ORIGINAL ARTICLE

The emergence of resistant pneumococcal meningitis—implications for empiric therapy

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Background: Following the emergence of penicillin and cephalosporin resistant pneumococcal meningitis in the United States, inclusion of vancomycin in empiric therapy for all suspected bacterial meningitis was recommended by the American Academy of Pediatrics. Few data are available to evaluate this policy.

Aims: To examine the management and clinical course in relation to antibiotic therapy of a large unselected cohort of children with pneumococcal meningitis in a geographic area where antibiotic resistance has recently increased.

Methods: Retrospective review of all cases of pneumococcal meningitis in a defined population (Sydney, Australia), 1994–99.

Results: A total of 104 cases without predisposing illnesses were identified; timing of lumbar puncture (LP) was known in 103. Resistance to penicillin increased from 0 to 20% over the study period. Only 57 (55%) had an early LP (prior to parenteral antibiotics); 55 (96%) had organisms on Gram stain. Severe disease (intensive care admission or death) increased significantly from 57 cases with early LP (28%) to 33 with delayed LP (42%) to 13 with no LP (62%). Evidence of pneumococcal infection was available within 24 hours in 85% of those with delayed or no LP. Outcome was not related to empiric vancomycin use, which increased from 5% prior to 1998 to 48% in 1999.

Conclusion: LP is frequently delayed in pneumococcal meningitis. Based on disease severity, empiric vancomycin is most justified when LP is deferred. If an early LP is done, vancomycin can be withheld if Gram positive diplococci are not seen.

Worldwide, there has been a rising incidence of decreased susceptibility to penicillin and third generation cephalosporins among pneumococci, although prevalence varies substantially even within countries.[1] In 1997, the prevalence of reduced susceptibility to penicillin among a sample of pneumococcal isolates from Australian laboratories was 25.4%, varying from 13% to 38% between regions. In addition, 10% of isolates had intermediate and 3.1% high level resistance to third generation cephalosporins.[2]

In pneumococcal meningitis, any degree of penicillin resistance is associated with failure of penicillin and chloramphenicol treatment.[3] While there have been treatment failures with third generation cephalosporins (TGC) in penicillin resistant pneumococcal meningitis,[4–7] successful treatment has also been reported.[8] Vancomycin penetrates inflamed meninges, but as inflammation decreases with treatment, levels in the cerebrospinal fluid (CSF) may fall.[9] Vancomycin and high dose cefotaxime are synergistic and prevent emergence of resistance.[10] The American Academy of Pediatrics (AAP) recommended in 1997: "Vancomycin plus cefotaxime or ceftriaxone should be administered initially to all children older than 1 month with definite or probable bacterial meningitis".[11] Application of this policy could lead to many children with aseptic meningitis or bacterial meningitis either not caused by *Streptococcus pneumoniae* or caused by penicillin sensitive pneumococci, receiving treatment with vancomycin. Whether this is appropriate will depend on both the local prevalence of antibiotic resistance in *Streptococcus pneumoniae* and how reliably pneumococcal meningitis can be distinguished from bacterial meningitis caused by other organisms on initial diagnostic tests.

As noted by the AAP review, data on the sensitivity of diagnostic tests for pneumococcal meningitis available before CSF culture (Gram stain and latex agglutination) are sparse. In a small study, three of six (50%) children over 6 years of age with pneumococcal meningitis, had Gram positive diplococci seen.[12] A larger study found a positive Gram stain in 81% of 77 children and adults.[13] However, in younger children, the Gram stain is positive in 90–100% of CSF specimens.[14 15] Pneumococcal antigen is identified by latex agglutination with a sensitivity of 60–67%.[16 17]

Concerns about the overuse of vancomycin are the emergence of vancomycin resistant enterococci or staphylococci, the cost of vancomycin and therapeutic monitoring, and the adoption of an unnecessary practice, which is difficult to reverse. This study examined a consecutive sample of pneumococcal meningitis in an area of rapidly increasing antibiotic resistance to determine whether a policy of basing empiric vancomycin use on initial CSF parameters was likely to be clinically acceptable.

METHODS

Case definition

Pneumococcal meningitis was defined as isolation of *Streptococcus pneumoniae* from CSF or from blood with a CSF pleocytosis (CSF white cell count (WCC) >10 cells per mm^3). If a lumbar puncture (LP) was not performed, meningitis was defined as isolation of *Streptococcus pneumoniae* from blood culture with clinical and imaging evidence of meningitis. Cases with predisposing illness (chemotherapy for malignancy or anatomical abnormalities of the ear, nose, or throat, maxillofacial, or central nervous system), who were deemed likely to

Abbreviations: AAP, American Academy of Pediatrics; CSF, cerebrospinal fluid; LP, lumbar puncture; TGC, third generation cephalosporin; WBC, white blood cell; WCC, white cell count

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have differing diagnostic pathways and indications for vancomycin, were examined as a separate group.

Case ascertainment

Eligible cases were 15 years of age or less and had a date of isolation of *Streptococcus pneumoniae* in the six years January 1994 to 31 December 1999. From January 1994 to June 1997, cases were ascertained by passive prospective laboratory notification, which included all microbiology laboratories in Sydney and surrounding urban areas.[18] From June 1997, active laboratory surveillance was in place over a wider geographic area.[19] For both time periods, case ascertainment was enhanced by cross referencing with all cases in the target age group with a discharge diagnosis of ICD-9 code meningitis, pneumococcal (320.1), all meningitis unspecified (320.0), and pneumococcal septicaemia.[20] Clinical data were obtained by a standard proforma from the medical records by a single research assistant (RG).

Antibiotic resistance

Antibiotic sensitivity methods were those reported by the local laboratory; confirmatory testing was not performed. Most laboratories were using E-test with the National Committee for Clinical Laboratory Standards interpretive criteria[21] for minimum inhibitory concentrations (MIC) as follows: penicillin susceptible ≤0.06 μg/ml, intermediate resistant 0.1–1 μg/ml, resistant ≥2 μg/ml; cefotaxime susceptible ≤0.5 μg/ml, intermediate resistant 1 μg/ml, resistant ≥2 μg/ml. Organisms with intermediate or high level resistance were included in the category non-susceptible. Other laboratories were using the calibrated dichotomous sensitivity testing method that reports a cut off at a radius of <6 mm around the penicillin disc as indicating intermediate or greater resistance.

Data analysis

The data were entered into Microsoft Excel and Access databases. Analysis was performed with SPSS and Statcalc in Epi-Info version 6.04b (1997).[22 23]

RESULTS

Study population

A total of 121 cases were identified during the study period. Of these, 16 had underlying illness (malignancy in six, anatomic abnormality in 10) and records were unavailable in one case, leaving 104 eligible cases (fig 1).

Cerebrospinal fluid examination

Of the 104 previously well children with available records, 91 (87%) had an LP performed, 57 (63%) prior to parenteral antibiotics and 33 (36%) after parenteral antibiotics were commenced; timing of antibiotic administration was unknown in one case (fig 1). Severity of illness, as measured by admission to intensive care, increased significantly from those who did not have parenteral antibiotics prior to LP (28%) to those who had a delayed LP performed (42%) to cases who never had an LP (62%) (χ^2 for trend = 4.7_{1df}; p = 0.03).

The mean total CSF white cell count (WCC) was 1306 per mm^3 (median 739). The WCC was <50 cells per mm^3 in nine children (10%), five of whom had organisms seen on Gram stain; another seven cases had a CSF WCC between 50 and 100 per mm^3. Thus the CSF WCC was less than 100 per mm^3 in 18% of cases. The average percentage of neutrophils was 73% (95% CI: 67 to 79). Of the 18 cases with less than 50% neutrophils, all except one had a CSF WCC of more than 100 per mm^3.

Table 1 shows CSF findings, according to prior antibiotic administration. There was no significant difference in the proportion with organisms seen on Gram stain of CSF between those who had (12/12) and those who had not (43/45) received oral prior to parenteral antibiotic therapy. Overall, 55/57 (96%) of children not receiving prior parenteral antibiotic therapy had organisms seen on Gram stain. Other CSF parameters did not assist early diagnosis in the two cases with a negative Gram stain. Latex agglutination, performed in one of the two, was negative, while the CSF glucose was normal (>3 mmol/l) in both and CSF protein was normal (0.17 g/l) in one and not recorded in the other. One child did not have CSF pleocytosis (white blood cells (WBC) 5×10^9 per litre and 42 red cells) and the other had only 13×10^9 WBC per litre with 9 red cells, so CSF would have appeared macroscopically clear. Nevertheless, blood and CSF cultures were positive at 24 hours in both. The proportion of cases with a positive Gram stain when parenteral antibiotics were given prior to LP was significantly lower (75%, p = 0.004, Fisher's exact test). Provisional evidence of pneumococcal infection from cultures of CSF or blood was available within 24 hours in 51 (89%) patients with LP prior to parenteral antibiotics, 25 (76%) of those with an LP after antibiotics had started, and all 13 (100%) of those who never had an LP.

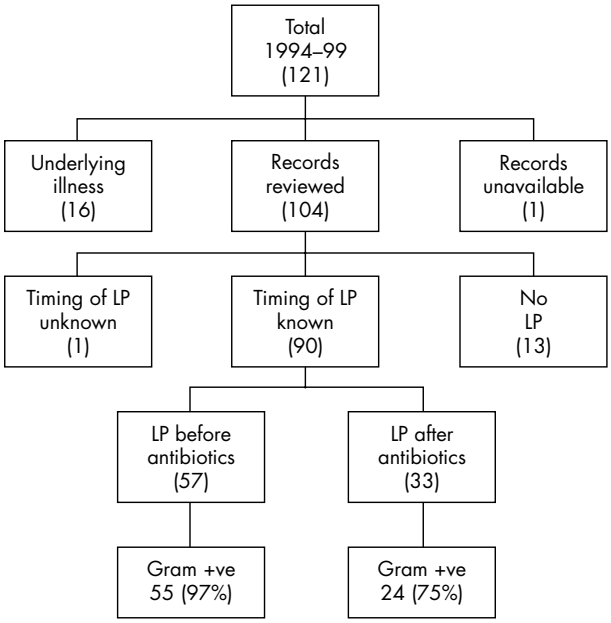

Figure 1 Pneumococcal meningitis cases in the Sydney region, 1994–99.

Antibiotic sensitivity

Among previously well children, there was a progressive increase in the prevalence of antibiotic resistance. The first isolate with intermediate resistance to penicillin was seen in 1996, increasing to 5/21 cases (24%) in 1999; the first two cases of high level penicillin resistance appeared in 1998. In children with underlying illness, the first CSF isolate with intermediate susceptibility to penicillin was seen in 1995; since 1995 6/12 (50%) have had penicillin non-susceptible isolates. The first isolate with intermediate resistance to third generation cephalosporins was seen in 1996. A total of six isolates with intermediate cephalosporin resistance were seen from 1996 (four in previously well children); two had high level penicillin resistance. Four of these six patients were treated with vancomycin within 24 hours, one child within 48 hours, and the other (a child with malignancy) died prior to sensitivity results being known.

Trends in vancomycin use

In children without underlying illness, vancomycin was rarely included in the initial antibiotic regimen prior to 1998 (3/63, 5%). This changed rapidly in 1998 (2/19, 11%) and 1999 (10/21, 48%). Vancomycin was more commonly included in the empiric regimen for children with malignancy, with 2/4

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Table 1 CSF findings according to prior antibiotic administration

Patient category	n	Gram stain positive	Ag positive/Ag tested	WBC >100/mm^3	Protein > 0.4 g/l	Glucose < 2.0 mM/l
No prior antibiotics	45	43 (96%)	29/33 (88%)	39 (80%)	33/44 (75%)	21/32 (66%)
Prior oral antibiotics only	12	12 (100%)	9/9 (100%)	10 (83%)	9/11 (82%)	5/12 (42%)
Prior parenteral antibiotics	33	24 (73%)	14/18 (74%)	27 (82%)	24/27 (89%)	16/31 (52%)
Total	90	79 (88%)	52/60 (87%)	76 (84%)	66/82 (80%)	42/75 (56%)

Table 2 Hospital course by antibiotic susceptibility of children with no underlying illness

	Penicillin sensitive	Penicillin intermediate resistance	Cefotaxime intermediate/penicillin high resistance
Number (103)	91	8	4
Age in months			
Median	13	13	9.5
Range	1–179	5–148	4–12
Days of fever (mean)	2.5	2	5
Died, n (%)	11 (12)	2 (25)	0
ICU, n=39 (38%)			
Number (%)	33 (36)	4 (50)	2 (50)
Median days (range)	3 (1–17)	1 (1–4)	9.5 (1–18)
Intubated			
Number (%)	21 (23)	3 (38)	1 (25)
Seizures			
Before admission (%)	13 (14)	2 (25)	0
After admission (%)	26 (29)	2 (25)	1 (25)

(50%) receiving it in 1994–95. Of the cases with a penicillin resistant pneumococcal isolate, vancomycin was included in the initial regimen in three cases and was added by 72 hours in all but one, who died less than 48 hours after admission.

Hospital morbidity in relation to antibiotic resistance

Of the 104 previously well cases with medical records available, 91 had pneumococcal isolates that were fully sensitive. Duration of fever was longer in the four cases with intermediate resistance to third generation cephalosporins, two of whom also had high level penicillin resistance (mean of 5 days), compared with 2.5 days for sensitive isolates and 2 days for isolates with intermediate resistance to penicillin only (table 2). Convulsions occurred in 15 cases (15%) before and 29 (28%) after admission, but this did not appear related to antibiotic sensitivity.

Where meningitis was caused by a penicillin non-susceptible isolate, admission to intensive care occurred in 6 /12 (50%) versus 33/91 (36%) cases (OR 1.8; 95% CI: 0.5 to 5.9; $p = 0.36$). There was a non-significant trend to longer mean stay in intensive care (9.5 days) among the four cases with high level penicillin or cephalosporin resistance. Of the 13 deaths, 11 (12.2%) occurred in children with pneumococcal meningitis caused by a fully sensitive isolate and two (20%) with penicillin intermediate resistance. Most deaths (57%) were within three days of admission (one prior to admission, one on day 1, four on day 2, and three on day 3), the remainder up to 19 days later. In those with an underlying illness, two had intermediate resistance to cefotaxime, of whom one received vancomycin and survived; the other died before sensitivities were available.

DISCUSSION

The role of vancomycin in therapy of pneumococcal meningitis is not well established.[24] On the one hand, it is clear that only slightly reduced susceptibility can result in penicillin treatment failure in pneumococcal meningitis. This is because achievable CSF penicillin levels are only just within the required range for effective therapy.[25] Third generation cephalosporins, in contrast, achieve relatively high CSF levels, particularly in the presence of meningeal inflammation, which should exceed the minimal bactericidal concentration for all but highly resistant pneumococci. In individual cases of treatment failure with third generation cephalosporins, vancomycin therapy has been successful.[26 27] However, vancomycin was considered suboptimal therapy for meningitis prior to the emergence of cephalosporin resistant pneumococci, as achievable CSF levels are modest.[28] Consequently, no randomised controlled trials of vancomycin therapy in pneumococcal meningitis are available, and evidence for efficacy of vancomycin is limited to observational studies.[29] An expert committee of the American Academy of Pediatrics concluded, based on the available in vitro and clinical data, that vancomycin should be included in empiric therapy of meningitis following the emergence of cephalosporin resistance among pneumococci. The committee did not agree on whether this recommendation should apply to all presumptive bacterial meningitis or need not be followed when there was convincing evidence of an alternative causative organism.[11] A major factor in this divergence of opinion was lack of data on the sensitivity and specificity of initial CSF parameters for diagnosis of pneumococcal meningitis.

This study provides data from a large population based series of cases on the presenting CSF parameters and severity

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of childhood pneumococcal meningitis in relation to antimicrobial susceptibility. Population based data avoid the biases associated with hospital based series, among which antibiotic resistant or severe cases may be over represented because of referral bias. It is apparent from these data that only 57% of cases have a lumbar puncture performed before parenteral antibiotics are commenced, so initial CSF parameters cannot be used to guide empiric therapy in many instances. However, when an early LP was performed, the Gram stain showed Gram positive cocci resembling pneumococci in 96% of cases, irrespective of prior oral antibiotic therapy. In the two cases where an early LP was done but Gram stain was negative, other CSF parameters were not diagnostically helpful and the CSF appeared macroscopically normal. Bacterial meningitis without CSF abnormalities on initial examination occurs in about 4% of cases overall, more commonly in neonates, and in older subjects with overwhelming infection or severe underlying disease.[15] Among a series of 87 children with meningitis caused by *Haemophilus influenzae* type b, *Neisseria meningitidis*, or *Streptococcus pneumoniae*, two had an initially normal CSF examination, one of whom had pneumococcal meningitis.[30] The lack of effect from oral antibiotic therapy on CSF findings in our study is also in keeping with other reports of bacterial meningitis.[15] Importantly, there was provisional evidence of a pneumococcal bacteraemia within 24 hours of admission in 83% of the 46 cases where LP was deferred or never done, who can be presumed to be more severely ill.

As patients with non-susceptible pneumococci will only be continued on therapy to which the isolate is not fully sensitive in vitro for a maximum of 48–72 hours (prior to laboratory reporting), evaluation of any detrimental effects from discordant antibiotic therapy is limited to the response to empiric therapy.[24] This study did not show any difference in hospital course for meningitis caused by penicillin non-susceptible isolates, although there was a trend towards longer duration of fever among those in the most resistant category. The power to detect a clinically important difference was limited. Five of the six children with cephalosporin resistant isolates (with or without high level penicillin resistance) received vancomycin within 24 hours of admission and a third generation cephalosporin was included in the initial therapy given to all children with pneumococci showing intermediate resistance to penicillin. In this study, there were no cases of meningitis caused by high level cephalosporin resistant pneumococci, though the two cases caused by high level penicillin resistant isolates were associated with intermediate cephalosporin resistance. It may be that such cases are more likely to fail therapy with a third generation cephalosporin. These data, though limited by small numbers of resistant cases, are in accord with other reports of pneumococcal meningitis caused by isolates with intermediate levels of antibiotic resistance only.[1]

When considering recommendations for empiric vancomycin therapy of presumptive bacterial meningitis, there are two major issues—the probability that an episode of meningitis is pneumococcal, and the local prevalence of cephalosporin resistance or high level resistance to penicillin in sterile site pneumococcal isolates.[29] Our data show that when commencement of antibiotic therapy can be postponed until the results of CSF examination are available, a negative Gram stain reduces the probability of pneumococcal meningitis to less than 5%. This means that, unless the prevalence of antibiotic resistance (as defined above) is >20%, the maximum probability of treatment failure with a third generation cephalosporin alone in a case where Gram stain is negative is less than 1% (probability of pneumococcal meningitis 0.05 × probability of high level resistance 0.2). In reality, the probability would be far lower as most Gram stain negative cases are not bacterial. In contrast, if LP is not performed but bacterial meningitis remains part of the differential diagnosis, the probability of pneumococcal meningitis is related to the age and clinical scenario. In most regions with *Haemophilus influenzae* type b (Hib) immunisation programmes, the proportion of childhood bacterial meningitis caused by pneumococci will be at least 30%. This means that the maximum probability of suboptimal therapy without vancomycin (assuming bacterial meningitis is present) will be >1% if the local prevalence of high level penicillin or cephalosporin resistance in pneumococci reaches >3%.

Thus, if early CSF examination is available, the gains from empiric vancomycin therapy in all presumptive bacterial meningitis, as recommended by the American Academy of Pediatrics,[11] seem small based on the lack of evidence of benefit from early vancomycin therapy in other studies[24] and our experience. In contrast, once high level penicillin or cephalosporin resistance emerges in pneumococcal meningitis, inclusion of vancomycin in empiric therapy for presumptive bacterial meningitis seems justified where LP is thought to be contraindicated, if our findings of LP being postponed in over 40% of cases (who have more severe illness) are widely applicable. This does not include the question of dexamethasone use prior to parenteral antibiotics in pneumococcal meningitis, which also has implications for vancomycin penetration into the CSF and disease severity.[31]

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Late post traumatic epilepsy

Estimates of the incidence of late epilepsy after head injury in children have varied considerably, probably because of differences in the populations studied. Rates of below 5% and above 20% have been reported. In Liverpool (RE Appleton and C Demellweek. *Journal of Neurology, Neurosurgery, and Psychiatry* 2002;**72**:669–72) the reported incidences were 0.9% in 1000 children admitted to hospital with head injuries, 3.4% in the 262 referred to the head injury rehabilitation team, and 9% in the 102 children who needed rehabilitation. The children referred to the rehabilitation team were followed up for periods varying from 19 months to 7 years.

Late post traumatic epilepsy occurred in 9 of the 102 children who received inpatient rehabilitation but in none of the others. Of the 102 children 90 had been admitted to the paediatric intensive care unit and 87 had needed mechanical ventilation. The nine children who developed late post traumatic epilepsy were aged 1.3–13.6 years at the time of head injury and the latent period between head injury and onset of late post traumatic epilepsy varied between 0.7 and 5.1 years. All had complex partial seizures or secondarily generalised tonic-clonic seizures or both and two also had simple partial sensory seizures. Four had hemiplegia and one tetraplegia. Five had learning difficulties and three behaviour difficulties. Only one child was neurologically normal and had neither learning nor behaviour problems. Seven had an abnormal EEG after the onset of late post traumatic epilepsy. MRI showed focal changes in four children, multifocal changes in three and was normal in two.

Ten of the 102 children had tonic-clonic seizures in the first week after injury, two of them immediately (within minutes) after injury. Three of the 10 (but neither of the two with immediate seizures) developed late post traumatic epilepsy. Fifteen children had either episodes of stiffening or paroxysmal autonomic changes in the first week but none of these developed late post traumatic epilepsy during the period of follow up. Two factors were significantly associated with the development of late posttraumatic epilepsy; they were early tonic-clonic seizures and low Glasgow coma scale score (<8) when first seen.

Late post traumatic epilepsy is not common even after severe head injury. First week tonic-clonic seizures and low initial Glasgow coma scale score increase the risk.

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