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REVIEW ARTICLE

Invasive pneumococcal disease; a serious and preventable infection

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INTRODUCTION

Streptococcus pneumoniae is not always a pathogen. It can colonize the nasopharynx harmlessly for a period of time in a "carrier". However, this bacterium has the ability to cause serious, life-threatening disease such as pneumococcal pneumonia, pneumococcal septicemia and pneumococcal meningitis, either in the "carrier" or in a contact. Collectively, any infection characterized by the presence of Streptococcus pneumoniae in a body site which is usually sterile, is called invasive pneumococcal disease (IPD). Further examples include pneumococcal septic arthritis and pneumococcal peritonitis.

The causative organism, Streptococcus pneumoniae, exists as around 90 distinct serotypes often with distinct geographic and demographic distributions. Not all serotypes are of clinical importance. Some are more likely to be responsible for the non-invasive pneumococcal infections pneumococcal otitis media and sinusitis. A large proportion of those serotypes responsible for IPD are covered by the current (and future) pneumococcal vaccines (see below).

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Diagnosis of IPD is difficult and often delayed. Delayed diagnosis may be due to either a mild initial non-specific presentation and/or inappropriate use of oral antibiotics which masks the true serious nature of the infection. If diagnosis is delayed, the consequences may be serious or fatal. Once the correct diagnosis is made, treatment with parenteral antibiotics and supportive management is relatively straightforward. Prevention is the preferred approach and two pneumococcal vaccines are currently available (see below).

Pathophysiology

Passage of Streptococcus pneumoniae from the nasopharynx directly into the bloodstream or to the lower respiratory tract sets in train a sequence of events that results in IPD. The cribriform plate separating the nasal passage from the brain is thin and there is some evidence that spread may occur directly to the nervous system (1). However, it is more likely that spread occurs via the bloodstream, invoking an inflammatory cascade that may be successful, in the case of pneumococcal bacteremia which may resolve spontaneously, or may be unsuccessful in the case of IPD.

The pathway leading to IPD involves invasion by the organism, the triggering of inflammatory pathways, pneumococcal toxicity and damage. Of

particular interest for invasion into the central nervous system are surface determinants such as choline binding protein (2). For meningitis exposure to the organism itself, or its toxins, is likely to be responsible for apoptosis-like programmed neuronal cell death (3). Susceptibility to IPD is highest in persons with underlying medical and surgical risk factors such as:

- Sickle cell disease
- Other impairments of the immune system
- Cerebro-spinal fluid leak
- Cochlear implant
- Some chronic diseases (respiratory, heart, kidney, liver)

However, the absolute total number of victims of IPD is much higher in those without high-risk factors but with other risk factors such as over-crowding or day-care attendance, or with no risk factors whatsoever.

Epidemiology

Although Streptococcus pneumoniae is not normally thought to cause outbreaks of disease, outbreaks of IPD have been reported (Table 1) (4-8). The mean age of adult patients admitted to hospital with pneumococcal meningitis is 53 years, with a range of 17 to 92 years and a male:female ratio of 1.3:1 (9). An earlier study showed no difference between the rate of IPD in male children and female children (10). In Germany there is evidence of regional differences in incidence, serotype distribution and antibiotic resistance rates in IPD in toddlers, with day-care attendance a notable risk factor (11). In France a prospective nationwide study performed between January 2001 and December 2003 enrolled 1084 infants and children with bacterial meningitis (12). Streptococcus pneumoniae was responsible for 33.4% of cases in those older than 28 days while it was the most frequent pathogen (49.5%) in those 2 to 12 months of age. Furthermore, the case-fatality rate for pneumococcal meningitis was 10.8%.

But it is the results of national surveillance in the USA that indicate the endemic nature of pneumococcal infection and the propensity for transmission of Streptococcus pneumoniae from the pediatric population to the adult population and to very young infants (13-15). This remarkable observation that pediatric pneumococcal immunization has resulted not only in significant reductions in IPD in the target age group but also significant reductions in the non-vaccinated adult age groups is leading to a deeper understanding of the life-cycle of the organism, and improvements in prevention strategies for IPD in all age groups.

Clinical presentation

The problem for clinicians is the often insidious nature of the presentation of IPD. The clinician may be deceived into thinking that their patient is suffering from a minor viral illness because of the non-specific nature of the early symptoms of IPD. By the time the gravity of the condition is obvious, it may be too late for antibiotics and supportive therapy to be effective. High fever, shock, rash and death may occur very quickly.

Pneumococcal bacteremia may present as a fever and with prompt antibiotic therapy, it is likely to resolve with no consequences. Nevertheless, it is important to check for evidence of an underlying medical or surgical risk factor before dismissing the patient. Pneumococcal infection may be the external manifestation of splenic dysfunction or some other impairment of immune function. Conversely, pneumococcal bacteremia may progress to more serious IPD. It is therefore important to perform a blood culture and to treat the patient with parenteral antibiotics until it is known that the blood culture is negative.

Pneumococcal pneumonia presents with fever, shortness of breath and possibly chest pain. It may be difficult to differentiate pneumococcal pneumonia from other forms of pneumonia, and indirect methods of diagnosis such as immunoassay and polymerase chain reaction may complement

traditional microbiological methods (16,17). Radiology may be non-specific or may display the classical "round" pneumonia.

Pneumococcal meningitis, like other forms of IPD, affects all age groups. However, as with other forms of IPD, there are peaks of infection in the very young and in the elderly. The classical presentation of pneumococcal meningitis is an insidious onset leading through vomiting and fever to impaired consciousness, meningism and death without appropriate treatment. Delayed diagnosis is associated with increased morbidity but not necessarily with increased mortality (18). The longer-term consequences of pneumococcal meningitis include profound deafness in 15.5% (19), brain damage in 9.7% (20), focal neurological signs in 6% (21) and epilepsy in 7% (20). In adults, death from pneumococcal meningitis occurs in between 16% and 37% of patients while neurological sequelae occur in between 30% and 52% of survivors (9).

Burden of IPD

Rates of IPD are high in the very young and in older adults (22). Paradoxically, the greatest *number* of cases of IPD occur in patients with no identifiable risk factors. The typical pre-vaccination age-related incidence pattern of pediatric IPD is demonstrated by the rates for England and Wales between 1996 and 1998 (Table 2) (23). The reported rates of pediatric IPD in Europe range from a low in Sweden of 1.7 per 100,000 for those <2 years of age and 4.2 per 100,000 for those 2 to 15 years of age (24), to a high in Spain of 174 per 100,000 for those <2yrs (25) and 56.2 per 100,000 for those <5 years of age (26). For adults in the USA the "baseline" rates of IPD in 1998/99 were (13):

- 11.2 per 100,000 for those 20 to 39 years of age
- 21.5 per 100,000 for those 40 to 64 years of age
- 60.1 per 100,000 for those 65+ years of age.

Antibiotic resistance and antibiotic treatment of IPD

The antibiotic resistant strains of Streptococcus pneumoniae are likely to be the strains responsible for IPD as is, for example, the case in Portugal (27). While the resistance may not always be "high-level", there is nevertheless concern that a life-threatening or disabling infection could be inadequately treated with ineffective antibiotics. This leads to the use of antibiotic combinations and "more powerful" antibiotics than may be necessary. Penicillin resistance has been detected in 39% of invasive pneumococcal isolates in Argentina (28). A 7-year-old German bone transplant recipient is reported to have died as a consequence of penicillin- and cefotaxime-intermediate Streptococcus pneumoniae contracted in Spain (29).

A recent Cochrane Systematic Review shows no clinically important differences between third generation cephalosporins and combination ampicillin/chloramphenicol for the treatment of acute community-acquired bacterial meningitis (30). Suspected pneumococcal meningitis should, in general, be treated with either of these regimens for 10 to14 days. However, if the lumbar puncture is delayed, vancomycin should be added to cover for penicillin or cephalosporin resistant Streptococcus pneumoniae (31). Rifampicin may be an acceptable alternative to add (32). Pneumococcal pneumonia may respond to penicillin alone but is increasingly likely to require a combination. In Kilifi, Kenya, the incidence of pneumococcal bacteremia is as high as 241 per 100,000 infants <1 year of age and is also associated with a high mortality rate, underlining the importance of treating this entity satisfactorily with the appropriate antibiotics (33).

Table 1. *Outbreaks of IPD*

Time period	Setting	Serotype(s) and ages	Reference
1990 to 2000	USA	4, 14 and 23F responsible for 67% of the 12 of the 26 outbreaks	(4)
8 day period	Baltimore family child-care home	Cluster of 6 cases of serotype 12F in infants and children 8 to 26 months of age	(5)
November 1995 to January 1996	Iowa, following an influenza outbreak	Severe pneumococcal pneumonia in 13 children	(6)
13 September to 22 October 1999	Ibadan, Nigeria	14 paediatric cases	(7)
January 2003 to March 2004	Alaska	14 cases, age range 1 to 72 years; serotype 12F in 64%	(8)

Table 2. *Number reports of paediatric IPD by age 1996 to 1998 (3 years), England and Wales and annualised incidence rates according to clinical presentation*

Age group	Meningitis		Other IPD		Total IPD reports	
	No. (%)	Rate/10^5	No.	Rate per 10^5	No.	Rate per 10^5
< 2 months	50 (28)	15.4	131	40.2	181	55.6
2-5 months	131 (53)	20.1	114	17.5	245	37.6
6-11months	126 (36)	12.9	224	22.9	350	35.8
12-17 months	58 (18)	6.1	266	27.9	324	33.9
18-23 months	20 (15)	2.1	113	11.8	133	13.9
24-47 months	50 (15)	1.3	273	6.9	323	8.1
48-59 months	14 (13)	0.7	96	4.8	110	5.5
5-9 years	16 (8)	0.2	187	1.8	203	1.9
10-14 years	20 (17)	0.2	96	1.0	116	1.2
Total	485 (24)	1.6	1500	5.0	1985	6.6

Vaccination against *Streptococcus pneumoniae*

There are two pneumococcal vaccinations currently available: the 23-valent pneumococcal polysaccharide (PPS) vaccine and the 7-valent pneumococcal conjugate vaccine (PCV). From 13 observational studies, the estimate of 23-valent PPS vaccine efficacy against IPD was 53% (95% confidence interval 46% to 59%) compared with 38% (95% confidence interval −4% to 63%) from nine randomized controlled clinical trials (RCTs) (34). Estimates of 23-valent PPS protection against all-cause pneumonia from five heterogeneous studies showed an efficacy of 32% (95% confidence interval 7% to 50%) compared with 3% (95% confidence interval −16% to 19%) from 13 RCTs.

The safety, immunogenicity, efficacy and effectiveness of a 4-dose schedule of 7-valent PCV in preventing IPD has been firmly established by means of a large RCT (35), (36), (37), (38), (39). It appears that fewer doses may also be effective (40). 7-valent PCV is also effective in preventing a proportion (around 6%) of all acute otitis media (41,42). The vaccine has an excellent safety profile (43). Seven-valent PCV protects against infection caused by pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. Its efficacy against all IPD is dependent upon the serotype coverage against individual serotypes (44).

Herd protection

What is perhaps the most remarkable feature of 7-valent PCV is its ability to protect members of

the community not actually vaccinated themselves (13). The decline in IPD in the USA in various adult age groups from the "pre-vaccination" era (1998/99) to the "post-vaccination" era (2001) was significant at:

- 32% for those 20 to 39 years of age
- 8% for those 40 to 64 years of age
- 18% for those 65+ years of age.

Although a slight increase in non-vaccine serotype disease is noted, this is relatively small in comparison with the overall large decreases in both the target and the non-target age groups. The effect also extends to infants too young to be vaccinated (15) and to antibiotic-resistant disease (14). When herd protection is taken into account, the cost-effectiveness of 7-valen PCV becomes apparent (45).

CONCLUSION

IPD is the systemic clinical manifestation of infection by Streptococcus pneumonia. The organism also causes non-invasive mucosal infections such as acute otitis media. What is revealed by a successful pediatric immunization program with 7-valent PCV is the extent to which the organism is being transmitted throughout the community and between age groups. The effectiveness of this vaccine appears to be dependent as much on prevention of pneumococcal transmission as the absolute immunogenicity in the vaccine. This provides an efficient opportunity to protect many vulnerable members of the society and to prevent the feared consequences of bacterial meningitis.

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