

A comparison of bacteremic pneumococcal pneumonia with nonbacteremic community-acquired pneumonia of any etiology – Results from a Canadian multicentre study

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BACKGROUND: Bacteremic pneumococcal pneumonia has not been the subject of a multicentre Canadian Study.

OBJECTIVES: To compare bacteremic community-acquired *Streptococcus pneumoniae* pneumonia with nonbacteremic community-acquired pneumonia of any etiology.

METHODS: A prospective cohort study was conducted at 15 centres in eight Canadian provinces from January 1996 to January 1998.

RESULTS: Fifty-six of the 450 patients (12.4%) had one or more blood cultures positive for *S pneumoniae*. Compared with the 394 blood culture-negative patients, the bacteremic patients were younger (55.6 years versus 63.4 years; $P=0.002$). At presentation, bacteremic patients had a higher mean oral temperature ($38.1\pm 1.2^{\circ}\text{C}$ versus $37.7\pm 1.2^{\circ}\text{C}$; $P=0.026$), a higher pulse rate (108.4 ± 22.1 beats/min versus 102.1 ± 20.6 beats/min; $P=0.033$), a lower diastolic blood pressure reading (66.8 ± 12.7 mmHg versus 73.8 ± 15.8 mmHg; $P=0.001$) and a higher percentage of white blood cells that were band forms (22.1% versus 14.2%; $P=0.0007$). The time from onset of symptoms until admission to hospital was shorter among the bacteremic patients (4.6 ± 3.7 days versus 7.0 ± 13.9 days; $P=0.005$). Three capsular polysaccharide types accounted for 53.4% of the isolates: type 14, 29.2%; type 4, 12.1%; and type 22 F, 12.1%. Two of 44 isolates were resistant to penicillin.

CONCLUSIONS: While some differences in patient characteristics and presentation occur when patients with bacteremic pneumococcal pneumonia are compared with nonbacteremic patients with community-acquired pneumonia, there is considerable overlap, and clinical presentation does not allow one to distinguish the bacteremic patients from the nonbacteremic patients.

Key Words: Bacteremia; Epidemiology; Pneumonia; Resistance; *Streptococcus pneumoniae*

Streptococcus pneumoniae accounts for 60% of all cases of bacteremic community-acquired pneumonia (CAP) (1). While bacteremic pneumococcal pneumonia has been described in several studies (2), there has never been a Canada-wide study of the clinical features, processes and

Une comparaison entre la pneumonie bactériémique à pneumocoques et la pneumonie non bactériémique de toute étiologie acquise dans la collectivité : Les résultats d'une étude multicentre canadienne

HISTORIQUE : La pneumonie bactériémique à pneumocoques n'a fait l'objet d'aucune étude multicentre canadienne.

OBJECTIFS : Comparer la pneumonie bactériémique à *Streptococcus pneumoniae* acquise dans la collectivité à la pneumonie non bactériémique de toute étiologie acquise dans la collectivité.

MÉTHODOLOGIE : Une étude prospective de cohorte a été menée dans 15 centres de huit provinces canadiennes entre janvier 1996 et janvier 1998.

RÉSULTATS : Cinquante-six des 450 patients (12,4 %) présentaient au moins une analyse sanguine positive au *S. pneumoniae*. Par rapport aux 394 patients dont l'analyse sanguine était négative, les patients bactériémiques étaient plus jeunes (55,6 ans par rapport à 63,4 ans; $P=0,002$). À la présentation, les patients bactériémiques affichaient une température orale moyenne plus élevée ($38,1\pm 1,2^{\circ}\text{C}$ par rapport à $37,7\pm 1,2^{\circ}\text{C}$; $P=0,026$), une fréquence plus élevée du pouls ($108,4\pm 22,1$ battements/min par rapport à $102,1\pm 20,6$ battements/min; $P=0,033$), une tension artérielle diastolique moins élevée ($66,8\pm 12,7$ mmHg par rapport à $73,8\pm 15,8$ mmHg; $P=0,001$) et un plus fort pourcentage de globules blancs à noyau incurvé (22,1 % par rapport à 14,2 %; $P=0,0007$). Le délai entre l'apparition des symptômes et l'hospitalisation était plus court parmi les patients bactériémiques ($4,6\pm 3,7$ jours par rapport à $7,0\pm 13,9$ jours; $P=0,005$). Trois types de polysaccharide capsulaire représentaient 53,4 % des isolats : type 14, 29,2 %; type 4, 12,1 %; et type 22 F, 12,1 %. Deux des 44 isolats étaient pénicillinorésistants.

CONCLUSIONS : Bien qu'on remarque certaines différences dans les caractéristiques et la présentation des patients lorsque les patients atteints de pneumonie bactériémique à pneumocoques sont comparés à des patients non bactériémiques atteints de pneumonie acquise dans la collectivité, il existe un chevauchement considérable, et la présentation clinique ne permet pas de distinguer les patients bactériémiques des patients non bactériémiques.

outcomes of care of this entity. The present prospective study of CAP at 15 teaching hospitals in eight Canadian provinces gave us the opportunity to accomplish the above goals and, in addition, to compare patients who had bacteremic pneumococcal pneumonia with those who had negative blood cultures

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for this organism. Further aims of the present study were to determine the serotypes and the antimicrobial susceptibility of the strains of *S pneumoniae* recovered from these patients.

PATIENTS AND METHODS

Patient population and study design

This was a prospective, observational study of CAP requiring initial hospitalization; the study commenced on January 11, 1996, and the last patient was terminated in January 1998. Investigators at 15 teaching hospitals in eight Canadian provinces enrolled patients. Eligible patients were those who were admitted to the hospital with a diagnosis of pneumonia and who met the following criteria:

- 16 years of age or older;
- A new pulmonary infiltrate on chest radiograph not attributable to an alternate cause;
- At least one of:
 - symptoms or signs suggestive of pneumonia (chest pain, cough, rales, rhonchi, and/or signs of consolidation); and/or
 - oral temperature of 38.5°C or higher, or 36.5°C or lower.

After informed consent was obtained, a study nurse identified and enrolled patients admitted during day 11 to 30 or 31 (the first 10 days were used for another study that the group was involved in) of each month. The study nurse completed the data collection forms and made daily visits (for a maximum of seven days of follow-up while in hospital) to record progress in terms of the evolution of the pneumonia and any complications that may have occurred during the hospital stay. All data were verified against the original chart by a study monitor during a site visit.

Antibiotic therapy

Antibiotic therapy was categorized as monotherapy if a single antimicrobial agent was administered and as combination therapy if more than one agent was administered. Combination therapy was further categorized as concurrent if the agents were administered during the same time period for five or more days and as sequential if they overlapped by three days or less.

The first antibiotics that a patient received were termed first-line therapy; a change to an antibiotic of a different class was termed second-line therapy; and so forth for third- and fourth-line therapy.

Diagnostic workup

Blood cultures were recommended for all patients in the study. The collection of acute and convalescent (four to six weeks after discharge) blood samples was recommended, but the decision was the investigator's. Other aspects of the diagnostic workup were handled by the attending physician.

Microbiology procedures

Blood and sputum samples were processed for culture at each site's laboratory using standard methods. All serum samples were tested for antibodies to *Mycoplasma pneumoniae*, influenza

viruses A and B, parainfluenza viruses 1, 2 and 3, adenovirus and respiratory syncytial virus (RSV) using a standard complement fixation technique in microtitre plates at the Halifax site. The adenovirus and RSV antigens were purchased from Flow Laboratories (USA); influenza A and B, parainfluenza 1, 2 and 3, and *M pneumoniae* antigens were purchased from MA Bioproducts (USA).

Patients with bacteremic pneumococcal pneumonia had serum samples tested for immunoglobulin G and immunoglobulin M antibodies to *Chlamydia pneumoniae* (AR-39 strain); *Chlamydia psittaci* (avian strain 6BC, feline pneumonitis strain FP, turkey strain TT3 and pigeon strain CP3); *Chlamydia pecorum* (ovine polyarthritis strain); and *Chlamydia trachomatis* (pooled antigens of serovars BED, CJHI and FGK using the microimmunofluorescence test [tests completed by Dr R Peeling, Laboratory Centre for Disease Control, Winnipeg, Manitoba] (3). These patients also had serum samples (24 acute and convalescent serum samples, and 22 single serum samples) tested for antibodies to *S pneumoniae* pneumolysin, pneumolysin immune complexes, C-polysaccharide, surface protein A, *Hemophilus influenzae* and *Branhamella catarrhalis* by Dr M Leinonen, National Public Health Institute, Oulu, Finland (4-6).

All serum samples from the patients with bacteremic pneumococcal pneumonia were tested for antibodies to *Legionella pneumophila* serogroups 1 to 4 by Dr Victor Yu, Pittsburgh, Pennsylvania, using an enzyme-linked immunosorbent assay method (7), and antibodies to *Coxiella burnetii* phase I and II antigens were determined using a microimmunofluorescence test as previously described (8). All patients had a urine sample collected within 24 h of admission, which was tested for *L pneumophila* serogroup 1 antigen (at each study site) using an enzyme-linked immunosorbent assay technique (Binax Inc, USA) (9).

Susceptibility testing of *S pneumoniae*

Minimal inhibitory concentrations (MICs), microbroth dilution testing and susceptibility category break points were determined as described by the National Committee on Clinical Laboratory Standards (10). Antibiotics tested included: penicillin, amoxicillin, amoxicillin/clavulanic acid, cefuroxime, ceftriaxone, imipenem, meropenem, trovafloxacin, moxifloxacin, levofloxacin, ciprofloxacin, erythromycin, doxycycline, tetracycline, trimethoprim/sulfamethoxazole, vancomycin and clindamycin. Penicillin resistance was defined to be penicillin-nonsusceptible *S pneumoniae* (MIC 0.1 µg/mL or greater) or penicillin-resistant *S pneumoniae* (MIC 2 µg/mL or greater).

S pneumoniae capsular polysaccharide typing

S pneumoniae isolated from the blood of patients with CAP were typed for capsular polysaccharide at the Streptococcal National Reference Centre in Edmonton, Alberta.

Data analysis

Data was entered into SPSS 8.0 (SPSS Inc, USA). Differences between patient subpopulations were tested using χ^2 test or Student's *t* test for continuous variables. All analysis was conducted using SPSS software. Proportions were compared using the χ^2 test or Fisher's exact test, and the difference between means of continuous data was determined using Student's *t* test (11).

TABLE 1
Comparison of demographic features of 56 patients having bacteremic *Streptococcus pneumoniae* pneumonia with 394 patients having blood culture-negative community-acquired pneumonia

Demographic feature	Bacteremic patients (n=56)	Patients with blood cultures negative (n=394)	P
Mean (\pm SD) age (years)	55.6 \pm 19.1	63.4 \pm 18.1	0.003
Male (n, %)	31 (55.4)	209 (53.0)	
White (n, %)	49 (87.5)	368 (93.4)	
Chronic obstructive pulmonary disease, asthma or bronchiectasis (n, %)	28 (50.0)	183 (46.4)	
Active cancer (n, %)	4 (7.1)	87 (22.1)	0.009
Smoked in past year (n, %)	29 (51.7)	99 (37.9)	
Influenza vaccine (n, %)	22 (39.3)	188 (47.7)	
Pneumococcal vaccine (n, %)	3 (5.4)	20 (5.1)	
Alcoholism (n, %)	9 (16.1)	40 (10.2)	
Current smoker (n, %)	19 (33.9)	112 (28.4)	

TABLE 2
Physical signs in 56 patients with bacteremic pneumococcal pneumonia compared with 394 patients with blood culture-negative community-acquired pneumonia (CAP)

Physical sign	Patients with bacteremic pneumococcal pneumonia (n=56)	Patients with blood culture-negative CAP (n=394)	P
Mean (\pm SD) oral temperature ($^{\circ}$ C)	38.1 \pm 1.2	37.7 \pm 1.2	0.026
Mean (\pm SD) respiratory rate (breaths/min)	26.7 \pm 8.3	26.6 \pm 7.5	
Mean (\pm SD) pulse rate (SD) (beats/min)	108.4 \pm 22.1	102.1 \pm 20.6	0.033
Mean (\pm SD) systolic blood pressure (mmHg)	132.3 \pm 27.9	126.6 \pm 29.0	
Mean (\pm SD) diastolic blood pressure (mmHg)	66.8 \pm 12.7	73.8 \pm 5.8	0.001
Crackles (n, %)	14 (25)	130 (33)	
Wheezes (n, %)	13 (23.2)	94 (23.9)	
Pleural rub (n, %)	2 (3.6)	10 (2.5)	
Consolidation (n, %)	7 (12.5)	42 (10.7)	

RESULTS

Four hundred fifty of the 850 patients (52.9%) enrolled in the study had one or more blood cultures processed, 56 of which (12.4%) were positive for *S pneumoniae*. These 56 patients were compared with 394 patients who had negative blood cultures (Table 1). The bacteremic patients were younger and less likely to have pre-existing cancer than the nonbacteremic patients. There was no difference in the frequency of presenting symptoms when the two groups were compared (data not shown). Table 2 shows that the mean temperature at the time of admission was significantly higher among the bacteremic patients ($P=0.026$), as was the mean pulse rate ($P=0.033$), while the mean diastolic blood pressure was lower ($P=0.001$).

The mean (\pm SD) time from the onset of symptoms until hospitalization was 4.6 \pm 3.7 days for the bacteremic patients

TABLE 3
Comparison of outcomes and time to presentation for 56 patients with bacteremic pneumococcal pneumonia and 394 patients with blood culture-negative pneumonia

Outcome/time	Patients with bacteremic pneumococcal pneumonia (n=56)	Patients with blood culture-negative CAP (n=394)	P
Died (n, %)	3 (5.4)	42 (10.7)	
Admitted to intensive care (n, %)	11 (19.6)	50 (12.7)	
Mean (\pm SD) length of stay (days)	8.1 (11.3)	7.7 (6.5)	
Mean (\pm SD) number of days between onset of symptoms and presentation	4.6 (3.7)	7.0 (13.9)	0.005

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versus 7.0 \pm 13.9 days for the nonbacteremic patients ($P<0.005$). The mortality rate was lower for the bacteremic group (5.4%) than for the nonbacteremic group (10.7%) (P =not significant [NS]) (Table 3). The intensive care unit (ICU) admission rate was similar in both groups – 19.6% for the bacteremic group and 12.7% for the nonbacteremic group. Seven of the 11 bacteremic patients (63.6%) admitted to the ICU required assisted ventilation, compared with 25 of 50 nonbacteremic patients (50%). The length of hospital stay was similar in both groups. Three of the bacteremic patients (5.4%) died, while 42 of the nonbacteremic patients (10.7%) died (P =NS).

The mean white blood cell count of the bacteremic patients was $17.4 \times 10^9/L$, compared with $14.2 \times 10^9/L$ for the nonbacteremic patients (P =NS). The percentage of white cells that were band forms was higher among the bacteremic patients than among the nonbacteremic patients (22.1% \pm 18.5% versus 14.2% \pm 14.2%) ($P=0.0007$). There was a tendency toward multilobar pneumonia among the bacteremic patients (16 of 56, 28.5%) versus the nonbacteremic patients (72 of 394, 18.2%) (P =NS).

Forty-four per cent of the bacteremic patients waited 4 h or more from presentation to the emergency room until receipt of antibiotics, compared with 58.3% of the nonbacteremic patients ($P=0.055$). The bacteremic patients received intravenous antibiotics for 8.4 \pm 6.4 days, while the nonbacteremic patients received antibiotics for 6.7 \pm 6.0 days ($P=0.04$).

Twenty-one patients (37.5%) with bacteremic pneumococcal pneumonia received treatment with a single antibiotic, compared with 39.8% of the nonbacteremic group. A second-generation cephalosporin was used as the single agent for 14 of 21 bacteremic patients (66.7%); two (9.5%) received a macrolide and four (19%) received other antibiotics. Thirty-five bacteremic patients (62.5%) received combination therapy, compared with 219 nonbacteremic patients (55.5%) ($P=0.029$). A second-generation cephalosporin and a macrolide were used to treat 29 of 35 bacteremic patients (82.8%) who received combination therapy. Fifty-three bacteremic patients (94.6%) received second-line antibiotic therapy, compared with 349 nonbacteremic patients (88.5%) (P =NS). However, more bacteremic patients received a third-line antibiotic than nonbacteremic patients (Table 4). Eventually, 34 of the bacteremic patients (60.7%) received penicillin ($n=27$) or amoxicillin ($n=7$).

TABLE 4
Number (%) of 56 bacteremic pneumococcal pneumonia patients and 394 nonbacteremic patients with community-acquired pneumonia (CAP) who received second-, third- and fourth-line antibiotic therapy

Antibiotic therapy	Patients with bacteremic pneumococcal pneumonia (n=56)	Patients with blood culture-negative CAP (n=394)	P
Second-line	53 (94.6)	350 (88.8)	NS
Third-line	25 (44.6)	112 (28.4)	0.014
Fourth-line	5 (8.9)	18 (4.6)	NS

The capsular polysaccharide types for 41 of the isolates are shown in Table 5. Three serotypes accounted for 53.4% of the isolates – type 14, 29.2%; type 4, 12.1%; type 22 F, 12.1%.

Forty-four isolates were tested for susceptibility to 24 different antibiotics (Table 6). Only two of the isolates were resistant to penicillin, one of which was also resistant to cefotaxime, ceftriaxone and cefuroxime. Both of these isolates were from Ontario sites. There was no erythromycin resistance observed. One of the patients with penicillin-resistant *S pneumoniae* was a 73-year-old woman with chronic obstructive pulmonary disease and a one hundred pack-year history of tobacco smoking. She was treated with erythromycin and ciprofloxacin, and was discharged after a 15-day hospital stay. The second patient was a 50-year-old man with a history of alcoholism who was treated with ceftriaxone and discharged after a four-day hospital stay.

Table 7 shows the results of the serodiagnosis of pneumococcal pneumonia among 46 of the bacteremic patients who had serum specimens available for testing. Eighty-three per cent of those with acute and convalescent samples had a positive test, while 31.8% of those with an acute phase sample only had a positive test. Overall, 58.7% of the patients tested had a positive serological test indicating infection with *S pneumoniae*. Seven patients (15.2%) had evidence of infection with another pathogen. These pathogens included respiratory syncytial virus (RSV) and influenza A in one patient, RSV and *C pneumoniae* in another patient, and one of influenza A, influenza B, *Coxiella burnetii*, *C pneumoniae* and parainfluenza virus 3 in five patients. Fifty-one nonbacteremic patients (22.8%) had two or more pathogens identified as the etiology of the pneumonia.

DISCUSSION

Fifty-six of the 450 patients (12.4%) who had blood cultures performed had bacteremic *S pneumoniae* pneumonia. This is higher than the 4.2% rate (47 of 1118 patients) reported in a study carried out at a single hospital in Halifax from November 1981 to May 1990 (1). In another North American study carried out in Boston, Massachusetts; Pittsburgh, Pennsylvania; and Halifax from October 1991 to March 1994, 63 of 1343 patients (4.6%) requiring hospitalization for CAP had *S pneumoniae* isolated from the blood (12). Marston et al (13) found that 5.5% of 2776 patients with CAP hospitalized in two counties in Ohio had *S pneumoniae* bacteremia. Mundy et al (14) noted that 31 of 385 patients (8%) with CAP requiring admission to the Johns Hopkins Hospital, 180 of whom had human immunodeficiency virus infection, had pneumococcal bacteremia.

TABLE 5
Capsular polysaccharide types for 41 isolates from patients with bacteremic pneumococcal pneumonia

Type	n	%
3	1	2.4
4	5	12.1
6A	1	2.4
8	3	7.3
9N	1	2.4
9V	3	7.3
10A	2	4.8
12F	1	2.4
14	12	29.2
16F	1	2.4
18C	2	4.8
19F	1	2.4
20	2	4.8
22F	5	12.1
33F	1	2.4

Risk factors for pneumococcal pneumonia that have been mentioned in other studies are dementia, seizure disorders, current cigarette smoking, congestive heart failure, cerebrovascular disease, institutionalization, chronic obstructive pulmonary disease, lung cancer, corticosteroid use and alcoholism (15). Musher et al (2) found that 58% of 52 patients with bacteremic pneumococcal pneumonia had a history of alcohol abuse, compared with 35% of 48 patients with nonbacteremic pneumococcal pneumonia (P=0.03). Most of the patients (98%) in Musher's study were male and all were hospitalized at a Veterans Affairs Medical Center, both of which may be confounding factors. We did not find these factors to be significant in our study.

The mortality rate of 5.3% among our patients with bacteremic pneumococcal pneumonia is low and may be due in part to enrolment bias. Since providing informed consent was necessary for all patients to participate, very ill patients were often not enrolled in the study. Another possible explanation for the low mortality rate is the shorter time between onset of symptoms and presentation for the bacteremic patients – 4.6 days versus 7.0 days for the nonbacteremic patients. In a previous study of all patients with bacteremic pneumococcal pneumonia, we found that the mortality rate was 19% (1). Kalin et al (16) studied 460 patients with bacteremic pneumococcal pneumonia from September 1, 1993 to August 31, 1995 at five centres in Halifax; Huntington, West Virginia; Barcelona, Spain; Manchester, United Kingdom; and Stockholm, Sweden. The overall mortality rate was 12%, ranging from 6% in Halifax to 20% in Barcelona and Huntington. Musher et al (2), in their study of 52 bacteremic pneumococcal pneumonia patients at a Veterans Affairs Medical Center in Houston, Texas from September 1996 through 1999, found that the seven-day mortality rate was 19%, while the 30-day and 90-day mortality rates were 21% and 27%, respectively (2). In a study carried out during the preantibiotic era from 1929 to 1935, Tilghman and Finland (17) found that 77.5% of 582 bacteremic patients died.

TABLE 6
Minimal inhibitory concentrations of various antibiotics required to inhibit 50% (MIC₅₀) and 90% (MIC₉₀) of 44 isolates of *Streptococcus pneumoniae* from patients with bacteremic pneumococcal pneumonia

Antibiotic (cut-point for resistance)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	Range (µg/mL)	Resistance (%)
Penicillin (0.12 to 1 – nonsusceptible; 2 or greater – resistant)	0.03	0.03	0.03 to 0.12	4.5%
Amoxicillin (1)	0.03	0.06	0.03 to 0.12	0
Amoxicillin/clavulanic acid (1/0.5)	0.06	0.06	0.03 to 0.12	0
Cefuroxime (1)	0.25	0.25	0.25 to 2	2.2
Ceftriaxone	0.03	0.06	0.03 to 1.0	2.2
Cefotaxime	0.03	0.03	0.03 to 1.0	2.2
Imipenem	0.03	0.06	0.03 to 0.06	0
Meropenem	0.03	0.03	0.03 to 0.06	0
Trovafloxacin	0.12	0.25	0.06 to 0.25	0
Gatifloxacin	0.12	0.12	0.06 to 0.25	0
Grepafloxacin	0.25	0.25	0.12 to 0.25	0
Moxifloxacin	0.25	0.25	0.12 to 0.25	0
Levofloxacin	1	1	0.5 to 1.0	0
Ofloxacin	2	2	1.0 to 2.0	0
Ciprofloxacin	1	1	0.5 to 2.0	0
Erythromycin (0.5)	≤0.12	0.12	0.12	0
Doxycycline	≤1	1	1	0
Tetracycline (4)	≤1	1	1	0
Trimethoprim	2	4	0.25 to 32	0
Trimethoprim/sulfamethoxazole	0.25	0.50	0.25 to 4	16
Vancomycin	≤0.50	0.50	0.5	0
Chloramphenicol (8)	2	4	2 to 4	0
Clindamycin (0.25)	≤0.25	0.25	0.25	0
Dalfopristin/quinapristin	0.50	0.50	0.25 to 0.5	0

TABLE 7
Results of testing for antibodies to pneumolysin, C-polysaccharide, pneumococcal surface protein and pneumolysin immune complexes in 46 patients with bacteremic pneumococcal pneumonia

Phase	n	Number of positive results (%)
Acute and convalescent serum samples	24	20 (83.3)
Acute phase only	22	7 (31.8)
Total	46	27 (58.7)

Austrian and Gold (18), in a study carried out just after penicillin had been introduced as a therapy for pneumococcal pneumonia, noted that 24.7% of patients with pneumococcal bacteremia died and that 60% of all deaths among patients treated with penicillin occurred during the first five days, suggesting that antimicrobial therapy has little or no effect on the outcome of infection among those destined to die within five days. Hook et al (19) noted that there was a 30.5% overall mortality rate from pneumococcal bacteremia and a 76% mortality rate among those admitted to ICUs. Some of these findings remain to be explained but likely reflect both host and micro-organism factors.

There were no statistically significant differences in symptoms when patients with pneumococcal bacteremia were compared with those with pneumonia and negative blood cultures

for *S pneumoniae*. Twenty-five per cent of the bacteremic patients had diarrhea. Severe diarrhea can occur in pneumococcal pneumonia (20,21) and was termed 'croupous colitis' by Osler (20). It has been suggested that this diarrhea is due to invasion of the intestinal wall and the mesenteric lymph nodes by *S pneumoniae* (22).

Pleuritic chest pain was slightly more frequent among those with bacteremia – 46.4% versus 38.9% for the nonbacteremic patients. This is lower than the findings in our previous study, in which 62% of the bacteremic patients complained about pleuritic chest pain (1). In a study of 1343 patients requiring hospitalization for the treatment of CAP, Fine et al (23) found that 39.4% patients had pleuritic chest pain. It seems likely that pleuritic chest pain does occur in a greater proportion of patients with bacteremic pneumococcal pneumonia than other patients with CAP.

There were, however, differences in physical findings – the bacteremic patients had a higher temperature and pulse rate, and a lower diastolic blood pressure than the nonbacteremic patients.

There are now 90 serotypes of *S pneumoniae* recognized (24), and the lower numbered serotypes are more pathogenic for man (17). Indeed, in the 1930s, serotypes 1, 2, 3 accounted for 75% of bacteremias (17). In a study of 7000 episodes of invasive pneumococcal disease from Europe, South America and North America, 12 serotypes (or groups) accounted for 80.9% of all isolates (25). Types 14, 22F, 6, 19 and 3 were the most common and

accounted for nearly 40%; types 23, 1, 9 and 4 for about 25%; and types 8, 18, 7 and 5 for approximately 15% of all isolates.

This study also demonstrated important geographic and age-related variations in the distribution of serotypes. Even though the number of isolates that we serotyped was small, the distribution generally confirms what is stated above. Type 14 was the most common serotype, accounting for 29.2% of the isolates; indeed, types 14, 6, 19 and 3 collectively accounted for 36.4% of our isolates. Types 9 and 4 accounted for 21.8%, and types 8, 18 and 7 accounted for 12.1% of the isolates. We also noted geographic variation; six of the 12 type 14 isolates were from patients at the Winnipeg site, and three of the five 22F isolates were from patients at the Halifax site. Thirteen isolates were typed from the Winnipeg site and 10 from the Halifax site. In a previous study at the Winnipeg site, Mirzanejad et al (26) found that, over an eight-year period, type 14 was the most common cause of pneumococcal bacteremia, accounting for 32 of 217 isolates (14.7%).

Henriques et al (27) serotyped 354 isolates from the patients with bacteremic pneumococcal pneumonia studied by Kalin et al (16). They noted that serotype 14 was most common, accounting for 14% of the isolates, followed by type 9V at 11%, type 3 at 9%, type 23F at 9% and 7F at 8%. They also noted a marked difference in the serotype distribution according to country of origin of the patient, with serotype 3 dominating in Spain and the United States, and type 14 dominating in Sweden and Canada.

During 1997 and 1998, Zhanel et al (28) tested 1180 *S pneumoniae* isolates collected across Canada for susceptibility to a variety of antibiotics. They found that 251 (21.2%) were penicillin nonsusceptible (intermediate susceptibility plus resistance). Davidson et al (29) examined 1320 isolates of *S pneumoniae* collected from sites across Canada in 1994/1995, as well as 1044 isolates in 1996. They found that the percentage of penicillin-nonsusceptible isolates increased from 8.5% in 1994/1995 to 13.3% in 1996. How do we reconcile these observations with our data, in which only two of 44 bacteremic isolates (4.5%) collected during 1996/1997 were penicillin-nonsusceptible? There are several possible explanations; for instance, we examined isolates only from adults with bacteremic pneumococcal pneumonia. Age younger than four years is one of the factors associated with penicillin-resistant *S pneumoniae* (30,31).

In the studies cited above (28,29), the *S pneumoniae* isolates were from a variety of respiratory tract sites and included all ages. It is also possible that the penicillin-nonsusceptible isolates are less virulent and hence would be under-represented in any study that examined only blood isolates. Against this argument is the observation by Plouffe et al (32) that the incidence of drug-resistant, bacteremic *S pneumoniae* isolates increased to 14% during their study of 590 patients at 10 adult care hospitals in Franklin County, Ohio from January 1991 to April 1994. The most recent and comprehensive data comes from a 1995 to 1998 study of 4013 cases of invasive *S pneumoniae* in the United States (33). In 1998, 24% of the isolates were resistant to penicillin, and over the period of the study, the proportion of the isolates that were resistant to three or more classes of drugs increased from 9% to 14% (33).

A method of diagnosing pneumococcal pneumonia that does not depend on sputum culture is desirable. In most studies of CAP, at least 30% of the cases are of unknown etiology despite

an intensive diagnostic workup (14,34). The pneumococcal serological studies used in this and other studies (35-38) are of great interest, because they offer the possibility of making an etiological diagnosis of pneumococcal pneumonia in the absence of sputum specimens and in those with negative blood cultures. However, these studies need validation against a gold standard. Bacteremic pneumococcal pneumonia is one such standard.

It is noteworthy that three studies (36-38) that used serological methods in addition to blood and sputum cultures in the diagnosis of pneumococcal pneumonia had the highest rates of infection due to this micro-organism. In these studies, 42.8% (36), 32% (37) and 55% (38) of the cases of pneumonia were due to *S pneumoniae*, compared with 15.3% and 17.9% for studies that did not use this methodology (34,14). We found that 83.3% of the bacteremic patients who had acute and convalescent serum samples tested met the criteria for the serological diagnosis of *S pneumoniae* infection. This is almost identical to the 88% sensitivity found by Porath et al (35) in a study of 22 bacteremic pneumococcal pneumonia patients. If an acute phase sample only was available, the sensitivity in our patients was only 31.8%. We conclude that, at present, serological testing is not useful as a method of diagnosing pneumococcal pneumonia.

We found that 15% of the 46 patients with serum available for serological testing had evidence of infection with another pathogen. Marston et al (13) found that 14 of 154 patients (9%) with bacteremic pneumococcal pneumonia had evidence of infection with another pathogen. They noted that one patient had group A streptococcus bacteremia, one had *Staphylococcus aureus* bacteremia, two had four-fold rises in antibody titre to *Legionella* species, five had *M pneumoniae*, three had *C pneumoniae*, one had influenza A and one had RSV.

In the current study, in addition to *S pneumoniae*, RSV and influenza A were found in one patient; RSV and *C pneumoniae* were found in one patient, and influenza A, influenza B, *C burnetii*, *C pneumoniae* and parainfluenza virus 3 were each found alone in five patients. In a previous study, eight of 47 patients (17%) had a potential pathogen in addition to *S pneumoniae* isolated from the sputum, and eight of 32 patients (25%) had serological evidence of infection with another pathogen: parainfluenza 3, three patients; influenza A, one patient; influenza B, one patient; RSV, one patient; cytomegalovirus, one patient; and *C burnetii*, one patient (1). Collectively, these observations indicate that a proportion of patients with bacteremic pneumococcal pneumonia are infected with a second, and occasionally even a third, pathogen.

CONCLUSIONS

While the clinical picture of bacteremic *S pneumoniae* pneumonia is very similar to that of CAP with blood cultures negative for *S pneumoniae*, a number of significant differences were noted in the present study in terms of age, underlying disease, vital signs and time from onset of symptoms until presentation. Although outcomes between bacteremic *S pneumoniae* pneumonia and nonbacteremic pneumonia were similar, there was a tendency toward better outcomes for the bacteremic *S pneumoniae* patients. A possible explanation is that the nonbacteremic patients presented seven days after the onset of symptoms, while bacteremic *S pneumoniae* pneumonia patients presented 4.6 days after the onset of symptoms.

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