Review

Mark L. Graber*, Monika Patel and Stephen Claypool

Sepsis as a model for improving diagnosis

https://doi.org/10.1515/dx-2017-0036
Received October 15, 2017; accepted January 4, 2018; previously published online February 6, 2018

Abstract: Diagnostic safety could theoretically be improved by high-level interventions, such as improving clinical reasoning or eliminating system-related defects in care, or by focusing more specifically on a single problem or disease. In this review, we consider how the timely diagnosis of sepsis has evolved and improved as an example of the disease-focused approach. This progress has involved clarifying and revising the definitions of sepsis, efforts to raise awareness, faster and more reliable laboratory tests and a host of practice-level improvements based on health services research findings and recommendations. We conclude that this multi-faceted approach incorporating elements of the 'learning health system' model has improved the early recognition and treatment of sepsis, and propose that this model could be productively applied to improve timely diagnosis in other time-sensitive conditions.

Keywords: diagnostic error; learning health systems; misdiagnosis; sepsis.

Introduction

Diagnostic error is a ubiquitous problem that occurs in every healthcare setting. The National Academy of Medicine concluded that these errors are common and that 'Each of us is likely to experience one or more diagnostic errors in our lifetime, sometimes with devastating consequences' [1]. Efforts to address the problem to date have focused largely on high-level, global issues like raising awareness and promoting adoption of system-related or cognitive strategies to minimize the risk of error [2–4]. A major sticking point is the difficulty of actually measuring the incidence of diagnostic error in practice [5]. As a result, at the present time there is little evidence that these 'global' strategies have had appreciable clinical impact.

An alternative strategy to address diagnostic error is to focus on a single specialty or a specific disease. We propose that sepsis may be an instructive model for this approach, given the increasing evidence that the timeliness of sepsis diagnosis is improving and research evidence that early diagnosis and treatment substantially improves the odds of survival. In this review, we consider how these improvements have been achieved. Improving sepsis mortality reflects progress realized across multiple domains, including enhanced awareness, the development of better diagnostic tests, research advances allowing better definitions and the generation of evidence-based consensus guidelines and tools and ultimately their implementation by healthcare organizations.

The sepsis problem

Sepsis has a devastating annual impact on patients around the world [6, 7]. Depending on the clinical criteria used, there are roughly 850,000 septic patients seen in US emergency departments (EDs) every year, just under 1% of all patients seen [8]. Sepsis is the cause of 20–30% of hospital deaths each year in the US and costs the healthcare system over $24 billion [9]. The Sepsis Alliance, the largest sepsis advocacy group in the US, believes that this disease is the leading cause of death in US hospitals [6]. The key area of focus in the fight against sepsis is early recognition and treatment of infection. The time-sensitive aspect of this disease is crucial because after the onset of severe sepsis, mortality rates increase by 7–10% per hour [10]. Delayed treatment has consistently been found to be the cause of unnecessary death and disability. Around 70% of sepsis cases are community-acquired, and public education and awareness campaigns encourage individuals to seek out treatment early enough to prevent unnecessary harm. The burden then falls to our healthcare system to make the diagnosis as quickly as possible, a goal that in the past has been challenging to meet.

***Corresponding author: Mark L. Graber,** MD, Society to Improve Diagnosis in Medicine, NY, USA; and RTI International, Research Triangle Park, NC, USA, E-mail: graber.mark@gmail.com
Monika Patel: Candidate for the Bachelor's Degree of Arts in Science and Technology Studies, Cornell University, Ithaca, NY, USA
Stephen Claypool: Wolters Kluwer Health, Minneapolis, MN, USA

Clarifying definitions

The beginning of wisdom is to call things by their right names

– Confucius

Credit for improving the diagnosis of sepsis begins with the advances in health services research that have helped define the syndrome and identify septic patients using clinical criteria. Agreement on definitions has been challenging because there is no definitive, 'gold standard' diagnostic test for this potentially fatal syndrome. As a result, there has been substantial variability in how sepsis is defined clinically, how to recognize different stages of sepsis (e.g. early sepsis, severe sepsis, septic shock) and how cases are captured by administrative billing codes. This variability has created controversy over the actual incidence of sepsis, whether the incidence is changing over time and whether or not survival is actually improving. To make the point, studies have identified a two- to four-fold difference in sepsis incidence and a three-fold difference in mortality, depending on the definitions used [11, 12]. Despite the fact that the methods used to identify sepsis yield disparate results, and despite the debate on sepsis incidence, the actual incidence is likely not changing, as evidenced by analysis of the core clinical data [13]. Thus, variability in incidence and mortality are inherent artifacts of the differences in the methods we use to define sepsis. Fortunately, a great deal of time and emphasis has been devoted to understanding the purposes and perspectives of various definitions [14, 15], which has led to more useful and more widely accepted operational definitions. The improved clarity and agreement on these definitions by the research and clinical community has created the standardization needed for meaningful research and its application in clinical practice.

The first national consensus definition of sepsis, 'Sepsis-1', emerged from a conference convened by the American College of Chest Physicians and the Society of Critical Care Medicine in 1991. Sepsis-1 recognized sepsis as a manifestation of infection-related inflammation, termed systemic inflammatory response syndrome (SIRS) [16]. Patients with two or more SIRS criteria were defined as having sepsis, which could proceed to severe sepsis (with organ dysfunction) and with hypotension, to septic shock.

Over the next several years, new physiology-based scoring systems were put into use that contributed to standardizing criteria for sepsis evaluation. These included the Acute Physiology and Chronic Health Evaluation (APACHE) II score [17], the Simplified Acute Physiology Score (SAPS) II [18] and the Logistic Organ Dysfunction System (LODS) [19]. ICD-9 codes for severe sepsis and septic shock were added in 2002 and 2003, respectively, allowing sepsis definitions and case-finding using administrative data sets. The Sepsis-1 definition and criteria were re-evaluated by a second consensus conference with minor changes in 2001 (unofficially known as 'Sepsis-2'), by which time there had been sufficient research to appreciate that the SIRS-based criteria were valuable but associated with an unacceptable number of both false-positive and false-negative results. Indeed, roughly half of all inpatients manifest system inflammatory signs but were not septic [20]. Many conditions were found to activate the same inflammatory pathways, including acute pancreatitis, trauma, alcohol withdrawal and many other conditions. In short, the Sepsis-1 definition detects sepsis with high sensitivity, but it has many false positives due to limited specificity [21].

The most recent iteration of sepsis definitions [22], 'Sepsis-3', moved away from the use of SIRS-based criteria [23]. The Sepsis-3 definition is based on recognition of sequential, sepsis-related, organ functional assessment (SOFA) or a simplified, 'quick' version termed q-SOFA which includes just three parameters reflecting altered mental status, hypotension and increased respiratory rate (Table 1). Sepsis-3 has improved specificity compared to Sepsis-1, but poorer sensitivity, and patients with sepsis are frequently not detected by Sepsis-3 until late in the illness [27]. Sepsis-3 thus identifies a different, 'sicker' cohort of patients, with greater degrees of organ failure and a higher mortality rate. Over half of the patients meeting Sepsis-1 criteria fail to meet Sepsis-3 standards [28].

Although treatment implications are the same in both Sepsis-1 and Sepsis-3 definitions, the two definitions offer different perspectives for understanding the sepsis problem and unique advantages and disadvantages for prognostication, research and epidemiologic studies (Table 1), and it seems likely that both will see continued use until the next iteration evolves [26, 29].

Using the long-standing principle that tests that screen a population for a disease should have high sensitivity so that cases are not missed, whereas confirmatory tests to establish the diagnosis should have high specificity to minimize erroneous diagnoses, perhaps the best utilization of the SIRS-base (Sepsis-1) and SOFA-based (Sepsis-3) definitions would be to use SIRS criteria as a surveillance tool and SOFA criteria to confirm the diagnosis. With this model, all patients within at-risk cohorts would receive routine SIRS-based screening. Prompt treatment and further evaluation would be ordered for all positive cases without waiting for confirmation, but patients

Table 1: Comparison of Sepsis-1 and Sepsis-3.

	Sepsis-1 **1992 [16, 24, 25]**	**Sepsis-3** **2016 [23]**
Definition	The combination of pathologic infection and physiological changes known collectively as the systemic inflammatory response syndrome	Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection Septic shock: a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than from sepsis alone
Clinical criteria	Infection + two or more SIRS markers	Increase in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more q-SOFA: two or three of these criteria: Glasgow Coma Scale score of 13 or less, systolic blood pressure of 100 mmHg or less and respiratory rate of 22/min or greater
Epidemiologic applications	Identifies the widest spectrum of disease, from SIRS through sepsis, severe sepsis and septic shock	Narrower spectrum of sicker patients with fewer false positives and higher mortality
Prognostication	Mortality increases progressively from sepsis to severe sepsis to septic shock	Selects the highest mortality populations, without designating 'severe sepsis or septic shock'
Accuracy	High sensitivity, low specificity, therefore many false positives	High specificity, low sensitivity and often positive later in the course of sepsis; many false negatives
Recommended utilization	Surveillance/screening	Confirmatory diagnosis

Modified from Sprung and Trahtemberg [26].

would not be diagnosed with sepsis until they also meet Sepsis-3 criteria.

Enhanced awareness

If sepsis is indeed a success story of improved diagnosis, efforts to raise awareness have played an outsized role. Awareness campaigns have educated the public at large and have motivated healthcare organizations and their staff to act more aggressively in diagnosis. Designating sepsis as a public health crisis has fostered collaboration and coordination amongst local communities, healthcare providers, medical associations, leading businesses, insurance companies and the government.

Non-profit foundations have taken a leadership role in advocacy. The Rory Staunton Foundation [30], the Coalition for Sepsis Survival [22], the Patient Safety Movement [31] and several others have all developed awareness campaigns focused on early diagnosis.

The impact of this work is evident at the state level, with major initiatives ongoing in New York, Colorado, Illinois and Ohio [30, 32–34]. The Rory Stanton Foundation is the driving force behind the adoption in 2013 of 'Rory's Regulations' in New York State [33]. 'Rory's Regulations' mandate that New York State hospitals use evidence-based protocols when diagnosing and managing sepsis and report on their protocol adherence and clinical outcomes [7]. Similar legislation is pending in New Jersey and Pennsylvania. In Colorado, the Coalition for Sepsis Survival has raised public awareness through partnerships between hospitals and local radio and TV stations [34]. Similarly, Ohio has made demonstrable progress in sepsis management, achieving an 8% reduction in mortality rate through an aggressive education campaign to raise awareness of the disease amongst all levels of healthcare [32]. In Illinois, 'Gabby's Law' requires hospitals to develop evidence-based protocols for the early recognition and treatment of sepsis [35].

The Agency for Healthcare Research and Quality (AHRQ) has served as a sponsor and clearinghouse for efforts to improve diagnosis at the national level through interprofessional meetings, practice initiatives, toolkit development and health services research support. International focus has been provided by the World Health Organization's declaration of sepsis as a global health priority, bringing the need for further action to the forefront of public and political attention [7].

The 'Surviving Sepsis Campaign' (SSC), an international collaboration of leading professional societies and now in its fourth iteration, has been one of the most effective forces in the sepsis battle. As described below (see

Practice improvements directed at early detection), the Campaign has played a major role in promoting awareness, developing standards and guidelines and helping translate advances from research into practice improvement.

The Centers for Disease Control and Prevention launched Get Ahead of Sepsis in August 2017, an educational initiative to protect Americans from the devastating effects of sepsis [36]. This initiative emphasizes the importance of early recognition and timely treatment of sepsis, as well as the importance of preventing infections that could lead to sepsis.

Sepsis awareness campaigns have used a wide range of tools to improve workplace awareness, including posters, identification badge cards with the sepsis bundle elements printed on the backside and even apps [37]. The 'Sepsis Guide' app and *Septris*, an app-based game, are fun and innovative ways to test and improve clinical knowledge about the disease [38, 39].

Better tests

Historically, efforts to identify septic patients centered on the use of blood cultures to detect bacteremia and subsequent sensitivity testing if cultures are positive [40]. The limitations of this approach to diagnosis of sepsis are now well understood, given that culture results are seldom available until the second or third day, false-positive (contaminated) cultures are common and only a minority of patients in septic shock will actually have positive blood cultures. The critical need for earlier, more accurate information has created the impetus to explore alternative approaches to diagnosis, focusing on biomarkers of sepsis, or molecular techniques that can shorten the time to identify pathogenic bloodstream organism from days to hours [41].

Markers of inflammation

Sepsis invokes a systemic inflammatory response that involves a wide range of circulating and cellular inflammatory markers. Although many of these have been investigated for their potential to improve diagnosis, procalcitonin has been the most-studied candidate marker [42]. Procalcitonin increases early-on in the systemic response and has a relatively long half-life, and the absolute levels increase progressively as patients advance from sepsis to advanced sepsis and on to septic shock. Rising levels correlate with bacteremia and poor outcomes and are more reliable than considering a single value. All of these characteristics contribute to its value as a screening test. A recent systematic review concluded that procalcitonin reliably distinguishes infection-related from non-infection-related inflammatory disease response, with a pooled sensitivity and specificity near 80% [43]. However, a randomized trial and another meta-analysis found that using clinical algorithms based upon procalcitonin levels did not affect mortality [44]. Elevated levels (false positives) may also be seen in Addisonian crisis (adrenal failure), certain paraneoplastic syndromes and in patients receiving treatment with certain immunoglobulins or monoclonal antibodies. Therefore, its diagnostic value is controversial. Perhaps the best role for procalcitonin may be as a tool to distinguish infectious from noninfectious conditions, thereby facilitating the decision to de-escalate antibiotic therapy [45]. Presepsin is another soluble marker of the systemic inflammatory response that parallels sepsis severity and predicts clinical outcomes and may be useful for early diagnosis [46].

Molecular tests

Another revolutionary approach to the rapid diagnosis of sepsis are tests using the polymerase chain reaction to amplify genes associated with bacterial or fungal infection. Coupled with novel detection systems, these tests detect bacterial infection with a high sensitivity and specificity within hours, and without incubation. A further advantage is that many of these tests also identify genetic patterns of antibiotic resistance, allowing the choice of the most appropriate antibiotic regimen [47].

More study is needed, though, to understand the role of presepsin and molecular testing in sepsis evaluation.

Practice improvements directed at early detection

To impact outcomes, the many advances in improving awareness and early detection ultimately need to translate into more effective practices on the front lines of the sepsis battle. This work has centered on adoption and use of checklist-based and electronic screening algorithms to identify sepsis at the earliest possible stage. The Surviving Sepsis Campaign (SSC), a collaboration of the European Society of Intensive Care Medicine, the Society of Critical Care Medicine and the International Sepsis Forum, worked with the Institute for Healthcare Improvement (IHI) and published guidelines for diagnostic evaluation

of patients suspected to have sepsis [21, 48]. The National Quality Forum ratified a measure based upon the SSC's guidelines, NQF #500, and it was subsequently adopted by Centers for Medicare and Medicaid Services (CMS) for reporting by US hospitals (CMS Sep-1). These guidelines and performance improvement efforts are associated with improved patient outcomes for sepsis. A recent meta-analysis of 50 observational studies revealed that performance improvement programs resulted in a reduction in mortality [odds ratio (OR) 0.66; 95% confidence interval (CI) 0.61–0.72] [49]. Nurse-driven screening programs are most commonly implemented using either SIRS or Modified Early Warning System (MEWS) scoring [50].

These manual screening methods can improve sepsis outcomes, including mortality [51–53]. Today, using change management methodology to teach nursing staff to routinely screen for sepsis remains the gold standard for detecting insidious cases of sepsis. These programs work; a program using nurse specialists focused on detecting and managing sepsis in patients on the wards and admitted through the ED resulted in all-sepsis mortality rates declining from 12% to 9% [37].

Nurse-based, manual screening is labor intensive, though, and therefore expensive. Furthermore, processes that rely on staff can be late in detecting sepsis, so electronic alerting has frequently been deployed to detect sepsis. Electronic surveillance should, in theory, detect signs of sepsis as soon as vitals and lab abnormalities are available, potentially reducing delays in diagnosis. Indeed, electronic surveillance is known to be very sensitive when SIRS-based criteria are used for alerting parameters, but it is also highly non-specific. Similarly, MEWS-based screening suffers from poor specificity. The majority of hospitalized patients with SIRS criteria do NOT have sepsis [54]. This is because many diseases and medicines cause abnormal vital signs and lab tests. For example, patients with acute pancreatitis, chronic obstructive pulmonary disease (COPD) exacerbations, diabetic keto-acidosis, alcohol withdrawal, trauma, heart failure, end-stage liver disease, pulmonary embolism and even post-operative recovery will all have SIRS or MEWS abnormalities. Similarly, many medicines cause false-positive alarms; albuterol causes tachycardia, warfarin elevates the international normalized ratio (INR) and heparin elevates the partial thromboplastin time (PTT). Almost all patients in the hospital have vitals or lab abnormalities, otherwise they would be treated as outpatients. The net effect of all these confounders is that roughly one-half of the inpatients meet SIRS criteria [55]. If an electronic alerting system is being used to identify sepsis, it causes numerous false-positive alerts; the computer thinks they have sepsis but too often they are just sick from other medical conditions.

Therefore, it is no surprise that a meta-analysis of all eight sepsis alerting studies conducted up to 2015 concluded that none of the alerting systems improved mortality [56]. These programs likely failed because of alert fatigue; clinicians tire of false-positive alerts, so they tend to ignore or over-ride alerts that are too-frequently incorrect.

To reduce false-positive alerts, electronic triggers must consider comorbid medical conditions and medicines when interpreting medical chart abnormalities. Surveillance systems must know when medical conditions are the cause of abnormalities versus when the abnormalities should be attributed to sepsis. These systems need to think like expert physicians. When physicians interpret abnormalities, they consider the impact of chemotherapy on cell counts, they understand how biliary obstruction changes liver tests, they know that sickle cell pain crises cause tachycardia – they know when to NOT attribute abnormalities to sepsis. Although it is complicated, computerized algorithms can be designed to think the same way. They can be developed to have both a high sensitivity and a high specificity and to positively impact outcomes. An expert system incorporating these principles achieved a sensitivity of 95% and a specificity of 82% and resulted in a 50% reduction in sepsis-related mortality in an inpatient setting [57]. According to the systematic review, this is the first and only electronic surveillance tool shown to significantly improve mortality and reduce the risk of death from sepsis [50].

In summary, both checklist-based bundles and electronic screening algorithms that account for comorbid conditions lead to earlier detection of sepsis and improved clinical outcomes.

The advances in sepsis-related care are welcome, but have come at a cost, and further progress has probably been impeded by the many practical challenges encountered implementing early-detection approaches. Efforts to standardize care invariably encounter problems defining the population of patients at risk, and this remains a major issue in the battle for early recognition of sepsis, as evidenced by the continuing efforts to settle on a satisfactory definition. Secondly, compliance with bundles takes time, effort and resources, all in short supply in the chaotic environment of most EDs. Other unintended consequences include the patients who receive fluids as part of the early-treatment requirements, in patients with heart failure or renal insufficiency, and turn out to be 'false positives' in terms of actually having sepsis. Even when sepsis detection programs are ideally implemented, one wonders whether the staff time has been taken away from some other priority area, which now suffers.

Discussion

Although the changing definitions and methodology used to study the issue raise valid questions about the validity of observed trends [13, 58], this article focuses on the increasing evidence that the diagnosis of sepsis is improving [59–61]. This progress serves as an instructive model of how to improve diagnosis, and patient outcomes, one disease at a time. The 'learning health systems' model provides a framework for understanding this improvement cycle, where advances in science provide evidence that can be translated into improved practice [62–64] (Figure 1). New and improved primary care delivery systems [63] and post-operative recovery programs [65] illustrate effective implementations of 'learning health systems', and we suggest that the advances in the early diagnosis of sepsis illustrate another application of this data-driven approach:

- Basic science research has provided us with better tests,
- Health services research has gathered the evidence base for improved tools, guidelines and protocols and
- Completing the implementation science cycle, these tools, tests and guidelines have been incorporated into practice to improve care, the impact of which can be measured.

The role of advocacy and raising awareness should not be underestimated as a critical element in this story, providing the motivation necessary for clinical uptake. Indeed, it is unlikely that the improved outcomes now being seen would have been realized with any one of these levers acting alone; it required all of the levers to combine synergistically.

Another lesson emerging from the study of the sepsis story is the importance of measurement in driving progress. At every stage of the cycle, measurement was essential for improvement, culminating in the measure of greatest interest, improved survival. Moreover, it is likely that the improvement cycle now operational in regard to sepsis diagnosis will yield further improvements in outcomes in future years. Hopefully, this same approach can be replicated for other conditions and diseases where early and accurate diagnosis is a major determinant of patient outcomes. Stroke, aortic dissection, glaucoma and many other infections, such as necrotizing fasciitis, as well as all in-hospital causes of impending critical illnesses that cause respiratory failure, hemodynamic instability and altered mental status should be prime targets for similar efforts going forward.

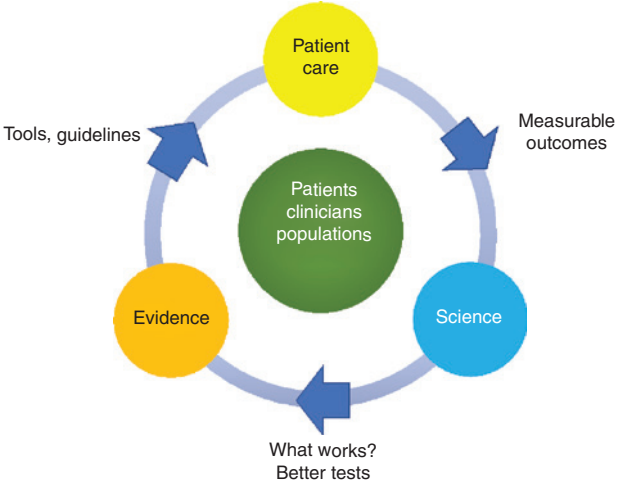

Figure 1: Elements of a learning health system [62] and its application to improving the diagnosis of sepsis.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Institute of Medicine. Improving diagnosis in health care. Washington, DC: National Academies Press, 2015.
2. Singh H, Graber M, Kissam S, Sorensen AV, Lenfestey NF, Tant EM, et al. System-related interventions to reduce diagnostic errors: a narrative review. BMJ Qual Saf 2012;21:160–70.
3. Graber M, Kissam S, Payne V, Meyer A, Sorensen A, Lenfestey N, et al. Cognitive interventions to reduce diagnostic error: a narrative review. BMJ Qual Saf 2012;21:535–57.
4. McDonald K, Matesic B, Contopoulos-Ioannidis D, Lonhart J, Schmidt E, Pineda N, et al. Patient safety strategies targeted at diagnostic errors – a systematic review. Ann Int Med 2013;158:381–9.
5. Singh H, Graber M, Hoffer T. Measures to improve diagnostic safety in clinical practice. J Patient Saf 2016;doi: 10.1097/PTS.0000000000000338.
6. Gorman A. The new war on sepsis. Kaiser Health News. 2017; June 21, 2017. Available at: http://khn.org/news/the-new-war-on-sepsis/. Accessed 30 Aug 2017.
7. Reinhart K, Daniels R, Kissoon N, Machado F, Schachter R, Finfer S. Recognizing sepsis as a global health priority – a WHO resolution. N Engl J Med 2017;377:414–7.

8. Wang H, Jones A, Donnelly J. Revised national estimates of emergency department visits for sepsis in the United States. Crit Care Med 2017;45:1443–9.
9. Lagu T, Rothberg M, Shieh M, Pekow P, Steingrub J, Linenauer P. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003–2007. Crit Care Med 2011;40:754–61.
10. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
11. Stevenson E, Rubenstein A, Radin G, Wiener R, Walkey A. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. Crit Care Med 2014;42:625–31.
12. Rhee C, Klompas M. What is the national burden of sepsis in US emergency departments? It depends on the definition. Crit Care Med 2017;45:1569–71.
13. Rhee C, Dantes R, Epstein L. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. J Am Med Assoc 2017;318:1241–9.
14. Angus D, Seymour C, Coopersmith C, Deutschman C, Klompas M, Levy M, et al. A framework for the development and interpretation of different sepsis definitions and clinical criteria. Crit Care Med 2016;44:e113.
15. Seymour C, Coopersmith C, Deutschman C, Gesten F, Klompas M, Levy M, et al. Application of a framework to assess the usefullness of alternative sepsis criteria. Crit Care Med 2016;44:e122–30.
16. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.
17. Knaus D, Draper E, Wagner D, Zimmerman J. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
18. Le Gall J, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. J Am Med Assoc 1993;270:2957–63.
19. Le Gall J, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, et al. The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU scoring group. J Am Med Assoc 1996;276:802–10.
20. Iwashyna T, Odden A, Rohde J, Bonham C, Kuhn L, Malani P, et al. Identifying patients with severe sepsis using administrative claims: patient-level validation of the angus implementation of the international consensus conference definition of severe sepsis. Med Care 2014;52:e39–43.
21. Rhodes A, Evans L, Alhazzani W, Levy M, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2016. Int Care Med 2017;43:304–77.
22. Coalition for Sepsis Survival. Colorado State Sepsis Initiative. Available at: https://coalitionforsepsissurvival.org/. Accessed 24 Jan 2017.
23. Singer M, Deutschman C, Seymour C, Shankar-Hari-M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). J Am Med Assoc 2016;315:801–10.
24. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644–55.
25. Martin G, Mannino D, Easton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–54.
26. Sprung C, Trahtemberg U. What definition should we use for sepsis and septic shock. Crit Care Med 2017;45:1564–7.
27. Williams J, Greenslade J, McKenzie J, Chu K, Brown A, Lipman J. SIRS, qSOFA and organ dysfunction: insights from a prospective database of emergency department patients with infection. Chest 2016;151:586–96.
28. Sterling S, Puskarich M, Glass A, Guirgas F, Jones A. The impact of the sepsis-3 septic shock definition on previously defined septic shock patients. Crit Care Med 2017;45:1436–42.
29. Vincent J-L, Martin G, Levy M. qSOFA does not replace SIRS in the definition of sepsis. Crit Care 2016;20:210.
30. Rory Staunton Foundation for Sepsis. Available at: https://rorys-tauntonfoundationforsepsis.org/. Accessed 24 Jan 2018.
31. Patient Safety Movement. Actionable Patient Safety Solution #9: Early Detection and Treatment of Sepsis. Available at: http://patientsafetymovement.org/wp-content/uploads/2016/02/APSS-9_-Early-Detection-_-Treatment-of-Sepsis.pdf. 2017.
32. Commins J. Sepsis: Ohio Provides Hospitals with a Battle Plan. Health Leaders Media. 2017; Available at: http://www.healthleadersmedia.com/technology/sepsis-ohio-provides-hospitals-battle-plan. Accessed 24 Jan 2018.
33. Hershey T, Kahn J. State sepsis mandates – a new era for regulation of hospital quality. N Engl J Med 2017;376:2311–3.
34. Survival CfS. Saving 10,000 Colorado Lives and $200 Million in Healthcare Costs: A Colorado Strategy for Improving Healthcare, 2015.
35. Kacich, T. Rauner signs 'Gabby's Law' at emotional ceremony. News Gazette, 2016. Available at: http://www.news-gazette.com/news/state/2016-08-18/rauner-signs-gabbys-law-emotional-ceremony.html. Accessed 24 Jan 2018.
36. Centers for Disease Control and Prevention. Get Ahead of Sepsis 2017. Available from: https://www.cdc.gov/sepsis/get-ahead-of-sepsis/index.html. Accessed 24 Jan 2018
37. Schorr C, Odden A, Evans L, Escobar G, Gandhi S, Townsend S, et al. Implementation of a multicenter performance improvement program for early detection and treatment of evere sepsis in general medicine-surgical wards. J Hosp Med 2016;11:32–9.
38. Evans K, Daines W, Tsui J, Strehlow M, Maggio P, Shieh L. Septris: a novel, mobile, online, simulation game that improves sepsis recognition and management. Acad Med 2015;90:1–5.
39. Apps D. Sepsis Guide: Surviving Sepsis Quick Reference, 2012.
40. Murray P, Masur H. Current approaches to the diagnosis of bacterial and fungal bloodstream infections in the intensive care unit. Crit Care Med 2012;40:3277–82.
41. Srinivasan L, Harris M. New technologies for the rapid diagnosis of neonatal sepsis. Curr Opin Pediatr 2012;24:165–71.
42. Ratzinger F, Schuardt M, Eichbichler K, Tsirkinidou I, Bauer M, Haslacher H, et al. Utility of sepsis biomarkers and the infection probability score to discriminate sepsis and systemic inflammatory response syndrome in standard care patients. PLoS One 2013;8:e82946.
43. Wacker C, Prkno A, Brunkhorst F, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lance Inf Dis 2013;13:426–35.
44. Shehabi Y, Sterba M, Garrett P, Rachakonda K, Stephens D, Harrigan P, et al. Procalcitonin algorithm in critically ill adults with

undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med 2014;190:1102–10.
45. Lee J, Cho S, Suh J, Jang B, Lee S-M, Kim J, et al. The use of procalcitonin test in patients with sepsis: a systematic review and meta-analysis. Am J Respir Crit Care Med 2016;193:A3659.
46. Masson S, Caironi P, Fanizza C, Thomae R, Bernasconi R, Noto A, et al. Circulating presepsin (soluble CD14 subtype) as a maker of host response in patients with severe sepsis or septic shock: data from the multicenter, randomized ALBIOS trial. Intensive Care Med 2015;41:12–20.
47. Rutanga J, Nyirahabimana T. Clinical significance of molecular diagnostic tools for bacterial bloodstream infections: a systematic review. Interdiscip Perspect Infect Dis 2016;2016,6412085.
48. Dellinger R, Levy M, Rhodes A, Annane D, Gerlach H, Opal S, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165–228.
49. Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. PLoS One 2015;10:e0125827.
50. Alberto L, Marshall A, Walker R, Aitken L. Screening for sepsis in general hospitalised patients: a systematic review. J Hosp Infection 2017;96:305–15.
51. Gyang E, Shieh L, forsey L, Maggio P. A nurse-driven screening tool for the early identification of sepsis in an intermediate care unit setting. J Hosp Med 2015;10:97–103.
52. MacQueen I, Dawes A, Hadnott T, Strength K, Moran G, Holschneider C, et al. Use of a hospital-wide screening program for early detection of sepsis in general surgery patients. Am Surg 2015;81:1074–9.
53. Nguyen K, Cook L, Greenlee E. Mortality reduction in patients with severe sepsis and septic shock through a comprehensive sepsis initiative. Crit Care 2014;18:28.
54. Churpek M, Zadravecz F, Winslow C, Howell M, Edelson D. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunction in ward patients. Am J Respir Crit Care Med 2015;192:958–64.
55. Smythe M, Daniels R, Perkins G. Identification of sepsis among ward patients. Am J Respir Crit Care Med 2015;192:910–1.
56. Van Der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13:138–47.
57. Manaktala S, Claypool S. Evaluating the impact of a computerized surveillance algorithm and decision support system on sepsis mortality. J Am Med Inform Assoc 2016;24: 88–95.
58. Rudd K, Delaney A, Finfer S. Counting sepsis, an imprecise but improving science. J Am Med Assoc 2017;318:1228–9.
59. De Backer D, Dorman T. Surviving sepsis guidelines: a continuous move toward better care of patients with sepsis. J Am Med Assoc 2017;317:807–8.
60. Kaukonen K, Bailey M, Suzuki S, Pilcher D. Mortality related to severe sepsis and septic shock amoung critically ill patients in Australia and New Zealand. J Am Med Assoc 2014;311:1308–16.
61. Levy M, Rhodes A, Phillips G, Townsend S, Schorr C, Beale R, et al. Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5 year study. Crit Care Med 2015;43:3–12.
62. Olsen L, Aisner D, McGinnis J. The learning healthcare system: workship summary. Washington, DC: Institute of Medicine, 2007.
63. Greene S, Reid R, Larson E. Implementing the learning health system: from concept to action. Ann Int Med 2012;157:207–10.
64. Institute of Medicine. Best care at lower cost: the path to continuously learning health care in America. Washington, DC: National Academies Press, 2013.
65. Gramlich L, Sheppard C, Wasylak T, Gilmour L, Ljungqvist O, Basualdo-Hammond C, et al. Implementation of enhanced recovery after surgery: a strategy to transform surgical care across a health system. Implement Sci 2017;12:67.