J Crit Care 83 (2024) 154848

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Sepsis phenotypes in the era of individualized medicine

ARTICLE INFO

Keywords
Sepsis
Septic shock
Phenotypes
Individualized medicine

Sepsis and septic shock are common causes of intensive care unit (ICU) admission and mortality in critically ill patients. In the last decades, we have progressively moved towards a precision medicine and an individualized approach to the different clinical scenario. Sepsis does not equally manifest in all patients and, in this perspective, some authors suggested a stratification based on different phenotypes. Phenotypic differences can be associated with molecular deviations in host response leading to variation in clinical expression and outcomes. However, to our knowledge, no phenotypic classification has been validated in the literature and various research biases limit a consensus in this field. In general, we can identify septic phenotypes (SPs) classified by inflammatory status/laboratory alterations or clinical presentation (Table 1).

Inflammatory status/laboratory alterations

In parallel to acute respiratory distress syndrome (ARDS) models, SPs have been classified by inflammatory status and biological alterations. Seymour et al. attempted to identify distinct murine SPs using clinical data from biotelemetry-enhanced cecal ligation and puncture (CLP) prior to physiologic deterioration [1]. The authors identified two phenotypes named Class 1 and Class 2. Class 2 exhibited a shorter time to deterioration with a hyperinflammatory profile including higher serum concentrations of interleukin (IL)-6 and IL-10 at 24 h after CLP than Class 1. A pediatric study classified three hypothetical inflammation pathobiology phenotypes: type 1, characterized by immune paralysis associated with multiorgan failure (MOF); type 2, characterized by thrombocytopenia associated MOF; and type 3, characterized by sequential MOF with hepatobiliary dysfunction [2]. Type 2 showed a higher mortality rate (40%) than type 1 (21%) and type 3 (17%). Kudo and colleagues analyzed 3694 ICU patients with severe sepsis and septic shock and four clusters were identified. Cluster dA ($n = 323$) had severe coagulopathy with high serum concentrations of fibrinogen degradation products (FDP) and D-dimer, severe organ dysfunction, and high mortality rate. Cluster dB ($n = 629$) had severe disease with moderate coagulopathy. Clusters dC ($n = 1147$) and dD ($n = 1595$) had moderate and mild disease with and without coagulopathy, respectively [3].

Clinical presentation

A retrospective study reviewed 320 septic patients admitted to a medical ICU. The authors reported four phenotypes based on clinical features [4]. Phenotype 1 showed MOF; phenotype 2 usually had a neurological dysfunction; phenotype 3 showed a respiratory dysfunction; and phenotype 4 included all other patients. Phenotype 1 had the highest rate of mortality (48.4%), followed by the neurological dysfunction phenotype (39.7%). A retrospective but robust clinical study analyzed 20,189 septic patients and four phenotypes were identified [5]. Phenotype α included patients with a low rate of vasopressor administration; phenotype β included old patients with high incidence of comorbidities; phenotype γ had more inflammation and respiratory failure; phenotype δ showed more liver failure and septic shock. Interestingly, the 28-day and 365-day mortality rates were highest among the δ phenotype *versus* the three phenotypes ($p < 0.001$).

Bhavani and colleagues analyzed 12,473 patients with suspected infection; these patients were compared with 8256 patients in validation cohorts [6]. Four sub-phenotypes were identified: (1) Group A ($n = 3483$, 28%) had hyperthermia, tachycardia, tachypnea, and hypotension; (2) Group B ($n = 1578$, 13%) shared the characteristics of Group A with a less severe presentation; (3) Groups C ($n = 4044$, 32%) and (4) Group D ($n = 3368$, 27%) had lower body temperature, heart rate, and respiratory rate, with Group C being normotensive and Group D being hypotensive patients. Group A included young patients requiring high vasopressor doses and having a low rate of comorbidities; group B included young patients with high prevalence of congestive heart failure, diabetes and chronic kidney disease; group C and D were older than other groups with the patients in Group D requiring highest vasopressor use. In logistic regression, 30-day mortality was significantly higher in Group A and Group D ($p < 0.001$ and $p = 0.03$, respectively), which was probably associated with the increased need in vasopressor in these two groups. This study had some strengths and limitations. On one hand, the detailed classification of phenotypes and sub-phenotypes was an opportunity for the intensivists to individualize the management of septic patients. On the other hand, the retrospective nature of the study may introduce bias and limitations in data collection.

In the light of these findings, we summarized the state of the art

https://doi.org/10.1016/j.jcrc.2024.154848

Available online 19 June 2024

Table 1
Classification of septic phenotypes based on current literature. List of abbreviations: SP, septic phenotype; MOF, multiple organ failure; ND, neurological dysfunction; RD, respiratory dysfunction; HR, heart rate; RR, respiratory rate; LD, liver dysfunction; rhTM, recombinant human thrombomodulin.

Authors	Sample size (n.)	Population	Type of SPs	Classification	Findings
Shald[4] et al.	320	ICU septic patients	Clinical presentation	**SP 1**: MOF **SP 2**: ND **SP 3**: RD **SP 4**: other patients	SP 1 showed higher mortality rate
Bhavani[6]et al.	12,473	Patients with sepsis/ suspected infection	Clinical presentation	**SP A**: higher temperature, HR, RR **SP B**: lower temperature, HR, RR **SP C**: older patients **SP D**: older patients, high doses of vasopressors	SP A and D showed higher mortality rate
Seymour[5] et al.	20,189	Septic patients	Clinical presentation	**SP α**: low doses of vasopressors **SP β**: older patients **SP γ**: higher rate of inflammation and RD **SP δ**: LD and septic shock	SP δ showed higher mortality rate
Seymour[1] et al.	191	Animal study	Inflammatory status/ laboratory alterations	**Class 1**:hypoinflamatory profile **Class 2**:hyperinflammatory profile	Class 2 showed a rapid clinical deterioration
Carcillo[2] et al.	100	Pediatric study	Inflammatory status/ laboratory alterations	**Type 1**. immune paralysis + MOF **Type 2**: thrombocytopenia + MOF **Type 3**: LD + MOF	Type 2 showed higher mortality rate
Kudo[3] et al.	3696	ICU septic shock patients	Inflammatory status/ laboratory alterations	**Cluster dA**: severe coagulopathy **Cluster dB**: moderate coagulopathy **Cluster dC**: mixed cases **Cluster dD**: mixed cases	Treatment with rhTM lower mortality rate in clusters with severe coagulopathy

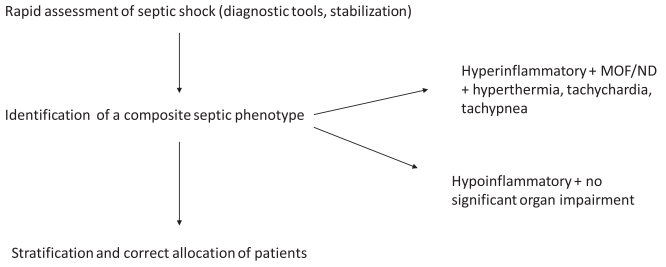

Fig. 1. Proposed flowchart for a rapid assessment of septic phenotype in the clinical practice. List of abbreviations: MOF, multiorgan failure; ND, neurological dysfunction.

about SPs (Fig. 1). Few studies classified SPs by inflammatory status/ laboratory alterations or clinical presentation. We believe that a first step should be to gather both classifications identifying some composite phenotypes (*i.e.* hyperinflammatory + MOF + hyperthermia + significant tachypnea/tachycardia; hypoinflammatory + no significant coagulopathy + normal or mild increased respiratory rate/heart rate; etc). Secondly, there is a need to validate these composite SPs in large observational and prospective studies, to avoid the biases inherent to retrospective studies.

In conclusion, we suggest that a prompt identification of different SPs could facilitate the patient stratification in the era of individualized medicine.

CRediT authorship contribution statement

Elio Antonucci: Writing – review & editing, Writing – original draft, Investigation. **Marc Leone:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Seymour CW, Kerti SJ, Lewis AJ, Kennedy J, Brant E, Griepentrog JE, et al. Murine sepsis phenotypes and differential treatment effects in a randomized trial of prompt antibiotics and fluids. Crit Care 2019;23(1):384.
[2] Carcillo JA, Halstead ES, Hall MW, Nguyen TC, Reeder R, Aneja R, et al. Three hypothetical inflammation pathobiology phenotypes and pediatric Sepsis-induced multiple organ failure outcome. Pediatr Crit Care Med 2017;18(6):513–23.
[3] Kudo D, Goto T, Uchimido R, Hayakawa M, Yamakawa K, Abe T, et al. Coagulation phenotypes in sepsis and effects of recombinant human thrombomodulin: an analysis of three multicentre observational studies. Crit Care 2021;25(1):114.
[4] Shald EA, Erdman MJ, Ferreira JA. Impact of clinical sepsis phenotypes on mortality and fluid status in critically ill patients. Shock 2022;57(1):57–62.
[5] Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA 2019;321(20):2003–17.
[6] Bhavani SV, Semler M, Qian ET, Verhoef PA, Robichaux C, Churpek MM, et al. Development and validation of novel sepsis subphenotypes using trajectories of vital signs. Intensive Care Med 2022;48(11):1582–92.

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