Host-targeted approaches to sepsis due to community-acquired pneumonia

Catia Cilloniz[a,b,**] and Antoni Torres[a,c,*]

[a]Pulmonology Department, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain
[b]Faculty of Health Sciences, Continental University, Huancayo, Peru
[c]CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

eBioMedicine
2022;86: 104335
Published Online 2 December 2022
https://doi.org/10.1016/j.ebiom.2022.104335

Sepsis, a life-threatening condition, is the main complication of severe community-acquired pneumonia (CAP) observed in approximately one in three patients with severe CAP.[1] The complexity and heterogeneity of the biological mechanisms underlying sepsis illustrate the need to identify clearly defined phenotypes based on differential host immune responses recognizable in a clinical setting.[2] These phenotypes would provide new opportunities to increase the efficacy of the therapeutic strategies applied to severe CAP complicated by sepsis. For example, two main sub-phenotypes related to acute respiratory distress syndrome (ARDS, which develops in almost a third of CAP patients receiving mechanical ventilation) have been identified: the hyper-inflammatory and hypo-inflammatory phenotypes. These have distinct clinical and biological features, outcomes, and responses to different therapies.[3]

Seymour et al.[4] proposed four clinical phenotypes of sepsis by applying machine learning methods to large retrospective observational cohorts, consisting of three cohorts of patients from the United States. The first two cohorts included data from patients in the SENECA study who were adults (aged ≥18 years) and met the criteria for sepsis within the first 6 h of attendance at the emergency department of one of 12 hospitals (from 2010 to 2012 for the derivation cohort and from 2013 to 2014 for the validation cohort); the third cohort included patients with severe CAP from the Genetic and Inflammatory Markers of Sepsis (GenIMS) study. These serotypes were correlated with different patterns of host immune response, as well as clinical outcomes, such as short-term mortality. These results illustrate the importance of identifying and characterizing severe CAP sepsis phenotypes that may help us to predict outcomes and apply personalized care to patients.

Several risk assessments have been developed to identify patients at risk of sepsis. A Spanish study published in 2017 reported that 62% of patients with CAP presented with sepsis, according to the Sepsis 3 definition.[5] The authors reported that the quick Sequential Organ Failure Assessment (qSOFA) and the Confusion, Respiratory Rate, and Blood Pressure (CRB) scores proved more clinically useful than the criteria for the systemic inflammatory response syndrome (SIRS) as tools for prompt management of patients with CAP in emergency departments. However, the host response to sepsis may be altered in various ways—perhaps explaining the highly heterogeneous clinical presentation that increases the difficulties of early diagnosis of sepsis.[6] A variety of biomarkers have also been investigated, with a special focus on the capacity of biochemical and/or immunological biomarkers, alone or in combination, to discriminate between infectious and non-infectious causes of sepsis, as well as their prognostic capacity. In severe CAP, C-reactive protein (CRP) and procalcitonin (PCT) are the biomarkers most commonly investigated. There is extensive evidence of their important role as adjunctive tools to assist the clinical diagnosis of pneumonia, together with clinical parameters and the use of severity scores. In the case of PCT, serial measurements could guide antimicrobial stewardship. However, the current recommendation of the CAP guidelines is not to initiate empiric therapy based on biomarker levels.[7]

An important study of patients with severe CAP and a high inflammatory response (C-reactive protein >150 mg/L at admission) reported that the use of methylprednisolone (0.5 mg/kg twice a day for five days) was related to a lower rate of treatment failure (13% vs. 31%, including radiographic progression, late mechanical ventilation, and septic shock). The authors also reported a 5% absolute—albeit non-significant—reduction in mortality in patients who received corticosteroids.[8] These results were further confirmed in a recently published multicenter study of severe patients with CAP who received corticosteroids (prednisone, methylprednisolone, and dexamethasone).[9] The authors reported a significant reduction in 30-day mortality in patients who presented with an elevated inflammatory response and/or septic shock and required mechanical ventilation.[9]

Studies of host immune transcriptome profiles may also play a key role in paving the way towards personalized treatment approaches for patients with CAP with distinct host immune responses. Scicluna et al.[10]

*Corresponding author. Department of Pneumology, Hospital Clinic of Barcelona, C/ Villarroel 170, 08036 Barcelona, Spain.
**Corresponding author. Department of Pneumology, Hospital Clinic of Barcelona, C/ Villarroel 170, 08036 Barcelona, Spain.
E-mail addresses: atorres@clinic.cat (A. Torres), catiacilloniz@yahoo.com (C. Cilloniz).

identified four sepsis endotypes (Mars 1 to 4) using blood genomic analysis (the second validation cohort included 265 severe CAP cases). The Mars1 sepsis endotype was associated with the highest mortality; it showed a decreased expression of genes related to the innate and adaptive immune responses and an increased expression of specific cellular metabolic pathways (for example, the biosynthesis of haem). Mars2 and Mars4 endotypes had a high expression of genes involved in pro-inflammatory and innate immune reactions, while the Mars3 sepsis endotype was associated with the lowest mortality and an increased expression of adaptive immune or T-cell functions (the T-cell function includes the activation of other immune cells to fight the infection). As showcased by the aforementioned studies, increased understanding of the host immune response to severe CAP-induced sepsis (both at the systemic and pathogen-specific levels) and the possibility of distinguishing phenotypes associated with poor outcomes may soon enable the development and application of personalized precision medicine for one of the most lethal clinical situations. Such a development, in combination with a multidisciplinary approach, would improve the management and outcomes of patients with severe CAP complicated by sepsis, potentially saving hundreds and thousands of lives every year, leading to a dramatic reduction in the disease burden associated with CAP. Until such approaches are clinically accessible, it would be wise to take full advantage of all the preventive, diagnostic, and therapeutic tools currently at our disposal, by adapting them to the characteristics of individual health systems and clinical settings.

Contributors
All authors contributed equally.

Declarations of interest
The authors declare that they have no conflicts of interest.

References

1 Montull B, Menéndez R, Torres A, et al. Predictors of severe sepsis among patients hospitalized for community-acquired pneumonia. *PLoS One*. 2016;11:e0145929. https://doi.org/10.1371/journal.pone.0145929.
2 Vincent J-L, van der Poll T, Marshall JC. The end of "One Size Fits All" sepsis therapies: toward an individualized approach. *Biomedicines*. 2022;10:2260. https://doi.org/10.3390/biomedicines10092260.
3 Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. *Lancet*. 2022. https://doi.org/10.1016/S0140-6736(22)01485-4.
4 Seymour CW, Kennedy JN, Wang S, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA*. 2019;321:2003–2017. https://doi.org/10.1001/jama.2019.5791.
5 Ranzani OT, Prina E, Menéndez R, et al. New sepsis definition (Sepsis-3) and community-acquired pneumonia mortality. A validation and clinical decision-making study. *Am J Respir Crit Care Med*. 2017;196:1287–1297. https://doi.org/10.1164/rccm.201611-2262OC.
6 Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49:e1063–e1143. https://doi.org/10.1097/CCM.0000000000005337.
7 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200:e45–e67. https://doi.org/10.1164/rccm.201908-1581ST.
8 Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA*. 2015;313:677–686. https://doi.org/10.1001/jama.2015.88.
9 Ceccato A, Russo A, Barbeta E, et al. Real-world corticosteroid use in severe pneumonia: a propensity-score-matched study. *Crit Care*. 2021;25:432. https://doi.org/10.1186/s13054-021-03840-x.
10 Scicluna BP, van Vught LA, Zwinderman AH, et al. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respir Med*. 2017;5:816–826. https://doi.org/10.1016/S2213-2600(17)30294-1.