may be the most common clinical manifestation, pneumococcal pneumonia has the greatest impact on morbidity and mortality. Indeed, pneumonia is the leading cause of death of children from infection worldwide, accounting for 1 in 5 deaths, and *S. pneumoniae* is the leading cause of bacterial childhood pneumonia, particularly severe pneumonia.[18] Pneumococcal pneumonia, sepsis, and meningitis cause more deaths in children younger than 5 years than acquired immunodeficiency syndrome [AIDS], malaria, and measles combined,[19] particularly in resource-limited countries. *S. pneumoniae* is the leading

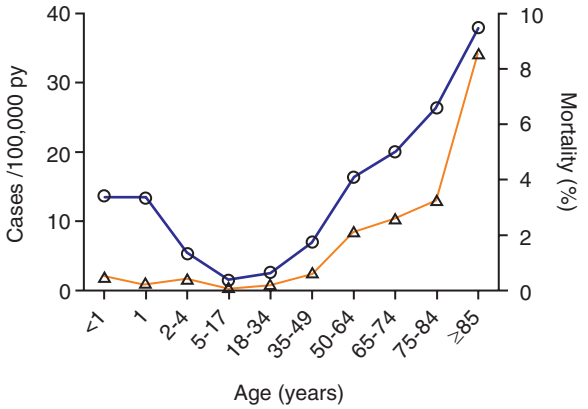


FIG. 199.2 Age-specific incidence and mortality with invasive *S. pneumoniae*, United States, 2016. The incidence of invasive pneumococcal infection has declined substantially since the introduction of pneumococcal conjugate vaccine in 2000, particularly in young children, such that the incidence is now highest in adults older than 65 years, exceeding that in children younger than 2 years.[3,12] However, the bimodal incidence pattern at the extremes of age is consistent with results since the 1920s.[1,18] Mortality is low in young children in the United States but highest in older adults, particularly those with underlying diseases. Blue line with circle represents cases per 100,000 person-years, and orange line with triangle represents mortality (%). *py,* Patient-years. *(Modified from Centers for Disease Control and Prevention. Active Bacterial Core Surveillance Report, Emerging Infections Program Network,* Streptococcus pneumoniae*; 2016.* http://www.cdc.gov/abcs/reportsfindings/survreports/spneu16.pdf.*)*

identified cause of bacterial pneumonia in adults in Kenya[20] and in adults in the United States.[21]

Invasive pneumococcal infections are most prominent at the extremes of life (Fig. 199.2).[22] Consistent results in multiple ethnic and geographic groups highlight the tremendous impact of age on the incidence of bacteremia.[1,18,23] In the pre–conjugate vaccine era (before 2000), pneumococcal bacteremia occurred at an approximately 10-fold higher rate among children younger than 2 years than among adults in the general population and in all populations studied, independent of ethnicity (e.g., White Mountain Apaches) or underlying disease (sickle cell disease, splenectomy, human immunodeficiency virus [HIV] infection).[24] These results are likely due to the limited ability of children under 2 years of age to generate protective antibodies to capsular polysaccharides. Infants in the first few months of life tend to be relatively spared in association with the passive transfer of capsule-specific mucosal immunoglobulin A (IgA) and innate factors to the upper respiratory tract by breast milk and specific immunoglobulin G (IgG) to serum transplacentally through

cord blood, levels of which decline by 6 months of age. Implementation of pneumococcal vaccination at 2, 4, and 6 months of age for infants in the United States (7-valent pneumococcal polysaccharide-protein conjugate vaccine [PCV7], then 13-valent pneumococcal polysaccharide-protein conjugate vaccine [PCV13] in 2010) has reduced invasive pneumococcal disease by over 90% in young children and by half in older adults.

Among children 6 months to 2 years of age, invasive pneumococcal disease is diagnosed primarily when blood cultures are obtained to evaluate for fever. Many of the affected children with "primary bacteremia" have no apparent focus of infection and are not hospitalized, and one-third resolve spontaneously. Hospitalization is more common with associated underlying cardiac, respiratory, and neurologic disease. Unlike in adults, among whom bacteremia is most often a complication of pneumonia (>80%), pneumonia in young children accounts for 28% to 77% of pneumococcal bacteremias in developing countries and 13% to 60% in more industrialized countries.[25] Primary bacteremia accounts for 61% to 70% of invasive pneumococcal disease in infants in the United States but is uncommonly diagnosed in developing countries. Whether the relatively low levels of serum antibodies to capsular polysaccharides or other protein antigens, or innate factors, in healthy adults underlie their relatively low incidence of pneumococcal disease is not well understood.[26,27]

Adults older than 65 years comprise about 15% of the population but experience one-third of all cases of invasive pneumococcal disease (approximately 15,000 episodes/yr, with ≥15% mortality). Hospitalization for pneumonia increases from 1.5% to 3.9% per year from age 65 to over 85, particularly among those with diabetes and organ dysfunction.[28] Most invasive cases result from complications of pneumonia (70% to >80%), but 5 to 10 times as many older adults experience pneumococcal pneumonia without bacteremia. In a recent prospective observational study, 8.8% of confirmed cases among adults over 65 years of age hospitalized with serotype-defined pneumococcal pneumonia were complicated by bacteremia,[29] as were 14% to 30% of such cases in a large prospective vaccine trial.[30] Thus the overall mortality associated with *S. pneumoniae* is likely much greater in the population than the numbers for invasive disease predict.[31] Mortality also increases substantially with age (see Fig. 199.2) and is more than two- to fivefold greater among adults with underlying disease (advanced lung, heart, kidney, or liver disease; diabetes; asplenia; solid and hematologic malignancies; immunosuppression) than in healthier older adults.[32]

Deaths from pneumococcal bacteremia tend to occur quickly, often in the first day to week[31,33,34] of hospitalization. Despite advances in antimicrobial therapy, the 5% to 10% early mortality with pneumococcal bacteremia has remained constant over the last century (Fig. 199.3). Although chronologic age itself is a factor, most pneumococcal disease and mortality in older adults occur in subjects with diabetes, underlying organ dysfunction (e.g., liver, kidney, heart, lung), humoral immune defects (hypogammaglobulinemia, chronic lymphocytic leukemia, multiple myeloma), and use of immunosuppressive medication (Fig. 199.4).[35–37] These data suggest an independent or additive contribution of underlying disease to the increased risk of serious infection with age.

Pneumococcal disease is not generally highly contagious. Pneumococci are transmitted from one person to another as a result of close contact,[38] such as among toddlers in daycare centers,[39,40] but many steps intervene between spread of organisms, colonization, and development of disease.[38] However, community-wide epidemics are well recognized in the meningitis belt in West Africa, where capsular serotype 1 predominates,[41] and smaller outbreaks of disease, often caused by capsular serotypes 1, 5, and 12F,[42,43] occur among adults in crowded living conditions, such as in military camps,[44] prisons,[45] shelters for the homeless,[46] and nursing homes.[47] In contrast, close contact in schools or the workplace is generally not associated with outbreaks of pneumococcal disease.[38,48] A very high incidence of invasive infections occurs at all ages among African Americans,[49] Native Americans,[50,51] and Alaska Natives[52] and

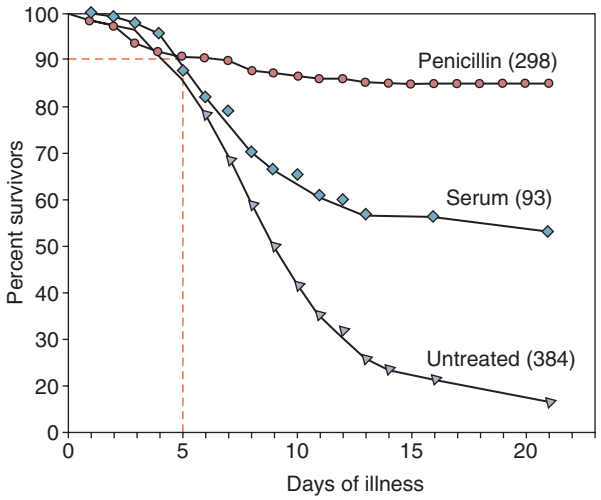


FIG. 199.3 Effect of therapy on survival with pneumococcal bacteremia in adults. Despite dramatic improvement in survival with immune horse serum against pneumococcal serotypes 1 and 2 in the 1920s, and then by penicillin and now multiple antibiotics and advanced supportive care, the 5% to 10% mortality of patients with pneumococcal bacteremia at 72 hours and 10% to 15% at 7 days has remained relatively constant.[33,362]

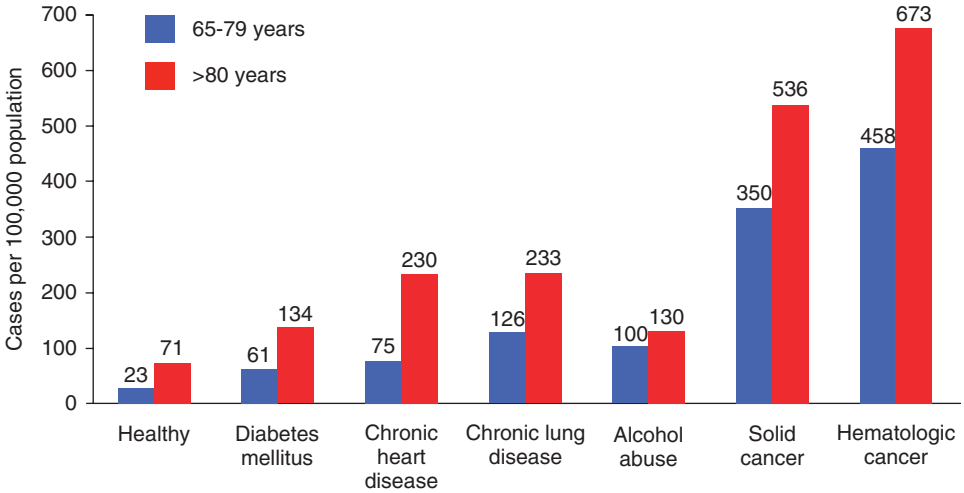


FIG. 199.4 Incidence of invasive pneumococcal disease in older adults by age group and illness. *(Modified from Kyaw MH, Rose CE Jr, Fry AM, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults.* J Infect Dis. *2005;192:377–386.)*

Australian Aboriginals,[53] presumably related to both socioeconomic genetic factors. Infants from these populations and other disadvantaged members of developed societies[54] are more likely to be colonized with high numbers of pneumococci, even within the first few weeks of life, adding exposure to their risk for disease.

Pneumococcal colonization and disease occur with a seasonal pattern, with a midwinter increase, although pneumococci can be recovered from healthy children and adults throughout the year. The incidence of pneumococcal otitis media clusters largely from November to April.[55,56] Bacteremia[57,58] shows a clear midwinter peak in temperate climates (Fig. 199.5). The association may relate in part to the colder temperatures and lower humidity, which appear to predispose to transmission of respiratory viruses such as influenza,[57–59] and perhaps closer contact indoors. However, in Houston, Texas, invasive disease in children coincides with the school year, from September through May, sparing the summer months and with no clear midwinter peak.[58] The seasonal distribution is less prominent in tropical climates.

PATHOGENETIC MECHANISMS

Colonization

The prevalence of pneumococcal colonization attests to the success of this organism in adapting to adherence and survival in the nasopharynx. The vast majority of colonizing episodes remain asymptomatic, but most symptomatic infections are likely initiated after asymptomatic colonization.[56,60] Nasopharyngeal colonization with pneumococci begins in the first weeks of life. The prevalence of colonization increases from less than 10% over the first several months of life to a peak at 70% to 100% at age 1 year, persists through the second and third year of life, and decreases thereafter to adult rates under 5%. Defining such rates depends on the sampling location, methods, and culture,[61] and, more recently, high-throughput sequencing of the 16S rRNA gene[62] and detection of the *lytA* gene by polymerase chain reaction (PCR). Duration of carriage can range from 1 week to 6 months. In adults, an individual serotype persists for shorter periods, usually 2 to 4 weeks,[63] but sometimes for several months.[1]

Living in resource-limited countries and the presence of siblings in the home are consistent risks for colonization.[54,64] Crowding (e.g., in home, daycare, barracks),[65] lower socioeconomic status, and ethnic background, as mentioned earlier, have been associated with high carriage rates, as have smoke exposure (passive or active smoking[45] and cooking fires in the home), antibiotic use (with associated risk of carriage of resistant organisms), and respiratory viral infections. Colonization is seasonal, peaking in the winter months but present in children year-round. Colonizing organisms can be transmitted from person to person by an aerosol route from coughing, with particles in the 1- to 5-μm size range depositing primarily in the upper respiratory tract[66] or acquired from saliva and shared drinking vessels.[67]

The frequency of pneumococcal colonization can be influenced by mucosal viral infections and the resident polymicrobial microbiome of co-colonizing organisms, which include other streptococci and *Neisseria* species, as well as *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus*, and other organisms. These bacteria interact and can compete for nutrients and binding sites, produce inhibitory molecules, and modify both local innate and specific immune responses.[64,68] Bacterial components can have specific interactions with host mucosal constituents.[64,69] A more diverse nasopharyngeal microbiome was associated with an increased likelihood of colonization in subjects experimentally challenged nasopharyngeally with pneumococcus.[70] Pneumococcal neuraminidases A and B may modify neighboring bacteria and cleave sialic acid on host mucins and glycopeptides to facilitate exposure of *N*-acetylglucosamine receptors on resting epithelial cells that bind pneumococcal surface-associated proteins, such as pneumococcal surface adhesion protein A. Local inflammation induced by pneumolysin, rhinovirus or influenza infections, and conditions that elicit proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1, facilitate pneumococcal binding, uptake, and likely migration of the bacteria across the epithelium and endothelium.[68] Such inflammation elicits upregulation of epithelial platelet-activating factor receptor that binds bacterial cell wall phosphorylcholine (ChoP), which intercalates through the capsule. Moreover, sialic acid, lacto-*N*-neotetraose, and polymeric immunoglobulin receptors on activated epithelial cells bind surface-expressed CbpA to advance transcytosis.[69]

Other innate host macrophage receptors, including scavenger receptor A, mannose receptor, and particularly, macrophage receptor with collagenous structure (MARCO), have been proposed in murine models to enhance mucosal clearance of *S. pneumoniae*. The role of MARCO may be to enhance interactions between the organisms and other innate receptors, such as Toll-like receptor 2 and nucleotide oligomerization domain protein 2, to promote cytokine and chemokine production.[71] In addition to its cytotoxic and complement-modifying activities, pneumolysin, largely conserved among strains, appears to engage Toll-like receptor 4, and, in conjunction with the cell wall, to limit mortality after mucosal challenge.[72] Finally, specific host IgA bound to the pneumococcal capsule, and potentially to other surface proteins, can be cleaved by bacterial IgA1 protease. The bound but cleaved IgA modifies the surface charge and can enhance binding of encapsulated pneumococci that otherwise bind less well to the epithelium.[73] Pneumococci themselves may also respond to local environmental conditions by increasing expression of ChoP and CbpA to enhance adherence to mammalian cells.[69] Lower expression of capsule may expose epithelial-binding cell

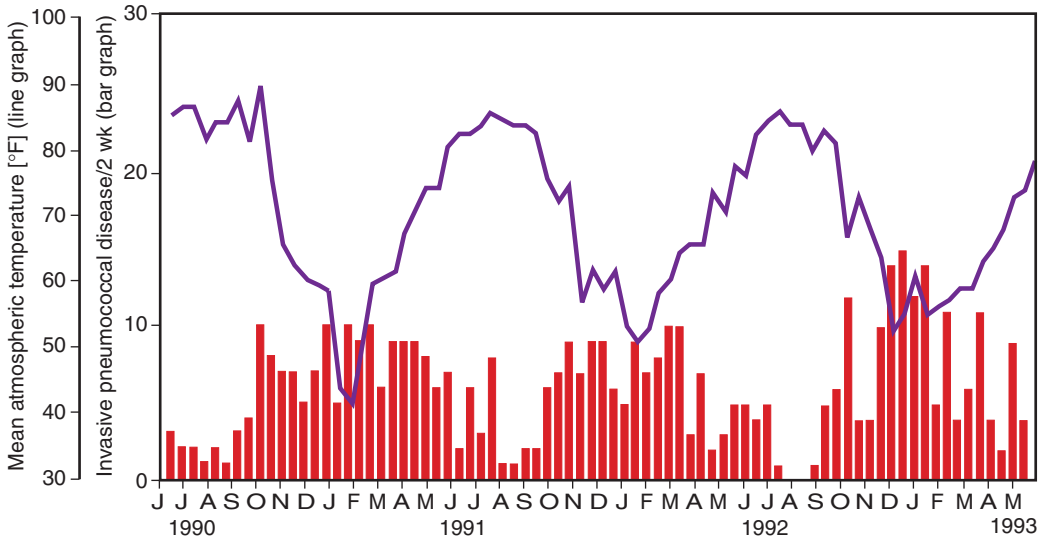


FIG. 199.5 Seasonal distribution of invasive pneumococcal disease. The bar graph indicates the total cases of bacteremic pneumococcal pneumonia and pneumococcal meningitis during each 2-week period over a period of 3 years at four tertiary care hospitals (adult and pediatric) in Houston, Texas. The line graph shows mean ambient temperature, indicating its association with the prevalence of invasive pneumococcal disease.[363]

wall–bound ligands, but higher capsule expression may facilitate bacterial escape from mucin binding and shedding.[21] Thus *S. pneumoniae* adapt to and interact with their mucosal milieu to effect colonization, but the presence of inflammation may promote the conversion from asymptomatic colonization to local and systemic disease. When symptomatic infections do accompany colonization, they typically occur within a few weeks of acquiring a new strain rather than from chronic carriage, because antibody production generally follows soon after colonization in children[56] or in adults.[74]

Pneumococcal Capsular Serotypes and Progression From Colonization to Disease

The serotypes of colonizing pneumococci can vary by age and geography and are predictive of the incidence, syndrome, and outcome of pneumococcal infections. Only a relatively small number of the more than 92 capsular serotypes typically cause serious disease, particularly among unvaccinated children. Differences among these capsular types account for approximately 60-fold differences in the invasiveness of the organism.[75–78] Indeed, capsular serotype appears to be a primary determinant of which strains are likely to remain as colonizers (e.g., 3, 6A, 6B, 9N, 19F, and 23F), which are more likely to progress from carriage to cause more invasive disease (e.g., 1, 5, 7F, 8, 14, 18C, 33F, and 38), and, among those causing invasive disease, which are more likely to cause fatal infections.[64,76,79–82] Based on a process called phase variation, organisms that express less capsule in vitro are more likely to colonize, whereas those producing more capsule show greater resistance to phagocytosis.[83] The clinical distinctions among organisms are associated with their interaction with the host. Colonizing strains are proposed to resist nonopsonic phagocytosis but to be cleared by alveolar macrophages and by complement in blood and, perhaps, lung, thereby resulting in a lower incidence of invasive disease.[84] In contrast, invasive serotypes are less common colonizers that, if not cleared by neutrophils, show increased adhesion-mediated binding to and translocation across the epithelium and are more resistant to killing by alveolar macrophages and complement. However, when colonizing strains do cause invasive disease (e.g., serotypes 3, 6A, 6B, 9N, 19F, and 23F), mortality is higher than with infection with the usual invasive strains, perhaps related to decreased host resistance.

Although the serotype distribution varies by age, these differences are likely not sufficient to explain the increases in mortality (1) from infancy to adulthood, (2) from age 65 to older than 80 years, or (3) in the presence of underlying disease among adults older than 65 years.[35] Disease in immunocompromised adults is more often caused by pediatric serotypes.[85] Thus the interaction between microbial factors, particularly expression of capsular serotype,[81] and the integrity of anatomic and immune host defense[35,82] determine the development of disease and mortality, but serotype appears to be the primary determinant of outcome in young healthy adults.

These morbid outcomes highlight the importance of understanding, potentially preventing, or at least successfully managing pneumococcal colonization and thereby its consequences. In this context, use of the polysaccharide-protein conjugate vaccines over the past 18 years has been associated with decreased rates of colonization in immunized children.[86,87] This decrement in childhood colonization and disease has been accompanied by a progressive reduction in adult invasive disease with the pediatric vaccine serotypes.[88] Colonization itself may serve as an immunizing event, and antibodies to pneumococcal neuraminidase A, PspA, and capsular polysaccharides have been detected in serum after carriage.[64,69,74,89] These antibodies, as well as antibody-independent $CD4^+$ T-cell–mediated responses,[90] perhaps involving Th17 $CD4^+$ T cells,[84,91,92] may also mediate protection against subsequent colonization and the development of disease and provide alternative approaches to immunization.

Immunologic Mechanisms of Defense Against and Susceptibility to *S. pneumoniae* Infection

After successful initial colonization, a range of immunologic mechanisms in the host contribute to protection against disease, and a panoply of bacterial factors conspires to evade these defenses. Critical to the process of defense against disease are the interplay among innate immune factors, including complement, antibodies to the bacteria, and the activity of phagocytes. Each is required and none is sufficient alone to clear this invasive mucosal pathogen. The development of pneumococcal disease among patients with specific congenital or acquired immune defects reveals the role of these factors in defense against serious pneumococcal infections.

Antibodies are essential for defense against pneumococcal disease. Antibodies to capsular polysaccharides, the primary virulence factor,[75–78] are implicated in protection against disease. In support of their protective role, (1) anticapsular antibodies appear in the bloodstream 5 to 8 days after the onset of infection, when fever spontaneously resolves in the absence of treatment; (2) administration of immune horse serum with capsule type-specific antibody in the preantibiotic era was moderately effective in treating pneumococcal pneumonia (see Fig. 199.3)[33]; (3) capsular polysaccharide vaccines elicit both specific antibody and protection against invasive infection; and (4) capsule-specific antibodies support dose-dependent uptake and killing of pneumococci in vitro[93–96] and protection of experimental animals after pneumococcal challenge in vivo.[97] Failure to produce capsule-specific antibodies in young children and compromised adults results in increased rates of invasive disease.[37,98–101] Similarly, Bruton (X-linked) agammaglobulinemia in children and common variable immunodeficiency in adults (all deficient in immunoglobulin M [IgM], IgG, and IgA)[21,102] predispose to serious pneumococcal infection, as may deficiencies of IgG2 subclass with selective IgA deficiency[103] and selective defects in responses to polysaccharide antigens.[104,105]

Other than indirect evidence of an association between antibody to pneumolysin[106] or PspA,[107] few data in humans support a protective role for antibody to antigens other than capsular polysaccharides. Maternally derived antibodies to a range of pneumococcal proteins were associated with either an increase or a decrease in infant colonization.[108] Epidemiologic evidence suggests that antibody-independent immune mechanisms provide protection in the population.[109] Indeed, in the preantibiotic era, a proportion of patients recovered from pneumococcal pneumonia without producing measurable amounts of anticapsular antibody. Moreover, young children with documented primary bacteremia and only mild symptoms can clear the infection at a time when their ability to make anticapsular antibodies is very limited. Thus antibody-independent mechanisms, including the effects of $CD4^+$ Th17 T cells during colonization, may also contribute to defense against this pathogen.

Antibodies defend against infection by binding through their variable Fab regions to bacterial surface components, including polysaccharide capsules and proteins. Upon binding, the effector constant Fc region of the antibody engages Fc receptors on phagocytic cells, such as neutrophils and macrophages, thereby providing a bridge between the phagocyte and the organism. Supporting antibody-dependent phagocytosis and killing of the organism, complement also binds to the surface of *S. pneumoniae* and to complement receptors on the phagocyte. Complement activation by each of the three activation pathways (classical, lectin, and alternative) and deposition on the surface of pneumococci (particularly complement protein C3b) occurs by both antibody-dependent and antibody-independent mechanisms and is largely required for effective uptake and killing of the organism.[110] In general, all three elements are required for clearance of pneumococci: complement, phagocytes, and antibodies; no two alone are sufficient.

Capsule-specific antibodies are proposed to derive from selected subsets of B cells.[111] The ability of polysaccharides to bind and cross link surface antibodies may directly activate naïve and IgM memory B cells, initiating an IgM response. Thus pneumococcal polysaccharides are considered "T-independent" antigens. Decreases in these B-cell subsets are associated with advanced HIV disease[112] and limited IgM responses to pneumococcal vaccine. Impaired vaccine responses and a high incidence of invasive pneumococcal disease characterize patients with common variable immunodeficiency.[113] A decreased frequency of response to pneumococcal vaccine among patients with splenectomy may be related to immunosuppression and underlying malignancy.[114] Very limited IgM responses to pneumococcal vaccine are common with HIV infection[115] and in elderly and, particularly, frail adults.[116]

Although considered T-independent antigens, pneumococcal polysaccharides may also engage and depend upon $CD4^+$ T cells to provide help. Activated T cells can engage B cells directly as well as secrete cytokines to enhance these early responses and to support the switch from production of IgM to IgG and IgA. The mechanisms by which polysaccharides stimulate T cells are controversial. The presence of proteins, particularly those linked directly and covalently to the polysaccharide on the organism or with conjugate vaccines, appears to be required to help B cells produce antibodies in sufficient amounts and of sufficient quality to control these infections. Such enhancement may derive from binding of protein-linked polysaccharides to polysaccharide-specific B cells by their surface antibody. Uptake and processing of the linked protein by these B cells provides protein-derived peptides bound to major histocompatibility complex (MHC) class II molecules on the B-cell surface. Activation of $CD4^+$ helper T cells by these MHC-bound peptides on the B cell may then support the development of these polysaccharide-specific B cells to produce antibodies that bind avidly to the capsular polysaccharides.[117,118] In this scenario, the processed protein stimulates the T cells. Alternatively, the linked protein may serve to anchor the polysaccharide to MHC class II molecules on the B-cell surface, allowing the polysaccharide itself to stimulate the T cell and enhance antibody production by that B cell.[119] The key to understanding the limitations of antibody responses to capsular polysaccharides and to enhancing these responses with vaccines lies in characterizing and exploiting these protein-polysaccharide interactions. Indeed, the introduction of vaccines with proteins covalently conjugated to polysaccharides has revolutionized vaccine development and efficacy against *S. pneumoniae* and other encapsulated pathogens by generating capsule-specific antibodies to opsonize and kill the organisms.[120,121]

The spleen is the principal reticuloendothelial organ that clears unopsonized pneumococci from the bloodstream.[122,123] In humans, highly opsonized particles are removed from the circulation in part by the liver. However, particularly with limited opsonization, the spleen assumes the most prominent role.[124] Presumably, the slow passage of blood through the spleen and prolonged contact time with reticuloendothelial cells in the cords of Billroth and the splenic sinuses allow the relatively less efficient removal of nonopsonized particles through natural immune mechanisms.[125] Overwhelming pneumococcal infection occurs in children and adults from whom the spleen has been removed or in whom it does not function normally, with an incidence 5- to 15-fold greater than that in other adults and greater yet in children.[37,122,126] The herald event in an outbreak of pneumococcal pneumonia in a metropolitan prison was the rapid, septic death of two prisoners who had undergone splenectomy.[45] Pneumococcal disease progressed so rapidly in these cases that pneumonia was not initially detectable clinically or even with certainty by chest radiographs before autopsy. The 35- to 100-fold increase in the incidence of pneumococcal bacteremia or meningitis in children with sickle cell disease is probably due to splenic dysfunction, although other factors, such as antibody and complement abnormalities, may also contribute.[123,127] Complications of these high-grade infections can include adrenal insufficiency with Waterhouse-Friderichsen syndrome and peripheral symmetrical gangrene with necrosis of multiple digits and limbs.

FACTORS THAT PREDISPOSE TO PNEUMOCOCCAL INFECTION

S. pneumoniae is a prototypic extracellular bacterial pathogen. Host defenses against infection rely, as noted earlier, on the interaction between antibody, complement, and phagocytic cells, specifically neutrophils. Both primary (or congenital) and secondary clinical conditions and underlying mechanisms may hamper the immunologic capacity of the host and predispose to pneumococcal infection (Table 199.2). Although these risks include defects in anatomy, antibody production, complement, and phagocytes (typically low neutrophil number rather than impaired function), cell-mediated abnormalities in T and natural killer cells do not figure prominently among them. These predisposing conditions do, however, include underlying liver, kidney, heart, and lung dysfunction; diabetes; alcoholism; and malignancies, particularly in older adults, which may invoke a more subtle constellation of predisposing risks.

TABLE 199.2 Conditions That Predispose to an Increased Incidence and/or Severity of Pneumococcal Infection

ABNORMALITY	PRIMARY	SECONDARY
Anatomic	Congenital CSF leak	Poor eustachian tube drainage Traumatic CSF leak Cochlear implants COPD Asthma Preceding viral/influenza infection
Antibody defects	Congenital agammaglobulinemia Common variable immunodeficiency IgG2 subclass deficiency (± selective low IgA) Selective hyporesponsiveness to polysaccharides Hyper-IgM syndrome Hyper-IgE syndrome	CLL Multiple myeloma HIV infection
Low complement	Classical pathway (low C2, C1, C4) Alternative pathway (low factors I, H, and B) Low C3 (all pathways) MBL deficiency and polymorphisms	Nephrotic syndrome Complement consumption
Neutropenia	Cyclic neutropenia	Drug-induced neutropenia Aplastic anemia
Neutrophil dysfunction	Fcγ receptor IIa (*R131* allele) (low avidity for IgG2) Chédiak-Higashi syndrome	Diabetes
Reticuloendothelial cell defects	Congenital asplenia Hyposplenia	Splenectomy Sickle cell disease Portal hypertension
Combined/other	IRAK4 deficiency (decreased cytokines)	Extremes of age HIV/AIDS Sickle cell disease (spleen, antibody, ± complement) Chronic organ dysfunction (lung, liver, kidney, heart) Chronic alcohol use Solid-organ and bone marrow transplantation Lymphoma
Environmental		Environmental smoke Smoking (tobacco) Crowding (daycare, homeless shelters, prison, military training) Stress (military training) Cold season

C, Complement component; *CLL,* chronic lymphocytic leukemia; *COPD,* chronic obstructive pulmonary disease; *CSF,* cerebrospinal fluid; *HIV/AIDS,* human immunodeficiency virus/acquired immunodeficiency syndrome; *Ig,* immunoglobulin; *IRAK4,* interleukin-1 receptor-associated kinase 4; *MBL,* mannose-binding lectin.

In addition to the potential defects in antibody production considered previously, the heat-labile complement components of humoral immunity are essential for defense. Of the many possible defects in complement, only those factors required to generate C3b for binding to the bacterial surface and inactivated C3b (iC3b) for phagocytosis and killing by phagocytes are associated with pneumococcal infection.[110] Because the pore-like membrane attack complex (MAC; complement component C6, C7, C8, or C9) that lyses gram-negative organisms cannot pierce the thick pneumococcal cell wall, pneumococci are not killed by serum alone, and defects in these components do not predispose to these infections. In contrast, genetic deficiencies in complement component C3, essential for the activity of each of the three complement activation

pathways (classical, lectin, and alternative) are associated with recurrent pneumococcal infection.[110,128] Deficiencies in complement components C1, C4, and most commonly C2, whether congenital or acquired, are expected to increase susceptibility to pneumococcal infection,[129] although they do so only rarely. The absence of mannose-binding protein in serum, which triggers the lectin complement pathway, may be associated with susceptibility to pneumococcal bacteremia.[130,131] However, in addition to host defects in complement production, *S. pneumoniae* expresses a range of proteins that promote degradation of C3 (PhpA) and interfere with deposition of opsonins (PspA, pneumolysin), with activation and generation of convertase (pneumolysin, factor H–binding inhibitor of complement [Hic], and PspC) and with ligands for complement receptors on phagocytes (Hic, PspA/PspC, CbpA, and pneumolysin). These data highlight the importance of the complement system in defense of the host and survival of the bacteria.[110]

Neutropenia of whatever cause is associated with *S. pneumoniae* infection, although functional leukocyte defects, such as leukocyte adhesion deficiency syndrome (MAC-1 deficiency) generally are not,[101,132] due to the redundancy of killing pathways in neutrophils. Similarly, defective bacterial killing by polymorphonuclear leukocytes (PMNs), as seen in chronic granulomatous disease, does not predispose to infection with *S. pneumoniae*; the absence of catalase renders this organism susceptible to the interaction between its endogenous H_2O_2 and myeloperoxidase and the halide present in PMNs. At the time of initial hospitalization for acute leukemia, patients are more likely to have infection caused by other gram-positive pathogenic bacteria,[133] akin to the pretreatment situation in multiple myeloma.[134] Limitations in antibody binding to Fc receptors, particularly among subjects with homozygous expression of the *R131* allele of the neutrophil Fcγ receptor II that binds the Fc region of IgG2 only poorly,[135] can predispose to these infections.

The susceptibility of elderly persons to pneumococcal pneumonia is multifactorial; the bacteria can exploit the defects described earlier as well as those accompanying impaired functional status, such as weakening of the gag and cough reflexes, malnutrition, and organ dysfunction. The effect of alcoholism is also multifactorial and involves lifestyle (such as cold exposure and malnutrition), suppression of the gag reflex, and possibly deleterious effects on PMN function, although in most instances these alterations have been difficult to attribute to the effect of alcohol alone and may well involve liver disease as well.[136,137] Heffron[1] cited studies from the preantibiotic era showing a 30% to 50% incidence of alcohol abuse in patients with pneumococcal pneumonia, results confirmed in more recent studies (about one-third of such patients).[23,34,138] A disproportionately high number of patients with pneumococcal infection have diabetes mellitus,[23,34,138–140] a condition in which PMN chemotaxis is reduced[141] and phagocytic function is defective,[142] as well as dysfunction of other organ systems and underlying hematologic malignancies that often accompany aging (see Fig. 199.4).

Regarding antibody production in older adults, both the differentiation potential of hematopoietic stem cells and the numbers of naïve T cells and B cells decrease with advancing age,[143–145] as may the subsets of IgM memory B cells proposed to respond preferentially to polysaccharide antigens.[111,146–149] These perturbations and decreased responses to capsular polysaccharides have been most closely related to weight loss and frailty rather than to age alone.[150,151] Studies have been begun to distinguish between innate age-dependent "immunosenescence" and the effects of accumulated underlying disease and frailty on age-related immune dysfunction, particularly decreased responses to vaccination.

As mentioned earlier, prior respiratory viral infection, especially that caused by influenza virus, plays a prominent role in predisposing to pneumococcal infection.[57,58,152,153] Upregulation of surface receptors during viral infection enhances pneumococcal adherence[154,155] and invasion. Bacteria show greater epithelial adherence and impaired clearance from the airways because of virus-induced damage. Pneumococcal disease is greatly increased in people with altered pulmonary clearance, such as those who have chronic bronchitis, asthma, or chronic obstructive pulmonary disease, and cigarette smoking, including passive exposure,[48] particularly among otherwise noncompromised nonelderly adults. In the United States, socioeconomic factors may contribute substantially to the increased risk for these infections among persons of African-American descent, whereas the very high incidence among certain Native American populations, such as the Navajo, likely reflects genetic and environmental factors.[50,51,156]

HIV Infection

Pneumococcal pneumonia occurs 10 to 25 times more commonly with untreated HIV infection than in the general age-matched population (approximately 90 cases/1000 person-years).[157,158] Rates of invasive pneumococcal disease (e.g., bacteremia) were increased by approximately 80- to 100-fold with advanced untreated HIV disease (overall 176 vs. 3.8/100,000 patient-years for HIV vs. general population, respectively),[159] with recurrence in approximately 20% of cases.[160,161] HIV-associated risk factors for pneumococcal disease include stage of HIV disease, $CD4^+$ T-cell number,[37] drug and alcohol use, smoking,[158] organ dysfunction, previous pneumonia, and African-American ethnicity,[162,163] often with impaired antibody responses. Despite a greater than 90% decline in other opportunistic infections, effective antiretroviral treatment has limited the incidence of bacterial pneumonia and pneumococcal disease by only half,[158,164–168] or even shown no benefit.[169–171]

HIV infection is complicated by impaired IgG antibody responses, especially primary responses, to immunization[172–174] with pneumococcal and other vaccines.[175] That preimmunization levels may be lower, for instance, with influenza or measles[175,176] suggests a paradoxical loss of specific antibody despite hypergammaglobulinemia. Indeed, selective antigen-specific deficits after immunization were proposed to underlie the increased incidence of pneumonia and, relatively, pneumococcal infection after administration of 23-valent polysaccharide vaccine among HIV-infected adults in Uganda.[177] Pneumococcal vaccine failures were associated with low vaccine responses[178] and opsonic activity.[179] As discussed later, current pneumococcal vaccines show limited or transient protection against invasive disease, highlighting the need to limit HIV-associated immunodeficiency and circumvent related defects with more effective vaccine platforms.

CLINICAL SYNDROMES

S. pneumoniae causes infection of the middle ear, sinuses, trachea, bronchi, and lungs by direct spread of organisms from a nasopharyngeal site of colonization and causes empyema by direct extension to the pleural space from the lungs. Infections of the heart valves, bones, and joints are initiated by hematogenous spread, and those of the central nervous system (CNS) and peritoneal cavity by either route. The spectrum of invasive disease[180] includes primary bacteremia without an apparent source or focus of infection. In a population-based study of pneumococcal bacteremia in Israeli adults,[181] 71% of patients had recognizable pneumonia by plain chest radiograph, 8% had meningitis, and 4% had otitis media or sinusitis; 18% had primary bacteremia without an obvious source, a finding that is more common in children than adults.

Otitis Media

Diagnosis of otitis media depends on visualizing the tympanic membrane and testing its function.[182] Virtually every study of culture-proven acute otitis media has shown *S. pneumoniae* to be the most common isolate or second only to nontypeable *H. influenzae*, although nearly all of these studies were carried out in populations that had not received conjugate polysaccharide vaccine (see below). Among children ages 6 months to 4 years before widespread use of pneumococcal conjugate vaccine, *S. pneumoniae* was implicated in 40% to 50% of cases in which an etiologic agent was isolated or in 30% to 40% of all cases. PCR of middle ear fluid from children with otitis media suggests that 50% of specimens that used to be regarded as sterile may be caused by *S. pneumoniae* or *H. influenzae*.[183] Pneumococci have historically been the most prevalent pathogens in otitis media in adults as well.[184] Prior infection by a respiratory virus may play a major contributory role by causing congestion of the opening to the eustachian tube, which prevents expulsion of bacteria by normal clearance mechanisms. Prospective longitudinal studies[56,60,185] have shown that, when otitis media occurs, it follows within a few weeks after colonization by a new pneumococcal serotype and before the appearance of circulating anticapsular antibody.

Sinusitis

Acute bacterial rhinosinusitis has the same pathogenesis as, and is initially caused by, the same organisms as acute otitis media, with

S. pneumoniae and *H. influenzae* predominating.[186] Obstruction of orifices by viral infection, atmospheric pollutants, or allergens, together with accumulation of fluid in the paranasal sinus cavities, even during simple colds,[187] provides a medium for bacterial proliferation and subsequent acute sinus infection. Acute bacterial sinusitis is most consistently differentiated from viral causes by the persistence of symptoms (≥10 days), severity of symptoms and signs (temperature ≥39°C, purulent discharge or pain for greater than 3 days), and worsening of symptoms (fever, headache, increased nasal discharge) after initial improvement following a simple upper respiratory tract infection.[188] Evolution from acute to chronic sinusitis is associated with more complex bacteriologic findings.

Meningitis

Except during an outbreak of meningococcal infection, *S. pneumoniae* is the most common cause of bacterial meningitis in adults.[189–191] In countries that have implemented effective vaccination programs for *H. influenzae* type b, pneumococci have become the most common sporadic cause of meningitis in children older than 6 months, as well. Even after the widespread use of pneumococcal conjugate vaccine in children, *S. pneumoniae* remains the most common cause of bacterial meningitis in the United States, but the burden of disease has shifted from young children to older adults.[191]

Meningitis may result from hematogenous spread or by direct extension of bacteria from the sinuses or the middle ear.[192,193] Favoring the role of direct extension are the association between acute otitis media or sinusitis and infection of the CNS and the well-documented role of *S. pneumoniae* as the most common cause of recurrent bacterial meningitis associated with head trauma, cerebrospinal fluid (CSF) leak, cochlear implants,[194] or any other break in the integrity of the dura.[195] Favoring hematogenous spread is the association between pneumococcal pneumonia or bacteremia without a known focus and meningitis. In addition, an autopsy study of the temporal bones of children who died of bacterial meningitis[196] showed no evidence for extension from the middle ear, supporting the possibility that even after otitis media, meningitis may develop as a result of bacteremia. Although hematogenous spread to the choroid plexus was originally thought to be responsible for most cases of pneumococcal meningitis, it is now proposed that infection upregulates platelet-activating factor on vascular endothelial surfaces in the meninges and that pneumococci adhere and are internalized by this mechanism.[197] Direct spread to the CNS via lymphatics may also be responsible.[198] Communication through the cochlear aqueduct between the inner ear and the subarachnoid space[198,199] may explain deafness, a common complication in patients with hematogenous bacterial meningitis.

Once pneumococci appear in the meninges or subarachnoid space, the capacities to escape phagocytosis and produce inflammation are central to the disease process. Intracisternal injection of pneumococcal cell wall constituents in rabbits (principally peptidoglycan, also teichoic acid) causes the CSF abnormalities of bacterial meningitis, presumably through a variety of inflammatory mediators (e.g., complement protein C5a, tumor necrosis factor, interleukin-1, interleukin-6).[189,193,200] Interactions with Toll-like receptors 2 and 4 may initiate some protective response, but also stimulate further inflammation.[198]

No distinctive clinical features distinguish meningitis due to *S. pneumoniae* from that due to other bacteria. Examination of a Gram stain from a centrifuged specimen of CSF provides the correct diagnosis in a large majority of cases[201] with confirmation by appropriate culture. However, bacterial numbers and diagnostic sensitivity are substantially decreased if antibiotics have been given more than 4 hours in advance of CSF sampling. Immunologic detection of pneumococcal capsular material ("bacterial antigen") generally does not add information beyond what is determined by Gram staining[202]; the value of available single and multiplex PCR methods is currently under study.

Acute Exacerbation of Chronic Bronchitis

S. pneumoniae is the third most common bacterial cause of exacerbation in patients who have chronic bronchitis,[203,204] following *H. influenzae* and *M. catarrhalis.* Exacerbations are highly associated with acquisition of a new pneumococcal strain.[205]

Pneumonia

Overview

In the preantibiotic era, pneumococcus was identified as the cause in up to 90% to 95% of cases of community-acquired pneumonia (CAP).[1] More recent studies from Europe have attributed 25% to 40% of pneumonia cases to *S. pneumoniae,* results based, in part, on techniques that have not been validated.[206,207] Recent studies from the United States implicate pneumococcus as a cause of about 5% to 10% of CAP cases, even when an intensive effort has been made to identify the causative organism,[208] consistent with incidence of for rigorously identified cases in the Netherlands (5.4%).[30] The earlier widespread use of conjugate pneumococcal vaccine in children and a lower rate of cigarette smoking in U.S. compared with European adults may contribute to these geographic differences.

Pathogenesis

Unrecognized aspiration of oropharyngeal bacteria likely initiates most cases of lower respiratory infections. That many organisms are present in the nasopharynx but *S. pneumoniae* most often causes clinical pneumonia speaks to the relative virulence of this organism. Pneumonia develops when potentially protective mechanisms fail to prevent both the access of pneumococci to the alveoli and their subsequent replication. Bacteria proliferate in alveolar spaces and spread via the alveolar septa. In these sites, pneumococci activate complement, generate cytokine production, and upregulate receptors on vascular endothelial surfaces. Exudative fluid and WBCs accumulate in the septa and alveoli and extend to uninvolved areas through the interalveolar pores of Kohn. This filling of alveoli with microorganisms and inflammatory exudate defines the presence of pneumonia, and a clinical diagnosis is made when fluid accumulation is great enough to be seen radiographically as a nonlucent region of "infiltration" or "consolidation" (Fig. 199.6).

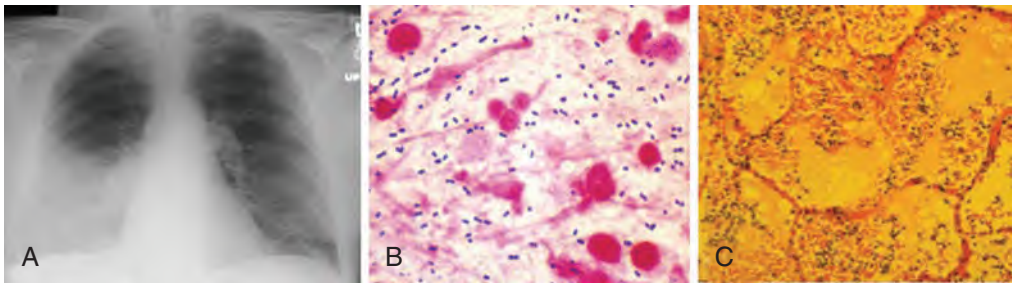


FIG. 199.6 Radiographic, microbiologic, and pathologic features of pneumococcal pneumonia in a 62-year-old man. A 62-year-old man described sudden-onset chills, fever, cough, and purulent sputum for 2 days. He smoked two packs of cigarettes per day, had alcohol binges, and had congestive heart failure. He was acutely ill, had a temperature of 103.4°F (39.7°C), respiratory rate of 32 breaths/min and labored breathing, blood pressure of 106/62 mm Hg, and pulse of 112 beats/min. He had decreased breath sounds and density to percussion in the right posterior chest. (A) Chest radiograph. (B) Gram stain of sputum with many neutrophils and gram-positive diplococci (note that bacteria are not within the phagocytes). (C) Histology of lung tissue from this man's autopsy when he died on day 2 of hospitalization while treated with ceftriaxone and azithromycin with supplemental oxygen in the intensive care unit.

Predisposing Factors

In a recent prospective study of pneumococcal pneumonia in a veteran population,[34] nearly all patients had two or more predisposing conditions, such as cigarette smoking, chronic obstructive pulmonary disease (both affect pulmonary clearance), alcohol abuse, liver disease (hepatitis, cirrhosis, or both), diabetes mellitus (these three latter conditions adversely affect PMN function), recent intravenous drug use, congestive heart failure, malignancy, HIV infection (greatly suppressed ability to produce IgG), or neurologic disease (decreased ability to swallow, decreased gag reflex, and increased aspiration). One-third of patients had been discharged from a hospital within the preceding 6 months. The increase in adult pneumococcal pneumonia during winter[58] and the striking association with viral infections in children and adults has long been noted.[58,152,153,209] Among patients hospitalized for influenza and found to have pneumonia, 25% were coinfected with *S. pneumoniae.*[210]

Symptoms and Physical Findings

The acute onset of cough (92%), fatigue (63%), shortness of breath (47%), and dyspnea (23%) with documented or subjective fever (92%), chills (77%), sweats, purulent sputum, and pleuritic chest pain (79%), as described by Heffron in 1938,[1] remain the most frequent symptoms of pneumococcal pneumonia.[31,211,212] These are all more prominent in younger than in older patients.[213,214] Patients with pneumococcal pneumonia usually appear ill and have a grayish, anxious appearance that may differ from that of persons with viral or mycoplasmal pneumonia. The temperature may be elevated to 102°F to 103°F, the pulse to 90 to 110 beats/min, and the respiratory rate to greater than 20 breaths/min and labored, with use of accessory muscles. Elderly patients may have a less well-defined clinical syndrome and only a slight or no temperature elevation, which may delay or obscure the diagnosis, but they are more likely to have an increased respiratory rate.[213,214] Fully one-half of patients admitted to a Department of Veterans Affairs hospital with CAP did not have a temperature >99.4°F in the first 48 hours of admission.[208]

Physical examination may reveal diminished respiratory excursion (splinting) on the affected side because of pain. Dullness to percussion is present in about half of cases. Crackles or abnormal lung sounds are heard on careful auscultation in nearly all cases, but in patients who have chronic lung disease, it is often difficult to be certain that such sounds signify the presence of pneumonia. Increased tactile fremitus, often overlooked, is very useful in detecting consolidation. Bronchial or tubular breath sounds may be heard if dense consolidation is present. Flatness to percussion at the lung base, with an inability to detect the expected degree of diaphragmatic motion based on the patient's respiratory excursion, and decreased tactile fremitus strongly suggest the presence of pleural fluid. Normal vital signs substantially reduce the likelihood of pneumonia, but no set of physical findings can reliably replace the chest radiograph in diagnosing the presence or absence of pneumonia.[215] Accordingly, the presence of cough, fever, increased respiratory rate, and abnormal lung sounds indicates the need for a chest radiograph. Indeed, patient management depends upon the results of chest imaging, limiting both overdiagnosis of pneumonia and antibiotic use.[216] The finding of a new heart murmur, particularly a diastolic murmur, raises concern about endocarditis, a rare but serious complication. The presence of fever with headache, confusion, obtundation, or neck stiffness suggests the presence of meningitis and is a compelling indication for a lumbar puncture.

Radiographic Findings

In most cases of pneumococcal pneumonia, chest radiography reveals an area of infiltration involving one or more segments within a single lobe (see Fig. 199.6A).[34] Consolidation, defined as a dense infiltrate (e.g., showing the presence of air bronchograms), is more frequent in bacteremic cases.[34,217] Necrotizing changes can be seen on chest radiographs in about 2% of patients and by computed tomography in 10%.[34,218] Only rarely does *S. pneumoniae* infection cause a thick-walled lung abscess.[219] Although pleural effusion may be detected by careful search in up to 57% of patients with pneumococcal pneumonia, only 10% have sufficient amounts of fluid to aspirate. Empyema is present in only 2% to 8% of patients.[31,220]

General Laboratory Findings

Twenty-five percent of patients with pneumococcal pneumonia have hemoglobin at 10 mg/dL or less.[34] The WBC count is elevated in the majority of patients (>12,000/mm^3) but normal in one-quarter; a WBC count less than 6000/mm^3, occurring in 5% to 10% of adults hospitalized for pneumococcal pneumonia, indicates a very poor prognosis.[221] Low serum albumin may result from predisposing malnutrition or from sepsis-related catabolism and fluid shifts.[34] Elevations of serum bilirubin to 3 to 4 mg/dL may result from hypoxia, hepatic inflammation with elevated transaminases, and breakdown of red blood cells in the lung. Levels of lactate dehydrogenase may be elevated. The likelihood that underlying disease is present must always be considered when evaluating abnormal laboratory findings. Laboratory abnormalities in empyema are reviewed in Chapter 68.

Diagnostic Microbiology

Microscopic examination of Gram-stained sputum is both sensitive and specific if the sample is available and contains large numbers of PMNs (>25/high-power field) and very few epithelial cells (<1 per 10–20 PMN), and if the patient has not received more than 6 to 12 hours of antibiotics (see Fig. 199.6B).[222,223] Sensitivity declines after 6 hours of antibiotic therapy, so every effort should be made to obtain a sample before that time. Although often unavailable, with adequate sputum specimens and in the absence of prior antibiotic treatment, Gram staining and culture both reveal pneumococci in expectorated sputum from about 60% of patients with pneumococcal pneumonia, and 30% to 40% of patients with CAP.[31,222] When a patient who has pneumonia cannot initially provide an expectorated specimen, inhalation of humidified air or hypertonic saline may be used to obtain one, but these should not delay therapy. Antibiotics should be given promptly and at the point where the diagnosis of pneumonia is made. An earlier requirement to administer antibiotics within 4 hours of a patient's arrival at an emergency room has recently been rejected.[224] We suggest that reasonable attempts to determine an etiologic agent should be made for all adults sufficiently ill to be hospitalized; upcoming guidelines for management of CAP recommend such efforts only for those with severe pneumonia.

If accepted terminology is strictly followed, a presumptive diagnosis of pneumococcal pneumonia is then made if *S. pneumoniae* is identified by sputum culture, whereas the diagnosis is regarded as proven if pneumococci are isolated from blood or another normally sterile body site. About 20% to 25% of patients hospitalized for pneumococcal pneumonia have detectable bacteremia.[1] A guide to interpreting results of blood and sputum culture is shown in Table 199.3.

In addition to analysis of sputum and blood cultures, other diagnostic techniques focus on the detection of pneumococcal antigen. Most commonly used is the rapid point-of-care urine immunochromatographic membrane test (BinaxNow *S. pneumoniae* urinary antigen test; Alere, Waltham, MA) for C-polysaccharide approved by the US Food and Drug Administration (FDA). In 22 studies of more than 4600 patients with pneumococcal pneumonia, the test has a sensitivity of 75% (range, 58%–93%), specificity of 95% (range, 58%–93%), a positive predictive value of 79% (range, 25%–100%), and a negative predictive value of 93% (range, 74%–100%), showing greater sensitivity than other methods,[31] particularly in those with bacteremia. The test can remain positive for weeks and is not useful in children because of positive results with heavy pharyngeal colonization.[226] False-positive results have rarely been reported.[227,228] A technique to detect PPSs from the 13 serotypes present in the 13-valent conjugate vaccine in the urine is more sensitive than BinaxNow,[229] but these serotypes have become much less common causes of pneumonia because of the use of the 13-valent conjugate vaccine, so this test is not likely to be useful diagnostically. Other techniques include the following:

(1) Quantitative PCR for DNA that encodes *lyt*A of *S. pneumoniae* in sputum or nasal secretions[230,231] modestly increases the diagnostic yield compared with standard bacteriologic techniques, as may multiplex PCR assays,[232] the predictive values of which are being determined in community settings. This test also was useful in HIV-infected subjects in South Africa but has yet to be validated in non-AIDS patients in a developed country.

TABLE 199.3 Microscopic Examination and Culture of Sputum and Blood Diagnosis of Pneumococcal Pneumonia

GRAM STAIN	SPUTUM CULTURE	BLOOD CULTURE	COMMENT
+	+	+	Generally regarded as confirmed diagnosis of invasive pneumococcal pneumonia but does not exclude contribution by another etiology, such as influenza virus infection or lung cancer
+	+	–	Good evidence for presumptive (nonbacteremic) pneumococcal pneumonia if a clinical syndrome suggesting pneumonia is present, microscopic examination of Gram-stained sputum is characteristic (see Fig. 199.5), and culture shows strongly predominant growth of pneumococci with no other likely pathogenic bacteria
±	–	+	With symptoms and signs of pneumonia and an infiltrate on the chest radiograph, findings are taken to indicate invasive pneumococcal pneumonia even if organisms are not found in sputum
+	–	–	In the presence of the appropriate clinical syndrome, still remains suggestive of pneumococcal pneumonia because organisms can be missed on culture as a result of sampling error and overgrowth of streptococci from saliva; however, gram-positive cocci may be streptococci of the mouth
–	+	–	In the presence of the appropriate clinical syndrome, this yields a diagnosis of presumptive (nonbacteremic) pneumococcal pneumonia
–	–	–	Does not support a diagnosis of pneumococcal pneumonia but does not exclude it because of numerous difficulties in obtaining a valid sputum sample

(2) A quantitative assay to detect pneumococcal capsular polysaccharide directly in nasopharyngeal and blood specimens.[233]

(3) Quantitative PCR that has been studied on sputum in CAP patients who can provide a sputum specimen. Although they used excellent negative and positive controls to standardize the assay, the authors found multiple isolates of common bacterial pathogens that are readily identifiable by traditional techniques, so the assay is evolving for clinical application.[234]

Levels of C-reactive protein and procalcitonin are often elevated in patients with bacterial pneumonia but do not discriminate *S. pneumoniae* from other bacteria.

Complications

Pleural fluid appears in a substantial proportion of cases of pneumococcal pneumonia but is usually reactive. The fluid is tapped when of sufficient amount to cause respiratory distress or when response to treatment is delayed, suggesting the presence of an empyema. Some authorities suggest that, in every case of pneumonia, if sufficient fluid is present a pleural tap should always be done. When bacteria reach the pleural space, either hematogenously or as a result of extension to the visceral pleura, empyema results; this is seen in 2% to 8% of cases.[220] Persistence of fever, even if "low grade," and leukocytosis after 4 to 5 days of appropriate antibiotic treatment for pneumococcal pneumonia is suggestive of empyema, and this diagnosis is even more likely if the radiograph shows persistence of pleural fluid. The presence of frank pus in the pleural space, a positive Gram stain, or fluid with pH of 7.1 or less are each indications for aggressive and complete drainage with prompt insertion of a chest tube, followed by immediate removal of infected material by pleuroscopy or open thoracotomy if drainage is not complete, if the patient remains febrile or with leukocytosis, or both.[235]

Other Infectious Syndromes

S. pneumoniae is implicated in a wide variety of infectious states. Isolated or epidemic *conjunctivitis* is essentially the primary condition in which unencapsulated pneumococci play a role.[10] A case of pneumococcal *endocarditis*[236] is seen once or twice per decade at a large tertiary care hospital in the United States; 14 cases were identified in Denmark (population of 5 million) in a 10-year period.[237] Alcoholic dependence is common in these cases, most infections involve previously normal heart valves, and the disease tends to be fulminating.[236–238] Purulent *pericarditis*[239] caused by pneumococci has also become exceedingly rare, whether it occurs as a separate entity or together with endocarditis. Pneumococci cause a small proportion of *peritonitis,* occurring by hematogenous or local inoculation of the peritoneal cavity.[240] Preexisting ascites can serve as a site of diminished resistance, with pneumococci reaching the peritoneum by hematogenous spread, even in the absence of a documented source of infection elsewhere. Local inoculation occurs either when pneumococci are carried to the peritoneal cavity via the female reproductive tract, with or without clinically recognizable infection (e.g., salpingitis), or as a result of bowel perforation. Pneumococcal infections of the female reproductive organs[241–243] occur with or without peritonitis. *Septic arthritis* develops spontaneously in a natural or prosthetic joint[244] or as a complication of rheumatoid arthritis.[245] Multiple joints are involved in less than 25% of cases,[246] and the functional outcome is often bad. *Osteomyelitis* in adults tends to involve the vertebral bones.[247] *Epidural and brain abscesses* are rarely described.[248] *Soft tissue* infections[249,250] are found in persons who have connective tissue diseases or HIV infection. Bacteremic pneumococcal *cellulitis* generally occurs in patients who have severe underlying diseases, and a respiratory focus is often apparent.[251] Finally, the development of pneumococcal pneumonia or bacteremia or the appearance of *unusual infections* in a young adult should prompt testing for HIV infection.[252,253]

Noninfectious Syndromes

Noninfectious sequelae may complicate infections,[254,255] including pneumococcal pneumonia.[222] Consistent with earlier reports of cardiovascular complications of CAP,[254,255] among 170 US veterans hospitalized for pneumococcal pneumonia, 33 (19.4%) had at least one major cardiac event, including acute myocardial infarction, arrhythmia, or worsening congestive heart failure.[222] Possible mechanisms for these cardiac events include (1) increased local inflammatory response in a vulnerable coronary artery atherosclerotic plaque, with plaque rupture and subsequent infarction[256]; (2) sepsis causing increased demand ischemia in myocardial muscle exacerbated by ventilation-perfusion mismatch and hypoxemia; or (3) actual invasion of or damage to myocardium by pneumococci.[257] Pneumococcal bacteremia may also be complicated by peripheral symmetrical gangrene with necrosis of digits and limbs, as well as hemolytic-uremic syndrome.[258]

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE

Definitions of Antibiotic Susceptibility

Before 1977, with isolated exceptions, virtually all *S. pneumoniae* were inhibited by penicillin at a concentration of 0.06 μg/mL or less. In 1977–1998, pneumococcal antimicrobial resistance was described in South Africa and was associated with clinical failures of treatment, particularly in the cases of meningitis. Isolates with a minimal inhibitory concentration (MIC) of 0.06 μg/mL or less were called penicillin susceptible, or resistant if the MIC was 0.12 μg/mL or greater.[259] Definitions of susceptibility to penicillin were changed in 2008 to reflect the site of infection, particularly for meningitis, and the route of therapy.[260–263] Current accepted definitions of susceptibility and resistance to penicillins

TABLE 199.4 Current Definitions of Susceptibility or Resistance of Pneumococci to Penicillins or Cephalosporins

	PENICILLIN[a]	CEFTRIAXONE[b]
Non-CNS, Oral		
Susceptible	≤0.06 μg/mL	—
Intermediate	>0.06 and ≤1 μg/mL	—
Resistant	>1 μg/mL	—
Non-CNS Parenteral		
Susceptible	≤2 μg/mL	≤1 μg/mL
Intermediate	>2 and ≤4 μg/mL	>1 and ≤2 μg/mL
Resistant	>4 μg/mL	>2 μg/mL
CNS		
Susceptible	≤0.06 μg/m	≤0.5 μg/mL
Intermediate	—	>0.5 and ≤1 μg/mL
Resistant	>0.06 μg/mL	>1 μg/mL

[a]Also applies to amoxicillin.
[b]Also applies to cefotaxime.
CNS, Central nervous system.

and cephalosporins, summarized in Table 199.4, may be overly conservative for penicillin and ceftriaxone for CNS infections.

Mechanisms of Antibiotic Susceptibility and Resistance

Penicillin inhibits the replication of *S. pneumoniae* by binding one or more enzymes needed to synthesize peptidoglycan, including higher-molecular-weight transpeptidases and a lower-molecular-weight carboxypeptidase, resulting in bacterial autolysis. The binding is covalent, and a serine ester–linked, enzymatically inactive penicilloyl complex is formed. Six peptidoglycan synthesis enzymes, which are also called penicillin-binding proteins (PBPs), have been identified (1a, 1b, 2a, 2b, 2x, and 3). Resistant isolates are characterized when penicillin shows decreased affinity for one or more of these enzymes due to mutations in the genes that encode them.[264] Alterations in PBP2b are more likely to account for low-level resistance, whereas mutations in PBP2x have been associated with high-level resistance.[265] Alterations in PBP2x and 1a also render pneumococci more resistant to third-generation cephalosporins, such as cefotaxime or ceftriaxone.[266]

Pneumococci develop antibiotic resistance by transformation, the unique capacity to acquire genetic material from other bacteria with which they coexist in close proximity. In fact, the altered sequence in the gene for PBP2b in many penicillin-resistant isolates appears to have been acquired from *Streptococcus mitis.*[267] Extensive diversity among isolates[268] or within the transpeptide-encoding region of the pneumococcal genome[265,266] indicates that many discrete mutational events have occurred, some of which reflect acquisition and others, rearrangement of DNA. Alterations in several PBPs within an individual isolate result in a mosaic array of PBPs. Nevertheless, the major source of resistance worldwide has been the geographic spread of a few clones that seem to have special capacity to spread and to colonize.[269] In this context, a strain that was prevalent in Spain during the 1992 Olympics was imported into and rapidly spread throughout Iceland.[270] Similarly, the dominant factor in the emergence of antibiotic-resistant pneumococci in the United States has been human-to-human spread of relatively few clonal groups that harbor resistance determinants to multiple classes of antibiotics[271] and have spread worldwide.

Geographic spread is greatly facilitated by antibiotic pressure, which explains why many of the widespread colonizing clones exhibit antibiotic resistance, including the clonal spread of a penicillin-resistant *S. pneumoniae* serotype 19A.[272] A prominent site for this selection in the United States is daycare centers, in which a remarkably high proportion of children are receiving antibiotics. Conditions in these centers (1) suppress susceptible microbiota, thereby creating a niche for resistant organisms; (2) spare antibiotic-resistant pneumococci; (3) increase the prevalence of antibiotic-resistant viridans-group streptococci, thus setting the stage for further transformation of pneumococci to antibiotic resistance; and (4) provide close contact among small children, which allows the spread of organisms. Similar conditions for emerging resistance are present in nursing homes.

Decreased susceptibility to penicillin is associated with resistance to other antimicrobial agents, because resistance usually results from acquisition of a cassette of genetic elements. Even low-level increases in MICs for penicillin are associated with resistance to other widely used antibiotics, including macrolides, trimethoprim-sulfamethoxazole, tetracyclines, and, to a lesser extent, quinolones.

Understanding the complexity of macrolide resistance is important clinically. Macrolides insert into a pocket of the 23S subunit of the 50S ribosome, specifically by attaching at domain V of the peptidyl transferase loop, thereby blocking protein assembly. In doing so, these drugs—generally regarded as bacteriostatic drugs against gram-positive pathogens, such as *S. aureus*—are bactericidal against *S. pneumoniae.* Acquisition of genetic material, designated *ermB* or *mefA,* often together with genes that encode penicillin resistance, may lead to resistance. The gene *ermB* encodes an enzyme that methylates a base in domain V of the 23S rRNA (nucleotide A2058), thereby altering the ribosomal pocket. Because the macrolide no longer fits into the pocket, increasing its concentration has little effect, resulting in high-level resistance (≥64 μg/mL). The gene *mefA* encodes an efflux pump that extrudes macrolides. High antibiotic concentrations might be expected to overcome the pump, forcing enough antibiotic into the bacterium to exert an antibacterial effect. This resistance is at a lower level (usually ≤16 μg/mL) and, at a sufficient dose, a macrolide might be expected to be effective. The debate about whether such resistance is clinically meaningful[273] is based on the fact that the majority of macrolide-resistant isolates in the United States have *mefA,* and that present doses of macrolides may be effective despite the in vitro finding that an isolate is resistant. Other mutations are responsible for resistance in a small percentage of isolates.[274]

Prevalence of Resistance

Despite earlier overestimates of the frequency of pneumococcal resistance to β-lactam antibiotics, currently, about 65% of non-CNS isolates in the United States are susceptible to penicillin or amoxicillin given orally, 17% are intermediately resistant, and 17% are resistant (Tables 199.4 and 199.5).[275] About 96% of all pneumococci are susceptible to penicillin given parenterally, 4% are intermediate, and <1% are resistant.[276] In cases of meningitis, 65% of organisms are susceptible to penicillin and 35% are resistant (no intermediate resistance is defined). For ceftriaxone, in non-CNS infections, 96% of organisms are susceptible, 4% are intermediate, and <1% are resistant; in CNS infections, these percentages are 88%, 7%, and 5%, respectively.[277] With the notable exception of the Netherlands and Germany, where accepted standards of practice strictly limit antibiotic usage,[278] rates of resistance are higher in most European countries than in the United States, and greater yet where antibiotic usage is uncontrolled.

Pneumococci with low MICs for penicillin remain susceptible to most other antibiotics. As resistance to penicillin increases, resistance to other commonly used antibiotics also increases. In the United States, about 35% of all pneumococci are resistant to macrolides, 10% to clindamycin, 30% to trimethoprim-sulfamethoxazole, 18% to doxycycline, and 2% to the newer quinolones.[279] *ermB* and *mefA* strains are present in equal proportions, but *ermB* gene-related macrolide resistance is higher in Europe. In general, greater than 98% of isolates remain susceptible to fluoroquinolones, probably because these drugs are not used to treat children. In Canada, an increase in resistance has paralleled increased quinolone use,[280] and in high-usage locales, such as chest clinics[281] or nursing homes,[282] the rate of resistance may exceed 5%. A remarkable incidence of colonization by a single clone of *S. pneumoniae* (sequence type 156; serotype 19A or 23) was documented in a long-term care facility in Israel; many of the colonized patients had not, themselves, previously received a quinolone.[283] Pneumococcal resistance to vancomycin, the oxazolidinones (linezolid), ceftaroline, the ketolides (such as telithromycin and cethromycin), the glycylcyclines (such as tigecycline), or daptomycin has not yet been documented.

TABLE 199.5 Estimated Likelihood of in vivo Bacteriologic Response of *S. pneumoniae* to Antibiotics in Patients With Non-CNS Infections Using Standard Therapy in the United States

ANTIBIOTIC	LIKELIHOOD (%)
Penicillin (parenteral), ampicillin, piperacillin	95[b]
Amoxicillin	95[b]
Cefuroxime, cefpodoxime, cefdinir	85[b]
Cefotaxime, ceftriaxone, cefepime	97[b]
Imipenem, meropenem, ertapenem	97
Azithromycin, clarithromycin	80[c]
Clindamycin	93
Telithromycin	100
Trimethoprim-sulfamethoxazole	65
Doxycycline	84
Vancomycin	100
Quinolones[d]	98

[a]See text discussion and Musher and coworkers.[260] These estimates of bacteriologic coverage are not equivalent to National Committee for Clinical and Laboratory Standards–defined in vitro susceptibility nor the likelihood of cure in vivo, which depend on both microbiologic and host clinical factors.
[b]With high doses of these drugs, almost all pneumococci are expected to be susceptible.
[c]This estimate balances the 25% rate of resistance in vitro and a generally high rate of clinical response.
[d]Quinolones = levofloxacin and moxifloxacin.

THERAPY

The basic principles of treating pneumococcal infection are similar to those for treating other bacterial infections: (1) prompt diagnosis and administration of an antibiotic that provides a level sufficient to inhibit or kill the infecting organism, (2) continuation of treatment at least until the host is able to complete the curing and healing processes, (3) drainage of infections of closed spaces if necessary, (4) knowing what response to expect, and (5) being prepared to reevaluate if this response is not observed. Application of these principles is by no means simple. Obstacles include (1) for most pneumococcal diseases, therapy is begun before the etiologic agent is known or no microbiologic studies are done; (2) even if *S. pneumoniae* is known to be causative, antibiotic susceptibility is not known when treatment is begun; (3) the appropriate duration of therapy is not evidence based; (4) in otitis media and sinusitis, the most common infections caused by *S. pneumoniae,* drainage is not usually done; and (5) many physicians do not clearly understand the natural history of disease or what response to expect after treatment has begun.

Otitis Media

Treatment of otitis media is the leading indication for antibiotic use in children. For children under 2 years of age with first-episode otitis media requiring antibiotics (bulging of the tympanic membrane, other signs of acute infection, *and* middle ear effusion), the American Academy of Pediatrics and the American Academy of Family Physicians recommend amoxicillin, 90 mg/kg in two daily doses for 10 days (<2 years old) or 5 to 7 days (>2 years old)[284] for *S. pneumoniae,* the most common identifiable cause of this infection and the one associated with the greatest morbidity. Treatment of recurrent or recently treated disease with amoxicillin-clavulanate is directed to β-lactamase–producing *H. influenzae,* because this medication has no additional effect on penicillin-resistant *S. pneumoniae,* for which cephalosporins may be more effective.

Sinusitis

Because the pathogenesis and causative organisms of acute bacterial rhinosinusitis are comparable to those of otitis media, the same therapeutic considerations apply. Treatment guidelines are largely empirical, without knowing whether *S. pneumoniae* is present or, if present, its antibiotic susceptibility.[92,285] First-line therapy with amoxicillin is likely beneficial in 80% to 90% of cases. However, amoxicillin-clavulanate is increasingly recommended as first-line therapy in children and adults because of a high frequency of β-lactam resistance among isolates of *H. influenzae.*[188] High-dose amoxicillin-clavulanate (180 mg/kg/day orally in two or three divided doses, not to exceed a total of 4 g/day) is considered for severe infections, immunocompromised hosts, and extremes of age, and when the frequency of penicillin nonsusceptibility is high (>10%). Because clavulanic acid causes diarrhea, a proposed option is to mix 500 mg of amoxicillin together with another 500 mg of amoxicillin plus 125 mg clavulanic acid three to four times daily. Quinolones may be used in adults but are not approved for children. If subsequent therapy with ceftriaxone fails, referral to an otolaryngologist is appropriate.

Pneumonia

Outpatient Therapy

When a microbiologic diagnosis is sought, *S. pneumoniae* has been the most common organism isolated.[21] The response to therapy generally appears to be excellent irrespective of the drug selected; specifically, penicillins with or without β-lactamase inhibitors, macrolides, doxycycline, or a newer fluoroquinolone (as opposed to ciprofloxacin) all seem to be equally effective,[224] although clinical failures may complicate macrolide treatment of outpatient pneumonia caused by macrolide-resistant pneumococci.[286]

Inpatient Therapy

Guided but not bound by published guidelines,[224] the importance of the decision to hospitalize a patient with pneumonia, even directly to intensive care, cannot be overemphasized. The severity index established by the Pneumonia Outcomes Research Team (PORT)[287] is preferred over the more accessible but less reliable CURB-65 (*c*onfusion, blood *u*rea nitrogen, *r*espiratory rate, systolic *b*lood pressure)[288] criteria. However, clinical judgment should outweigh the results of a scoring system in considerations of hospitalizing the patient, at least for the initiation of therapy. Because the PORT score is so highly dependent on age of the patient, clinical judgment becomes more important in younger adults.

Pneumonia caused by pneumococci that are susceptible or intermediately resistant to penicillin responds to treatment with penicillin, 1 million units intravenously every 4 hours; ampicillin, 1 g every 6 hours; or ceftriaxone, 1 g every 24 hours. A principal concern is whether pneumonia caused by a relatively uncommon pneumococcus judged to be resistant by present definitions will respond to such therapy, whether higher doses of β-lactam antibiotics are needed, or whether treatment should be changed to another class of antibiotic, such as a quinolone. Patients who are treated for pneumococcal pneumonia with an effective antibiotic generally have substantially reduced fever and feel much better within 48 hours. If a patient has responded to treatment with a β-lactam antibiotic, this therapy should be continued independent of susceptibility results. However, if a clear response is not observed and the organism is resistant, therapy should be changed in accordance with susceptibility testing results. Several retrospective case-control studies and prospective trials suggest that patients with pneumococcal infection have better outcomes if a macrolide is added, especially if they are critically ill.[289–291] Proposed mechanisms for these observations include immunomodulatory or antiinflammatory effects of the macrolide,[292] treatment of coinfections (e.g., *Mycoplasma, Chlamydia, Legionella*), increased bacterial kill rates, or decreased adherence of organisms.

The optimal duration of therapy for pneumococcal pneumonia is uncertain. Pneumococci are not readily detected in sputum microscopically or by culture more than 24 hours after the administration of an effective antibiotic.[293] Experience obtained early in the antibiotic era showed that 5 to 7 days of therapy sufficed, even when blood cultures were positive. Antibiotic therapy for pneumococcal pneumonia should be continued for 2 days after achieving clinical stability (temperature <99°F, respiratory rate ≤24 breaths/min, oxygen saturation >90%, blood pressure >90 mm Hg), generally for a total of 5 to 7 days.[294] Failure of a patient to defervesce within 3 to 5 days should stimulate a review of the organism's antibiotic susceptibility, search for another organism,

attempts to exclude a loculated infection such as empyema, or search for a noninfectious source. Once clinically stable, patients have a less than 1% chance of failure, defined by death or immediate readmission, but if discharged with two or more abnormal signs, they have a 46% risk of death or readmission.[31,294] The time to achieve clinical stability is no different among bacteremic and nonbacteremic patients with pneumococcal pneumonia,[295] so treatment duration should be comparable in both settings.

Meningitis

Pneumococcal meningitis is the syndrome in which antimicrobial resistance is most likely to have adverse clinical outcomes. Pneumococcal meningitis has been treated with 12 to 24 million units of penicillin every 24 hours or 2 g ceftriaxone every 12 hours. Either regimen is effective against antibiotic-susceptible *S. pneumoniae* and may be effective against intermediately resistant ones; pharmacokinetic considerations and achievable CSF levels favor the use of ceftriaxone or cefotaxime. During treatment of resistant strains, β-lactam antibiotics are likely not to achieve therapeutic levels in CSF, justifying the recommendation that vancomycin be given together with ceftriaxone or cefotaxime until susceptibility results are reported. In patients who have documented penicillin and cephalosporin allergies, unless the history suggests a class 1, life-threatening reaction, ceftriaxone or cefotaxime should be used. Meropenem is an alternative for the β-lactams; imipenem is not typically recommended because of the risk of seizures.

An important randomized clinical trial in adults with severe meningitis showed that the addition of dexamethasone, 10 mg four times daily for 4 days, decreased morbidity and mortality from pneumococcal meningitis,[296] although benefits had not been consistently demonstrated previously in adults or children.[297] If administered, steroids should be given before or with the first dose of antibiotics and should not be continued beyond the recommended 4 days. Repeat spinal taps may be needed if there is any suggestion of a delayed clinical response.

Endocarditis

Pneumococcal endocarditis is associated with rapid destruction of heart valves. All patients with this disease should be seen by a cardiologist and a cardiovascular surgeon as soon as the diagnosis is suspected. Because of the (albeit unlikely) possibility of β-lactam resistance, initial therapy should include vancomycin and ceftriaxone until the results of minimal bactericidal concentration testing are known.

PREVENTION OF PNEUMOCOCCAL INFECTIONS

Despite the availability of effective vaccines in children against invasive disease caused by *S. pneumoniae* and *H. influenzae* type b, these encapsulated pathogens remain leading causes of bacterial death worldwide in young children.[19] Interventions to prevent pneumococcal disease and death in children include minimizing crowding, limiting indoor air pollution from fires for cooking and heating (and avoiding chronic secondary smoke exposure from cigarettes[48]), and promoting maternal health, sanitation, and access to care.[80] Optimizing nutrition by reducing prematurity and low birth weights, exclusive breastfeeding, and micronutrient supplementation (with zinc and, likely, vitamin A) are also beneficial. Case management includes early diagnosis, assessment of severity, early therapy, and the use of oxygen in severe cases. Immunization for measles and perhaps influenza also should reduce the incidence of pneumococcal disease.[298]

Vaccination with capsular polysaccharides is the mainstay of control of pneumococcal disease. Two pneumococcal polysaccharide vaccines are approved for use in the United States: (1) a pneumococcal polysaccharide vaccine, PPSV23, marketed as Pneumovax (Merck, Whitehouse Station, NJ), or Pnu-Immune (Wyeth, Collegeville, PA), consisting of capsular material from 23 pneumococcal types that historically caused about 75% to 85% of pneumococcal disease in children or adults, and (2) a protein-conjugate pneumococcal vaccine, PCV, initially marketed as Prevnar or Prevnar 7 (PCV7; Wyeth) and now replaced by Prevnar13 (PCV13; Pfizer, Philadelphia, PA), containing capsular polysaccharide from the 13 most common types that caused disease in children, each covalently linked to a nontoxic protein congener of diphtheria toxin (cross-reacting material 197 [CRM197]).[299] PPSV23 and PCV13 share serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23, whereas PPSV23 also contains serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F, but serotype 6A is unique to PCV13. The more limited immunogenicity and efficacy of the polysaccharide vaccine in very young children is overcome by the ability of the conjugate to enhance levels, generation of IgG1 rather than IgG2 antibodies, avidity, and memory for pneumococcal capsular polysaccharide antibodies in children by engagement of dendritic cell–dependent and T-cell–dependent mechanisms,[118,119] with greater than 90% protection against invasive disease.[300,301]

Antibody Responses to Pneumococcal Capsular Polysaccharides

The primary goal of pneumococcal vaccination is to elicit antibodies to the primary virulence factor of *S. pneumoniae,* its polysaccharide capsules. Both younger and older adults often show evidence of prior exposure to a range of pneumococcal serotypes. Among persons older than 65 years, each serotype was recognized by IgG (>1 μg/mL) from 5% to 35% of subjects.[27,96] After vaccination of adults, capsule-specific IgM and IgG, as well as IgA, can be detected after about 7 days and IgG peaks at 1 to 2 months.[27,94,302–304] About 80% of older adults showed appreciable responses to 18 or more of 23 serotypes and 50% to 15 or more serotypes after receiving PPSV23,[27] with 65% to 95% showing greater than 1 μg/mL of specific IgG to each serotype. Levels of specific IgG then wane to near baseline levels over the next 5 to 7 years.[305] However, no reliable cutoff for a protective level has been established in adults. Levels of capsule-specific IgG show some correlation with the ability of these sera to support opsonophagocytosis and killing of the organism. Multiple factors contribute to these functional outcomes, including antibody isotype, subclass and avidity, and phagocyte function, each of which may be compromised in older adults.[116,306]

That IgG appears as soon as IgM after primary vaccination and that these capsule-specific IgG cells are class-switched and show substantial somatic hypermutation of the antigen-binding immunoglobulin genes may suggest that the vaccine is stimulating memory cells in these adults.[307,308] However, whether pure polysaccharides generate memory responses is controversial. The substantial response to the polysaccharide PPSV23 in adults, compared with low levels in young infants, may be due to memory or to greater immune maturation. With classic memory responses to proteins (e.g., tetanus toxoids), booster responses are of greater magnitude than those to primary immunization. In contrast, responses to revaccination with PPSV23, which has been best studied among the elderly, are of similar or even lower magnitude than those to the original challenge.[302,305] Whether the latter responses to revaccination with PPSV23 represent blunting of secondary responses ("hyporesponsiveness"), as has been described with meningococcal polysaccharides, in older adults is debated.[305,309,310] However, recent data suggest that revaccination within 1 year, rather than many years, after primary immunization and giving the conjugate vaccine as the first dose, independent of which vaccine is given second, is associated with enhanced antibody levels among adults older than 70 years, compared with giving PPSV23 first.[311] These data and recent efficacy results[30] underlie the recent CDC Advisory Committee on Immunization Practices (ACIP) recommendation to use PCV13 for primary immunization in older adults followed by PPSV23; the former may provide a more immunogenic base for revaccination and the latter elicits broader serotype coverage. Nevertheless, because of the effectiveness of PCV7 and now PCV13 in reducing transmissible pneumococcal carriage and disease in children, herd protection results in an ever-decreasing proportion of clinical disease in adults caused by PCV13 serotypes.[312]

Pneumococcal Conjugate Vaccine Efficacy in Children

Despite earlier evidence of protection against death from pneumonia in children in Papua, New Guinea,[313] young children, particularly those younger than 2 years, do not respond adequately to the PPSV23 vaccine used in adults. The defect may relate in part to engagement of T cells and impaired ability of children to produce the IgG2 subclass predominantly elicited by polysaccharides. Their ability to now recognize and respond to the capsular polysaccharides within the conjugate vaccine

elicits robust antibody responses, predominantly of the IgG1 subclass that supports opsonophagocytosis of *S. pneumoniae* with complement. After three to four doses of 7- or 9-valent vaccines delivered early in life (ages 2, 4, 6, and 12 months in the United States), protection against invasive pneumococcal disease caused by vaccine serotypes ranged from 77% to 97% in the United States, South Africa, and the Gambia.[300,314–316] Such protection against bacteremia in children younger than 2 years[300] includes low-birth-weight and preterm infants[317] and persists over time.[318] Across countries, overall protection against vaccine serotypes ranges from 39.9% in Spain to 99.1% in the United States.[319] For all vaccine-related invasive serotypes, protection had a median of 65.5% for all international sites and 94% in the United States,[312] and 45% for invasive pneumococcal disease of all serotypes in the United States.

Conjugate vaccine protection extended to other syndromes in young children. Protection was significant but more modest against otitis media in children: 6% (0.4%–16%) against all-cause otitis, 34% (21%–45%) against confirmed pneumococcal otitis, and 57% (44%–67%) against otitis caused by vaccine serotypes.[301,320,321] Of greatest importance, the conjugate vaccine provides substantial protection against pneumonia in children,[322] both clinically diagnosed and, particularly, radiologically confirmed pneumonia, which is the leading cause of death from pneumococcal disease in children.[323] All-cause pneumonia was reduced by 4.3% (−3.5% to 11.5%), but 30% (4.4%–34%) with disease confirmed by chest radiographs. These results were confirmed in the Gambia in West Africa, where, among children younger than 1 year, a 9-valent conjugate supported 7% (1%–12%) protection against clinical pneumonia but 37% against radiographically confirmed pneumonia.[314] Consistent with these results, use of the protein-polysaccharide conjugate vaccine (PCV7 and PCV13) in young children has also yielded dramatic and sustained decreases in hospitalizations for pneumonia.[324,325] Indeed, in the period after the introduction of PCV7 and its broad uptake in the population (1997–2009), the annual incidence of invasive pneumococcal disease fell most dramatically in children under 2 and adults 65 years and older (Fig. 199.7),[312] as did all-cause hospitalization for pneumonia in the United States,[324] as well as specifically for pneumococcal pneumonia in children under 18 years (Fig. 199.8).[325] Based on these remarkable findings, an advancing goal is to introduce effective, accessible, and affordable vaccines against the pneumococcus in resource-limited settings (Fig. 199.9).

Finally, meningitis, which has the highest case fatality and long-lasting sequelae, has also decreased by 26% to 64% in children younger than 2 years, in association with use of the pediatric vaccine, as well as by 54% among adults older than 65 years by herd protection. Some of the concomitant increase in nonvaccine serotypes with PCV7 (especially 19A, 22F, and 35B)[277] are included in PCV13 (e.g., 19A). Results of testing the use of an additional dose of PPSV23 after PCV13 in children have shown mixed results, some of which are promising.[309]

Efficacy of 23-Valent Pneumococcal Polysaccharide and 13-Valent Polysaccharide Conjugate Vaccine in Adults

Protection against pneumococcal disease in adults, particularly older adults, needs to be considered in the context of bacteremia and pneumonia. In two field trials in South Africa in the 1970s, pneumococcal polysaccharide vaccines showed significant efficacy against pneumococcal pneumonia among otherwise healthy, young gold miners with a high incidence of disease.[326,327] Based on these results, the 14-valent, then the 23-valent polysaccharide vaccines were licensed. Currently, in the United States, one-half to two-thirds of persons older than 65 years and with relevant underlying illnesses have received PPSV23 (and one-third have received PCV13).[328] Case-control and indirect cohort

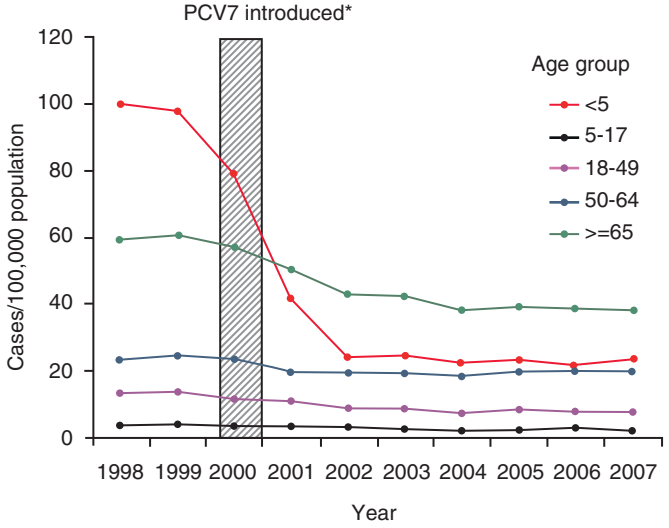


FIG. 199.7 Broad protection of children and adults by immunization of children with pneumococcal conjugate vaccine. An active vaccination program in infants and toddlers by using 7-valent pneumococcal conjugate vaccine (PCV7) beginning in 2000 greatly reduced the incidence of invasive pneumococcal disease in persons of all age groups (45%) from 1998 to 2007, including in adults who did not receive this vaccine.[312] The incidence of all invasive pneumococcal disease and of that caused by the seven vaccine serotypes declined by 76% and almost 100% in children younger than 5 years, respectively, and by 37% and 92%, respectively, in adults age 65 years or older. *(Modified from Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine.* J Infect Dis. *2010;201:32–41.)*

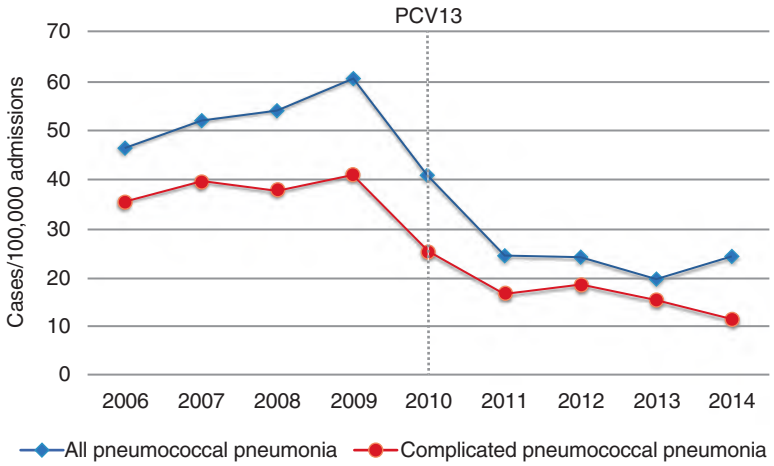


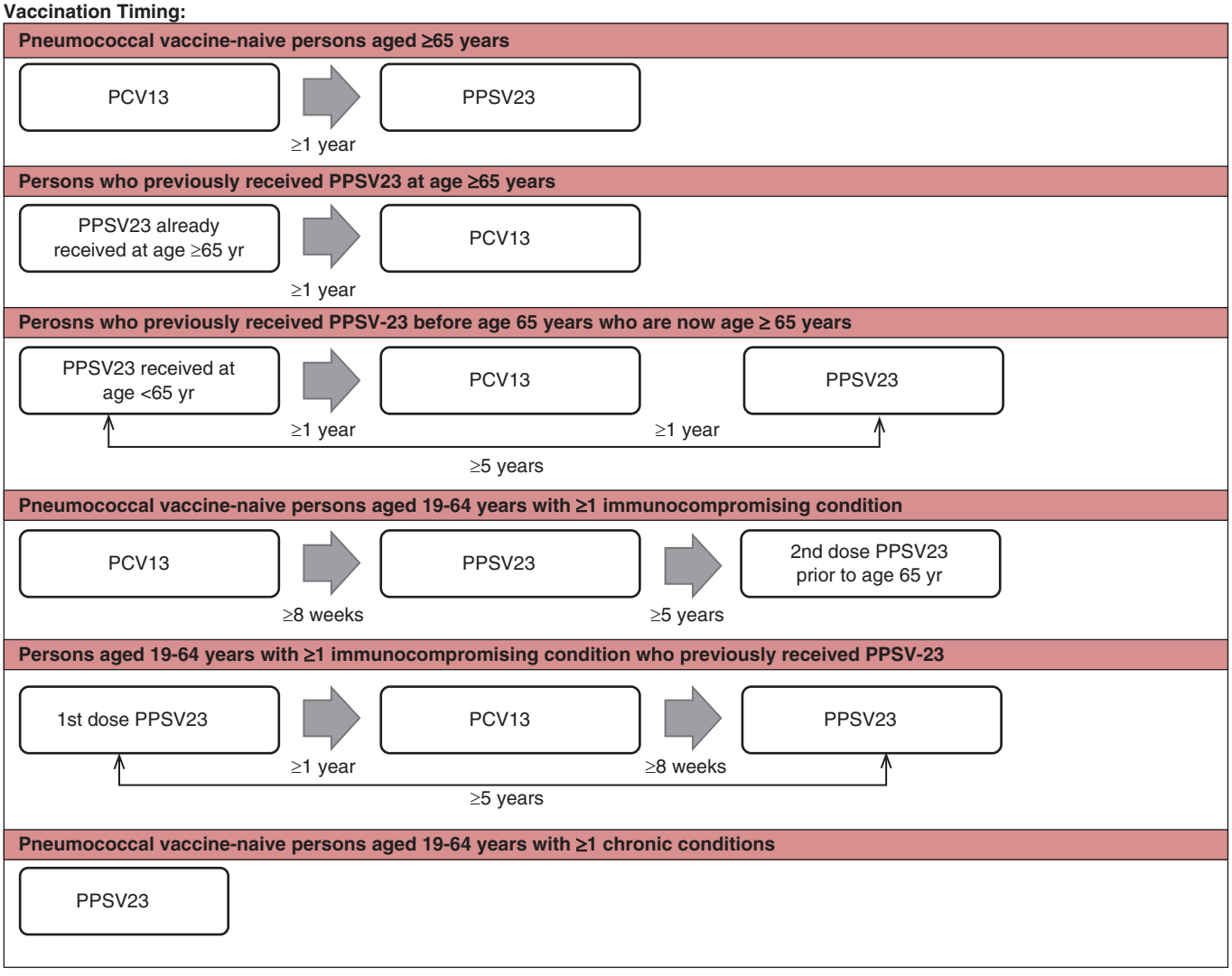
FIG. 199.8 Hospitalization rate for pneumococcal pneumonia in children <18 years old in eight US cities, 2006–2014. Children's hospitals in eight cities were prospectively monitored for microbiologically confirmed cases of pneumococcal pneumonia in the period surrounding the introduction of PCV13 in 2010. *(From Olarte L, Barson WJ, Barson RM, et al. Pneumococcal pneumonia requiring hospitalization in US children in the 13-valent pneumococcal conjugate vaccine era.* Clin Infect Dis. *2017;64:1699–1704.)*

Indications for Adult Pneumococcal Vaccination

Indications:

PPSV-23 Alone	Both PCV-13 and PPSV-23
Patients 19-64 years with ≥1 choronic condition below:	**All patients ≥65 years**
Cigarette smoking	**Patients 19-64 years with ≥1 immunocompromising condition below:**
Chronic heart disease (CHF, cardiomyopathy)	Cerebrospinal fluid leak
Chronic lung disease (asthma, COPD)	Cochlear implant
Diabetes mellitus	Congenital or acquired immunodeficiency
Alcoholism	HIV infection
Chronic liver disease (cirrhosis)	Functional or anatomic asplenia
Reside in nursing home or long-term care facility	Chronic renal failure or nephronic syndrome
	Malignancy
	Solid organ transplant
	Immunosuppression (glucocorticoids, radiation)

Vaccination Timing:



Refer to http://www.cdc.gov/vaccines/acip/index.html

FIG. 199.9 Recommendations for pneumococcal vaccination (PCV13 and PPSV23) in adults age 19 years and older. *Schedule is integrated from references* **359**–361 and 364–366. CHF, *Congestive heart failure;* COPD, *chronic obstructive pulmonary disease;* HIV, *human immunodeficiency virus;* PCV13, *pneumococcal conjugate vaccine (Prevnar);* PPSV23, *pneumococcal polysaccharide vaccine (Pneumovax).*

studies performed postlicensure revealed that the vaccine is protective against invasive disease, particularly bacteremia, in immunocompetent older adults. In the largest study, Shapiro and coworkers[329] showed that invasive pneumococcal disease caused by vaccine serotypes was reduced by 56%, consistent with other studies of invasive disease (54%–81%).[36,330–333] Shapiro and coworkers highlighted clinical protection, a decreasing effect with advancing age, and suggested a waning protective effect over time from initial immunization, consistent with waning levels of specific antibody. However, such protection was not afforded to older adults with immunocompromising conditions, among whom vaccine efficacy has not been confirmed.

Pneumococcal pneumonia comprises the major burden of pneumococcal disease, and most pneumococcal pneumonia and deaths are not associated with bacteremia. Evidence in support of a beneficial

effect of PPSV23 in prevention of pneumococcal pneumonia in older adults is limited,[331,334,335] although diagnosing *S. pneumoniae* as the specific cause of CAP in the absence of bacteremia can be problematic. Among nine clinical trials of PPSV23 against all-cause pneumonia,[336–340] three have shown benefit.[341–343] Among the latter, 1006 nursing home residents in Japan were randomized to receive PPSV23 or placebo.[341] All-cause pneumonia and pneumococcal pneumonia were significantly lower in the vaccine group compared with the control group (cases/1000 person-years: 55 vs. 91 and 12 vs. 32, respectively; both $P < .001$). Moreover, death rates from pneumococcal pneumonia, but not all-cause pneumonia, were lower in the vaccine group. Thus although there is no consensus as to whether PPSV23 reliably prevents all-cause CAP, only a minority of cases are due to *S. pneumoniae.* Use of more sensitive and specific tests to diagnose pneumococcal pneumonia with current methods—PCR assay of respiratory samples and serotype-specific urine antigen detection—may help to resolve this question.

Perhaps the most striking recent advance in pneumococcal vaccine is a prospective, randomized, placebo-controlled trial of PCV13 among almost 85,000 adults age 65 years or older in a community in the Netherlands.[30] Using culture and vaccine serotype–specific urine antigen detection, the study is the first to show efficacy by PCV13 against bacteremia in adults (75%), and, of note, against CAP as well (45.6%), both limited to vaccine serotypes (Table 199.6), with this robust trial design. The 139 vaccine serotype–related cases represented 9% of all CAP in the population, for which no overall efficacy was detected. The study was done prior to the introduction of conjugate vaccine in children in the Netherlands, so the vaccine serotypes likely represented a higher proportion of adult disease than is now present in the United States. Nevertheless, the demonstration of protection against vaccine serotypes with a conjugate vaccine provides proof of concept that pneumococcal pneumonia may be a vaccine-preventable disease in older adults at risk. These data led to time-limited approval of PCV13 for older adults, and recent observational results consider these promising findings in the US community setting.[29] Less clear is whether the broad introduction of conjugate vaccine in adults has led to an additional decrement in adult cases of pneumococcal pneumonia and bacteremia independent of the community protection effects of childhood immunization. Additional strategies are in development to address prevention of the additional, and now majority, of serotypes causing pneumonia and bacteremia in adults that are not currently included in the pediatric-directed PCV13 now used in adults.

Impact of Infant Immunization on Adult Disease

In addition to the direct effects of pneumococcal vaccination of adults, a beneficial indirect effect of vaccination of children has been a progressive and significant decline in both invasive disease and pneumonia[312] in adults, particularly older adults. These effects appear to be a consequence of the decreased frequencies of invasive disease, and, particularly, decreased colonization in vaccinated children,[88,312,344] because the decrement in adults is largely limited to PCV7 and now PCV13 vaccine and vaccine-related serotypes and does not extend substantially to nonvaccine serotypes. This protective effect beyond the vaccinated group is called "herd protection," in which adults experience a lower incidence of disease based on decreased exposure from fewer infected infants, rather than because these adults have increased vaccine-associated immune protection themselves.

Consistent with these results, use of the protein-polysaccharide conjugate vaccine in young children has also yielded dramatic and sustained decreases in hospitalizations for pneumonia in adults as well as children.[324] Hospitalizations for pneumonia declined by 22% in adults age 85 years or older and 51% in adults of all ages, despite no appreciable changes in immunization of the adults themselves, accounting for an estimated 168,000 fewer hospitalizations for pneumonia annually in the United States overall. In 2007, PCV13 serotypes accounted for about one-third of invasive disease in adults age 65 years or older, and the 11 serotypes unique to PPSV23 accounted for 25%.[345] These proportions have continued to decline in children and older adults since PCV13 was introduced in 2010,[346] highlighting the need to extend the vaccine-associated serotype coverage in adults.

Vaccine Protection During HIV Infection

With almost 35 million people living with HIV/AIDS worldwide and their very high incidence of pneumonia and bacteremia, this population comprises perhaps the largest acquired risk group for pneumococcal disease. Antibody responses to PPSV23 are impaired in untreated adults.[347,348] A large prospective, randomized, placebo-controlled trial of 23-valent polysaccharide vaccine among HIV-infected adults in Uganda showed no protection against invasive disease.[177] In fact, the rate of all-cause pneumonia was significantly increased after immunization compared with that in placebo recipients. Pneumococcal vaccine failures were associated with an impaired IgG response to vaccine capsular serotypes.[178,179] However, among HIV-infected children in South Africa, a similarly designed trial of 9-valent conjugate vaccine revealed 53% vaccine efficacy (95% confidence interval, 21%–73%) against invasive disease caused by vaccine serotypes.[315] This efficacy waned rapidly within the first year after vaccination.

Compared with the 23-valent polysaccharide vaccine, the immunogenicity of the 7-valent conjugate vaccine may be somewhat higher among HIV-infected adults with initial immunization,[349] as has been described in patients with splenectomy,[350] but the magnitude of the differences is limited.[351] Alternating two sequential doses of the 23-valent polysaccharide and the 7-valent conjugate vaccine showed higher levels of capsule-specific antibody for three of four serotypes with the conjugate, but the second dose of 7-valent vaccine was beneficial for only one serotype (type 4).[352] In no case was an initial dose of PCV7 detrimental to subsequent responses to either vaccine.

Ultimately, the most powerful data in support of the conjugate vaccine in adults derive from a trial among HIV-infected adults in Malawi who had a previous episode of invasive pneumococcal disease[353] and among whom 20% or greater experienced a second episode.[177,354] This randomized, placebo-controlled, double-blind clinical trial with two doses of PCV7 showed a relative risk of 0.25 (range, 0.08–0.71) against vaccine serotypes in the first year compared with placebo. However, the risk against any invasive pneumococcal disease was not significant because

TABLE 199.6 Effect of PCV13 on Community-Acquired Pneumococcal Pneumonia and Invasive Disease Caused by Vaccine Serotypes Among Adults 65 Years and Older in the Netherlands (2008–2013)

	PCV13 (*n* = 42,237)	PLACEBO (*n* = 42,255)	PROTECTION	*P*
	Cases			
Pneumonia	49	90	45.6%	0.006
Invasive disease	7	28	75.0%	0.0067
	Incidence (100,000/yr)		**No. Needed to Vaccinate[a]**	
Pneumonia	57.6	105.8		656
Invasive disease	8.2	32.9		20,400

Currently, PCV13 is used in approximately 35% of cases and PPSV23 is used in approximately 65%.
No effect on all community-acquired pneumonia cases or mortality among 13 total deaths.
[a]To prevent a single case of the indicated illness.
Data from Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. *2015;372:1114–1125.*

TABLE 199.7 Recommendations for Pneumococcal Vaccines in Adults >19 Years of Age (Advisory Committee on Immunization Practices, 2014)

		PCV13	PPSV23	
RISK GROUP	**UNDERLYING MEDICAL CONDITION**	**Recommended**	**Recommended**	**Revaccination 5 Years After First Dose**
Immunocompetent persons	Chronic heart disease[b]		×	
	Chronic lung disease[c]		×	
	Diabetes mellitus		×	
	Cerebrospinal fluid leak	×	×	
	Cochlear implant	×	×	
	Alcoholism		×	
	Chronic liver disease, cirrhosis		×	
	Cigarette smoking		×	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathy	×	×	×
	Congenital or acquired asplenia	×	×	×
Immunocompromised persons	Congenital or acquired immunodeficiency[d]	×	×	×
	Human immunodeficiency virus infection	×	×	×
	Chronic renal failure	×	×	×
	Nephrotic syndrome	×	×	×
	Leukemia	×	×	×
	Lymphoma	×	×	×
	Hodgkin disease	×	×	×
	Generalized malignancy	×	×	×
	Iatrogenic immunosuppression[e]	×	×	×
	Multiple myeloma	×	×	×

[a]All adults age 65 years or older should receive a dose of PCV13 if not previously vaccinated with PPSV23, followed by PPSV23 after 12 months. Adults 65 years or older who have been vaccinated with PPSV23 after age 65 should receive a dose of PCV13 at least 12 months from the initial vaccination. Adults vaccinated with PPSV23 before age 65 should receive a dose of PCV13 at age 65 at least 12 months after initial vaccination and then receive PPSV23 in 12 months.
[b]Including congestive heart failure and cardiomyopathies, excluding hypertension.
[c]Including chronic obstructive pulmonary disease, emphysema, and asthma.
[d]Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4), and phagocytic disorders (excluding chronic granulomatous disease).
[e]Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

most cases were due to nonvaccine serotypes, and there was no protection against death or all-cause pneumonia. Counterbalancing the results of this efficacy study with the broader prevalence of serotypes in the community, the ACIP recommended the use of a two-dose schedule with a first dose of 13-valent conjugate vaccine, followed 8 weeks or more later with the 23-valent vaccine for patients with HIV infection and adults with immunocompromising conditions.[15] Ongoing studies will reveal whether this rapid succession of doses enhances both the magnitude and persistence of capsule-specific antibody. Current evidence is mixed on the immunogenicity of reimmunization with either PPSV23 or PCV7 (now PCV13) among HIV-infected patients who received a PPSV23 dose 3 to 7 years earlier, even with effective antiretroviral therapy.[355–357]

Vaccine Recommendations

Children are recommended to receive PCV13 at 2, 4, and 6 months of age with a booster dose at 12 to 15 months. Current recommendations for pneumococcal vaccination in adults have evolved over the last several years (Table 199.7).[358] On August 13, 2014, the ACIP recommended routine use of PCV13 for adults age 65 years or older.[359] Rather than receiving a single dose of PPSV23, pneumococcal vaccine–naïve persons or those with unknown age status or those age 65 years or older are recommended to receive PCV13 first, followed by PPSV23 6 to 12 months later. Adults age 19 to 64 years with chronic conditions should receive a dose of PPSV23. Those in this age category with more severe immunocompromising conditions, including HIV infection, should be given PCV13 followed by PPSV23 at least 8 weeks later. In all cases, revaccination with PPSV23 should be delayed until 5 years after the initial PPSV23 dose. Among adults older than 50 years, both PPSV23 and PCV13 are now licensed by the FDA as options.[345] Persons previously vaccinated with PPSV23 are recommended to be vaccinated with PCV13 1 year or more after the most recent PPSV23 vaccination. Persons due for a second PPSV23 injection should have it administered at least 12 months after PCV13 and 5 years or more after the initial PPSV23 dose.[360] Of note, for all immunocompromised adults older than 19 years, those with functional or anatomic asplenia, or immunocompetent adults with CSF leak or cochlear implants, a sequential two-dose regimen is recommended, with a dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later (see Table 199.7).[361] Primary immunization of children should include three doses of PCV13 between 2 and 6 months of age or two doses between 7 and 11 months of age, with each receiving a booster dose at 12 to 15 months of age. Children 12 to 23 months of age are given two doses; those 24 to 59 months of age, one dose; and those with chronic or immunocompromising conditions, two doses between 24 and 71 months of age, each without a booster dose.[358]

Revaccination with PPSV23 is indicated for children age 2 years or older and adults with functional or anatomic asplenia and immunocompromising conditions, if given 8 weeks or more after the last dose of PCV13. Of note, for those with chronic conditions, revaccination with PPSV23 is not recommended in either age group because of lack of data supporting the clinical benefit of revaccination. All of these recommendations will likely continue to change as diagnostic methods improve, serotype prevalence changes within groups, and results of clinical trials are revealed. Enhancing our understanding of the epidemiology, microbiology, pathogenesis, and immunology of *S. pneumoniae* will drive the development of more efficient and effective vaccines and approaches to prevention and management of pneumococcal colonization and disease.