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ORIGINAL ARTICLE

Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia

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ABSTRACT

Rationale Host and bacterial factors as well as different treatment regimens are likely to influence the outcome in patients with bacteraemic pneumococcal pneumonia.

Objectives To estimate the relative contribution of host factors as well as bacterial factors and antibiotic treatment to mortality in bacteraemic pneumococcal pneumonia.

Methods A cohort study of 1580 adult patients with community-acquired bacteraemic pneumococcal pneumonia was conducted between 2007 and 2009 in Sweden. Data on host factors and initial antibiotic treatment were collected from patient records. Antibiotic resistance and serotype were determined for bacterial isolates. Logistic regression analyses were performed to assess risk factors for 30-day mortality.

Results Smoking, alcohol abuse, solid tumour, liver disease and renal disease attributed to 14.9%, 13.1%, 13.1%, 8.0% and 7.4% of the mortality, respectively. Age was the strongest predictor, and mortality increased exponentially from 1.3% in patients <45 years of age to 26.1% in patients aged ≥85 years. There was considerable confounding by host factors on the association between serotype and mortality. Increasing age, liver disease and serotype were associated with mortality in patients admitted to the ICU. Combined treatment with β-lactam antibiotics and macrolide/quinolone was associated with reduced mortality in patients in the ICU, although confounding could not be ruled out.

Conclusions Host factors appear to be more important than the specific serotype as determinants of mortality in patients with bacteraemic pneumococcal pneumonia. Several host factors were identified that contribute to mortality, which is important for prognosis and to guide targeted prevention strategies.

Key messages

What is the key question?

- To what extent do host and bacterial factors contribute to mortality in bacteraemic pneumococcal pneumonia?

What is the bottom line?

- This study shows that host factors such as age, alcohol abuse, liver disease, renal disease and solid tumour contribute to mortality in patients with bacteraemic pneumococcal pneumonia, while the association between pneumococcal serotype and mortality is mitigated by adjustment for host factors.

Why read on?

- These findings suggest that host factors appear to be more important than specific serotype as determinants of mortality in patients with bacteraemic pneumococcal pneumonia, which supports targeted intervention strategies.

INTRODUCTION

Streptococcus pneumoniae (the pneumococcus) is the main cause of community-acquired pneumonia (CAP) and a large contributor to morbidity and mortality worldwide.[1] Studies have reported that the risk of dying in patients with pneumococcal disease is dependent on host factors such as age and comorbidities as well as bacterial factors such as serotype, antibiotic resistance and bacterial clonal type.[2–9] Studies also report conflicting results on the effect of combination antibiotic therapy or monotherapy in patients with pneumococcal disease,[10–14] where some studies indicate a beneficial effect in particular of combining β-lactam and macrolide antibiotics.[11–13]

There are currently 93 pneumococcal serotypes described with different propensity to cause invasive pneumococcal disease (IPD).[8 15–17] Licensed conjugated pneumococcal vaccines are based on a limited number (7–13) of these serotypes. It is therefore important to investigate serotype-specific mortality to guide vaccination strategies. A large Danish study including more than 18 000 patients with IPD reported that the risk of a fatal outcome in this patient group depended on the serotype even after adjustment for age and comorbidity.[3] Furthermore, a recent meta-analysis of bacteraemic pneumococcal pneumonia reported a higher risk of death in patients with certain serotypes, indicating serotype as an important clinical predictive factor.[9] Nevertheless, when mortality risks of individual serotypes are investigated, the numbers of cases in each serotype category are small even in large studies and it might be difficult to perform adequate adjustment for host factors.

It is important to assess the relative risk attribution of both host and bacterial factors to mortality in order to understand the natural history of the disease and to guide targeted intervention

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strategies. Also, in epidemiological studies focusing on the aetiological rather than the predictive role of risk factors, caution is needed when selecting variables to include in multivariate models in order to perform proper adjustment for confounders.[18] Previous studies of IPD that have focused on risks for mortality associated with host factors have either not been large enough to perform adjustment for confounders or have not used an aetiological analytical approach to assess the contribution of host factors.[2 6 7]

We performed a large population-based cohort study of bacteraemic pneumococcal pneumonia in Sweden to investigate the relative contribution of host factors, bacterial factors and antibiotic treatment regimen to 30-day mortality. Careful consideration was given to the relationship between variables to perform adjustment for confounding factors in multivariate models in order to assess the effect of each individual exposure on mortality.

METHODS

Study design

In Sweden it is mandatory for clinicians and laboratories to report IPD episodes to the Swedish Institute for Communicable Disease Control where isolates have been serotyped on a continuous basis since 2006. A cohort study was commenced in 2007 in which questionnaires were sent to clinicians to obtain data on diagnosis (ie, pneumonia, meningitis), comorbidities and clinical management of IPD episodes (see also online supplementary methods). During the study period between 1 January 2007 and 31 December 2009, 92% of reported IPD episodes were serotyped. All Swedish counties except two participated in the study (national coverage 82%). The current study is restricted to 1580 patients with pneumonia aged ≥18 years with serotyped pneumococci isolated from blood cultures obtained within 48 h after hospital admission and adequately completed questionnaires (figure 1). This accounts for 58% (2025/3504) of all serotyped IPD episodes during this time period. If patients had repeated episodes, only the first one was included. To obtain complete data on mortality, the database was linked to Statistics Sweden using the unique personal identification number given to all Swedish citizens.[19] The Swedish national guidelines on the clinical management of CAP published in 2005 recommend that all patients with suspected pneumonia assessed at a hospital should have a chest x-ray and two blood cultures performed.[20] Treatment regimens should be based on the severity of pneumonia graded according to CURB-65 where patients with non-severe CAP (0–2 points) are recommended treatment with penicillin G, patients with 3 points are recommended treatment with penicillin G or a cephalosporin and patients with very severe CAP (4–5 points) are recommended treatment with a cephalosporin in combination with a macrolide or penicillin G in combination with moxifloxacin/levofloxacin. The guidelines were largely unchanged during the study period except that CURB-65 was replaced by CRB-65 in 2008.[21]

Laboratory analyses

Serotyping was performed by gel diffusion and/or capsular reaction testing, as previously described.[16] Antibiotic resistance was determined with disc diffusion and E-test. Non-susceptibility for penicillin was defined as a minimal inhibitory concentration of ≥0.12 mg/l and for erythromycin a zone diameter of ≤21 mm.[22]

Statistical analyses

Mortality was defined as death within 30 days from the sampling date. Most comorbidities were analysed as dichotomous variables (see online supplementary methods). Data on age, sex, serotype and mortality were complete. For smoking, alcohol abuse and comorbidities, data were incomplete in the questionnaires in 5.8–21.1% of patients (table 1). Missing data are common in epidemiological studies and simulation studies have shown that complete-case analyses often induce bias.[23] We therefore performed multiple imputation analyses using chained equations with 20 imputation sets (see online supplements for details).[24] Logistic regression modelling was used and variables associated with mortality in univariate analyses at a p value of <0.1 were considered for inclusion in the multivariate models. Since the aim was to assess the effect of each exposure on mortality, careful consideration was given to the relationship between different variables using graphic models, which formed the basis of what variables to include in the multivariate models to perform proper adjustment for confounders.[18 25] For example, if it is known which host factors affect serotype acquisition,[8] it would be improper to adjust for serotype in a model that assesses the effect of host factor on mortality since it removes the part of the host factor effect mediated through the serotype. Serotype was assessed individually for serotypes with

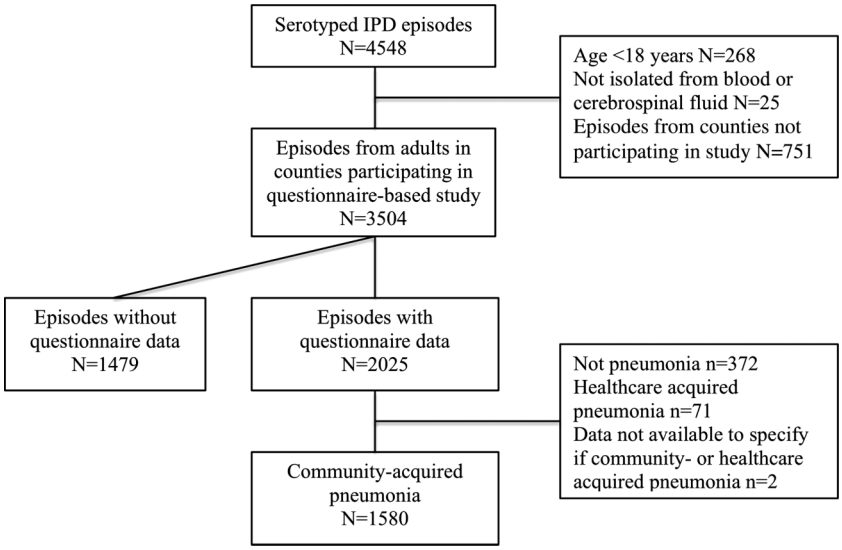

Figure 1 Flow chart of patients with serotyped invasive pneumococcal disease (IPD) in Sweden 2007–2009.

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Table 1 Host factors associated with 30-day mortality in patients with bacteraemic pneumococcal pneumonia

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Age				
≥85	203 (12.9)	52 (26.1)	**26.74 (8.20 to 87.12)**	**29.43 (9.00 to 96.27)**
75–84	323 (20.4)	40 (12.4)	**10.69 (3.27 to 35.02)**	**11.30 (3.45 to 37.06)**
65–74	301 (19.1)	25 (8.3)	**6.85 (2.04 to 22.99)**	**7.10 (2.12 to 23.85)**
55–64	341 (21.6)	20 (5.9)	**4.71 (1.38 to 16.05)**	**4.84 (1.42 to 16.49)**
45–54	182 (11.5)	6 (3.3)	2.58 (0.64 to 10.46)	2.59 (0.64 to 10.50)
<45	230 (14.6)	3 (1.3)	1.00 (ref)	1.00 (ref)
≥65	827 (52.3)	118 (14.3)	**4.16 (2.73 to 6.32)**	**4.29 (2.82 to 6.54)**
<65	753 (47.7)	29 (3.9)	1.00 (ref)	1.00 (ref)
Sex				
Men	767 (48.5)	78 (10.2)	1.22 (0.87 to 1.72)	**1.55 (1.09 to 2.22)**
Women	813 (51.5)	69 (8.5)	1.00 (ref)	1.00 (ref)
Smoking				
Yes	337 (21.3)	33 (9.8)	1.46 (0.96 to 2.23)	**1.79 (1.02 to 3.14)**
No	909 (57.5)	65 (7.2)	1.00 (ref)	1.00 (ref)
N/S	334 (21.1)	49 (14.7)		
Alcohol abuse				
Yes	113 (7.2)	18 (15.9)	**2.39 (1.40 to 4.08)**	**3.82 (1.85 to 7.85)**
No	1214 (76.8)	93 (7.7)	1.00 (ref)	1.00 (ref)
N/S	253 (16.0)	36 (14.2)		
Heart disease				
Yes	438 (27.7)	72 (16.4)	**3.00 (2.09 to 4.31)**	1.42 (0.93 to 2.17)
No	1038 (65.7)	59 (5.7)	1.00 (ref)	1.00 (ref)
N/S	104 (6.6)	16 (15.4)		
Pulmonary disease				
Yes	382 (24.2)	40 (10.5)	1.48 (0.99 to 2.20)	0.96 (0.61 to 1.48)
No	1086 (68.7)	82 (7.6)	1.00 (ref)	1.00 (ref)
N/S	112 (7.1)	25 (22.3)		
Liver disease				
Yes	84 (5.3)	15 (17.9)	**2.80 (1.54 to 5.08)**	**2.25 (1.04 to 4.87)**
No	1369 (86.7)	108 (7.9)	1.00 (ref)	1.00 (ref)
N/S	127 (8.0)	24 (18.9)		
Severe†	23 (1.5)	8 (34.8)	**6.06 (2.58 to 14.25)**	**5.15 (1.74 to 15.26)**
Mild	61 (3.9)	7 (11.5)	1.86 (0.85 to 4.07)	1.70 (0.64 to 4.47)
No	1369 (86.7)	108 (7.9)	1.00 (ref)	1.00 (ref)
Renal disease				
Yes	91 (5.8)	18 (19.8)	**3.12 (1.83 to 5.30)**	**1.84 (1.02 to 3.33)**
No	1372 (86.8)	104 (7.6)	1.00 (ref)	1.00 (ref)
N/S	117 (7.4)	25 (21.4)		
Diabetes				
Yes	207 (13.1)	22 (10.6)	1.31 (0.81 to 2.12)	0.98 (0.57 to 1.66)
No	1282 (81.1)	105 (8.2)	1.00 (ref)	1.00 (ref)
N/S	91 (5.8)	20 (22.0)		
Blood malignancy				
Yes	115 (7.3)	5 (4.4)	0.48 (0.20 to 1.17)	0.47 (0.19 to 1.19)
No	1325 (83.9)	113 (8.5)	1.00 (ref)	1.00 (ref)
N/S	140 (8.9)	29 (20.7)		
Solid tumour				
Yes	114 (7.2)	27 (23.7)	**3.84 (2.41 to 6.11)**	**2.63 (1.53 to 4.50)**
No	1353 (85.6)	97 (7.2)	1.00 (ref)	1.00 (ref)
N/S	113 (7.2)	23 (20.4)		
Chronic autoimmune disease				
Yes	119 (7.0)	7 (6.4)	0.72 (0.31 to 1.65)	0.79 (0.32 to 1.96)
No	1348 (85.3)	118 (8.5)	1.00 (ref)	1.00 (ref)
N/S	122 (7.7)	22 (18.0)		
Hypogammaglobulinaemia				
Yes	18 (1.1)	3 (16.7)	1.72 (0.51 to 5.82)	1.53 (0.41 to 5.76)
No	1289 (81.6)	104 (8.1)	1.00 (ref)	1.00 (ref)
N/S	273 (17.3)	40 (14.7)		

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Table 1 Continued

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Chronic immunosuppressive therapy				
Yes	158 (10.0)	17 (10.8)	1.45 (0.85 to 2.48)	1.12 (0.60 to 2.09)
No	1306 (82.7)	108 (8.3)	1.00 (ref)	1.00 (ref)
N/S	116 (7.3)	22 (19.0)		
Splenectomy				
Yes	11 (0.7)	1 (9.1)	1.60 (0.27 to 9.59)	1.23 (0.19 to 7.89)
No	1334 (84.4)	107 (8.0)	1.00 (ref)	1.00 (ref)
N/S	235 (14.9)	39 (16.6)		
Charlson Index‡				
≥4	74 (4.7)	16 (21.6)	**6.03 (3.43 to 10.59)**	**3.21 (1.75 to 5.90)**
3	85 (5.4)	13 (15.3)	**3.45 (1.83 to 6.51)**	1.89 (0.96 to 3.72)
2	205 (13.0)	16 (7.8)	**1.91 (1.08 to 3.37)**	1.12 (0.62 to 2.03)
1	313 (19.8)	21 (6.7)	1.49 (0.86–2.58)	0.86 (0.48–1.54)
0	562 (35.6)	25 (4.5)	1.00 (ref)	1.00 (ref)
N/D	341 (21.6)	56 (16.4)		

*Adjusted ORs: to avoid adjustment for variables on the causal pathway between exposure and outcome, age was adjusted for gender; gender was adjusted for age; smoking was adjusted for age, sex and alcohol abuse; alcohol was adjusted for age, sex and smoking; each comorbidity was adjusted for age, sex, smoking, alcohol and other comorbidities associated with mortality at a p value of <0.1 in univariate analyses (ie, heart disease, pulmonary disease, liver disease, renal disease and solid tumour); and Charlson Index was adjusted for age, sex, smoking and alcohol.
†Liver disease was divided into mild and severe disease where cirrhosis, liver failure and primary liver malignancy were classified as severe disease.
‡Charlson Index based on heart disease, pulmonary disease, liver disease, renal disease, diabetes, blood malignancy, solid tumour and connective tissue disease. N/D since data on disease status were not specified for one or more of the abovementioned diseases.
N/D, not defined; N/S, not specified in questionnaire.

more than 50 isolates using serotype 14 as the reference type, and also grouped in three different ways: (1) according to high (serotype 1, 5 and 7F), medium (serotype 4, 9V, 14 and 18C) and low (serotype 3, 6A, 6B, 8, 19F and 23F) invasive disease potential[8 15]; (2) according to high (serotypes 3, 6A, 6B, 9N, 19A, 19F, 23F), medium (serotypes 9V, 12F, 14, 22F) and low (serotype 1, 4, 5, 7F, 8) serotype-specific case fatality rates (CFR) as reported by meta-analysis[9]; or (3) according to serotypes included in the 13-valent conjugated vaccine approved for use in adults (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).[26] The Charlson Index was used to assess the importance of multiple comorbidities and to adjust for comorbidities in the model with individual serotypes.[3 27] Population attributable proportions (PAP) were calculated for exposures associated with mortality where PAP=exposure prevalence among diseased×(adjusted OR − 1)/adjusted OR.[18]

RESULTS

Host factors and mortality risk

The overall 30-day mortality was 9.3% among the 1580 patients with bacteraemic pneumococcal pneumonia. Among the host factors, increasing age, male gender, smoking, alcohol abuse, liver disease, renal disease, solid tumour and higher Charlson Index were associated with an increased mortality risk in adjusted analyses (table 1). Age was the strongest predictor of death, which increased exponentially from 1.3% in patients <45 years of age to 26.1% in patients aged ≥85 years. Even in analyses restricted to 476 patients with no recorded comorbidity, mortality was strongly associated with increased age (1.5% in patients <65 years vs 11.9% in patients ≥65 years, p<0.001). The PAP for 30-day mortality was 14.9% for smoking, 13.1% for alcohol abuse, 13.1% for solid tumours, 8.0% for liver disease and 7.4% for renal disease. Heart disease was associated with increased mortality in crude analyses but not after adjustment for other host factors. The risk of death was not statistically different between patients with arrhythmia (13.7%), valvular dysfunction (23.8%), cardiovascular disease (15.9%) or heart failure (19.6%) (p=0.54). Patients with different pulmonary diseases had different mortality risks: asthma (4.4%), chronic obstructive pulmonary disease (8.1%), lung cancer (28.0%) and other pulmonary diseases (8.5%) (p=0.003). However, pulmonary disease was not associated with an increased risk of mortality in multivariate analysis even if asthma was excluded (OR 1.10, 95% CI 0.70 to 1.73). The analyses were not sensitive to the number of imputations used or specific combinations of imputed datasets, except for the uncommon exposures splenectomy and hypogammaglobulinaemia (see online supplementary table S1).

Serotype and mortality risk

For individual serotypes the mortality ranged from 2.3% for serotype 7F to 19.2% for serotype 6B (table 2). In the analyses, serotype 14 was used as reference and only serotype 6B was associated with an increased risk in unadjusted analyses. After adjustment for age, sex and Charlson Index, none of the serotypes had a significantly different mortality OR compared with serotype 14. In the crude analyses where serotypes were grouped, there were highly significant trends of increased mortality both for patients infected with serotypes with lower invasive disease potential and those infected with serotypes previously reported to infer a higher mortality (p values for trend <0.001) (table 2). However, in the multivariate model, these associations were mitigated by adjustment for host factors and were no longer significantly associated with mortality (p values for trend 0.09 and 0.11). Adjustment for age removed confounding to a larger extent than adjustment for comorbidities, which indicates that age was the strongest confounder of the association between serotype and mortality (data not shown). The prevalence of serotypes with low CFR potential decreased with increasing age and Charlson Index score, and serotypes with high CFR potential increased in older age groups and in patients with a higher Charlson Index score (p values for

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Table 2 Thirty-day mortality risk according to serotype and antibiotic resistance in patients with bacteraemic pneumococcal pneumonia

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Individual serotype				
9V	191 (12.1)	10 (5.2)	0.62 (0.28 to 1.40)	0.83 (0.36 to 1.93)
7F	177 (11.2)	4 (2.3)	0.26 (0.09 to 0.79)	0.51 (0.16 to 1.59)
4	158 (10.0)	8 (5.1)	0.60 (0.25 to 1.43)	0.88 (0.36 to 2.16)
3	142 (9.0)	17 (12.9)	1.54 (0.76 to 3.12)	1.85 (0.87 to 3.93)
23F	97 (6.1)	11 (11.3)	1.44 (0.65 to 3.21)	1.23 (0.54 to 2.81)
22F	79 (5.0)	7 (8.9)	1.10 (0.44 to 2.76)	1.25 (0.48 to 3.23)
6B	78 (4.9)	15 (19.2)	**2.69 (1.27 to 5.69)**	2.09 (0.96 to 4.57)
6A	76 (4.8)	10 (13.1)	1.71 (0.75 to 3.92)	1.17 (0.49 to 2.75)
19A	55 (3.5)	4 (7.3)	0.89 (0.29 to 2.75)	0.69 (0.21 to 2.22)
14	209 (13.2)	17 (8.3)	1.00 (ref)	1.00 (ref)
Other	318 (20.1)	44 (13.8)	–	–
Serotype category according to CFR‡				
High	509 (32.2)	63 (12.4)	**3.28 (1.89 to 5.70)**	1.63 (0.89 to 2.98)
Medium	484 (30.6)	35 (7.2)	**1.81 (1.00 to 3.28)**	1.27 (0.67 to 2.42)
Low	412 (26.1)	17 (4.1)	1.00 (ref)*	1.00 (ref)**
Serotype category according to invasiveness§				
Low	461 (29.2)	58 (12.6)	**4.21 (1.89 to 9.40)**	1.67 (0.70 to 4.00)
Medium	591 (37.4)	40 (6.8)	2.13 (0.94 to 4.82)	1.19 (0.49 to 2.87)
High	212 (13.4)	7 (3.3)	1.00 (ref)*	1.00 (ref)***
PCV 13 serotypes ¶				
Yes	1277 (80.8)	107 (8.4)	**0.60 (0.41 to 0.89)**	0.78 (0.51 to 1.19)
No	303 (19.2)	40 (13.2)	1.00 (ref)	1.00 (ref)
Penicillin non-susceptible††				
Yes	45 (2.9)	6 (13.3)	1.52 (0.63 to 3.65)	1.07 (0.42 to 2.74)
No	1535 (97.2)	141 (9.2)	1.00 (ref)	1.00 (ref)
Erythromycin non-susceptible††				
Yes	69 (4.4)	5 (7.4)	0.75 (0.30 to 1.90)	0.83 (0.32 to 2.16)
No	1511 (95.6)	141 (9.4)	1.00 (ref)	

Significant results in bold.
p Value trend: *<0.001, **0.09, ***0.11.
†Adjusted ORs: individual serotypes and antibiotic resistance adjusted for age, sex and Charlson Index score; grouped serotypes adjusted for age, sex, smoking, alcohol and comorbidities associated with mortality at a p value of <0.1 in univariate analyses (ie, heart disease, pulmonary disease, liver disease, renal disease and solid tumour).
‡Serotypes classified as associated with low (serotype 1, 4, 5, 7F, 8), medium (serotypes 9V, 12F, 14, 22F) and high (serotypes 3, 6A, 6B, 9N, 19A, 19F, 23F) case fatality rate in a recent meta-analysis.[9] There were 175 patients infected with serotypes not included in this classification.
§Serotypes classified as associated with high (serotype 1, 5 and 7F), medium (serotype 4, 9V, 14 and 18C) and low (serotype 3, 6A, 6B, 8, 19F and 23F) invasiveness.[8 15] There were 316 patients infected with serotypes not included in this classification.
¶Serotypes included in 13-valent pneumococcal conjugate vaccine: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
††Non-susceptibility for penicillin was defined as minimal inhibitory concentration ≥0.12 mg/l and for erythromycin a zone diameter of ≤21 mm.[22].
CFR, case-fatality rates; PCV, pneumococcal vaccine.

trend <0.001) (figure 2). Furthermore, individual serotypes with low CFR potential tended to cluster in patients without comorbidities (serotype 4 was less prevalent in patients with heart disease and serotype 7F was less common in patients with heart disease, blood malignancy and chronic immunosuppressive therapy). On the other hand, serotypes with high CFR potential tended to cluster in patients with comorbidities (serotype 6A in patients with liver disease and solid tumours, serotype 6B in patients with blood malignancies and serotype 23F in patients with heart disease) (see online supplementary table S2). Serotypes not included in the 13-valent conjugated pneumococcal vaccine were associated with higher death rates in unadjusted but not in adjusted analyses (table 2). The association in the unadjusted analysis was confounded by comorbidity and age because serotypes in the 13-valent vaccine were associated with younger age and patients without comorbidities (p=0.01 and p<0.001, respectively). The 7-valent conjugated pneumococcal vaccine was introduced in the Swedish childhood vaccination programme during the course of the study (in most Swedish counties on 1 January 2009), which could have influenced the serotype distribution. However, there was no evidence of a differential serotype effect on mortality before and after the introduction of the vaccine (p value for interaction=0.19). The prevalence of penicillin and erythromycin non-susceptibility among the pneumococcal isolates was uncommon (2.9% and 4.4%, respectively) and was not associated with mortality (table 2).

Antibiotic treatment and risk factors for patients admitted to the ICU

The effect of initial combination antibiotic therapy on mortality was assessed in 1484 patients receiving intravenous β-lactam antibiotics (penicillin, cefotaxime, ceftriaxone, cefuroxime, piperacillin-tazobactam or carbapenem; table 3). None of the 26 patients treated with β-lactam antibiotics in combination with macrolide and only one of 31 patients treated with β-lactam antibiotics in combination with a quinolone died (table 3). However, this was not statistically different from the death rate of 9.3% in 1098 patients treated with β-lactam antibiotics only. Since the initial empirical antibiotic regimen is likely to have been influenced by disease severity, we further restricted the analyses to patients admitted to the ICU. In ICU patients

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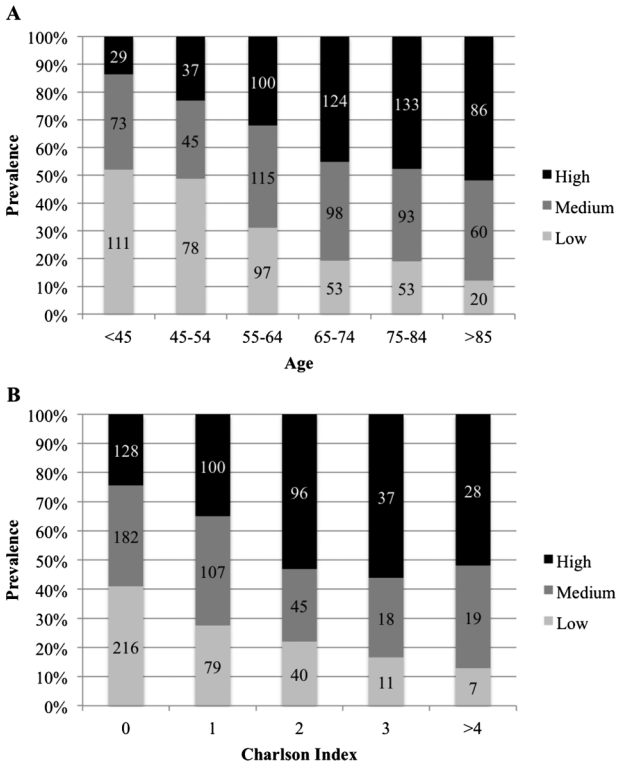

Figure 2 Association between serotype category according to case fatality rate potential[9] (high=black, medium=dark grey, low=light grey) and (A) age and (B) Charlson Index. Absolute numbers presented within bars.

the death rate was 18.8% (54/288) and age and liver disease were associated with mortality in adjusted analyses (table 4). Serotype category, with serotypes previously reported to infer a higher mortality, was also associated with increased mortality in adjusted analyses in these patients (p value for trend=0.04). None of the 25 ICU patients receiving initial treatment with β-lactam antibiotics in combination with a macrolide or quinolone died. In contrast, 31 of 147 patients (21.1%) receiving β-lactam monotherapy had a fatal outcome (OR 0.11, 95% CI 0 to 0.64). There was no difference in the prevalence of pneumococci non-susceptible to penicillin between the two groups (table 5). However, patients receiving combination therapy with macrolides or quinolones tended to be younger, to have fewer comorbidities and were infected with serotypes with lower CFR, indicating that the reduced risk of death in this patient group may be explained by confounding (table 5).

DISCUSSION

Pneumococci are major contributors to mortality worldwide; however, more knowledge on how this genomically diverse species contributes to disease is needed. In this cohort study we assessed the contribution of bacterial and host factors as well as antibiotic treatment to mortality in adult patients with community-acquired bacteraemic pneumococcal pneumonia. Few studies have had a sufficiently large sample size to investigate the effect of comorbidities on mortality risk in IPD using multivariate analyses.[6 28 29] The large size and population-based design of this study with comprehensive follow-up argues in favour of the reliability of our results. Careful consideration was given to the relationship between variables in the selection of exposures to include in multivariate analyses using graphic models—for example, to avoid adjustment for variables that are on the causal pathway between the exposure of interest and the outcome—in order to be able to assess the effect of each exposure on mortality. This is particularly important for public health measures where it is crucial to understand the relative contribution of different exposures. We found that increased age, alcohol abuse, smoking, liver disease, renal disease and solid tumours were associated with an increased risk of mortality. Interestingly, age was a very strong contributor to mortality even in patients without recorded comorbidities. This could be due to unmeasured or misclassified comorbidities, but another plausible explanation is immunosenescence.[30 31] Ageing is associated with changes in both the innate and adaptive immune response, such as an increase in functionally impaired macrophages and a shift from Th1 to Th2 cytokine response.[30] Interestingly, a recent study reported age-related impairment of alveolar macrophages and Toll-like receptor levels during pneumonia caused by *S pneumoniae* in mice.[32] Furthermore, ageing is associated with a procoagulant state and mitochondrial damage causing cellular apoptosis during sepsis.[31] Our data are consistent with previous studies where increasing age was associated with mortality in patients with IPD[2 6] and with studies where mortality was reported to increase exponentially with age.[7 33 34] Indeed, the absolute mortality risk in patients without underlying disease was low among patients aged <65 years (1.5%) compared with those aged ≥65 years (11.9%), which is in line with current pneumococcal vaccine indications for adults in many

Table 3 Thirty-day mortality risk according to initial monotherapy versus combination antibiotic treatment in patients with bacteraemic pneumococcal pneumonia*

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR† (95% CI)
β-lactam iv+aminoglycoside	242 (15.3)	31 (12.8)	1.43 (0.93 to 2.20)	1.95 (1.16 to 3.27)
β-lactam iv+macrolide	26 (1.6)	0 (0)	0.27 (0 to 1.52)‡	N/A
β-lactam iv+quinolone	31 (2.0)	1 (3.2)	0.33 (0.04 to 2.41)	0.93 (0.11 to 7.78)
β-lactam iv+macrolide/quinolone	57 (3.6)	1 (1.8)	0.17 (0.02 to 1.27)	0.24 (0.03 to 2.07)
β-lactam iv+other antibiotics	30 (1.9)	2 (6.7)	0.70 (0.16 to 2.97)	0.60 (0.07 to 5.03)
β-lactam iv only	1098 (69.5)	102 (9.3)	1.00 (ref)	1.00 (ref)

*Initial intravenous (iv) β -lactam monotherapy compared with combined therapy. β-lactam iv=penicillin, cefotaxime, ceftriaxone, cefuroxime, piperacillin-tazobactam or carbapenem. Macrolide=erythromycin, clarithromycin or azithromycin. Quinolone=levofloxacin or moxifloxacin. Other antibiotics=ampicillin, ceftazidim, ciprofloxacin, cloxacillin, clindamycin, vancomycin, metronidazole or doxycyclin.
†Adjusted ORs: antibiotic regimen adjusted for age, sex, smoking, alcohol and comorbidities associated with mortality at a p value of <0.1 in univariate analyses (ie, heart disease, pulmonary disease, liver disease, renal disease and solid tumour) and serotype.
‡Calculated with exact logistic regression.
N/A, not applicable.

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Table 4 Risk factors significantly associated with 30-day mortality in patients with bacteraemic pneumococcal pneumonia admitted to the ICU (n=288)

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Age				
≥85	12 (4.1)	6 (50.0)	**11.67 (2.86 to 47.57)**	**11.56 (2.83 to 47.19)**
75–84	51 (17.7)	20 (39.2)	**7.53 (2.75 to 20.57)**	**7.74 (2.81 to 21.28)**
65–74	68 (23.6)	13 (19.1)	2.76 (0.98 to 7.72)	2.79 (0.99 to 7.82)
55–64	81 (28.1)	9 (11.1)	1.46 (0.49 to 4.31)	1.47 (0.50 to 4.34)
<55	76 (26.4)	6 (7.9)	1 (ref)	1 (ref)
Heart disease				
Yes	72 (25–0)	21 (29.2)	**2.19 (1.16 to 4.15)**	0.96 (0.44 to 2.07)
No	181 (62.9)	26 (14.4)	1.00 (ref)	1.00 (ref)
N/S	35 (12.2)	7 (20.0)		
Liver disease				
Yes	21 (7.3)	7 (33.3)	**3.01 (1.12 to 8.05)**	**4.23 (1.38 to 12.93)**
No	233 (80.9)	36 (15.5)	1.00 (ref)	1.00 (ref)
N/S	34 (11.8)	11 (32.4)		
Renal disease				
Yes	19 (6.6)	8 (42.1)	**3.74 (1.43 to 9.76)**	2.50 (0.84 to 7.45)
No	234 (81.3)	34 (14.5)	1.00 (ref)	1.00 (ref)
N/S	35 (12.2)	12 (34.3)		
Serotype category according to CFR‡				
High	104 (36.1)	25 (24.0)	**4.03 (1.33 to 12.26)**	3.29 (0.99 to 10.88)
Medium	98 (34.0)	15 (15.3)	2.30 (0.72 to 7.33)	2.13 (0.61 to 7.48)
Low	55 (19.1)	4 (7.3)	1.00 (ref)*	1.00 (ref)***
Serotype category according to invasiveness§				
Low	92 (31.9)	22 (23.9)	4.09 (0.90 to 18.60)	3.96 (0.76 to 20.72)
Medium	111 (38.5)	16 (14.4)	2.19 (0.47 to 10.14)	2.40 (0.45 to 12.74)
High	28 (9.7)	2 (7.1)	1.00 (ref)**	1.00 (ref)****
Initial antibiotic therapy				
β-lactam iv+macrolide/ quinolone¶	25 (8.7)	0 (0)	**0.11 (0 to 0.64)**††	N/A
β-lactam iv only¶	147 (51.0)	31 (21.1)	1.00 (ref)	

p Value trend: *0.007, **0.02, ***0.04, ****0.06.
†Adjusted ORs: age was adjusted for gender; each comorbidity was adjusted for age, sex and other comorbidities associated with mortality at a p value of <0.1 in univariate analyses (ie, heart disease, liver disease and renal disease).
‡Serotypes classified as associated with low (serotype 1, 4, 5, 7F, 8), medium (serotypes 9V, 12F, 14, 22F) and high (serotypes 3, 6A, 6B, 9N, 19A, 19F, 23F) case fatality rate in a recent meta-analysis.[9]
§Serotypes classified as associated with high (serotype 1, 5 and 7F), medium (serotype 4, 9V, 14 and 18C) and low (serotype 3, 6A, 6B, 8, 19F and 23F) invasiveness.[8 15]
¶iv=intravenous. β-lactam iv=penicillin, cefotaxime, ceftriaxone, cefuroxime, piperacillin-tazobactam or carbapenem. Macrolide/quinolone=erythromycin, clarithromycin, azithromycin, levofloxacin or moxifloxacin.
††Calculated with exact logistic regression.
CFR, case-fatality rates; N/A, not applicable; N/S, not specified in questionnaire.

countries.[35 36] In the current study alcohol abuse, smoking, liver disease, renal disease and solid tumour attributed 7.4–14.9% to the mortality, indicating that these patient groups are important vaccination targets for reducing mortality in pneumococcal disease. Heart disease was associated with increased mortality in unadjusted but not adjusted analyses, indicating confounding by other host factors. Previous studies have reported an increased mortality risk in multivariate models for patients with pulmonary disease,[6 37] immunosuppression,[2 29] liver disease,[29 38] cardiac failure[29] and solid tumours.[29] Possible reasons for discrepancies between studies are differences in study design, study populations, definition of variables, cohort effects and how the multivariate modelling was performed.

The observed effect of serotype on mortality was mitigated after adjustment for host factors (particularly age), which shows the importance of adequate adjustment for host factors in analyses of pneumococcal disease when investigating serotype-specific mortality. Also, serotypes associated with a high CFR were more prevalent among older patients and among patients with underlying diseases, while the opposite was observed for serotypes with low CFR potential. This is in line with our previous findings that certain serotypes act as 'opportunistic pathogens' infecting older patients and patients with underlying diseases.[8] We therefore hypothesise that certain serotypes have a propensity to infect older and non-healthy individuals, but the status of the patient is likely to be more important for the outcome of disease. Despite being one of the largest studies to investigate mortality in patients with serotyped pneumococcal pneumonia, the present study did not enable adequate investigations of mortality risk associations to individual serotypes combined with satisfactory adjustment for host factors. However, the mortality risk point estimates of individual serotypes generally corresponded well with the results of a recent meta-analysis of bacteraemic pneumococcal pneumonia which also used serotype 14 as a reference.[9] Other studies reporting an association between serotype and mortality have made an insufficient adjustment for host factors,[5 8 9] while the largest study to date comprising 18 858 Danish patients with IPD observed distinct differences in serotype-specific mortality even after adjustment for age and comorbidity.[3]

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Table 5 Host and bacterial factors in ICU patients treated with intravenous (iv) β-lactam monotherapy and β-lactam plus macrolide/quinolone

	β-lactam iv only (n=147)	β-lactam iv+macrolide/quinolone (n=25)	p Value
Age			
Mean	63.7	57.8	0.09
≥65	72 (49.0)	10 (40.0)	0.40
<65	75 (51.0)	15 (60.0)	
Sex			
Men	69 (46.9)	12 (48.0)	0.92
Heart disease			
Yes	43 (29.3)	3 (12.0)	0.08
No	82 (55.8)	19 (76.0)	
N/S	22 (15.0)	3 (12.0)	
Liver disease			
Yes	16 (10.9)	0 (0)	0.13
No	110 (74.8)	23 (92.0)	
N/S	21 (14.3)	2 (8.0)	
Renal disease			
Yes	9 (6.1)	2 (8.0)	0.69
No	114 (77.6)	21 (84.0)	
N/S	24 (16.3)	2 (8.0)	
Serotype category according to case-fatality rate†			
High	55 (37.4)	7 (28.0)	0.07*
Medium	53 (36.1)	9 (36.0)	
Low	22 (15.0)	8 (32.0)	
Penicillin non-susceptible‡			
Yes	4 (2.7)	1 (4.0)	0.55
No	143 (97.3)	24 (96.0)	

*p Value for trend.
†Serotypes classified as associated with low (serotype 1, 4, 5, 7F, 8), medium (serotypes 9V, 12F, 14, 22F) and high (serotypes 3, 6A, 6B, 9N, 19A, 19F, 23F) case fatality rate in a recent meta-analysis.[9]
‡Non-susceptibility for penicillin was defined as minimal inhibitory concentration ≥0.12 mg/l and for erythromycin a zone diameter of ≤21 mm.[22]

Interestingly, we observed that none of the patients admitted to the ICU receiving initial treatment with macrolides or quinolones in combination with β-lactam antibiotics died. Several studies of pneumococcal disease have reported a reduced mortality risk for patients receiving combination therapy with β-lactam and macrolide antibiotics, especially in patients with severe disease (unfortunately we did not have sufficient information to stratify patients according to severity score indices).[11–13] However, other studies have reported no effect of combination therapy.[10 14] Antibiotic resistance could not explain our findings since only 2.9% of the isolates in our study were non-susceptible to penicillin and there was no difference in the prevalence of non-susceptible pneumococci between patients who received monotherapy or combination therapy. However, patients who received combination therapy tended to be younger and to have fewer comorbidities, so confounding cannot be ruled out as a possible explanation.

We obtained questionnaires from 58% of serotyped IPD episodes. The demographic data on patients with serotyped IPD with and without questionnaires were similar, indicating that the data from the questionnaires were a valid representation of IPD episodes in Sweden: mean ages were 65.6 vs 66.9 years, 48.5% vs 49.7% were men and serotypes categorised as high, medium and low CFR were prevalent in 38.3% vs 41.9%, 33.2% vs 32.7% and 28.5% vs 25.4% of cases with or without questionnaires, respectively (see online supplementary table S3). Missing data regarding exposure status ranged from 5.8% to 21.1% depending on the variable. Missing data are common in epidemiological studies and can be addressed by performing complete-case analysis which might induce bias[23] or, as was done in this study, by performing multiple imputation. We followed the recommendation of van Buuren *et al*[39] in the selection of variables for the imputations, and sensitivity analyses demonstrated that our results were not sensitive to either the number of imputations or specific imputed sets used. We therefore believe that our results are robust, except for more uncommon exposures such as splenectomy and hypogammaglobulinaemia. Furthermore, our aim was to investigate risk factors in community-acquired disease, but we did not have data on previous hospitalisations and hence it is possible that some patients hospitalised within the last month were included in our study population. Also, we did not have adequate data to produce a severity score index which is necessary to be able to study the effect of timing of initial antibiotic treatment. Moreover, the PAP estimates should be interpreted with caution since we could not obtain CIs for these estimates due to the use of multiple imputations. Finally, the conjugated pneumococcal vaccine was introduced in the Swedish childhood vaccination programme during the course of the study (in most Swedish counties it was introduced only 1 year before the termination of the study). We did not find evidence that vaccination had an effect on the serotype-specific mortality in this population, and hence vaccination is unlikely to have influenced our results.

In conclusion, in a large population-based cohort we performed careful adjustment to assess the role of host and bacterial factors in the aetiology of mortality in adult patients with bacteraemic pneumococcal disease. Our results indicate that host factors determine the pneumococcal serotype with which a patient is infected as well as being the main determinants of the

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outcome. This information is useful with regard to the prognosis of patients with pneumococcal disease as well as for policy-makers of intervention strategies.

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Contributors PN performed the analyses and drafted the report. JD and EM contributed to acquisition and management of data. ÅÖ and BHN are the guarantors of the study and contributed to the study concept and design. All authors contributed to the revision of the report and approved the version submitted.

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