# Predicting Poor Outcome of Pneumonia

R. Menéndez[a] and A. Torres[b]

[a]Servicio de Neumología, Hospital Universitario La Fe, Valencia, Spain.
[b]Servicio de Neumología, Hospital Clínic, Barcelona, Spain.

The appearance of antibiotics in the mid-20th century produced a drop in mortality from pneumonia that led to predictions of the disappearance of the "captain of death." Nevertheless, while the forecast fall in mortality did occur initially, analysis of trends for infections throughout the last century is less encouraging.[1] One of the most intriguing observations is that mortality rates for pneumonia over nearly 60 years of antibiotic use have hardly changed at all and have remained within a range that varies very little. That is, it appears that the fall in mortality rates due to antibiotic treatment cannot be further improved even after our achievement of a better understanding of the pharmacokinetics and mechanisms of action of antibiotics. For this reason, analysis of the factors that affect poor outcome and mortality of pneumonia is still fully valid.

The information available up until the 1990s on risk factors for mortality was based on univariate studies, some multivariable studies, and meta-analyses that have found the factors pertaining to the micro-organism, the host, and clinical, analytical, and radiological findings that are most frequently related to mortality.[2] Regarding microorganisms, one of the most widely-considered concerns in studies on community-acquired pneumonia (CAP) is the appearance of increasing resistance to antibiotics. However, despite the increase in resistance of *Streptococcus pneumoniae,* analyses using multivariable statistical studies, which eliminate confounding factors, persistently show mortality to be associated with patient-dependent factors and not with microorganism resistance.[3,4]

The integrated study of factors that predict mortality has given rise to the appearance of prognostic scales. Thus, the most significant advance of the 1990s in predicting poor outcome was the publication of the risk index by Fine et al[5] and, more recently, the CURB-65 index.[6] Such indexes have provided a common, uniform and universal language for use when calculating the probability of death for a patient with CAP in any country in the world. Furthermore, prognostic indexes can be applied without identifying the microorganism causing the disease—a step we know to be difficult and uncommon in normal practice. Another less apparent aspect of these indexes is that they have focused on relating poor outcome to characteristics of the patient rather than the microorganism.

The information provided by the Fine or CURB-65 indexes (the most popular ones) is static. That is, they both calculate a probability for death, but they cannot predict the patient's response once treatment has been started—an essential prognostic factor.

A more novel approach at present is to identify risk factors in terms of response to therapy, as this provides information regarding the likelihood of poor outcome in both high- and low-risk classes.[7]

The scarcity until recently of studies on response to therapy in CAP may be due to several reasons: lack of an agreed definition, the small number of studies on the natural history of pneumonia, and the considerable variability in the courses taken by different pneumonias, or variability in clinical manifestations. Initial descriptions used terms such as "nonresolving pneumonia" and empirical and arbitrary periods of time to define it.[8-11] This is a key aspect because a specific period of time is required for an antibiotic to take effect and this depends on the microorganism responsible, the initial severity, and the host. The most commonly accepted time for defining therapeutic failure is 72 hours from the start of antibiotic treatment based on the studies of Montravers et al,[12] who found that bacterial load falls drastically over that interval when treatment is effective. Interestingly, studies by Spanish researchers are the ones that have achieved a deeper analysis of the clinical aspects and causes of therapeutic failure.[7,13,14]

The usefulness of predicting therapeutic failure as additional information to the prognostic indexes is considerable. In high-risk classes, it identifies patients with a probability of dying at least 3 times that of other patients in the same category. In low-risk classes, it is also helpful in finding patients who may suffer a poor outcome even though mortality in that subgroup is not as high.

Studies on the factors related to therapeutic failure show predictable, curious, and even unexpected findings.[7] The predictable findings include initial

Correspondence: Dr. R. Menéndez.
Servicio de Neumología. Hospital Universitario La Fe.
Avda. de Campanar, 21. 46009 Valencia. España.
E-mail: rmenend@separ.es

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severity, multilobar pneumonia, and the presence of pleural bleeding. As would be expected, the effect of the initial antibiotic treatment influences the response to treatment. Menéndez et al[15] found less therapeutic failure with treatments that adhere to guidelines (14% compared to 20%) and, independently, found less therapeutic failure where initial treatment was with fluoroquinolones, possibly due to their effectiveness against CAP of mixed etiology or to their therapeutic spectrum. According to Rosón et al,[14] inappropriate initial treatment was one cause of early failure in CAP caused by *Legionella* species and gram-negative bacteria. Adherence to guidelines when deciding on the initial therapy has proven useful in improving the prognosis in terms of mortality.[15]

Among the curious findings that have been noted by Menéndez and colleagues[7] are a protective effect of vaccination against influenza and a relatively high percentage of therapeutic failure in the low-risk classes. The beneficial effect of the influenza vaccine on response to treatment had not been mentioned previously in the literature although such vaccination is known to reduce mortality in pneumonia. An unexpected finding reported by the same group was the lower percentage of failure in patients with chronic obstructive pulmonary disease, which contrasts with findings in other settings such as liver diseases. This has raised as yet unanswered questions.

What is clear is that analysis of therapeutic response requires a more in-depth study of the relationship between host and microorganism. Indeed, it is possible for a CAP to have a poor outcome despite antibiotic treatment with an appropriate spectrum and a sensitive microorganism.

One hypothesis being investigated holds that an imbalance in the host's response, with overproduction of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL) 1β, should be related to a worse prognosis.[16] Excess TNF-α production leads to metabolic and/or physiologic manifestations, such as hypotension, myocardial dysfunction, hypoperfusion of vital organs, and lactic acidosis.[16-18] An increase in IL 6 and TNF-α and a correlation with mortality have been found in severe CAP.[19]

It is not fully understood what determines an excessive inflammatory response with negative effects on outcome, although several factors may be involved: *a)* the microorganism itself and the bacterial load possibly influencing the increased production of cytokines; *b)* antibiotic treatment; and *c)* the characteristics and susceptibility of the host. Ioanas et al[20] found that, in cases of therapeutic failure, high levels of IL 6 and IL 8 persist up to the third day of treatment. Since cytokine production is genetically determined, one line of research focuses on linking genetic polymorphisms to the host's response to the infection and its subsequent outcome.[21]

While this hypothesis is being examined, in clinical practice we need both clinical markers that can evaluate therapeutic response and treatments that can modulate it. C-reactive protein and procalcitonin are the most promising markers as persistence of high concentrations has been found to be associated with treatment failure. Serum procalcitonin has been shown to be a more specific bacterial marker than C-reactive protein. Procalcitonin levels increase 4 hours after an infection rather than during inflammation. As well as being useful for diagnosing infection in infectious exacerbation of chronic obstructive pulmonary disease and in ventilator-associated pneumonia, high concentrations of procalcitonin on the first day and persistence to the third and seventh days of treatment have been found to predict therapeutic failure.[22]

It remains to be shown whether therapeutic intervention can halt the excessive inflammatory response, when therapy is indicated, and which patients are candidates to receive it in order to improve their outcome. Initial results have been positive. Monton et al[23] found that use of glucocorticoids in treating severe pneumonia reduced the inflammatory response, with reduction of IL 6 and TNF-α, and lowered the associated mortality rate. In a randomized trial in the setting of severe CAP requiring intensive care, Confalonieri et al[24] found that the prognosis improved for patients treated with hydrocortisone. The immunomodulating effect on the inflammatory response by antibiotics, specifically the macrolides, merits thorough study by means of clinical trials in the context of CAP.[25]

At the beginning of the 21st century, attention is being focused on patient response and there is an urgent need for biological markers of this response. It is highly likely that, in this decade, we will be able to monitor the inflammatory response sufficiently well in advance to be able to intervene. This would provide 2-fold therapeutic action in CAP: antibiotics to fight the microorganism and drugs to interact with the host's inflammatory response.

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