Guideline

AME evidence series 001—The Society for Translational Medicine: clinical practice guidelines for diagnosis and early identification of sepsis in the hospital

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Abstract: Sepsis is a heterogeneous disease caused by an infection stimulus that triggers several complex local and systemic immuno-inflammatory reactions, which results in multiple organ dysfunction and significant morbidity and mortality. The diagnosis of sepsis is challenging because there is no gold standard for diagnosis. As a result, the clinical diagnosis of sepsis is ever changing to meet the clinical and research requirements. Moreover, although there are many novel biomarkers and screening tools for predicting the risk of sepsis, the diagnostic performance and effectiveness of these measures are less than satisfactory, and there is insufficient evidence to recommend clinical use of these new techniques. As a consequence, diagnostic criteria for sepsis need regular revision to cope with emerging evidence. This review aims to present the most updated information on diagnosis and early recognition of sepsis. Recommendations for

clinical use of different diagnostic tools rely on the Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework. Because most of the studies were observational and did not allow a reliable assessment of these tools, a two-step inference approach was employed. Future trials need to confirm or refute a particular index test and should directly explore relevant patient outcome parameters.

Keywords: Sepsis; early identification; diagnosis

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Definition of sepsis

The Surviving Sepsis Campaign (SSC) has the goal to improve the outcome of patients with sepsis and therefore it is important to define criteria for an early identification and treatment of these patients (1). Sepsis is most commonly defined as a systemic inflammatory response syndrome (SIRS) plus documented or suspected infection (2). Historically, several "versions" of this definition have been proposed, all aiming to reflect the common underlying mechanisms of the inflammatory response induced by infection (*Table 1*). The first version of the ACCP/SCCM [1992] definition is easily incorporated for bedside clinical use, but its specificity is vigorously debated (3). The second version adopted by both the 2001 SCCM/ESICM/ACCP/ATS/SIS and 2012 SSC guidelines is more complex and included some novel biomarkers such as procalcitonin (PCT) (2,4). Diagnosis of sepsis is based on five broad categories: general parameters, inflammatory markers, hemodynamic variables, organ dysfunction and indicators of tissue perfusion. This complex definition reflects the heterogeneous clinical presentations of sepsis, which is also shown in meta-analyses of diagnostic criteria through its tests for heterogeneity (5,6). The definitions do not specify how many items should be met before sepsis is considered to be present. Also, clinicians need to memorize too many items, which limits the applicability of the new definition for clinical use and research purposes. This sepsis definition also is not "clear-cut" but merely helps clinicians identifying a patient who "looks septic". As a result, clinical research still relies on the "old" ACCP/SCCM definition to screen patients with sepsis.

More recently, defining sepsis on the basis of organ dysfunction has been found to be helpful for the identification of patients requiring intensive and secondary-line treatments (7,8), leading to a new definition of severe sepsis and septic shock (Sepsis-3). In this perspective, sepsis has been defined as a "life-threatening organ dysfunction caused by dysregulated host response to infection", identifying, as we will see below, the *condition-sine-qua-non* for its diagnosis in the presence of an acute and sepsis-related organ failure. Organ dysfunction is identified as an acute change in sequential organ failure assessment (SOFA) score of two points or more following infection (9). The concept of the quick SOFA (qSOFA) clinical score based on mental status, respiratory rate and systolic blood pressure (SBP) was introduced in order to provide rapid and repeated assessments of patients without laboratory tests. The major difference of these definitions compared to the previous ones was that they were not only based on expert opinion; instead a broad analysis of clinical and laboratory parameters of patients from five large independent cohorts was performed to develop these definitions (5,9). Sepsis-3 definitions are not universally accepted and many controversies have surfaced (10-12). Clinical data utilized for the development of the Sepsis-3 definitions were mainly recorded in patients hospitalized in US intensive care units (ICU). Analysis was driven by mortality as the main outcome measure. However, the presence of organ failure at infection onset or the development of an infection-associated organ failure during the patient physical course appears to be a more attractive outcome for analysis. Furthermore, the sepsis-3 appears to focus on a more restrictive definition rather than on therapeutic interventions at earlier stages of sepsis where SIRS is detectable. The justification of sepsis-3 requires further clinical investigation to prove that delayed intervention is not implicated in this cohort of sepsis-3 patients.

Classification and staging of sepsis

According to the 2012 SSC guidelines, sepsis can be categorized by ascending severity into sepsis, severe sepsis and septic shock (4). Severe sepsis is defined as

Table 1 Definitions of sepsis

ACCP/SCCM 1992 (3)	SSC 2012 and 2001 SCCM/ESICM/ACCP/ATS/SIS (2)
Infection, documented or suspected, and two or more of the following:	Infection, documented or suspected, and some of the following:
Temperature >38 or <36 °C	General variables
Heart rate >90 min^{-1}	Fever >38.3 °C
Respiratory rate >20 min^{-1} or $PaCO_2$ <32 mmHg	Hypothermia (core temperature <36 °C)
WBC count >12,000 μL^{-1}, <4,000 μL^{-1}, or >10% immature (band) forms	Heart rate >90 min^{-1} or more than two SD above the normal value for age
	Tachypnea
	Altered mental status
	Significant edema or positive fluid balance (>20 mL/kg over 24 h)
	Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
	Inflammatory variables
	Leukocytosis (WBC count >12,000 μL^{-1})
	Leukopenia (WBC count <4,000 μL^{-1})
	Normal WBC count with greater than 10% immature forms
	Plasma C-reactive protein more than two SD above the normal value
	Plasma procalcitonin more than two SD above the normal value
	Hemodynamic variables
	Arterial hypotension (SBP <90 mmHg, MAP <70 mmHg, or an SBP decrease >40 mmHg in adults or less than two SD below normal for age)
	Organ dysfunction variables
	Arterial hypoxemia (PaO_2/FiO_2 <300 mmHg)
	Acute oliguria (urine output<0.5 mL $kg^{-1}\cdot h^{-1}$ for at least 2 h despite adequate fluid resuscitation)
	Creatinine increase >0.5 mg/dL or 44.2 mmol/L
	Coagulation abnormalities (INR >1.5 or aPTT <60 s)
	Ileus (absent bowel sounds)
	Thrombocytopenia (platelet count <100,000 μL^{-1})
	Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
	Tissue perfusion variables
	Hyperlactatemia (>3 mmol/L)
	Decreased capillary refill or mottling

WBC, white blood cell; PCT, procalcitonin; SD, standard deviation; INR, international normalized ratio; aPTT, activated partial thrombin time; $PaCO_2$, arterial partial pressure of carbon dioxide; SBP, systolic blood pressure; MAP, mean arterial pressure; PaO_2/FiO_2, oxygen index.

sepsis complicated by acute and sepsis-induced organ dysfunction. The method to evaluate for organ dysfunction is adapted from the SOFA score, which includes a scoring system to evaluate, on a daily basis, the function of the main six organs or systems (cardiovascular, renal, liver, coagulation, respiratory and neurological) (*Table 2*) (13,14). In general, organ dysfunction within severe sepsis criteria does correspond normally with organ failure according to the SOFA score, i.e., to a SOFA score equal to or greater than two points for each subcomponent. Central nervous system dysfunction was not incorporated into the assessment of sepsis severity, because of the use of sedative agents as major confounders on the neurological status of the most severe patients. The new definitions of sepsis (Sepsis-3) had

Table 2 Comparison of organ dysfunction between SOFA and severe sepsis

Organs	SOFA >1 point	Severe sepsis
Kidney	Creatinine >1.2 mg/dL	Urine output <0.5 mL·kg^{-1}·h^{-1} for more than 2 h despite adequate fluid resuscitation; creatinine >2.0 mg/dL
Lung	PaO_2/FiO_2 ≤400 mmHg	Acute lung injury with PaO_2/FiO_2 <250 mmHg in the absence of pneumonia as infection source or <200 mmHg in the presence of pneumonia
Liver	Bilirubin >1.2 mg/dL	Bilirubin >2 mg/dL
Coagulopathy	Platelet count ≤150,000/μL	Platelet count <100,000/μL; international normalized ratio >1.5
Central nervous system	GCS <13	NA
Cardiovascular system	Mean arterial pressure <70 mmHg	Sepsis-induced hypotension; lactate above upper limits of laboratory normal

GCS, Glasgow coma scale; NA, not applicable; SOFA, sequential organ failure assessment.

removed the term "severe sepsis" considering that sepsis is by definition a severe life-threatening disease. Sepsis-3 explicitly includes the SOFA score to identify infected patients at risk of having sepsis, and at increased risk of mortality (9). Septic shock, according to the original ACCP/SCCM definition, is defined as "a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes" and associated with an infection (2). It can be identified in a septic patient with hypotension requiring vasopressors to maintain MAP >65 mmHg and a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. Interestingly, in addition to clinical criteria, the Delphi consensus process by the task force included a serum lactate level of >2 mmol/L as part of the definition of septic shock. The inclusion of hyperlactatemia highlights the role of lactate in the understanding of this syndrome (15).

Analogous to the TNM classification used for staging malignant tumors, some authors have proposed the PIRO (predisposition, infection, response and organ dysfunction) system to better evaluate sepsis and its severity. It was originally formulated as IRO in the Fifth Toronto Sepsis Roundtable Talk, with P (predisposition) added thereafter (16). Although some investigators argued that PIRO was only attractive in its conceptual framework (17), recent evidence supported it as an accurate predictor of mortality. The PIRO system indeed outperformed the SOFA score in predicting mortality (AUC: 0.86; 95% CI: 0.80 to 0.92 *vs.* 0.78; 95% CI: 0.71 to 0.87) of patients with severe sepsis and of septic shock patients in the emergency department (18). However, inferior results were obtained from other studies with AUCs ranging between 0.68 and 0.744, from various emergency department cohorts (18-21). To date, no randomized controlled trials (RCT) have explored how patient-important outcomes (e.g., mortality, long term physical and cognitive behavior, return to previously normal function etc.) are influenced by applying the PIRO system. More studies are needed to determine its clinical utility.

Early identification of sepsis

Sepsis may benefit from early identification (1), thus many biomarkers and screening strategies to identify patients with sepsis have been investigated (22,23). The reference standard used in these studies was defined in the ACCP/SCCM, 2001 SCCM/ESICM/ACCP/ATS/SIS and 2012 SSC guidelines. The index test (i.e., potential diagnostic biomarkers) included, among others, presepsin (sCD14-ST) (24), PCT, Neutrophil CD64 (25), sTREM-1 (26), lipopolysaccharide-binding protein, pro-adrenomedullin, pro-vasopressin and a variety of inflammatory cytokines (27-29). Furthermore, the efficacy of many scoring systems and screening tools for detecting early sepsis has been evaluated (30,31). These include BioScore system (32), computer-weighted bedside scoring system (33), three-step sepsis screening tool (34), and spot check tissue oxygen saturation (StO_2) (35). However, the clinical usefulness of these screening tools has not been established. In the next sections, benefits and pitfalls of early identification of sepsis within the Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework will be discussed (36).

Assessment of diagnostic testing in the GRADE framework

Clinical usefulness of screening tools for early

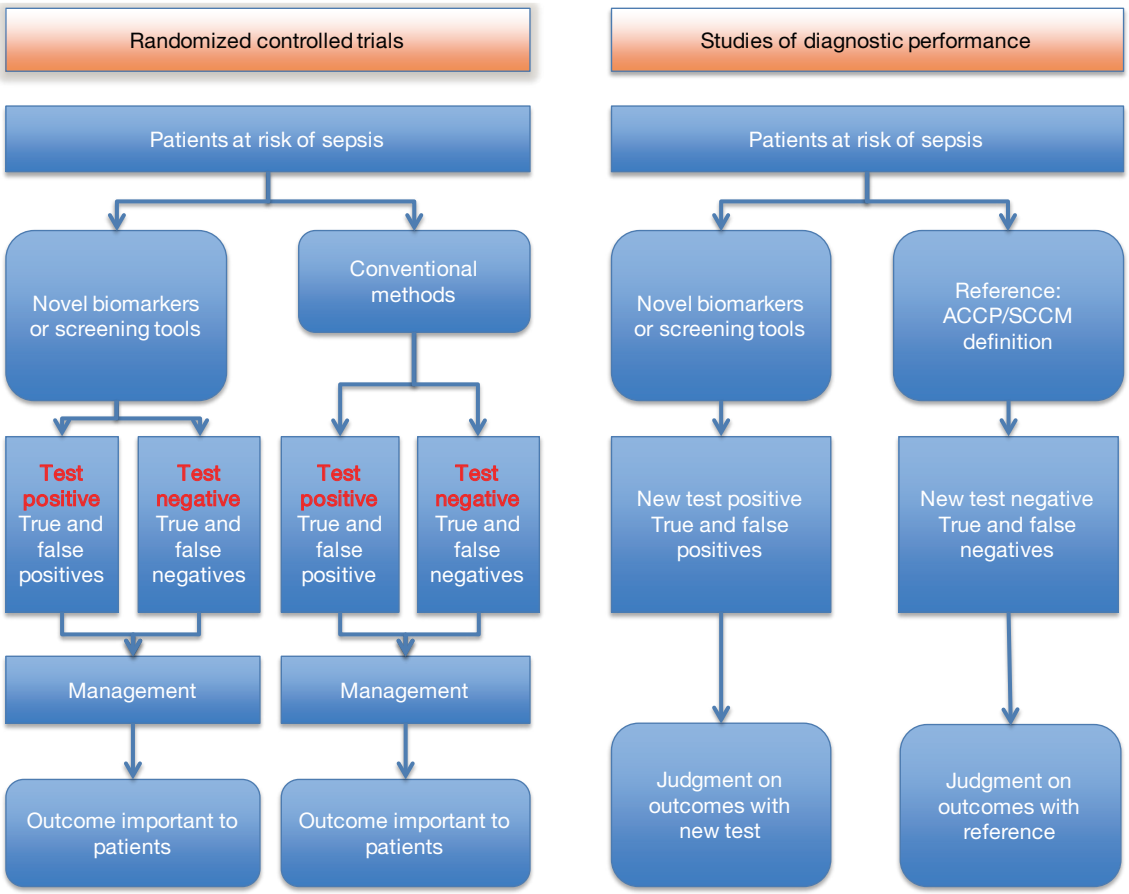

Figure 1 Two methods to evaluate the clinical usefulness of a diagnostic test. Randomized controlled trials can provide the highest quality of evidence because they directly compare patient-important outcomes between the group managed with index test and the control group. Observational cohort studies provide diagnostic accuracy and allow judgment on impact of each diagnostic result (true positive, false positive, false negative, and true negative) on relevant patient outcomes.

identification of sepsis can be investigated by RCTs and cohort studies (*Figure 1*). RCTs also allow evaluating potential pitfalls in the early diagnosis of sepsis. For example, a three-step sepsis screening tool can be assessed with one arm assigned to the control and the other to the screening. Benefits may include the early use of antibiotics or early initiation of a "resuscitation bundle", whereas potential drawbacks may involve, as an example, anxiety of being diagnosed with sepsis, pulmonary edema due to fluid overload and more expensive treatment. Furthermore, inherent false positives and negatives will stir up the debate on benefits and harms. Such problems should be tackled by well-designed RCTs which directly evaluate patient important outcomes including mortality, ICU and hospital length of stay and organ-failure free days. This is the so-called "one step reference". Inferences become more complicated when "two step" diagnostic performance studies are used. The first step assesses the accuracy of the new biomarker (or the new diagnostic strategy) and related quality of evidence. The second step involves subjective judgment on the impact of test results on clinically relevant outcomes, which may range from survival, to other clinical end-points (such as reduction or prevention of organ failures, reduction of length of stay, and reduction of antibiotic therapy).

Evidence from RCTs

A PubMed search from inception to May 2016 looked for RCTs investigating the effect of early identification of sepsis by using biomarkers and screening tools on patient important outcomes. The search strategy included:

Table 3 Patients' outcomes and possible impact on management

Test results	Presumed influence on patient-important outcomes	Directness of evidence for outcomes important to patients
True positives	Early use of resuscitation bundle to reduce mortality from 37% to 30%	Some uncertainty
True negatives	Less patients' anxiety, and cost for further testing	Major uncertainty
False positives	Unnecessary resuscitation, cost, anxiety, antibiotic exposure	Some uncertainty
False negatives	Delayed resuscitation, possible adverse outcomes	Major uncertainty
Balance between presumed outcomes, test compliance and cost	New biomarkers with high accuracy may warrant their use in early recognition of sepsis and septic shock	

((((((early diagnosis[Title/Abstract]) OR screening[Title/Abstract]) OR screen[Title/Abstract]) OR early identification[Title/Abstract])) AND ((randomized[Title/Abstract]) OR randomization[Title/Abstract])) AND ((sepsis[Title/Abstract]) OR septic[Title/Abstract]). The initial search identified 62 studies. However, we found no RCTs that fulfilled the inclusion criteria.

PCT has been investigated in RCTs for its usefulness in patients with established sepsis (37,38). Although PCT was employed mainly as a biomarker to guide subsequent treatment in target populations with established diagnosis of sepsis or severe sepsis, it was also shown to be valuable for differentiating sepsis from SIRS due to non-infectious etiologies (39-41). Thus, it is discussed here within the scope of diagnosis of sepsis. A systematic review and meta-analysis published in 2013 showed that PCT-guided therapy significantly reduced the duration of antimicrobial therapy with no effect on mortality, or length of ICU and hospital stay. The risks of bias in included studies were mostly low or unclear (42-48). Only one study by Jensen and coworkers was considered to have high risk of bias in terms of selective reporting (46). A recent RCT, not included in Prkno's systematic review, showed that PCT-guided therapy in patients with undifferentiated infection or suspected sepsis did not achieve a clinically significant 25% reduction in duration of antibiotic treatment (49). Taken together, PCT-guided therapy has no significant adverse consequences. It may shorten the duration of antibiotic exposure and therefore could reduce financial cost and development of antibiotic resistance.

Evidence from observational cohort studies

Many biomarkers and screening tools have been used for diagnostic purpose in observational cohort studies for their diagnostic performance. This performance should be evaluated by weighting their benefits and risks in the GRADE framework. Benefits and potential harms were evaluated in the context of each possible outcome of the diagnostic test: true positives, false positives, true negatives and false negatives (*Table 3*). A major issue is whether early recognition of sepsis may reduce mortality or other negative outcomes (true positives). One large observational study reported a decrease in mortality risk (from 37% to 30.8%) when complying with a sepsis resuscitation bundle. Although still robust after adjustment for known confounding factors, this study included historical controls and therefore some unmeasured confounders cannot be excluded (50). The study served as the primary evidence for the effect of early use of a sepsis bundle (4). However, it actually compared patients resuscitated according to bundle target with those without bundle target. Thus, it remains to be proven whether early initiation of therapy is of significant benefit. True negatives allow clinicians and patients to reduce uncertainty or anxiety related to diagnosis, cost and ICU admission. The potential benefits of true negative outcomes are debated. False positive (e.g., patients testing positive for sepsis but actually not septic) will result in unnecessary resuscitation procedures, more antibiotic exposure, and higher cost. Extensive evidence shows that a persisting positive fluid balance is associated with adverse outcomes (51-56). Therefore, inappropriate fluid management based on false positive results may create an unwarranted positive fluid balance with a corresponding higher mortality risk. Finally, initiation of resuscitation may be delayed in false negatives but it is not known whether this has any impact on patient-important outcome parameters. The potential clinical benefit and cost-effectiveness of early

Table 4 Biomarkers or screening tools for early identification of sepsis

Tests	Study type	Subjects (n)	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Presepsin (sCD14-ST)	Meta-analysis of 8 studies (57)	1,815	0.89 (0.86–0.92)	0.86 (0.79–0.91)	0.78 (0.68–0.85)
	Meta-analysis of 9 studies (58)	2,159	0.89 (0.84–0.94)	0.78 (0.76–0.80)	0.83 (0.80–0.85)
Neutrophil CD64	Meta-analysis of 8 studies (59)	1,986	0.95	0.76 (0.73–0.78)	0.85 (0.82–0.87)
sTREM-1	Prospective study (26)	74	–	–	–
Infection probability score	Prospective study (60)	298	0.51	0.575	0.671
lipopolysaccharide-binding protein	Prospective study (61)	90 episodes	0.566	–	–
Screening tool[¶]	Prospective study (34)	920	–	0.965	0.967
StO_2	Prospective study (35)	500	–	0.857	0.784
Bioscore	Prospective study (32)	320	0.914 (0.862–0.951)	90.8	73.9
Screening tool with lactate	Prospective study (62)	258	–	0.34 (0.28–0.41)	0.82 (0.69–0.90)
NOSEP score	Prospective study (33)	104 episodes	0.82	0.60	0.84
Automated electronic sepsis alert systems[‡]	Systematic review of 8 studies (63)	42,317	–	0.636 (0.316–0.878)	0.996 (0.99–0.998)
EWS	Retrospective study (30)	500	0.89 (0.84–0.94)	0.926 (0.742–0.987)	0.77 (0.728–0.806)

[¶], a numeric score [0-4] for each of the SIRS criteria; [‡], there was no meta-analysis performed and sensitivity and specificity were extracted from one representative study. EWS, early warning score; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; AUC, area under curve; NOSEP, computer-weighted bedside scoring system; SIRS, systemic inflammatory response syndrome.

resuscitation (i.e., before diagnosis of sepsis is confirmed) needs further evaluation.

Biomarkers and screening tools for early recognition of sepsis

To be clinically useful, the diagnostic performance of a test is of vital importance. Sensitivity, specificity, likelihood ratios that are based on pre- and post-test odds/probabilities of sepsis in individual patients should be investigated in target populations. In this section, the diagnostic performance of each tool is extracted from the literature. In case of meta-analyses, pooled data have been employed (*Table 4*).

The diagnostic performance of biomarkers and screening tools varied widely in these studies. Screening by assigning numeric scores for each of the SIRS criteria appears to be most accurate for determination of sepsis (34). However, such screening scores actually employ the diagnostic criteria of sepsis and thus cannot guarantee early recognition of sepsis (sepsis prediction). Other screening strategies have moderate to good diagnostic accuracy but a substantial number of patients may be misclassified. More recently, the qSOFA score has been recommended to use for early recognition of patients with sepsis who require urgent monitoring or interventions (9). Since the impact of false positives and negatives on patient-important outcomes is still largely unexplored, these screening strategies cannot be fully recommended for clinical use until further prospective studies are done to address the abovementioned outcomes.

Use of automated electronic sepsis alert system (AeSAS) to improve sepsis management represents an area of active research (63). Advances in electronic medical system technology and sophisticated machine learning techniques will "upgrade" prediction models making them more accurate and individualized (64-66). AeSAS employs two or more SIRS criteria as alert threshold (67-70). Other studies use additional threshold such as SBP (71), and a lactic acid concentration >2 mmol/L (72,73). Two studies employed recursive partitioning tree analysis involving a variety of variables such as shock index, mean arterial blood pressure, international normalized ratio (INR), white blood cell (WBC) count, absolute neutrophil count, bilirubin, albumin, hemoglobin and sodium (74,75). One high-quality RCT, however, failed to identify any beneficial effect of this alerting system on patient-important outcomes (67). Up to now, AeSAS have only poor to moderate diagnostic performance and no beneficial effect on mortality risk and length of ICU stay.

Special considerations in low-income and middle-income countries (LIMC)

Because most of the literature focuses on identification of sepsis in developed countries, some screening tools and strategies may not be applicable to LIMC (76). For example, it has been reported that approximately 37% hospitals in African and Sub-Saharan African countries have no access to lactate measurement (77). As a result, the diagnosis of septic shock involving lactate criterion cannot be readily made in substantial number of hospitals in LIMC. Instead, there are other non-invasive, cheap and easy methods for screening inadequate tissue perfusion. Capillary refilling time can be a good alternative to blood lactate in measuring peripheral perfusion. In addition, pulse oximetry is also sensitive to poor perfusion with arterial oxygen saturation below 90% indicating hypoxemia and hypoxia (78).

With respect to the causes of sepsis, the Sepsis-3 was based on a large in-hospital cohort in the USA and respiratory and postoperative infections were the primary causes of sepsis. However, the community-acquired infections are more common in LIMC, with higher prevalence of gastroenteritis, septic abortion, skin and soft tissue infections. Sepsis and septic shock caused by these infections usually have different pathogens as compared with those used for the development of Sepsis-3. For example, salmonella was found to be the most prevalent isolate in a meta-analysis of 19 bacteremia studies in Africa (79). Some reports from LIMC show that dengue is an important cause of septic shock requiring ICU admission (80,81). Mycobacteria and HIV are prevalent in some areas of LIMC and their coexisting with sepsis and septic shock may impose great challenges to the treatment of this syndrome. Collectively, early recognition of sepsis in LIMC cannot be performed with screening tools as those being used in developed countries. Of note, there are some specific pathogens that can cause the form of sepsis and septic shock. Identification of such pathogens should take priority.

Conclusions

Sepsis is a heterogeneous syndrome characterized by a complex immune-inflammatory response to presumed or proven infection. However, due to some common features of this disorder, sepsis is treated and researched in one paradigm. In the absence of a gold standard, the diagnosis of sepsis remains challenging and subject to change. As a result, the clinical diagnosis of sepsis is ever changing to meet the clinical and research requirements. The original diagnosis criteria that were developed two decades ago were criticized for their lack of specificity. The later definition was deemed too complex and unsuitable for clinical purpose. The Sepsis-3 definitions better captures increased mortality risk of sepsis with organ dysfunction in response to infection, but the late progression or a highly time-dependent definition of septic conditions might result in delay of effective therapeutic intervention.

Early recognition of sepsis is an important research target. There are many novel biomarkers and screening tools for predicting the risk of sepsis. However, their diagnostic performance and effectiveness are poorly documented and thus cannot be recommended for clinical use. In the future, electronic medical record systems may allow better prediction of sepsis by using sophisticated machine learning techniques. Due to its heterogeneity and clinical impact, sepsis represents an exceptional example of the necessity of applying precision medicine, both for its early diagnosis and individualized treatment. The years to come encompass such important challenge.

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Footnote

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