PAPERS AND SHORT REPORTS

Pneumococcal bacteraemia: 325 episodes diagnosed at St Thomas's Hospital

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Abstract

Three hundred and twenty five episodes of pneumococcal bacteraemia occurred at St Thomas's Hospital during 1970-84, accounting for 13·3% of all episodes of bacteraemia. Twice as many cases occurred in male as in female patients, and common predisposing factors included chronic chest disease, alcoholism, haematological malignancies, cirrhosis, and sickle cell anaemia. Mortality was 28·6% overall but only 11·8% among patients who received antibiotic treatment for at least 24 hours. Most patients (261) had pneumonia, 26 had meningitis, and eight were children with occult bacteraemia. The commonest serotype of pneumococcus in adults was type 3 (39 episodes), and these strains were associated with a high mortality. Other factors determining a fatal outcome included underlying disease (such as cirrhosis, malignancy, and chronic chest disease) and extrapulmonary infection. Almost half the survivors were treated for 10 days or less and became afebrile within 48 hours.

Introduction

Streptococcus pneumoniae is a common isolate from blood cultures; only *Escherichia coli* and *Staphylococcus aureus* are isolated more often. There has been renewed interest in Britain in pneumococcal vaccine for those at increased risk of fulminating pneumococcal infections, such as patients who have undergone splenectomy and those with sickle cell disease. Knowledge of the common serotypes found in bacteraemia is therefore of practical importance. In the United Kingdom there have been few studies of bacteraemic pneumococcal disease and all have been of only small numbers of patients.[1-3] We report a prospective survey of all episodes of pneumococcal bacteraemia at St Thomas's Hospital from January 1970 to March 1984.

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Methods

Laboratory methods and the collection of patient data were as described previously.[4 5] The pneumococcus was identified by its colonial morphology and its sensitivity to Optochin. Discs impregnated with penicillin and tetracycline were used to assess sensitivities. The antibiotic content of the penicillin disc was changed towards the end of the survey from 1 unit to 0·25 unit to detect reduced susceptibility. The Streptococcus Reference Unit, Division of Hospital Infection, Colindale, typed the isolates.

Results

During the period studied, 325 of 2442 (13·3%) episodes of bacteraemia were caused by *Str pneumoniae*. The figure shows the annual incidence and the number of episodes per 1000 admissions during 1970-82 (this information was not available for 1983-4). Considerable seasonal variation was seen with almost half the cases occurring from December to March.

PATIENTS

Table I shows the age and sex distributions of the patients together with related mortalities. The overall mortality was 28·6% (28·1% among male patients and 29·6% among female patients). Twice as many male as female patients had pneumococcal bacteraemia. Table II shows the factors predisposing to infection.

Two thirds of the patients (225) were admitted to the general medical wards; the other third were either moribund on arrival or were admitted to the intensive care unit. Nine patients had sickle cell anaemia or trait, and three died of fulminating pneumococcaemia with no localised infection. Of three patients who had undergone splenectomy, one died immediately after an operation for trauma and the two others (who survived) had Hodgkin's disease and developed bacteraemic pneumonia 19 days and two years after operation. None had received pneumococcal vaccine or prophylaxis with penicillin.

TABLE I—*Age, sex, and mortality among patients with pneumococcal bacteraemia diagnosed at St Thomas's Hospital 1970-84*

Age (years)	No of episodes	No of deaths (%)	No of episodes (and deaths) among: Male patients	Female patients
0-9	26	4 (15·4)	14 (1)	12 (3)
10-19	10		4	6
20-29	17	5 (29·4)	14 (4)	3 (1)
30-39	17	4 (23·5)	11 (2)	6 (2)
40-49	35	8 (22·9)	27 (7)	8 (1)
50-59	66	15 (22·7)	53 (12)	13 (3)
60-69	78	26 (33·3)	51 (18)	27 (8)
70-79	52	18 (34·6)	31 (10)	21 (8)
80-89	20	11 (55·0)	11 (6)	9 (5)
90-99	4	2 (50·0)	1 (1)	3 (1)
Total	325	93 (28·6)	217 (61)	108 (32)

TABLE II—*Factors predisposing to infection*

Factor	No of patients
Chronic chest disease	63
Alcoholism	59
Vagrancy*	35
Haematological malignancy	28
Corticosteroid treatment	28
Cirrhosis	13
Recent surgery	13
Diabetes mellitus	11
Malignancy other than lung	10
Sickle cell disease or trait	9
Congestive cardiac failure	9
Lung malignancy	7
Renal failure	7
Neutropenia†	4
Drug addiction	4
Jaundice (not cirrhosis)	4
Recent viral respiratory illness	4
Splenectomy	2
Others	13

*Homeless, rootless people; alcoholic vagrants were included under both vagrancy and alcoholism.
†Two patients also included in haematological malignancy category.

CLINICAL PRESENTATION

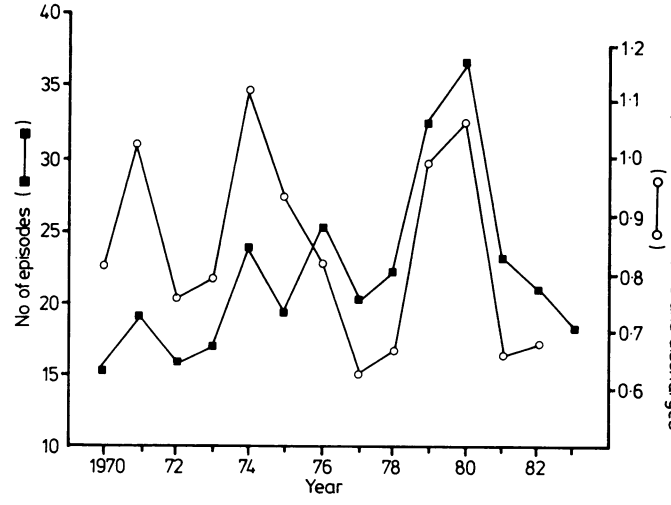
Table III shows the clinical presentation of the 325 episodes of pneumococcal bacteraemia.

Pneumonia and empyema—Most patients with pneumococcaemia had pneumonia (n=261). Twenty six patients had fluid in the pleural space; in eight this was found on admission and yielded pneumococci when cultured. In four of these eight the fluid was frank pus (pleural empyema); none survived beyond 12 hours. In the other four the fluid was serous, and they all survived. The remaining 18 patients developed a pleural effusion during treatment. This effusion was invariably sterile when aspirated and cultured, and all of these patients survived.

Meningitis—Meningitis occurred in 26 patients, 10 of whom died (three cases were diagnosed at necropsy). Predisposing illness was noted in only 11 of these patients: three were alcoholic, three had sickle cell anaemia, two had cirrhosis, one had carcinoma of the maxillary antrum, one had chronic chest disease, and one had lymphoma. Sixteen of the 26 patients had no other focus of infection; seven of these 16 were aged under 10 (three with sickle cell anaemia). In 10 patients there were other foci of infection in addition to the meninges; one of these 10 died of fulminant infection with pneumococcal endometritis 36 hours after a normal delivery of her baby, who also died with pneumococcaemia and the respiratory distress syndrome.

Laboratory diagnosis of meningitis was straightforward: all patients had cerebral spinal fluid leucocytosis (0·11-12·16 $\times 10^9$ cells/l), and characteristic Gram positive diplococci were readily detected in smears of the centrifuged deposit, often in large numbers.

Endocarditis—Six of the seven patients with endocarditis were either alcoholics or had cirrhosis, and in five the diagnosis was made at necropsy. The two others underwent emergency operations to replace heart valves. The valves that were infected were: mitral (two patients); aortic (two); mitral, aortic, and tricuspid (two); and mitral and tricuspid (one). In only one patient was there no other focus of infection. He had alcoholic cirrhosis and died shortly after an operation for haemorrhage from a gastric ulcer. Although aspiration of stomach contents had occurred, pneumonia was not detected either clinically during life or at necropsy. The six other patients all had pneumonia (one with empyema), and four had meningitis.



Annual incidence of pneumococcaemia at St Thomas's Hospital.

Source unknown—Forty one patients had no recognisable focus of infection. Eight children, who were all aged less than 4, had occult bacteraemia and presented with fever and leucocytosis; three had febrile convulsions and four mild upper respiratory tract symptoms; all survived. *Str pneumoniae* was also isolated from the noses of three patients. Two of these three strains were the same serotype as the pneumococcus isolated from the patient's blood (the third strain was not typed). In 14 patients the disease was fulminant; all died before a source could be identified, and none underwent necropsy. Their underlying conditions were sickle cell anaemia (three patients), haematological malignancy (two), other malignancy (two), cirrhosis (two), congestive cardiac failure (two), diabetes mellitus (one), and cerebrovascular accident (one). Seven patients who had recently had operations developed bacteraemia without an apparent source. These

TABLE III—*Clinical presentation of 325 episodes of pneumococcal bacteraemia*

Clinical presentation																				Total No (%)
Pneumonia	+	+	–	+	–	+	+	+	+	–	–	+	–	–	–	–	–	+	–	261 (80·3)
Meningitis	–	–	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	26 (8·0)
Endocarditis	–	–	–	–	–	+	+	–	+	+	–	–	–	–	–	–	–	–	–	7 (2·2)
Peritonitis	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	4 (1·2)
Empyema	–	+	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	4 (1·2)
Endometritis	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1 (0·3)
Pharyngitis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	1 (0·3)
Cellulitis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	1 (0·3)
Arthritis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	1 (0·3)
Not known	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	12 (3·7)
Not known (fulminant)	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	14 (4·3)
Not known (age <4 years (occult))	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	8 (2·5)
Not known (after operation)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	7 (2·2)
No (%) of patients	246 (78)	2 (1)	16 (5)	4 (1)	1 (<1)	3 (1)	1 (<1)	1 (<1)	2 (1)	1 (<1)	3 (1)	1 (<1)	8 (3)	14 (4)	7 (2)	1 (<1)	1 (<1)	1 (<1)	12 (4)	325
No of deaths	56	2	3	2	1	2	1	1	2	1	3	1	0	14	4	0	0	0	0	93

patients may have had early pneumonia and been treated before radiological changes appeared. The sources for the 12 remaining patients, none of whom died, were unknown. Seven patients were receiving corticosteroids (two had neutropenia), three had sickle cell anaemia or trait, one was alcoholic, and one had cirrhosis.

BACTERIOLOGICAL FINDINGS

Resistance to penicillin was not detected, and only 11 of 312 (3·5%) isolates tested were resistant to tetracycline. Table IV shows the results of serotyping. The commonest serotypes were 3, 8, 14, and 1, which accounted for half of the isolates. Altogether 259 (83%) isolates were serotypes included in the 14 valent pneumococcal vaccine (Pneumovax, Merck, Sharp and Dohme), which has been withdrawn, and 293 (94%) were serotypes included in the new 23 valent vaccine that is not yet available in the United Kingdom. Of the 22 serotyped isolates from children under 6 years, type 23 was the commonest (five isolates); the others were types 9 (three isolates), 14 (three), 8 (three), 18 (two), and 1, 4, 6, 19, 24, and 33 (one each). Serotype 3 was the commonest in adults yet was not isolated in the children or the 23 patients with leukaemia and lymphoma.

TABLE IV—*Serotypes of pneumococci isolated*

Serotype	No of adults (and deaths)	No of children aged < 6 years (and deaths)	Total	No of mucoid strains
3	39 (17)		39	27
8	36 (6)	3	39	5
14	33 (7)	3	36	
1	31 (4)	1	32	1
6	17 (6)	1 (1)	18	4
7	16 (5)		16	
4	14 (2)	1	15	
9	12 (5)	3	15	
23	9 (3)	5	14	1
19	11 (5)	1 (1)	12	
18	9 (5)	2	11	1
12	9 (3)		9	
25*	2 (1)		2	1
2	1		1	
22	8 (4)		8	
5	7 (2)		7	
20	5 (2)		5	1
17	4 (2)		4	
Fifteen other types†	27 (7)	2	29	
Not typed	11 (3)	2 (2)	13	3
Total	301 (89)	24 (4)	325	44

*Not included in 23 valent vaccine.
†These comprised 10, 11, 15, 24*, 32*, 33, 34*, 35*, 36*, 38*, 39*, 40*, 42*, 48*, and one non-typable isolate.

TREATMENT AND OUTCOME

Nineteen patients (5·8%) died soon after admission and did not receive any antibiotics. Forty seven patients received initial treatment before the results of blood culture were available but did not receive definitive treatment (because of death or withdrawal of treatment); 259 patients (79·7%) received both initial and definitive treatment.

The commonest initial treatment regimens were: ampicillin or amoxycillin (89 of the 306 patients (29%)), penicillin (77 (25%)), ampicillin or amoxycillin and flucloxacillin (41 (13%)), ampicillin or amoxycillin and gentamicin (22 (7%)), and penicillin and gentamicin (9 (3%)). The commonest definitive regimens were: penicillin (138 of the 259 patients (53%)), ampicillin or amoxycillin (68 (26%)), and penicillin and gentamicin (13 (5%)).

The mean duration of antibiotic treatment for the 232 survivors was 12·1 days (range 5-61 days). Most patients (195 (84%)) were treated for five to 15 days, and almost half (104 (45%)) were treated for 10 days or less. Two groups were treated for longer: those with a pleural effusion (mean 15·9 days) and those infected with mucoid strains of serotype 3 pneumococci (mean 15·3 days). More than half the patients had a normal temperature by the third day of treatment. A pleural effusion was often associated with slow resolution of temperature; 14 of 22 patients with an effusion took a week or longer to respond.

The overall mortality from pneumococcaemia was 28·6% (93/325), with no difference between the sexes. Of the 93 patients who died, 56 were moribund on admission. Twenty eight of the 44 patients admitted to the intensive care ward with particularly severe disease also died. In contrast, only nine of the remaining 225 patients died. Only 31 of the 264 (11·8%) patients who were treated for at least 24 hours died. Most deaths (65 (70%)) occurred within 24 hours after admission. The clinical state of the patient on admission was thus an important factor influencing the outcome. Extrapulmonary infection resulted in a higher mortality: 56 of 246 patients with pneumonia alone died, whereas 37 of the 79 patients with infection at another site died ($\chi^2 = 16{\cdot}96$, $p < 0{\cdot}002$). Other factors influencing the outcome included cirrhosis (10 out of 13 patients died) and bacteraemia with a type 3 strain of pneumococcus (17 out of 39 died, $\chi^2 = 4{\cdot}86$, $p < 0{\cdot}05$). Infection with a serotype 3 strain that produced mucoid colonies increased the chance of a fatal outcome (14 of 27 died, $\chi^2 = 7{\cdot}78$, $p < 0{\cdot}01$) and was more likely to cause fatal, fulminant, or severe disease requiring admission to the intensive care ward ($\chi^2 = 21{\cdot}68$, $p < 0{\cdot}0001$). Three of the nine episodes in patients with sickle cell anaemia were fatal, resulting from fulminant infection.

Discussion

Of the few studies of serious pneumococcal disease in the United Kingdom, this was the largest prospective analysis of bacteraemic infection. *Str pneumoniae* was the third most common isolate from all blood cultures, which agrees with a recent report on bacteraemia by the Public Health Laboratory Service.[6] The report noted a dramatic rise in the incidence of pneumococcal bacteraemia in the years 1975-80. We, however, saw a sharp decline in incidence over the next three years, 1981-3. Seasonal influence on the incidence of pneumococcal bacteraemia is well known.[7]

Common predisposing conditions included chronic chest disease, alcoholism, cirrhosis, haematological malignancies, and sickle cell anaemia. Vagrants, whether known alcoholics or not, were a particularly susceptible group. Surgical or functional asplenia was uncommon. We did not seek a predisposing viral infection of the respiratory tract.

The most common site of infection was the lung. Bacteraemia has been reported to accompany 25-37% of cases of pneumococcal pneumonia.[8-12] Twenty six patients had fluid in the pleural space in association with pneumonia. We used the term empyema to describe only frank pus in the pleural space. The development of empyema may be preceded by two stages.[13] The first is exudative (thin pleural fluid with few pus cells), and without treatment this may progress to a fibrinopurulent or transitional stage with thicker, more turbid fluid before ending in true empyema. These stages may be continuous. The four patients with pleural empyema all died with sepsis. Of the remaining patients, four presented with serous fluid containing pneumococci in the pleural space and 18 developed an effusion during treatment. When this was aspirated and cultured it was invariably sterile. This has been noted before[14] but seems to cause confusion. A sterile effusion often resulted in slow resolution of temperature and caused clinical concern (antibiotic treatment in these patients was prolonged). Less than 10% of effusions in pneumococcal pneumonia progress to empyema,[15] which is an avoidable complication if specific treatment is given early.[7 15] Before antibiotics were introduced 7-11% of all cases of pneumococcal pneumonia were complicated by empyema,[16] but subsequently the incidence of pneumococcal empyema sharply declined.[17-19] None of our patients with pleural effusion died, but in a study by Austrian and Gold three out of 15 patients with a sterile effusion died.[11]

The incidence of pneumococcal meningitis in the United Kingdom has changed little.[6] It was 8% in our study, which was lower than in two previous reports from the United Kingdom.[3 6] Alcoholics and patients with cirrhosis had the most severe disease, with endocarditis and pneumonia as well as meningitis. Laboratory diagnosis did not present any difficulty. The only patient with meningitis who relapsed was a child with sickle cell anaemia.

The source of pneumococcaemia in 41 patients was not apparent: some presented moribund or died rapidly of fulminant infection, and without a necropsy no source could be detected. Occult pneumococcaemia in children has been reported often in America,[20-23] but there has been only one

substantial study in the United Kingdom.[24] Our findings agree with this study. All children whom we studied were aged under 4 and were admitted with febrile convulsions, minor infections of the upper respiratory tract, or vomiting. Each child was febrile with leucocytosis. Response to treatment with penicillin was prompt. As in the British report the organism was isolated from a non-inflamed upper respiratory tract in three of our patients; in two this isolate was the same serotype as the isolate from the blood culture (the third was not typed). The prevalence of this clinical phenomenon in this country is probably greater than our study suggests. Paediatric admissions to St Thomas's Hospital averaged only about 1400 each year during the study. In America many episodes of occult bacteraemia in children go unrecognised.[23 25] These findings underline the importance of culturing blood from children to prevent occult pneumococcaemia being incorrectly diagnosed as a viral infection.

Bacteraemia without a localised source occurred in some patients after operation, which was often on the upper gastrointestinal tract and usually an emergency procedure. These episodes were probably due to early pneumonia.

The pneumococcus, in our experience, is highly sensitive to penicillin, though resistance to both penicillin and chloramphenicol has been reported.[26-28] In our laboratory about 1% of all pneumococcal isolates show relative resistance to penicillin (minimum inhibitory concentration of penicillin $\geq 0{\cdot}25$ mg/l). Such isolates may have escaped detection in the early part of our series when the disc with a high pencillin content was used.

Serotypes of pneumococci vary with time,[29] geographic location,[30] and underlying disease,[31] and differences in type exist between children and adults.[30] The serotyping reported in the 1980-1 Public Health Laboratory survey of systemic pneumococcal disease suggested that in the period that was studied type 1 isolates were the most common, at least in adults.[32] Overall the predominant serotype at St Thomas's Hospital in adults was type 3, but in 1980 three times as many isolates of type 1 as type 3 were present. The common serotypes found in young children were similar to those elsewhere, with no type 3 among the small number of patients studied; types 23, 8, 9, and 14 were the most common. In the Public Health Laboratory survey there were no type 8 isolates in young children. Data on the serotypes isolated in bacteraemic pneumococcal disease are important in the light of the availability of polyvalent pneumococcal vaccine. Altogether 83% of isolates were of serotypes included in the 14 valent vaccine, but the new 23 valent vaccine will provide even more comprehensive cover. A serious problem with the old vaccine was its relatively poor efficacy in children under the age of 2.[33] These points do not, however, detract from the value of this useful and underused prophylactic agent.[34] It may prove difficult to give vaccine to some of those at greatest risk of infection such as vagrants and alcoholics.

In this study microbiologists seldom influenced the initial treatment, which almost invariably included a penicillin. Definitive treatment was usually determined by consultation with a laboratory doctor. Penicillin alone was used almost twice as often in definitive treatment as in initial treatment. The duration of antibiotic treatment was usually short, but occasionally it was prolonged, probably inappropriately, because of the development of a sterile pleural effusion and associated fever. Persistent fever in an otherwise well patient was also seen after treatment for meningitis. It was eventually, and usually reluctantly, attributed to the antibiotics; this has been well described.[35 36] The optimum duration of antibiotic treatment for pneumococcal disease is unknown, but relapses are rare and it is doubtful if continuing antibiotics is of any benefit when there is a sterile effusion and fever.

Overwhelming infection accounted for most deaths from pneumococcaemia. The increased mortality in elderly patients and in those with underlying disease such as cirrhosis, malignancy, and sickle cell anaemia has been noted before. We found, in agreement with other reports[11 37] that alcoholism had little prognostic value unless associated with conditions such as neutropenia and hepatic insufficiency. Death may still occur despite apparently appropriate antibiotic treatment with or without the help of all the facilities of a modern intensive care unit.

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