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Contributions to an understanding of community-acquired pneumonia

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Community-acquired pneumonia of diverse aetiology: prognostic features in patients admitted to an intensive care unit and a "severity of illness" score

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Abstract. In a retrospective study of 73 patients with community-acquired lobar pneumonia of diverse aetiology admitted to an intensive care unit, an attempt was made to identify those factors among the demographic and clinical features and results of initial laboratory investigations that were predictive of the ultimate outcome. A lower mean white cell count ($p = 0.03$), platelet count ($p = 0.02$), total serum protein ($p = 0.005$) and albumin ($p = 0.02$) and a higher mean serum creatinine ($p = 0.03$) and phosphate level ($p = 0.02$) appeared to be predictive of a poor prognosis. The most significant variable predictive of mortality, was the presence of bacteraemia ($p = 0.0005$). Severity of illness scoring systems by omitting microbiological data appear to underestimate predicted patient mortality. The mortality rate of critically ill patients with community-acquired lobar pneumonia remains high, despite advances in antimicrobial chemotherapy and intensive care unit facilities, particularly in the presence of certain negative prognostic factors of which the presence of bacteraemia is the most important.

Key words: Community-acquired lobar pneumonia – Intensive care unit – Bacteraemia

Community-acquired pneumonia is a frequent reason for the admission of patients to hospital medical wards with the pneumococcus (*Streptococcus pneumoniae*) being the most common causative organism [1–4]. The introduction of penicillin was associated with a marked reduction in both the morbidity and mortality associated with pneumococcal disease. However, there remains a number of clearly defined features [5–8] which, when present at the time of admission to hospital, appear to predict a poor prognosis in patients with pneumococcal pneumonia. The eventual outcome in cases with these negative prognostic features appears, moreover, to have been little improved by the advances in antimicrobial chemotherapy [9, 10] and critical care medicine [11, 12]. Although it is possible that similar negative prognostic factors may exist in lobar pneumonia due to bacteria other than the pneumococcus, adequate documentation of these is not available [13].

We reviewed the aetiology, clinical features and outcome of all cases of community-acquired lobar pneumonia admitted to our intensive care unit during a 42-month period. The object of the study was to determine the applicability of the well-known negative prognostic features in pneumococcal disease to a heterogeneous group of patients with lobar pneumonia of diverse aetiology, and to assess their association with a severity of illness scoring index.

Patients and methods

We retrospectively analysed the records of all patients with community-acquired lobar pneumonia admitted to the Hillbrow Hospital Intensive Care Unit between January 1982 and July 1985. The Hillbrow Hospital is an urban general hospital admitting mainly black patients from the Johannesburg area. Lobar pneumonia was defined as an acute respiratory illness with clinical and radiologic evidence of unilobar or multilobar pulmonary consolidation. The analysis was based on the initial clinical and radiological features, and the results of laboratory investigations in each patient at the time of admission to hospital

Demographic and clinical features analysed included the age and sex, alcohol and smoking habits, the duration of illness prior to hospital admission, initial arterial blood pressure, heart rate and rate of respiration and the number of affected pulmonary lobes. Laboratory investigations analysed included the initial haemoglobin level and indices of red blood cell morphology, the leucocyte and platelet counts and the blood urea, creatinine, electrolytes, glucose, urate, calcium and phosphate levels. Indices of hepatic function measured included the serum levels of bilirubin, hepatic enzymes, total serum protein and albumin.

The entity of "lobar pneumonia" was chosen as the entry criterion into the study in order to include patients with mainly the "common bacterial causes" of pneumonia. This entity would exclude many cases of pneumonia due to aspiration, *M tuberculosis*, and the so-called "atypical" infections caused by *Mycoplasma pneumoniae*, chlamydiae and *Coxiella burnetti*, in which lobar consolidation is less common, as well as many cases of legionellosis. We specifically excluded cases with associated extrathoracic complications.

Patients were admitted to the intensive care unit, either because they required mechanical ventilation, or because they were judged to be in an unstable condition requiring intensive medical and nursing care. Although during the study period scoring of the severity of patient illness on admission to our ICU was not routinely undertaken, scoring was done retrospectively using the Simplified Acute Physiology Score System (SAPS) [14–17]. As by convention occasional missing data were recorded as normal values. No patient had received antibiotic therapy prior to arrival at the hospital, and all patients entered the intensive care unit within 24 h of admission to hospital.

Bacteriological cultures of blood taken at the time of admission were performed according to standard microbiological techniques, using BACTEC bottles 6B and 7C for the BACTEC 460 instrument (Johnston Laboratories, Towson, Md). Wherever possible specimens of respiratory tract secretions obtained at the time of admission were gram-stained and cultured. Bacteria such as *S. pneumoniae, Staphylococcus aureus*, the gram negative bacilli belonging to the Enterobacteriaeceae family, *Pseudomonas* species *Haemophilus influenza* were specifically sought. Whenever it was deemed appropriate, specimens of serum were tested for the presence of antibodies to *Legionella pneumophila* by the indirect fluorescent antibody test using a polyvalent heat killed antigen suspension [18] and *Mycoplasma pneumoniae* by complement fixation. Criteria accepted as predictive of a putative aetiologic agent in deep cough sputum samples were the presence of significant polymorphonuclear leucocyte exudate in the secretions, the predominance of a specific morphologic type of bacterium on microscopy and its subsequent demonstration in abundance on culture. Antecedant antimicrobial therapy disqualified specimens for assessment.

The therapeutic measures instituted in each patient at the time of admission to the intensive care unit were also analysed. These included data regarding antimicrobial therapy and the use of inotropic agents, and corticosteroids, as well as the need for mechanical ventilation and peritoneal dialysis.

Two procedures were used for the analysis of the data. Categorical variables were analysed by means of the χ^2-test. For the analysis of the continuous variables the patient population was divided into its three largest subgroups, namely patients with blood cultures yielding *S. pneumoniae*, patients with blood cultures yielding *K. pneumoniae*, and patients with negative blood cultures. A two-way analysis of variance was performed using "cuture groups" and "outcome" as the categorising variables. The value of those continuous variables showing apparent differences between the groups were compared with each other by means of the *t*-test, modifying the level of significance according to the procedure described by Bonferroni [19]. Those continuous variables showing no statistically significant difference between the groups were studied further as to their possible importance as predictors of mortality in the group as a whole by comparing their values in "survivors" and "non-survivors" by means of the *t*-test.

Results

Seventy-three patients with community-acquired lobar pneumonia were admitted to the intensive care unit during the study period. There were 57 males and 16 females. Their age ranged between 20 years and 74 years, with a mean age of 44.6 years. Thirty-five patients admitted to alcohol abuse, and 40 patients were known to be current smokers. All patients had been well prior to admission to hospital, but 4 had well controlled diabetes mellitus, and 1 patient with systemic lupus erythematosis was being treated with corticosteroids.

Table 1. Full blood count results of 73 cases

Measurement	Mean	Range
Haemoglobin	13.6 g/dl	(8.0–19.2 g/dl)
Leucocyte count[a]	8.8×10^9 l	($0.6–48.0\times10^9$ l)
Platelet count	233×10^9 l	($17–801\times10^9$ l)

[a] Leucocyte count: $>11.0\times10^9$ l – 22 patients; $4–11.0\times10^9$ l – 22 patients; $<4.0\times10^9$ l – 29 patients

The temperature ranged from 34.6 °C to 40.4 °C with a mean of 37.9 °C. The mean systolic blood pressure was 101 mmHg, and 17 patients were found to be shocked (systolic blood pressure less than 90 mmHg with poor peripheral perfusion). The mean heart rate was 120 beats per minute, and the mean respiratory rate 39 breaths per minute.

Results of routine haematological studies are given in Table 1. Twenty-two patients had leucopaenia (white cell count less than 4.0×10^9/l) and 24 were found to have thrombocytopaenia (platelet count less than 140×10^9/l). The range of the serum urea level was 2.9 to 48.5 mmol/l (mean 12.8 mmol/l), and that of the serum creatinine 17 to 998 μmol/l (mean 183 μmol/l). The range of the serum sodium was 116 to 148 mmol/l (mean 132 mmol/l). Twenty-two patients had a serum sodium of less than 130 mmol/l.

Bacteria were cultured from the blood in 46 cases. The organisms cultured were *S. pneumoniae* in 21, *K. pneumoniae* in 20, and *Escherichia coli, Serratia marcescens* and *Proteus mirabilis* in 1 case each. In the 27 patients with negative blood cultures, the sputum

Table 2. Bacteriology of 73 cases

Aetiological agent	Diagnostic criteria		
	Blood culture	Sputum	Total
Streptococcus pneumoniae	21	5	26
Klebsiella pneumoniae	20	3	23
Staphylococcus aureus	2	1	3
Others	3[a]	2[b]	5
Unknown			16
		Total	73

[a] *Escherichia coli* (1), *Serratia marcescens* (1), and *Proteus mirabilis* (1)

[b] *Serratia marcescens* (1) and *Acinetobacter anitratus* (1)

Table 3. Antimicrobial therapy of 73 cases

Antimicrobial agents	Adult dosage[a]	No. patients treated[b]
Aminoglycosides[c]	3 – 15 mg/kg daily[c]	69
Penicillin G	1.2 – 10 million units daily	66
Cephalosporins[d]	2 – 12 gm daily	49
Erythromycin	2 – 4 gm daily	35
Metronidazole	500 – 700 mg 6 – 8 hourly	19
Clindamycin	1.1 – 2.4 gm daily	14
Chloramphenicol	4 gm daily	9
Other[e]		5
Cloxacillin	0.5 – 1 gm 6 hourly	3
Vancomycin	2 – 4 gm daily	2

[a] Dosages were modified appropriately in renal failure and for peritoneal dialysis; [b] Most patients received more than one antimicrobial agent; [c] Gentamicin 3 – 6 mg/kg daily in 3 doses, tobramycin 3 – 6 mg/kg daily in 3 doses, or amikacin 15 mg/kg daily in 2 doses; [d] Cephradine 2 – 8 gm daily in 6 hourly doses, cefoxitin 3 – 12 gm daily in 4 hourly doses, moxalactam 6 – 12 gm daily in 8 hourly doses, or cefotaxime 4 – 12 gm daily in 6 hourly doses; [e] Piperacillin (3), trimethoprim (1), and fucidic acid (1)

examination was deemed to have yielded putative pathogens in 11 cases. Bacteriological data is given in Table 2. Serological titres for *L. pneumophila* and *M. pneumoniae* infection did not meet the criteria for a positive diagnosis in any of the patients tested.

Details of antimicrobial chemotherapy used are shown in Table 3. Sixty-three of the 73 cases required mechanical ventilation, 57 required inotropic support (isoprenaline and/or dopamine) and 23 patients were given corticosteroids. Eight patients were peritoneally dialysed for renal failure.

The two-way analysis of variance showed no statistically significant difference between the 3 culture groups with regard to any variable tested, although the variable "temperature" was remarkable in that the respective mean temperature was higher in the patients who died in the *K. pneumoniae* group (38.2°) and *S. pneumoniae* group (38.1 °C) and lower in the patients who died in the negative culture group (36.8 °C); the values of $p = 0.0203$ and $p = 0.0376$ respectively did not, however, quite reach statistical significance according to the Bonferroni procedure [19].

Thirty-nine of the 73 patients (53%) died, 23 of them within the first 5 days. The mean SAPS for the group as a whole was 10.8 with a range from four to eighteen. The scoring of occasional missing data as normal values, as by convention, may have resulted in a slight underestimation of severity of patient illness. The predicted mortality rate (%) for a score of 11 has been found to be approximately 24.5 ± 4.1% [15]. Figure 1 demonstrates the range of SAPS and the associated patient mortality. The mean SAPS in non-survivors (39 patients) was 10.5 (range 5 – 18) and in survivors (34 patients) was 11.1 (range 4 – 17]. Neither age, sex, duration of illness prior to hospitalisation, nor alcohol and smoking habits were found to be of assistance in predicting the prognosis. Similarly neither initial blood pressure, heart and respiratory rate, nor the number of affected pulmonary lobes were found to be of prognostic significance.

The comparative laboratory findings in non-survivors as opposed to survivors, expressed as the respective means in each case, followed in brackets by the relevant statistical significance levels were: leucocyte count 6.6×10^9/l and 11.2×10^9/l ($p = 0.03$); platelet count 189×10^9/l and 278×10^9/l ($p = 0.02$); serum creatinine 216 µmol/l and 146 µmol/l ($p = 0.03$); total protein 58.9 g/l and 65.6 g/l ($p = 0.005$); serum albumin 25.5 g/l and 28.2 g/l ($p = 0.02$) and serum phosphate 1.2 mmol/l and 0.87 mmol/l ($p = 0.02$).

The strongest predictor of outcome was the presence of bacteraemia ($p = 0.0005$). Of the 46 patients with positive blood cultures, 32 patients died (70%), whereas only 7 of the 27 patients in the blood culture negative group died (26%). The mean SAPS in bacteraemia positive patients was 11.0 and in those patients with negative blood cultures, 10.4. Figure 2 shows the respective score values and mortality in bacteraemia and nonbacteraemic patients. Within almost each SAPS value significantly more deaths oc-

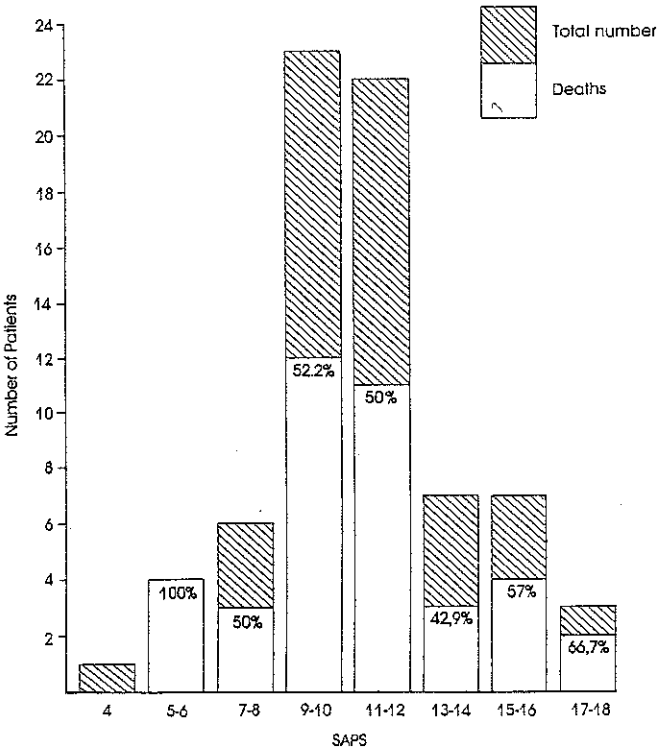

Fig. 1. Relationship between SAPS and outcome in 73 patients with community-acquired lobar pneumonia. The *clear area* within each bar represents the fatality rate in that group of patients

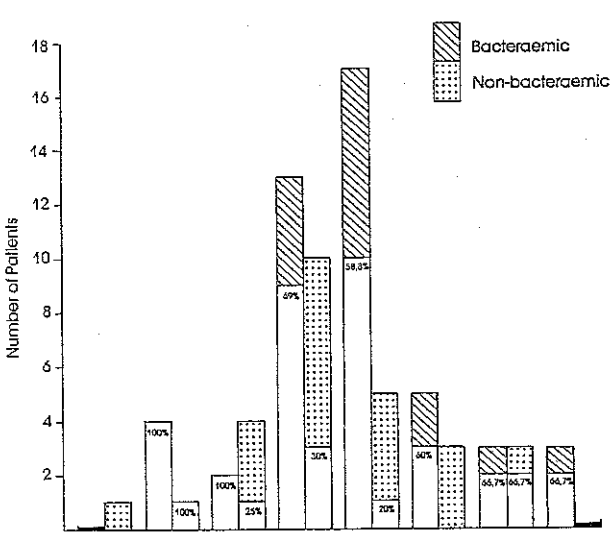

Fig. 2. Relationship between SAPS and outcome in bacteraemic (*cross-hatched bars*) and non-bacteraemic (*dotted bars*) patients with community-acquired lobar pneumonia. The *clear area* within each bar represents the fatality rate in that subgroup of patients

curred in bacteraemic patients. The importance of bacteraemia appears not to have been adequately addressed by the scoring system.

As anticipated, certain therapeutic measures which were employed in the more critically ill patients were associated with a higher mortality, namely corticosteroids ($p = 0.004$), inotropic agents ($p = 0.0001$) and peritoneal dialysis ($p = 0.006$).

Discussion

Despite adequate antimicrobial chemotherapy and advances in intensive care unit facilities, the mortality from pneumococcal disease remains significant [9–12], and there are several well-known factors which, when present at the time of admission to hospital, appear to be associated with a relatively poor prognosis [5–8]. These include advanced age, prolonged period of symptoms prior to the institution of therapy, the presence of pre-existing disease, chronic alcoholism, certain pneumococcal serotypes, extensive pulmonary involvement, the absence of leucocytosis, the presence of intra- or extrathoracic complications, and the presence of bacteraemia. Although it is possible that these negative prognostic factors are applicable in cases of pneumonia due to organisms other than the pneumococcus, adequate documentation of this has not been available.

Although a recent study [20] has attempted to address this question, it included a relatively small number of patients with positive blood cultures, and no documented cases of gram negative infection. In our study we attempted to adequately address the question of prognostic factors in lobar pneumonia of diverse microbiological aetiology. In addition, we have documented the homogeneity of the different subgroups of pneumonia by showing no significant differences between the groups with regard to a number of variables tested.

We documented the importance of a low initial white cell count as a negative prognostic factor in our study group. Its relevance in a heterogeneous group of patients is not unexpected. The significance of a low leucocyte count has been known since the pre-antibiotic era [8], and is often described in pneumococcal disease [7, 8]. Endotoxin is known to cause a decrease in the leucocyte count [21] and the lack of leucocytosis in gram negative infections has been variously attributed to either peripheral sequestration of white blood cells within visceral capillaries [21] or to poor bone marrow reserve and folate deficiency which are characteristic findings in alcoholics [22].

We found, in addition, that a relatively low initial platelet count was an apparent predictor of a poorer prognosis. While this association with pneumococcal disease is not commonly described, it is frequently present in gram negative infections [23]. Thrombocytopaenia, however, may be an early indicator of disseminated intravascular coagulation which is characteristically associated with gram negative infection, but is also known to occur in serious gram positive disease, and endotoxin is known to be associated with a decrease in the platelet count [23, 24].

Estimations of the serum albumin level have been used as indicators of a patient's nutritional status [25–27], a diminished level being clearly associated with dietary protein deficiency. While the resistance to infection may be decreased in malnourished patients [28, 29], it is known that acute infections may, through the action of interleukin-1, precipitate a drop in the serum albumin level [30]. Although the serum albumin level was low in both survivors and non-survivors in our study, it was significantly lower, as was the total serum protein, in the non-survivors. More recently, studies have confirmed the importance of a low serum albumin level as a negative prognostic factor [31] and its value as a predictor of the need for ICU admission [32].

The finding of a higher serum creatinine and inorganic phosphate level as well as the need for peritoneal dialysis in non-survivors, are clearly indices of renal failure. The importance of renal failure as a negative prognostic factor is well known [20].

The strongest negative prognostic factor identified in our study was the presence of bacteraemia. The importance of bacteraemia in predicting outcome in patients with pneumococcal pneumonia has been known

for many years [7, 33], and remains relevant at the present time [34]. It has been shown that the incidence of bacteraemia has an inverse relationship to the white cell count, and is more commonly associated with pre-existing systemic disease, as well as in patients with post-pneumonic complications [7].

Mortality rates of patients with pneumonia treated in intensive care units are often in excess of 50% [11, 35], and in this regard our mortality rate of 53% compares favourably. Contributing to the high mortality rate in our study group may be the high incidence of infection with *K. pneumoniae*, known to be associated with a higher mortality rate [36], as well as the high percentage of bacteraemic patients, the most powerful predictor of a poor prognosis.

Several studies [14–16] have demonstrated the accuracy and importance of severity of illness scoring systems among critically ill patients. A recent one has evaluated three systems, including SAPS, and found them all to be reliable in assessing mortality in seriously ill patients with bacterial pneumonia [16]. The various systems appear to adequately address most of the negative prognostic features we have found, including the importance of a low white cell and platelet count, a low serum albumin, and parameters of renal failure. Microbiologic data, however, is not an important consideration in the systems. The presence of bacteraemia was the most important predictor of mortality in our patient population, and within almost each SAPS value, the mortality of bacteraemic patients was significantly higher, a fact not addressed by the scoring system. We would suggest that absence of any microbiological data, particularly the presence or absence of bacteraemia, may significantly underestimate the mortality, particularly among bacteraemic patients.

Most deaths in our patients occurred within the first 5 days (59%). It has been shown in pneumococcal disease that despite new modalities in therapy, the initial 5-day mortality rate remains unchanged, largely due to severe physiological damage induced by the organism before specific therapy has a chance to act [29]. This appears, therefore, to be the case in all cases of pneumonia. Despite effective antimicrobial chemotherapy, and advances in critical care management of patients, the mortality rate of severely ill patients with community-acquired lobar pneumonia of diverse microbiological aetiology remains unacceptably high, particularly in the presence of several documented risk factors, of which the presence of bacteraemia is the most ominous.

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MEDICAL INTELLIGENCE



COMMUNITY-ACQUIRED PNEUMONIA DUE TO PENICILLIN-RESISTANT PNEUMOCOCCI

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UNTIL 1967 all strains of pneumococcus (*Streptococcus pneumoniae*) were thought to be highly sensitive to penicillin.[1,2] In that year Hansman and Bullen[3] described a patient with hypogammaglobulinemia and bronchiectasis in whom a strain of pneumococcus that was relatively insensitive to penicillin was isolated from the sputum. Reports followed of the occurrence of strains with an even greater resistance to penicillin[4,5] as well as resistance to other antibiotics to which the pneumococcus had previously been sensitive.[6-8]

Previous studies in South Africa have shown that infections due to resistant pneumococci, as well as asymptomatic carrier states, have occurred almost exclusively in black children under three years of age, usually with a history of recent antibiotic therapy.[9,10] All the infections were nosocomially acquired.

We have recently treated, in the intensive care unit of the Hillbrow Hospital in Johannesburg, three adult patients with community-acquired pneumonia due to pneumococci that were resistant to penicillin as well as to other antibiotics. The outcome was uniformly fatal. Our experience confirms the high mortality associated with disease caused by these organisms and the need for routine antibiotic-sensitivity testing of all cultured pneumococci.

METHODS

The results of all blood cultures submitted to the microbiology laboratory at the Hillbrow Hospital during 1983 were analyzed. The sensitivity of each cultured pneumococcus to various antibiotics was studied. Strains of pneumococcus (*S. pneumoniae*) were isolated and identified by standard methods. Serotyping was performed by the Quellung method, with antiserum samples supplied by the Statens Serumsinstitut, Copenhagen. Disk susceptibility was determined by the modified Kirby–Bauer technique, with use of Mueller–Hinton agar supplemented with 5 per cent lysed horse blood.[8] The antibiotics tested were penicillin G, methicillin, erythromycin, clindamycin, chloramphenicol, tetracycline, rifampin, and vancomycin. Susceptibility to penicillin G was initially determined by measuring the zone of inhibition surrounding a 5-μg disk of methicillin.[11] The minimal inhibitory concentration of each drug was determined by the tube dilution method, with use of serum broth to which appropriate concentrations of penicillin G had been added. An inoculum of 10^5 cfu per milliliter was used. The minimal bactericidal concentration of each drug was determined by subculture on Mueller–Hinton agar supplemented with 5 per cent lysed horse blood.

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RESULTS

During 1983 there were 85 patients treated at Hillbrow Hospital whose blood cultures were positive for pneumococcus. The organisms cultured from three of these patients were found to be resistant to penicillin as well as other antibiotics. This represents 3.5 per cent of all pneumococci cultured from the blood of patients at the hospital during that year. Brief case histories of these three subjects are given below. Each of them presented to the hospital during the month of August. Antigenic typing showed that in two patients the resistant pneumococci were Serotypes 19A and 6B, respectively; in the third they belonged to Serogroup 6. The primary isolations of the resistant pneumococci from the latter two patients were not temporally related. Details of the antibiotic sensitivities of the organisms are shown in Table 1.

The pneumococci cultured from the remaining 82 patients were fully sensitive to penicillin as well as to the other antibiotics against which they were tested.

Patient 1

A 24-year-old black woman with systemic lupus erythematosus and membranoproliferative glomerulonephritis was admitted to the intensive care unit with right-upper-lobe pneumonia. She had been receiving prednisone (30 mg daily) but no antibiotic therapy. The blood pressure was 105/70 mm Hg, and the heart rate 110 per minute. The rectal temperature was 35°C. The hemoglobin was 8.2 g per deciliter, with a white-cell count of 5.8×10^9 per liter. The blood urea was 40.1 mmol per liter (241.6 mg per deciliter), and the serum creatinine was 1047 μmol per liter (11.8 mg per deciliter). Antinuclear factor was present in the serum in a titer of 1/640, and anti-DNA antibodies were also detected. A Gram stain of the sputum was unhelpful in identifying a definite causative organism.

The patient required mechanical ventilation, and adequate oxygenation could be achieved only with high concentrations of inspired oxygen and high positive end-expiratory pressure. Peritoneal dialysis was begun. Intravenous antibiotic therapy was commenced with penicillin G (2 million units every six hours), and one dose of tobramycin (80 mg) was given. Despite all therapeutic measures, irreversible hypotension developed, and the patient died within 24 hours. A pneumococcus (Serotype 19A) that was resistant to penicillin as well as to several other antibiotics (Table 1) was cultured from blood taken at the time of admission.

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Table 1. Antibiotic Sensitivities of Cultured Pneumococci.

Drug*	Patient Number		
	1	2	3
Serotype/serogroup	19A	6†	6B
Penicillin			
MIC	2	0.5	4
MBC	4	1	4
Methicillin			
MIC	32		32
MBC	32		32
Chloramphenicol			
MIC	16		8
MBC	16		8
Tetracycline			
MIC	64		16
MBC	64		32
Erythromycin			
MIC	<0.06		>128
MBC	0.12		>128
Clindamycin			
MIC	<0.06		>128
MBC	<0.06		>128
Rifampin			
MIC	<0.06		64
MBC	<0.06		>128
Vancomycin			
MIC	1	0.03	1
MBC	1	0.03	1

*MIC denotes minimal inhibitory concentration, and MBC minimal bactericidal concentration.

†Further serotyping as well as more detailed drug-sensitivity testing could not be performed, because the organism was lost on subculture. On disk susceptibility testing, the organism appeared to be sensitive to all the drugs tested except penicillin/methicillin.

Patient 2

A 52-year-old, previously healthy black man was admitted to the intensive care unit with right-upper-lobe pneumonia. The blood pressure was 90/60 mm Hg, and the heart rate 130 per minute. The rectal temperature was 38.1°C. The hemoglobin was 16.4 g per deciliter, with a white-cell count of 4.2×10^9 per liter. The serum urea, electrolyte, and creatinine levels were normal.

The patient required mechanical ventilation, and intravenous antibiotic therapy with penicillin G (2 million units every four hours) and tobramycin (80 mg every eight hours) was begun. A Gram stain of the sputum was unhelpful in identifying a definite causative organism.

A penicillin-resistant pneumococcus (Serogroup 6) was cultured from blood taken at the time of admission, and the antibiotic therapy was therefore changed to vancomycin (500 mg intravenously every six hours) and rifampin (300 mg orally twice daily) on the second day. With the onset of renal failure the vanocomycin was replaced by clindamycin (600 mg intravenously every six hours). However, despite all therapeutic measures and an initially good response, the patient died after 18 days with refractory hypotension.

Patient 3

A 36-year-old, previously healthy black man was admitted to the intensive care unit with right-upper-lobe pneumonia. The blood pressure was 104/80 mm Hg, and the heart rate 120 per minute. The rectal temperature was 38.9°C. Peripheral perfusion was poor. The hemoglobin was 9.9 g per deciliter, with a white-cell count of 12.3×10^9 per liter. The serum urea, electrolyte, and creatinine levels were normal. Blood-gas analysis showed hypoxia, hypocapnia, and a severe metabolic acidosis (bicarbonate less than 5 mmol per liter). A Gram stain of the sputum was unhelpful in identifying a definite causative organism.

The patient required mechanical ventilation, and peritoneal dialysis was instituted because of severe metabolic acidosis, which was refractory to large doses of intravenously administered sodium bicarbonate. The patient rapidly went into shock and hypothermia, and the blood pressure could be maintained only with large doses of inotropic agents (dopamine and isoproterenol). Intravenous antibiotic therapy was begun with penicillin G (2 million units every four hours) and tobramycin (80 mg every eight hours). In spite of all therapeutic measures, the patient died three days later. A pneumococcus (Serotype 6B) that was resistant to penicillin and multiple other antibiotics (Table 1) was cultured from blood taken at the time of admission.

Discussion

The pneumococcus remains the commonest cause of community-acquired pneumonia.[12] After the introduction of penicillin there was a striking reduction in the morbidity and mortality associated with disease caused by the organism,[9] which was extremely sensitive to the drug (minimal inhibitory concentration ≤ 0.01 μg of penicillin G per milliliter). Recently, strains of pneumococcus have emerged that demonstrate resistance to penicillin as well as to other antibiotics. Some strains of pneumococcus have even been found for which the minimal inhibitory concentration of penicillin is as high as 10 μg per milliliter. This represents a minimal inhibitory concentration 1000 times greater than that for susceptible organisms. The emergence of pneumococci that are resistant to penicillin as well as to several other antibiotics has been a particular problem in South Africa.[7,10] Previous epidemiologic studies have shown these resistant strains to belong to Serotypes 6A and 19A.[10]

Our cases represent community-acquired infections in adults, caused by penicillin-resistant pneumococci. Community-acquired disease due to these organisms appears to be occurring with increasing frequency in black children in Johannesburg (Oppenheim BA, Koornhof HJ: unpublished data).

The nasopharyngeal-carrier rates for resistant pneumococci among adults within the Johannesburg community is unknown. A study[13] performed in 1978 in a predominantly pediatric population in Johannesburg showed a carrier rate for multiply resistant organisms (minimal inhibitory concentration ≥ 1 μg of penicillin per milliliter) of 0.7 per cent. In addition, the rate of acquisition of the carrier state among 152 healthy household contacts of children known to be colonized

with these organisms was found to be 4.6 per cent. In a more recent study among 303 children in Johannesburg, Klugman and Koornhof (unpublished data) have shown that pneumococci of intermediate resistance (minimal inhibitory concentration, 0.1 to 1 μg of penicillin per milliliter) and high resistance (minimal inhibitory concentration $\geq$1 μg of penicillin per milliliter) were harbored by 13.5 and 0.7 per cent, respectively. The source of these resistant pneumococci within the community is thought to be children discharged from pediatric hospitals, who are nasopharyngeal carriers.[10]

The morbidity and mortality of patients infected with penicillin-resistant pneumococci are high, particularly if only beta-lactam antibiotics are used. Effective antibiotic therapy for these organisms depends on the degree of penicillin resistance and the pattern of resistance to other agents. In cases of intermediate resistance (minimal inhibitory concentration of penicillin, 0.1 to 1 μg per milliliter), high-dose penicillin therapy may be adequate. Appropriate alternatives for highly resistant organisms may include erythromycin, chloramphenicol, tetracycline, vancomycin, and rifampin.[9]

Whether intermediate resistance of pneumococci to penicillin has direct clinical relevance in patients with pneumonia and bacteremia requires further elucidation. One of our patients was infected with a pneumococcus of intermediate resistance (minimal inhibitory concentration, 0.5 μg per milliliter), and two had still more resistant organisms. In Patient 1, preexisting systemic lupus erythematosus was being treated with corticosteroids, and in Patient 2, the pneumonia was associated with an initially low white-cell count (4.2×10^9 per liter), which itself carries a poor prognosis.[14] Their deaths cannot, therefore, be attributed solely to the failure of penicillin therapy. However, infection with pneumococci with minimal inhibitory concentrations of penicillin higher than 1 μg per milliliter carries an extremely high mortality,[7,10,15,16] and in Patient 3 the minimal inhibitory concentration of penicillin for the organism was 4 μg per milliliter. It is likely, therefore, that this patient did not at any time receive adequate antimicrobial therapy.

Although resistant pneumococci have occurred most frequently in South Africa, they have also emerged in other countries, including England, Australia, Canada, the United States, New Guinea,[9,10] and France.[17] When infections with penicillin-resistant pneumococci occur in the typical setting — in a young black child after hospitalization — the correct bacteriologic diagnosis may possibly be suspected and appropriate antibiotic therapy commenced early. In the setting of community-acquired pneumococcal pneumonia in adults, the possibility of penicillin resistance will usually not be considered. Penicillin has long been considered the antibiotic of choice for suspected pneumococcal infections and commonly constitutes the initial therapy in community-acquired pneumonia. Although such an approach remains reasonable, our cases confirm the need for routine surveillance for resistant organisms by antibiotic-sensitivity testing of all cultured pneumococci.

A polyvalent vaccine made of pneumococcal capsular polysaccharide has been available for some years. The existence of potent antibiotic therapy and the absence of adequately controlled clinical trials confirming its efficacy within all segments of the population[18] may be reasons for the failure of its acceptance in routine use. However, the increasing emergence of multiply resistant organisms as reported here, and the severe morbidity and mortality associated with disease caused by them, are cogent reminders that reevaluation of the role of immunoprophylaxis against pneumococci is required.

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