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Original article

Clinical aspects and cost of invasive *Streptococcus pneumoniae* infections in children: resistant vs. susceptible strains

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Abstract

Invasive *Streptococcus pneumoniae* infections in children are associated with serious consequences in terms of morbidity and mortality. The main objective of the study was to determine if invasive infections caused by penicillin-resistant *Streptococcus pneumoniae* (PRSP) differed in clinical presentation, outcome, risk factors, or cost from those caused by penicillin-susceptible strains (PSSP) in children. All patients aged 18 or less with invasive *Streptococcus pneumoniae* infections admitted to two teaching hospitals in Montreal between 1989 and 1998 were included in the study. We present a case–control study in which for each index case of PRSP, 3 controls with PSSP infections were matched for age, sex, and site of infection. One hundred and forty-four patients were included in the analysis (36 cases, 108 controls). There was no difference between the two groups in terms of initial clinical presentation (vital signs, laboratory results) or total length of stay. Mortality was 2.7% in both groups. Hospital antibiotic cost was higher in the PRSP group (211 Canadian dollars (CAD) vs. 74 CAD; $P = 0.02$). Antibiotic consumption in the preceding month was significantly associated with PRSP infection. Underlying diseases or day-care attendance were not shown to be significant risk factors for acquiring invasive PRSP infection. There were no differences between invasive infections caused by PRSP and PSSP in terms of clinical presentation, morbidity or mortality in a paediatric population.

Keywords: *Streptococcus pneumoniae*; Penicillin resistance; Meningitis; Bacteraemia

1. Introduction

Streptococcus pneumoniae is a major cause of pneumonia as well as the leading cause of bacterial meningitis, bacteraemia and otitis media in children [1]. Serious invasive infections occur more commonly in children younger than 2 years of age and may have important consequences in terms of morbidity and mortality [2].

The increasing prevalence of penicillin-resistant strains of *S. pneumoniae* worldwide is of growing concern. Increased cost of therapeutic alternatives to penicillin need to be evaluated, as does the question of morbidity associated with the emergence of resistance. Some studies have reported that the clinical presentation and outcome of infections caused by penicillin-resistant *Streptococcus pneumoniae* (PRSP) and penicillin-sensitive (PSSP) strains of *S. pneumoniae* were similar [3–11]. The cost of PRSP invasive infections has not been previously evaluated in children.

A retrospective matched case–control study was undertaken to determine if invasive infections caused by PRSP or PSSP in children differed in risk factors, clinical presentation, costs of treatment or outcome.

2. Material and methods

2.1. Patient selection

All patients aged 18 years or less who presented to the emergency room or who were admitted to one of two

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tertiary care teaching hospitals in Montreal, Canada with invasive *S. pneumoniae* infections between 1989 and 1998 were eligible. The patients were identified via the microbiology laboratory records. Those who had a positive culture for *S. pneumoniae* from a normally sterile body fluid and whose strains were still available in the microbiology laboratory at the time of the study were included.

2.2. Case and control definitions

2.2.1. Case

Patient infected with *S. pneumoniae* with a minimal inhibitory concentration (MIC) for penicillin of $\geqslant 0.12$ mg/l. Non-susceptible strains were defined as having an MIC of 0.12–1 mg/l and resistant strains defined as having an MIC of $\geqslant 2$ mg/l.

2.2.2. Control

Patient infected with *S. pneumoniae* with MIC for penicillin of $\leqslant 0.06$ mg/l. For each index case identified, 3 controls were matched according to sex, site of positive culture (blood only or CSF and blood) and age. Cases were matched to the closest controls in terms of age.

2.2.3. Clinical information

Charts from cases and controls were retrospectively reviewed. Information collected included age, sex, initial presentation (temperature, heart and respiratory rates, oxygen saturation, peripheral white blood cell count), clinical course (time to defervescence, admission to intensive care unit (ICU), length of stay (LOS) in ICU and total LOS, antibiotics received), risk factors (documentation in the admission record of use of antibiotics in preceding month, day-care centre attendance and underlying diagnosis), diagnoses on discharge and mortality. Serotypes of the isolates were also recorded when available.

2.3. Cost calculation

Hospital costs were calculated using data obtained from the Quebec Ministry of Health (SOFI system, Système Opérationnel et Financier Informatisé). The following mean daily costs were used: admission to ICU: 500 Canadian dollars (CAD), admission onto a general paediatric ward: 180 CAD per day. Antibiotic costs were calculated according to the hospital's pharmacy price list. Cost of administration of each dose of intravenous antibiotic was estimated to be 5 CAD (tubing, nursing, pharmacy). Only the cost of parenteral antibiotics provided by the hospital was taken into account. Costs of emergency and of outpatient visits, and physicians fees were not included. Hospital and antibiotics costs were stable within the study period, no significant increases were noted, mostly due to government controlled prices.

2.4. Antimicrobial susceptibility testing

MIC testing was carried out for all strains by broth microdilution as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) guidelines [12].

2.5. Data analysis

Student's *t*-test and Wilcoxon rank sum test were used for comparison of means and medians when appropriate. All *P*-values were two-sided. Proportions were compared using chi-square and risk factors were analyzed using Mantel-Haenszel matched odds ratio using Epi-Info (version 6.0, CDC, Atlanta, USA).

3. Results

3.1. Description of cases

Thirty-six cases (24 with intermediate resistance to penicillin, 12 with high level resistance) and 108 controls were included in the study. The distribution of available serotypes for both PRSP and PSSP are described in Table 1. Seventy-two percent of the serotypes in the PRSP group are included in the heptavalent pneumococcal conjugate vaccine compared with 82% of the serotypes in the PSSP group. All resistant strains with an MIC > 1 mg/l were also resistant to cefuroxime; 4/12 (33%) were resistant to erythromycin and clarithromycin, and none were resistant to levofloxacin, or moxifloxacin. All strains were sensitive to ceftriaxone.

The cases had a mean age of 3.08 years (range: 0.4–13.8 years, median: 1.94 years). The controls had a mean age of 2.88 years (range: 0.32–17.19, median: 1.74). Both groups had a male to female ratio of 1:1.11. All 36

Table 1
Serotypes of penicillin-resistant and -sensitive *S. pneumoniae*

Serotypes	PRSP (%)	PSSP (%)
4	0	6 (5.6)
6B	5 (13.8)	17 (15.7)
9V	5 (13.8)	3 (2.8)
14	6 (16.7)	34 (31.5)
18C	0	10 (9.3)
19A	4 (11.1)	1 (0.9)
19F	2 (5.6)	11 (10.2)
23F	8 (22.2)	7 (6.5)
Others	1 (2.8)	13 (12.0)
Unavailable	5	6

cases had a positive blood culture and CSF was also positive in 3 cases. There were no differences in the proportions of cases and controls by years during the study period.

3.2. Clinical events

All cases and controls were seen in the emergency room and had similar initial presentations upon arrival (Table 2). Diagnoses on discharge were similar in both groups. Bacteraemia with no other focus of infection was diagnosed in 36% of the cases compared with 39% of the controls. The second most frequent diagnosis was pneumonia occurring in 33% of the cases and 27% of the controls (Table 2).

Cases and controls had similar time to defervescence with means of 1.6 and 1.9 days, respectively. The percentage requiring hospital admission was similar in both groups, as was the length of hospital stay, proportion admitted to ICU, and days of ICU stay (Table 2). The proportion of the hospital days spent in the ICU was higher for the cases group (0.2 vs. 0.09, $P < 0.01$). If one patient with a 33 days ICU-stay was removed from the analysis, the difference was non-significant. This patient remained in the ICU for reasons unrelated to pneumococcal infection. One death oc-

Table 2
Clinical picture, empirical antibiotics used and previous antibiotics consumption

	Cases	Controls	
Clinical picture			
Number	36	108	
Initial temperature (°C)[a]	39.6 (37.8–41)	39.7 (37.2–41.6)	
Respiratory rate (per min)[a]	34 (20–60)	37 (18–84)	
Heart rate (bpm)[a]	132 (32–180)	144 (100–200)	
Pulse oxymetry (%)[a]	93.1 (56–100)	95.3 (86–100)	
WBC ($\times 10^9$/mm^3)[a]	22.8 (2.2–39.3)	23.0 (0.1–74.3)	
Patients with WBC $> 20 \times 10^9$ (%)	21 (60%)	58 (54%)	
Temperature back to normal (days)[b]	1.6 (0–8, 1)[b]	1.9 (0–13, 1)	
Deaths	1	3	
Patients not admitted (%)	10 (28%)	37 (34%)	
Total length of stay (days)[b]	6 (0–58, 4)	5 (0–58, 2)	
ICU stay (days)[b]	1.2 (0–33, 0)	0.4 (0–13, 0)	
Patients admitted to ICU (%)	4 (11%)	11 (10%)	
Length of stay in ICU if admitted to ICU (days)[b]	10.75 (1–33, 4.5)	4.18 (1–13, 2)	
ICU day/admission day	0.20	0.09	$P < 0.0001$, OR = 2.6 (95% CI: 1.62–4.19)
Diagnoses on discharge			
Bacteremia alone	13 (36.1%)	42 (38.9%)	
Pneumonia	12 (33.3%)	29 (26.9%)	
Meningitis	4 (11.1%)	9 (8.2%)	
Acute otitis media	1 (2.8%)	6 (5.6%)	
Sinusitis	2 (5.6%)	8 (7.4%)	
Cellulitis	3 (8.3%)	12 (11.1%)	
Bone/joint infection	1 (2.8%)	2 (1.9%)	
Empiric antibiotic used			
Cefuroxime	10 (28%)	36 (33%)	
Ceftriaxone	16 (44%)	32 (30%)	
Amoxycillin	3 (8%)	19 (18%)	
Pencillin	2 (6%)	7 (6%)	
Other	4 (11%)	12 (11%)	
None	1 (3%)	2 (2%)	
Antibotics used in previous month			
Total (%)	18 (50%)	15 (14%)	OR = 5.75 (95% CI: 2.18–15.16)
Pencillins	6	3	
Cephalosporins	1	3	
Macrolides	2	1	
TMP-SMZ	7	4	
Unknown	2	4	

[a] Mean (range).
[b] Mean (range, median).

curred among the cases and 3 in the controls. All deaths occurred in patients with bacteraemia without identified focus. All had an underlying co-morbid condition: acute leukaemia (2), extreme prematurity (1) and sickle cell anaemia (1). Upon discharge from hospital, 6 of 9 patients with meningitis had a documented hearing loss (4 with severe and 2 with mild deficit). Only one of these patients had an infection with PRSP. All other patients without meningitis had a good outcome.

There was no statistically significant difference in initial empiric antibiotic therapy (Table 2). Five of 36 cases (13.9%) were initially treated orally and 1 case was never treated. Cases who received penicillin or oral antibiotic therapy as initial treatment did not experience any adverse event because of delay in appropriate treatment. Twelve cases had *S. pneumoniae* with MIC to penicillin $\geqslant 2$ mg/l. Of those, 6 cases received a third generation cephalosporin while the remaining 6 cases received various antibiotics: ampicillin (2), penicillin G (1), cefuroxime (3) as initial empirical therapy. Six cases that were initially suboptimally treated, all had bacteraemia and no meningitis. All had a good outcome and only one case not receiving a third generation cephalosporin had his therapy changed to a third generation cephalosporin when the penicillin MIC was known.

All costs are in CAD (1 CAD = 0.7 USD). The cost for antibiotics alone was determined for both groups. The case average cost for antibiotic therapy was three times that of the cost for controls: 211.42 CAD (median 55.10 CAD, range 0–1856.50) for the cases and 74.65 CAD (median 28.0, range 0–868.95) for controls ($P = 0.02$). The patients with PRSP were more likely to have received ceftriaxone and the patients with PSSP were more likely to have received penicillin as definitive treatment. Only 6 cases (3 with meningitis) and 9 controls (5 with meningitis) received vancomycin as initial therapy. The total costs including hospitalization and antibiotics was greater for the cases but did not reach statistical significance: 1668.60 CAD (median 744.98) for cases and 1087.60 CAD (median 387.55) for controls ($P = 0.18$).

3.3. Risk factors

The proportion of children less than 5 years of age who attended day-care centres were similar in the cases and the controls (10/29 or 24% of cases vs. 18/84 or 21% of controls). The percentages with underlying medical conditions were also similar. Eight of 36 (22%) of cases and 25/108 (14%) of controls had previous medical conditions. These conditions were asthma, sickle cell anaemia, HIV, transplants, splenectomy, congenital heart disease, and neoplasm.

Documented antibiotic use in the month preceding presentation differed between the groups (Table 2). Fifty percent of the cases compared with 14% in the controls had received antibiotics (OR = 5.75, 95% CI: 2.18–15.16). The numbers were too small to determine the significance of class of antibiotic received.

4. Discussion

Resistance rates in *S. pneumoniae* isolates from the respiratory tract vary according to geographical location from 7.8% in Germany to 66.5% in France [13]. In Canada, the resistance rate of *S. pneumoniae* reached a peak in 1998 at about 17% and is now declining [14]. However, non-invasive isolates are known to be more resistant than invasive ones. In a US survey 22.2% of *S. pneumoniae* strains isolated from blood or CSF were non-susceptible to penicillin compared with 39.1 and 55.3% in respiratory and ear isolates, respectively [15]. In Canada, the rate of nasopharyngeal colonization by a PRSP strain was found to be 17% in children attending day-care centres [16]. Some previous reports found young age to be a risk factor for PRSP compared with PSSP infections [7,17,18]. In this study, cases and controls were matched for age. However, when the age of cases was compared with the age of all patients with PSSP infections in the database (total of 178 patients), there was no significant difference by group. Einarsson reported that adults with pneumonia caused by PRSP had a milder clinical presentation than those with pneumonia caused by PSSP [19]. Published data has suggested that more resistant pneumococcal strains may be less invasive than sensitive strains [15]. Our data confirm previous reports in children who have shown that clinical presentation does not differ between infections due to PSSP or PRSP [4,6,10,20].

The clinical course was similar in both groups, as was the LOS in hospital contrary to a previous report where adults with pneumonia caused by PRSP spent a longer time in hospital [19]. A similar proportion of cases and controls were admitted to the ICU and length of ICU stay was not different.

In our study, the outcome was similar in both groups despite the fact that some patients with PRSP were initially treated with suboptimal therapy. Of note, all cases of PRSP meningitis received initial empirical therapy effective against PRSP. Deaths occurred evenly in both groups, and only in patients with underlying illnesses. Data published in 1987 found that there was increased mortality in adults with bacteraemia pneumonia due to PRSP, however this finding was not confirmed when taking other factors into consideration [21]. Similar studies in children have shown no difference in terms of outcome [4,6].

Cost of treatment has previously been evaluated in adults and found to be higher for infection due to PRSP mainly because of longer LOS [19]. Our data also found increased cost for PRSP infection but mainly because of

antibiotic cost: ceftriaxone for PRSP and penicillin G for PSSP. Unlike adults, children with *S. pneumoniae* bacteraemia are frequently treated as outpatients, which reflects the lack of severe underlying medical condition [21].

We did not find that day-care centre attendance was a risk factor for PRSP invasive infections but our study was limited by the fact that it was a retrospective chart review. Day-care attendance was not available for 7 of 36 cases and 26 of 108 controls less than 5 years of age. Patients, for whom the information was not noted on initial presentation, were considered as not attending day-care centres. Our data showed that antimicrobial use in the previous month was a risk factor for invasive infection with PRSP. Published data in the literature supports our findings [6,8,9,11,16–28], and the use of β-lactams [6,22,25,26,28] and trimethoprim-sulphamethoxazole [8,18] have been implicated most of the time.

The majority of the children in this study did not have recognized indications for polysaccharide pneumococcal vaccination (136 of 144). The impact of the arrival of the conjugate pneumococcal vaccine on the incidence of invasive infections in children will have to be evaluated in the long term, but preliminary results are encouraging with regards to severe invasive infections such as meningitis or bacteraemia [29].

In conclusion, our data indicates that PRSP and PSSP invasive infections in children are similar in clinical presentation, course of illness and mortality but that PRSP infections are more costly, mainly in terms of antibiotics usage. The consumption of antibiotics in the previous month was the only risk factor identified and has a potential for modification. Many studies comparing PRSP and PSSP were conducted in populations with underlying medical conditions and it is difficult to completely overshadow these pre-existing problems. Invasive *S. pneumoniae* infections in children who are in the vast majority of cases healthy, offer the possibility of studying the impact of penicillin resistance without the interference from other factors.

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