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Biomarkers

François Ventura
Intensive Care Unit
Hirslanden Clinique des Grangettes
Chêne-Bougeries, Switzerland
Division of Anesthesiology
Geneva University Hospitals
Genève, Switzerland

Pierre Tissières
Service de Réanimation Pédiatrique et Médecine Néonatale
Centre Hospitalier Universitaire CHU du Kremlin-Bicêtre
Le Kremlin-Bicêtre, France

Jérôme Pugin
Division of Intensive Care
Geneva University Hospitals
Genève, Switzerland

Sepsis Diagnosis: Clinical Signs, Scores, and Biomarkers

A checklist of criteria to assess the usefulness of a biomarker to be integrated into sepsis guidelines.

Introduction

Septic shock is a subset of sepsis, with circulatory collapse and metabolic dysfunction associated with high mortality. Worldwide, 48.9 million people develop sepsis each year, and 11 million die of septic shock (Rudd et al. 2020).

The definition of sepsis has evolved over time. In 1992, in the first set of definitions, sepsis was defined as a suspected bacterial infection associated with a systemic inflammatory response syndrome (SIRS) (Bone et al. 1992). In 2003, sepsis was defined as a suspected bacterial definition associated with a more complete SIRS definition (Levy et al. 2016). In 2016, a third set of definitions of sepsis was proposed: sepsis was defined as a bacterial infection causing organ dysfunction (Singer et al. 2016). Since October 2021, the latest set of sepsis definitions was proposed by the Surviving Sepsis Campaign (SSC) (Evans et al. 2021). Sepsis was defined as a bacterial infection associated with a dysregulated response of the body with SIRS and organ dysfunction. Guidelines for the management of sepsis were first proposed by the SSC in 2004 (Dellinger et al. 2004); they have since been revised regularly, with the latest update published in October 2021 (Evans et al. 2021).

The Diagnosis of Sepsis

In adults and in children, the diagnosis of sepsis is based on an early diagnosis of a bacterial infection and the identification of a dysregulated response of the body with organ dysfunction (Evans et al. 2021; Weiss et al. 2020). There are two different diagnostic approaches and two different therapeutic approaches to be made in parallel: the control of infection with antimicrobials and the source of infection, and the treatment of the dysregulated response of the body and organ dysfunction, with volume resuscitation, organ support, and adjuvant therapies.

Diagnosis of (suspected) infection

In the case of (suspected) sepsis, it is recommended to confirm or rule out bacterial infection and to continuously reassess the infectious diagnosis, to initiate, modify or stop antibiotic therapy (Evans et al. 2021). Unfortunately, bacterial cultures take between 24 and 48 hours to give meaningful results to the clinician and do not help to make decisions as to start antibiotics or not. They may also be false negatives due to prior antibiotic therapy or inadequate sampling. It is, however, a strong recommendation in the sepsis management guidelines that antibiotic therapy should be initiated as soon as possible, at least less than 45 to 60 minutes after suspicion of sepsis (Evans et al. 2021). Initiating broad-spectrum antibiotics in all patients with suspected sepsis will result in unnecessary treatments in 60 to 70% of patients who end up not having sepsis, in part because signs are similar between severe viral and bacterial infections and also with severe inflammatory processes (Klein Klouwenberg 2015).

Biomarkers have been extensively studied to help diagnose rapid bacterial infection in patients with suspected sepsis. They may be used to increase specificity to restrict antibiotic treatment only to patients with a bacterial infection. In addition, they should have a good negative predictive value to rule out a bacterial infection in patients with suspected sepsis and prevent unnecessary antibiotic treatments. The matrix presented in **Table 1** describes four clinical conditions: adequately treated sepsis, inadequate sepsis treatment at risk for aggravation, unnecessary antibiotic therapy at risk of bacterial resistance, and adequate no (or suspended) antibiotic therapy.

Once antibiotic therapy has been initiated, it should be reassessed daily (pursue, modify or stop) based on the results of bacterial cultures and clinical evolution (Evans et al. 2021).

Biomarkers sepsis diagnosis matrix		Clinical evaluation/suspicion	
		SEPSIS Infection	NO SEPSIS No infection
Biomarkers-based antibiotics	Positive biomarkers Antibiotics	Accurate management (True positive)	Inadequate treatment Risk of AMR (False positive)
	Negative biomarkers No Antibiotics	Inadequate treatment Risk of septic shock (False negative)	Accurate management (True negative)

Table 1. Biomarker-based antibiotics and sepsis diagnosis matrix

Diagnosis of dysregulated response of the body

The diagnosis of dysregulated response of the body is based on SIRS criteria and/or organ dysfunction according to the SSC 2021 guidelines (Evans et al. 2021). SIRS score evaluate three non-specific clinical parameters: temperature, heart rate, and respiratory rate, as well as two laboratory results: circulating blood leukocytes and $PaCO^2$. The dysregulated organ response is based on two clinical scores, the National Early Warning Score (NEWS) and the Modified Early Warning Score (MEWS)

(strong recommendation, moderate quality evidence) (Evans et al. 2021). The gold standard for the dysregulated organ response is the Sequential Organ Failure Assessment (SOFA) score which assesses the function of six organs impacted by sepsis (lung, circulation/heart, brain, liver, kidney, coagulation), combining five clinical parameters and four laboratory results. The qSOFA (quick SOFA) is a simple and fast version of the SOFA which takes < 5 minutes. However, the 2021 SCC guideline suggested that the qSOFA should no longer be used (Evans et al. 2021). In paediatrics, the organ failure score is the Pediatric Logistic Organ Dysfunction (PELOD) score which assesses the function of six organs (Goldstein et al. 2005).

Clinical Signs, Scores, and Biomarker

The consequence of the four different definitions of sepsis, the absence of a gold standard specific test for early diagnosis, and the change in clinical scores to be used have led to confusion among clinicians. More than half of the clinicians use a mixture of all these scores (Ventura 2021); 89.7% measure circulating blood leucocytes, 92.3% CRP, 84.6% PCT, and 100% lactate in case of suspicion of sepsis. Only 35.9% use the Sepsis-3 definition alone, 34.2% still calculate the qSOFA, and 44.7% use the complete SOFA score. This indicates that in daily practice, clinicians use more biomarkers than scores. The ideal biomarker of infection and sepsis should have a sensitivity similar to the non-specific, highly sensitive clinical approach but should carry a better specificity, with a very good negative predictive value to rule out infection and sepsis. Ideally, biomarkers should be able to detect sepsis even before clinical suspicion, which is only possible by routine monitoring (daily measurements) in hospitalised patients at high risk for nosocomial sepsis. This is the concept of pre-symptomatic diagnosis of nosocomial sepsis. Finally, a biomarker should be able to help with the decision of antibiotic de-escalation, coupled with clinical evaluation.

One or more biomarkers should help in the diagnosis of sepsis and nosocomial sepsis in the three chronological phases: the pre-sepsis or pre-symptomatic phase (with daily monitoring of hospitalised patients at risk), the clinical onset of sepsis phase, and the post-sepsis phase (**Table 2**).

Discussion

It is fundamental to carry out future clinical studies on sepsis biomarkers analysing their specificity (PPV and NPV with cut-offs), their capacity to make a pre-symptomatic diagnosis, and their potential in the de-escalation of antibiotics. We propose a checklist (**Table 3**) with the basic requirements that biomarkers of sepsis should meet and a standard protocol for biomarker sepsis studies so that future studies can be comparable and can answer the urgent questions raised by the major public health problems of sepsis and antimicrobial resistance. This standard protocol should include three specific protocols according to the three phases of sepsis (pre-sepsis, sepsis, post-sepsis) the studies would like to investigate.

Conclusion

Both classical sepsis and infection biomarkers and new biomarkers should be studied or re-studied using a standardised approach to determine which biomarker(s) answer(s) clinicians' questions. The biomarker result should be obtainable within 45 to 60 minutes to initiate (or not) antibiotic therapy quickly, as required by the SSC 2021 guidelines (Evans et al. 2021) for adults and the SSC 2020 for children (Weiss et al. 2020). A point-of-care test (POCT), with a 10-20 minute dosing time, can allow such a rapid result, and it must be able to fulfil to a large extent the ASSURE criteria (Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment free) for a sepsis diagnosis test (Bissonnette and Bergeron 2010). Economic studies should also be able to determine the financial consequences of sepsis biomarker testing on public health costs. The objective of all these studies could allow one or several infection and sepsis biomarkers that tick all the boxes on the checklist (**Table 3**) to be included in the next adults and paediatrics international Surviving Sepsis Campaign guidelines. ■

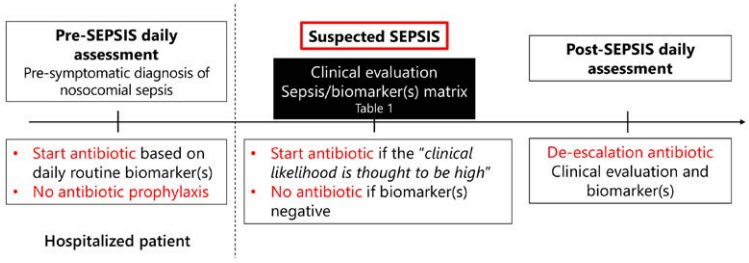

Table 2. Sepsis phase

Ideal criteria for a sepsis biomarker	
Affordable	
Price 10-50 US$	☐
Economic study published	☐
Sensitive	
Standard protocolized study	☐
As high as clinical symptoms	☐
Pre-symptomatic diagnosis	☐
Antibiotic de-escalation	☐
Specific	
Standard protocolized study	☐
Cut-off and VPP > 90%	☐
Cut-off and VPN > 90-95%	☐
TP, TN, FP, FN rate	☐
Sepsis/AMR Matrix	☐
User-friendly testing	☐
Rapid	
Results in 45-60 minutes	☐
Dosing time 10-20 minutes	☐
Equipment free (or light)	
Point of Care testing POCT	☐
Pediatrics	
Capillary blood	☐
Blood volume 30-50 ul	☐
Certified	
European IVDR	☐
FDA 510K	☐
Australia	☐

Table 3: Checklist - Tick the box: Ideal criteria for a sepsis biomarker

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References

For full references, please email editorial@icu-management.org or visit https://iii.hm/1jjm

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