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Monotherapy in Severe Community-Acquired Pneumonia

Is It Worthy?

Severe community-acquired pneumonia (SCAP) is the term used to refer to those patients with community-acquired pneumonia (CAP) who are admitted to an ICU. The frequency of SCAP is variable, ranging from 5% to 35%, which indicates the lack of uniformity used in the criteria for ICU admission. In one study, SCAP represented 10% of admissions in a specialized respiratory ICU.

The definition of SCAP has been a matter of study in the last few years. Probably the most accurate criteria are those described by Ewig et al. The presence at ICU admission of one of two major criteria (requirement of mechanical ventilation or the presence of septic shock) or two of the three minor criteria (systolic BP ≤ 90 mm Hg, multilobar involvement, PaO₂/fraction of inspired oxygen ratio < 250) defines a SCAP population with 78% sensitivity and 94% specificity. These criteria have been recently validated, with similar results found and compared favorably to other scores such as the pneumonia severity index or the British Thoracic Society rules. In summary, although not perfect, this rule is probably the best that we have to detect those patients with CAP who will benefit from ICU admission. In addition, this rule can be useful to stratify patients for research, including randomized clinical trials.

The mortality of patients with SCAP is very high, ranging from 20 to 50%, which again indicates disparities between definitions of SCAP, the presence of comorbidities, age, and empirical antibiotic therapy.
treatment. More than 40 prognostic factors have been identified to be associated with death from CAP in multivariate analysis. For clinical management, they can be classified into basic (before admission), baseline (at admission), and disease progression factors. Of all these factors, the most important in order to potentially reduce treatment failure or mortality are the inadequacy of antimicrobial therapy and the delay in appropriate therapy. The latter is self-explanatory. For example, two studies have demonstrated an increased mortality if antibiotic treatment is started 4 h or 8 h after emergency department arrival, respectively. But what is the adequacy of initial antimicrobial treatment? Initial antimicrobial treatment refers to the correct antimicrobial coverage (including resistances) of potential causal microorganisms using correct dosages. Since in 50% of cases the etiology of SCAP in which definite microbial etiology was identified, the presence of pulmonary comorbidities, and the presence of HIV. In addition, geographic and seasonal variations explain differences in the presence of atypical microorganisms, Legionella, viruses, and resistances to antibiotics. All these factors have to be considered when recommending initial antibiotics in SCAP. Patients coming from nursing home facilities should be treated for nosocomial pneumonia.

All of the current guidelines published more recently recommend a combination of antibiotics to treat SCAP. A β-lactam plus a macrolide or a respiratory quinolone (levofloxacin or moxifloxacin) are the two most recommended options. When Pseudomonas is suspected a β-lactam with antipseudomonal activity plus ciprofloxacin is the best therapeutic option. Some findings suggest that respiratory quinolones could be a better option than macrolides. In one study, moxifloxacin had slightly better clinical efficacy when compared to a combination of third-generation cephalosporin plus a macrolide. In a recent study of a large series of hospitalized patients with CAP, the administration of a respiratory quinolone proved to be protective for treatment failure.

None of the guidelines have recommended monotherapy for the initial treatment of SCAP. One of the reasons explained in the guidelines for avoiding monotherapy is the lack of experience in ICU-admitted CAP patients. An additional important reason to take into account is the body of evidence that suggests that a combination of antibiotics may improve mortality in bacteremic pneumococcal pneumonia. For example, two retrospective studies in multivariate analyses found that combining at least two antibiotics showed a better outcome compared to monotherapy. Explanations for this finding are the potential hidden presence of primary atypical pneumonia or Legionella etiologies associated with Streptococcus pneumoniae and the anti-inflammatory effects of some families of antibiotics such as macrolides. Detractors of these studies argue about the lack of control for confounders and their retrospective nature. However, in a recent observational and prospective multinational study, Baddour et al confirmed the protective effect of combination therapy in bacteremic pneumococcal pneumonia when septic shock was present.

In the current issue of CHEST (see page 172), the results of an open randomized clinical trial comparing levofloxacin in monotherapy to a combination of cefotaxime plus ofloxacin are presented. This clinical multinational investigation is original and innovative since as mentioned above, there are no randomized controlled trials studying monotherapy in a homogeneous population of ICU-admitted patients with SCAP. The clinical success was similar in both study arms (79%) in the per protocol population. Similar satisfactory bacteriological response was found in the two groups. Specifically, patients with septic shock prior to inclusion were excluded. Patients with treatment failure could be included unless one of the antibiotics under study was previously administered. The conclusion of the authors is that levofloxacin was at least as effective as the combination in SCAP, unless patients required vasopressors or mechanical ventilation.

Despite the undoubted merit of the study, there are several aspects that deserve special consideration:

1. The antibiotic combination chosen by the authors is probably not the best that we currently have in our antibiotic armamentarium to treat SCAP. This is honestly recognized by authors. The most recent guidelines on CAP recommend the association of a third-generation, nonantipseudomonal cephalosporin with a macrolide or a respiratory quinolone, mainly levofloxacin or moxifloxacin. Consequently, we cannot say that monotherapy with levofloxacin is as effective as the standard recommended combination.

2. Patients with septic shock were specifically excluded. That means that the conclusions of the study cannot be extrapolated to all patients with SCAP. Septic shock may be present in up to 30% of patients with SCAP.

3. Specific criteria of severity were not prospectively used. In fact, the real inclusion criterion was ICU admission. These criteria are subjective and...
depend on each ICU and hospital availabilities and necessities. For future studies, the specific criteria for SCAP described in the literature should be used.3 This will ensure the selection of a more heterogeneous population.

(4) Finally, 29 of 139 of levofloxacin-treated patients presented failure at the test-of-cure visit. Similar results were observed with the combination. Apparently, results were similar, but there were seven cases of insufficient response (7 of 29 patients, 24%) during treatment in the levofloxacin group vs one case (1 of 27 patients, 3%) in the combination group. Although the numbers are low, this finding is worrisome and needs further evaluation.

Another recent study from Fogarty et al23 investigated the safety and the efficacy of levofloxacin compared to ceftriaxone plus erythromycin, followed by amoxiclavulanate plus clarythromycin, in the treatment of serious CAP in adults. In this study, the term serious was not equivalent to ICU-admitted patients. The overall clinical efficacy was similar in both study arms (close to 85%). However, we cannot compare this study to the article commented here25 since the two populations investigated are probably different in terms of severity.

The capital question in this entire issue is whether or not antibiotic monotherapy can be used confidently for the treatment of SCAP. We cannot answer this question from this study because of all the reasons mentioned above.

Why is it important to avoid combination in such a small and severe group of CAP patients? Using a combination of antibiotics in SCAP is not going to have an important impact on antibiotic resistances, but it may improve treatment failure and mortality. In addition, cost should not be an issue to consider in these patients at all.

We must continue to recommend a combination of antibiotics to treat SCAP and to avoid monotherapy, at least in the first 5 days of treatment. Further studies should be addressed to determine the clinical efficacy and safety of de-escalation therapy and to find out which is the best antibiotic combination.

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The “Goldilocks” Principle

The article by Jaklitsch and colleagues (see page 237) is an important contribution to the challenge of making appropriate surgical decisions in the care of patients with non-small cell lung cancer (NSCLC). To use “Goldilocksian” analysis, the challenge for thoracic surgeons is to get the operation neither too hot (a resection of more lung than necessary) nor too cold (an insufficient resection), but to get it just right.

To put this issue into perspective, through the first decades of the twentieth century there were only a few, anecdotal reports of lung resection for lung cancer. The description by Graham and Singer1 in 1993 of the performance (and not unimportantly the patient’s survival) of the first pneumonectomy for lung cancer established a role for surgical resection in the treatment of lung cancer patients. In fact, surgical resection became relatively standard with pneumonectomy being the cancer operation of choice. Over time, however, experience has showed that an anatomic lobectomy was technically feasible and resulted in the same outcomes as the more extensive operation, for patients with a similar stage of disease, if the primary tumor was limited to a lobe. This then resulted in a transition in the thoracic surgery community to lobectomy as the preferred procedure to preserve the maximum amount of pulmonary reserve. At present, pneumonectomy is reserved for patients with such centrally located cancers that even the technique of sleeve resection does not allow a lobectomy to encompass all disease. Resections less than lobectomy, which leave behind intrapulmonary lymphatics as well as parenchyma, such as wedge resection and segmentectomy have been generally considered to be marginally or completely inadequate cancer procedures and employed sparingly and selectively for patients with limited pulmonary reserve and/or comorbid conditions leading to the assessment of the patient as a poor candidate for a “major” operation.

The authors used a large database to accumulate and analyze 14,555 patients with stage 1 or 2 NSCLC who were operated on for cure with either a lobectomy or one of the lesser resections. Their comparative analysis has convincingly demonstrated that for patients with early stage lung cancer (definitely stage 1 patients and probably stage 2 patients), a lobectomy remains the operation of choice for those patients < 71 years old. Below this age, the survival curve for lobectomy patients is significantly better than that for a lesser resection. This would be considered old news. However, the new information is that the survival curves are similar above the age of 71 regardless of the operative procedure. In other words, patients > 71 years of age treated with lobectomy compared to patients treated with a limited resection did not receive a survival benefit. Survival following operation was quite similar whether the patient received either of these operative alternatives.

This information is compelling, and it will certainly influence my selection of operation for elderly patients with stage 1 NSCLC. Knowing there is no cancer survival benefit for the patient from a lobectomy, the choice is a wedge resection that is less morbid because it is technically simpler, resulting in a shorter operation with less risk of blood loss, and maximizes the remaining lung volume.

A few caveats need to be identified. First, a limited resection, be it a wedge resection or a segmentectomy, must be a sufficient cancer operation as defined by the authors. That is, the margins of the surgical specimen must be free of cancer. This must be determined by frozen section analysis at the time of operation, and if there is any question of residual disease being left behind then further lung tissue must be resected. A limited resection with cancer in the margin of resection cannot be considered to be a sufficient cancer operation. This means that if this criterion cannot be met in older patients with large and/or sufficiently proximal primary cancers, then a lobectomy should be performed in the absence of physiologic contraindications.

My second caveat is that while the authors have demonstrated that on a population basis there is an age-dependent transition in the risk/benefit ratio favoring a “lesser” operation above age 71 years, I have to believe that individual patients may have