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WHAT'S NEW IN INTENSIVE CARE

What's new in sepsis recognition in resource-limited settings?

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Introduction

Sepsis is a life-threatening condition characterized by one or more organ dysfunctions due to a dysregulated host response to infection [1] or, in certain cases, due to direct pathogen effects. Sepsis is not only associated with bacterial or fungal infections but also with any other infection such as viral disease, protozoal (e.g., malaria), or tropical infections. Although the literature suggests that sepsis is predominantly a healthcare issue in resource-rich countries, the global burden of acute infections is highest in resource-limited areas [2]. Successful sepsis management relies on various components of which early recognition is essential. Evidence and recommendations for sepsis recognition are mainly based on research performed in resource-rich settings [3]. However, resource-rich and -limited countries differ in healthcare accessibility [4] and infectious disease epidemiology [5–7]. It is therefore unreasonable to directly translate evidence between these settings.

The Global Intensive Care working group of the European Society of Intensive Care Medicine together with the Mahidol-Oxford Research Unit formed an international team of physicians to revise existent recommendations for sepsis management in resource-limited settings [8]. In this manuscript, we summarize recommendations on sepsis recognition. A detailed description of the guideline team, conflicts of interest, methods, rationales, and references is given in the Online supplement.

Results and recommendations for sepsis recognition in resource-limited settings

Four clearly defined questions regarding sepsis recognition in resource-limited settings were formulated using the GRADEpro Guideline Development Tool [9]. The literature search was performed using the same techniques as described for the Surviving Sepsis Campaign guidelines [3]. Specific attention was paid to identify publications originating from resource-limited settings. The quality of evidence was classified as high (grade A) to very low (grade D) and recommendations as strong (grade 1—*'we recommend'*) or weak (grade 2—*'we suggest'*) [9]. Factors influencing this classification were the level of scientific evidence, certainty about the benefit/risk ratio, certainty in or similar values, resource implications, availability and feasibility, affordability, and safety for resource-limited settings (Table 1).

With regard to sepsis recognition, we recommend defining sepsis in adults as the combination of acute infection and the presence of two of the following three parameters: (a) respiratory rate ≥22 bpm, (b) systolic blood pressure ≤100 mmHg, (c) any acute change in mental state; these criteria have not been validated to recognize sepsis from non-bacterial infections such as malaria, dengue, or other tropical infectious diseases. Until data confirm their predictive value in malaria, we recommend diagnosing malaria-induced sepsis if malaria and one or more of the following signs occur: impaired consciousness, prostration, respiratory distress, multiple convulsions, hypoglycemia, severe malarial anaemia, renal impairment, jaundice, malaria-induced shock, significant bleeding, hyperparasitemia. Similarly, until further data are available, we recommend diagnosing dengue-induced sepsis if dengue infection and any of the

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For the Global Intensive Care working group of the European Society of Intensive Care Medicine (ESICM) and the Mahidol-Oxford Research Unit (MORU) in Bangkok, Thailand.Group members of the Sepsis in Resource-Limited Settings expert consensus recommendation group are listed in the supplement.

Group members of the subgroup 'Sepsis Recognition' are listed in "Appendix".

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Table 1 Recommendations for sepsis recognition in resource-limited settings (with grading)

1	Recognition of sepsis	Define sepsis as the combination of acute infection and two of the following parameters: respiratory rate ≥22 bpm, systolic blood pressure ≤100 mmHg, any acute change in mental state (1B); these criteria have not been validated to recognize patients with sepsis from non-bacterial infections such as malaria, dengue, or other tropical infectious diseases (ungraded); diagnose malaria-induced sepsis if malaria and one or more of the following clinical signs occur: impaired consciousness, prostration, respiratory distress, multiple convulsions, hypoglycemia, severe malarial anaemia, renal impairment, jaundice, malaria-induced shock, significant bleeding, hyperparasitemia (1B); diagnose dengue-induced sepsis if dengue infection and any of the following clinical symptoms occur: shock, respiratory distress, severe bleeding, or any organ dysfunction (1B); healthcare workers, irrespective of their proficiency, be alert to consider sepsis in adults and children with acute infection of any etiology (1C); recognition of sepsis in children is based on different severity indicators (ungraded)
2	Identification of the underlying type of infection	Take a structured patient history and perform a systematic head-to-toe physical examination to identify the underlying type of infection (1A); recognition of local infectious disease epidemiology is crucial (ungraded); depending on their availability, perform additional diagnostic evaluations such as laboratory testing and/or radiographic or ultrasound imaging to identify the source of infection (1B)
3	Identification of the causative microbiological pathogen	If available, obtain microbiological cultures before antimicrobial therapy as long as this does not relevantly delay antimicrobial therapy (1A); take two or more sets of blood cultures and tissue/body secretions from the site of suspected infection (1A); perform microscopy and Gram staining of secretions sampled from the suspected source of infection (1B); if available, test for antibiotic susceptibility of cultured bacteria to guide antibiotic therapy (1B); if resources to test for antibiotic susceptibility are not routinely available, perform intermittent microbiological screening of antimicrobial susceptibility of selected pathogens to inform empirical antimicrobial strategies (2C); use rapid diagnostic tests to diagnose malaria (1A); alternatively, use light microscopy of stained blood smears performed by experienced staff (1A); use direct (early disease phase) or indirect (intermediate or later disease phase) laboratory methods to diagnose specific virus infections such as dengue, influenza, or ebola virus disease (1A); all patients with an acute infection who are positive for the human immunodeficiency virus, suffer from immunosuppression of other causes (e.g., malnutrition), had previous tuberculosis infection and/or close contact with a person suffering from tuberculosis should be screened for tuberculosis co-infection (1A); use light emitting diode microscopy of two sputum smears or field PCR for the diagnosis of pulmonary tuberculosis (1A); perform tuberculosis cultures in HIV-positive patients (1A)
4	Recognition of septic shock	Define septic shock as the presence of two or more clinical indicators of systemic tissue hypoperfusion independent of the presence of arterial hypotension (1B); if available, measure arterial lactate levels (1A); in patients with dengue sepsis, use a change in arterial blood pressure amplitude of ≤20 mmHg to diagnose shock (1C); do not rely solely on the use of arterial hypotension to diagnose septic shock, as arterial hypotension is typically a preterminal event and associated with an exceedingly high mortality in sepsis patients in resource-limited settings (1C)

PCR polymerase chain reaction, *HIV* human immunodeficiency virus

following symptoms occur: shock, respiratory distress, severe bleeding, or any organ dysfunction; we recommend that healthcare workers, irrespective of their proficiency, be alert to consider sepsis in adults and children with acute infection of any etiology. Recognition of sepsis in children is based on different severity indicators; these are summarized in another set of the expert consensus recommendations that will be published separately.

With regard to identification of the underlying type of infection, we recommend taking a structured patient history and performing a systematic head-to-toe physical examination (online supplement Table 3) to identify the underlying type of infection; thereby, consideration of local epidemiology of infectious diseases is crucial. Depending on their availability/affordability, we recommend performing additional diagnostic evaluations such as laboratory testing and/or radiographic or ultrasound imaging to identify the source of infection, as guided by the history and physical examination.

With regard to identification of the causative microbiological pathogen, we recommend, if available/affordable, obtaining microbiological cultures before antimicrobial therapy as long as this does not relevantly delay antimicrobial therapy. We recommend taking two or more sets of blood cultures and/or tissue/body secretions from the site of suspected infection. We recommend performing microscopy and Gram staining of secretions sampled from the suspected source of infection. If available/affordable, we recommend testing for antibiotic susceptibility of cultured bacteria to guide antibiotic therapy.

If resources to test for antibiotic susceptibility are not routinely available, we suggest performing intermittent microbiological screening of antimicrobial susceptibility of selected pathogens to inform empirical antimicrobial strategies. We recommend using rapid diagnostic tests to diagnose malaria; alternatively, we recommend light microscopy of stained blood smears performed by experienced staff. We recommend using direct (early disease phase) or indirect (intermediate or later disease phase) laboratory methods to diagnose specific virus infections such as dengue, influenza, or ebola virus disease. All patients with an acute infection who are positive for the human immunodeficiency virus, suffer from immunosuppression of other causes (e.g., malnutrition), had previous tuberculosis infection and/or close contact with person suffering from tuberculosis should be screened for tuberculosis co-infection. We recommend light emitting diode microscopy of two sputum smears for the diagnosis of pulmonary tuberculosis. Whenever available/affordable, we recommend using polymerase chain reaction (PCR) tests to diagnose tuberculosis or performing tuberculosis cultures in HIV-positive patients.

With regard to recognition of septic shock, we recommend defining septic shock as the presence of two or more clinical indicators of systemic tissue hypoperfusion independent of the presence of arterial hypotension. If available/affordable, we recommend measuring arterial lactate levels in patients with sepsis. In dengue sepsis, we recommend using a reduction in the arterial blood pressure amplitude $\leq$20 mmHg to diagnose shock. We recommend against relying solely on arterial hypotension as a diagnostic criterion for the diagnosis of septic shock, as arterial hypotension is typically a preterminal event and associated with an exceedingly high mortality in sepsis patients in resource-limited settings.

Conclusion

Sepsis is not only associated with bacterial or fungal infections but also with any other infection such as viral disease, protozoal (e.g., malaria), or tropical infections. We provided a set of simple, readily available, and affordable recommendations on how to recognize sepsis, identify the underlying type of infection, identify the causative microbiological pathogen, and recognize septic shock in resource-limited settings. As most evidence originates from resource-rich settings, there is an urgent need for related research in resource-limited settings.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4222-x) contains supplementary material, which is available to authorized users.

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