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The problem of early mortality in pneumococcal pneumonia: a study of risk factors

To the Editor:

The mortality of pneumococcal pneumonia, and especially the number deaths that occur soon after presentation, remains unacceptably high [1]. In 1964, Austrian and Gold [2] observed that 60% of deaths in patients with invasive pneumococcal pneumonia (IPP) occurred within the first 5 days. Unfortunately, this does not appear to have changed over the subsequent five decades [3].

Different factors related to the mortality of pneumococcal disease have been described, including host factors such as age, comorbidities or immunosuppressive conditions [4], and organism-related factors such as serotype, bacterial load or viral co-infection [3, 5–7]. These factors have all been primarily identified to predict overall mortality, but information regarding the determinants of early mortality is scarce. It has been hypothesised that early deaths are more likely to be due to an inappropriate inflammatory response triggered by *Streptococcus pneumoniae* than to the micro-organism itself [8]. Thus, the factors that influence the early mortality may differ from those associated with late mortality. We performed the present study in order to assess factors associated with early and late mortality in IPP.

This is a multicentre longitudinal study of adults hospitalised because of IPP in three hospitals in Catalonia, Spain. In these hospitals, all microbiological strains isolated in sterile samples are collected systematically. IPP was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography and isolation of *S. pneumoniae* in blood and/or pleural fluid cultures. The strains were serotyped by Quellung reaction and/or dot-blot assay. Serotypes were grouped according to high (serotypes 3, 6A, 6B, 9N, 19A, 19F and 23F), medium (9V, 12F, 14 and 22F) and low (1, 4, 5, 7F and 8) serotype-specific case fatality rates [6]. Antibiotic therapy was administered at the discretion of the attending physician and the hospital guidelines. Treatment was considered appropriate if at least one antibiotic administered during the first 48 h showed full sensitivity against the isolated strains. To identify the risk factors for early mortality (death within 5 days of admission), late mortality (hospital mortality >5 days after admission) and survival, a multinomial logistic regression analysis was performed.

Over the study period (from 1996 to 2013), 1588 consecutive adults with IPP were diagnosed. Overall, 221 patients (13.9%) died in hospital. 121 (54.5%) died in the first 5 days after admission; 80 (36.1%) of them died in the first 48 h. Patients with early mortality were older (mean age 67.1 years) and 65.5% had an

underlying chronic medical illness. At presentation, 91.8% of these cases had respiratory failure, 68.9% septic shock and 37% required intensive care unit admission.

1328 (83.6%) pneumococcal strains were available for serotyping. The pneumococcal serotypes most commonly associated with mortality were serotypes/serogroups 3, 6 and 19F (early and late mortality developed, respectively, in 11.3% and 11.3% of infections by serotype 3, 14.3% and 7.1% by serogroup 6, and 22.2% and 14.8% by serotype 19F).

1300 patients (98.8%) received appropriate empirical therapy. β-lactams associated with macrolide were used in 28.2% of patients. No difference in mortality was observed in relation to the use of macrolide combination.

In the multivariate analysis, after adjustment by age, sex, different comorbidities and pneumococcal vaccine status, the independent risk factors for early mortality were: heavy alcohol consumption (relative risk ratio (RRR) 2.28), chronic heart disease (RRR 2.71), chronic neurological disease (RRR 2.26) and infection caused by high case fatality rate serotypes (RRR 1.98). The risk factors for late mortality were: heavy alcohol consumption (RRR 2.25), HIV infection (RRR 4), haematological cancer (RRR 3.06) and solid cancer (RRR 4.17) (table 1). When we included the specific serotypes in the model, the only serotypes associated were: infection by serotype 19F as a risk factor for early (RRR 5.88, 95% CI 1.69–20.48) and late (RRR 6.44, 95% CI 1.82–22.85) mortality, infection by serotype 3 as a risk factor for late mortality (RRR 2.77, 95% CI 1.32–5.82) and infection by serotype 1 as a protective factor against both early (RRR 0.1, 95% CI 0.02–0.87) and late (RRR 0.12, 95% CI 0.03–0.84) mortality. When we restricted the analysis to non-immunocompromised patients only (n=1010), risk factors for early mortality did not change (data not shown). In the subgroup of immunocompromised patients (n=578), the only risk factor for early mortality was high case fatality rate serotypes (RRR 2.937, 95% CI 0.996–8.660).

The results of this large study of adults with IPP show that the proportion of deaths occurring in the first 5 days remains unacceptably high, above 50% of total deaths. Furthermore, the determinants of early mortality seem to be different from the factors predisposing to later mortality.

In our study, serotypes grouped as having a high case fatality rate were found to be a significant risk factor for early mortality. The association of specific serotypes and mortality has been reinforced in recent years

TABLE 1 Multivariate analysis: risk factors for early and late mortality in invasive pneumococcal pneumonia

	RRR (95% CI)	p-value
Early mortality		
Age (18–50 years *versus* >50 years)	0.48 (0.17–1.33)	0.157
Male sex	1.51 (0.76–3.02)	0.24
Previous pneumococcal vaccination	1.16 (0.6–2.24)	0.66
Alcohol consumption	2.28 (1.11–4.66)	0.024
Chronic heart disease	2.71 (1.42–5.19)	0.003
Chronic liver disease	0.85 (0.35–2.05)	0.713
Chronic neurological disease	2.26 (1.05–4.85)	0.037
HIV infection	1.77 (0.56–5.58)	0.329
Haematologic cancer	1.93 (0.73–5.09)	0.182
Solid cancer	2.13 (0.96–4.73)	0.062
High case fatality rate serotypes[#]	1.98 (1.07–3.63)	0.029
Late mortality		
Age (18–50 years *versus* >50 years)	0.53 (0.22–1.31)	0.17
Male sex	1.22 (0.59–2.51)	0.24
Previous pneumococcal vaccination	0.7 (0.32–1.52)	0.366
Alcohol consumption	2.25 (1.12–4.53)	0.023
Chronic heart disease	0.65 (0.24–1.76)	0.401
Chronic liver disease	0.91 (0.4–2.07)	0.813
Chronic neurological disease	0.96 (0.28–3.33)	0.954
HIV infection	4 (1.55–10.3)	0.004
Haematologic cancer	3.07 (1.21–7.76)	0.018
Solid cancer	4.18 (1.96–8.92)	<0.001
High case fatality rate serotypes[#]	1.81 (0.96–3.42)	0.069

RRR: relative risk ratio. [#]: serotypes grouped as high case fatality rates are serotypes 3, 6A, 6B, 9N, 19A, 19F and 23F.

[4–6]. Nevertheless, several authors continue to assert that mortality is primarily associated with host factors [3, 7]. In our view, the results of this study reinforce the idea that micro-organisms are also an important determinant of mortality. The association of these serotypes and early mortality could be connected to the hypothesis that early deaths are due to an inappropriate inflammatory response from the host. Serotypes with high case fatality rates have been found to be heavily encapsulated [6, 9] and induce a greater inflammatory response [10]. Nevertheless, we have also in mind that this phenomenon is complex and probably involves many other factors not entirely explained [11].

In addition to pathogen-related factors, host aspects also play a role in the severity of the illness. Different studies have found that increased age, alcohol abuse, smoking, chronic medical illness, and immunosuppressive conditions were associated with an increased risk of mortality [4, 7, 12]. However, few studies have addressed the relationship between comorbidities and early mortality [3, 13]. In our study, we found that chronic heart disease and severe neurological disease were independent risk factors for early mortality. In contrast, some immunosuppressive conditions carried a high risk of later mortality. The reasons for different factors being associated with different stages of mortality are not clearly understood. We can hypothesise that, although some immunodeficiency conditions may promote pneumococcal infection, they may also decrease the inflammatory response of the host to this infection. If so, this seems more likely to contribute to late mortality than early mortality, which is more related to inflammatory mechanisms.

Studies report conflicting results concerning the benefit of combination antibiotics in pneumococcal pneumonia [14, 15]. We did not find any differences in the mortality attributable to the use of combination therapy with macrolides. This evidence reinforces the hypothesis that early deaths are less dependent on antibiotic than other factors [2].

Our study has some limitations. First, the study included only patients with IPP, and therefore it is difficult to generalise the findings to all cases of pneumococcal pneumonia. Secondly, other factors that might modulate the clinical presentation of pneumococcal pneumonia, such as the genetic properties of *S. pneumoniae* or the host, or the effect of viral co-infections, have not been evaluated [5]. Finally, we have not evaluated the inflammatory response of the host or anti-inflammatory therapy, so we cannot fully support our hypothesis concerning the effect of encapsulated serotypes or immunosuppressive conditions on mortality.

Despite these limitations, our study demonstrated that early mortality remains a problem in pneumococcal pneumonia, but its determinants differ from factors associated to later mortality.

@ERSpublications
Comorbidity and infections by encapsulated serotypes are the main risk factors for death in pneumococcal pneumonia http://ow.ly/KSnlB

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Risk factors for the misdiagnosis of tuberculosis in the UK, 2001–2011

To the Editor:

In the past 20 years, following several decades of decline, the number of tuberculosis (TB) cases in the UK has increased. The characteristics of TB cases have changed, from a disease that was predominantly pulmonary and widespread in the population [1], to one that is concentrated in major urban areas affecting immigrants, the homeless, prisoners and drug users [2], with a high proportion of extrapulmonary disease [3]. The signs and symptoms of TB are shared with many other diseases. Therefore, knowledge of the epidemiology of TB and current associated risk factors is essential in informing a diagnosis [4].

In this analysis, the demographic characteristics of misdiagnosed cases (those notified and subsequently denotified) were compared with those correctly diagnosed at the outset. Knowledge of these details may inform improved clinical management of patients presenting with symptoms from the differential diagnosis in which TB and other diseases are included.

The Public Health England Enhanced Tuberculosis Surveillance (ETS) System collects demographic and clinical data on TB cases in England, Wales and Northern Ireland. The definition of TB used by ETS is based either on a positive culture of *Mycobacterium tuberculosis* complex in a clinically ill patient or on clinical and/or radiological signs and/or symptoms compatible with TB, together with a clinician's decision to treat the patient with a full course of anti-tuberculosis therapy. Cases may subsequently be denotified if found not to be TB on further investigation. Follow-up information on treatment outcome is requested 12 months after commencement and includes a prompt for denotification of the case if appropriate.

All cases notified between 2001 and 2011 were included in the analysis. Cases were identified as "true" TB cases (any TB case reported to ETS that was not subsequently denotified or reported as not having had TB at the 12-month treatment outcome follow-up), or "misdiagnosed" cases (any case that was subsequently denotified or reported as not having had TB at the 12-month treatment outcome follow-up).

Data were analysed using Stata V.13.1 (StataCorp, College Station, TX, USA). Risk factors included in the analyses were: sex, age group, location, ethnicity, place of birth (UK- or non-UK-born), site of disease, history of TB and time from entry to the UK until TB diagnosis. Logistic regression was used to obtain odds ratios, and variables associated with the outcome at $p<0.05$ in the univariable analysis were considered for multivariable analysis in a forward stepwise fashion, starting with the ones most strongly associated with the outcome. The category with the lowest risk of misdiagnosis was used as the baseline. Statistical significance