Recognition of Sepsis in Resource-Limited Settings

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4.1 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 with any other infections such as viral disease, protozoal disease (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. In this chapter, we summarize recommendations on sepsis recognition, identification of the underlying infection and causative microbiological pathogen, as well as recognition of septic shock in resource-limited settings (Table 4.1).

4.2 Sepsis Recognition

Sepsis is a life-threatening condition due to acute infection that is characterized by one or more organ dysfunctions. From a pathophysiological perspective, organ dysfunction results from a dysregulated response of the host's immune system to the microbiological pathogen [3] and, in certain cases, from direct effects of the pathogen (e.g., sequestration of parasitized red blood cells in malaria, endothelial damage by NS1 [nonstructural protein 1] in dengue, tissue damage by bacterial toxins). Sepsis is not only associated with bacterial or fungal infections but with any other infection such as viral disease, protozoal diseases (e.g., malaria), or other tropical infections. As the benefits of sepsis therapy are delicately time-sensitive with improved mortality and other outcomes observed in patients receiving appropriate therapy early in the course [3, 4], it is critical to recognize sepsis as early as possible upon patient's presentation. Early indicators of severe disease which relate to a fatal outcome select patients needing early and urgent treatment.

The results of a large US health record database including approximately 150,000 patients with suspected acute infection revealed that a quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) score could help to identify patients with sepsis outside of an intensive care environment. The qSOFA score indicates the potential presence of sepsis if two of the following three indicators are fulfilled: (1) respiratory rate $\geq$22 bpm, (2) systolic blood pressure $\leq$100 mmHg, and (3) any acute change in mental state. Addition of further parameters did not relevantly improve the predictive power of this model [5]. These parameters are also included in different early warning scores [6], whose reasonable power to predict increased mortality of acutely ill patients was confirmed by studies from resource-limited settings [6–9]. A recently published study from Uganda reported that a prognostic index including respiratory rate ($\geq$30 bpm), pulse rate ($\geq$100 bpm), a mean arterial

Table 4.1 Recommendations for the recognition of sepsis 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, and any acute change in mental state (1B); these criteria have not been validated to recognize patients with sepsis from nonbacterial 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 anemia, renal impairment, jaundice, malaria-induced shock, significant bleeding, and 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, should 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), and had previous tuberculosis infection and/or close contact with person suffering from tuberculosis should be screened for tuberculosis coinfection (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)

(continued)

Table 4.1 (continued)

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)

Abbreviations: *PCR* polymerase chain reaction, *HIV* human immunodeficiency virus

blood pressure ≥110 or ≤70 mmHg), body temperature (≥38.6 or ≤35.6 °C), and any acute change in mental state could adequately predict hospital mortality in patients with sepsis [10].

It is important to note that the definition of sepsis was established largely based on adult patients suffering from bacterial or fungal infections. The definition has so far not been validated for other infections such as malaria, dengue fever, or tropical infectious diseases, which are highly prevalent in some resource-limited settings. As pathophysiology of malaria and bacterial infections differs [11], it is well conceivable that these criteria have a lower reliability to recognize patients with sepsis due to malaria. A prospective observational study from Uganda reported that out of 216 hospitalized patients with community-acquired infection and the systemic inflammatory response syndrome, only 4% suffered from acute malaria infection [12]. These data indicate that patients with malaria may potentially manifest with alternative signs of infection and might have been unrecognized as such. In 2015, the World Health Organization recommended diagnosing severe malaria in adults with *Plasmodium falciparum* asexual parasitemia and one or more of the following clinical signs: (1) impaired consciousness, (2) prostration (defined as the inability to sit, stand, or walk unassisted), (3) respiratory distress due to acidosis or pulmonary edema, (4) more than two convulsions within 24 h, (4) hypoglycemia, (5) severe malarial anemia, (6) renal impairment, (7) jaundice, (8) malaria-induced shock (for definition see below), (8) significant bleeding, and (9) hyperparasitemia [13]. A malaria prognostic index (including Glasgow Coma Scale <11, admission parasitemia >315,000/μL, pigmented parasites >20%, total bilirubin >58 μmol/L, lactate >5 mmol/L) has shown a high sensitivity (95–100%) and specificity (88–91%) to predict death in Asian adults with falciparum malaria [14]. A post hoc analysis of four studies suggested that normothermia, tachypnea, impaired consciousness, oligo-anuria, shock, and hypo-/hyperglycemia independently predicted death in adults with falciparum malaria [15].

Similarly, in dengue infection, the development of shock, respiratory distress, severe bleeding, or any organ dysfunction has been recommended by the World Health Organization to characterize severe dengue and an increased risk of death [16]. The clinical usefulness and diagnostic reliability of this classification were confirmed in a multicenter study performed in seven countries including 2259 patients from Southeast Asia and Latin America [17].

As the burden of infection-related death in resource-limited areas is highest in children, particularly in those aged <5 years [18], recognition and management of sepsis in this age group is of particular importance. As children differ in several physiologic aspects from adults, the indicators of their life-threatening organ dysfunction may differ as well. These parameters are summarized in a separate part of these expert consensus recommendations dedicated to pediatric sepsis.

One of the key challenges in resource-limited areas is the lack of well-trained healthcare workers, particularly physicians specialized in emergency and critical care medicine [19, 20]. Therefore, it appears unreasonable to limit recognition of sepsis to physicians only. Both physicians and nonphysicians (e.g., medical officers, nurses, and advanced level practitioners) need to be aware of and be able to recognize sepsis. However, they may require specific training and/or experience to do so [21]. Given that the vast majority of children with sepsis in resource-limited areas are presumably managed by non-pediatricians, it is also important that healthcare staff in resource-limited areas is aware of and trained in the specific characteristics of sepsis recognition in children [22]. A shortage in resources should not impede reliable and timely recognition of sepsis as this can generally be achieved using clinical skills only. Similarly, severity of diseases caused by malaria and dengue can be assessed largely by clinical signs. However, to recognize specific symptoms of malaria-induced sepsis or to calculate the malaria prognostic index, it is necessary to determine base deficit, lactate, and total bilirubin and creatinine or urea levels, which may not be routinely available in resource-limited settings.

Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to acute infection or, in certain cases, due to direct effects of the pathogen. Sepsis is not only associated with bacterial or fungal infections but with any other infection such as viral disease, protozoal infections (e.g., malaria), or tropical infections (ungraded). We recommend defining sepsis in adults as the combination of acute infection and the presence of two of the following three parameters: (1) respiratory rate $\geq$ 22 bpm, (2) systolic blood pressure $\leq$ 100 mmHg, and (3) any acute change in mental state (1B). These criteria have not been validated to recognize patients with sepsis from nonbacterial infections such as malaria, dengue, or other tropical infectious diseases (ungraded). Until data confirm the predictive value of the new sepsis definition in malaria, we recommend diagnosing 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 anemia, renal impairment, jaundice, malaria-induced shock, significant bleeding, and hyperparasitemia (1B). Until data confirm the predictive value of the new sepsis definition in dengue, we recommend diagnosing dengue-induced sepsis if dengue infection and any of the following clinical symptoms occur: shock, respiratory distress, severe bleeding, or any organ dysfunction (1B). We recommend that healthcare workers, irrespective of their proficiency, should 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). These are summarized in another chapter of this book.

4.3 Identification of the Underlying Type of Infection

Recognition of acute infection is paramount for both sepsis diagnosis and management. Acute infection can be caused by various microbiological pathogens—bacteria, viruses, parasites, or fungi. The epidemiology of infectious diseases differs globally. While bacterial and fungal infections are observed everywhere in the world, malaria, dengue, and tropical infectious diseases are typically encountered in Central and South America, sub-Saharan Africa, and southern parts of Asia [23]. Although clear data on the epidemiology of sepsis are missing, the global mortality of malaria and thereby the burden of malaria-induced sepsis appear to be exceptionally high in resource-limited countries, particularly in sub-Saharan Africa, India, and Southeast Asia [24]. Tuberculosis is a chronic but sometimes acute bacterial infection caused by *Mycobacterium* spp., highly prevalent in many resource-limited areas [25]. While in high- and upper-middle-income countries, only lower respiratory tract infections are ranked (sixth) among the top ten causes of death; three and four infectious diseases (excluding HIV/AIDS) are among the top ten causes of death in lower-middle- and low-income countries, respectively. In low-income countries, lower respiratory tract infections represent the most common cause of death followed by HIV/AIDS and diarrheal diseases [26]. Viral causes of sepsis, such as dengue, often occur in epidemics.

Clinical skills of structured history taking and systematic physical examination are essential to identify the underlying type of infection. Nonspecific signs of infection include fever, chills, fatigue, malaise, and muscle/joint aches. If associated with a low risk of harm for the patient, sites of suspected infections (e.g., abscess, joints, effusion) can be punctured or incised to verify the infectious focus and sample secretions or tissue for laboratory work-up [2]. Selected laboratory parameters can assist in making the diagnosis of acute infection (e.g., the white blood cell count) but are neither highly sensitive nor specific [27–32]. Diagnostic imaging techniques, where available and preferably portable (e.g., X-ray, ultrasound) [33–35], can be used to answer specific diagnostic questions. Given its increasing portability and availability, the role of ultrasound to diagnose abdominal, joint/soft tissue, and lung infections in resource-limited countries is emphasized [36].

As mainly clinical skills are required, a lack of resources does not relevantly impede identification of the underlying infection. Given that the majority of laboratories in resource-limited settings are capable of routinely determining the white blood cell count [36–38], this parameter may be useful to support the diagnosis of an acute infection. Although ultrasound has been increasingly available in resource-limited settings [36], in many healthcare facilities, ultrasound is not always available, as machines are routinely operated only by selected healthcare workers [39]. In addition, installation of ultrasound services in resource-limited hospitals is usually associated with substantial costs. Maintenance of ultrasound machines is another challenge in these settings. Similarly, X-ray machines are frequently immobile and require supply materials such as X-ray films.

We recommend taking a structured patient history and performing a systematic head-to-toe physical examination to identify the underlying type of infection (1A).

Thereby, recognition of local epidemiology of infectious diseases is crucial (ungraded). 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 (1B).

4.4 Identification of the Causative Microbiological Pathogen

Definitive (as opposed to empiric) antimicrobial therapy requires identification of the microbiological pathogen of infection [3]. Appropriate antimicrobial therapy is one of the cornerstones of successful sepsis management [3, 4, 40–42]. Knowledge of the causative organism and its susceptibility to antimicrobial agents is a prerequisite for appropriate antimicrobial therapy [3]. Different diagnostic techniques are required for identification of the infectious agents causing bacterial infection, tuberculosis, malaria, and viral diseases.

Microbiological methods are used to specify bacteria and fungi from sampled body fluids and blood as well as to test their susceptibility to antibiotic agents. Microscopy and Gram staining are simple and rapid techniques to identify bacteria and fungi in the sputum, urine, cerebrospinal fluid, ascites, and other body secretions [43–49]. The appearance and staining of bacteria can categorize (Gram positive/negative) and identify selected bacterial species (e.g., meningococci, pneumococci, staphylococci), thus allowing for prompt adjustment of empiric antibiotic therapy. Microbiological cultures of body secretions are the gold standard to grow and specify bacteria. Cultivating bacteria from the blood requires special media known as blood cultures. To achieve a reasonable sensitivity, two or more sets of blood cultures from different puncture sites or indwelling catheters need to be sampled in a sterile fashion [50]. As the shorter time period between the sepsis diagnosis and administration of an appropriate antimicrobial agent may reduce mortality [4], sampling of blood or body secretions for microbiological work-up should not relevantly delay initiation of antimicrobial therapy (e.g., <45 min [3]). The knowledge of antimicrobial susceptibility of the causative pathogen is of crucial importance as any potential resistance of microbiological pathogens against antimicrobial agents may result in inadequate antibiotic therapy. While antimicrobial resistance is a global challenge, the incidence of multidrug resistance is particularly high in many resource-limited areas with rates of resistant bacteria approaching as high as 50% [51–55]. This could explain partially why an observational study from Uganda did not observe a difference in mortality between sepsis patients who received and did not receive an empiric antibiotic therapy [56]. Similarly, resistance of *Plasmodium falciparum* to certain antimalarial drugs such as artemisinin has spread throughout mainland Southeast Asia and has also been detected in sub-Saharan Africa [57–59].

Patients with an acute infection who have a risk of being (co-) infected with tuberculosis should be screened for tuberculosis. Common risk factors are HIV

infection, malnutrition, previous tuberculosis infection, and close contact to persons suffering from tuberculosis (e.g., household members, prisoners, healthcare personnel) [60–62]. A study from Uganda reported that one in four HIV-infected patients with severe sepsis had *Mycobacterium tuberculosis* bacteremia [63]. The 2007 WHO international policy on tuberculosis detection recommends light-emitting diode microscopy of two sputum smears for the diagnosis of pulmonary tuberculosis infection [64]. In children, gastric aspirates can be examined alternatively to induced sputum samples. A novel field nucleic acid amplification test (Xpert MTB/RIF) yields diagnostic results and information on rifampicin resistance under 2 h [65]. Despite a more rapid and frequent diagnosis of tuberculosis with this technique, concerns remain as relevant patient outcomes have not been affected so far. Although sputum examination using Ziehl-Neelsen microscopy for acid-fast bacteria is insensitive in HIV-positive subjects, it is frequently performed in laboratories of resource-limited areas, as conventional fluorescence or light-emitting diode microscopy is not commonly available. WHO guidelines recommend performance of tuberculosis cultures in HIV-positive patients [64].

Light microscopy and rapid diagnostic tests are the laboratory methods commonly used to diagnose malaria. Light microscopy of Giemsa-stained blood smears is the standard method applied in many endemic areas to identify *Plasmodium* spp. and estimate parasite density [66, 67]. Depending on the examiner's experience, sensitivity varies but was shown to be very high in expert hands [68]. However, this method is labor intensive and requires specific training [69]. Antigen-detecting rapid diagnostic tests, on the other hand, do not depend on laboratory infrastructure and can be performed by non-laboratory medical personnel [70]. The sensitivity and specificity of rapid diagnostic tests are high (93–98%) and superior to that of light microscopy [71]. As rapid diagnostic tests only yield qualitative results, parasite density cannot be assessed with this method [70]. In addition, depending on the regional malaria epidemiology, different rapid diagnostic tests are required to detect and distinguish between plasmodium species [70].

Laboratory diagnosis of viral diseases, such as dengue, influenza, or Ebola, typically depends on the duration of the illness. During the early phases of infection, virus identification is achieved by direct methods (e.g., detection of viral components or cell cultures), whereas during later phases (after 5–7 days) indirect methods (e.g., serologic detection of serum IgM) are used [16, 72]. For certain viruses, rapid antigen detection tests are available yielding results within a few hours [16].Many of these tests have shown a high sensitivity and specificity such as a point-of-care rapid diagnostic test to detect the Ebola virus [73].

Laboratories in resource-limited areas often lack regular supply of materials to perform microbiological cultures and test for antibiotic susceptibility due to irregular availability of these materials on the local and national markets as well as due to the high cost [36–38]. On the other hand, microscopy and Gram staining are available in many of the laboratories [36–38]. Microscopic analysis and Gram staining can specify selected bacteria and fungi but do not give information on antibiotic susceptibility. In cases where routine microbiological cultures and susceptibility

testing are not available, determination of the most common pathogens (e.g., pneumococci, staphylococci, *Escherichia coli*, *Mycobacterium tuberculosis*, *Plasmodium falciparum*, etc.) for each infection site as well as their antimicrobial susceptibility may help to optimize empiric antimicrobial therapy. Accordingly, the World Alliance Against Antibiotic Resistance recommends collection of information on antibiotic resistance in each country/region [74].This recommendation is in line with that of the World Health Organization to regularly monitor drug efficacy for the first-line antimalarial drugs at regular intervals [75].

Laboratory methods to identify malaria are commonly available at healthcare facilities in areas where malaria is endemic [36–38]. The costs of rapid diagnostic tests are higher than those of light microscopy, despite that their use in Africa has increased substantially during the recent years [76]. Regarding tuberculosis detection using polymerase chain reaction tests or virus identification, laboratory tests yielding a high sensitivity and specificity typically require complex technologies, infrastructure requirements, and staff expertise and imply high costs. On the other hand, serologic tests are more affordable although they similarly require specific laboratory facilities which may not be available in many resource-limited settings [36–38]. This may change in cases of viral disease epidemics such as the recent Ebola virus disease epidemic in Western Africa [77]. None of the tests are associated with any direct risks for the patient. However, contamination of microbiological cultures and false-positive or false-negative results of laboratory tests bear the risk of over- or undertreatment, both of which may be associated with harm.

If available/affordable, we recommend obtaining microbiological cultures before antimicrobial therapy as long as this does not relevantly delay antimicrobial therapy (1A). We recommend taking two or more sets of blood cultures and/or tissue/body secretions from the site of suspected infection (1A). We recommend performing microscopy and Gram staining of secretions sampled from the suspected source of infection (1B). If available/affordable, we recommend testing for antibiotic susceptibility of cultured bacteria to guide antibiotic therapy (1B). 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 (1C). We recommend using rapid diagnostic tests to diagnose malaria (1A). Alternatively, we recommend light microscopy of stained blood smears performed by experienced staff (1A). 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 (1A). All patients with an acute infection who are positive for the human immunodeficiency virus, suffer from immunosuppression of other causes (e.g., malnutrition), and had previous tuberculosis infection and/or close contact with person suffering from tuberculosis should be screened for tuberculosis coinfection (1A). We recommend light-emitting diode microscopy of two sputum smears for the diagnosis of pulmonary tuberculosis (1A). Whenever available/affordable, we recommend using polymerase chain reaction tests (e.g., Gene Xpert) to diagnose tuberculosis or perform tuberculosis cultures in HIV-positive patients (1A).

4.5 Recognition of Septic Shock

Shock is defined as inadequate systemic tissue perfusion with cellular dysoxia/hypoxia [78]. Septic shock has recently been defined as arterial hypotension requiring vasopressor therapy to maintain mean arterial blood pressure at 65 mmHg or greater together with a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation [79]. Systemic tissue hypoperfusion is a critical cofactor in the development of organ dysfunction and death in patients with sepsis [3, 79]. Recognition of septic shock is therefore essential to recognize sepsis patients with a particularly high risk of death.

Critically ill patients with abnormal peripheral perfusion (e.g., cold and clammy skin) following initial resuscitation have more severe metabolic derangements and organ dysfunction than subjects with normal peripheral perfusion [80]. In early septic shock due to bacterial infection, prolonged capillary refill time is strongly associated with organ dysfunction and mortality [81]. Similarly, prolonged capillary refill time is an indicator of disease severity and a high risk of death in malaria [82] and dengue infection [83]. The extent of skin mottling in the lower extremities is associated with organ dysfunction and mortality in sepsis [84]. Given that of all internal organs the kidneys exhibit the highest autoregulatory threshold, renal blood flow is the first to decline in case of decreased cardiac output or peripheral vasodilation [85]. Thus, any episode of oliguria (<0.5 ml/kg/h) potentially indicates renal hypoperfusion. Observational studies found that the longer time during which urine output remains <0.5 mL/kg/h is associated with higher morbidity and mortality in critically ill patients [86]. Elevated lactate levels also predict increased morbidity and mortality in patients with sepsis [87, 88]. Moreover, the duration of hyperlactatemia and the rate of lactate clearance are associated with organ dysfunction and mortality in sepsis. Studies from resource-limited settings confirmed that hyperlactatemia is associated with a high degree of illness severity and an increased mortality from sepsis independent of the underlying pathogen [14, 89]. If patients with sepsis and signs of systemic tissue hypoperfusion develop arterial hypotension [defined as a systolic arterial blood pressure < 90 mmHg or a mean arterial blood pressure < 65 mmHg], the risk of death was shown to be excessively high in resource-limited settings [89–91]. Per the authors' experience, occurrence of arterial hypotension in septic patients with systemic tissue hypoperfusion is typically a preterminal sign, as the therapeutic requirements in these patients often exceed the capabilities of resource-limited healthcare facilities. In patients with severe malaria, arterial hypotension is rare and when present is often associated with bacterial coinfection [11, 13, 92]. The World Health Organization defined dengue shock by the presence of an arterial blood pressure amplitude (systolic minus diastolic arterial blood pressure) ≤20 mmHg [16]. In dengue shock, systolic arterial blood pressure remains normal or even elevated but can drop rapidly preceding terminal cardiovascular collapse [16]. Studies have suggested that the following clinical symptoms result from early plasma leakage and herald dengue shock: abdominal pain, hepatomegaly, high or increasing hematocrit levels, rapid decrease in platelet count, serosal effusions, mucosal bleeding, and lethargy or restlessness [16].

A shortage of resources does not impede the ability to recognize septic shock as the diagnosis is mainly based on clinical indicators. Specific training of healthcare workers to recognize these clinical signs is, however, essential. Using skin mottling to assess skin perfusion in dark complexed patients may not be feasible. However, assessment of capillary refill time is a meaningful alternative that demonstrated similar predictive value for organ dysfunction and death in sepsis [81]. Costs for lactate measurements may be relevant and, in some settings, may even impede use of arterial lactate in sepsis patients. There are no direct patient risks related to diagnosing shock by using clinical techniques. Despite its strong predictive power, arterial lactate measurements are not routinely available or affordable in many resource-limited healthcare facilities [36–38].

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 (1B). If available, we recommend measuring arterial lactate levels in patients with sepsis (1A). In patients with dengue sepsis, we recommend using a reduction in the arterial blood pressure amplitude $\leq$20 mmHg to diagnose shock (1C). 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 (1C).

4.6 Conclusions

Sepsis is not only associated with bacterial or fungal infections but with any other infection such as viral disease, protozoal disease (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.

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