Sepsis endotypes: The early bird still gets the worm

Jack Varon and Rebecca M. Baron *

Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, MA 02115, United States

eBioMedicine 2022;76: 103832
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.103832

Despite decades of research, therapy for sepsis remains limited to supportive care, including early identification and intervention directed towards elimination of the physical focus of infection (commonly referred to as source control), and appropriate antibiotics. While advances have been made with respect to sepsis prevention, early recognition, and molecular understanding of sepsis pathways, there are no targeted therapies for sepsis.[1] Over 100 clinical trials attempting to modulate the immune response to sepsis have failed.[2] This failure is, in large part, due to the heterogeneity of the sepsis syndrome.[3] Patients vary by pathogen, site of infection, comorbidity, host response, and duration of infection prior to receiving care. There is significant interest in strategies to rationally subgroup sepsis patients based on underlying biology. Multiple investigators have attempted to use transcriptional data to create gene expression profiles for both prognostic and predictive enrichment.[4]

In this issue of *eBioMedicine*, Baghela and colleagues present a critical and timely addition to the sepsis endotype literature.[5] They studied 266 patients with suspected sepsis from Colombia, the Netherlands, Canada, and Australia, and obtained samples from the Emergency Department within two hours of presentation for care. Also included in their study were 82 intensive care unit (ICU) patients enrolled early in the ICU course and 44 heathy controls. Using an unsupervised machine learning approach, they sorted patients into five endotypes: Neutrophilic-Suppressive (NPS), associated with neutrophil activation and immune suppression; Inflammatory (INF), associated with an increased pro-inflammatory response, *e.g.*, increased NF-κB expression; Innate Host Defence (IHD), associated with interleukin signaling; Interferon (IFN), associated with increased IFN-α,β,γ; and Adaptive (ADA), associated with a variety of pathways including increased adaptive immunity. Each endotype was characterized by a signature of approximately 200 genes and was validated in a subset of the ED cohort. The NPS and INF endotypes identified those with more severe sepsis. In particular, the NPS endotype exhibited longest hospital stays, highest sequential organ failure assessment (SOFA) scores, and had worst overall survival. Conversely, the ADA pathway was associated with a more benign course. These endotypes were also observed in the ICU subjects, with the exception of the more benign ADA endotype which was not identified in the ICU.

The authors have created a unique and important body of work. Most importantly, while others have derived meaningful, well-validated endotypes from gene signatures in sepsis, theirs is the first study of this scale to investigate the transcriptome of patients with suspected sepsis so soon after initial presentation. Early recognition and treatment are key tenets of current sepsis management.[1] Thus, it stands to reason that rapid identification of patients with concerning endotypes could benefit from enhanced monitoring and triage to a higher level of care. Likewise, the rapid identification of patients likely to have mild disease might spare unnecessary and potentially harmful treatments. In particular, broad-spectrum antibiotics are typically administered within six hours of presentation. Calls to push antibiotic administration to within one hour of presentation have been met with mixed responses, given concern for administration of antibiotics that later turn out to be unnecessary.[6] Early endotyping could help guide these decisions. In terms of recruitment for future clinical trials, the ability to rapidly assign patients to endotypes dramatically increases the possibility of predictive enrichment. This may address and mitigate the role that heterogeneity has played in the failure of investigational therapies for sepsis.[3]

Along the same lines, the biological underpinnings of these endotypes also suggest the evaluation of therapies in more selected patient populations. For example, while the role of interferon-γ (IFN-γ) in sepsis is complex and can drive late secondary infections,[7] the marked deficiency in IFN-γ signaling in the NPS endotype with the worst clinical outcomes might suggest benefit in these patients of IFN-γ therapy. Patients with the Inflammatory (INF) endotype, characterized by increased inflammatory responses and poorer outcomes, may respond to immune suppression. A reasonable next step would be to assess for heterogeneity of treatment effects in existing as well as future transcriptomic data sets. For example, Antcliffe and colleagues conducted a post-hoc analysis of the VANISH trial of corticosteroids in septic shock and demonstrated worsened survival with corticosteroids in patients with sepsis response syndrome 2 (SRS2), a gene signature

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103776

*Corresponding author.
E-mail address: Rbaron@partners.org (R.M. Baron).

corresponding with immune competence.[8] These findings have obvious implications for the future design of clinical trials and support the routine collection of clinical trial biospecimens beginning early in the course of illness.

To realize a future of personalized care for patients with sepsis, we believe several steps must be taken. First, the five endotypes identified by Baghela and colleagues must be validated in other cohorts. This will require clinical research infrastructure nimble enough to recruit patients rapidly after presentation to the ED or ICU on a broader scale. As more data is generated, efforts should be made to come to a consensus on biologically meaningful endotypes in sepsis to guide further research. Second, to practically guide enrollment in clinical trials or impact clinical decision making, data on endotypes must be available quickly. The authors hint at one potential approach, indicating that a 40-gene classification tool has good receiver operator characteristics in defining the five endotypes that they derived. Conceivably, patients could be more rapidly assayed by polymerase chain reaction for a subset of genes. Another approach would be to more rigorously correlate clinical data points (including vital signs and laboratory values) with sepsis endotypes than was feasible in this study. For example, Sinha and colleagues were able to accurately sort patients into phenotypes previously derived, in part, from circulating inflammatory biomarker data using only readily available clinical data.[9] Such an approach would also make the application of these endotypes feasible in more resource-limited settings. Third, further research must be done to generate insight into the biological mechanisms driving each endotype, particularly the NPS and INF endotypes associated with the worst outcomes. These insights will be crucial in developing rational strategies for endotype-directed treatment. Finally, it will be critical to study the stability of these endotypes in patients over time, as previous sequential transcriptomic analysis has shown that gene signatures can be dynamic and patients can shift between endotypes over the course of their illness.[10]

Future trials in sepsis are unlikely to be successful without a strategy of predictive enrichment based on the underlying biology of endotypes. Such a strategy will depend on rapid and early phenotyping of patients with sepsis. With their early approach, Baghela and colleagues have taken us one step closer to a precision approach to sepsis.

Contributors

JV wrote the draft and both authors edited and finalized the manuscript.

Declaration of interests

JV declares no conflict of interest. RMB sits on Advisory Boards for Merck and Genentech pertaining to work not directly relevant to this commentary.

References

1 Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. *Nat Rev Dis Prim*. 2016;2(1):16045.

2 Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med*. 2014;20(4):195–203.

3 Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. *Nat Rev Nephrol*. 2020;16(1):20–31.

4 Leligdowicz A, Matthay MA. Heterogeneity in sepsis: new biological evidence with clinical applications. *Crit Care*. 2019;23(1):80

5 Baghela A, Pena OM, Lee AH, et al. Predicting sepsis severity at first clinical presentation: the role of endotypes and mechanistic signatures. *eBioMedicine*. 2021. https://doi.org/10.1016/j.ebiom.2021.103776.

6 Rhee C, Chiotos K, Cosgrove SE, et al. Infectious diseases society of America position paper: recommended revisions to the national severe sepsis and septic shock early management bundle (SEP-1) sepsis quality measure. *Clin Infect Dis*. 2021;72(4):541–552.

7 Kim EY, Ner-Gaon H, Varon J, et al. Post-sepsis immunosuppression depends on NKT cell regulation of mTOR/IFN-γ in NK cells. *J Clin Investig*. 2020;130(6):3238–3252.

8 Antcliffe DB, Burnham KL, Al-Beidh F, et al. Transcriptomic signatures in sepsis and a differential response to steroids. from the VANISH randomized trial. *Am J Respir Crit Care Med*. 2019;199(8):980–986.

9 Sinha P, Churpek MM, Calfee CS. Machine learning classifier models can identify acute respiratory distress syndrome phenotypes using readily available clinical data. *Am J Respir Crit Care Med*. 2020;202(7):996–1004.

10 Burnham KL, Davenport EE, Radhakrishnan J, et al. Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. *Am J Respir Crit Care Med*. 2017;196(3):328–339.