Current Trends in *Streptococcus pneumoniae* Infections and Their Treatment

Avinash K. Shetty · Yvonne A. Maldonado

Abstract Invasive pneumococcal disease (IPD) is a major cause of pediatric morbidity and mortality in resource-rich and low and middle-income countries (LMICs). *Streptococcus pneumoniae* can cause a wide spectrum of invasive and non-invasive disease. In resource-rich countries, implementation of 7-valent pneumococcal conjugate vaccine (PCV7) has been a significant public health achievement. Dramatic decrease in pediatric IPD incidence occurred after PCV7 implementation, but emergence of multi-drug-resistant non-vaccine serotypes (especially 19A) remains a concern. The recently introduced 13-valent PCV (PCV13) has the potential to further reduce the burden of IPD due to serotypes not contained in PCV7. Given the diversity of pneumococcal serotypes and the possibility of serotype replacement disease, innovative approaches to development of pneumococcal vaccines are needed. Continued surveillance of pneumococcal serotypes and antimicrobial resistance is crucial to evaluate the impact of PCV13 vaccine. Improved access to PCVs is crucial to reduce morbidity and mortality related to IPD in LMIC.

Keywords *Streptococcus pneumoniae* · Invasive disease · Treatment

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Introduction

Invasive disease caused by *Streptococcus pneumoniae* (pneumococcus) is a major cause of morbidity and mortality in children [1, 2, 3•, 4••]. The World Health Organization (WHO) estimates that 1.2 million infants die of invasive pneumococcal disease (IPD) each year, primarily in low and middle-income countries (LMICs) [5, 6]. In 2000, *S. pneumoniae* accounted for 14.5 million episodes of serious disease in children aged <5 years resulting in 826,000 deaths representing 11 % (8–12 %) of all deaths in children aged 1–59 months (excluding deaths in HIV-infected children) [1]. Children aged <2 years, adults ≥65 years of age, and immunocompromised individuals remain at highest risk for IPD, defined as isolation of *S. pneumoniae* from a normally sterile body fluid [7]. Seven pneumococcal serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) cause most cases of IPD in children worldwide [2, 8, 9]. The extent of disease due to different serotypes can vary by age, ethnicity, country, time, and clinical presentation [4••]. The emergence of multi-drug resistant (MDR) *S. pneumoniae* is a major concern [10, 11]. The introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in the US in 2000 has resulted in a significant decline in the incidence of IPD in all ages, especially in children aged <2 years [4••, 12]. Reduction in IPD among adults was noted, likely due to herd immunity [3•]. The success of PCV7 was accompanied by emergence of non-PCV7 serotypes especially 19A, warranting the development of 13-valent PCV (PCV13) [13–16, 17••]. In this article, we review the changing epidemiology, pathogenesis, clinical manifestations, treatment and prevention of *S. pneumoniae* infections in children.

Etiology

Streptococcus pneumoniae is an encapsulated, lancet-shaped, alpha-hemolytic, catalase-negative Gram-positive

diplococcus that is part of the human nasopharyngeal (NP) flora [18–20]. A total of 94 immunologically distinct capsular serotypes of *S. pneumoniae* have been described including the recently identified serotypes 6C, 6D, 20A/20B, and 11E [2, 21]. In the US, historically most IPD were associated with serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F contained within PCV7 [22, 23]. Prior to PCV7 introduction, penicillin-resistance in pneumococci was most commonly associated with serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F [24]. After PCV7 use, serotype 19A is the most frequent etiology of IPD, but has emerged in unvaccinated population causing acute otitis media (AOM) [25, 26].

Epidemiology

NP Carriage and Transmission

Streptococcus pneumoniae colonizes the nasopharynx, usually with other co-pathogens, such as *Haemophilus influenzae* and *Moraxella catarrhalis* [27]. Pneumococcus is ubiquitous and primarily transmitted from person to person via contact with respiratory droplets [28, 29]. Young children remain the primary source of transmission to household contacts and adults [3•]. The microorganism is generally not considered contagious, although community outbreaks can rarely occur in certain populations [30]. The precise period of communicability is unclear but likely to be <24 h after initiation of appropriate therapy [28].

Pneumococcal carriage in the nasopharynx begins during the first weeks of life and peaks during the first 2 years of life [31, 32]. Infants become colonized with pneumococcus around 6 months of age [18]. Epidemiologic studies suggest that NP pneumococcal carriage is a dynamic process acting as a reservoir for person to person transmission [19, 20]. Highest carriage rates (40–60 %) are observed in young children, especially those attending day care centers [6]. Carriage rates decrease with increasing age ranging from 12 % in older children to 6–10 % in adolescents and 3–4 % in adults [33]. Carriage rates in children can vary from 21 % in resource-rich settings to >90 % in LMIC [28]. Pneumococcal carriage rates are also affected by race, socioeconomic status, seasonality, overcrowding, exposure to day care centers and passive smoke [6, 32, 34]. In institutional settings and during winter, point prevalence and longitudinal studies have reported maximal carriage rates varying from 21–59 to 65 %, respectively [6, 34].

Most individuals are colonized with one pneumococcal serotype at a time, although co-colonization by multiple serotypes can occur in up to 30 % in settings with high pneumococcal carriage rates [32, 35]. Duration of carriage can vary from days to months and is highly dependent on the serotype [36]. Some serotypes (e.g., serotype 1, 4, 5, and 7F) colonize the nasopharynx rarely or to a lesser degree than others [37•, 38]. The duration of the first colonizing serotype is often the longest; reacquisition of the same serotype is possible [18]. After colonization with one of the pneumococcal serotypes, a new strain may replace other competing serotypes and persists for weeks to months [18].

Serotype-specific acquired immunity to pneumococcal carriage has been noted, which likely explains the varied colonization rates between children and adults [39]. Recent acquisition of a new serotype is an important predictor of development of subsequent IPD compared to duration of carriage or specific clonal genotypes [40]. The survival strategy of *S. pneumoniae* in humans is dependent on selection of specific clones with either an invasive phenotype or a persistent colonization phenotype (non-invasive phenotype) [29]. Low immunogenicity serotypes (6, 14, 19 and 23) can persist in the nasopharynx for longer duration, more likely to be reacquired, serving as a reservoir for transmission, promoting pneumococcal survival and harbor antimicrobial resistance [3•, 19].

Pathogenesis

NP colonization with *S. pneumoniae* is a critical first step in the pathogenesis of IPD [6, 20]. The direct link between colonization and subsequent disease manifestation in the same individuals has been supported by some longitudinal studies [18, 41]. In one study, 15 % of children who acquired a new strain developed otitis media within 1 month of acquisition of the new strain [18]. The mechanism of infection is by hematogenous route or contiguous spread, with migration of bacteria from the nasopharynx to adjacent structures such as middle ear, sinuses, and airways [4••]. The complex mechanisms involved in clearance or invasive disease resulting from pneumococcal carriage needs further elucidation [20, 29].

A wide array of pneumococcal virulence factors work collaboratively to cause invasive disease [42]. The most crucial virulence determinant of *S. pneumoniae* is the polysaccharide capsule that mediates invasion. The capsular antigen enables the microorganism to exhibit antigen variation, confers serotype specificity, prevents mucosal clearance, shows antiphagocytic and adherence properties, and sterically inhibits complement and immunoglobulin-binding to host receptors [43]. Pneumococcal virulence factors such as the capsule and pneumococcal surface molecules such as choline binding protein A and phosphorylcholine play a dual role in colonization and virulence [20]. Capsular switching from vaccine serotype to non-vaccine serotype can occur as a result of genetic recombination and lead to serotype replacement disease [4••]. Following PCV7, vaccine escape serotypes have emerged

due to recombinant exchanges [44]. The emergence of many clones of pneumococcal serotype 19A is a result of capsular switching [15]. Other factors such as lack of efficacy of PCV7 against serotype 19A, antimicrobial resistance, and clonal expansion have led to the genetic diversity of 19A and emergence worldwide as the predominant serotype causing IPD [15, 25, 45].

Incidence of IPD

During the pre-PCV7 era, *S. pneumoniae* accounted for an estimated 16,250 cases of IPD each year in children aged <5 years in the US; PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) accounted for 80 % of cases of IPD in children aged <5 years, and for 50 % of cases in individuals ≥6 years of age [24, 46]. The epidemiology of IPD changed significantly after infant PCV7 vaccination program [12, 14, 47, 48]. A population- and laboratory-based active bacterial core (ABC) surveillance system report a reduction in incidence of IPD among children aged <5 years from 99 cases per 100,000 population during 1998–1999 to 21 cases per 100,000 population in 2008 (79 % reduction) [17••]. The overall reduction in IPD rates resulted from dramatic declines (99 %) in IPD due to PCV7 vaccine serotypes in children aged <5 years and an overall decline by 95 % among individuals of all age groups [49, 50]. In one report, of the 753 cases of IPD reported in children fully immunized with PCV7, vaccine failures were observed in 4 % cases; the remainder of cases was caused by non-vaccine serotypes [51].

Since 2002, the overall IPD rates have been estimated at ∼22 to 25 annual cases per 100,000 children aged <5 years [46]. Further, PCV7 proved to be a cost-effective intervention given the estimated $10,400 cost per life-year saved after taking into consideration the indirect effects on IPD incidence [52]. Indirect benefits of infant PCV7 was noted resulting in an overall reduction of 45 % among unvaccinated individuals of all age groups due to herd immunity [47, 48, 53]. Based on 2009 data from the Centers for Disease Control and Prevention (CDC) [17••], overall rates of IPD have declined 34, 14, and 37 % in persons aged 18–49, 50–64, and ≥65 years, respectively. IPD due to PCV7 vaccine serotypes were observed in children aged <5 years and an overall decline by 95 % among individuals of all age groups [49, 50].

Serotype Replacement and Emergence of Antimicrobial Resistance

Pneumococcal serotypes can vary with time, patient age and geographic setting [21]. Following PCV7 implementation in resource-rich countries, non-PCV7 serotypes have increased among asymptomatic carriers ("serotype replacement")

[13]. Also, an increase in incidence of IPD due to non-vaccine types (especially serotype 19A) was noted in the US and several other countries in Europe and Asia-Pacific region [12, 15, 25, 45, 54]. The absolute rate increase in IPD due to serotype 19A is estimated at ∼5 cases per 100,000 population compared with decline in the rate of IPD due to PCV7 serotypes [55, 56]. In the US, most serotype 19A disease results from proliferation of preexisting sequence type (ST) 199, but a new strain, designated ST 320, is prevalent in many countries [15, 57]. The factors governing serotype replacement are complex given the natural variability in IPD and pneumococcal serotypes over time and the absence of increase in non-PCV7 serotype replacement IPD with PCV7 use in some studies [19, 53, 58].

Antibiotic Resistance Trends Among Replacement Serotypes

Prior to implementation of PCV7, five serotypes contained in PCV7 comprised 80 % of penicillin-non-susceptible isolates [24]. Following the PCV7 program, studies reported a 57 % decrease in the overall incidence of IPD (and 81 % decrease in children aged <2 years) due to non-susceptible pneumococcal serotypes contained in the PCV7 [17••, 59]. In addition, erythromycin-resistant and MDR pneumococcal strains also declined [17••].

However, a corresponding increase in disease caused by penicillin-non-susceptible, non-PCV7 pneumococcal serotypes was observed [12, 15, 17••, 57, 59, 60]. Most cases penicillin-resistant pneumococcal infections are caused by seven serotypes (6A, 6B, 9V, 14, 19A, 19F, and 23F) of which five are included in PCV7 (6B, 9V, 14, 19F, and 23F) whereas all of these important serotypes are included in PCV13 [4••]. In the US MDR pneumococcal serotype 19A is a common cause of IPD in the post PCV7 era [3•, 4••, 12, 17••, 25, 61].

Risk Factors for IPD

Before PCV7, children aged <2 years were at highest risk for disease given the high carriage rates in this age group, and other contributory factors such as poor natural immunity to the polysaccharide capsule and increased risk of exposure to viral respiratory infections [4••, 19]. Table 1 summarized the various host, pathogen, and environmental risk factors for IPD in children [3•, 4••, 17••, 19, 28, 29].

Clinical Syndromes

Streptococcus pneumoniae can cause a wide spectrum of clinical syndromes ranging from invasive disease (e.g., bacteremia, sepsis, meningitis, community-acquired

Table 1 Risk factors for invasive pneumococcal disease

Host

  Age <2 years pr > 65 years

  Ethnic groups/indigenous populations

    African-American, Native American, Alaskan Eskimo

    Micronesian

    Aboriginal (Australia, New Zealand)

  Absence of breastfeeding

  No prior pneumococcal vaccinations

  Co-morbid disease (e.g., cerebrospinal fluid leaks, cardiac or renal disease, diabetes mellitus), cochlear implants

  Antecedent viral respiratory infections (e.g., influenza)

  Primary and secondary immune deficiency

    human immunodeficiency virus infection

    sickle cell disease

    congenital or acquired asplenia

    complement deficiencies

    congenital or acquired antibody deficiency

    malignancy or other forms of immunosuppression

Pathogen

  Recent acquisition of new pneumococcal virulent strain

Environment

  Childhood day care attendance

  Recent antibiotic use

  Winter season

  Parental smoking

  Overcrowding situations

Data from [3•, 4••, 17••, 19, 28, 19]

Table 2 Clinical spectrum of pneumococcal disease in children

Common presentations	Unusual presentations
Otitis media and sinusitis	Infective endocarditis
Bacteremia	Periorbital cellulitis
Sepsis	Buccal cellulitis
Meningitis	Primary peritonitis
Pneumonia	Pericarditis
Osteomyelitis and septic arthritis	Mastoiditis
	Hemolytic–uremic syndrome
	Neonatal sepsis

Data from [4••, 22, 23, 61–63]

pneumonia) to other common localized infections (e.g., otitis media, sinusitis). Table 2 depicts the common and uncommon clinical presentations of pneumococcal disease in children [4••, 22, 23, 61–63]. The incubation period may vary depending on the infection type, but can range from 1 to 3 days [28].

Bacteremia

Historically, pneumococcal bacteremia in infants and young children was a commonly reported disease [4••]. In the pre-PCV7 era, in children aged ≤4 years, the annual incidence of pneumococcal bacteremia was ∼242 cases per 100,000 individuals; infants aged ≤12 months were at greatest risk (∼72 % of reported cases) [64]. A variety of clinical presentations may be associated with bacteremia including meningitis, pneumonia, osteomyelitis or septic arthritis as well as otitis media [4••].

In the post-PCV7 era, the incidence of pneumococcal bacteremia has declined significantly in both children and adults [4••, 46, 48, 53]. However, studies have noted an increase in percentage of episodes of bacteremia caused by vaccine-related pneumococcal serotypes (those of the same serogroup but not of the same serotype as PCV7) from 6 % in the pre-PCV period to 35 % in the post-PCV7 period [65]. In a recent ABC surveillance report, a reduction in the rate of bacteremia without focus source from 67.9 % in the pre-PCV7 period to 10.1 % in the post-PCV7 period was noted [46].

Pyogenic Meningitis

Globally, meningitis due to *S. pneumoniae* is estimated to cause >60,000 deaths in children aged <5 years [1]. *S. pneumoniae* is the most common cause of pyogenic meningitis in the US, with a bimodal age distribution [66]. During post-PCV7 era, rates of pneumococcal meningitis decreased significantly among children and adults [12, 14, 48, 67]. In 2004, data from the Nationwide Inpatient Sample from 1994 to 2004 indicated that *S. pneumoniae* was the most common pathogen causing bacterial meningitis accounting for 21,396 hospitalizations and 2,684 deaths (12.5 %) [67]. Following infant PCV7, there was a 66 % decrease in hospitalization rates for pneumococcal meningitis per 100,000 individuals (7.7 % in 1994–1997 to 2.6 in 2001–2004) in children under the age of 2 years. In children aged 2–4 years, there was a 51.5 % decrease in hospitalizations rates per 100,000 individuals (0.9 % in 1994–1997 to 0.5 in 2001–2004). In addition, hospitalization rates due to pneumococcal meningitis also decreased by 33 % for individuals ≥65 years of age [67]. Overall, PCV7 prevented an estimated 3,330 hospitalizations and 394 deaths related to pneumococcal meningitis in persons of all ages during 2001–2004 [67].

In a population-based surveillance project conducted from 1998 to 2005 at eight US sites, the overall rate of pneumococcal meningitis due to PCV7 serotypes decreased significantly (from 59 % in 1998–1999 to 23 % in 2004–2005) [12]. However, non-PCV7 serotype-associated disease rates increased significantly (from 28 % in 1998–1999 to 65 % in 2004–2005), with most increase attributed to serotypes 19A and 22F [12]. Despite the observation of serotype

replacement disease, the overall incidence of pneumococcal meningitis due to PCV7 serotypes has declined by 30 % to 0.79 cases per 100,000 people [12].

The spread of *S. pneumoniae* to the meninges typically occurs via the hematogenous route [4••, 32]. The clinical features can vary from an insidious onset of illness after an upper respiratory tract infection to a rapidly fulminant course resulting in death within 24 h of presentation [4••]. Substantial morbidity and mortality can occur despite early recognition of illness. Neurologic sequelae (e.g., sensorineural hearing loss, paresis, and cognitive impairment) has been reported in 25–56 % of survivors, and fatalities can occur in 5–15 % of cases [4••].

Pneumonia

Streptococcus pneumoniae is the most common cause of CAP in children and adults worldwide [36]. In Latin America and Caribbean, where PCV7 was not implemented in national vaccination programs during 1980–2008, a recent meta-analysis found that serotype 14 was the most common cause of pneumococcal CAP, followed by serotypes 1 and 5 [68]. In the post-PCV7 era, pneumococcal serotype 1 is the most prevalent etiologic agent of pneumococcal CAP, followed by serotypes 19A, 3 and 14 [69, 70]. Risk factors for pneumococcal pneumonia include primary or secondary immunodeficiency disorders, sickle cell disease, nephrotic syndrome, chronic lung disorders, chronic smoke inhalation, malnutrition, and viral respiratory infections, especially influenza [4••, 29]. Bacteremia may be present in 20–40 % of all cases of pneumococcal pneumonia [4••, 50].

The clinical presentation of pneumococcal pneumonia can vary from a mild non-specific respiratory tract infection to a severe illness characterized by fever, cough, and dyspnea needing hospitalization [4••, 29]. Complications can occur in 40–50 % of hospitalized children including pleural effusion, empyema, necrotizing pneumonia and lung abscess [22, 32]. Bacteremic pneumonia is more severe disease resulting in acute respiratory failure, empyema, and meningitis [4••]. In a recent meta-analysis, the risk of mortality was found to be higher in patients with bacteremic pneumonia caused by pneumococcal serotypes 3, 6A, 6B, 9N, 19A, 19F, and 23F than patients infected with serotype 14 whereas lower mortality was associated with serotypes 1, 4, 5, 7F, and 8 than 14 [71].

Studies have shown a modest impact of PCV7 on the incidence of pneumococcal CAP [4••, 72]. During the post-PCV era, a decrease in hospitalizations rates and outpatient visits for community-acquired pneumonia has been reported [72]. In one CDC report from pre-PCV7 period (1997–1999) to 2006, hospitalization rate for all-cause pneumonia declined 35 % among children under age 2 years but not in children aged 2–4 years [72]. A Cochrane Database Systematic Review found a 27 % pooled PCV7 vaccine efficacy for preventing radiograph-proven pneumonia and 6 % for clinically diagnosed pneumonia in children aged <2 years [73].

Although PCV7 resulted in significant decreases in the rates of IPD and pneumococcal pneumonia in children, there has not been an effect on the incidence of empyema [4••]. Studies have documented an increase in the incidence of empyema resulting in hospitalizations [74, 75]. In one report, a 2.17-fold overall increase in the rates of empyema complicating pneumococcal CAP was observed; in children ≤2 years of age there was a 2.01-fold increase (from 3.5 cases per 100,000 children in 1996–1998 to 7 cases per 100,000 children in 2005–2007) and in children 2–4 years of age, there was a 2.81-fold increase (from 3.7 cases per 100,000 children in 1996–1998 to 10.3 cases per 100,000 children in 2005–2007) [74]. In another study, a 70 % increase in the annual rate of empyema-associated hospitalization was noted from 1997 to 2006 (increase from 2.2 cases per 100,000 children in 1997 to 3.7 cases per 100,000 children in 2006) [75].

Non-PCV7 serotypes 1, 3, and 19A are most commonly associated with cases of pediatric pneumonia [25]. In a recent US study, the most common serotypes associated with empyema was serotype 3 (26.5 %) and 19A (22.4 %), followed by serotypes 7F (14.3 %) and 1 (12.2 %) [76]. Non-PCV7 serotype 1 has been linked to pediatric empyema cases [77, 78]. Genotypic analysis using multi-locus sequence typing of pneumococcal serotype 1 isolates have shown that ST 306, a newly detected genotype, emerged after PCV7 implementation whereas STs-227, -228, and -304 were previously existing genotypes [78, 79]. The potential of pneumococcal serotype 1 to cause empyema may be attributed to the presence of zwitterionic polysaccharides present in the pneumococcal capsule [37•].

Bone and Joint Infections

In children with microbiologically confirmed orthopedic infections, pneumococcus is the etiology in ∼4 % of osteomyelitis and ∼20 % of septic arthritis [4••]. Bone and joint infections constitute 3–6 % of IPD [4••, 80, 81]. The pathogenesis involves hematogenous spread of microorganisms, and the most commonly involved bones include the femur and humerus [80]. Rarely, other bones such as the vertebra may be infected [4••]. The knee and hip are most commonly affected in septic arthritis [80]. Pneumococcal osteomyelitis and septic arthritis may be associated with positive blood culture for *S. pneumoniae* in approximately 50 % of cases [80]. After PCV7 was introduced, there was a 50 % decrease in pediatric osteomyelitis and septic arthritis due to *S. pneumoniae* compared with pre-PCV7 period [16].

Hemolytic–Uremic Syndrome

Other unusual presentations of IPD include HUS [55, 62]. The clinical course in pneumococcal HUS can be severe with higher dialysis requirements and mortality rate compared with typical HUS following enterotoxigenic *Escherichia coli* [32]. In the pre-PCV era, serotype 14 was most commonly implicated, but during the post-PCV7 era, serotype 3 has emerged as a major cause followed by serotypes 1, 7F and 19A [62, 82].

Otitis Media and Sinusitis

AOM is one of the most frequent infections encountered in pediatric practices, accounting for an estimated 13 million episodes each year among US children and resulting in health care expenditures of billions of dollars [83]. AOM often occurs in infants and young children aged between 3 and 24 months after a preceding viral upper respiratory infection, which results in impairment of the mucociliary apparatus and Eustachian tube dysfunction [84]. The peak age incidence for AOM is 3–24 months, which coincides with the peak incidence of community-acquired viral infections in children [85]. Otoscopic findings are crucial in making a clinical diagnosis of AOM [86].

Streptococcus pneumoniae is the most common microorganism causing AOM (35–40 % of cases) followed by non-typeable *H. influenzae* (30–35 %) and *M. catarrhalis* (15 %) [83]. After introduction of PCV7, there has been a decrease in ambulatory visits for otitis media, rates of frequent otitis media, and tympanostomy-tube placement among young children [87]. In addition, a transient decline in the prevalence of *S. pneumoniae* infection and a relative increase in *H. influenzae* infection was noted during the post-PCV7 period [83, 88]. However, the emergence of vaccine-related replacement serotype 19A with high-level amoxicillin resistance resulting in treatment failure has been a concern [89]. In the PCV7 era, considerable variability has been noted in the prevalence of penicillin-resistant *S. pneumoniae* [83]. In addition, β-lactamase producing strains of 35–45 % of *H. influenzae* strains account for 35–45 % of cases while almost 100 % of *M. catarrhalis* isolates are β-lactamase positive [90].

Treatment

The emergence of MDR *S. pneumoniae* has complicated the treatment of pneumococcal infections [10, 11, 25, 26]. Over the past three decades, pneumococcal strains have emerged worldwide that are not susceptible to β-lactams (penicillin and ampicillin, third-generation cephalosporins such as ceftriaxone and cefotaxime), and other antimicrobial agents such as macrolides (including erythromycin, clarithromycin, and azithromycin), clindamycin, and trimethoprim–sulfamethoxazole (TMP–SMX) [10, 11]. In the PCV7 era, the emergence and spread of MDR CC320/271 strains with serotype 19A is a major therapeutic challenge [25, 91].

Antimicrobial Susceptibility Testing and Penicillin Breakpoints

The role of pharmacokinetic and -dynamic properties has proven invaluable to determine breakpoints for all antimicrobial agents used to treat pneumococcal infections [11]. In 2008, new breakpoints for penicillin G to treat non-meningeal infections were published by the Clinical and Laboratory Standards Institute [92] defining susceptibility and non-susceptibility for meningeal and non-meningeal pneumococcal isolates [93]. The breakpoints for intravenous penicillin G to treat meningitis were unchanged (susceptible, $\leq$0.06 μg/ml; resistant, $\geq$0.12 μg/ml). However, the breakpoints for intravenous penicillin G to treat non-meningeal infection were changed (susceptible, $\leq$2.0 μg/ml; intermediate, $\geq$ 4.0 μg/ml; resistant, $\geq$ 8.0 μg/ml). The breakpoints for oral penicillin to treat non-meningeal pneumococcal infection remain the same (susceptible, $\leq$ 0.06 μg/ml; intermediate, 0.12–1.0 μg/ml; resistant, $\geq$ 2.0 μg/ml) [92, 93]. With the exception of meningitis, in vitro results are not predictive of treatment outcome in pneumococcal disease [11].

During 2006–2007, the CDC estimated that the percentage of IPD non-meningeal pneumococcal isolates defined as susceptible, intermediate, and resistant to penicillin changed from 74.7, 15.0, and 10.3 % under the old breakpoints to 93.2, 5.6, and 1.2 %, respectively, under the revised 2008 breakpoints [93]. Using the revised penicillin susceptibility breakpoint of $\leq$2 μg/ml for non-meningeal infections, the SENTRY Antimicrobial Surveillance Program found that 93 % of all pneumococcal isolates would be susceptible to parenteral penicillin [94]. However, using the revised penicillin susceptibility breakpoint of $\leq$0.06 μg/ml for meningeal infections, only 68 % of isolates were susceptible [94]. The SENTRY Program in 2008 found that rates of resistance to erythromycin, clindamycin, and TMP–SMX were 37.1, 20.3, and 22.5 %, respectively among respiratory pneumococcal isolates [95].

Mechanisms of Antimicrobial Resistance

The mechanism of penicillin resistance in pneumococci is alteration in the cell wall penicillin-binding proteins (PBPs) [10, 96]. Alterations in PBP1a, 2x and 2b results in increased MICs to β-lactam agents and decrease drug affinity [10]. With the exception of meningitis, higher concentrations of β-lactam antibiotics at non-meningeal

sites of infection (e.g. otitis media, sinusitis, pneumonia) can bind and inhibit the enzyme and retain clinical effectiveness against penicillin-non-susceptible pneumococcal strains [10]. Resistance to quinolone and TMP–SMX to *S. pneumoniae* occurs from mutations within the bacterial genome [10].

Treatment of Pneumococcal Meningitis

Antimicrobial therapy in pneumococcal meningitis is challenging given the presence of pneumococcal strains non-susceptible to penicillin G, cefotaxime, ceftriaxone [10, 11, 96]. In addition, achievable therapeutic concentrations of antibiotics are lower in cerebrospinal fluid (CSF) [96]. Therefore, treatment of proven or suspected pneumococcal meningitis in infants aged >1 month and children includes combination therapy with vancomycin plus cefotaxime or ceftriaxone [28, 96]. Combination therapy also provides optimal empiric coverage for other bacteria causing meningitis in children such as *N. meningitidis*. Patients who are allergic to penicillin or cephalosporin may be treated with vancomycin and rifampin [28]. Monotherapy with vancomycin or rifampin is not recommended because of concerns of achieving sustained bactericidal concentrations in the CSF (with vancomycin) and risk of development of resistance (with rifampin) [28]. Other alternative agents used for therapy of meningitis due to cephalosporin-resistant pneumococcal strains include carbapenems (e.g., imipenem, meropenem) [28].

Therapy can be adjusted once antibiotic susceptibility testing results are available. If the pneumococcal isolate is susceptible to penicillin (MIC <0.06 μg/ml), vancomycin must be discontinued and penicillin, cefotaxime, or ceftriaxone should be continued alone [28]. For isolates non-susceptible to penicillin (intermediate or resistant) but susceptible to extended-spectrum third-generation cephalosporins, vancomycin should be discontinued and cefotaxime or ceftriaxone must be continued [28]. For isolates non-susceptible to both penicillin and cefotaxime and ceftriaxone (intermediate or resistant) and susceptible to rifampin, addition of rifampin is recommended if there is clinical worsening after 24–48 h on vancomycin plus cefotaxime or ceftriaxone therapy, positive CSF culture for pneumococcus on repeat lumbar puncture or isolate showing high MIC (≥4 μg/ml) to cefotaxime or ceftriaxone [28]. Given the unreliable meningeal penetration of vancomycin, third-generation cephalosporin therapy is continued with vancomycin plus rifampin in cases of meningitis due to *S. pneumoniae* resistant to penicillin, cefotaxime and ceftriaxone [28]. In cases of meningitis caused by highly penicillin- or cephalosporin-resistant pneumococcal strains, use of fluoroquinolone (e.g., moxifloxacin) with in vitro activity against *S. pneumoniae* is an alternative therapeutic option for patients not responding to standard therapy; in such cases, fluoroquinolone must be used in combination with a third-generation cephalosporin or vancomycin [97]. The recommended dose of vancomycin therapy for bacterial meningitis is 60 mg/kg/day in four divided doses, but to maintain a target trough concentration of about 15–20 μg/ml to achieve adequate CSF concentrations, the dose and frequency of vancomycin may have be individualized [98].

A repeat lumbar puncture to document sterility after 48 h of therapy is recommended in patients not responding to appropriate therapy, CSF culture positive for penicillin non-susceptible *S. pneumoniae* (by oxacillin disk or quantitative MIC testing) and pending results of cefotaxime or ceftriaxone quantitative susceptibility testing, and prior dexamethasone therapy, which may limit the ability to assess clinical response [28]. The recommended duration of parenteral antimicrobial therapy for uncomplicated meningitis is 10 days [28]. The role of adjunctive corticosteroid (dexamethasone) therapy in the treatment of pneumococcal meningitis in infants (> 6 weeks of age) and children is controversial [28]. If considered, dexamethasone should be administered before or concomitant with the first doses of antibiotics.

Treatment of Non-meningeal IPD

Previously healthy children with non-meningeal IPD (e.g., bacteremia, pneumonia) requiring hospitalizations (but not critically ill) can be treated with β-lactam antibiotics such as parenteral penicillin, ampicillin, cefuroxime, cefotaxime, and ceftriaxone [28]. Critically ill patients with suspected non-meningeal invasive disease due to pneumococcus (e.g., severe necrotizing or multilobar pneumonia with hypoxia or shock) must receive parenteral vancomycin plus a β-lactam agent (such as ceftriaxone or cefotaxime) to treat possible strains that are non-susceptible to penicillin, ceftriaxone or cefotaxime [28]. Vancomycin must be discontinued once the results of susceptibility testing become available and the organism is susceptible to penicillin or third generation cephalosporins. A pediatric infectious disease consultation is recommended for treatment of non-meningeal IPD due to pneumococcal strains that are non-susceptible to penicillin G, cefotaxime or ceftriaxone.

Acute Otitis Media

For uncomplicated AOM and acute sinusitis, current American Academy of Pediatrics [99] and the American Academy of Family Physicians guidelines recommend high-dose amoxicillin (80–90 mg/kg/day divided twice daily) as the drug of choice in most instances. Given its excellent pharmacodynamic profile, high-dose amoxicillin

can achieve adequate concentrations in the middle ear or sinus fluid that exceed the MICs to most penicillin-non-susceptible pneumococcal strains and achieve bacteriologic eradication [84, 99]. In selected circumstances, patients with AOM may be observed without the need for antimicrobial therapy. The recommended duration of treatment for young infants with AOM or children with severe disease is 10 days, but in children older than 6 years of age who have mild or moderate disease, 5–7 days of therapy is sufficient [28, 99].

In the absence of clinical improvement, treatment failure must be reassessed at 3–5 days after initial therapy and prescribed alternative oral agents such as high-dose amoxicillin-clavulanate, cefdinir, cefpodoxime, or cefuroxime or a 3-day course of intramuscular (im) ceftriaxone [28]. These alternative agents have activity against penicillin-non-susceptible pneumococci as well as β-lactamase-producing *H. influenzae* and *M. catarrhalis.* To reduce the frequency of diarrhea, a 14:1 formulation of amoxicillin-clavulanate is recommended at 80–90 mg/kg/day of the amoxicillin component. A 3-day course of im ceftriaxone can be used to treat patients who fail courses of oral antibiotic therapy [28].

Macrolide therapy with azithromycin or clarithromycin is reserved for patients with severe hypersensitivity reaction to β-lactams. In children with severe disease or those not responding to second-line therapy, obtaining a diagnostic culture via myringotomy or tympanocentesis is prudent for making appropriate therapeutic decisions [28, 84]. Pneumococcal serotype 19A has been implicated as an important otopathogen in cases of AOM treatment failure [89]. Clindamycin, rifampin, or other alternative antimicrobial agents are indicated for MDR resistant strains of *S. pneumoniae* [28].

Alternative Antimicrobial Agents for Treatment of Resistant *S. pneumoniae* Infection

In some cases, alternative agents (e.g., linezolid, quinupristin–dalfopristin or fluoroquinolones such as levofloxacin) may be indicated after careful consideration of the risks and benefits and in consultation with a pediatric infectious disease specialist. Linezolid is a synthetic oxazolidinone active in vitro against resistant Gram-positive bacteria, including MRSA, vancomycin-resistant enterococcus, and MDR *S. pneumoniae* [100]. Initially approved for clinical use by the FDA in 2000, linezolid is bacteriostatic and inhibits bacterial protein synthesis by binding to domain V of the 23S ribosomal RNA of the 50S subunit [101]. Linezolid has been shown to be effective in the treatment of skin and skin–structure infections, bacteremia, or pneumonia in children but concerns about toxicity and potential development of resistance [101]. Linezolid is available in oral and parenteral formulations. Adverse effects include hematologic toxicity (anemia and thrombocytopenia) and peripheral neuropathy during chronic use [101].

Newer Antimicrobial Agents

The concern of evolving antimicrobial resistance to pneumococci and other Gram-positive pathogens has led to the development of several new antibiotics to treat CAP and other serious infections [102••]. New antimicrobial agents available for treatment of resistant Gram-positive infections include daptomycin, tigecycline, and telavancin [100]. Ceftaroline is a novel fifth-generation cephalosporin with broad-spectrum of activity against both Gram-positive and -negative pathogens including MRSA and resistant pneumococci [100]. Newer agents in ketolides (a subclass of macrolides) under development include telithromycin, cethromycin, and solithromycin [102••]. However, most new agents currently under development are derivatives of currently existing classes of antimicrobial agents raising the concerns of cross-resistance [11].

Prevention

Although the PCV7 vaccination program stated in 2000 has made a substantial impact in preventing pneumococcal disease in the US, non-PCV7 serotype replacement disease has necessitated the development of PCV with expanded serotype coverage [8, 17••]. In February 2010, a new PCV13 was recommended in place of PCV7 for routine pediatric immunization in the US from 6 weeks through 71 months of age [17••]. A single supplemental dose is recommended in all children aged 14–59 months who have been previously immunized with age-appropriate PCV7 series [17••]. The AAP Red Book [28] has published recommendations related to the use of PCV13 in children unimmunized or incompletely immunized with PCV13 as well as immunization of children 6–18 years of age with high-risk conditions.

In 2007, the ABC Surveillance Group reported that 64 % of 427 IPD cases observed in studies were caused by pneumococcal serotypes contained in PCV7, especially serotype 19A (42 %) [17••]. PCV13 includes all the seven serotypes included in PCV7, with an additional six serotypes (1, 3, 5, 6A, 7F, and 19A) that cause a majority of IPD [17••]. PCV13 has the potential to address the variation in serotype distribution, and further reduce the burden of IPD [8]. Data from the UK indicate that IPD due to serotypes contained in PCV13 has been reduced by 50 % in children less than 2 years of age [16]. In LMIC, serotypes 1 and 5 are common causes of IPD. Due to efforts from the Global Alliance for Vaccines and Immunization, eight

LMIC (Nicaragua, Honduras, Guyana, Sierra Leone, Kenya, and Democratic Republic of Congo, Mali, and Yemen) have introduced PCV13 during 2010–2011 [8]. A 10-valent PCV has also been developed and gained WHO pre-qualification in 2009 [4••, 8].

Given the diversity of pneumococcal serotypes, capsular switching potential, and the possibility of serotype replacement disease in both IPD and carriage, innovative approaches are needed to develop newer vaccines, such as conserved pneumococcal protein vaccines (CPPVs) [4••, 8, 19]. A number of CPPVs are currently being developed targeting combinations of conserved virulence proteins including pneumococcal surface protein A and pneumolysin, triple antigen vaccine based on antigens StKP, PcsB and PsaA, inactivated whole cell vaccine, and common protein vaccines [4••, 8].

Conclusion

IPD remains an important cause of morbidity and mortality in children, especially in LMIC where PCV has not been implemented. NP carriage of *S. pneumoniae* is a precursor to disease. *S. pneumoniae* can cause a wide spectrum of invasive and non-invasive disease. In resource-rich countries, implementation of PCV7 has been a significant public health achievement. However, serotype replacement disease due to MDR non-vaccine serotypes remain a concern. The recently introduced PCV13 with expanded serotype coverage has the potential to further reduce the burden of IPD due to serotypes not contained in PCV7. Continued surveillance of pneumococcal serotypes and antimicrobial resistance is crucial to evaluate the impact of PCV13 vaccine. Improved access to PCVs is crucial to reduce morbidity and mortality related to IPD in LMIC.

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