Pneumococcal disease in childhood

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***Streptococcus pneumoniae* is the most common cause of serious bacterial infections in children worldwide. Problems with antibiotic resistance have lead to changes in antibiotic policies for children with possible pneumococcal disease. Demonstration of the efficacy of a pneumococcal conjugate vaccine has lead to consideration of its inclusion in routine infant vaccination schedules.**

In children, *Streptococcus pneumoniae* is a frequent cause of bacteraemia, septicaemia, community-acquired pneumonia, acute otitis media and sinusitis. It is also a frequent cause of bacterial meningitis in children under 2 years of age (Overturf et al, 2000). The incidence of childhood disease resulting from *Haemophilus influenzae* type b (Hib) and, in the UK, disease resulting from *Neisseria meningitidis* group C, has fallen dramatically following the introduction of Hib and meningococcal C conjugate vaccines (Wenger et al, 1998; Ramsay et al, 2001). *S. pneumoniae* is now therefore the most common vaccine-preventable infection in childhood.

BIOLOGY OF PNEUMOCOCCAL INFECTION

S. pneumoniae is a Gram-positive coccus, often identifiable as a lancet-shaped diplococcus and in chains of varying lengths. Encapsulated forms are the only forms identified in clinical material. The capsule is composed of one of 90 serologically distinct types and has antiphagocytic properties. The host mounts an antibody response to the capsule, which is protective (Kalia, 1998), and this is the basis for vaccination with capsular polysaccharide. The bacterial cell wall induces inflammation by stimulation of cytokine production (Heumann et al, 1994) and by activation of complement (Winklesein and Tomasz, 1978). Other virulence factors are shown in *Table 1*.

S. pneumoniae binds to cells of the upper and lower respiratory tract. Adherence enables asymptomatic carriage for weeks without any overt inflammation but with production of a serotype-specific immunity. In invasive disease, adherence proceeds to internalization of the bacteria into the host cell by a receptor-mediated endocytosis. Intercurrent viral infections can generate local inflammatory factors, possibly upregulate platelet-activating factor receptors, and this may enhance adherence and invasion.

TABLE 1.
***Streptococcus pneumoniae* virulence factors**

Cell component	Location	Biological action
Capsular polysaccharide	Capsule	Virulence
		Anti-phagocytic but not toxic
		Type-specific antibody is protective
Cell wall polysaccharide	Cell wall	Pro-inflammatory
		Attaches to platelet-activating factor receptors on activated endothelium
Autolysin	Cell wall	Cell wall lysis when growth ceases
		Essential for release of pneumolysin
Pneumolysin	Intracytoplasmic	Toxic to the host cells
		Activates complement
Pneumococcal surface protein A	Surface of cell wall	Function unclear Needed for full virulence

From Catterall (1999)

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EPIDEMIOLOGY

The greatest risk of invasive pneumococcal disease is in children under 2 years of age and in the elderly. Incidence figures vary in different countries (*Table 2*). This is likely to reflect the different ethnic and socioeconomic settings but also the different reporting practices and culture sampling and surveillance methods used in different countries.

The epidemiology has been best studied in the USA, and *S. pneumoniae* is estimated to cause a minimum of 1400 cases of meningitis, 17 000 cases of bacteraemia, 71 000 cases of pneumonia and 5–7 million cases of otitis media annually (Overturf et al, 2000). Globally, it is thought to be responsible for 1 million deaths in children under 5 years of age annually (Leowski, 1986).

The burden of invasive disease in children, i.e. meningitis and bacteraemia, is more easily defined than that of non-invasive diseases, such as pneumonia and otitis media. The latter are more difficult to quantify as often a pathogen is not sought in typical cases and treatment is given empirically. However, pneumonia and otitis media are responsible for substantial morbidity and health-care costs. Otitis media is a frequent cause of GP attendance and antibiotic use in children, and *S. pneumoniae* may comprise up to 50% of bacteria causing otitis media (Dowell et al, 1999). Complications of acute otitis media include glue ear, chronic suppurative otitis media and hearing loss, while rarer sequelae include mastoiditis, venous sinus thrombosis and meningitis. Community-acquired pneumonia is also a common clinical syndrome in childhood, and *S. pneumoniae* is a frequent cause of this. Septicaemia and empyema may complicate pneumonia. In countries such as the UK, the contribution of *S. pneumoniae* to otitis media and pneumonia is largely undefined.

MORBIDITY AND MORTALITY

The case fatality rate as a result of pneumococcal infections in children varies from 1–16% in different studies (Bohr et al, 1985; Eskola et al, 1992; Shackley et al, 2000) and is substantially higher in adults over 70 years of age (>50%). A recent UK study indicated a mortality of 1% and incidence of sequelae of 7% (Shackley et al, 2000). The consequences of pneumococcal meningitis are considerable. Following pneumococcal meningitis, neurological sequelae include hearing impairment, hydrocephalus, convulsions and mental retardation. These sequelae have been described in 29–56% of children (Fortnum, 1992). A meta-analysis of outcomes after bacterial meningitis in children indicated that children with pneumococcal meningitis were more than twice as likely to develop neurological sequelae as children with Hib meningitis and more than six times as likely as children with meningococcal meningitis (Baraff et al, 1993).

HIGH-RISK GROUPS FOR INVASIVE PNEUMOCOCCAL INFECTION

Children with sickle cell disease and sickle combination haemoglobinopathies, congenital and surgical asplenia, and human immunodeficiency virus (HIV)-infected children are at greatest risk of invasive disease. Infants and children in out-of-home care in the USA (Overturf et al, 2000) and Finland (Takala et al, 1995) have also been shown to be at greater risk of disease. Certain ethnic groups, such as children of native American descent and Alaskan natives, also have very high rates of disease (Overturf et al, 2000).

TABLE 2.
Incidence of pneumococcal disease in different countries

Country	Reference	Data collection period	Annual incidence/ 100 000/year (age)
England/Wales	Sleeman et al (2001)	1995–9	48.1 (<1year)
			21.2 (<5 years)
Finland	Eskola et al (1992)	1985–89	45.3 (<2 years)
			24.2 (<5 years)
Germany	Reinert et al (1999)	1997	10.1 (≤5 years)
Spain	Diez et al (1999)	1996–97	26.5 (< 1 year)
			13.7 (< 5 years)
USA	Centers for Disease Control and Prevention (1997, 1999)	1999	162.7 (<1 year)
			205.4 (1–2 years)
			33.2 (2–4 years)

DRUG-RESISTANT *S. PNEUMONIAE*

There has recently been a significant increase in drug-resistant *S. pneumoniae* (DRSP) in the USA as well as in other developed countries (Campbell and Silberman, 1998). This has significant implications for the choice of empirical antibiotics in children with possible pneumococcal disease. For example, in the USA, recommendations now dictate use of vancomycin in addition to a third generation cephalosporin for empirical treatment of childhood meningitis (American Academy of Pediatrics, Committee on Infectious Diseases, 1997).

Penicillin resistance results from multiple alterations in the penicillin-binding proteins (PBP) which affect the binding affinity of penicillin. These alterations are the result of stable genetic mutations and are chromosomally mediated. A majority of DRSPs belongs to selected serotypes, i.e. 6, 9, 14, 19 and 23 (Tomasz, 1997). Resistance is graded into bands based on minimum inhibitory concentrations (MIC). These were selected on the basis of the efficacy of penicillin in treating *S. pneumoniae* meningitis. Strains are deemed penicillin susceptible if their MIC is ≤0.06 mg/ml, intermediately resistant if their MIC is 0.1–1.0 mg/ml and highly resistant if their MIC is >2.0 mg/ml.

Some alterations in PBP may also affect the susceptibility of isolates to other β-lactam agents, especially cephalosporins, and hence penicillin resistance can be associated with cephalosporin resistance. Erythromycin resistance is reported as high as 19% in the USA (Thornsberry et al, 1997), and there is cross-resistance to other macrolides. The mechanism of resistance may be modifications of the ribosome or the presence of a macrolide efflux system. The incidence of macrolide resistance is higher in penicillin-resistant isolates. The incidence of fluoroquinolone resistance remains very low, possibly because of limited use of these antibiotics.

KEY POINTS

- *Streptococcus pneumoniae* is a frequent cause of otitis media, pneumonia, bacteraemia and meningitis in childhood. The morbidity, mortality and health-care cost of pneumococcal disease is therefore significant.
- Antibiotic resistant strains of *S. pneumoniae* are being increasingly recognized, with significant implications for antibiotic prescribing in children.
- Consideration is now being given to the routine use of new and effective pneumococcal conjugate vaccines in infants.
- Further epidemiological studies are warranted in those countries where the burden of pneumococcal disease has yet to be quantified.

The clinical implications of penicillin resistance are greatest for meningitis. It should be noted that the peak serum concentrations for standard doses of oral β lactams may be 3–7-fold higher than the MIC of even a resistant strain. Thus, studies comparing the outcome of penicillin-susceptible *vs* penicillin-resistant pneumococcal disease (non-meningitis) have not shown any significant differences in outcome (Freidland and Klugman, 1992; Tan et al, 1998). However, antibiotic concentrations are lower in CSF than in serum, and the difference between antibiotic concentration and MIC will be correspondingly less. Although there are case reports of clinical relapse in cases with penicillin-resistant strains, large series have not actually shown significant differences in outcome of meningitis (Arditi et al, 1998; Fiore et al, 2000). It should be noted that in these studies (which are from the USA) vancomycin was often used early in the management of meningitis so that the outcome without use of vancomycin remains uncertain.

In the UK, resistance to penicillin has risen from 0.3% in 1989 to 7.5% in 1997, and the proportion resistant to erythromycin has risen from 3.3% in 1989 to 11.8% in 1997 (Public Health Laboratory Service, 2001). Thus, although penicillin resistance is not a major problem at present, it is likely to increase over time. Currently, antibiotic resistance should be considered in children arriving from countries with a high prevalence of antibiotic resistance, children with previous heavy antibiotic exposure, children who are immunosuppressed and in those who are not responding to therapy. This is particularly relevant in cases of meningitis, and if these risk factors are present, then the addition of vancomycin to a third generation cephalosporin should be considered until antibiotic susceptibilities have been clarified.

CONCLUSIONS

S. pneumoniae is an important pathogen in childhood, which results in considerable morbidity, use of health-care resources and, in the case of meningitis, a mortality which exceeds that of the other common childhood pathogens, Hib and *N. meningitidis*. Better epidemiological data are required in those countries such as the UK which are now considering the use of the new and effective pneumococcal conjugate vaccines. HM

Conflict of interest: Dr Heath is a consultant for Wyeth Vaccines on pneumococcal vaccines.

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