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INTERNATIONAL NOTES

Pneumococcal Bacteremia in Adults over a 10-Year Period at University Hospital, Leiden

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The medical records on all cases of pneumococcal bacteremia in adults at the University Hospital, Leiden, over a 10-year period (1976–1986) were retrospectively reviewed. In this series of 147 episodes (an annual incidence of 0.8 episodes/10,000 adults), overall mortality was 25.9%. Factors significantly related to a higher mortality rate were shock, respiratory insufficiency, preexisting renal failure, and rapidly fatal underlying disease. Several laboratory abnormalities — such as a low percentage of band forms, an elevated level of serum lactate dehydrogenase, and hyperbilirubinemia — were significantly related to a poor outcome. Multilobar pneumonia and meningitis were both associated with high mortality, although not to a statistically significant degree. Discriminant analysis showed the presence of shock as the most powerful predictive factor of death. Surprisingly, prior splenectomy did not correlate with higher mortality. Treatment with β -lactam antibiotics favorably influenced the outcome of illness in patients with ultimately fatal and nonfatal underlying disease, while the use of these agents in patients with rapidly fatal underlying disease did not correlate significantly with a good prognosis.

The pneumococcus (*Streptococcus pneumoniae*) is one of the microorganisms most pathogenic for humans. Despite the advent of penicillin, the pneumococcus has remained a major cause of disease. It is the foremost cause of community-acquired pneumonia and of bacterial meningitis in the elderly [1–4]. The latter infection still has a disturbingly high fatality rate.

In this paper, data are presented on the incidence of and the case-fatality rate for pneumococcal bacteremia in an adult population. These data are based on a retrospective analysis of records of patients from whose blood *S. pneumoniae* was isolated. The aim of this retrospective study was to discern risk fac-

tors predictive of a poor outcome in patients who present with pneumococcal bacteremia.

Patients and Methods

The records of adult patients from whose blood *S. pneumoniae* was isolated between January 1976 and January 1986 at the University Hospital, Leiden (UHL), were reviewed. UHL is a 900-bed hospital in which both general health care and all specialties are covered. Patients were identified by a search for cases of pneumococcal bacteremia in the computerized registry of the microbiology laboratory. A total of 147 episodes in 142 patients were found. The records of three patients could not be retrieved; however, since their age and sex and the outcome of their illness were known, their data were included in the calculation of incidence and mortality. One patient's record provided insufficient data. Thus, a total of four patients were not included in further analyses.

Blood cultures were usually performed if the patient had fever (i.e., a rectal temperature of $>38.5^{\circ}\text{C}$). Isolates of *S. pneumoniae* were identified by standard laboratory techniques; isolates are not routinely typed in the Netherlands.

Episodes were categorized as community acquired (present on admission) or nosocomial (both the

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manifestation of illness and positive blood cultures at least 3 days after admission). Meningitis was defined by the isolation of *S. pneumoniae* from CSF or the detection of pneumococcal antigen in CSF. Empyema was defined by the isolation of *S. pneumoniae* from pleural fluid. Endocarditis was defined by the criteria of Von Reyn et al. [5]. Arthritis was diagnosed clinically. The diagnosis of pneumonia and sinusitis was in all cases confirmed by roentgenography. Pneumococcal peritonitis was defined by the isolation of *S. pneumoniae* from ascites. Respiratory insufficiency was defined as a PaO₂ of <7 kPa or a PaCO₂ of >7 kPa. Shock was defined as systolic blood pressure less than 90 mm Hg in addition to other clinical signs of shock. Death was considered directly related to pneumococcal bacteremia when, as judged by clinical and pathologic criteria, the bacteremia was the prime cause.

The underlying disease of the patients was classified (according to McCabe and Jackson [6]) as rapidly fatal, ultimately fatal, or nonfatal. Blood counts and chemical tests were assessed on the SMA-12 multichannel autoanalyzer (Technicon, Tarrytown, N.Y.); data obtained on the day of the positive blood culture or the day thereafter were used in this analysis. Antimicrobial therapy was scored with regard to the choice of antibiotic.

Statistical analysis for comparison of two groups was performed by the χ^2 test for dichotomous variables and Student's *t* test for continuous variables (sometimes after a logarithmic transformation). For identification of the risk factors most predictive of a poor outcome of pneumococcal bacteremia, 10 variables were studied: age, prior splenectomy, previous renal failure, underlying disease, chest roentgenographic abnormalities, origin of infection, meningitis, shock, respiratory insufficiency, and antibiotic use. These variables were studied in cross-tabulations against death or survival with stepwise discriminant analysis [7].

Results

Characteristics of patients. Between January 1976 and January 1986, 147 episodes of pneumococcal bacteremia were registered at UHL, for an average of 14.7 episodes per year. For an estimated adult adherence population (a population calculation used by the Dutch government for hospitals with a large number of referrals, e.g., university hospitals) of 180,000 patients per year, the annual inci-

dence of pneumococcal bacteremia is ~ 0.8 cases/10,000 adults. In terms of admissions (average, 17,335 adults per year), the figures are indicative of 0.8 episodes/1,000 admissions.

The characteristics of the patients studied are summarized in table 1. The mean age of the entire study

Table 1. Characteristics of patients and outcome of 143 episodes of pneumococcal bacteremia.

Characteristic (unit of measure)	Median \pm SD value (range) for indicated group*		P
	Nonfatal (n = 106)	Fatal (n = 37)	
Age (y)	58.5 \pm 20.6 (15-91)	46.0 \pm 20.2 (20-92)	.50
Sex (no. of episodes)			
M	45	13	
F	61	24	.55
Origin of infection (no. of episodes)			
Hospital	29	14	.32
Community	77	23	
Duration of illness before therapy (d)	2.0 \pm 3.1	2.0 \pm 6.9	.49
Temperature ($^{\circ}$ C)	39.2 \pm 0.8	39.0 \pm 1.1	.62
Blood pressure (mm Hg)			
Systolic	120 \pm 26	102 \pm 33	<.01
Diastolic	70 \pm 18	70 \pm 23	.15
Pulse (min ⁻¹)	115 \pm 21	120 \pm 25	.32
Symptoms (no. of episodes) [†]			
Chest pain	32	5	<.02
Chills	34	4	.07
Leukocytes ($\times 10^9$ /L)	10.6 \pm 8.8	13.0 \pm 9.2	.13
Band forms (%)	31 \pm 22	22 \pm 18	<.02
Lactate dehydro- genase (U/L)	176 \pm 281	290 \pm 1247	<.001
Alkaline phosphatase (U/L)	95 \pm 139	93 \pm 86	.93
Erythrocyte sedi- mentation rate (mm/1st h)	71 \pm 39	66 \pm 43	.60
Bilirubin (μ mol/L)	15 \pm 24	28 \pm 110	<.001
Sodium (mmol/L)	134 \pm 5	133 \pm 8	.40

* For some characteristics, only median values or median \pm SD values are shown.

[†] These data concerned 140 episodes instead of 143.

population was 52 years, with a range from 15 to 92 years. Of the 147 episodes, 69 (47%) occurred in 67 patients over 60 years of age. Of the 143 evaluable bacteremic episodes, 58 occurred in male and 85 in female patients ($P < .01$). In 43 episodes (30%) pneumococcal infection originated in the hospital, whereas in 100 episodes it was community acquired. Nosocomial pneumococcal infection was rare on the various surgical wards ($n = 5$) but was more frequent on the medical wards ($n = 38$). Pneumococcal bacteremia was secondary to pneumonia in 91 episodes. In the other 52 episodes, bacteremia was due to pneumococcal infection outside the lung (in 24 cases, without an identifiable portal of entry).

Underlying disease and splenectomy. The number of patients classified as having underlying disease is shown in table 2. The group classified as hav-

ing nonfatal underlying disease included 11 patients with no known underlying illnesses.

Fifteen episodes occurred in patients who had been splenectomized; the total number of splenectomies performed at this hospital in the 10-year period was 354. The interval between splenectomy and pneumococcal infection ranged from 3 days to 34 years. In seven of the 15 bacteremic episodes in splenectomized patients, primary bacteremia was present; i.e., no apparent portal of entry could be identified.

Complications. A wide range of complications occurred in a large number of patients. These events are summarized in table 3.

Treatment. Treatment with a β -lactam antibiotic was considered appropriate. Thus, 129 episodes were treated appropriately. In nine of 14 episodes not treated with a β -lactam antibiotic, drugs were withheld for the following reasons: clinically insignificant bacteremia (two cases), terminal oncologic disease (five), and bacteremia occurring as a fulminant lethal event (two). In the other five of these 14 episodes, an aminoglycoside, a sulfonamide, trimethoprim-sulfamethoxazole, or a tetracycline was given.

Outcome and analysis of risk factors. Bacteremic episodes ended fatally in 38 cases; with a total of 147 episodes, the overall mortality rate was 25.9%. With exclusion of the nine untreated cases, the corrected mortality rate for treated pneumococcal bacteremia dropped to 22.5%. Analysis of the study population by decade of age showed no significantly

Table 2. Relations between potential risk factors and outcome of pneumococcal bacteremia.

Risk factor, category	No. of episodes from indicated group with factor			P*
	Total (n = 143)	Nonfatal (n = 106)	Fatal (n = 37)	
Underlying disease†				
RFD	28	11	17	
UFD	50	41	9	<.001
NFD‡	65	54	11	
Splenectomy				
Yes	15	13	2	.38
No	128	93	35	
Preexisting renal failure				
Yes	8	1	7	<.001
No	135	105	30	
Preexisting hepatic failure				
Yes	5	3	2	.83
No	138	103	35	
Chest roentgenographic abnormality				
Pneumonia only	80	56	24	
Pneumonia with complications	11	9	2	.43
Extrapulmonary infection	52	41	11	

* P values pertain to differences between two groups—the nonfatal and the fatal.

† RFD = rapidly fatal diseases; UFD = ultimately fatal disease; and NFD = nonfatal disease.

‡ The NFD group included 11 patients with no known underlying diseases.

Table 3. Complications during 143 episodes of pneumococcal bacteremia and outcome of illness.

Complication	No. of deaths/ no. of episodes		P*
	Complication present	Complication absent	
Multilobar pneumonia	15/38	22/105	.19
Empyema	2/11	35/132	.80
Arthritis	1/4	36/139	1.0
Endocarditis	1/5	36/138	1.0
Meningitis	7/15	30/128	.10
Shock	18/25	19/118	<.001
Respiratory insufficiency	8/15	29/128	<.02
Cardiac arrhythmia	6/13	31/130	<.15
Peritonitis	1/1	36/142	<.58

* P values pertain to differences in mortality between two groups—complication present and complication absent.

poorer outcome for any decade. The relative number of deaths in male and female patients was also similar (table 1). Of a large number of clinical features, only a low systolic blood pressure and an absence of pleuritic chest pain were significantly related to mortality rate. Laboratory data analysis showed a significant association between a low percentage of band forms in the blood smear, a high serum level of lactate dehydrogenase, and a high serum level of bilirubin on the one hand and a poor outcome on the other. As indicated in table 2, splenectomy proved not to be a significant risk factor. Rapidly fatal underlying disease was a highly significant risk factor for poor prognosis, as was preexisting renal failure ($P < .001$ for both). As indicated in table 3, shock and respiratory insufficiency were the only complications significantly related to a poor outcome ($P < .001$ and $P < .02$, respectively). Complications proved to be additive in determining a poor outcome.

Despite the fact that all treated bacteremic episodes in patients with rapidly fatal underlying disease were treated with β -lactam antibiotics, the fatality rate was 60%. This outcome was significantly poorer than that for β -lactam-treated patients with ultimately fatal or nonfatal underlying disease ($P < .001$). Treatment of the latter groups with β -lactam agents resulted in mortality rates of 0 and 12%, respectively.

Stepwise discriminant analysis showed the most prognostic factors to be (in descending order) the presence of shock, the existence of rapidly fatal underlying disease, the presence of meningitis, and the involvement of multiple lobes. Analysis of these four variables yielded 32 correct predictions of 37 fatal outcomes (87%) and 87 correct predictions of 106 nonfatal outcomes (82%).

Discussion

In this retrospective study of 147 episodes of pneumococcal bacteremia, the case-fatality rate was 25.9% for all episodes and 22.5% of episodes treated with antibiotics. Patients with rapidly fatal underlying disease had a poor prognosis if they manifested pneumococcal bacteremia. Apart from rapidly fatal underlying disease, a number of other risk factors were found, including preexisting renal failure, presence of shock, presence of respiratory insufficiency, absence of pleuritic chest pain, low number of band forms, and elevated serum levels of lactate

dehydrogenase and bilirubin. In these respects our results are similar to those of studies from other countries during the antibiotic era [8–16]. As the most powerful predictive factors of a poor outcome of illness, we found first of all the presence of shock, which was followed in significance by rapidly fatal underlying disease, the presence of meningitis, and multilobar pneumonia.

Some divergence from prior studies exists, however. First, we did not find increased mortality with advanced age [8, 17]. A partial explanation could be that in our study many relatively young patients (under 50 years of age) had rapidly fatal underlying disease. Another factor of possible influence is that elderly patients may currently tend to seek medical attention more promptly than in previous years [18]. Second, we did not find a significantly higher mortality among patients with nosocomial bacteremia than among those with community-acquired bacteremia; this result is in contrast to those of recent studies of veterans [19]. Third, an intriguing observation not previously made is that pneumococcal bacteremia occurred significantly more frequently in women than in men. However, case-fatality rates were similar for the two sexes. Fourth, mortality among splenectomized persons at UHL was only 0.6%, whereas Singer [20], in his study of more than 2,795 splenectomized persons, reported a much higher mortality rate of 2.52%. This difference in death rate cannot be explained by a higher degree of vaccination in our group, since only one of the splenectomized persons had been vaccinated before developing pneumococcal bacteremia. One hypothesis is that in a small country like the Netherlands these patients are able to seek medical attention at a comparatively early stage, resulting in prompt treatment.

In our series, appropriate therapy did not have an effect on the course of illness in patients who were particularly at risk—i.e., those with rapidly fatal underlying disease. This observation confirms the importance of underlying disease in the treatment and outcome of infections [6]. It also emphasizes the urgent need for specific preventive measures in this high-risk group.

In conclusion, our study shows no major geographic differences with regard to the incidence, outcome, or clinical picture of pneumococcal bacteremia. However, some points of divergence with prior studies exist; these discrepancies may be related to country size, patient population, and other factors.

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