

WHAT'S NEW IN INTENSIVE CARE



# Research in community-acquired pneumonia: the next steps

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Severe community-acquired pneumonia (SCAP) is usually defined as CAP admitted to an intensive care unit (ICU). The mortality associated with SCAP is still very high, particularly in patients needing mechanical ventilation (30%) [1]. Indeed, these patients represent an important target population for future research. In this ICM research document we focus on three major aspects of SCAP: (1) Influenza pneumonia; (2) adjunctive anti-inflammatory treatments; and (3) medium and long-term outcomes.

## Influenza pneumonia: cutting-edge epidemiology in future pandemics

To determine the timing and spread of influenza, health agencies in Spain and abroad have used a sentinel surveillance system. Using high-quality data, it has been possible to establish the composition of a seasonal influenza vaccine, to track changes in circulating influenza viruses and to design an alert system for potential pandemic viruses. However, mechanisms for detecting triggers of severe influenza are still lacking. For this reason, the World Health Organization (WHO) introduced a sentinel surveillance system for hospitalized patients who met the definition of syndromic Severe Acute Respiratory Infection (SARI) [2]. While the rationale is extremely valid, the results regarding the feasibility of this concept are inconclusive. In the ICU setting the information is scarce; the Intensive Care Global Study on Severe Acute Respiratory Infection (IC-GLOSSARI), launched by the European Society of Intensive Care Medicine (ESICM), reported that SARI is very common in the ICU and is associated with high morbidity and mortality rates [3].

In recent years the information provided on pandemic preparedness has been extremely useful, although it has mainly been based on trends in the community and Primary Care settings [4]. The aim is to describe not only attack rates but also their severity; we believe that the implementation of the four “S”s concept for outbreaks (Seasonality, Sentinel critical care, Severity and geopolitical hospital Settings) would improve the detection of pandemics and would also help to determine strategies, triage, and priorities for optimizing patient care during hospital admission [5].

Particularly notable is the increase in the number of patients with influenza who are admitted to hospitals with bacterial co-infections. One might expect the high mortality associated with influenza to be due to the severity of the virus, but little is known about co-pathogenic mechanisms. In a large multicenter study our group recently found that co-infection was an independent risk factor for ICU, 28-day, and hospital mortality [6]. Biomarkers, used on a “one value-one intervention” basis, have the potential to rule out bacterial co-infections, but more complex models of analysis can be envisaged which include combinations or panels of biomarkers with biological plausibility and decision-tree analyses that will help to determine a wider range of clinical variables such as treatment failure, patient’s risk stratification and composite outcomes for clinical cure in randomized clinical trials [7]. Future research in SCAP should focus on all these aspects.

## Coadjuvant treatments: will we be able to reduce acute mortality in SCAP?

SCAP-related mortality is still very high, particularly in patients with increased inflammatory response despite rapid, adequate antibiotic treatment.

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1. Studies of corticosteroids in these populations suggest that their use reduces treatment failure [8], the development of ARDS, and mortality rates [9]. Due to their potential side effects, however, corticosteroids may not be cost-effective. These publications suggest that they are beneficial in patients with high systemic inflammatory response, but as they may increase mortality [10] in hospitalized patients with influenza in the presence of rhinovirus, adenovirus, RSV and metapneumovirus, their true value remains to be established. Only new RCTs or individual meta-analyses will be able to determine their real benefit.
2. Macrolides are antibiotics with potent immunomodulatory effects. Retrospective analyses in SCAP have demonstrated that their inclusion in therapeutic regimes seems to reduce mortality [11]. However, many doubts and questions regarding the use of macrolides need to be resolved in the coming years: for instance, are they more effective than quinolones when combined with beta-lactams? And which particular SCAP target population will benefit most from macrolide treatment?
3. Immunoglobulins (Ig) have been administered in sepsis and in septic shock, but their use is controversial. Survival Sepsis Campaign guidelines [12] do not recommend Ig administration. The Cigma study [13] is a phase II study comparing 15% enriched IgM in patients with SCAP needing mechanical ventilation, with a primary end-point of ventilator-free days. The provisional results suggest a significant reduction in mortality in certain subgroups of patients. There is now a clear need for a large phase III trial in target populations with CAP: i.e., patients who are mechanically ventilated, and those with high levels of systemic inflammation or low levels of IgM.

### Medium and long-term prognosis in pneumonia

After an episode of CAP, patients of all ages present an increased risk of long-term adverse events and mortality compared to the general population [14]. Short-term prognosis usually comprises the period up until 30 days and follow-up periods of 1 year or more have been reported in the literature as long-term [15]. In fact, the risk may even persist until 10 years after the episode, as has been described after sepsis; indeed, CAP is one of the main causes of sepsis. The most widely recognized causes of mortality related to medium and long-term prognosis

include cardiovascular diseases, new lung infections and cancer. The potential mechanisms involved are: the direct adverse effect of microorganisms, the inflammatory host response, platelet activation and alterations of the endothelium or disruption of atheroma plaque. The study of biomarkers to monitor cardiovascular risk (both during the episode and at discharge) is becoming crucial for diagnosis, although several questions remain unanswered: for example, the identification of the best biomarker and/or panel of biomarkers, the precise factors triggered in each patient, its duration after the acute episode, and the associated risk factors [16]. All are important questions for designing interventional strategies and personalized treatments in order to curb poor prognosis. Currently, although proadrenomedullin (proADM) and other cardiovascular biomarkers have shown high prognostic power for community-acquired pneumonia (CAP) outcomes, their application in the clinical setting has been slow.

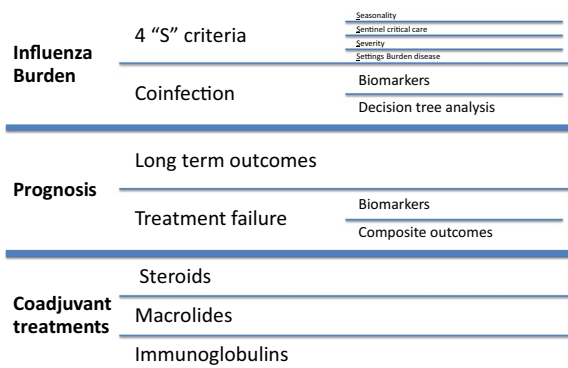
MicroRNA (miRNA) analysis has emerged as a useful tool for sepsis diagnosis and for prognosis. miRNAs are small non-coding RNAs which can act as master regulators of gene expression; they are able to modulate almost all biological processes and are essential for maintaining cellular homeostasis. Dysregulation of miRNA expression has been associated with aberrant gene expression and may lead to pathologic conditions [17]. Studies investigating immune responses and inflammatory responses from the perspective of the potential inhibition of translation or transcription of miRNA will be very welcome.

### Conclusions

In conclusion, our main recommendation for SCAP research is that it should focus on reducing its short- and long-term mortality. The next steps can be summarized as follows:

- To investigate the epidemiology (risk and prognosis factors and etiology) of the four “S”s—Seasonality, Sentinel critical care, Severity and geopolitical Settings—in SCAP.
- To establish which patients with SCAP would benefit from coadjuvant anti-inflammatory or immunomodulatory treatment in order to reduce short-term mortality.
- To investigate biomarkers and phenotypes of SCAP patients with a higher risk of dying during hospital admission (short-term) and after hospital discharge.

## Landscape analysis of CAP research



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