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High mortality of invasive pneumococcal disease compared with meningococcal disease in critically ill children

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Abstract *Objective:* To ascertain outcome, patterns of disease, incidence of concurrent infection, superinfection and penicillin resistance in children requiring intensive care for *Streptococcus pneumoniae* infection and compare it to a similar disease pattern, namely *Neisseria meningitidisb* infection. *Design and setting:* Prospective cohort study in a regional paediatric intensive care unit (PICU). *Patients and participants:* Children with invasive pneumococcal and meningococcal disease requiring intensive care. *Measurements and results:* The study included 22 children with invasive pneumococcal disease (IPD), median age 14 months (interquartile range 3–52), median Paediatric Index of Mortality (PIM) 0.051 (0.028–0.066), median length of PICU stay 8.5 days (4–13). Four patients died, three (13.5%) attributable to IPD. Incidence of concurrent infection 27%. There were no superinfections. All *S. pneumoniae* were sensitive to cefotaxime; one isolate (3.7%) was resistant to penicillin. There were 186 children with meningococcal disease (MD), with a higher PIM (median 0.068, 0.033–0.108), older age (29 months, 10.7–77.9) and shorter length of PICU stay (median 3 days, 2–6). Eight (4.3%) children died from MD. Incidence of concurrent and superinfection was 18% and 6%, respectively in children with MD. All *N. meningitidis* cases were sensitive to cefotaxime and penicillin. The standardized mortality ratio was considerably higher with IPD (2.0) than with MD (0.52). *Conclusions:* In invasive pneumococcal disease preventative measures including early recognition, immediate antibiotic therapy and vaccination need to be taken in the community, similar to the control of meningococcal disease. Invasive pneumococcal disease should command the same respect as meningococcal disease.

Keywords Aerobic Gram-negative bacilli · Critically ill children · Methicillin-resistant *Staphylococcus aureus* · *Neisseria meningitidis* · Paediatric intensive care · *Streptococcus pneumoniae*

Introduction

Streptococcus pneumoniae is common in the mucosa of the nasopharynx and throat of healthy children, at rates of 7–99% depending on health, socio-economic status, study population and the patient's age, tending to decrease with increasing age [1, 2]. In contrast, carriage rates for *Neisseria meningitidis* are 10–25% in teenagers and adults, with a decreasing incidence with decreasing age [3]. *S. pneumoniae* is one of the most pathogenic microorganisms. It causes not only upper respiratory tract infections such as conjunctivitis, otitis media, sinusitis and bronchitis but also invasive pneumococcal disease (IPD), including pneumonia, septicaemia and meningitis. The pathophysiology of *S. pneumoniae* is similar to that of *N. meningitidis* [3, 4, 5]. The mortality rate of IPD in chil-

Table 1 Demographic and clinical characteristics of the paediatric intensive care patients with invasive pneumococcal disease (*IPD*) and meningococcal disease (*MD*), 1 January 1999–1 October 2003 (*IQR* interquartile range, *PIM* Paediatric Index of Mortality)

	IPD (*n*=22)	MD (*n*=186)	*p*
Sex: M/F	55%/45%	57%/43%	0.8[b]
Admissions	24	186	
Age, median (months; IQR)	14 (3–52)	29 (10.7–77.9)	<0.001*
Length of stay, median (days; IQR)	8.5 (4–13)	3 (2–6)	<0.001*
Mechanically ventilated	100%	80.1%	<0.001[b]
Inotropic support	50%	63.4%	0.03[b]
PIM, median (IQR)	0.051 (0.028–0.066)	0.068 (0.033–0.108)	0.02*
Actual mortality	4 (18.2%)[c]	8 (4.3%)[d]	0.03[b]
Time to death, median (days; (IQR)	8 (5–13)	2.5 (1–3)	0.02*
PIM predicted mortality	1.5 (7%)	15.3 (8.2%)	
Standardized mortality ratio[e]	2.0[f]	0.52[g]	

[a] Wilcoxon-Mann-Whitney test
[b] Fisher's exact test
[c] Attributable mortality: 3 (13.5%)
[d] Odds ratio (IPD–MD)=4.3 (95% confidence interval 1.4–12.9)
[e] Standardized mortality ratio=attributable mortality/PIM-predicted mortality
[f] 95% CI: 0.41–5.85
[g] 95% CI: 0.23–1.03

dren varies between 1% and 11.8% [6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. This is similar to the experience with meningococcal disease (MD) [16]. Analogous to MD, there is a characteristic seasonable distribution for IPD, with a peak incidence during the winter/spring months [3, 6]. Likewise, viral infections are known to be immuno-suppressive and pave the way for bacterial co-infections due to *N. meningitidis* and especially *S. pneumoniae* [6, 17]. A recent European surveillance study on resistant *S. pneumoniae* isolates from blood and cerebrospinal fluid (CSF) shows that penicillin resistance varies widely, with the highest incidence in Spain with 11%, followed by Belgium, Ireland and the United Kingdom with 4%, and less than 1% in The Netherlands, Germany and Scandinavia [18, 19]. The highest incidence of penicillin-resistance is generally observed in children, especially those with upper respiratory tract infections, who have often received multiple courses of antibiotics [18, 20].

A prospective observational cohort study was undertaken in children with IPD requiring intensive care to ascertain outcome, concurrent and superinfection, and penicillin-resistance amongst *S. pneumoniae*, and compare it to *N. meningitidis* infection which has a similar disease and clinical pattern.

Patients and methods

Setting

The study was undertaken on a paediatric intensive care unit (PICU) at the Royal Liverpool Children's Hospital, United Kingdom, a university-affiliated, multi-disciplinary, regional referral centre. The PICU is a 20-bedded facility with an annual admission rate of 1000 children.

Patients

A prospective observational cohort study of children admitted into PICU with IPD or MD between 1 January 1999 and 1 October 2003 (56 months). The study was approved by the Institutional Ethics Review Board. IPD was defined by the isolation of *S. pneumoniae* from normally sterile body fluids, for example, blood, CSF and lower airway secretions, with laboratory and clinical parameters of severe sepsis [21]. Meningococcal disease was diagnosed on the isolation [culture and/or polymerase chain reaction (PCR)] of *N. meningitidis* from blood or CSF (rarely) and clinical parameters of infection. Of the 4,710 PICU admissions during the study period 23% fell into the category of septicaemia, meningitis/encephalitis or pneumonia, and no causative pathogen was identified in 3.9% of the total PICU population (46 with septicaemia, 26 with meningitis, 112 with pneumonia).

The demographic and clinical characteristics of patients in the IPD and MD groups are summarized in Table 1. In the IPD group the median length of stay was 8.5 days (IQR 4–13) and that of survivors 9 days (4–16). One IPD patient developed renal failure requiring dialysis due to haemolytic uraemic syndrome as a consequence of IPD. Three children with pneumococcal respiratory infections had underlying neurological co-morbidity (muscular dystrophy, transverse myelitis, subacute necrotizing encephalomyelopathy). *S. pneumoniae* was isolated from the 22 patients in the following sites: blood (*n*=7), blood and CSF (*n*=2), CSF (*n*=3), lower airway secretions (*n*=7), pneumococcus and respiratory syncytial virus (RSV) in lower airway secretions (*n*=3). All the patients fulfilled the 2001 Consensus Conference definition of severe sepsis or septic shock. There were no differences in outcome, inflammatory markers, PIM or inotropic requirement according to the site of positive microbiological culture. In children with MD all microbiological diagnoses were made on blood results, apart from three on CSF. Only two children with MD had underlying neurological co-morbidity (hydrocephalus).

Endpoints

The endpoints were: (a) mortality, (b) inflammation markers [C-reactive protein (CRP), leucocytes and platelets, (c) concurrent and superinfections and (d) antibiotic sensitivity.

Clinical management of severe pneumococcal and meningococcal infections

Corticosteroids were used in patients with meningitis, as well as in children with septic shock who did not respond to the treatment. No novel/experimental therapies, for example, activated protein C and tissue plasminogen activator, were used in either group.

Microbiology

Diagnostic samples of blood, lower airway secretions and CSF were taken on clinical indication. Surveillance samples of throat and rectum were obtained on admission and then twice weekly. The diagnostic samples of blood, lower airway secretions and CSF were inoculated onto universal media of blood and chocolate agar [22]. All diagnostic samples for *N. meningitidis* were sent for PCR. The sensitivity of all isolates was tested using the E-test [23]. *S. pneumoniae* isolates were not serotyped unless penicillin-resistant [24]. RSV nasopharyngeal aspirates were tested by the Directigen RSV test (Becton Dickinson, Maryland, USA), an in vitro enzyme-linked immunosorbent assay (ELISA) membrane test for RSV antigen [25]. Surveillance samples of throat and rectal swabs were processed qualitatively and semi-quantitatively to detect the level of carriage of potential pathogens [26].

Antibiotic policies

Patients with signs of infection received intravenous cefotaxime (150 mg/kg per day in four doses for up to 7 days) as first-line therapy for 48 h whilst awaiting culture results. Clinical status on presentation governed whether supplementary intravenous cover with an aminoglycoside, gentamicin (7.5 mg/kg per day in three doses for up to 7 days) was added. Once the causative microorganism was confirmed as *S. pneumoniae* or *N. meningitidis* gentamicin was discontinued. When the surveillance samples revealed abnormal flora including aerobic Gram-negative bacilli (AGNB) selective decontamination of the digestive tract (SDD) using enteral polymyxin, tobramycin and amphotericin B was administered in order to prevent superinfections [27].

Definitions

Internationally accepted definitions were utilized for infections, sepsis and abnormal carriage [21, 26, 27, 28].

Analytic methods

Data were collected prospectively. Prediction of mortality using the Paediatric Index of Mortality (PIM) was obtained on the patient's first contact with the PICU team [29]. Results are expressed as a fraction of the total study population, median with inter-quartile range (IQR), mean with standard deviation, 95% confidence interval, or standard error of the mean. Continuous data were analysed using Student's *t* test or the Wilcoxon-Mann-Whitney test. Categorical data were analysed using Fisher's exact test. Correlations were assessed using Spearman's rank test (two-tailed). Kinetic data were studied with two-way analyses of variance for repeated measurements with Bonferroni's correction for post hoc analysis. Statistical calculations were performed with the Statistical Program for Social Science release 11.0.0 (Chicago, Ill., USA). A *p* value

less than 0.05 was considered statistically significant. The standardized mortality ratio (SMR) defined as the actual or attributable mortality divided by the PIM-predicted mortality was calculated for each group.

Results

Mortality

Four patients who were positive for *S. pneumoniae* died, with IPD being the cause of death in three children (13.5%). One patient died on day 5 of treatment on PICU from cerebral oedema due to pneumococcal meningitis complicated by cerebritis. One patient admitted with pneumococcal septicaemia died on day 4 of multiple organ systems failure. Pneumococcal pneumonia was the cause of death due to respiratory failure in a patient with Duchenne's muscular dystrophy on day 11. A patient with 75% burns died on day 19 from multiple organ system failure, which was not associated with an earlier pneumococcal lower airway infection. A post-mortem examination found pulmonary haemorrhages as part of disseminated intravascular coagulation, but no evidence of lung infection. All eight deaths in the MD group were due the *N. meningitidis* infection. Four children died from fulminant cardiovascular collapse and one each from cerebral oedema, pulmonary haemorrhage, acute respiratory distress syndrome, multiple organ systems failure.

There were no differences in age, PIM, or even length of PICU stay between the survivors and non-survivors in either the IPD or the MD group (all *p* values >0.34), but numbers were small with IPD. Death occurred earlier in MD than IPD (*p*=0.02; Table 1). Death was correlated to inotropic requirement in MD (*p*=0.03), but not in IPD (*p*=0.2). There was no association between age and death in those with IPD (*p*=0.15), with MD (*p*=0.52), or when both groups were analysed together (*p*=0.33).

Inflammatory response

CRP levels, white blood cell count (WCC) and platelets count of the children with IPD compared to those with MD over the course of their PICU stay are shown in Figs. 1, 2 and 3, respectively. There were no differences in the inflammatory markers over the course of their PICU stay between survivors and non-survivors in either the IPD or the MD groups (all *p* values >0.15), but numbers were small with IPD. There was no correlation between admission WCC and death in either IPD (*p*=0.79) or MD (*p*=0.61). The prevalence of leucopaenia, defined as WCC lower than 4×10^9/l on PICU admission, was 19.2% and 12.4% in the IPD and MD populations, respectively, but there was no difference in admission WCC between groups (*p*=0.72).

Fig. 1 Temporal profile of C-reactive protein (*CRP*) levels of critically ill children with invasive pneumococcal disease compared to those with meningococcal disease (mean, standard error of the mean). The number of patients (*n*) in each group on admission, at 48 h and at 96 h is shown. **p=0.001 (Bonferroni's method: *p*<0.016)
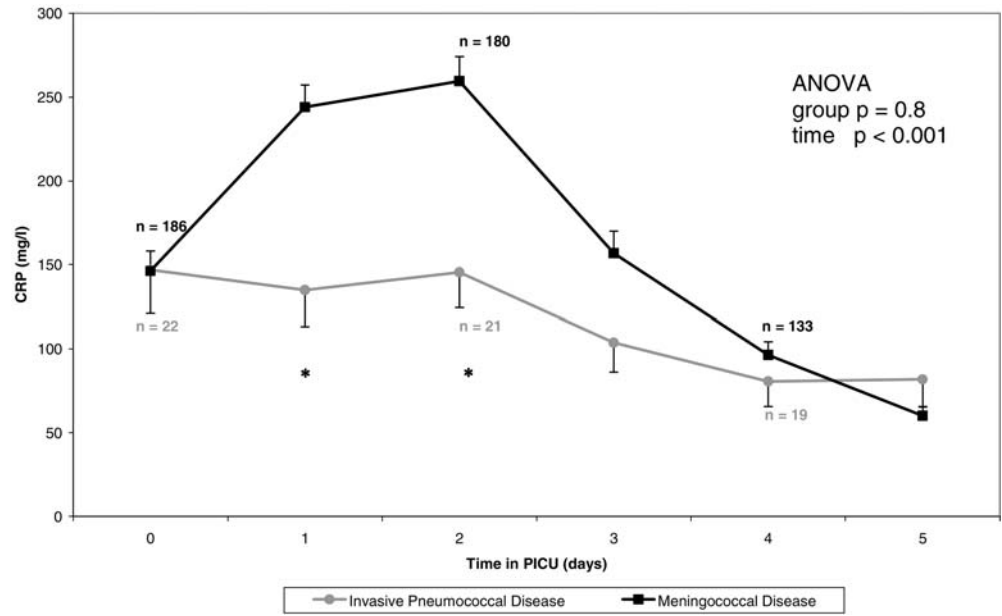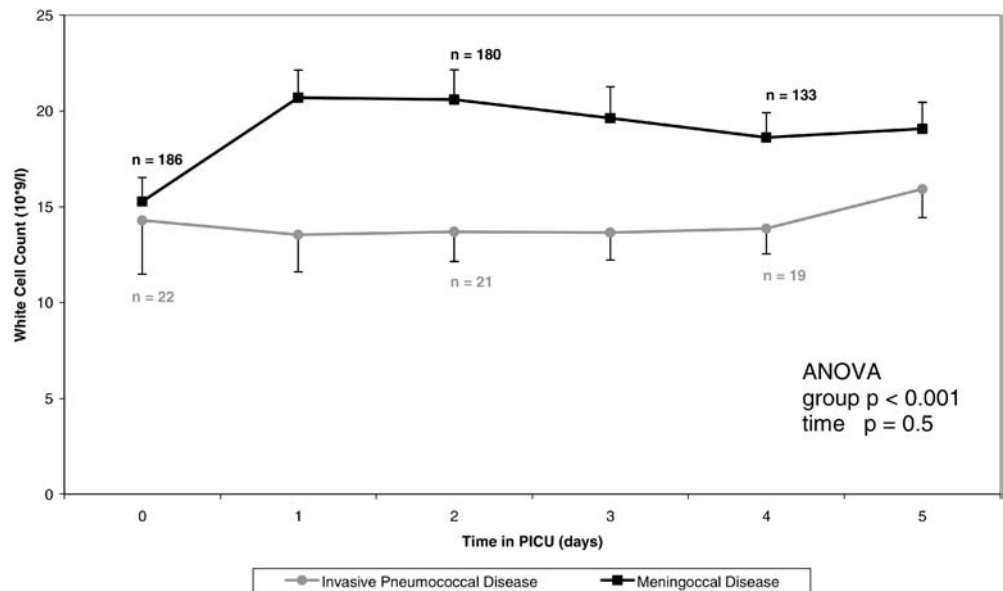

Fig. 2 Temporal profile of the white cell count in critically ill children with invasive pneumococcal disease compared to those with meningococcal disease (mean, standard error of the mean). The number of patients (*n*) in each group on admission, at 48 h and at 96 h is shown


Concurrent and superinfection

All patients were admitted with *S. pneumoniae*, demonstrating that the infection developed in the community (i.e. imported into PICU). The incidence of concurrent infection was high (27%) in the IPD group. Three children had one other primary endogenous infection, two due to *Pseudomonas aeruginosa* and one due to *Moraxella catarrhalis*. Three children had a concurrent viral (RSV) infection. There were no bacterial or fungal superinfections (secondary endogenous or exogenous). One child (4.2%) acquired RSV bronchiolitis while on PICU. In contrast, in the MD group the incidence of concurrent

infection was 17.8% (one-half bacterial and one-half viral), of bacterial superinfection 5.9%, and 5.8% acquired a viral infection (RSV or parainfluenza). There was no significant difference in concurrent infection rate between groups (*p*=0.57).

Abnormal flora on admission

In the IPD group 43% were admitted with abnormal AGNB in throat and/or gut surveillance swabs, compared to 45% in the MD group. *Klebsiella*, *Enterobacter*, *Citrobacter* and *P. aeruginosa* were the predominant ab-

Fig. 3 Temporal profile of the platelet count in critically ill children with invasive pneumococcal disease compared to those with meningococcal disease (mean, standard error of the mean). The number of patients (*n*) in each group on admission, at 48 h and at 96 h is shown
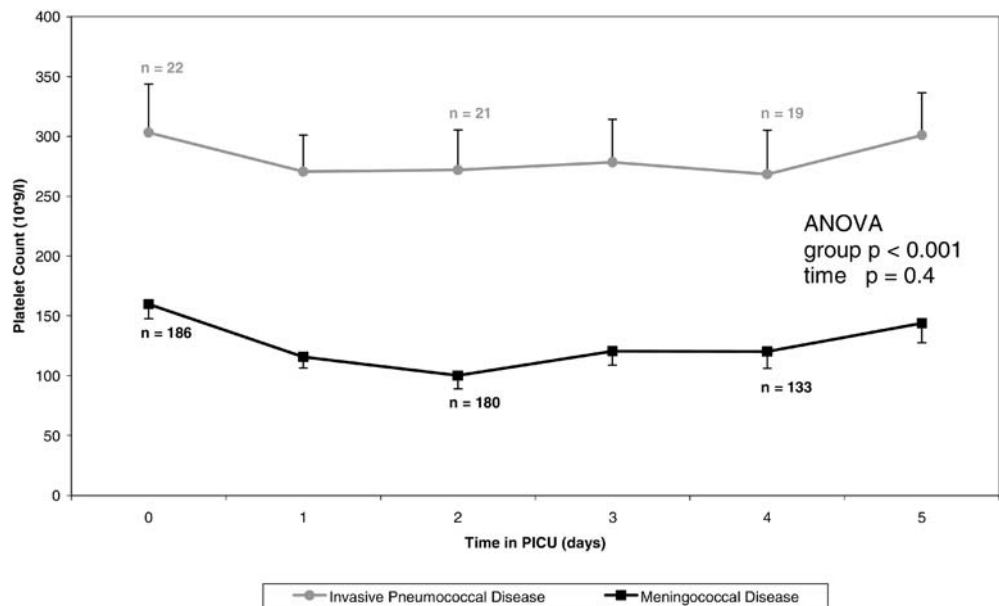
normal AGNB. One IPD patient was a carrier of methicillin-resistant *Staphylococcus aureus* (MRSA).

Antibiotic susceptibility

Twenty-seven isolates were obtained from the 22 patients with IPD, all of which were sensitive to cefotaxime, the first choice of treatment. No isolates were resistant to the macrolides and glycopeptides. Two isolates were resistant to ciprofloxacin and one was intermediate for ciprofloxacin. One isolate (serogroup 9; 3.7%) obtained from lower airway secretions was resistant to penicillin. There was no penicillin resistance in the MD group.

Discussion

Four findings emerge from this prospective comparative cohort study between IPD and MD children requiring paediatric intensive care: (a) The crude mortality was 18.2% and the mortality due to IPD was 13.5%, which was higher than the comparative MD group (4.3%). (b) Inflammation markers in IPD were high during the first week of treatment on PICU but were lower in the first 3–4 days than the children with MD. (c) The concurrent infection rate (27%) was similar to the comparative MD group (17.8%), but there were no superinfections. (d) Penicillin-resistance was not a problem amongst either *S. pneumoniae* or *N. meningitidis* isolates.

In this study although there were four deaths, only three children died on the PICU due to IPD, giving an attributable mortality of 13.5%. This is similar to the mortality quoted in the literature [6, 7, 8, 9, 10, 11, 12, 13,

14, 15, 16]. However, it was appreciably higher than the comparative group with MD (4.3%). Age may have played a role, as the children with IPD were younger than their counterparts with MD (median 14 vs. 29 months old, *p*<0.001), but no correlation was observed. Perhaps the IPD group had a more severe and protracted disease course than the MD patients, as suggested by their longer length of stay in the PICU (median 8.5 vs. 3 days, *p*<0.001) and more required mechanical ventilation (100% vs. 80.1%, *p*<0.001). On the other hand, more children required inotropic support with MD (63.4% vs. 50%, *p*=0.03). Additionally, on admission to PICU the risk of death (PIM) was higher in the MD group (*p*=0.02). The use of SMR should calibrate for disease severity and allow comparison between groups and units [30, 31, 32, 33, 34, 35]. The SMR was different, at 2.0 and 0.52 for IPD and MD, respectively.

The severe generalized inflammation status in both IPD and MD patients often lasted for more than 1 week, but did not explain the basis for IPD patients performing worse than their MD counterparts. On the contrary, the MD patients had a more intense initial inflammatory response and similar ongoing response, and yet still fared better. Figures 1 and 2 show that the CRP and WCC were significantly higher in the MD than the IPD group. The platelets were significantly lower due to endotoxin release by *N. meningitidis* than in the IPD group (Fig. 3) [36]. Conceivably the MD group had a better outcome because of better initial, early management. Certainly in the United Kingdom over the past 5–10 years there has been heightened public and medical awareness of MD. This has most probably impacted on earlier recognition and therefore earlier appropriate management and treatment of the disease [37, 38].

Although concurrent infection may have adversely affected the IPD group, the incidence was no greater than in the MD group. There were six patients in the IPD group with concurrent infections, three viral and three bacterial, and this is in line with two recent studies on community acquired pneumonia and sepsis in hospitalized children [39, 40]. The intense inflammation response causing a profound immunosuppression during the first week is a likely cause for these concurrent primary endogenous infections with micro-organisms present in the admission flora [26].

Illness severity is a well described independent risk factor for abnormal carriage of AGNB and MRSA [41]. The two groups had similar abnormal carriage rates (IPD 43% and MD 45%), indirectly suggesting similar disease severities on PICU admission. Yet one group fared substantially better. The intense inflammation status associated with invasive infections promotes acquisition and subsequent carriage of hospital flora including AGNB and MRSA [42, 43]. An abnormal carrier state may lead to superinfections and associated mortality in the subset of ventilated patients with ongoing immune suppression [42, 43]. There was a low superinfection rate in our study in both groups. In our unit a policy of restrictive antibiotic usage and SDD using enteral antimicrobials as a technique to eradicate abnormal carriage may have played a role in minimizing superinfections [44]. Previous studies have suggested that mortality in IPD is related to superinfections [17, 42], but this did not play a role in this IPD study group. Only one isolate (3.7%) was resistant to penicillin whilst cefotaxime, the drug of first choice, was invariably active. It is therefore unlikely that penicillin-resistance amongst *S. pneumoniae* impacted on outcome in our study. A recent prospective study in severely ill adults with pneumococcal bacteraemia showed that combination antibiotic therapy improved survival over monotherapy [45]. Many of our IPD patients had received combination antibiotic therapy (cefotaxime and gentamicin) initially which was later rationalized to monotherapy once cultures and sensitivities were available. Unfortunately the numbers were too small to address this aspect. Similarly the sample size was too small to determine a correlation with regards to corticosteroid therapy and outcome [46].

All the cases of IPD had clinical and laboratory evidence of widespread sepsis and fulfilled criteria for severe sepsis or septic shock [21]. The low number of cases with microbiologically confirmed IPD in this study may be an underestimate. A considerable number of the sepsis cases with an unidentified pathogen (3.9% of the PICU population) may have been caused by *S. pneumoniae*, as during most of the study period only culture techniques were used to diagnose IPD. Molecular techniques including PCR may improve the diagnosis of IPD and increase the number of IPD cases identified, as commonly used antimicrobials given in the community and the referring hospital render clinical samples of blood, tracheal aspirate and CSF sterile. PCR was routinely used to confirm MD cases. Added to this, MD's more clearly definable clinical signs (especially the purpuric rash) allowed it to be considered more readily.

It can be argued that the relative paucity of exposure to IPD as opposed to MD within the unit could have influenced the treatment and therefore the mortality. It has been recognized in medical practice that improvement in outcome may reflect a relationship between quantity and quality [32, 33, 34, 35]. However, experience within the PICU with critically ill children with sepsis is substantial (over 200 cases per year), and therefore lack of exposure is unlikely to play a major role.

The sample size may be a limitation in this study. Although the prospective study covered a long period (56 months), only 24 admissions (22 children) with microbiologically confirmed IPD were diagnosed. This utilization of only culture-confirmed pneumococcal disease cases may also have limited the study. The small sample size of 22 children requiring intensive care including mechanical ventilation for IPD compared to 186 children with MD may unfavourably bias this comparison, but the difference in outcome speaks for itself. Serogrouping of *S. pneumoniae* isolates was not routinely performed, and we were therefore unable to specify which serogroups were common to our study population.

Recent studies have demonstrated substantial declines in the number of cases of IPD following the introduction of a polyvalent pneumococcal vaccine [47, 48]. Pneumococcal vaccination is not routinely used in the United Kingdom. The age of the children with IPD in this study (median 14 months, IQR 3–52) reveals that most would have benefited from vaccination. Early recognition and earlier, more pro-active aggressive treatment of MD at base hospitals/healthcare centres has improved mortality in those presenting to PICU [37, 38]. Perhaps this approach would impact on IPD similarly.

Conclusion

IPD and MD show clinical similarities. Despite the absence of resistance and superinfections developing during intensive care treatment, the mortality and SMR in those with IPD was still much higher than in those MD. We believe that IPD should command the same respect and be treated in an identical way as MD, i.e. prevention in the community, including vaccination and immediate antimicrobials [18, 49, 50].

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