Common Sense Approach to Managing Sepsis

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KEYWORDS

• Sepsis • Resuscitation • Hemodynamic monitoring • Antibiotics • Critical care • Fluids

KEY POINTS

- Sepsis is frequent and deathly.
- The clinical management of patients with sepsis may be guided by applying the Surviving Sepsis Campaign guidelines together with common sense and flexibility based on patient-specific and setting-specific characteristics.
- Use 250-mL to 500-mL fluid boluses; continue only if there is clinical improvement.
- Use norepinephrine.
- Give broad-spectrum antibiotic early; de-escalate when the microbe is identified or the patient improves.

Sepsis is a syndrome, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] It is a global health challenge resulting in many deaths, prolonged suffering among survivors and relatives, and high use of resources both in developed and developing countries.[2,3]

Patients with sepsis may progress in disease severity from infection with a modest degree of organ dysfunction and in-hospital mortality of approximately 10% to severe circulatory impairment (ie, septic shock), to mortality rate above 40%.[4] This chain of progression represents a window of opportunity, in which correct identification of the patient and appropriate interventions and monitoring are likely to improve outcomes. Thus the recently updated clinical practice guidelines from the Surviving Sepsis Campaign (SSC) categorize sepsis and septic shock as medical emergencies for which treatment and resuscitation should begin immediately.[5] The diagnosis and care of patients with sepsis is complex because of the pathophysiologic involvement

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of several organ systems and many of the biological processes are far from understood.[6,7] Diagnosis and care are also complex because patients present with sepsis to different settings in the health care system (eg, prehospital, emergency department, operating room, ward, or intensive care unit [ICU]). The patients, therefore, have to be identified and cared for by different health care professionals.[7] Together this may lead to delayed diagnosis and less optimal treatment and care pathways for patients with sepsis.

The key items in the initial management of the patient with sepsis are microbiological culture and antibiotics, hemodynamic monitoring and interventions, source control, and supportive care, which for the severe cases most often occur in an ICU.

This narrative review discusses how to optimize the management of patients with sepsis by the application of the updated SSC guidelines and common sense.

THE SURVIVING SEPSIS CAMPAIGN GUIDELINES AND CARE BUNDLES

The 2016 SSC guidelines article represent the work of a consensus committee of 55 international experts representing 25 international organizations.[5] The guidelines are based on the best available evidence systematically synthesized and presented using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach,[8] which was facilitated by methods experts. The 93 specific suggestions and recommendations are rarely supported by high-quality evidence. Only 7 are based on high-quality evidence, 28 on moderate evidence, and 58 on low-quality or very-low-quality evidence. Only 4 of the 26 statements on initial management, that is, screening, diagnosis, initial resuscitation, antibiotics, and source control, are based on moderate or high-quality evidence; the vast majority is based on low-level or very-low-level evidence. Also, there are 4 strong recommendations based on low-level evidence,[5] 1 of which is on initial fluid management, that is, the use of a fixed volume of 30 mL/kg for all patients with septic shock.

To operationalize the guidelines, SSC care bundles were developed together with the Institute for Healthcare Improvement. After the 2015 revision, the bundles now consist of 7 specific management goals to be completed before 3 hours or 6 hours within diagnostics (lactate measurement and blood culture), interventions (broad-spectrum antibiotics, fixed volume fluids, and vasopressors), and reassessment of the circulation in case of severe impairment (http://www.survivingsepsis.org/Bundles/Pages/default.aspx). In the 2016 guidelines, only 2 of the 7 items included in the revised bundles were graded as moderate quality of evidence (use of antibiotics and vasopressors); the remaining 5 were graded as low quality or very low quality of evidence.[5] Adherence in clinical practice to the items in the bundles has repeatedly been found to be low even with the use of focused implementation strategies.[9–11] The low compliance rates may indicate that the SSC guidelines are not standard of care in all settings.

HOW SHOULD THE SURVIVING SEPSIS CAMPAIGN GUIDELINES BE USED?

There has been vivid debate about how clinicians and heath care systems should use clinical practice guidelines, such as the SSC guidelines. On one hand, guidelines may be seen as a tool to provide the clinical application of the evidence base synthesized by experts through clear recommendation.[12] On the other hand, often guidelines are outdated, may contain few recommendations based on high-quality evidence, and may be used for legal or restrictive administrative purposes.[12] Guidelines may be colored by academic and fiscal conflicts of interest, and some investigators have argued that they cause regression toward the mean of care — poor performing

centers improve while good performing ones get worse — and that guidelines hamper the conduct of clinical trials because uncertainties are rarely acknowledged in the guidelines.[13,14]

Some of the arguments from the guidelines pros and cons may be dampened by increasing emphasis on the World Health Organization definition of a clinical practice guideline (Version: 10 March 2003): "Guidelines are systematically developed evidence-based statements which assist providers, recipients and other stakeholders to make informed decisions about appropriate health interventions." Thus, clinical practice guidelines should assist and not mandate care; they are guidance to the clinicians. Applying this to the SSC, the 2016 guideline article is an extensive, fully updated document that may assist clinicians in delivering the best care to the patients with sepsis while adding flexibility based on patient-specific and setting-specific characteristics.

Where the SSC guidelines should advise clinicians, the SSC bundles may be another issue, because these quality-improvement tools may easily be used to mandate and measure care. Observational data suggest that adherence to the SSC guidelines and bundles is associated with improved outcome, despite low adherence to the items in bundles.[9–11] This challenges the outcome results, in particular because none of the bundles' items has been shown to improve outcomes in randomized trials, and observational data may overestimate the relative intervention effects by as much as 30%.[15,16] When coupled to outcome reports based on observational data with inherent high risk of bias,[9] then a self-fulfilling prophecy may be created. Interventions based on low-quality evidence recommendations may be mandated and further supported by low-quality evidence as is the case, for example, in fixed-volume fluid resuscitation in the SSC bundles and guidelines.[5] Forcing care based on lower-quality evidence may cause harm as suggested with certain antibiotics for pneumonia,[17] and the inclusion of tight blood sugar control in the original SSC bundle items.[18] It is, therefore, appropriate to raise concerns about mandating sepsis care items without high-quality evidence.[19]

HOW TO MANAGE THE PATIENT WITH SEPSIS?

What should clinicians managing patients with sepsis do when international standards are based on such uncertain evidence? With the Hippocratic Oath, they have promised to abstain from doing harm. For patients with septic shock, this is particularly difficult because of the uncertain risk-benefit ratio for interventions used in the initial management. In addition, the decision of whether or not to administer an intervention has to be balanced against the potential dire consequences of delaying interventions in these patients.[7] On the other hand, a constant theme in recent years is that less is often more in critical care. As many standard interventions and therapeutic targets in critical care are being challenged, simplifying care becomes increasingly rational both from patient, organizational, and financial perspectives.[7] How to use some of the specific items of the SSC guidelines together with a commonsense approach to aid clinical management of patients with sepsis while trying to balance the potential benefit and harm of the items is discussed.

IDENTIFICATION OF PATIENTS WITH SEPSIS

Although the updated definitions of sepsis and septic shock (Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3])[1] should be applied in the broader context, the clinician standing in front of a sick patient should not rely solely on these or the previous syndrome criteria, because they were developed

at a population level. Any patient with potential infection who seems very sick, that is, with new-onset warning signs or organ dysfunction (Fig. 1), will likely benefit from additional diagnostic work-up focusing on the circulation, markers of organ dysfunction, blood and other relevant cultures, and the most likely focus of infection. Importantly, the progression of sepsis is time dependent, so clinical reassessment should be planned within a short time frame and communicated to the entire clinical team.

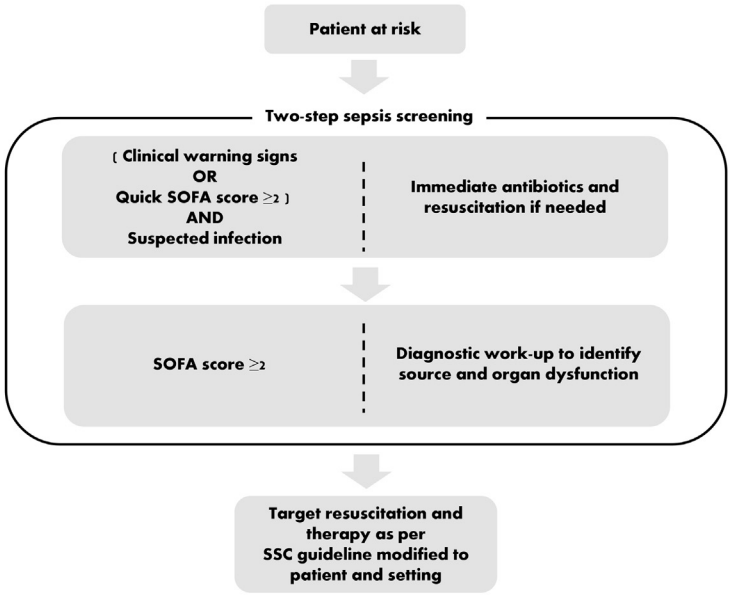
INITIAL RESUSCITATION AND ONGOING CIRCULATORY MANAGEMENT

Because patients with septic shock have been consistently documented to have higher mortality than those with sepsis,[4] vigilant hemodynamic monitoring and intervention continue to be a central part of management of these patients and of the SSC guidelines. There is low-quality or very-low-quality evidence for 14 of the 20 statements in the guidelines on initial resuscitation, fluids, vasoactive drugs, and steroids. This is an obvious challenge, because some of the interventions used in these patients were shown ineffective or even harmful when a higher level of evidence was obtained from clinical trials and systematic reviews.[20–25]

Fluid Therapy

- For initial resuscitation, the SSC guidelines recommend at least 30 mL/kg of crystalloids be given to all patients with sepsis-induced hypoperfusion in the first 3 hours.[5] The physiologic rationale may be that all patients with sepsis-induced hypoperfusion are hypovolemic, but this may not be correct.[26] The evidence to support this recommendation is weak and comes from observational data and the notion that this volume was the average baseline fluid volume observed in the recent early goal-directed therapy (EGDT) trials (median 28 mL/kg given in the 3 trials combined),[27] in which overall low mortality was observed. Thus, more than half of the patients received less than the recommended 30 mL/kg, which may be in line with a large cohort study from a national US registry showing an average fluid volume of 4.4 L given on the first day in ICU.[28] Thus, the initial 30 mL/kg of fluids may not be current practice in many settings. More worrying, the only randomized trial done on fluid bolus versus no fluid bolus in sepsis-induced hypoperfusion indicated increased mortality with fluid bolusing.[29] This trial was done in children in sub-Saharan Africa, so the generalizability to adults with sepsis in more developed settings is unknown.
- For ongoing fluid therapy, the SSC recommends using fluid challenges as long as hemodynamic factors continue to improve. The physiologic rationale is likely that fluids given to maximize cardiac output are beneficial, which may have some support in the perioperative setting.[30] But the EDGT protocol, in which fluids, inotropes, and blood were given to optimize hemodynamic factors, was no better than usual care in patients with early septic shock in the recent large multicenter trials, neither overall nor in several subgroups based on disease or shock severity.[27] Furthermore, the recent CLASSIC trial showed that a protocol restricting fluid input after the initial resuscitation was feasible in ICU patients with septic shock and was associated with improved kidney function compared with a standard care protocol.[31] The hemodynamic parameters were identical in the 2 groups after randomization, indicating that additional fluid after the initial resuscitation did not result in improved circulation, at least not in terms of blood lactate level, vasopressor dose, or urine output.[32]
- A common-sense approach to fluid therapy in patients with sepsis-induced hypoperfusion is to give 250-mL to 500-mL boluses followed by regular

A



B

Organ system	Clinical warning signs	Quick SOFA variables	SOFA variables
Central nervous system	Altered mental state	Altered mental state	Glasgow Coma Scale Score
Respiration	Dyspnea High respiratory rate Hypoxia Expectoration of pus	Respiratory rate (>22 min^{-1})	PaO_2/FiO_2-ratio
Cardiovascular	Cold extremities Mottling Tachycardia Lactate above 2 mM Delayed capillary refill	Systolic blood pressure (<100 mm Hg)	Mean arterial pressure Administration of vasopressors (type and rate of infusion)
Renal	Low urine output High s-potassium High s-creatinine Metabolic acidosis		S-creatinine Urine output
Coagulation	Bleeding Suggillations Petechiae		Platelet count
Liver	Jaundice		S-bilirubin
Other	Fever Chills Shivering Patient feeling severe acute sickness		

Fig. 1. Identifying sepsis among patients at risk being it in the ward, emergency department, operating room, or ICU. (*A*) Proposed flow chart for identifying sepsis in patients with clinical warning signs and suspected infection. Quick SOFA, SOFA variables, and suggested clinical warning signs are presented (*B*). SOFA, Sequential (Sepsis-related) Organ Failure Assessment. (*Modified from* Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801–10.)

reassessments of the circulation (Table 1). If a patient has had a documented fluid loss, then a fixed volume may be given to replace the documented loss. Although many patients improve their circulation with some fluid, those who do not should not receive any more because these patients may be at particular

Table 1
A common sense approach to the initial management of patients with sepsis

Identification of patients with sepsis	All patients with potential infection who seem very sick should have a diagnostic work-up focusing on the circulation, markers of organ dysfunction, blood culture, and the most likely focus of infection.
Fluid therapy	Use 250–500 mL fluid boluses; continue only if the circulation improves. Use fixed volume to substitute documented loss. Use crystalloid solutions (ie, isotonic saline and buffered solution) guided by repeated assessment of base excess and sodium in plasma. Avoid hydroxyethyl starch and gelatin solutions. Aim for fluid restriction and negative fluid balances as soon as the circulation has stabilized.
Vasopressor agents	Use norepinephrine. Early infusion of norepinephrine may be considered for severe hypotension, for example, MAP <50 mm Hg, and for those who have no documented loss of fluid. Peripheral infusion may be considered into a large vein proximal to the antecubital or popliteal fossae while waiting for central access or if a short infusion time is expected. Initially aim for MAP of 65 mm Hg; lower may be acceptable provided a patient is awake and adequately perfusing.
Inotropic agents	It is less likely that inotropic agents result in overall benefit, while the risk of adverse effects is high. Dobutamine may be tried in case of ongoing severe tissue hypoperfusion with signs of low cardiac output. In case of adverse effects, in particular tachycardia, the infusion should be decreased or stopped.
Blood transfusion	Transfuse at Hb threshold of 7 g/dL unless the patient has acute myocardial ischemia during which a higher Hb threshold may be considered.
Hemodynamic monitoring	Use repeated assessment of simple circulatory parameters, including blood pressure, heart rate, temperature gradients on the extremities, mottling, capillary refill time, and lactate.
Antibiotic therapy	Give an broad-spectrum antibiotic as soon as possible De-escalate when the microbe is identified or the patient is improving.

risk of being harmed by too much fluid. For ongoing fluid therapy, increasing evidence suggests a more restrictive approach should be used in preference to a more liberal strategy.[33]

- Crystalloid solutions can be used alone because the synthetic colloid solutions cause kidney and coagulation impairment[34–36] and have been shown to increase mortality with varying certainty (high certainty for hydroxyethyl starch and low for gelatin).[23,37] Albumin is likely safe in sepsis but has no obvious benefits and is an expensive and limited resource.[38] The SSC guidelines do suggest consideration of albumin use in patients expected to require large volumes of fluid.[5]
- As for the crystalloid solutions, both isotonic saline and buffered solutions may be used because they appear to cause no differences in outcome.[5,39] It may be rational to give patients with severe acidosis buffered solutions and isotonic saline to those at risk of severe hyponatremia.[40] Thus, ongoing fluid therapy may be guided by repeated assessment of plasma levels of base excess and sodium.

- Aiming at negative fluid balances may be of value for patients who have a positive fluid balance and are hemodynamically stable because such strategies may shorten the time of mechanical ventilation without increasing mortality.[33]

Vasopressors

- Norepinephrine is recommended as the first-line vasopressor in patients with septic shock in the SSC guidelines and in other clinical practice guidelines.[5,41] This choice should be uncontroversial because dopamine is associated with harm compared with norepinephrine,[21] and the overall benefit versus harm of other alternatives (eg, vasopressin analogs and phenylephrine) has been inadequately assessed.[41] The more challenging questions are when to start the norepinephrine infusion and what endpoints should be targeted where evidence from trials are limited.
- Early infusion of norepinephrine may be considered for sepsis patients with severe hypotension, for example, mean arterial pressure less than 50 mm Hg because very severe hypotension may pose a direct threat to a patient's life. In particular, patients with no documented fluid loss should be considered for early norepinephrine. In those who have a higher mean arterial pressure (MAP) and/or documented loss of fluid, IV fluid bolus(es) may be given before the initiation of norepinephrine, as described previously.
- A peripheral venous infusion may be considered to facilitate early initiation of norepinephrine while waiting for central access or if a short infusion time is expected. Taken together, the results of a cohort study and a systematic review of case series suggest that peripheral infusion of vasopressors may be safe if given into a large vein proximal to the antecubital or popliteal fossae for a few hours only, during which the infusion site should be monitored.[42,43] Such an approach has been suggested in the guidelines of the Canadian Association of Emergency Physicians.[44]
- Initially, aim for MAP of 65 mm Hg. To obtain this, patients should be allowed to have values of MAP both below and above 65 mm Hg; if not, patients will likely have time-averaged means of MAP well above the target as has been observed in recent MAP target trials.[45,46] The overshoot observed in these trials hampers interpretation of their results. Thus, there is no good evidence to support any particular level of MAP, but increasing doses of norepinephrine seem to result in increased rates of adverse effects (eg, atrial fibrillation).[45,46] Therefore, the lowest possible MAP target should be accepted as long as the patient is awake and makers of perfusion and kidney function remains unaltered. With this approach, some patients can be handled with MAP target below 65 mm Hg, whereas other patients (eg, those with chronic hypertension) may need a higher target.[45]

Inotropes

- The use of inotropes in patients with septic shock should be carefully considered because there are no placebo-controlled trials showing their efficacy, and safety. Recent trials in patients with septic shock and in patients with impaired heart function prior to or after cardiac surgery indicated no beneficial effects from levosimendan and even harm in those with septic shock.[47–49] Based on a physiologic rationale, the SSC guidelines suggest using dobutamine in patients with evidence of persistent tissue hypoperfusion despite adequate fluid loading and the use of vasopressor agents.[5] One strategy of applying this concept was extensively accessed in the EGDT trials; however, outcomes were not improved by the

use of dobutamine in patents in the EGDT groups who had a persistently low central venous oxygen saturation ($ScvO_2$) compared with patients in the usual-care groups.[27] Judging the effects of dobutamine based on the EGDT trial is not straightforward; however, the results of a recent propensity-adjusted cohort study suggested increased mortality with the use of dobutamine in patients with septic shock.[50] Taken together, it is less likely that the use of inotropes (ie, dobutamine, levosimendan, and milrinone) improves patient-important outcomes yet the risk of harm is imminent.

Blood Transfusion

- Transfusion with red blood cells should be performed at a hemoglobin (Hb) level of 7.0 g/dL.[5,24,25,51] There is limited evidence that extenuating circumstances should alter this threshold level except for ongoing myocardial ischemia, during which a higher Hb threshold for transfusion may be considered.[52] There is limited evidence for the use of alternative triggers of transfusion other than Hb.

Hemodynamic Monitoring

- The repeated assessment of circulatory parameters is likely to be important in guiding therapy; this may be done using simple markers of perfusion including lactate (see **Table 1**). Urine output may be used, but it may result in overtreatment, because oliguria may be due to causes other than a low renal blood flow in sepsis.[26]
- On the other hand, it is less likely that more advanced hemodynamic monitoring improves outcomes of patients with septic shock. No hemodynamic target used to guide therapy has been shown to improve outcomes of patients with sepsis. Guidance by $ScvO_2$ monitoring, at least as part of the EGDT protocol,[27] and guidance using cardiac output, at least in general ICU patients and those with early shock,[53,54] does not lead to improved outcomes. The use of alternative strategies, such as echocardiography, has not been tested in trials of sepsis resuscitation. Furthermore, the validity of some of the measures obtained by echocardiography may be questioned.[55,56] The use of markers predictive of fluid responsiveness has shown proof-of-concept,[57,58] but it is still unknown if outcomes are improved by applying these in the management of patients with sepsis.

ANTIMICROBIAL THERAPY

- Broad-spectrum antibiotic therapy should be given as soon as possible to patients with septic shock because this, together with source control, is the only specific intervention against sepsis.[5] The choice of antimicrobial cover should be made according to the likely focus of infection and knowledge about the local antibiogram, in particular the likelihood of infections with multiresistant bacteria. If needed, more than 1 antibiotic may be given to broaden the cover, but there is limited evidence supporting the use of combination therapy with the specific aim of covering the suspected microbe with more than 1 antibiotic.[59]
- Antibiotic cover should be narrowed as soon as the pathogenic microbe has been identified or the patient has improved.[5] If repeated sampling of procalcitonin is used, there is evidence to suggest that antibiotics may be stopped when procalcitonin is normal or has decreased below 80% of the peak value.[60,61] This protocol will likely reduce the use of antibiotics without adverse effects on patient outcomes.

PERSPECTIVE

The clinical management of patients with sepsis and septic shock may be guided by applying the SSC guidelines together with common sense and flexibility based on patient-specific and setting-specific characteristics. A balanced approach is particularly important in areas of uncertainty of which there are still many, as exemplified by the low number of recommendations in the guidelines supported by high-quality evidence.[5] These areas of uncertainty should be broadly acknowledged for clinicians, clinical researchers, and policy makers to act cautiously and together point to the interventions needed to be tested in trials. The aim should be to assess as many current and novel interventions for sepsis as possible in large, multicenter, randomized trials with the lowest possible risk of bias. The results of such trials should improve clinical practice guidelines and patient care and outcomes.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801–10.
2. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–71.
3. Prescott HC, Langa KM, Liu V, et al. Increased 1-year healthcare use in survivors of severe sepsis. Am J Respir Crit Care Med 2014;190:62–9.
4. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:775–87.
5. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77.
6. Perner A, Gordon AC, De Backer D, et al. Sepsis: frontiers in diagnosis, resuscitation and antibiotic therapy. Intensive Care Med 2016;42:1958–69.
7. Perner A, Rhodes A, Venkatesh B, et al. Sepsis: frontiers in supportive care, organisation and research. Intensive Care Med 2017;43:496–508.
8. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.
9. Levy MM, Rhodes A, Phillips GS, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Intensive Care Med 2014;40:1623–33.
10. Noritomi DT, Ranzani OT, Monteiro MB, et al. Implementation of a multifaceted sepsis education program in an emerging country setting: clinical outcomes and cost-effectiveness in a long-term follow-up study. Intensive Care Med 2014;40:182–91.
11. Rhodes A, Phillips G, Beale R, et al. The surviving sepsis campaign bundles and outcome: results from the international multicentre prevalence study on sepsis (the IMPreSS study). Intensive Care Med 2015;41:1620–8.
12. Shekelle P, Aronson MD, Melin JA. Overview of clinical practice guidelines. UpToDate 2017. 9-5-2017. Ref Type: Online Source.
13. Girbes AR, Robert R, Marik PE. Protocols: help for improvement but beware of regression to the mean and mediocrity. Intensive Care Med 2015;41:2218–20.

14. Bonten MJ. Dangers and opportunities of guidelines in the data-free zone. Lancet Respir Med 2015;3:670–2.
15. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JP. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. BMJ 2016;352:i493.
16. Ziff OJ, Lane DA, Samra M, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015; 351:h4451.
17. Kett DH, Cano E, Quartin AA, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis 2011;11:181–9.
18. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–97.
19. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care–reasons for caution. N Engl J Med 2014;370:1673–6.
20. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. Intensive Care Med 2015;41:1549–60.
21. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779–89.
22. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012;367:124–34.
23. Haase N, Perner A, Hennings LI, et al. Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ 2013;346:f839.
24. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381–91.
25. Holst LB, Petersen MW, Haase N, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ 2015;350:h1354.
26. Perner A, Prowle J, Joannidis M, et al. Fluid management in acute kidney injury. Intensive Care Med 2017;43(6):807–15.
27. The Prism Investigators, Rowan KM, Angus DC, Bailey M, et al. Early, goal-directed therapy for septic shock - a patient-level meta-analysis. N Engl J Med 2017;376(23):2223–34.
28. Marik PE, Linde-Zwirble WT, Bittner EA, et al. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Med 2017;43:625–32.
29. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483–95.
30. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA 2014;311:2181–90.
31. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 2016;42: 1695–705.
32. Hjortrup PB, Haase N, Wetterslev J, et al. Effects of fluid restriction on measures of circulatory efficacy in adults with septic shock. Acta Anaesthesiol Scand 2017; 61:390–8.

33. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med 2017;43:155–70.
34. Rochwerg B, Alhazzani W, Gibson A, et al. Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. Intensive Care Med 2015;41:1561–71.
35. Haase N, Ostrowski SR, Wetterslev J, et al. Thromboelastography in patients with severe sepsis: a prospective cohort study. Intensive Care Med 2015;41:77–85.
36. Mittermayr M, Streif W, Haas T, et al. Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration. Anesth Analg 2007;105:905–17, table.
37. Moeller C, Fleischmann C, Thomas-Rueddel D, et al. How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. J Crit Care 2016;35:75–83.
38. Perner A, Junttila E, Haney M, et al. Scandinavian clinical practice guideline on choice of fluid in resuscitation of critically ill patients with acute circulatory failure. Acta Anaesthesiol Scand 2014;59:274–85.
39. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA 2015;314:1701–10.
40. Burdett E, Dushianthan A, Bennett-Guerrero E, et al. Perioperative buffered versus non-buffered fluid administration for surgery in adults. Cochrane Database Syst Rev 2012;(12):CD004089.
41. Moller MH, Claudius C, Junttila E, et al. Scandinavian SSAI clinical practice guideline on choice of first-line vasopressor for patients with acute circulatory failure. Acta Anaesthesiol Scand 2016;60:1347–66.
42. Cardenas-Garcia J, Schaub KF, Belchikov YG, et al. Safety of peripheral intravenous administration of vasoactive medication. J Hosp Med 2015;10:581–5.
43. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care 2015;30:653.e9-17.
44. Djogovic D, MacDonald S, Wensel A, et al. Vasopressor and inotrope use in Canadian emergency departments: evidence based consensus guidelines. CJEM 2015;17(Suppl 1):1–16.
45. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370:1583–93.
46. Lamontagne F, Meade MO, Hebert PC, et al. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. Intensive Care Med 2016;42:542–50.
47. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. N Engl J Med 2016;375:1638–48.
48. Landoni G, Lomivorotov VV, Alvaro G, et al. Levosimendan for hemodynamic support after cardiac surgery. N Engl J Med 2017;376(21):2021–31.
49. Mehta RH, Leimberger JD, van DS, et al. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med 2017;376(21):2032–42.
50. Wilkman E, Kaukonen KM, Pettila V, et al. Association between inotrope treatment and 90-day mortality in patients with septic shock. Acta Anaesthesiol Scand 2013;57:431–42.

51. Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683–93.
52. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2016;(10):CD002042.
53. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. Cochrane Database Syst Rev 2013;(2):CD003408.
54. Takala J, Ruokonen E, Tenhunen JJ, et al. Early non-invasive cardiac output monitoring in hemodynamically unstable intensive care patients: a multi-center randomized controlled trial. Crit Care 2011;15:R148.
55. Wetterslev M, Moller-Sorensen H, Johansen RR, et al. Systematic review of cardiac output measurements by echocardiography vs. thermodilution: the techniques are not interchangeable. Intensive Care Med 2016;42:1223–33.
56. Wetterslev M, Haase N, Johansen RR, et al. Predicting fluid responsiveness with transthoracic echocardiography is not yet evidence based. Acta Anaesthesiol Scand 2013;57:692–7.
57. Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 2009;37:2642–7.
58. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med 2016;42:1935–47.
59. Sjovall F, Perner A, Hylander MM. Empirical mono- versus combination antibiotic therapy in adult intensive care patients with severe sepsis - a systematic review with meta-analysis and trial sequential analysis. J Infect 2017;74:331–44.
60. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74.
61. De Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819–27.