Sepsis – What's new in 2019?

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Purpose of review
Sepsis-3 guidelines have implications in a deeper understanding of the biopathology of the disease. Further, the review focuses on timely topics and new literature on fluid resuscitation, the value of steroids in sepsis, and new therapeutic options such as angiotensin II, vitamin C, and thiamine as well as the emerging role of procalcitonin (PCT) in managing antibiotics.

Recent findings
Traditional therapies such as type of crystalloid fluid administration and steroid therapy for sepsis are currently under re-evaluation. Angiotensin II is investigated for reversing vasodilatory shock. The role of capillary endothelium leak and cellular metabolism can be affected by vitamin C and thiamine levels. Biomarker level trends, specifically PCT, can aid clinical suspicion of infection.

Summary
Sepsis-3 shifts the focus from a noninfectious inflammatory process and an emphasis on a dysregulated host response to infection. Hyperchloremic crystalloid resuscitation is associated with poor clinical outcomes. Steroid administration can reverse shock physiology; however, mortality benefits remain uncertain. Angiotensin II, vitamin C, and thiamine are novel treatment options that need further validation. PCT assays can help discern between infectious and noninfectious inflammation.

Keywords
angiotensin II, chloride, sepsis, thiamine, vitamin C

INTRODUCTION

There are 1.5 million sepsis cases in the United States and it is responsible for one out of every three hospital deaths [1]. The economic impact is estimated at over $20 billion annually in the United States, and approximately $55 million each day [2]. Septic shock is associated with mortality as high as 50% [3]. Although easy 'cures' are elusive, diagnosis and treatment for sepsis continue to advance. In this review, we will discuss the implications of the Sepsis-3 criteria and epidemiologic importance of this concept. Further, we will discuss recent data regarding intravenous (IV) fluid administration, the use of steroids, and new drug therapies including vitamin C, thiamine, and angiotensin 2. Although it is unclear which of these will be practice changing, they raise important concerns in the management of sepsis.

SEPSIS-3

Sepsis is a diagnosis based on clinical criteria. Defined as 'life-threatening organ dysfunction caused by a dysregulated host response to infection,' [4▪] its objective identification is based on a change in the [sepsis-associated] Sequential Organ Failure Assessment (SOFA) score [5] of two points or more for patients in an ICU and a quick SOFA (qSOFA) score of two or more for patients outside of the ICU, when there is presumed or suspected infection [4▪]. Table 1 specifies the SOFA, qSOFA, and Systemic Inflammatory Response Syndrome (SIRS) criteria. These were the basis of a clinical diagnosis of sepsis since the original 'Sepsis-1'criteria were established in 1992 [6]. A subsequent revision established parameters to support a SIRS response, but retained SIRS, suggested restraint from using laboratory measurement of various inflammatory markers (aside from abnormalities of white blood cell count) to define sepsis, and introduced a framework for evaluating sepsis based on predisposition, pathogen, host response, and organ dysfunction [7]. The evolution of these criteria and considerations

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KEY POINTS

- New criteria for sepsis codify an evolution in the understanding of the disorder.
- Resuscitation remains an important component of sepsis management, and balanced crystalloids appear superior to hyperchloremic solutions.
- Steroid administration reverses shock in some sepsis patients, but specifics as to which patients will benefit are uncertain.
- Angiotensin II, vitamin C, and thiamine are all therapeutics demonstrating uncertain, albeit promising results.
- PCT monitoring may help distinguish sepsis from nonseptic inflammation.

reflects an increased understanding of the role and biology of sepsis.

Sepsis-3 separates severe infection from sepsis based on the presence of organ dysfunction, previously the criteria for 'severe sepsis.' Unhitching sepsis from SIRS excludes patients with nonspecific changes in inflammatory criteria, removes the emphasis on inflammation, emphasizes the dysregulated response to infection, and establishes organ dysfunction, rather than less significant changes in physiology, as the essential criteria for sepsis. SIRS has proven to be insensitive and nonspecific for clinically important outcomes [3,8] and the Sepsis-3 authors sought to correlate their criteria to mortality and length of stay in the ICU, using large databases. The inflammation of SIRS is likely adaptive, and in sepsis is associated with concomitant anti-inflammatory responses. qSOFA criteria specifically relate to the most likely manifestations of organ dysfunction in each of the main organ systems: neurologic, cardiovascular, and respiratory. Abandoning an emphasis on inflammation frees discussion and research to seek clarification about the essential pathobiology of sepsis. Since publication in 2016, these criteria have been replicated in the emergency department [9], and in low and middle-income countries [10], but continue to be controversial [11▪,12▪].

Septic shock in Sepsis-3 encompasses circulatory dysfunction, based on a mean arterial pressure less than 65 mmHg or sustained need for vasopressor therapy in the absence of hypovolemia, and an elevated serum lactate level (>2 mmol/l). The authors describe septic shock as 'a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.' Adding metabolic abnormalities to the definition highlights the roles of cellular dysfunction and energy failure. Although these criteria correlate with increased odds of mortality, it is still unclear whether septic shock is any different from a very bad case of sepsis.

Although SIRS is not a part of the Sepsis-3 criteria, it is still useful to describe a host inflammatory response to damage or infection. It has a role in describing physiology that might lead to sepsis, and is also relevant in the context of understanding responses to tissue damage from noninfectious sources. Sepsis-3 does not impeach the idea of SIRS. It unhitches it from a serious and severe, albeit different, clinical entity. There is still no gold standard that can define sepsis. None of these clinical criteria are meant to be perfect in discriminating patients with the disease from those without, nor in calibrating their risks across a spectrum. Rather, the new criteria dispel incorrect assumptions and allow further exploration of the uncertainties in the pathobiology of the disease. They enhance the potential of improving precision around incidence and outcomes, where there exists opportunity for improvement.

FLUID RESUSCITATION/ACUTE KIDNEY INJURY

An important component for the management of sepsis is fluid resuscitation. Several recent trials investigated crystalloid administration. As with any therapeutic, there are hazards and benefits to fluid administration. Excess negatively impacts cardiac and renal physiology. During resuscitation, when a patient's circulation is no longer fluid responsive, hazard outweighs benefit [13,14]. Cardiac myocytes overstretch, resulting in worsening myocardial performance. Pulmonary edema affects arterial oxygenation, and interstitial edema impairs cellular oxygenation [13,14]. 2016 Society of Critical Care Medicine (SCCM) guidelines support conservative fluid management in acute respiratory syndrome (ARDS) with resolution of shock, and after resolution of shock [15▪▪,16]. There is evidence for conservative fluid management during organ dysfunction, and lower cardiac filling pressures result in improvements in lung function for patients in ARDS [13]. Many experts suggest a cautious approach to fluid resuscitation in sepsis, and an emphasis on late conservative fluid management with timely 'de-resuscitation' [17].

There may be clinical significance to the type of resuscitative fluid used in sepsis. The two major subgroups of crystalloids commonly administered are 0.9% normal saline and crystalloids with lower chloride concentration (e.g., Lactated Ringers, Plasma-Lyte 148, Drug Manufacturer Baxter, Deerfield, Illinois USA). Our body's serum plasma has a

Table 1. Sequential Organ Failure Assessment, quick Sequential Organ Failure Assessment and Systemic Inflammatory Response Syndrome criteria, and sepsis criteria

SIRS	SOFA	Score 1	Score 2	Score 3	Score 4	qSOFA
Temperature $<36^{\circ}C$ (96.8°F) or $>38^{\circ}C$ (100.4°F)	Respiration PaO_2/FiO_2 (mmHg)	<400	<300	<200 With respiratory support	<100 With respiratory support	SBP ≤100 mmHg
Heart Rate >90/min	Coagulation Platelets, X $10^3/mm^3$	<150	<100	<50	<20	Respiratory rate ≥22/min
Respiratory Rate > 20/min or $PaCO_2$ < 32 mmHg (4.3 kPa)	Liver Bilirubin, mg/dl (μmol/l)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (>204)	Altered mentation Glasgow Coma Scale Score ≤ 13
White blood cell count $< 4 \times 10^9$/L or $> 12 \times 10^9$/l or > 10% immature neutrophils (bands)	Cardiovascular Hypotension	MAP < 70 mmHg	Dopamine ≤ 5 μg/kg/min Or any dose Dobutamine	Dopamine > 5 μg/kg/min Epinephrine ≤ 0.1 μg/kg/min Norepinephrine ≤ 0.1 μg/kg/min	Dopamine > 15 μg/kg/min Epinephrine > 0.1 μg/kg/min Norepinephrine > 0.1 μg/kg/min	
	Central nervous system Glasgow Coma Scale Score	13–14	10–12	6–9	< 6	
	Renal Creatinine, mg/dl (μmol/l) or Urine output (ml/day)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or < 500 ml/day	> 5.0 > (440) or < 200 ml/day	
Sepsis-1 (6): Two or more SIRS criteria in response to the presence of infection.						
Sepsis-2 (7): Two or more SIRS criteria, along with the presence or suspicion of infection. Additionally, general, inflammatory, hemodynamic, organ dysfunction, and tissue perfusion variables establish criteria to support a diagnosis.						
Sepsis-3 (4): Presumed or suspected infection along with a change in SOFA score of 2 or more points (or a score ≥ 2 if baseline is unknown) in the ICU, or qSOFA score of 2 or more outside the ICU.						

For SOFA, no points are awarded if the criteria exceed the thresholds for 1 point; for the SOFA cardiovascular category, adrenergic agents should be administered at least 1 h.
MAP, mean arterial pressure; qSOFA, quick SOFA; SIRS, Systemic Inflammatory Response Syndrome; SOFA, [Sepsis-associated] Sequential Organ Failure Assessment.
Adapted with permission from (Crit Care Med, 1992. 20(6):864–874; Angus, D., Crit Care Med, 44(3):e113–e121) and [5].

chloride concentration ranging from 94 to 111 mmol/l, whereas the 0.9% normal saline has a concentration of 154 mmol/l, Lactated Ringers 109 mmol/l, and Plasma-Lyte 98 mmol/l. Chloride-rich saline may produce detrimental effects on renal function and worsening effects on mortality [18–20]. High chloride concentration leads to renal vasoconstriction in animal models [21].

Two recent trials compared balanced (Lactated Ringers, Plasma-Lyte) crystalloids with saline for resuscitation. [22▪,23▪] In both cases, a modest difference in composite outcomes suggested a weak effect favoring the lower chloride solutions. The primary endpoint of major adverse kidney events within 30 days was 14.3 vs. 15.4% [odds ratio (OR) 0.9, 95% confidence interval (CI) 0.82–0.99, $P = 0.04$] in favor of the balanced crystalloids group for the balanced crystalloids versus saline in critically ill adults (SMART) trial [22▪]. The balanced crystalloids versus saline in noncritically ill adults (SALT-ED) trial focused on noncritically ill patients in the emergency department and similarly reported a weak effect favoring balanced crystalloids for major adverse kidney events (4.7 vs. 5.6%; OR, 0.82; 95% CI, 0.70–0.95; $P = 0.01$) [23▪]. In neither trial were the cumulative volumes of crystalloids particularly large: medians of 1000 ml and 1079 ml, respectively. Such a volume of saline would be expected to raise serum chloride little more than 2 mEq/dl, suggesting any effect would be surprising. Even the modest number of 94 patients needed to treat may be clinically important in this context. The subgroups with preexisting renal disease and sepsis demonstrated further benefit suggests that the potential for this low-cost intervention should be investigated further. Concerns of causing hyperkalemia by giving Ringers solution (potassium 4.0 mEq/l) may be exaggerated in comparison to risks of renal failure or death.

STEROIDS IN CRITICAL ILLNESS

Administration of steroids in sepsis is a common, but largely unsettled, practice. Although it is clear that mineralocorticoid and glucocorticoid secretion, disposition, and response are altered during sepsis, there are arguments for and against administration. Steroids reduce vasoconstrictor use and improve SOFA scores [24▪▪], and might improve mortality in septic shock [25,26]. They also lead to hypernatremia, hyperglycemia, and neuromuscular weakness [24▪▪]. Among concerns is the identification of patients likely to benefit [26]. The specific role of mineralocorticoids in combination with glucocorticoids, an ideal diagnostic approach, and translation of reversal of shock to more patient-important outcomes remain unresolved. Mortality may not be the best investigational endpoint [27], as mechanisms underlying steroid benefit remain unclear.

Two recent clinical trials addressed steroids in sepsis with mixed results. A trial of hydrocortisone and fludrocortisone demonstrated a mortality benefit in the first 24 h of sepsis (43 vs. 49.1%, relative risk 0.88, 95% CI 0.78–0.99) [28▪], whereas the second trial assessed hydrocortisone by continuous infusion, demonstrating no benefit on mortality (27.9 vs. 28.8%, OR 0.95, 95% CI 0.82–1.1) [29▪]. Both trials included patients on vasopressor therapy, but doses of norepinephrine were higher in the positive study, suggesting that the early use of steroids, in the sickest patients, may reduce mortality. The SCCM guidelines continue to recommend IV hydrocortisone for septic shock unresponsive to fluid resuscitation [15▪▪,24▪▪,30].

ANGIOTENSIN II

After judicious resuscitation, the primary approach to maintaining arterial pressure in septic shock is through the use of vasoactives, ostensibly to reverse pathologic vasodilation. Vasoconstrictors can normalize what is measured (arterial pressure), but mixed evidence repeatedly suggests that this metric is imperfect. Currently, norepinephrine, vasopressin, and epinephrine are recommended vasoconstrictors in septic shock [15▪▪]. The prospect of another agent, acting by a separate mechanism, might improve resuscitation, particularly in patients refractory to traditional medications and in extreme, refractory shock states. A recent prospective, double-blinded, randomized trial of 344 patients demonstrated a significant mean arterial pressure response in favor of angiotensin II (69.9 vs. 23.4%, $P < 0.001$; OR, 7.95; 95%CI 4.76–13.3) [31▪]. The study targeted patients with high cardiac indices (>2.3 l/min/m^2) after fluid resuscitation [25 ml/kg crystalloid, mixed venous oxygen saturation (SvO_2) >70%]. Not all shock includes elevated cardiac output, and the negative effects of vasoconstriction on lower cardiac output states would not be unveiled by this study. There is no evidence that the drug changes mortality, incidence of acute kidney injury, or even total SOFA scores. Angiotensin II was awarded Food and Drug Administration (FDA) approval with a caution regarding increased venous and arterial thromboembolic events (12.9 vs. 5%) [32] and a statement that it should be used with concurrent venous thromboembolism prophylaxis. Sepsis frequently includes a hypercoagulable state, so that there may be real risks to administering a potentially prothrombotic drug.

VITAMIN C/THIAMINE

Vitamin C and thiamine enjoy renewed interest as therapies for sepsis. Vitamin C is thought to play an integral role for maintenance of the endothelium, and depletion may contribute to capillary leak [33–35]. Its administration may be beneficial in burns, trauma, and sepsis [34–36]. Thiamine (vitamin B1) depletion appears to be common in sepsis [37], and deficiencies may contribute to mitochondrial metabolic impairments, and cause lactic acidosis [38▪]. Repletion may increase lactate clearance [38▪,39]. New data suggest that IV vitamin C, hydrocortisone, and IV thiamine synergistically improve metabolic and functional circulatory impairments in septic shock [40▪]. The time to vasopressor reduction was 54.9 ± 28.4 h in the control group compared with 38.7 ± 6.5 h in treatment group, and mortality was dramatically reduced (adjusted OR 0.13; 95% CI 0.04–0.48) [40▪]. Extraordinary claims demand extraordinary evidence and these improvements, observed in a before/after study [40▪], await prospective trial replication. In addition, the relative low costs of vitamin C and thiamine are attractive. Among concerns, vitamin C can precipitate oxalate formation and worsen renal failure [40▪,41].

An additional observational study of thiamine given in septic shock improved lactate clearance and reduced 28-day mortality (hazard ratio 0.67, 95% CI 0.49–0.91) [38▪], results that await prospective replication. Early trial efficacy of this magnitude is rarely, if ever, validated over time. Such unprecedented efficacy would be welcome for a challenging disease, and an alternative to fluid resuscitation as a response to hyperlactatemia.

PROCALCITONIN

Early administration of antibiotics decreases mortality in sepsis. Delays in therapy for septic shock patients can lead to mortality rates as high as 7% per hour for the first 6 h [42]. De-escalation of therapy at the time of clinical improvement is less clear, and clinicians frequently rely on judgment. Procalcitonin (PCT) levels, produced predominately by the thyroid gland but also the lungs and intestines, rise during acute tissue inflammation and tissue injury [43,44]. PCT levels may prove to be a more accurate biomarker that can distinguish between nonspecific inflammation and bacterial infection. A PCT assay, recently approved by the FDA, has led to increasing use of this tool for both initiation and de-escalation of antibiotic therapy [45▪,46]. Evidence does not support a reduction in mortality when clinicians use PCT-based algorithms; however, results are from data too heterogeneous to provide guidance as to which patients may benefit. Overall, the data suggest that PCT guidance reduces unnecessary antibiotic exposure (7.35 vs. 8.85 days, 95% CI (−2.27 to −0.71); $P < 0.001$) [45▪]. SCCM guidelines endorse the use of the PCT assay to limit antibiotic exposure in patients with sepsis, and de-escalation of antibiotic therapy in patients originally presumed to have sepsis [15▪▪]. Although this assay is another added tool to limit antibiotic exposure and a trigger to treat infection prospectively, it should not replace clinician judgment. The Infectious Disease Society of America recommends clinical criteria alone in diagnosis, but follow-up in treatment can be accompanied by PCT to guide therapy [47,48].

CONCLUSION

Clinical approaches to sepsis continue to advance. A dysregulated host response to infection causing organ damage now helps to further define the disease. Sepsis-3 provides a framework for asking scientific questions and separating noninfectious inflammation from an infectious source. New evidence revisits established therapies for sepsis such as IV fluid administration and steroids, and new treatments including angiotensin II, vitamin C, thiamine, and the role of PCT as guide for antimicrobial therapy. Balanced crystalloids appear to be superior to hyperchloremic solutions. Steroid use has been controversial; however, early use in sepsis reverses shock in patients. Angiotensin II is a new vasoconstrictor to raise blood pressure, but may risk a prothrombotic state. Vitamin C and thiamine may improve metabolic abnormalities, but need further validation before routine use. PCT assays reduce antibiotic exposure and may help discern between sepsis and nonsepsis inflammation.

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Conflicts of interest

There are no conflicts of interest.

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