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Chapter I

Septic Shock Electronic Surveillance*

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Abstract

In a 2013 Healthcare Cost and Utilization Project Statistical Brief by the US Agency for Healthcare Research and Quality, septicemia was ranked as the #1 most expensive national inpatient hospital cost. This ranking comes in spite of substantial advances in the clinical management of sepsis over the past 15 years. While adherence with internationally established sepsis management protocols have demonstrated reduction in

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mortality and hospital/ICU length of stay, compliance with these protocols remains poor. Contributing factors may be delay in sepsis recognition and protocol implementation. A solution to this barrier is an automated sepsis detection and alert system embedded in the electronic medical record (EMR). In 2013, "alarm hazards" (e.g., excessive alarms, missed alarms, delayed alarms, etc.) was ranked as the #1 health technology hazard by the ECRI (Emergency Care Research Institute). Thus, sepsis surveillance systems must be developed and implemented in the context of alert fatigue, interruption, human error, and information overload. This chapter will describe essential elements in the electronic surveillance system development and implementation processes. Readers will learn about the critical elements of a septic shock detection algorithm and the data needed for each stage of sepsis management, such as early sepsis identification, notification of the clinicians, and tracking treatment processes. The chapter will describe the electronic components for this systems-level control of compliance with internationally established sepsis management protocols. A well-designed severe sepsis surveillance system has the potential to improve protocol compliance and patient outcomes, while reducing healthcare costs.

Detection of Sepsis: Historical Perspective and Current Status (Non-Computerized)

One of the earliest and most crucial steps in sepsis management was the standardization of sepsis and systemic inflammatory response syndrome (SIRS) definitions in August 1991 at a Consensus Conference between the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) [1]. The standardization of these clinical and physiological biomarkers allowed for early studies of the epidemiology of both sepsis and SIRS [2]. Prior to this, potential molecular biomarkers of sepsis, such as C-reactive protein (CRP), had been identified [3, 4]. In 1993, the first major report of an association between infection, sepsis, and high serum procalcitonin was published [5]. To date, hundreds of additional molecular biomarkers have been examined as potential diagnostic markers for sepsis detection [6]. Some of these molecular biomarkers—such as procalcitonin and CRP—seem to have limited utility in sepsis prognosis. However, none have been validated as diagnostic molecular biomarkers for sepsis detection. The cost-effectiveness of these molecular biomarkers is unclear [7, 8].

In one recent model of hypothetical patients with community-acquired pneumonia, procalcitonin protocol seemed to add $10 – 54 per patient to the cost of care compared to usual care [9].

For the past decade, a study by Martin et al. served as the reference for the epidemiology of sepsis in the United States [10]. A more recent large scale study of severe sepsis and septic shock in Australia and New Zealand demonstrated a significant decrease in mortality between the year 2000 to 2012 [11]. The US Agency for Healthcare Research and Quality (AHRQ) released a Statistical Brief calculating the aggregate cost of septicemia in the US to be $20.3 billion or 5.2% of the total aggregate cost for all hospitalizations [12]. Thus, septicemia is the most expensive inpatient condition to treat, outranking osteoarthritis (#2), complication of device, implant or graft (#3), acute myocardial infarction (#5), and cancer (did not make top 20).

As a result of collaborative work between SCCM and ACCP, consensus definitions for sepsis, severe sepsis, and septic shock have existed for over 20 years [1] with two major revisions [13, 14]. A landmark advancement in sepsis management occurred a decade later with the publication of early goal-directed therapy (EGDT) for the treatment of severe sepsis and septic shock [15]. In this single center research study, early identification and aggressive management of severe sepsis and septic shock in the emergency department (ED) was shown to significantly improve patient outcomes, including mortality. Soon thereafter, the US SCCM and the European Society of Intensive Care Medicine formed the Surviving Sepsis Campaign (SSC) to improve the care of these patients and to improve outcomes. At that time, the goal was to reduce worldwide mortality from severe sepsis and septic shock by 25% in 5 years [16]. This resulted in the publication of the first SSC guidelines for the management of severe sepsis and septic shock in 2004 [17].

With firmly established definitions and guidelines, a rationale exists for the use of computerized sepsis detection systems. At the turn of the century, early hospital alert systems were developed and validated for clinical trial enrollment purposes [18-20]. Likewise, the concept of a critical “golden hour” in the management of acute myocardial infarction and other traumas concurrently gained traction [21-23]. If similar critical hours exist in the management of severe sepsis and septic shock, it should be possible to detect and alert providers to these conditions to reduce response time in the hospital.

Computerized Attempts of Sepsis Detection

The introduction of computers into the hospital and ICU settings is still relatively recent. With the invention of the transistor in the 1940s (Nobel Prize in 1956), discussions of crude hospital EMR systems can be found dating back to the 1960s [24]. Rigorous study of the effect of early EMR systems on hospital practice began in the 1980s [25-27] and in ICU-specific settings a decade later [28-30]. However, due to lack of standardization of sepsis treatment protocols, development of early electronic sepsis surveillance systems did not begin until the 2000s.

In part due to the lack of computerized sepsis detection systems, many challenges hindered a sensitive sepsis detection system. Historically, the basic protocol for management of severe sepsis and septic shock was the administration of appropriate antibiotics, intravenous fluids, and advanced support (such as mechanical ventilation, vasopressors, and dialysis) when necessary [31]. However, the need for better sepsis clinical trials was recognized [32, 33]. Unfortunately, computerized sepsis detection systems could not be refined until standardized sepsis treatment protocols were developed. After the publication of the first SSC guidelines for the management of severe sepsis and septic shock, effectively standardizing sepsis treatment protocols, interest in computerized sepsis detection and alert systems increased dramatically. The current guideline for the diagnosis of sepsis divides the needed data into six clinical categories: general, inflammatory, hemodynamic, organ dysfunction, tissue perfusion, and severe sepsis-specific variables (Table 1). Early prospective electronic sepsis surveillance system studies focused on detection of sepsis, severe sepsis, and/or septic shock in non-ED/ICU settings, ED, and ICU settings [34-36]. These studies provided significant insight into the challenges of automated sepsis detection and alert, but failed to show significant improvement in clinical outcomes upon implementation of these systems. A large single center trial of an automated sepsis detection and alert system (based on modified SIRS criteria) also failed to show significant improvement in clinical outcomes [37]. However, this detection system's positive predictive value was only 41%, which may explain the lack of outcomes improvement. One of the earliest sepsis detection systems, termed the septic shock sniffer, was originally developed and validated at Mayo Clinic to enroll patients with septic shock into a time sensitive clinical trial in the critical care setting [20, 38].

Table 1. Data needs for a severe sepsis and septic shock electronic surveillance system based on current 2012 SSC international guidelines for management of severe sepsis and septic shock

Domain	Value	Rationale	Source in EMR
Age, Gender, Height & weight	any	Demographics implications	Demographics
Suspicion of infection	Presence of any culture order	Systemic infection (sign of sepsis)	Microbiology orders
Heart rate	> 90	SIRS criteria (sign of sepsis)	Monitored data
Respiratory rate	> 20	SIRS criteria (sign of sepsis)	Monitored data
Temperature	> 38 or < 36	SIRS criteria (sign of sepsis)	Monitored data
White blood count	> 12 or < 4	SIRS criteria (sign of sepsis)	Laboratory tests
Lactate	≥ 4.0	Sign of hypoperfusion (severe sepsis)	Laboratory tests
Systolic Blood Pressure	< 90	Sign of hypotension (severe sepsis)	Monitored data
Mean Arterial Pressure	< 70	Sign of hypotension (severe sepsis)	Monitored data
Bilirubin	> 4.0	Sign of organ dysfunction (severe sepsis)	Laboratory tests
Platelets	< 100k	Sign of organ dysfunction (severe sepsis)	Laboratory tests
INR	> 1.5	Sign of organ dysfunction (severe sepsis)	Laboratory tests
Mechanical Ventilation	Any use	Sign of organ dysfunction (severe sepsis)	Monitored data
PaO2/FiO2	< 300	Sign of organ dysfunction (severe sepsis)	Monitored data
GCS score	< 15	Sign of hypoperfusion (severe sepsis)	Nursing flow sheets
Creatinine Increase	> 0.5	Sign of organ dysfunction (severe sepsis)	Laboratory tests
Urine Output	< 0.5 mL/kg/hour for > 2 hours	Sign of organ dysfunction (severe sepsis)	Fluids in and out
Fluid resistant hypotension	SBP < 90 after sufficient fluid bolus	Sign of septic shock	Fluids in and out
Vasopressors	Any use	Sign of septic shock	Medications

The creation of this septic shock sniffer was possible due to the existence of a Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) Data Mart, which aggregates necessary components of patient's data that are usually stored in independent databases [39]. Briefly, this near real-time database copies and stores all ICU data on all ICU patients at Mayo Clinic. This data includes demographics, monitored data (vital signs, ventilator settings, etc.), laboratory tests, transfusions, microbiology, radiology, medications, physician notes, nursing flow sheets, respiratory data, and fluid balance data. Further validated methodology has been developed at Mayo Clinic to improve the severe sepsis and septic shock sniffer for clinical use in the ICU setting [40].

Limitations and Challenges of Early Computerized Systems

The early electronic sepsis surveillance systems described above suffered from a variety of limitations. In particular, many of these earlier studies placed more emphasis on algorithm development than attention to factors such as alert fatigue [41], interruption [42], human error [43], and information overload [44, 45]. Without careful consideration of these implementation factors, even a "perfect" sepsis detection and alert algorithm will fail to improve clinically significant outcomes, such as mortality and hospital/ICU length of stay. An inherent limitation of these earlier studies is also their single center design. Even the best single center, prospective study will potentially suffer from a variety of common epidemiologic biases and/or confounders [46]. These early electronic sepsis surveillance systems also needed to overcome numerous informatics challenges. Although less than one decade old, the timing of these studies overlaps with the rise of the concept and recognition of "big data" (i.e., large and complex sets of data that may be difficult to process and analyze using traditional systems). In less than a decade, the concept of big data has permeated fields ranging from biomedical research [47] to business/finance [48, 49] to healthcare and clinical research [50]. However, without sufficiently complex electronic infrastructure and personnel support, the same limitations and challenges outlined as implementation factors above are only amplified in clinical studies requiring use of big data.

Since these early electronic sepsis surveillance studies, many more single center studies have been conducted [51-56]. The scope of each of these studies varies significantly—study design, hospital setting, and number of patients—while suffering from the single center limitations and challenges outlined above. However, with sufficient experience systemic reviews of this topic are being published [57]. Likewise, a large multicenter/international study was recently conducted using SSC data [58] to produce a "sepsis severity score" [59]. This study was designed primarily for prognostication with population-level case mix adjustments, as opposed to patient-level, diagnostics purposes. Nonetheless, this study represents a landmark in the field of sepsis detection and alert systems.

Elements of an Advanced Computerized System

A "perfect" electronic sepsis surveillance system will not have close to the 99% sensitivity and specificity of FDA-approved rapid HIV tests [60]. This is due to differences in the complexity and nature of these tasks. When the ability of the SIRS criteria (an important element of any sepsis detection algorithm) to identify infection is compared against both clinical and microbiological gold standards; sensitivity, specificity, positive predictive value, and negative predictive value are all relatively poor [61]. For example, the sensitivity of the SIRS criteria against both gold standards (defined as dismissal diagnosis of sepsis or evidence of microbiological growth from any culture site) was 69%, while the specificity against these gold standards was 35% and 32%, respectively. Likewise, it is important to recognize that the accuracy of any test is dependent not only on the test characteristics, but also the prevalence of disease, among other factors [62]. Nonetheless, a perfect electronic sepsis surveillance system should achieve several goals.

First, an ideal electronic sepsis surveillance system should only generate actionable alerts in the context of alert fatigue, interruption, human error, and information overload. For example, electronic sepsis surveillance systems should not generate alerts for suspicion of infection or presence of SIRS criteria in isolation. This is because many patients in the critical care setting have suspicion of an infection due to SIRS criteria but may not have sepsis (e.g., drug fever or deep vein thrombosis). Furthermore, only a fraction of septic patients progress to severe sepsis (sepsis with the presence of organ

dysfunction) or septic shock. In the absence of significant comorbidities, it is only at the level of severe sepsis that mortality due to sepsis rises significantly [63]. Interestingly, it is also unclear if meaningful alerts could be generated in the context of septic shock. Although mortality in this extremely time-sensitive circumstance is even higher than severe sepsis, EMR-based detection of sepsis relies on existing EMR data. In other words, the presence of fluid resistant hypotension and/or the use of vasopressors (elements of the definition of septic shock) imply the presence of septic shock has already been identified by providers and action has been taken. Alerts in these contexts would potentially lead to alert fatigue, interruption, human error, and information overload. Thus, from the perspective of the clinical continuum from sepsis to septic shock, one of the clearest targets for actionable alerts is the critical golden hours during the progression from severe sepsis to septic shock. Adherence to existing, international SSC guidelines for severe sepsis and septic shock are known to significantly reduce mortality [58]. However, compliance with these guidelines is poor. There is frequently a delay between the generation of lab values, such as biomarkers of organ dysfunction, and clinician awareness of these values. Thus, preventing the progression of severe sepsis to septic shock is one mechanism to generate actionable sepsis alerts to reduce mortality in the critical care setting. The current SSC guidelines [14] are highly detailed, but contain a simplified set of two "bundles". The first bundle is comprised of a set of 4 elements to be completed within 3 hours upon suspicion and/or diagnosis of sepsis, while the second bundle is comprised of 3 elements to be completed within 6 hours. However, it should be noted that these bundle elements are not all mutually exclusive and can form a feedback loop. For example, it is expected that 30 mL/kg of crystalloid fluids will be administered within 3 hours for hypotension or elevated lactate. However, it is also expected that vasopressors will be administered within 6 hours if hypotension is not adequately reversed with fluids. Should hypotension persist (evidence of septic shock), it is thus possible to cycle between fluid administration and vasopressor use for periods of time much greater than 6 hours. Similarly, the first element of the 3-hour bundle is lactate measurement. However, both persistent hypotension and the third element of the 6-hour bundle (re-measure lactate if initial lactate was elevated) can result in feedback loop of repeated lactate measurements for an indefinite period of time. Secondly, an ideal electronic sepsis surveillance system must do more than detect sepsis. Once severe sepsis and/or septic shock have been identified, timely and appropriate response according to SSC guidelines remains crucial for positive patient outcomes [64]. Thus, identification of failure to comply

with these guidelines in a timely and appropriate manner is another potential mechanism for actionable sepsis alerts. Additionally, alerts need to be sent to the correct provider using the correction mechanism of alert delivery. This subject is particularly important in the context of alert hazards and has been studied in the context of the development of monitoring and alert systems for geriatric patients in the home setting [65, 66]. However, relatively limited investigation into methods of alert delivery to these patients' providers in the hospital setting has been performed [67]. Furthermore, this subject has been explored even less in the critical care setting [68, 69]. As the age of the average ICU patient is around 65 years and studies in the critical care setting are lacking [70], this example of geriatric patients is particularly relevant to highlight the specific need to perform systematic investigation of alert processes in the critical care/ICU setting. Specifically, most of the automated sepsis detection and alert systems previously referenced provided alerts to attending physicians using text paging as the mechanism of alert delivery. However, the questions of who should be the recipient of urgent and/or non-urgent alerts (attending physicians, residents/fellows, NPs/PAs, RNs, etc.) and how these alerts should be delivered—text paging, EMR-based messaging, email, or smartphone [71]—remain unresolved.

What EMR Data Is Needed?

To achieve the goals for an ideal electronic sepsis surveillance system, specific data requirements are necessary. The current 2012 SSC international guidelines for management of severe sepsis and septic shock provide a good starting point for these requirements [14]. These specific data requirements include a variety of variables/domains as diagnostic criteria for sepsis, as well as cutoff values for quantitative variables/domains, all of which can be extracted from the EMR. Conceptually, some of these variables/domains have varying degrees of usefulness along the sepsis "spectrum": suspicion of infection *or* SIRS, sepsis (suspicion of infection *and* SIRS), severe sepsis, or septic shock. It should be noted that not all of the numerous data elements listed in the current SSC guidelines are necessary to create an ideal electronic sepsis surveillance system. One example is hyperglycemia in the absence of diabetes. Although there are other important reasons to prevent hyperglycemia in critically ill patients, this value can change rapidly and is not required for the diagnosis of sepsis, severe sepsis, or septic shock. As glycemic state can

change rapidly, this limits the usefulness of this marker for quick detection of sepsis. Alternatively, decreased urine output for more than two hours despite adequate fluid resuscitation is a marker of organ/renal dysfunction (severe sepsis). However, the many hours potentially required to make this observation also limits the usefulness of this marker for timely detection of severe sepsis. It is therefore necessary to build an electronic sepsis surveillance system that includes other markers of organ dysfunction/severe sepsis, such as increased creatinine, increased bilirubin, and decreased platelet count. However, this implies that the detection algorithm must include the ability to detect changes in these variables rather the absolute values. Combined, carefully and correctly selected data from the EMR must be used to create the ideal system. In addition to previously discussed human-centric limitations and challenges—such as alert fatigue, interruption, human error, and information overload—there are also human-independent limitations to an ideal electronic sepsis surveillance system. In the context of "big data", the need for real-time, accurate data at the bedside ("point of care") is a crucial challenge. It is already known that the positive effect of point of care computer reminders on processes and outcomes of care in the hospital setting is limited (72). While some of this may be due to human-dependent factors, this does not entirely explain this observation. For example, there are uncertainties in the EMR systems, such as whether most of the variables/domains listed in Table 1 were ordered, if the timestamps represent time the test was ordered or the time the results were completed, and what the lag-time is in reporting new data. In a healthcare center of any size, complete data availability and interoperability of any electronic sepsis surveillance system may not exist across the ICU, ED, OR, and/or hospital floors (with or without telemetry). This can be due to lack of backend electronic infrastructure to support an electronic sepsis surveillance system in the context of an existing EMR system. The complexity of this problem is compounded when considering a multisite healthcare system, as data availability and interoperability across physical locations may be severely limited.

Workflow Changes, Educational Challenges, and Implementation

Knowledge is only the first step in the successful implementation of any complex technical system, medical or otherwise, which significantly modifies

or alters an existing, complex system. In this case, the SSC has provided the knowledge necessary to manage severe sepsis and septic shock. Thus, clinical knowledge of sepsis is not the primary barrier for implementation of an electronic sepsis surveillance system in the ICU and other hospital settings. Initial barriers include workflow and education changes. Even an ideal electronic sepsis surveillance system will not be accepted by clinicians (attending physicians, residents/fellows, NPs/PAs, RNs, etc.) unless the system is first introduced without substantially changing the existing workflow process for sepsis management. In the case of Mayo Clinic, this involved first creating METRIC Data Mart (a near real-time, EMR-independent information database), as well as the Ambient Warning and Response Evaluation (AWARE) system, an ICU-specific EMR viewer, for use as a platform in the critical care setting, on top of the existing EMR system [73]. Once a system has been introduced into the existing workflow, implementation changes must occur through educational interventions. The first steps involve active training sessions and prominently displayed poster-style reminders in the critical care setting. After these educational interventions and initial implementation, continued implementation efforts are required. This entails clear mechanisms and response to both unstructured (feedback button) and structured data (survey) for both the critical care and other monitored settings [74]. Each of these components of the implementation process, including post-marketing surveillance, is crucial for the success of an ideal sepsis electronic surveillance algorithm [75]. Essentially, implementation of an electronic sepsis surveillance system is similar to implementation of new therapeutics, medical devices, and even direct-to-consumer advertising.

Perspectives

After the publication of the first set of SSC guidelines for management of severe sepsis and septic shock in 2004 [17], one issue was identified with these guidelines: the lack of a clear, linear, bulleted management protocol to accompany the 16-page document [76]. As a result, the first SSC “bundles” for sepsis management were published the following year [16]. More importantly, this was a realization that lengthy, elaborate guidelines were not successfully implemented in the absence of a straightforward and human-interpretable summary of these processes in diagram format. From that point, although the second [13] and third (current) [13, 14] editions of the SSC guidelines

approximately doubled and tripled in size with respect to the initial guidelines, the SSC "bundles" were also updated and prominently incorporated into both the SSC guideline document and website.

Unfortunately, although the SSC bundles continue to mature, both the current SSC bundles and guidelines are *not* machine-readable/interpretable. For example, the fourth component of the 3-hour SSC bundle is to administer 30 mL/kg crystalloid for hypotension. However, for a computer to calculate the success or failure of completion of this intervention, several variables are required within this 3-hour window: blood pressure readings, fluid administration, and weight. Although blood pressure readings may be easily obtained, tracking fluid administration (specifically, bolus-only) is more complex. Additionally, in regard to EMR-interoperability, what if fluids are administered first in the ED setting, but then continued in the ICU setting? Does an electronic sepsis surveillance system have the capacity to track and understand fluid-bolus continuity across clinical departments? What if 30 mL/kg crystalloid for hypotension is achieved in 3.1 hours? In other words, what might be considered as a success by a clinician (aka human) would be considered a failure by the computer (aka machine). Even worse, a patient's weight might not be entered during the first 3 hours. In the absence of a weight to calculate the required fluid bolus, a computer would be forced to register all fluid boluses as failures. From a clinical perspective, this point may seem irrelevant, as many patient weights can be estimated. One solution is to collect all patient weights for the specific purpose of satisfying the algorithm. However, this concept is in opposition to earlier concepts of the implementation process: the machine should serve the clinician and not vice versa. Another solution is to expand the algorithm's ability to search for weights prior to 3 hours. But how far in advance of 3 hours and who decides this important cutoff value? Similar challenges related to this issue are also present in other elements of both the 3 and 6-hour SSC bundles.

Ultimately, as the rise of evidence-based medicine and education continues [77, 78], increased emphasis will be placed on adherence to "best practice" protocols, such as the SSC guidelines. However, the future of evidence-based medicine and education hinges on the question of the need/desire for clinicians to interpret free-text protocols versus reliance on potentially "black box" machine algorithms. For this shift to electronic surveillance systems to occur, best practice protocols must shift from clinical interpretation to computer/coding-friendly language. Otherwise, as the number and complexity of best practice protocols continues to expand, the benefits of human interpretable algorithms in evidence-based medicine will slowly be lost

to the inability to translate these algorithms into electronic systems that can handle volumes of data, which otherwise lead to alert fatigue, interruption, human error, and information overload. Thus, clinicians must eventually reassess the place for and implications of electronic surveillance systems in modern medicine.

It is also necessary to implement an electronic sepsis surveillance system using the correct delivery platform. One option is to implement these systems through existing commercial [79], open access [80], and/or custom EMR platforms. Another option is to use a custom delivery platform in parallel with an existing EMR system. For example, Mayo Clinic is implementing its electronic sepsis surveillance system in the critical care setting through AWARE, the ICU-specific patient viewer developed at Mayo Clinic and in use in routine clinical practice across its Minnesota, Arizona, and Florida locations, which have different core EMRs [81, 82]. Regardless of the delivery platform, an electronic sepsis surveillance system should interact synergistically with other electronic systems to reduce the alert hazards described above.

Future Algorithm Improvements for Electronic Surveillance

In the recent US multicenter ProCESS Trial, early-goal directed therapy (EGDT) was demonstrated to not significantly differ from "protocol-based standard therapy" or the current standard of care [83]. These results are supported by another recent multicenter trial in Australia and New Zealand (ARISE), comparing EGDT to "usual care" [84]. Taken together, these results indicate the success of sepsis diagnosis and management efforts over the past 20+ years. These results further indicate that some elements of the SSC bundle may not be essential in the management of septic patients.

It is also important to recognize the widespread scope of interest in improving sepsis outcomes. One current example not highlighted in this chapter is nursing. For many decades, the academic nursing community has published sepsis outcomes in nursing journals, in parallel with general medical journals [85]. Another example is veterinary medicine. In addition to sepsis outcomes, the veterinary literature routinely publishes interesting sepsis case reports on par or more interesting than those published in the general (human) medical journals [86]. In the area of dental hygiene, a recent randomized

clinical trial showed that routine dental care/treatment of critically ill patients in the ICU setting significantly reduces lower respiratory tract infections [87]. These studies represent examples of many diverse interests within the healthcare community devoted to improving sepsis outcomes now and in the future.

In order to develop a truly intelligent electronic sepsis surveillance system, it is necessary to consider more factors that have not yet been described in detail in this chapter, such as workflow analysis, ambience, and feedback [88]. In particular, existing electronic sepsis surveillance systems have focused specifically on sepsis detection and alert. However, such systems can be improved through implementation of automated detection and alert systems in the specific context of failure to rescue and treat sepsis in a timely and appropriate manner after diagnosis, which has already been shown to reduce mortality [58, 64]. As will be described below, failure to rescue and treat sepsis differs from failure to recognize sepsis in that this component of electronic sepsis surveillance focuses on response after the detection of sepsis. These concepts have not been explored in existing electronic sepsis surveillance systems.

In addition to the data needed and the implementation process, it is necessary to consider additional factors to develop a truly intelligent electronic sepsis surveillance system. One of these factors is the concept of "failure to rescue" (Figure 1). The US AHRQ (Agency for Healthcare Research and Quality) Patient Safety Network defines failure to rescue as "shorthand for failure to rescue (i.e., prevent a clinically important deterioration, such as death or permanent disability) from a complication of an underlying illness (e.g., cardiac arrest in a patient with acute myocardial infarction) or a complication of medical care (e.g., major hemorrhage after thrombolysis for acute myocardial infarction). Failure to rescue thus provides a measure of the degree to which providers responded to adverse occurrences (e.g., hospital-acquired infections, cardiac arrest, or shock) that developed on their watch. It may reflect the quality of monitoring, the effectiveness of actions taken once early complications are recognized, or both." [89]. This concept and term is derived from studies performed by Silber and colleagues over two decades ago in the surgical setting [90, 91]. Over the next decade, they extended these studies into perioperative areas such as anesthesiology [92] and nursing [93]. This concept of failure to rescue was recently applied to perform comparative analysis, at the hospital-wide level, across multiple institutions to assess availability of hospital resources and differences in performance [94]. However, like previous studies, the underlying population of interest was

surgical patients. With this recent study in mind, Silber and colleagues are now exploring failure to rescue as a component for standardizing patients for hospital audit/evaluation purposes and cost analysis [95]. However, the concept of failure to rescue outside the perioperative realm, including the ICU setting, remains largely unexplored.

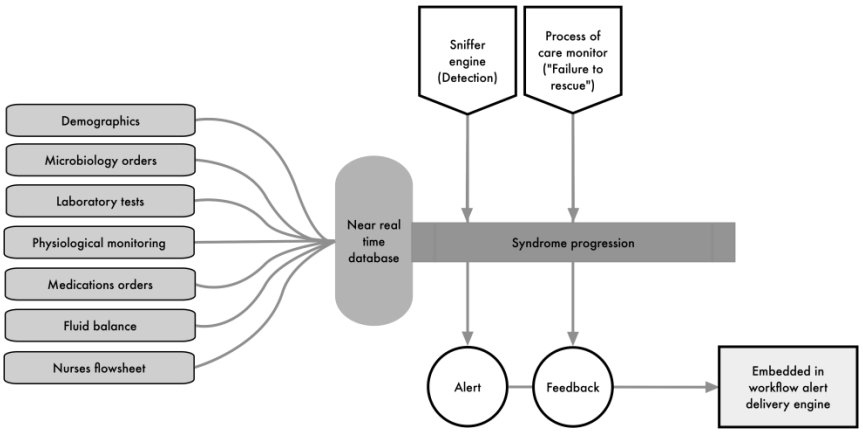

Figure 1. Flow diagram of sepsis management in the context of detection, failure to treat, and failure to rescue alerts, as well as physiologically relevant variables.

An electronic sepsis surveillance system with the capacity to identify failure to rescue and treat sepsis in a timely and appropriate manner after diagnosis—in addition to sepsis detection/recognition—has the potential to intelligently prevent alert fatigue, interruption, human error, and information overload. Along these lines, the methodology for this system has already been retrospectively validated for implementation at Mayo Clinic using an improved severe sepsis and septic shock "sniffer" for clinical use in the ICU setting [40]. Likewise, researchers at Mayo Clinic have already shown that activation of a sepsis response team, in combination with weekly feedback, increases the compliance with processes of care and reduces hospital mortality rate in the setting of septic shock [96]. Thus, future implementation of complex electronic surveillance systems, such as a sepsis sniffer with a failure to rescue component, can only occur in combination with these other mechanisms of diagnosis and management of septic patients.

The final element of future algorithm improvements in the context of electronic surveillance is the human interpretability of these algorithms. Guideline adherence can be improved by combining a refined sepsis alert and

detection system with existing electronic infrastructures to further improve sepsis outcomes. The development of the surveillance algorithm for the detection of failure to recognize and treat severe sepsis in the Mayo Clinic study described above made use of recursive data partitioning analysis. This technique is considered to be an advanced modeling and multivariate method, which has been described in detail elsewhere [97]. Briefly, statistical partitioning allows for the division of a data set into a complete, but non-overlapping, collection of components or parts using decision tress. It should be noted that other mathematical modeling approaches for sepsis detection and alert have been developed. For example, one unrelated study made use of a Dynamic Bayesian Networks-based model for early detection of sepsis in the ED setting [98]. Another group used machine learning-based models to develop a decision support system to make clinical predictions for patients with sepsis [99]. Thus, alternative modeling techniques may be applicable to the development of detection and alert systems specific to failure to rescue and treat sepsis.

Human interpretability of algorithms generated by a machine, such as supervised learning techniques (Bayesian networks, neural networks, and ensemble learning), or heuristic optimization techniques is often limited [100]. Thus, with increasing prevalence of complex technologies throughout the hospital setting, clinicians must eventually determine what is and is not an acceptable loss of human interpretability to "black box" algorithms. This will be particularly important if implementation of these algorithms results in improved patient outcomes. Ideally, this equilibrium will evolve in parallel with other improvements in the understanding of both the pathophysiology and clinical management of sepsis.

Bullet Points

(1) Detection of sepsis: historical perspective and current status (non-computerized)
   - Consensus conference criteria, early-goal directed therapy, and the Surviving Sepsis Campaign provided the basis for the clinical diagnosis and management of sepsis.

(2) Computerized attempts
- The earliest sepsis detection systems were developed primarily for clinical trial enrollment purposes, while recent, largely retrospective studies have focused on improvement of clinical outcomes in both critically and non-critically ill patients in ICU, ED, and hospital floor settings.

(3) Limitations and challenges of early systems
- In addition to retrospective and algorithmic limitations, a challenge of the above systems has been to address alert fatigue, interruption, human error, and information overload.

(4) Elements of an advanced system.
- An ideal electronic sepsis surveillance system should address all of the above challenges and delivery alerts to the correct providers to improve clinical outcomes, but still will not achieve 100% accuracy.

(5) Data needs
- The hospital EMR-infrastructure must be capable of integrating SSC international guidelines in the context of real-time data availability and interoperability across all relevant hospital settings (ICU, ED, and hospital floors).

(6) Workflow changes, educational changes, and implementation
- Implementation of a "perfect" electronic sepsis surveillance system will fail without the proper workflow and educational interventions to achieve acceptance from clinicians.

(7) Perspectives
- SSC guidelines are readable by humans, but not necessarily computer algorithms, which hampers the development of evidence-based electronic sepsis surveillance systems.

(8) Future algorithm improvements in the context of electronic surveillance
- In addition to detection/recognition, future algorithms must integrate the concepts of failure to rescue and treat sepsis with

advanced modeling techniques, which may also result in a decrease in the human interpretability ("black box") of these algorithms.

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