frontiers | Frontiers in Science

TYPE Frontiers in Science Viewpoint
PUBLISHED 30 January 2025
DOI 10.3389/fsci.2025.1557323

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Pietro Ghezzi,
University of Urbino Carlo Bo, Italy

*CORRESPONDENCE
R. Phillip Dellinger
dellinger-phil@cooperhealth.edu

RECEIVED 08 January 2025
ACCEPTED 23 January 2025
PUBLISHED 30 January 2025

CITATION
Dellinger RP and Bartock J. Transforming sepsis heterogeneity: challenges and progress. *Front Sci* (2025) 3:1557323. doi: 10.3389/fsci.2025.1557323

COPYRIGHT
© 2025 Dellinger and Bartock. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Transforming sepsis heterogeneity: challenges and progress

R. Phillip Dellinger[1,2]* and Jason Bartock[1,2]

[1]Critical Care Medicine Department, Cooper University Health, Camden, NJ, United States, [2]Department Medicine, Cooper Medical School of Rowan University, Camden, NJ, United States

KEYWORDS

sepsis, endotypes, phenotypes, precision medicine, artificial intelligence

A Viewpoint on the Frontiers in Science Lead Article

Deciphering sepsis: transforming diagnosis and treatment through systems immunology

Key points

- In sepsis, marked heterogeneity in genetic makeup, pathobiology, and acquired host characteristics is probably the primary reason that promising molecular biology-targeted therapies have failed when patients are enrolled in clinical trials based on their clinical manifestations (phenotypes).
- Endotypic classifications of septic patients based on differences in some combination of genomics, metabolomics, transcriptomics, and immune cell analysis—used in combination with phenotypic characteristics—may lead to successful treatment using innovative molecules that target pathobiological chains.
- The rapidly developing field of artificial intelligence has significant potential in advising therapeutic pathways in sepsis; machine learning may increase the predictive capability as more patient subtypes are matched with treatment decisions and outcomes.

Introduction

Sepsis care has shifted over the last 20 years. Whereas formerly patients with sepsis were largely ignored and poorly defined, the syndrome is now considered a medical emergency and it is general knowledge that early identification and early, standardized best treatment practices are important. However, the morbidity and mortality of sepsis remain unacceptably high (1), as illustrated in the case below.

Hypothetical case illustration

The following case is fictional and was created by the authors to illustrate the points made in their article. A 32-year-old physically active female, Gravida 1 Para 1, presented to

the emergency department (ED) complaining of fever and back pain for 2 days. She had recently undergone normal spontaneous vaginal delivery. She was alert and oriented with a blood pressure of 93/55 mmHg (mean arterial pressure 68 mmHg), regular pulse of 126 beats/min, respiratory rate of 18 breaths/min, and temperature of 39.1°C (102.3°F). Her abdomen was diffusely tender to palpation with vaginal erythema and a foul-smelling discharge. Extremity exam was normal. Laboratory investigations obtained shortly after ED arrival demonstrated a neutrophilic leukocytosis (42,000 cells/mm^3), elevated serum lactic acid (6.2 mmol/L), elevated d-dimer, international normalized ratio (INR) of 1.9 with baseline normal, thrombocytopenia (98,000 cells/mm^3) with baseline normal, and elevated serum creatinine (2.2 mg/dL). Within 1 hour after the lactate result, blood cultures were drawn and the sepsis bundle pathway was initiated with 30 ml/kg isotonic crystalloid resuscitation along with clindamycin, ampicillin, and gentamicin antibiotics based on a clinical diagnosis of post-partum endometritis. A transvaginal ultrasound was negative for retained products of conception. Despite crystalloid resuscitation, she became hypotensive and required hemodynamic support with increasing doses of norepinephrine.

Given her worsening shock, she was taken to the operating room where she underwent a total abdominal hysterectomy. The surgery revealed a boggy, foul-smelling uterus with pus within the cavity. Blood cultures were positive for pan-sensitive *Escherichia coli*.

Over the next 24 hours, her vasopressor requirements decreased; however, new bluish discolorations appeared bilaterally on the dorsum of her feet and forearms and the tip of her nose.

She developed acute renal failure requiring continuous renal replacement therapy. Her platelet count continued to drop with a nadir of 24,000 cells/mm^3 at 60 hours after ED arrival. Her distal extremity ischemia progressed, and she required bilateral above-the-knee amputations along with amputations of the gangrenous fingers bilaterally. She was discharged to a rehabilitation facility with a diagnosis of septic shock secondary to necrotizing endometritis, complicated by disseminated intravascular coagulation (DIC)-induced symmetrical peripheral gangrene due to microvascular thrombosis.

What could have been done differently in the case above to produce a better outcome? Nothing in our current armamentarium would probably have made a difference in this case. Sepsis bundles were applied in a complete and timely fashion.

But what if it was possible to predict, in advance of an infection being acquired, the risk for severe organ dysfunction (even specific organ dysfunctions, such as in the coagulation system in this case) once an infection occurred? This would open the door for patient instructions for self-administered antibiotics and immediate entry into the healthcare system at the first signs of an infection. Or, once an infection is diagnosed in the ED or hospital, what if it were possible to use immunological testing to identify the risk of specific organ dysfunctions and match that risk with proven innovative molecular therapy targeting a specific immunologically triggered dysfunction, such as DIC with microvascular thrombosis?

Failure of innovative therapy in clinical trials

The Surviving Sepsis guidelines provide guidance on supportive care, such as antibiotics, fluids, and source control (2). However, the results of therapy targeting molecular biology-driven immune dysfunction and its associated pathobiology and organ dysfunction have been overwhelmingly negative in clinical trials (3). The failure of these clinical trials probably relates to some combination of the following:

(i) Trial enrollment based on broad clinical and laboratory manifestations in a patient population with marked heterogeneity in molecular biology-driven pathogenesis. This clinical syndrome enrollment is in spite of sepsis being defined as life-threatening organ dysfunction due to a dysregulated host immune response to infection.

(ii) Primary sepsis interventions targeting the proinflammatory/procoagulant response in a disease state which is now recognized to have a significant anti-inflammatory component that may be recognizable early in the disease state and amenable to pro-immune therapy.

(iii) Clinical trials with novel molecules based on successful animal studies that do not represent the heterogeneity and complexity of human sepsis, e.g., with respect to co-morbidities, immune responses, and organisms/sites of infection.

Toward precision medicine in sepsis

In their lead article, Hancock et al. offer an in-depth review of the potential and promise of diagnostic testing and innovative precision therapy to improve sepsis monitoring and care (4). These authors point to the potential of combinations of genomics, metabolomics, transcriptomics, and immune cell analysis to identify specific sepsis endotypes (the classification of a patient's disease state based on the underlying pathobiological mechanisms) that may predict the development of phenotypic (clinical) organ dysfunctions. This could allow clinical trials to identify sepsis endotypes rapidly at presentation and test novel molecular therapies aimed at ameliorating or reversing the characteristic pathobiological mechanisms and clinical manifestations. If this goal is achieved, clinicians will be able to practice "precision medicine" that targets specific endotypic subsets of patients within the vastly heterogeneous overall sepsis population.

Hancock et al. offer the reader a playbook demonstrating how recent literature would support the use of systems biology (computational/mathematical analysis and modeling of immunology in complex biological systems) to derive immune endotypes that will function as a filter for the marked heterogeneity of sepsis populations (4). This endotyping might be used to predict organ

dysfunction and worse outcomes in general, or more specifically align with a particular organ dysfunction. For example, the authors highlight a recent study in which the two most severe endotypes identified, one neutrophilic suppressive (NPS) and one inflammatory (INF), were diametrically opposed in their underlying mechanisms (5). The authors further remind us of immune dysfunction variability over time following the onset of sepsis, which could lead to serial sampling to identify endotype changes and guide therapy modifications. This may be of particular significance regarding changing metabolomics downstream from genomic and transcriptomic signals.

Artificial intelligence and machine learning

Hancock et al. also discuss the potential importance of artificial intelligence (AI) and machine learning in gathering information from patients' electronic medical records, combining phenotypic manifestations with endotype classification, to recommend specific therapeutic choices. AI analysis of retrospective data could be used to build and then validate a specific clinical treatment pattern based on the desired outcomes. These recommendations could be made more precise over time by using machine learning to match more patient subtypes with treatment decisions and outcomes. From our perspective, this might involve a drop-down box in the medical records that (i) flags a patient as high risk for developing acute kidney injury or deteriorating clinically or (ii) recommends limitation of fluid administration while maintaining mean arterial pressure (MAP) using low-to-moderate dose vasopressor administration. This information might be further refined by offering the treatment team percentage estimates based on AI analysis, such as a 65% chance that the patient will develop organ dysfunction or a 70% chance that the outcome will be improved by fluid-driven, rather than vasopressor-driven, MAP maintenance.

Lower-income countries perspective

It must be recognized that lower-income countries have significant limitations in laboratory resources for endotyping and, therefore, alternative approaches allowing more precision in treatment decisions are needed. A recent study suggests that analytics-driven phenotypic classifications of sepsis that are much better defined than clinical trial entry criteria may play a significant role in guiding therapy in the future (6).

Potential applications to our hypothetical case

Our hypothetical septic patient presented with manifestations of DIC (thrombocytopenia, elevated INR, and elevated d-dimer). If it were possible at presentation to predict the likelihood that such a septic patient with early evidence of DIC (as a phenotypic manifestation) will develop microvascular thrombosis and peripheral ischemia before the onset of clinical manifestations, this might allow an intervention that would prevent or ameliorate the morbidity seen in this case. Phenotypic screening could be followed by endotype profiling, for instance by rapid genotypic testing or proteomic/metabolomic assays, or potentially a biomarker shown to be associated with microvascular thrombosis and peripheral ischemia. Subject to successful clinical trials, an intervention targeting this specific endotype (notionally, perhaps heparin or antithrombin 3) might prevent the life-changing morbidity described.

Conclusion

Sepsis care in the future will likely address clinical heterogeneity by using systems-based immunological endotyping, probably enhanced by phenotypic data, to allow risk stratification, early staging based on progression probability, and perhaps most importantly, best practices enhanced by precision therapy. There is a real possibility of utilizing AI to guide therapeutic options based on endotyping and machine learning to hone prediction and recommendation skills.

Acknowledgments

The case in this Viewpoint is fictional and was created by the authors to illustrate the points made in their article. Any resemblance to actual persons or events is fortuitous.

Statements

Author contributions

RD: Conceptualization, Writing – original draft, Writing – review & editing. JB: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. *Lancet* (2020) 395(10219):200–11. doi: 10.1016/S0140-6736(19)32989-7

2. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med* (2021) 49(11):e1064–143. doi: 10.1097/CCM.0000000000005337

3. Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med* (2014) 20(4):195–203. doi: 10.1016/j.molmed.2014.01.007

4. Hancock REW, An A, dos Santos CC, Lee AHY. Deciphering sepsis: transforming diagnosis and treatment through systems immunology. *Front Sci* (2025) 2:1469417. doi: 10.3389/fsci.2024.1469417

5. Baghela A, Pena OM, Lee AH, Baquir B, Falsafi R, An A, et al. Predicting sepsis severity at first clinical presentation: the role of endotypes and mechanistic signatures. *EBioMedicine* (2022) 75:103776. doi: 10.1016/j.ebiom.2021.103776

6. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliot CF, Xu Z, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* (2019) 321(20):2003–17. doi: 10.1001/jama.2019.5791