Increased Long-Term Mortality after an Episode of Community-Acquired Pneumonia—Time to Move beyond Descriptive Studies

Thomas J. Marrie* and Evangelos Michelakis
Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

(See the article by Mortensen et al. on pages 1617–24)

In this issue of *Clinical Infectious Diseases*, Mortensen et al. [1] report the results of an analysis of factors associated with long-term mortality in patients who survived 90 days after presentation to the hospital with community-acquired pneumonia (CAP) [1]. The population studied was the cohort of patients enrolled in the Boston and Pittsburgh portion of the Patient Outcomes Research Team pneumonia project, which is a collaborative effort among investigators in Boston, Pittsburgh, and Halifax, Nova Scotia, Canada [2]. Of the 1419 patients who were followed for a mean duration of 5.9 years, 608 (42.4%) died. A case-control method was used to determine whether there was increased long-term mortality among those who survived an episode of pneumonia. Control subjects were age-matched persons for whom data was obtained from US life tables. There was a significantly higher mortality among patients with CAP across all age groups than in the control population. In addition, the investigators analyzed the data to determine the factors that predicted long-term mortality. Sociodemographic factors associated with mortality were age (stratified by decade), high school graduation level or less, male sex, and nursing home residence. In addition, comorbid conditions (as represented by the Charlson comorbidity score), pleural effusion, and steroid use were independently associated with long-term mortality. Do-not-resuscitate status at the time of presentation, poor nutritional status, and glucocorticoid use were also associated with increased mortality. Fever at the time of presentation was associated with decreased mortality.

Long-term mortality following an episode of CAP has been the subject of a number of reports. Koivula et al. [3] examined the 12-year mortality among 122 older persons (≥60 years of age) who survived pneumonia, compared with that among 4045 residents of a Finnish town who had not had an episode of pneumonia. Thirty-nine percent of the patients who survived CAP were alive at 10 years, compared with 61% of the patients who had not had CAP. Total mortality, cardiovascular mortality, and pneumonia-associated mortality were all higher among the patients with CAP. Kaplan et al. [4] used an administrative database to examine the mortality among 158,960 Medicare recipients (≥65 years of age) hospitalized with CAP, compared with that among 794,333 hospitalized control subjects. The in-hospital and 1-year mortality rates were 11% and 40%, respectively, for the patients with CAP and were 5.5% and 29.1%, respectively, for the control subjects.

Advanced age and increasing number of comorbidities were major independent predictors of mortality. Carriere et al. [5] used an administrative database to study all adult patients hospitalized with pneumonia in the province of Alberta, Canada. They compared 4-year mortality among patients with pneumonia with that in the general adult population in Alberta not hospitalized for pneumonia. The 4-year mortality among those patients hospitalized during 1994–1995 (n = 9141) in each age-specific group was higher than that in the adult population not hospitalized with pneumonia (n = 1,950,997) that was followed longitudinally for the same duration of time. The significant difference in mortality rates between the pneumonia and nonpneumonia groups was mainly associated with the sharp drop in the survival probability among patients with pneumonia in the first year after the CAP episode (P<.0001).

*Present affiliation: Walter C. Mackenzie Health Sciences Center, Edmonton, Alberta, Canada.

Reprints or correspondence: Dr. Thomas J. Marrie, MD, FRCPC, Walter C. Mackenzie Health Sciences Center, 8840 112 St, Edmonton, Alberta, Canada T6G 2B7 (tom.marrie@ualberta.ca).

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Furthermore, the mortality for the subset of patients with pneumonia and without comorbidities was greater than that of the general population.

Brancati et al. [6] examined the 2-year mortality in a cohort of 119 patients who survived an episode of pneumonia. Thirty-eight patients (32%) died. Brancati et al. [6] found that 2-year mortality was independently associated with severe comorbidity, moderate comorbidity, and a hematocrit of <35%. Compared with patients aged 18–44 years, patients aged 45–64 (relative risk [RR], 0.84), 65–74 (RR, 1.28), and 75–92 years (RR, 1.99) were not significantly more likely to die during the 24 months after hospital discharge. However, the preponderance of the evidence indicates that there is an increased risk of mortality following an episode of CAP—the question is, why?

Because even those patients with CAP and without comorbidities also were associated with an increased mortality rate in the study by Mortensen et al. [1], we cannot attribute all of the increased deaths to the usual risk factors for pneumonia (independent risk factors for CAP in a population-based study were alcoholism [RR, 9], asthma [RR, 4.2], immunosuppression [RR, 1.9], institutionalization [RR, 1.8], and age of ≥70 versus 60–69 years [RR, 1.5] [7]) and to the comorbidities seen in this population. A study that specifically examined risk factors for pneumococcal infection found that dementia, seizure disorders, congestive heart failure, cerebrovascular disease, and chronic obstructive pulmonary disease were risk factors for this infection [8].

Mortensen et al. [1] found that a high school graduation level or less was associated with increased long-term mortality following an episode of CAP. A lower education level seems to be associated with increased mortality due to a variety of diseases, such as stomach cancer, lung cancer, liver cancer, cirrhosis, cerebrovascular disease, AIDS, chronic obstructive pulmonary disease, pneumonia and influenza, diabetes, ischemic heart disease, and nephrotic syndrome [9]. The effect differs according to sex. It is likely that a higher educational level is a surrogate marker for increased socioeconomic status and better health.

Is it possible or even likely that some or several of the acute-phase reactants that are part of the host’s response to pneumonia confer a short-term advantage but a long-term adverse effect in terms of increased mortality? C-reactive protein (CRP) is an acute-phase reactant synthesized in the liver in response to infection and inflammation [10]. It is elevated in patients with pneumonia, irrespective of etiology (pyogenic, viral, and atypical), and decreases by 50% within 3 days after initiation of treatment [11–13].

It is noteworthy that CRP was first described in 1930 by Tillett and Francis [14] as a third fraction derived from pneumococci (the other 2 were capsular polysaccharide and nucleoprotein) that precipitated in serum obtained from patients with lobar pneumonia and disappeared 1–3 days after crisis. In recent years, there has been an association between elevated CRP levels and both short- and long-term cardiovascular mortality [15–19]. An association has been demonstrated between CRP levels and myocardial infarction in patients with stable or unstable angina [15–17], as well as in healthy men [18]. Although it is likely that, in these instances, CRP is elevated because of the inflammatory reaction in the atherosclerotic plaque [19], there is evidence to suggest that an elevated CRP level—irrespective of inflammation in atherosclerotic plaque—may be associated with increased mortality. Tice et al. [20] studied women who were enrolled in a study of osteoporotic fractures. During the 6-year follow-up period, they noted that women with CRP levels in the highest quartile had an 8-fold greater risk of cardiovascular mortality than those in the lowest quartile. Women who smoked and had a CRP level above the lowest quartile had a 13-fold increased risk [20]. CRP levels were not associated with noncardiovascular mortality. It should be noted that studies of CRP and cardiovascular disease have involved detecting lower levels of CRP (i.e., lower than those that had been measured in patients with conditions such as pneumonia) using a high sensitivity assay [21].

Periodontal disease (ongoing inflammation) was associated with a 2-fold increase in mortality due to cardiovascular disease in an elderly population observed for 10 years [22]. In another study, a single, random, high-sensitivity CRP level was independently predictive of all-cause and cardiovascular mortality [23].

There is an ongoing debate about the importance of infectious burden and atherosclerosis. In 572 patients, the levels of antibodies to herpes simplex viruses 1 and 2, cytomegalovirus, Epstein-Barr virus, Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae, and Helicobacter pylori were determined [24]. The extent of atherosclerosis was assessed by coronary angiography, carotid duplex sonography, and evaluation of the ankle-arm index. Seropositivity was adjusted for age, sex, cardiovascular risk factors, and level of high-sensitive measurement of CRP. After a mean follow-up period of 3.2 years, among patients with advanced atherosclerosis, the cardiovascular mortality rate was 7% for those who were seropositive for 0–3 pathogens, versus 20% for those who were seropositive for 6–8 pathogens [24]. Some of these microbial agents are well-known causes of CAP [25]. For sometime now, there has been ongoing investigation of the role of C. pneumoniae infection as a risk factor for coronary artery disease [26]. It has been postulated that infection-related molecular mimicry could trigger atherosclerosis [27]. However, this is a complicated area of research, and carefully done prospective trials have not been able to confirm an association between infection and atherosclerosis [28].

A number of polymorphisms in or near
the TNF-α gene and the IL-10 gene are associated with variability in TNF-α production and, in turn, the inflammatory response to infection [29]. In patients with CAP, the TNF-α 238GA genotype is an independent risk factor for in-hospital mortality, whereas the lymphotixin-α+250AA genotype (LT-α) was a risk factor for septic shock, and the TNF-α−308: LT-α+250GC haplotype was protective against septic shock [30]. Homozygotes for a deletion in the angiotensin-converting enzyme gene (DD ACE) showed a markedly greater severity of meningooccal meningitis, compared with severity among heterozygotes [31]. Likewise, individuals with this deletion appear to be at risk for adult respiratory distress syndrome (ARDS) and for a poor outcome due to ARDS [32]. Among patients with pneumococcal disease (mostly pneumonia), those who were homozygous for IL-10 allele G had the highest risk of experiencing septic shock [29]. As with CRP, it is possible that a short-term benefit (albeit an enormous one) is accompanied by increased long-term mortality?

Another factor that probably explains some of the increased long-term mortality among patients surviving an episode of CAP is that ~17% of patients experience ≥1 recurrence, and each episode of pneumonia increases the mortality rate [33, 34].

The only way to determine the reasons for the increase in long-term mortality after an episode of CAP is by a longitudinal prospective comparative study of patients who have survived an episode of pneumonia and age- and sex-matched control subjects. Such a study should include—in addition to a variety of epidemiological parameters—successive measurement of various markers of inflammation and determination of their genetic regulation. In addition, a careful autopsy should be performed for each person who dies during the course of this study. This will be an expensive study but will likely shed light on a number of important biological phenomena that extend well beyond the disease that triggered the study.

References

30. Wunderink RG, Waterer GW, Aantor RM, Quesney MW. Tumor necrosis factor gene polymorphisms and the variable presentation


