Clinical Presentation, Processes and Outcomes of Care for Patients with Pneumococcal Pneumonia

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OBJECTIVE: To describe the presentation, resolution of symptoms, processes of care, and outcomes of pneumococcal pneumonia, and to compare features of the bacteremic and nonbacteremic forms of this illness.

DESIGN: A prospective cohort study.

SETTING: Five medical institutions in 3 geographic locations.

PARTICIPANTS: Inpatients and outpatients with community-acquired pneumonia (CAP).

MEASUREMENTS: Sociodemographic characteristics, respiratory and nonrespiratory symptoms, and physical examination findings were obtained from interviews or chart review. Severity of illness was assessed using a validated prediction rule for short-term mortality in CAP. Pneumococcal pneumonia was categorized as bacteremic; nonbacteremic, pure etiology; or nonbacteremic, mixed etiology.

MAIN RESULTS: One hundred fifty-eight (6.9%) of 2,287 patients (944 outpatients, 1,343 inpatients) with CAP had pneumococcal pneumonia. Sixty-five (41%) of the 158 with pneumococcal pneumonia were bacteremic; 74 (47%) were nonbacteremic with *S. pneumoniae* as sole pathogen; and 19 (12%) were nonbacteremic with *S. pneumoniae* as one of multiple pathogens. The pneumococcal bacteremia rate for outpatients was 2.6% and for inpatients it was 6.6%. Cough, dyspnea, and pleuritic pain were common respiratory symptoms. Hemoptysis occurred in 16% to 22% of the patients. A large number of nonrespiratory symptoms were noted. Bacteremic patients were less likely than nonbacteremic patients to have sputum production and myalgias (60% vs 82% and 33% vs 57%, respectively; $P < .01$ for both), more likely to have elevated blood urea nitrogen and serum creatinine levels, and more likely to receive pencillin therapy. Half of bacteremic patients were in the low risk category for short-term mortality (groups I to III), similar to the nonbacteremic patients. None of the 32 bacteremic patients in risk groups I to III died, while 7 of 23 (30%) in risk group V died. Intensive care unit admissions and pneumonia-related mortality were simi-

lar between bacteremic and nonbacteremic groups, although 46% of the bacteremic group had respiratory failure compared with 32% and 37% for the other groups. The nonbacteremic pure etiology patients returned to household activities faster than bacteremic patients. Symptoms frequently persisted at 30 days: cough (50%); dyspnea (53%); sputum production (48%); pleuritic pain (13%); and fatigue (63%).

CONCLUSIONS: There were few differences in the presentation of bacteremic and nonbacteremic pneumococcal pneumonia. About half of bacteremic pneumococcal pneumonia patients were at low risk for mortality. Symptom resolution frequently was slow.

KEY WORDS: pneumonia; pneumococcal; outcomes.

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Pneumonia due to *Streptococcus pneumoniae* continues to be a challenge. In the preantibiotic era it accounted for most cases of pneumonia.¹ Currently it causes about 6% to 10% of all cases of community-acquired pneumonia (CAP)²⁻⁴; however, it causes 60% of all cases of bacteremic pneumonia.

Although pneumococcal pneumonia has been studied for decades, there are still many unanswered questions about this illness, including the apparent differences in mortality rate between countries and the failure of antibiotic therapy to influence the high early mortality rate. In 1 study, the mortality rate from bacteremic pneumococcal pneumonia was 26% in Huntington, WV, while it was only 5% in Stockholm, Sweden.⁵ The mortality rate from bacteremic *S. pneumoniae* pneumonia is highest in the first 48 hours of hospitalization⁶ and is unchanged from the preantibiotic era.⁷ Furthermore, some investigators have found that even treatment in an intensive care unit (ICU) does not lower early mortality.⁸ Therapy of pneumococcal pneumonia used to be simple, but the emergence of antibiotic-resistant *S. pneumoniae* strains has complicated treatment of this common infection.^{9,10}

From October 1991 through March 1994, we conducted a prospective observational study of patients with ambulatory and hospitalized CAP at 1 site in Halifax, Nova Scotia, Canada; 2 sites in Boston, Mass, and 2 sites in Pittsburgh, Pa. Our objectives were to examine a variety of outcomes in patients with pneumococcal pneumonia (resolution of symptoms, time to return to work, time to return to usual activities) that have not been examined in previous studies. An additional objective of our study was to compare the clinical and other features of bacteremic pneumococcal pneumonia with nonbacteremic *S. pneumoniae* as a single pathogen, and cases of pneumo-

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nia in which *S. pneumoniae* was part of a polymicrobial etiology.

METHODS

This study of the clinical presentation, processes, and outcomes of care for patients with pneumococcal pneumonia was performed as part of the Pneumonia Patient Outcomes Research Team (PORT) multicenter, prospective cohort study of ambulatory and hospitalized patients with CAP. The study methodology has been previously described.¹¹

Study Sites and Patient Population

The Pneumonia PORT cohort study was conducted from October 1991 through March 1994, at 5 medical institutions in 3 geographic locations: the University of Pittsburgh Medical Center (UPMC); Massachusetts General Hospital (MGH), and Harvard Community Health Plan-Kenmore Center (HCHP), a 44,931-member staff-model center of a large health maintenance organization, in Boston, Mass; and Victoria General Hospital (VGH), a 637-bed university teaching hospital, in Halifax, Nova Scotia, Canada. The study was approved by the biomedical research review committee at each institution.

Study inclusion criteria were age ≥ 18 years, acute onset of symptoms suggestive of pneumonia, acute radiographic evidence of pneumonia within 24 hours of presentation, and provision of informed consent by the patient or patient proxy. Patients were ineligible for this study if they had been hospitalized within 10 days prior to initial presentation with CAP, were HIV positive, or were previously enrolled in the cohort study.

Of the 2,287 patients enrolled in the Pneumonia PORT cohort study, this investigation focused on patients in whom *S. pneumoniae* was the presumed or definite etiologic diagnosis of the pneumonia ($n = 158$). Patients were excluded from this investigation if they were assigned a microbiologic diagnosis other than *S. pneumoniae* ($n = 291$), if no diagnostic microbiologic tests were performed ($n = 695$), if a microbiologic etiology could not be assigned based on the available microbiologic data ($n = 1,102$), or if chart review data were incomplete ($n = 41$). The results of all sputum gram stains, sputum cultures, blood cultures, pleural fluid cultures, and acute and convalescent blood serologies obtained at the discretion of the managing physicians in the routine care of patients were recorded. The methods for performing each of these tests were those in place at the participating institutions; however, at all sites sputum was processed for culture only if there were ≤ 10 squamous epithelial cells/low power field on gram stain. Identification of *S. pneumoniae* was by standard methods. Based on these data, assignment of a definite diagnosis of *S. pneumoniae* pneumonia was made if there was a positive culture of blood, pleural fluid, or an otherwise sterile body fluid; a presumptive di-

agnosis was made on the basis of heavy or moderate growth of *S. pneumoniae* on sputum culture, or light growth of *S. pneumoniae* on sputum culture confirmed by the presence of gram-positive diplococci on sputum gram stain. Patients were also included as presumptive pneumococcal pneumonia if they were assigned a microbiologic diagnosis in which *S. pneumoniae* was the sole pathogen or 1 of multiple assigned pathogens. Multiple pathogens were felt to be the etiology if 2 or more pathogens were isolated from a sputum specimen and the gram stain revealed the presence of multiple organisms consistent with those isolated on culture.⁴ Pneumococcal bacteremia was defined as at least 1 blood culture positive for *S. pneumoniae*. All patients in whom a blood culture was not performed but who had a positive sputum culture for *S. pneumoniae* ($n = 20$) were considered nonbacteremic (we recognize that 1 or 2 patients in this group may be bacteremic given the 6.6% rate of pneumococcal bacteremia among patients who had blood cultures done). For the purposes of this investigation, patients were classified into 3 groups: (1) patients with pneumococcal bacteremia; (2) patients with pneumococcal pneumonia who had a microbiologic diagnosis in which *S. pneumoniae* was the sole pathogen (nonbacteremic, pure etiology); and (3) patients with pneumococcal pneumonia who had a microbiologic diagnosis in which *S. pneumoniae* was 1 of multiple pathogens (nonbacteremic, mixed etiology). One patient with a microbiologic diagnosis of multiple pathogens had a positive blood culture for *S. pneumoniae* and was assigned to the pneumococcal bacteremia group.

Baseline Patient Assessment

Baseline data on patient sociodemographic characteristics and clinical and laboratory findings were collected by clinical research associates by means of patient interview and medical record review as previously described.^{11,12}

Processes of Care and Medical Outcomes

Medical record reviews were used to record the following processes of care: antimicrobial use within 30 days of presentation, length of hospital stay and ICU admissions within 30 days of presentation. For this portion of our analysis, we excluded patients who were admitted to the coronary care unit [CCU] or who were admitted to ICU for cardiac monitoring. The reasons for all ICU and CCU admissions were recorded. In this study, we considered only the first ICU or CCU admission for respiratory failure, mechanical ventilation, or hemodynamic instability that occurred during the initial hospitalization.

Mortality 30 days following presentation was assessed for all patients. Detailed case summaries for all deaths were reviewed independently by 2 of the 5 investigators (CMC, MJF, WNK, TJM, DES) and used to assign the cause of death, using World Health Organization defi-

nitions.¹³ Medical record review was used to record data concerning selected new or worsening medical complications that occurred within 30 days of presentation. The complications were respiratory failure (with or without mechanical ventilation), congestive heart failure, shock, atrial fibrillation, anemia, thrombocytopenia, leukopenia, hepatic abnormalities, renal insufficiency, and suppurative infection (i.e., brain abscess, empyema, endocarditis, meningitis, osteomyelitis, and/or septic arthritis). Respiratory failure was defined as 1 or more of the following: $pO_2 \leq 60$ mmHg, O_2 saturation $\leq 90\%$ and/or $pCO_2 \geq 45$ mmHg at presentation. Shock was defined as systolic hypotension (blood pressure ≤ 90 mmHg) not corrected by intravenous fluids, or requiring pressor medications or an intraaortic balloon pump. Atrial arrhythmias included newly recognized atrial fibrillation, atrial flutter, supraventricular tachycardia, or multifocal tachycardia. Hepatic abnormalities were defined as newly elevated liver enzymes or worsening of chronically elevated liver enzymes. Renal insufficiency was defined as new or worsening renal function.

Thirty days following presentation, patients were asked about the presence or absence of the following 5 common pneumonia-related symptoms: cough, dyspnea, sputum production, pleuritic chestpain and fatigue. During the 30-day follow-up interview, patients were also asked to provide the date they had returned to work (if working at baseline) and to usual household activities.

Antimicrobial Susceptibility Testing

Antibiotic susceptibility data performed in the routine care of patients at each study site were recorded for all patients with pneumococcal bacteremia. At all sites, initial screening for penicillin resistance was performed using a 10 μ g oxacillin disk; those isolates with a zone of 19 mm or less were tested further to determine the penicillin minimum inhibitory concentration. Minimum inhibitory concentrations (MIC) were determined by broth microdilution in cation-adjusted Mueller-Hinton broth supplemented with 5% lysed horse blood according to the National Committee for Clinical Laboratory Standard guidelines. Intermediate resistance to penicillin was defined as an MIC from 0.12 to 1.2 μ g/mL and high level resistance as an MIC ≥ 2.0 μ g/mL. At 1 of the Pittsburgh sites (St. Francis Medical Center), MIC determinations were not done during the course of this study. At the Boston site, the E test was used to determine the penicillin MIC. At the Halifax site, MICs were performed from March 1992 onwards.

Analytical Methods

Comparisons of proportions were performed using the χ^2 statistic, or in cases of small proportions, Fisher's exact test was used. When appropriate, continuous variables were analyzed as categorical variables using clinically meaningful cut points. Comparison of return to work

and usual activities was done using the log-rank test. A 2-tailed P value $\leq .05$ was considered statistically significant for all analyses.

RESULTS

One hundred fifty-eight (6.9%) of 2,287 patients with CAP were assigned a diagnosis of pneumococcal pneumonia. Sixty-five (41.1%) of the 158 patients were bacteremic with *S. pneumoniae*, 74 (46.8%) had nonbacteremic pneumococcal pneumonia with *S. pneumoniae* as the sole pathogen, and 19 (12.0%) had nonbacteremic pneumococcal pneumonia with *S. pneumoniae* as one of multiple pathogens. There were 944 outpatients. Two (0.24%) were documented to be bacteremic with *S. pneumoniae*, compared with 63 (4.7%) of the 1,343 inpatients; however, only 77 of the outpatients had blood cultures performed. The pneumococcal bacteremia rate in this subgroup of outpatients was 2.6%, compared with 6.6% for inpatients. For the 19 patients in whom *S. pneumoniae* was part of a polymicrobial etiology, the combinations were *S. pneumoniae* and *Haemophilus influenzae* and *Staphylococcus aureus* (6 patients each); *Branhamella catarrhalis* (2); and *Enterococcus* sp and *H. influenzae*, *S. aureus* and *Pseudomonas aeruginosa*, *Enterobacter* sp, *Klebsiella pneumoniae*, and *Streptococcus agalactiae* (1 each).

Baseline Patient Characteristics

Overall, half of the patients were 65 years of age or older, 58.2% were men, and 85.4% were white. The vast majority (89.2%) of the patients were treated as inpatients. There were no significant differences in baseline demographic and clinical characteristics among the 3 study groups. Only 16.5% of the 133 patients for whom data were available had ever received pneumococcal vaccine. Seven percent of the bacteremic patients were admitted from a nursing home.

The most commonly reported respiratory symptoms were cough (86.6%) and dyspnea (75.2%), and the 2 most frequent nonrespiratory symptoms were fatigue (92.3%) and fever (82.4%). With the exception of sputum production, which was less common for bacteremic patients, there were no differences in frequency of respiratory symptoms among the three study groups. Nonrespiratory symptoms were also reported with similar frequency among the three groups except for myalgias, which were less frequently reported among bacteremic patients. A low serum albumin (<3.5 g/dL) and an elevated white blood cell count ($>11,000/\text{mm}^3$) were the most frequently recorded laboratory abnormalities in those for whom these tests were performed. A higher percentage of bacteremic patients had an elevated blood urea nitrogen (>30 mg/dL) (40.6% vs 17.7% and 22.2% for nonbacteremic, pure etiology and mixed etiology, respectively; $P < .05$), an elevated serum creatinine (42.6% vs 25.4% and 16.7% for nonbacteremic, pure etiology and mixed etiology, respec-

tively; $P \leq .05$) and a low albumin level (<3.5 g/dL) (83.0% vs 63.4% and 46.7% for nonbacteremic, pure etiology and mixed etiology, respectively; $P < .05$).

Review of the baseline pulmonary radiographs demonstrated a confirmatory pulmonary infiltrate in 94.2% of all patients. There were no significant differences among the 3 study groups in terms of pattern of infiltrate, presence of bilateral infiltrate, number of lobes, or the presence of pleural effusion.

Processes of Care and Medical Outcomes

Penicillin G and penicillin VK were more commonly used to treat bacteremic patients than to treat nonbacteremic patients (70.8% vs 27.0% and 10.5% for pure etiology and mixed etiology, respectively; $P < .05$) (Table 1). Most patients (77%) received intravenous followed by oral antibiotics, 13.9% received intravenous antibiotics only, and 8.9% received oral antibiotics only. A higher percentage of bacteremic patients received 3 or more antimicrobial agents than the 2 nonbacteremic groups (78.5% vs 51.4% and 73.7% for pure etiology and mixed etiology, respectively; $P = .003$). On discharge, penicillin V was more

commonly prescribed for bacteremic patients than for nonbacteremic patients (50.9% vs 17.9% and 6.3% for pure etiology and mixed etiology, respectively; $P < .05$); amoxicillin was more commonly prescribed for nonbacteremic patients than for bacteremic patients (17.9% and 18.8% for pure etiology and mixed etiology, respectively, vs 1.9%; $P < .05$). Antimicrobial susceptibility data were available for 60 of the 65 blood stream isolates. Only 2 isolates were resistant to penicillin; 1 isolate from St. Francis Medical Center was resistant by oxacillin disc diffusion. No MIC was determined. One isolate from MGH had an MIC of 0.125 $\mu\text{g/mL}$.

Overall, 13.3% of patients with pneumococcal pneumonia were admitted to an ICU for respiratory failure, mechanical ventilation, or hemodynamic collapse. The median length of hospital stay was 7 days (Table 2). No differences in ICU admissions or length of stay was demonstrated among the three study groups. There were no differences in rate of symptom resolution among the three groups; however, the median time from presentation to return to usual household activities was 21 days for bacteremic patients and 14 days for nonbacteremic, pure etiology patients ($P = .05$). Symptom resolution was slow as

Table 1. Antimicrobial Therapy Within 30 days

Antimicrobial Agents by Class*	Bacteremic Patients, % (n = 65)	Nonbacteremic Patients, %		All Patients, % (n = 158)	P Value
		Pure Etiology (n = 74)	Mixed Etiology (n = 19)		
Aminopenicillins					
Amoxicillin	3.1	23.0	31.6	15.8	.001
Amoxicillin and clavulanate	7.7	6.8	21.1	8.9	.13
Ampicillin	20.0	8.1	31.6	15.8	.021
Ampicillin and sulbactam	24.6	10.8	15.8	17.1	.10
Penicillins, extended spectrum					
Ticarcillin and clavulanate	1.5	5.4	0.0	3.2	.35
Penicillins, natural					
Penicillin G	64.6	21.6	5.3	37.3	.001
Penicillin V	52.3	20.3	10.5	32.3	.001
Cephalosporins					
First generation					
Cephalexin	3.1	2.7	5.3	3.2	1.00
Cefazolin	13.9	6.8	21.1	11.4	.16
Second generation					
Cefuroxime	35.4	43.2	52.6	41.1	.36
Third generation					
Ceftriaxone	7.7	4.1	0.0	5.1	.35
Ceftazidime	4.6	5.4	5.3	5.1	1.00
Other agents					
Ciprofloxacin	7.7	13.5	5.3	10.1	.40
Erythromycin	41.5	43.2	31.6	41.1	.65
Gentamicin	36.9	17.6	47.4	29.1	.008
Sulfamethoxazole-trimethoprim	7.7	23.0	10.5	15.2	.36
Other agents					
Clindamycin	6.2	9.5	26.3	10.1	.036
Vancomycin	9.2	8.1	5.3	8.2	.86
Metronidazole	10.8	2.7	0.0	5.7	.07

*Antimicrobial agents used in $\geq 2.0\%$ of patients within 30 days of presentation.

Table 2. Outcomes for 3 Groups of Patients with Pneumococcal Pneumonia

Outcome Measures	Bacteremic Patients, % (n = 65)	Nonbacteremic Patients		All Patients, % (n = 158)	P Value
		Pure Etiology (n = 74)	Mixed Etiology (n = 19)		
Admission to ICU, %	15.4	12.2	10.5	13.3	.80
Ventilated, no. and (% of those admitted to ICU)	7/10 (70)	5/9 (56)	1/2 (50)		
Median length of hospital stay, d*	7.5	6.5	7	7	.44
Pneumonia-related mortality, %	7.7	2.7	5.3	5.1	.40
Symptom resolution, %†					
Cough	62.5	41.0	45.5	50.0	.08
Dyspnea	47.4	48.2	44.4	47.5	.98
Sputum production	64.7	48.3	30.0	52.0	.11
Pleuritic chest pain	81.8	91.4	87.5	86.8	.50
Fatigue	40.8	37.1	23.1	37.1	.50
Return to daily household activities, d	21	14	‡	17	.048
Return to usual activities for workers, d	13	6	—	9	.16
Return to work, d	16	10	—	12	.26

*Length of initial hospital stay was computed for inpatients who were alive at 30 days: 58 bacteremic patients; 58 nonbacteremic, pure etiology patients, and 17 nonbacteremic, mixed etiology patients.

†Symptom resolution was defined as the absence of the symptom at 30 days for those patients who had the symptom at presentation. Denominator includes all patients who had data for the symptom recorded at baseline and at 30 days.

‡Data on these items available for only 3 patients in this group.

evidenced by persistence of symptoms at 30-day follow-up (Table 2). At that time, 50% of the patients complained of cough, 53% were dyspneic, 48% had sputum production, and 13% still had pleuritic chest pain. Sixty-three percent of the patients had fatigue.

The mortality rate at 30 days was 7.7% for bacteremic patients; 2.7% for nonbacteremic, pure etiology patients; and 5.3% for nonbacteremic, mixed etiology patients (Table 2). In all instances death was pneumonia-related. Table 3 shows the 30-day mortality rates according to risk group. Half of the bacteremic patients fell into the low risk group (I to III) for mortality. None of the 32 bacteremic patients in these low risk groups died compared with 4 (33%) of 12 in risk group V.

One hundred patients (63.3%) developed a complication within 30 days of presentation (Table 4). Anemia was more frequent among bacteremic patients (18.5%) than nonbacteremic patients (5.4% and 10.5% for pure etiology and mixed etiology, respectively; $P = .05$). Bacteremic patients were also more likely than either group of nonbacteremic patients to have renal insufficiency (24.6% vs

9.5% and 10.5% for pure etiology and mixed etiology, respectively; $P = .04$). Three of the 5 bacteremic patients with leukopenia had alcoholism, while none of the 2 nonbacteremic patients with leukopenia had alcoholism. Suppurative complications were relatively infrequent, but 3 patients (1.9%) had empyema, 1 (0.6%) had endocarditis, and 1 (0.6%) had septic arthritis.

DISCUSSION

About 7% of the 2,287 CAP patients in our study had *S. pneumoniae*. This is probably an underestimate of the number of cases due to this microorganism since diagnostic studies were pursued at the discretion of the attending physician. This rate of pneumococcal pneumonia as a percentage of all cases of CAP is far below the 20% to 60% rate quoted for North America and the 60% to 75% rate for Britain.¹⁴ There are several reasons for this discrepancy. The studies quoted probably do not reflect the current situation. A carefully done study by Mundy et al.³ at Johns Hopkins Hospital in Baltimore from November

Table 3. Mortality at 30 days According to Prediction Rule for Short-term Mortality¹¹

Risk Group	Bacteremic Patients (n = 64)	Nonbacteremic Patients		All Patients (n = 158)	P Value
		Pure Etiology (n = 74)	Mixed Etiology (n = 19)		
I, no. who died/no. in group	0/10	0/17	0/4	0/31	NA
II, no. who died/no. in group	0/14	0/13	0/2	0/29	NA
III, no. who died/no. in group	0/8	0/17	0/2	0/27	NA
IV, no. who died/no. in group	1/20	0/20	0/7	1/47	.001
V, no. who died/no. in group	4/12	2/7	1/4	7/23	1.00

NA, not applicable since there were no deaths in these groups.

Table 4. Complications (%) Occurring Within 30 days

Complications	Bacteremic Patients, % (n = 65)	Nonbacteremic Patients		All Patients, % (n = 158)	P Value
		Pure Etiology (n = 74)	Mixed Etiology (n = 19)		
None	26.2	43.2	47.4	36.7	.04
1	27.7	24.3	10.5	24.1	
2	3.1	9.5	10.5	7.0	
3	10.8	6.8	10.5	8.9	
≥4	32.4	16.2	21.2	23.4	
Pulmonary					
Respiratory failure	46.2	32.4	36.8	38.6	.25
Respiratory failure requiring mechanical ventilation	13.9	10.8	5.3	11.4	.60
Cardiovascular					
Congestive heart failure	16.9	10.8	5.3	12.7	.33
Shock	18.5	13.5	5.3	14.6	.34
Atrial Arrhythmias	13.9	6.8	15.8	10.8	.30
Hematologic					
Anemia (hematocrit <24.9%)	18.5	5.4	10.5	11.4	.05
Thrombocytopenia (<100,000/ μ L)	12.3	5.4	5.3	8.2	
Leukopenia (<3,000/ μ L)	7.7	2.7	0.0	4.4	
Miscellaneous					
Hepatic abnormalities	18.5	12.2	10.5	14.6	.50
Renal insufficiency	24.6	9.5	10.5	15.8	.04
Suppurative infection	6.2	2.7	0.0	3.8	.49
Empyema	1.5	2.7	0.0	1.9	.53
Endocarditis	1.5	0.0	0.0	0.6	.53
Septic arthritis	1.5	0.0	0.0	0.6	.53

1990 to November 1991 found that 15.1% of 201 HIV-uninfected patients with CAP requiring hospitalization had pneumococcal pneumonia. This was a marked decrease in the proportion of pneumonia due to *S. pneumoniae*, compared with a study done at Johns Hopkins Hospital during 1965-1966 in which 62% of patients had pneumococcal pneumonia.³ Another reason for the low rate of pneumococcal pneumonia in our study is that outpatients with pneumonia were included in the study population and this group had few diagnostic tests performed, so we do not know the true rate of *S. pneumoniae* pneumonia in this group. Among our inpatients, only 4.6% had bacteremic pneumococcal pneumonia; however, this compares favorably with 6.3% in Mundy's study,³ and with the 5.5% rate in a study of 2,776 patients with CAP requiring hospitalization in Franklin and Summit Counties, Ohio in 1991.¹⁵ The percentage of cases of CAP due to *S. pneumoniae* depends upon the diagnostic techniques used, the assiduousness with which specimens are collected, and the rapidity with which they are transported to the microbiology laboratory and processed for culture.

The most sensitive diagnostic test for diagnosis of pneumococcal pneumonia is detection of pneumolysin by polymerase chain reaction, or by detecting immune complexes of pneumolysin antigen-antibody^{16,17} or pneumolysin antibodies.¹⁷ Using these techniques, pneumococcal pneumonia was diagnosed in 32% to 55% of patients with

CAP.^{16,17} In our study, the rate of pneumococcal pneumonia was highest at the MGH, Boston site. The higher rate at the Boston site reflects a higher rate of sputum specimens processed for culture within 24 hours of presentation at this site; 50% of the patients hospitalized at MGH had such a specimen compared with 15% at VGH, Halifax. The pneumococcal bacteremia rate among inpatients was 6.4% at Halifax and 5.4% at MGH, Boston, indicating that the overall rate of pneumococcal pneumonia was probably the same at both sites.

Forty-one percent of the 158 patients with pneumococcal pneumonia were bacteremic. In Burman's study,¹⁶ in which a number of serological techniques were employed to diagnose pneumococcal pneumonia, 21% of the patients were bacteremic.

Streptococcus pneumoniae is found in the upper respiratory tract of healthy persons,¹⁸ so its isolation from sputum cannot be considered proof that the pneumonia is due to the pneumococcus. For this reason, some investigators do not use the results of sputum culture to assign etiology.¹⁹ However, in practice, clinicians equate isolation of *S. pneumoniae* from the sputum with pneumococcal pneumonia. It is thus important to compare definite (i.e., bacteremic) pneumococcal pneumonia with presumptive (i.e., nonbacteremic) pneumococcal pneumonia. There is also a third group of patients—those who have *S. pneumoniae* and other respiratory pathogens im-

plicated. We compared all 3 groups of patients. There were no differences in demographic features, comorbidities, or severity of illness at presentation.

Fine et al.¹¹ derived a prediction rule that stratifies patients with CAP into 5 classes with respect to the risk of death within 30 days. The mortality rates for the entire PORT study cohort of patients in risk classes I, II, and III were 0.1%, 0.6% and 0.9%, respectively. For classes IV and V, the rates were 9.3% and 27.0%.¹¹ Almost half (49.2%) of the patients with bacteremic pneumococcal pneumonia in the current study were in classes I to III, and none of them died within 30 days of presentation. In contrast, 33% of those in class V died. This is the first time that this prediction rule has been applied to patients with bacteremic pneumococcal pneumonia. It clearly illustrates that some of these patients fall into a low risk group for mortality. It is likely that our data underestimate the proportion of patients with bacteremic pneumococcal pneumonia who are in risk classes I to III, since most of the patients treated on an ambulatory basis did not have blood cultures done. The 2 outpatients with bacteremic pneumococcal pneumonia in our study responded well to treatment with oral antibiotics. However, additional data are needed before outpatient therapy of bacteremic pneumococcal pneumonia with oral antibiotics can be recommended.

The patients with bacteremic pneumococcal pneumonia were more likely to be treated with natural penicillins than were the other two groups. The sequence of events in terms of antimicrobial therapy was that at the time of admission empiric therapy usually consisted of 2 antibiotics.²⁰ The choice varied according to geographic site; e.g., cefuroxime plus erythromycin was most commonly used in Halifax, while cefuroxime plus gentamicin was most commonly used in Boston.²⁰ When the blood culture result was obtained, 64.6% of the bacteremic patients were then switched to penicillin alone. In contrast, patients with nonbacteremic, pure etiology, pneumococcal pneumonia were rarely treated with penicillin only. The reasons for this cannot be clearly ascertained from our study, but it is likely that physicians remained uncertain that *S. pneumoniae* was the cause of the pneumonia.

The current increase in penicillin-resistant *S. pneumoniae* in the United States has prompted infectious disease clinicians to change the way they treat pneumococcal infections. Seventy-two percent of respondents to an Infectious Diseases Society of America questionnaire indicated that they would select cefotaxime and/or ceftriaxone to treat patients with a presumptive diagnosis of pneumococcal pneumonia and probable bacteremia; 19% would select vancomycin.²¹ There was no high-level penicillin resistance among the 50 isolates tested from bacteremic patients; 2 (4%) isolates had intermediate resistance. Since our study enrolled patients from October 1991 through March 1994, the pneumococcal penicillin susceptibility data are already dated. Currently there is rapid evolution of penicillin-resistant *S. pneumoniae* in

North America. A study by Butler et al.²² of pneumococcal isolates recovered from normally sterile body sites of patients at 12 hospitals in 11 states during 1993-1994 found that 14.1% of 740 isolates were penicillin-nonsusceptible (intermediate resistance MIC ≥ 0.1 $\mu\text{g/mL}$) and 3.2% had high-level resistance (MIC ≥ 2.0 $\mu\text{g/mL}$). One of the participating hospitals in Butler's study was in Pennsylvania.

Overall, 13.3% of our patients were admitted to an ICU and 15.4% of bacteremic patients were admitted to an ICU, compared with 12.2% and 10.5% for the pure etiology and mixed etiology of two nonbacteremic groups, respectively. In studies that have focused on severe CAP requiring admission to ICU, *S. pneumoniae* is the most common etiology, accounting for 18 to 37% of the cases.^{23,24}

The pneumonia-related mortality rate was lowest (but not statistically significant) for the nonbacteremic, pure etiology group at 2.7% and highest for the bacteremic group at 7.7%. The mortality rate in bacteremic pneumococcal pneumonia has been related to factors that also apply to mortality for pneumonia in general, such as age,²⁵ alcoholism,²⁶ and involvement of two or more lobes radiographically.^{8,27} There are also organism-specific factors that influence mortality. In Austrian and Gold's study of 529 patients, the mortality rate for those infected with *S. pneumoniae* capsular polysaccharide type I was 8%, and for type III, it was 50%.⁶

The complication rate among the bacteremic patients was higher than among the nonbacteremic groups, but only achieved statistical significance for anemia and renal insufficiency. Tilghman and Finland,²⁷ in a study of 1,586 cases of pneumococcal pneumonia (582 were bacteremic) from 1929 to 1935 (preantibiotic era), showed that complications occurred twice as often in the bacteremic group. Twelve percent of their entire group had a suppurative complication; empyema was most common at 7%, followed by pulmonary abscess (2.7%), endocarditis (1%), and meningitis (1.2%). Our suppurative complication rate was 3.8% overall and 6.2% for the bacteremic group. Our empyema rate was 1.9%, while the rate of endocarditis was 0.6%. None of our patients had a complication of meningitis.

The leukopenia rate was 2.7 times higher in the bacteremic group than in the nonbacteremic groups (7.7% vs 2.7%), but the difference was not significant. In a review of 93 episodes of pneumococcal bacteremia, Perlino and Rimland²⁸ noted that 15 patients were leukopenic and 12 (80%) died compared with 40 (51%) of 78 of the nonleukopenic patients ($P < .05$). They also found that 12 of the 15 leukopenic patients had alcoholism; the bacteremia was fatal in 10 of these 12 patients. Three of our 5 bacteremia patients with leukopenia had alcoholism.

The Centers for Disease Control recently reported three outbreaks of pneumococcal pneumonia among residents of nursing homes in Massachusetts, Oklahoma, and Maryland.²⁹ Almost 8% of the bacteremic pneumococcal pneumonia patients in our study were from a

nursing home. This compares with 14% for the entire group of 1,343 inpatients with pneumonia. These data indicate that pneumococcal pneumonia is an important problem in nursing homes despite the policy of offering pneumococcal vaccine to nursing home residents. Pneumococcal vaccine was infrequently utilized (at least according to self-reports) by our patients.

While most of the discussion has focused on a comparison between bacteremic and nonbacteremic pneumococcal pneumonia, we also defined the symptoms of pneumococcal pneumonia. The slow resolution of these symptoms is reflected by the finding that 63% of patients complained of fatigue at 30 days, and about half still had symptoms of cough, dyspnea, and sputum production. Thirteen percent still had pleuritic chest pain. In a previous study, we found that older patients with pneumonia complained of fewer symptoms; patients aged 45-64, 65-74, and ≥ 75 years had 1.4, 2.9, and 3.3 fewer symptoms, respectively, than patients aged 18-44. Persistence of symptoms at 30-day follow-up was common.³⁰

Our study has several strengths and limitations. The strengths are the prospective nature of the study, its large size, geographic diversity (United States and Canada), use of a validated pneumonia-specific severity of illness scoring system, 30-day follow-up, and attention to important outcomes, such as time to return to usual activities, that have not been studied previously in this group of patients. The limitations are the observational nature of the study (some important investigations, such as blood and sputum cultures, were performed at the discretion of the attending physicians) and the incomplete enrollment (some patients did not wish to participate). These limitations may affect 1 of our key findings, namely that 50% of the bacteremic pneumococcal pneumonia patients were in the low risk group for mortality. However, a large multicenter study of pneumococcal bacteremia³¹ found that 51% had an APACHE II score (an acute physiology and chronic illness score) of <12 and a mortality rate of 2.6%.

In conclusion, among patients with CAP there is a low rate of bacteremic pneumococcal pneumonia, and 50% of these patients are at low risk for mortality. The time to return to usual household activities is significantly longer for bacteremic than nonbacteremic patients with pneumococcal pneumonia. Antibiotic therapy seems to be influenced by the results of blood cultures, since a significantly greater number of the bacteremic group received penicillin therapy. Finally, resolution of symptoms in patients with pneumococcal pneumonia can take more than 1 month.

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