Monitoring of the physical exam in sepsis

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Purpose of review
Monitoring of mental status and peripheral circulatory changes can be accomplished noninvasively in patients in the ICU. Emphasis on physical examination in conditions such as sepsis have gained increased attention as these evaluations can often serve as a surrogate marker for short-term treatment efficacy of therapeutic interventions. Sepsis associated encephalopathy and mental status changes correlate with worse prognosis in patients. Evaluation of peripheral circulation has been shown to be a convenient, easily accessible, and accurate marker for prognosis in patients with septic shock. The purpose of this article is to emphasize the main findings according to recent literature into the monitoring of physical examination changes in patients with sepsis.

Recent findings
Several recent studies have expanded our knowledge about the pathophysiology of mental status changes and the clinical assessment of peripheral circulation in patients with sepsis. Sepsis-associated encephalopathy is associated with an increased rate of morbidity and mortality in an intensive care setting. Increased capillary refill time (CRT) and persistent skin mottling are strongly predictive of mortality, whereas temperature gradients can reveal vasoconstriction and more severe organ dysfunction.

Summary
Monitoring of physical examination changes is a significant and critical intervention in patients with sepsis. Utilizing repeated neurologic evaluations, and assessing CRT, mottling score, and skin temperature gradients should be emphasized as important noninvasive diagnostic tools. The significance of these methods can be incorporated during the utilization of therapeutic strategies in resuscitation protocols in patients with sepsis.

Keywords
capillary refill time, sepsis, sepsis-associated encephalopathy, shock, skin mottling, skin temperature gradient

INTRODUCTION

Sepsis is characterized by organ dysfunction related to disruption of host response to an infection [1,2]. New definitions for sepsis and septic shock (Sepsis-3) were recently published, and sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, and septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [3]. Sepsis affects millions of people around the world and results in the death of approximately one in four affected patients [4,5]. Early identification and appropriate management in the initial hours after sepsis develops improves outcomes. Physical examination plays an important role in the diagnosis and management of sepsis.

In this review, we will evaluate selected physical examination characteristics that have been validated to replicate the findings of more invasive monitoring. Emphasis on physical examination in conditions such as sepsis have gained increased attention as these evaluations can often serve as a surrogate marker for short-term treatment efficacy of therapeutic interventions. The importance of physical examination in patients with sepsis and shock is further exemplified by the United States Center for Medicare and Medicaid Services (CMS) 'core measures' for treatment of patients with sepsis [6]. Within the initial 6-h bundle in the CMS sepsis core measures, physical examinations to assess areas such as mental status and tissue perfusion are explicitly recommended.

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KEY POINTS

- The physical examination is a reliable, inexpensive, and noninvasive first step to assess patients with sepsis.
- Reliance on simple bedside monitoring, such as evaluation of mental status, CRT, mottling score, and skin temperature must be emphasized and understood.
- Sepsis-associated encephalopathy often remains underdiagnosed; however, it is associated with increased morbidity and mortality and many survivors experience long-term cognitive deficits.
- Abnormal mental status, CRT, presence of mottling, and temperature variation in patients with sepsis is of great value in predicting more severe organ dysfunction.

MENTAL STATUS CHANGES IN SEPSIS

Sepsis is often characterized by an early and acute change in mental status, which can be associated with increased morbidity and mortality [7,8]. Patients can present with fluctuations in mental status, disorganized thinking, and inattention, therefore fitting the criteria for delirium. Although it is a multifactorial syndrome, delirium has several risk factors associated with it, such as the severity of illness, patient's characteristics (e.g., cognitive impairment and age); environmental factors (e.g., noise and sleep deprivation); medications (e.g., benzodiazepines and opioids); as well as metabolic disturbances such as fever, hypoglycemia, and sodium derangements [9–11]. Many conditions can induce delirium in critical illness, yet sepsis represents the most frequent and severe cause in the form of sepsis-associated encephalopathy (SAE) [12,13]. SAE is a multifactorial process leading to a condition of diffuse cerebral dysfunction caused by a systemic inflammatory response to an infection without evidence of an infection in the central nervous system. It is characterized by acute changes in mental status, cognition, alteration of the sleep–wake cycle, disorientation, disorganized thinking, or impaired attention [14].

SAE has a prevalence of up to 30% in septic patients at admission, and 30–70% of in-hospital patients with sepsis and a systemic inflammatory response syndrome [15,16]. It is also associated with an increased rate of morbidity and mortality in an intensive care setting [17,18]. In a recent meta-analysis, Salluh *et al.* [19▪▪] evaluated 42 studies and observed that delirium was identified in 31.8% of all critically ill patients. When compared with control patients without delirium, they found that patients with delirium had a significantly higher mortality during admission, with a risk ratio 2.19 [95% confidence interval (CI) 1.78–2.70]. Patients with delirium also had longer durations of mechanical ventilation, lengths of stay in the ICU and in the hospital, and an increased risk of cognitive impairment after discharge [19▪▪].

MONITORING OF SEPSIS-ASSOCIATED ENCEPHALOPATHY

Detection of acute brain dysfunction in ICU is based on repeated neurological examination. The detailed pathophysiology of SAE remains incompletely understood. In sepsis, there is increased transcription of several proinflammatory and anti-inflammatory cytokines and chemokines in the brain, including TNFα, IL1β, transforming growth factor beta, and monocyte chemoattractant protein 1 [20]. Sepsis also enhances activation of cerebral endothelial cells, which results in blood–brain barrier dysfunction and release of various mediators into the brain. In the early phase of sepsis, endothelial nitric oxide synthase-derived nitric oxide exhibits proinflammatory characteristics and causes activation and dysfunction of cerebrovascular endothelial cells [21]. The activated endothelium causes release of proinflammatory cytokines into the brain and can contribute to microcirculatory dysfunction, which can compromise cerebral perfusion [22]. Impaired cerebral blood flow is also common in sepsis, especially when shock is present [23▪,24]. In hemodynamically stable patients with sepsis, microcirculatory alterations can cause abnormal regional brain perfusion and lead to brain dysfunction [25]. Noradrenergic neurotransmission may also be involved in SAE, as dexmedetomidine, a selective agonist of alpha2-adrenoceptors expressed in the locus coeruleus, is associated with less brain dysfunction, fewer days of mechanical ventilation, and a lower 28-day mortality in septic patients when compared with lorazepam [26,27].

Detecting brain dysfunction in critically ill patients can be assisted by validated methods such as the Confusion Assessment Method for the ICU and the intensive care delirium screening checklist [12,28]. After detection of brain dysfunction, a comprehensive neurological examination evaluating cranial nerve function, neck stiffness, motor responses, muscular strength, and plantar and deep tendon reflexes should be pursued. Although sedative drugs may limit the interpretation of clinical findings, Sharshar *et al.* [29] evaluated brainstem responses in sedated critically ill patients. They showed that neurologic examination including the Glasgow Coma Scale, the Assessment to Intensive Care Environment score, cranial nerve examination, response to noxious stimuli, and cough

reflexes were independent of sedative dose. In their observational study, they revealed that loss of cough reflex was associated with 28-day mortality, and absent oculocephalic response was independently associated with altered mental status after withdrawal of sedation.

CAPILLARY REFILL TIME

The capillary refill time (CRT) measures the time required to recolor the tip of a finger, usually the index, after application of pressure. It is an attractive tool to use at the bedside as it is easy to learn and use, with good provider reproducibility. CRT reflects the duration of time needed for the patient's fingertip to regain color after direct pressure is applied to cause blanching. The assessment of CRT in patients with sepsis may seem counterintuitive as pathophysiologic derangements often lead to peripheral vasodilation resulting in warm, flushed extremities. Emerging literature, however, suggests that CRT may be an important bedside tool to assess adequacy of regional and global perfusion during the resuscitation phase of septic shock [30]. The normal range of CRT in adults is still being debated. In a study of 1000 participants, CRT was found to be strongly dependent on age, sex, and ambient temperature, with the upper limit of normal of 3.5 s (95th percentile) [31]. Many studies have shown that CRT more than 5 s following initial hemodynamic optimization differentiated between stable patients and those at higher odds for worsening organ failure [32–34].

In a recent study, Ait-Oufella *et al.* [35▪] revealed that after initial resuscitation in patients with septic shock, CRT was a strong predictor of 14-day mortality. A total of 59 patients were evaluated at intensive care admission and after initiation of vasopressor therapy within 24 h. In this study, a threshold of index CRT at 2.4 s predicted 14-day outcome with a sensitivity of 82% and specificity of 73% [35▪]. Skin CRT measured at 6 h after initial resuscitation was strongly predictive of 14-day mortality as the area under the curve was 84% (95% CI 75–94) for the index finger tip measurement and 90% (95% CI 83–98) for the knee area measurement. Patients who persisted with CRT more than 5.0 s at 6 h after initial resuscitation had an odds ratio (OR) of dying in 14 days of 18 (95% CI 3.6–89.6) when measured on the index finger and an OR of 61.2 (95% CI 6.5–578.9) when measured in the knee. This study revealed a strong correlation between CRT and tissue perfusion parameters such as arterial lactate, urinary output, and Sequential Organ Failure Assessment (SOFA) score.

Hernandez *et al.* [36] reported that in a population of septic shock patients, survival was characterized by normalization of CRT. Although perfusion-related variables such as CRT, lactate clearance, and central venous oxygen saturation exhibit markedly different normalization rates in septic shock survivors, they showed that there was a biphasic response with an initial rapid improvement. More than 70% of these patients had normalization of CRT at 6 h after initiation of treatment, even before normalization of lactate levels. Serial assessment of CRT with normalization at 6 h is independently associated with successful resuscitation when compared against traditional resuscitation goals, such as central venous oxygen saturation or lactate normalization. In the postresuscitation phase of critical illness, delayed CRT may also be a predictor of worsening organ failure and impeding shock [33].

SKIN MOTTLING

Mottling of the skin, a common clinical sign in septic and critically ill patients, is defined as patchy skin discoloration that typically manifests around the knees, elbows, and can extend to other peripheral circulation, such as the fingers and ears. It has a distinct patchy pattern and is a result of heterogenic small-vessel vasoconstriction that reflects abnormal skin microperfusion. Skin mottling can be easily evaluated at the bedside. To objectively analyze skin mottling, Ait-Oufella *et al.* [37] developed a clinical scoring system. In evaluating the area of mottling from the knees to the periphery, they utilized a range from 0 to 5, with higher scores indicating greater areas of skin mottling (Fig. 1). They reported that a higher mottling score within the first 6 h after resuscitation was a strong predictor of 14-day mortality during septic shock, suggesting a direct link among the initial event, severe infection, and ICU mortality. Moreover, this was independent of systemic hemodynamics such as mean arterial pressure or cardiac output. Although factors such as administration of vasopressors is believed to affect mottling, Ait-Oufella *et al.* showed that after stratification of drug dosage of vasopressor, the association of a high mottling score with mortality remained significant. This scoring system is also very easy to learn and has a very good interobserver agreement. This predictive value of the mottling score has also been reproduced in emergency departments and nonselected critically ill patients [38▪▪,39]. In a more recent study, the same group found that tissue oxygen saturation measurement around the knee in septic shock was associated with an increase in the mottling score [40].

More recently, Coudroy *et al.* [38▪▪] applied the same mottling score to investigate the incidence of mottling in a large cohort of 791 critically ill patients and its impact on ICU mortality. In this observational study, the authors reported skin mottling in 29% of

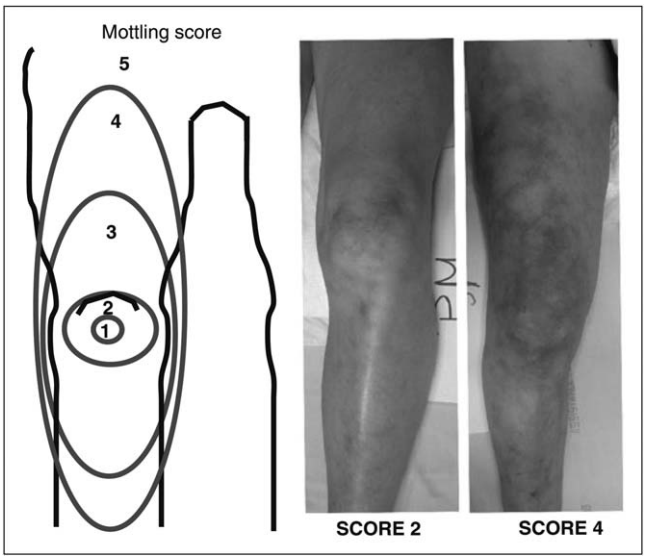

FIGURE 1. (a) The mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin. (b) Examples of the mottling score. Reproduced with permission [37].

all patients, 49% of patients admitted for septic shock, and 25% of patients admitted for acute respiratory failure. Patients with skin mottling had more severe disease, as was determined by higher SOFA and Simplified Acute Physiology Score II scores. In addition, they found that patients with skin mottling utilized significantly more supportive measures, such as mechanical ventilation, vasopressor infusion, or renal replacement therapy.

Assessment of mottling is a simple and highly reliable parameter, even in patients with nonextensive mottling, as it allows for continuous evaluation and quantitative measurements in patients in septic shock. In patients with cirrhosis, the mottling score remains a predictor of mortality during septic shock despite a lower sensitivity than noncirrhotic patients [41]. The lower sensitivity may be due to delayed mottling given the higher baseline skin perfusion in these patients. However, skin mottling can be challenging in persons with dark skin color, prior burns, or amputations.

TEMPERATURE GRADIENTS

Skin temperature has been shown to be an easily accessible parameter for patients with septic shock. There is difficulty in approaching only one objective parameter, however, as factors such as outside temperature can have a significant effect. Therefore, a difference between two temperatures can be used to adequately quantify significant changes. Body temperature gradients can better reflect changes in cutaneous blood flow than the absolute skin temperature itself in patients with sepsis and the critically ill [42,43]. Although septic shock is associated with peripheral vasodilation, cool extremities may be present in the early stage of sepsis. Temperature gradients can be determined by the difference between two different measurement points, such as forearm-to-fingertip ($T_{\text{skin-diff}}$), central-to-toe ($T_{\text{c-toe}}$), or peripheral-to-ambient. The advantage of measurements such as $T_{\text{skin-diff}}$ is that both spots of skin are similarly affected by the ambient temperature. Studies have suggested that although $T_{\text{skin-diff}}$ of 0 °C is normal, a $T_{\text{skin-diff}}$ of more than 4 °C is associated with severe vasoconstriction [33,44]. Thompson *et al.* [45] evaluated the time course of the clinical features of meningococcal disease in children and adolescents before the admission to the hospital, and they identified cold hands and feet together with abnormal skin color as the main important clinical sign of imminent sepsis within the first 12 h of the onset of illness. Lima *et al.* [33] showed that clinical assessment of peripheral perfusion, as measured by CRT and peripheral temperature variation, could discriminate hemodynamically stable patients with more severe organ dysfunction. They evaluated 50 patients, 21 of whom had septic shock, during the first 24 h following initial hemodynamic optimization. SOFA score was significantly higher, and the odds of unfavorable evolution were 7.4 (95% CI 2–19) times higher in patients with abnormal peripheral perfusion [33]. This study revealed that increased $T_{\text{skin-diff}}$ was related to outcome.

CONCLUSION

In patients with sepsis, noninvasive bedside monitoring through physical examination is important. The reliability and reproducibility of the clinical assessment requires the involved clinician to judge the diagnostic tools available for their ease of use and implementation. Laboratory testing is frequently relied on to determine improvements in the patient's status, but in certain environments, advanced testing may not be readily available. The clinician should have an array of bedside tools that can help assess patients with sepsis, and evaluations of mental status, CRT, mottling score, and temperature gradients should be emphasized and encouraged. We conclude that conventional hemodynamic parameters must be combined with the clinical assessment in patients with sepsis and recommend the clinicians repeat

physical examination following initial resuscitation interventions to fully assess the adequacy of their treatment.

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There are no conflicts of interest.

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- ■■ of outstanding interest

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