H. Lode

Bacterial community-acquired pneumonia: risk factors for mortality and supportive therapies

Received: 23 October 2008
Accepted: 27 November 2008
Published online: 10 December 2008
© Springer-Verlag 2008

This editorial refers to the article available at:
doi:[10.1007/s00134-008-1363-6](https://doi.org/10.1007/s00134-008-1363-6).

H. Lode (✉)
Research Center for Medical Studies (RCMS),
Hohenzollerndamm 2, 10717 Berlin, Germany
e-mail: haloheck@zedat.fu-berlin.de
Tel.: +49-30-88721639
Fax: +49-30-88719386
URL: www.rcms-berlin.de

Mortality in community-acquired pneumonia (CAP) of patients admitted to the hospital has not changed in the last 30 years [1]; especially in patients suffering from severe CAP, the mortality rate is still unacceptably high (>20%). Severe CAP was already defined in the 1987 American Thoracic Society [2] guidelines suggesting that the severe illness is characterized by the presence of any of ten different features. Although this definition was based on facts known to be associated with the need for intensive care, several studies have subsequently demonstrated that the use of only a single criterion was too liberal and as many as 45–68% of all patients admitted to the hospital have at least one feature of severe pneumonia [3]. A modified definition achieved more balanced operative indices. Using the modified criteria, the need for ICU admission requires the presence of two of three “minor” factors including blood pressure ≤ 90 mm Hg, multilobar involvement, arterial oxygen tension/fractional inspired concentration of oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio < 250 (admission) or one of two “major” factors including need

for mechanical ventilation or septic shock (present on admission or later during the hospital stay). With this proposed modified definition of severity, the sensitivity of predicting severe disease was 78%, the specificity was 94%, the positive predictive for increasing mortality was 75% and the negative predictive value was 95% [3]. Therefore, it seems that these five parameters will accurately identify patients with severe CAP [4]. In a more practical clinical approach, basically, all patients requiring ICU treatment are regarded as severe CAP [5].

In this issue of intensive care medicine, Rodriguez et al. [6] are reporting non-immunocompromised patients from the CAPUCCI study suffering from severe bacterial CAP (122 *S. pneumoniae*, 90 non-*S. pneumonia* pathogens) and receiving adequate antibiotic therapy. Despite appropriate antibiotic therapy of 184 patients with an etiological diagnosis, 43 (23.4%) patients died; risk factors for a fatal outcome in the multivariate analysis were shock (OR 13.0), acute renal failure (OR 4.8) and APACHE II-Score > 24 (OR 2.2). However, additional significant risk factors in the univariate analysis were bilateral infiltrates, need for mechanical ventilation and bacteremic CAP. From their findings, authors conclude that beside appropriate and early antibiotic therapy, additional attempts like adjuvant therapies in well-defined subgroups of patients could increase the survival of severe CAP-patients.

These conclusions are well taken; however, so far we have not identified specific groups of patients and also the right adjuvant therapy is open for discussion. Clinical failures related to CAP occur primarily during the first 72 h after hospital admission; severe sepsis is the primary etiology of clinical failure related to CAP [7]. Failure has been defined in the literature as “treatment failure” or “clinical failure”. “Treatment failure” definition was adopted by those interested in analysing the response of patients with CAP to a particular antibiotic treatment [8, 9]. When evaluating the efficacy of a particular

antibiotic, patients who deteriorated within 48 h of treatment initiation were usually excluded from the evaluation in order to allow the antibiotic time to take effect. Furthermore, in evaluating the particular antibiotic, immunocompromised patients who were likely to have poor outcomes were usually excluded from treatment trials. The general consensus is that the antibiotics need some time to eradicate the etiologic pathogens.

In the study population of Rodriguez et al., septic shock was apparently the most frequent cause of clinical failure with a high OR of 13.03. Previous studies evaluating patients from the community with severe sepsis identified CAP as the leading etiology [10]. A recent study showed that more than 20% of patients with CAP arrived at the hospital with severe sepsis and 2% of them had septic shock [11]. On the basis of these findings, an important factor in the fight for better survival of severe CAP-patients is obviously the time delay between the onset of first symptoms and admission to the hospital; most of the patients in the study of Rodriguez et al. were already in septic shock at the time of arrival in the hospital. At this time, the inflammatory process is already in full action and the damage of different target organs has already taken place. This explains the significance of three risk factors (shock, acute renal failure, and high APACHE II-Score) found in the study of Rodriguez et al. Is there a place for adjunctive therapies for severe CAP as it is the case in sepsis and septic shock? In a recent systematic review of this topic, Siempos et al. [12] analyzed the literature and came to the conclusions that there was no evidence suggesting a survival benefit by the administration of activated protein C, non-invasive mechanical ventilation, anticoagulants, immunoglobulins, granulocyte-colony-stimulating factor, statins, probiotics, chest physiotherapy, antiplatelet drugs, over the counter cough

medications, beta2-agonists, inhaled nitric oxide, and angiotensin-converting enzyme inhibitors in patients with CAP. However, these authors and others [13, 14] have reviewed the position of corticosteroids in the treatment of severe CAP. Corticosteroids have been proved to block several arms of the inflammatory cascade. Experimental studies consistently show that corticosteroids diminish plasma extravasation, inhibit the adhesion and migration of leukocytes across the capillary wall and prevent the release of proinflammatory mediators [15]. In patients with severe CAP, a systematic inflammation can occur, and hence administration of corticosteroids has been advocated for this purpose. In the literature, four eligible randomized controlled studies have been identified but all trials had only small sample sizes and one of them was characterized by its authors as a preliminary study [16]. Administration of corticosteroids in patients with severe CAP in these studies was associated with lower mortality compared with placebo; however, on the basis of these results the use of corticosteroids as adjunctive therapy in severe CAP should be characterized as a weak recommendation (two studies) and a strong recommendation (two studies) with either low or moderate-quality evidence. According to the GRADE system, available studies do not support the recommendation of corticosteroids as a standard of care for patients with severe CAP [13]. Further randomized controlled trials with this aim should enrol a larger number of severely ill patients.

In summary, the study of Rodriguez et al. is addressing an important and unresolved issue in the course of severe CAP-patients; we should educate our colleagues in the community to send the patients earlier to the hospital and we should establish prospective randomized controlled studies with potent immunomodulatory agents to overcome the septic process.

References

1. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG, Infectious Diseases Society of America, American Thoracic Society (2007) Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 44:S27–S72
2. American Thoracic Society (1993) Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and antimicrobial therapy. *Am Rev Respir Dis* 148:1418–1426
3. Ruiz M, Ewig S, Torres A, Arancibia F, Marco F, Mensa J, Sanchez M, Martinez JA (1998) Severe community-acquired pneumonia assessment of severity criteria. *Am J Respir Crit Care Med* 158:1102–1108
4. Rodriguez de Castro F, Torres A (2003) Optimizing treatment outcomes in severe community-acquired pneumonia. *Am J Respir Med* 2:39–54
5. Restrepo MI, Anzueto A (2006) The role of new therapies for severe community-acquired pneumonia. *Curr Opin Infect Dis* 19:557–564
6. Rodriguez A, Lisboa T, Blot S, Martin-Loeches I, Solé-Violan J, De Mendoza D, Rello J (2008) Mortality in ICU patients with bacterial community-acquired pneumonia: when antibiotics are not enough. *Intensive Care Med*. doi: [10.1007/s00134-008-1363-6](https://doi.org/10.1007/s00134-008-1363-6)
7. Aliberti S, Amir A, Peyrani P, Mirsaeidi M, Allen M, Moffett BK, Myers J, Shaib F, Cirino M, Bordon J, Blasi F, Ramirez JA (2008) Incidence, etiology, timing and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. *Chest* 134:955–962

8. Arancibia F, Ewig S, Martinez JA, Ruiz M, Bauer T, Marcos MA, Mensa J, Torres A (2000) Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. *Am J Respir Crit Care Med* 162:154–160
9. Menéndez R, Torres A, Zalacaín R, Aspa J, Martín Villasclaras JJ, Borderías L, Benítez Moya JM, Ruiz-Manzano J, Rodríguez de Castro F, Blanquer J, Pérez D, Puzo C, Sánchez Gascón F, Gallardo J, Alvarez C, Molinos L, Neumofail Group (2004) Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax* 59:960–965
10. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368–1377
11. Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC (2006) Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? *Chest* 129:968–978
12. Siempos II, Vardakas KZ, Kopterides P, Falagas ME (2008) Adjunctive therapies for community-acquired pneumonia: a systematic review. *J Antimicrob Chemother* 62:661–668
13. Salluh JJ, Póvoa P, Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT (2008) The role of corticosteroids in severe community-acquired pneumonia: a systematic review. *Crit Care* 12:R76
14. Pineda L, El Sohl AA (2007) Severe community-acquired pneumonia: approach to therapy. *Expert Opin Pharmacother* 8:593–606
15. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y (2004) Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *Br Med J* 329:480–488
16. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, Meduri GU (2005) Hydrocortisone infusion in patients with severe community-acquired pneumonia: results of a randomized clinical trial. *Am J Respir Crit Care Med* 171:242–248