DEVELOPMENT, TESTING, AND REFINING THE FAILURE TO RESCUE SEPSIS SNIFFER

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ABSTRACT

Background: Sepsis is one of the most lethal and expensive in hospital conditions in the Unites States and around the world. International consensus guidelines for the diagnosis and management of sepsis have been established. Compliance with these guidelines has been demonstrated to substantially improve outcomes such as hospital length of stay (LOS), intensive care unit (ICU) LOS, and mortality. However, there are significant delays in timely and appropriate recognition of sepsis, as well as delays in timely and appropriate treatment after diagnosis.

Objective: To develop and implement a sepsis detection and alert system for use in the ICU setting. Several knowledge gaps must be closed to achieve this goal.

Methods: First, an optimal electronic medical record (EMR)-based algorithm for the detection of failure to recognize severe sepsis was developed. An algorithm for the detection of failure of timely and appropriate treatment of severe sepsis was also developed. Second, the best method of alert delivery for failure to recognize and treat severe sepsis was developed. This process was performed in the context of alert fatigue, interruption, human error, and information overload. Third, to demonstrate efficacy, this surveillance system for the detection of failure to recognize and treat severe sepsis was implemented in the ICU setting.

Results: A failure to recognize and treat severe sepsis detection and alert system was successfully developed and implemented in the ICU setting.

Conclusion: The work presented in this thesis proved the feasibility of iterative development, testing, and real-world implementation of electronic surveillance of sepsis resuscitation. This research paves the way for meaningful EMR use to enhance the safety of hospitalized patients.

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OTHER ITEMS

List of Abbreviations

AHRQ	(US) Agency for Healthcare Research and Quality
AKI	Acute Kidney Injury
API	Application Programming Interface
ARISE	Australasian Resuscitation in Sepsis Evaluation (Trial)
AWARE	Ambient Warning and Response Evaluation
ACCP	(US) American College of Chest Physicians
CPOE	Computerized Physician Order Entry
CRP	C–Reactive Protein
CVP	Central Venous Pressure
DBMS	Database Management System
DNR/DNI	Do Not Resuscitate/Do Not Intubate
ECRI	Emergency Care Research Institute
ED	Emergency Department
EGDT	Early Goal-Directed Therapy
EMR	Electronic Medical Record
ICU	Intensive Care Unit
IQR	Interquartile Range
LOS	Length of Stay
METRIC	Multidisciplinary Epidemiology and Translational Research in Intensive Care (Research Group)
MICU	Medical intensive care unit (ICU)
MTR	Management to Reimbursement
NP	Nurse Practitioner
NPV	Negative Predictive Value

ODBC	Open Database Connectivity
OR	Operating room
PA	Physician Assistant
PGY	Post-Graduate Year
PPV	Positive Predictive Value
ProCESS	Protocolized Care for Early Septic Shock (Trial)
RCU	Respiratory Care Unit
RDBMS	Relational database management system (DBMS)
RN	Registered Nurse
SCCM	(US) Society of Critical Care Medicine
SOFA	Sequential Organ Failure Assessment
SQL	Structured Query Language
SSC	Surviving Sepsis Campaign

CHAPTER 1

Introduction

This book chapter has been published as Harrison AM, Park JG, Herasevich V. Septic Shock Electronic Surveillance. In: Septic Shock: Risk Factors, Management, and Prognosis. New York: Nova Science Publishers, 2015. The book and book chapter can be found at these links.

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 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].

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].

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

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.

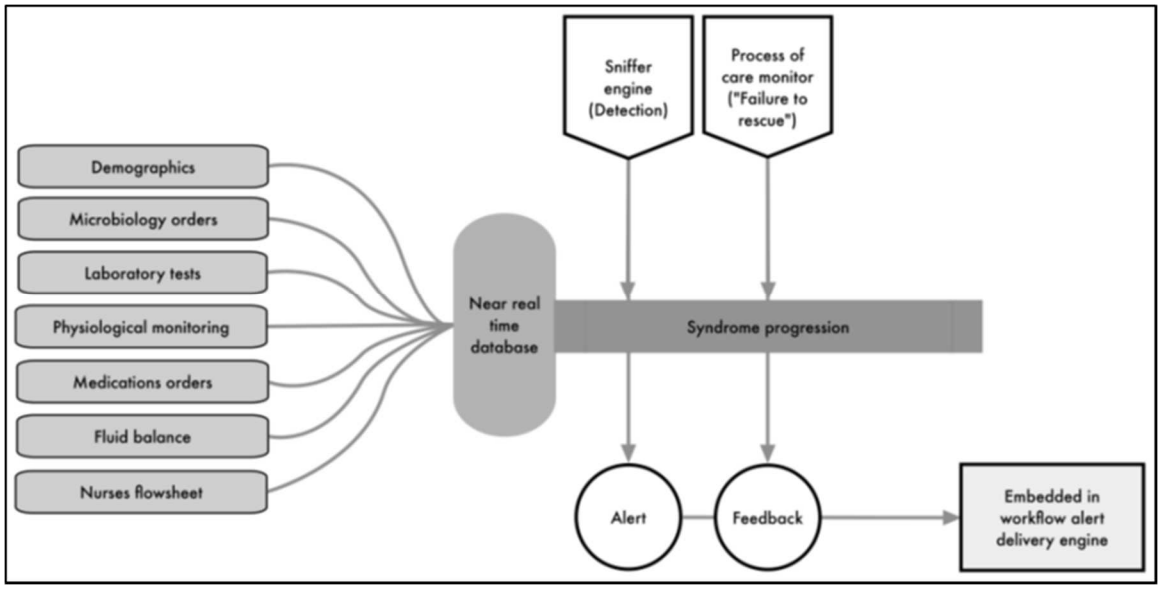

Figure 1: Flow diagram of sepsis management in the context of detection, failure to treat, and failure to rescue alerts, as well as physiologically relevant variables.

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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CHAPTER 2

Developing the surveillance algorithm for detection of failure to recognize and treat severe sepsis

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ABSTRACT

Objective: To develop and test an automated surveillance algorithm (sepsis "sniffer") for the detection of severe sepsis and monitoring failure to recognize and treat severe sepsis in a timely manner.

Patients and Methods: We conducted an observational diagnostic performance study using independent derivation and validation cohorts from an electronic medical record database of the medical intensive care unit (ICU) of a tertiary referral center. All patients aged 18 years and older who were admitted to the medical ICU from January 1 through March 31, 2013 (N=587), were included. The criterion standard for severe sepsis/septic shock was manual review by 2 trained reviewers with a third super-reviewer for cases of inter-observer disagreement. Critical appraisal of false-positive and false-negative alerts, along with recursive data partitioning, was performed for algorithm optimization.

Results: An algorithm based on criteria for suspicion of infection, systemic inflammatory response syndrome, organ hypoperfusion and dysfunction, and shock had a sensitivity of 80% and a specificity of 96% when applied to the validation cohort. In order, low systolic blood pressure, systemic inflammatory response syndrome positivity, and suspicion of infection were determined through recursive data partitioning to be of greatest predictive value. Lastly, 117 alert-positive patients (68% of the 171 patients with

severe sepsis) had a delay in recognition and treatment, defined as no lactate and central venous pressure measurement within 2 hours of the alert.

Conclusion: The optimized sniffer accurately identified patients with severe sepsis that bedside clinicians failed to recognize and treat in a timely manner.

INTRODUCTION

Sepsis is common and lethal in the United States and around the world.[1-3] Septicemia was also ranked as the most expensive in-hospital condition in the United States by the US Agency for Healthcare Quality and Research, based on 2011 data.[4] Current processes for sepsis management (including early goal-directed therapy [EGDT] and the data from the recent ProCESS [Protocolized Care for Early Septic Shock] and ARISE [Australasian Resuscitation in Sepsis Evaluation] trials) have been established.[5-7] The Surviving Sepsis Campaign (SSC) guidelines have refined the exact criteria for advanced disease, including organ dysfunction.[8] However, the fundamental process of sepsis management in these guidelines has not changed substantially, suggesting a barrier in implementation as the source of the continued sepsis problem. There is much room for improvement and optimization of existing computerized sepsis detection and alert systems. Although recent sepsis detection and alert systems have focused on clinical outcomes, these systems have failed to document improvement in clinically meaningful end points.[9-12] Thus, an improved approach is necessary to develop and validate a clinically useful sepsis alert system, especially for implementation in the critical care setting.

The aim of this study was to improve on previous studies in several ways. The first was by specifically targeting severe sepsis/septic shock (referred to as severe sepsis throughout the remainder of this article for brevity) to reduce the number of false-positive

alerts from isolated or non-septic systemic inflammatory response syndrome (SIRS).[13] The second was to target severe sepsis in the specific context of delay in recognition and treatment. This approach is derived from the concept of "failure to rescue" from the surgical literature, which suggests that hospital characteristics, as opposed to patient characteristics, are the primary determinant of adverse occurrences.[14,15] In this context, one example of delay in recognition and treatment would be progression to severe sepsis due to failure to adhere to established sepsis response and management protocols.[16] The third and final improvement was to target information overload, human error, interruption, and alert fatigue.[17,18] Combined, the objective of this study was to advance, test, and refine a delay in recognition and treatment of severe sepsis detection and alert system ("sniffer") for use in the critical care setting.

PATIENTS AND METHODS

Study Design and Setting

We conducted an observational diagnostic performance study that used independent derivation and validation cohorts for development and testing of the delay in recognition and treatment of severe sepsis sniffer. This study was performed at Mayo Clinic in Rochester, Minnesota, with Mayo Clinic Institutional Review Board approval.

Study Population and Data Collection

All patients aged 18 years and older who were admitted to the medical intensive care unit (ICU) at Mayo Clinic in Rochester, Minnesota, from January 1 through March 31, 2013, and provided research authorization were included in this study. This ICU setting has been described previously.[19] The purpose of this retrospective study was development of the sepsis sniffer algorithm. Thus, no patients admitted to the ICU with research consent were excluded from this study, including those patients with goal-

limiting care preferences, such as do-not-resuscitate/do-not-intubate (DNR/DNI) orders. Patients with ICU-acquired sepsis, which typically occurs several days after ICU admission, were effectively excluded from this study.[20, 21] It is unlikely that patient/proxy preferences, such as DNR/DNI status, would dramatically alter provisions of care, such as those related to transfer from the emergency department (ED) and/or hospital wards, in a way that would substantially confound the results of this study. At our institution, unless otherwise stated, patients with DNR/DNI orders receive central line placement when clinically indicated.

Patient data were collected using manual chart review and the METRIC (Multidisciplinary Epidemiology and Translational Research in Intensive Care) Data Mart, which has been described previously.[22] The data for the output response of severe sepsis was collected through manual review and scoring of all patient records by 2 trained reviewers (A.M.H., C.T.). Interobserver variability was solved by a third superreviewer (R.K.). This data set served as the criterion standard for the cohort. The data set for the full cohort (587 patients) was then randomly divided in half into derivation (293 patients) and validation (294 patients) cohorts. The derivation cohort was used for algorithm development and testing, while the validation cohort was reserved for final algorithm validation.

Algorithm Development

Sepsis Detection Component: For both manual review and scoring of patient records, as well as the first iteration of the severe sepsis sniffer (Algorithm 1), a standardized protocol for severe sepsis was used (Table 1). For the severe sepsis portion of this algorithm, this definition was divided into 3 components: suspicion of infection, SIRS, and organ hypoperfusion and dysfunction. A positive entry for all 3 of these components

within a 6-hour window between ICU admission and ICU discharge (up to 72 hours) was required for classification as severe sepsis positive. Because of the high frequency of microbial culture orders before ICU admission, particularly in patients admitted from the ED, the suspicion of infection domain was permitted to include 72 hours before ICU admission.

Delay in Recognition and Treatment Detection Component: The 2012 international guidelines for management of severe sepsis and septic shock from the SSC were used as the basis for development of the delay in recognition and treatment portion of the severe sepsis sniffer.8 Specifically, the protocol portion of these guidelines emphasize the timely need for lactate measurement, appropriate antibiotic administration, adequate fluid resuscitation, and placement of a central line for measurement of central venous pressure (CVP) and central venous oxygenation. The presence or absence of central line placement (peripherally inserted central catheter or central venous catheter) was not recorded. In cases in which CVP measurement was present at the time of ICU admission, this implies central line placement and/or CVP measurement before ICU admission but was not recorded for this ICU-specific study.

To develop a sniffer to minimize inappropriate alerts, a new data set (N=171) was created by pooling all severe sepsis alerts from the optimized algorithm using both the derivation and validation data sets (N=587). Of the 171 patients who had development of severe sepsis, 123 (72%) had no computerized physician order entry (CPOE) for severe sepsis management within the time window from ICU admission to severe sepsis alert plus 2 hours (Table 2). For reference, a CPOE for severe sepsis management in the ED and ICU was implemented at Mayo Clinic in 2005 and has remained the standard of care since.[23]

Table 1: Initial Severe Sepsis Sniffer Rules Definition

TABLE 1. Initial Severe Sepsis Sniffer Rules Definition[a,b]

Physiologic concept	EMR representation	Rule	Additional criteria
Suspicion of infection	Any culture order	Blood or lavage, stool or urine, or fluid or sputum	≥1 Event, including previous 72 h
Systemic inflammatory response	WBCs	<4.0 or >12.0 × 10^9/L	≥1 (WBCs or body temperature) event and ≥1 additional event from any of 3 remaining categories, within a 6 h window
	Body temperature	>38.0°C or <36.0°C	
	Respiratory rate	>20 breaths/min	
	Heart rate	>90 beats/min	
Organ hypoperfusion and dysfunction	Lactate	≥4.0 mmol/L	≥1 Event
	SBP	<90 mm Hg	≥1 Event
Shock	Vasopressors	Norepinephrine, epinephrine, dopamine, vasopressin, or phenylephrine	≥1 Event
	Fluid resistant hypotension	SBP <90 mm Hg despite ≥30 mL/kg crystalloid and/or 18.75 mL/kg colloid fluid bolus	Within a 3 h window
Delay in recognition and treatment	Lactate	>0 Measurements	Within 2 h of severe sepsis alert
	Central venous pressure	>0 Measurements	

[a]EMR = electronic medical record; SBP = systolic blood pressure; WBCs = white blood cells.
[b]The physiologic concepts represent the progression from sepsis to severe sepsis to septic shock. Within each physiologic concept is at least one EMR-based element (EMR representation), as well as each element's associated rule and additional criteria for use in the initial sepsis sniffer algorithm.

Table 2: Delay in Recognition and Treatment of Sniffer Development

TABLE 2. Delay in Recognition and Treatment Sniffer Development[a,b]

Variable	Cohort		
	Derivation	Validation	Total
Patients with severe sepsis	85/293 (29)	86/294 (29)	171/587 (29)
No severe sepsis CPOE	54/85 (64)	69/86 (80)	123/171 (72)
No lactate measurement	23/85 (27)	19/86 (22)	42/171 (25)
No CVP measurement	51/85 (60)	61/86 (71)	112/171 (65)
Delay (no lactate + CVP)	55/85 (65)	62/86 (72)	117/171 (68)
Delay + CPOE (overlap)	46/85 (54)	56/86 (65)	102/171 (60)

[a]CPOE = computerized physician order entry; CVP = central venous pressure.
[b]Data are presented as No. (percentage) of patients.

Algorithm Testing

Manual Chart Review: Critical appraisal of false-positive and false-negative alerts for both the sepsis detection and delay in recognition and treatment components of the sniffer began with comparison of the criterion standard against the first iteration of the improved severe sepsis sniffer (Figure 1). Critical appraisal of the first iteration of the sniffer (Algorithm 1 in the “Results” section) was performed by one reviewer (A.M.H.) manually examining all cases of disagreement between the sniffer and criterion standard for cases in which there was no interobserver disagreement. In all cases, the sources of disagreement were documented and used for generation of the second iteration of the sniffer (Algorithm 2 in the “Results” section). Critical appraisal of the second iteration of the sniffer was performed in an identical manner (Supplemental Figure, available online at http://www.mayoclinicproceedings.org), except for the inclusion of cases of disagreement between the sniffer and criterion standard in which there was interobserver disagreement (need for superreviewer and thus more complex). In all cases, the sources of disagreement were documented and used for generation of later iterations of the sniffer.

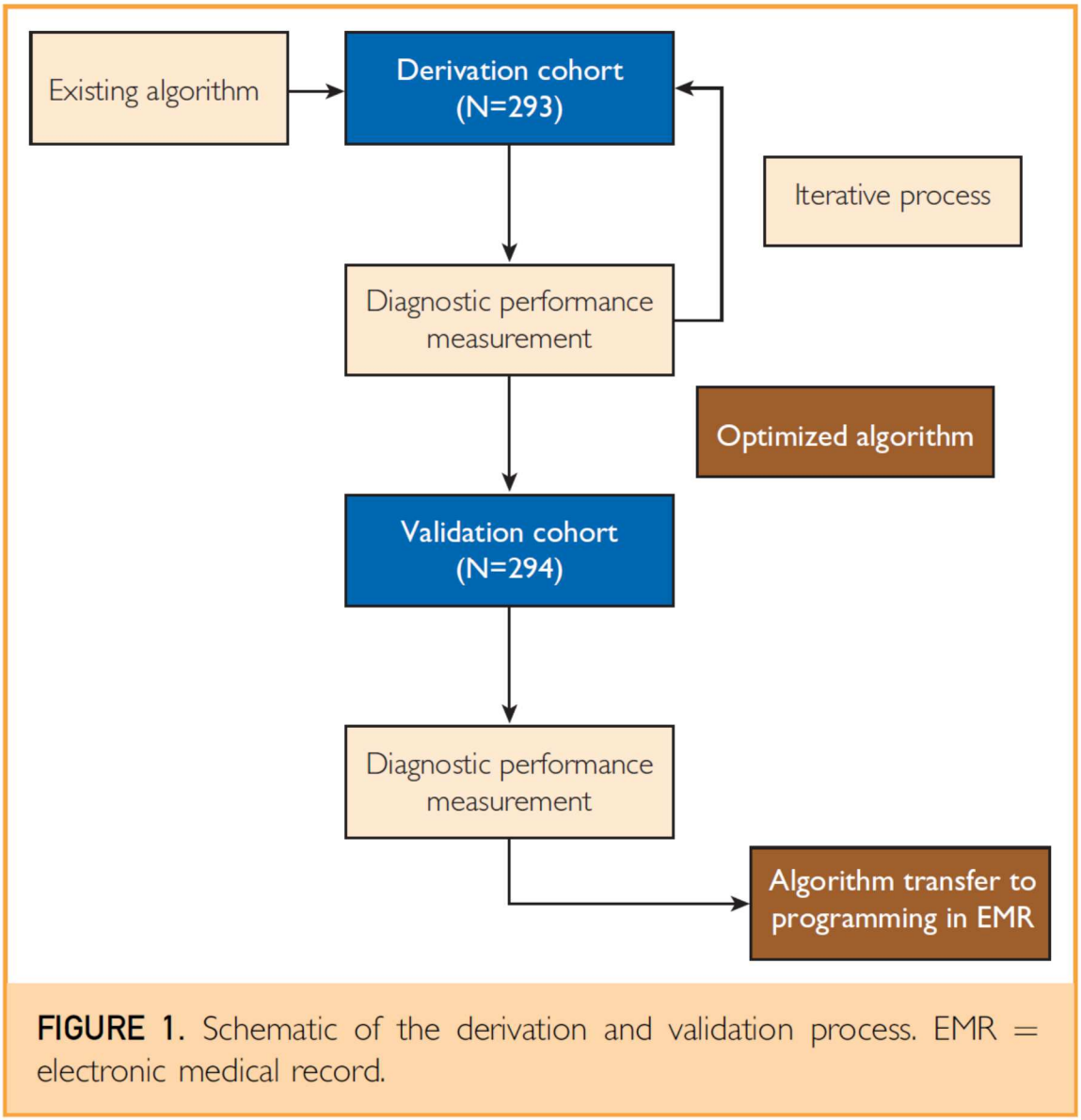


FIGURE 1. Schematic of the derivation and validation process. EMR = electronic medical record.

Figure 1: Schematic of the derivation and validation process

Recursive Data Partitioning: Optimization of both the sepsis detection and delay in recognition and treatment components of the sepsis sniffer algorithm was performed by recursive data partitioning using JMP statistical software (SAS Institute Inc). The recursive data partitioning feature is an advanced modeling and multivariate method that has been described in detail elsewhere.[24] Recursive data partitioning was performed

using all continuous and categorical variables in the existing sepsis sniffer algorithm as input factors.[25] For the purpose of node splitting criterion, all additional clinically relevant ICU data, available through METRIC Data Mart, were included as input factors.[22] Output response was the development of severe sepsis during the ICU stay.

Algorithm Refinement—Iterative Process

This recursive data partitioning process resulted in the generation of an optimized decision tree for the detection of severe sepsis and delay in recognition and treatment. On the basis of this result, a new sepsis sniffer was generated. Using this optimized algorithm, diagnostic performance measurements were recalculated and compared with those of the existing sepsis sniffer. In parallel, critical appraisal of false-negative and false-positive alerts was performed by manual review to determine the source of error. Both of these processes were repeated in iteration until an improved algorithm was generated. To optimize the original algorithm, these calculations were repeated following perturbation of the existing rules, as described previously. Next, this process was repeated in iteration until sufficient optimization was achieved. To validate the optimized sepsis sniffer algorithm, this process was repeated using the validation cohort. The results of these measurements were used to determine if the improved sepsis sniffer algorithm was superior to the original algorithm.

Outcome Measurement

The ability of the existing or improved severe sepsis algorithm to detect severe sepsis was evaluated using derivation and validation cohorts, which served as unique data sets. Diagnostic performance measurements—including the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each algorithm to detect sepsis—were then compared with the criterion standard of manual chart review.

To derive an optimized sepsis sniffer algorithm, the sensitivity, specificity, PPV, and NPV of the original sepsis sniffer algorithm to detect sepsis were calculated using the validation cohort.

Statistical Analyses

In addition to recursive data partitioning, JMP statistical software (JMP Pro version 11.1.1, SAS Institute Inc) was used for all statistical analyses. For all analyses, 2-sided significance testing was performed with P<.05 considered statistically significant. Analyses performed included the Student t test, the χ^2 test, and Cohen k coefficient, as appropriate.

RESULTS

For all study results, there was no statistically significant difference between the deviation and validation cohorts with respect to age (P=.79), sex (P=.54), hospital length of stay (LOS) (P=.44), ICU LOS (P=.70), Sequential Organ Failure Assessment score (P¼.72), and Acute Physiology and Chronic Health Evaluation III score (P=.23) (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). The k value for interrater agreement for severe sepsis was 0.74 (substantial agreement, 0.61-0.80).[26, 27] However, agreement between the criterion standard and the first iteration of the sepsis sniffer (Algorithm 1) was not as good. In particular, the sensitivity and NPV of Algorithm 1 were relatively low (Table 3). As a result, critical appraisal of false-positive and false-negative alerts was performed on the derivation cohort (N=293) for cases in which there was no interobserver disagreement (N=26). These results were used to perform optimization of the initial severe sepsis sniffer algorithm. At this point, critical appraisal for cases in which there was interobserver disagreement (need for

superreviewer and thus more complex) was not performed (N=18). For all other cases (N=249), there was agreement between the criterion standard and Algorithm 1.

Supplemental Table 1: Cohort characteristics

Variable	Derivation (N = 293)	Validation (N = 294)	*P* value
Age (± SD)	63.7 ± 18.5 years	63.3 ± 19.0 years	*.79*
Sex (% male)	52% (N = 151)	54% (N = 159)	*.54*
Hospital LOS, (± SD)	7.1 ± 6.7 days	7.6 ± 8.4 days	*.44*
ICU LOS, (± SD)	2.1 ± 2.6 days	2.2 ± 3.1 days	*.70*
SOFA score, Day 1 (± SD)	4.6 ± 3.5	4.5 ± 3.5	*.72*
APACHE III score, Hour 1 (± SD)	61.6 ± 25.6	59.1 ± 23.0	*.23*

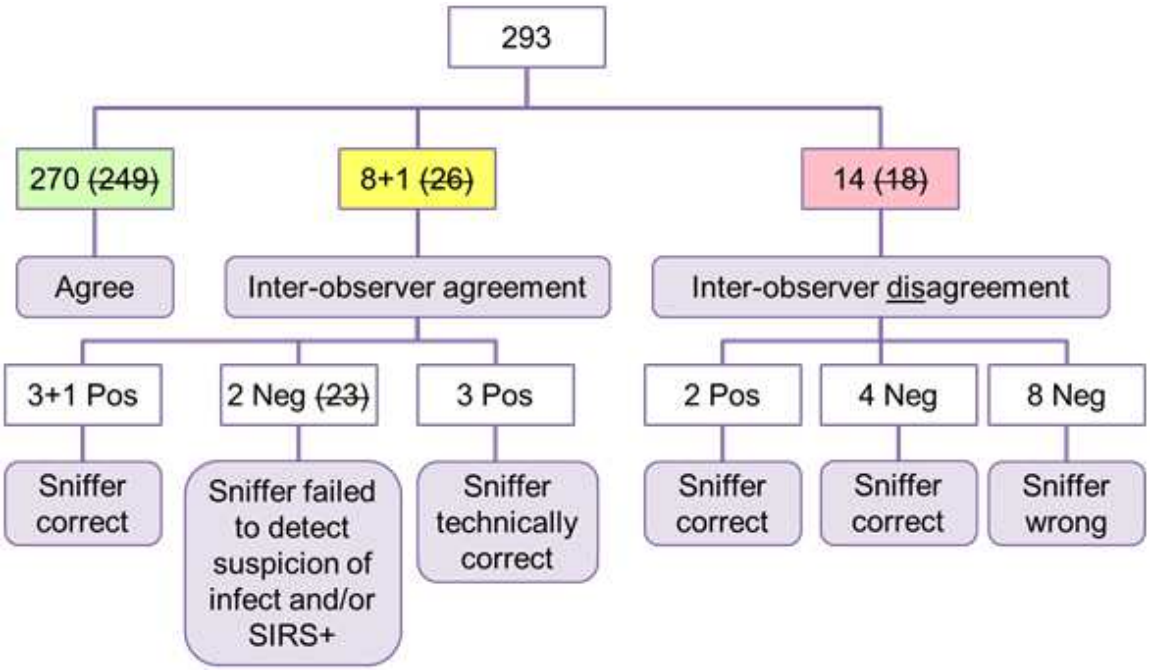
After optimization and debugging, the sensitivity and NPV of the second iteration of the sepsis sniffer (Algorithm 2) was considerably improved compared with Algorithm 1 (Table 3). The number of cases of disagreement between the criterion standard and Algorithm 2, for which there was no interobserver disagreement, was reduced from 26 to 9 (Supplemental Figure 1). The number of cases of disagreement between the criterion standard and Algorithm 2, for which there was interobserver disagreement, was also reduced from 18 to 14. Although fundamentally more complex (because of the need for the superreviewer), critical appraisal of all of these cases was performed. Most of these cases were likely either severe sepsis of short duration or failure of Algorithm 2 to detect suspicion of infection and/or identify positive SIRS criteria. However, the number of cases of agreement between the criterion standard and Algorithm 2, as compared with Algorithm 1, was increased from 249 to 270. Thus, this optimized and debugged sniffer was used to begin introducing and testing new variables as markers of organ dysfunction in subsequent sniffer iterations.

Table 3: All Iterations Performed for Sepsis Sniffer Optimization

TABLE 3. All Iterations Performed for Sepsis Sniffer Optimization

Algorithm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Algorithm 1 (initial)	59	97	92	83
Algorithm 2 (debugging)	82	97	93	92
Algorithm 3 (MAP)	82	95	90	92
Algorithm 4 (bilirubin)	82	96	92	92
Algorithm 5 (platelets)	82	95	89	92
Algorithm 6 (INR)	82	94	87	92
Algorithm 7 (mechanical ventilation)	82	93	86	92
Algorithm 8 (creatinine)	82	97	93	92
Algorithm 9 (PaO_2/FIO_2)	82	91	81	92
Algorithm 10 (urine output)	82	89	79	91
Algorithm 11 (GCS score)	82	92	83	91
Validation (using Algorithm 2)	80	96	92	91

GCS = Glasgow Coma Scale; INR = international normalized ratio; MAP = mean arterial pressure; NPV = negative predictive value; PPV = positive predictive value.



Supplemental Figure 1: Results of manual review of cases of disagreement between the gold standard (manual chart review) and Algorithm 2 (optimized algorithm). Note: "(XX)" represents the same analysis, but for Algorithm 1 (cases of inter-observer disagreement not examined). The absence of this notation indicates no change between Algorithm 1 and 2. Likewise, "+1" indicates the addition of a case that was not present in that category for Algorithm 1. "Pos" and "Neg" indicate a positive or negative Algorithm 2 (sepsis sniffer) result. "Sniffer technically correct" indicates cases where criteria were met, but the presence of only single data points to meet criteria and/or short ICU length of stay make a true diagnosis of sepsis unclear.

To test whether additional markers of organ dysfunction beyond high lactate level and low systolic blood pressure have the potential to be useful in detecting severe sepsis with the sepsis sniffer, 9 additional variables (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org) were identified on the basis of physiologic rationale and existing guidelines.[8] To test this hypothesis, each variable was introduced individually into the organ hypoperfusion and dysfunction domain of the second iteration of the sepsis sniffer (Algorithm 2) with the derivation data set. As with high lactate level and low systolic blood pressure, only 1 of 3 possible positive alerts in this category was necessary to trigger a positive alert in this domain. However, introduction of these variables into Algorithm 2 (debugged sepsis sniffer) did not increase the sensitivity, specificity, PPV, or NPV of the sniffer (Algorithms 3 through 11, Table 3). Thus, the approach of recursive data partitioning was also used for sepsis sniffer optimization.

For recursive data partitioning, all initial binary (positive or negative) variable results from Algorithm 2 and all 9 additional binary variables (Supplemental Table 2) were included in the analysis with the derivation data set. The binary criterion standard of severe sepsis

or no severe sepsis was used as the output for this analysis. Node splitting was performed in an unbiased fashion, with all splits determined by the statistical software. Maximization of the receiver operating characteristic curve value was used as the stopping criterion for node splitting. In this case, 6 node splits were required to maximize the receiver operating characteristic curve value (0.95). In order, these 6 splits were systolic blood pressure, SIRS criteria, suspicion of infection, high lactate level, and vasopressor use (twice) (Figure 2). On the basis of these results, Algorithm 2 was determined to be the best severe sepsis detection algorithm. To confirm this result, Algorithm 2 was applied to the validation cohort (N=294) and found to be in good agreement with the derivation cohort results (Table 3). This knowledge was then used to develop the delay in recognition and treatment portion of the sniffer.

Supplemental Table 2: Pathophysiologic Variable Rationale. Note: White background for original variables and gray background for nine additional variables.

Variable	Definition	Rationale
Suspicion of Infection	Any culture order	Infection drives sepsis
Heart rate (SIRS)	> 90	SIRS drives organ dysfunction
Respiratory rate (SIRS)	rate > 20	SIRS drives organ dysfunction
Temperature (SIRS)	> 38 or < 36	SIRS drives organ dysfunction
WBC count (SIRS)	> 12 or < 4	SIRS drives organ dysfunction
Lactate	≥ 4.0	Hypoperfusion (Sign of advanced disease)
Systolic Blood Pressure	< 90	Hypotension (Sign of advanced disease)
Vasopressors	Any use	Sign of septic shock
Fluid resistant hypotension	SBP < 90 after sufficient fluid bolus	Sign of septic shock
Mean Arterial Pressure	< 70 (at least 4 consecutive events)	Hypoperfusion (Sign of advanced disease)
Bilirubin	> 4.0	Marker of organ dysfunction
Platelets	< 100k	Marker of organ dysfunction
INR	> 1.5	Marker of organ dysfunction
Mechanical Ventilation	Any use	Marker of organ dysfunction
Creatinine Increase	> 0.5 (within 6 hour window)	Marker of organ dysfunction
PaO2/FiO2	< 300	Marker of organ dysfunction
Urine Output	< 0.5 mL/kg/hour for at least 2 hours	Hypoperfusion (Sign of advanced disease)
GCS score	< 15	Hypoperfusion (Sign of advanced disease)

When the delay in recognition and treatment component of the algorithm was applied, 42 of the 171 patients with severe sepsis (25%) had no lactate measurement from ICU admission to alert time plus 2 hours. Impressively, 112 of the 171 patients (65%) had no CVP measurement within this same time window. Combined, 117 patients (68%) had neither lactate level nor CVP measurement. Of the 171 patients with severe sepsis, 60% had both delay and no CPOE. Combined, 117 patients (68%) had neither lactate level or CVP measurement (delay in recognition and treatment). Thus, it was determined that the absence of both a lactate and CVP measurement within 2 hours of severe sepsis alert is sufficient criteria to serve as an alert trigger for delay in recognition and treatment (Table 1).

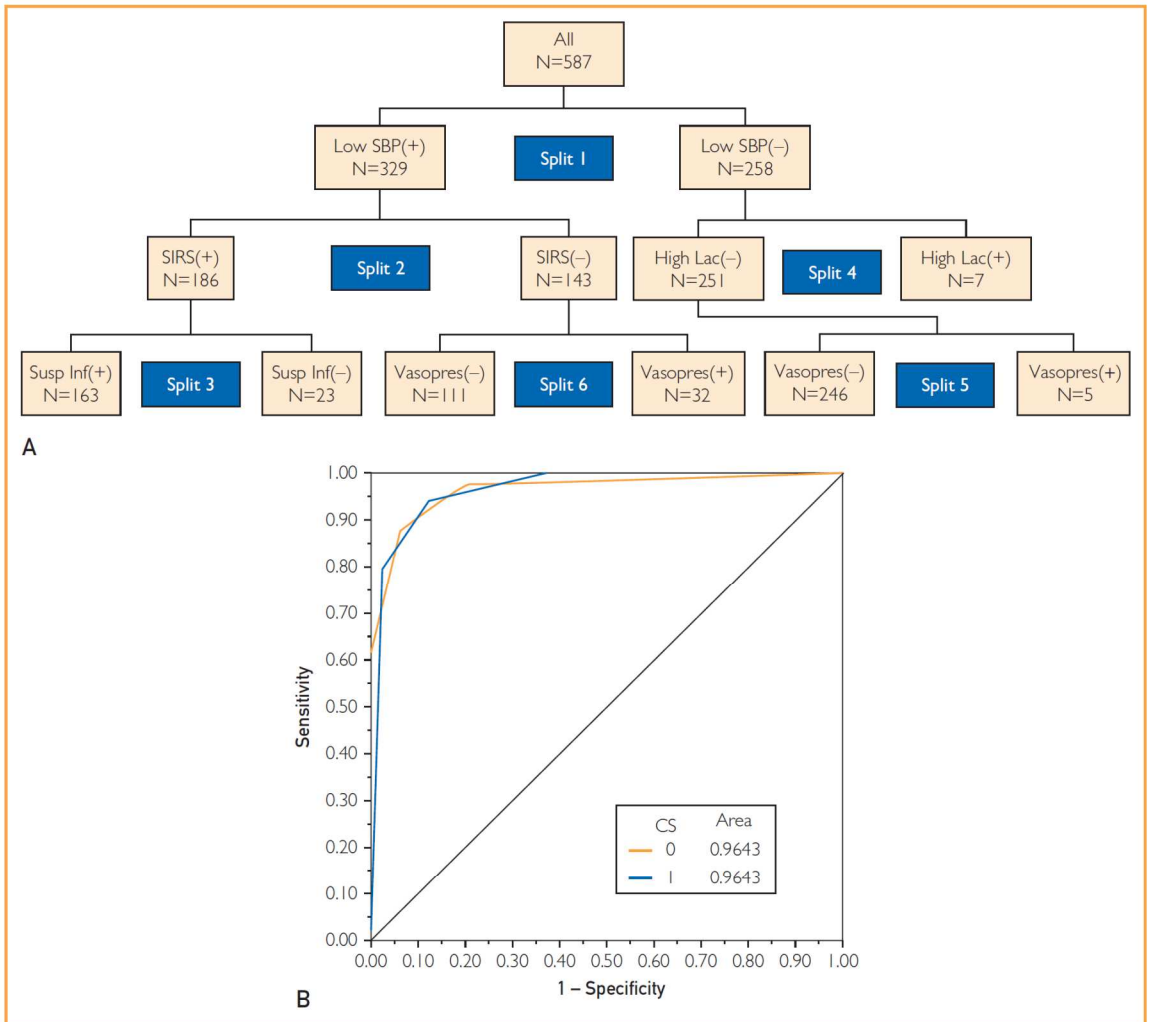


FIGURE 2. Recursive data partitioning. A, Results represented as a decision tree with the order of the 6 splits indicated. B, Receiver operating characteristic curve result using this optimized decision tree. CS = criterion standard; High Lac = high lactate level; SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome; Susp Inf = suspicion of infection; Vasopres = vasopressor use; (+) = present; (–) = absent.

Figure 2: Recursive data partitioning

DISCUSSION

Iterative optimization of an improved severe sepsis algorithm has led from a sensitivity and specificity of 59% and 97% (derivation cohort, Algorithm 1) to 80% and 96% (validation cohort, Algorithm 2), respectively, based on criteria of suspicion of infection, SIRS, organ hypoperfusion and dysfunction, and shock when applied to a validation cohort of medical ICU patients. In those patients with severe sepsis, the optimized delay

in recognition and treatment component of the sniffer identified that 68% of patients did not have a lactate level and CVP measurement in a timely manner. In order, low systolic blood pressure, SIRS positivity, and suspicion of infection were determined through recursive data partitioning to be of greatest predictive value.

There have been several prospective studies of various forms of sepsis detection and alert systems in recent years. In 2011, Sawyer et al[9] reported that the implementation of a real-time computerized sepsis alert in non-ICU patients was able to increase early therapeutic and diagnostic interventions among non-ICU patients at risk for sepsis. This study was a prospective, observational pilot study at a single academic center. Also in 2011, Nelson et al[10] reported that an automated algorithm for detecting potential sepsis increased the frequency and timeliness of some ED interventions for severe sepsis. This prospective, before-and-after study was also performed at a single academic center. In 2012, LaRosa et al[11] reported that a combined screening tool and alert system could improve compliance with sepsis bundle elements and improve survival from severe sepsis. This prospective study was also performed at a single academic center but in the ICU environment. Also in 2012, Hooper et al[12] performed a randomized trial of an automated modified SIRS monitoring system to facilitate early detection of sepsis in the ICU setting. Once again, this was a single academic center study, which failed to document improvement in outcomes such as time to first new antibiotic, time to adequate fluid resuscitation, ICU LOS, hospital LOS, and mortality. However, it is known that SSC guideline compliance is poor, even after implementation with educational interventions.[28] These pioneering studies have greatly advanced the state of automated sepsis detection and alert. However, there is still an important need for an optimized system.

As knowledge of sepsis management—as well as information overload, human error, interruption, and alert fatigue—improves, so will the accuracy of the sepsis sniffer. The delay in recognition and treatment component of the sniffer is one example. In one study of the SIRS criteria (only one component of this sepsis sniffer), the sensitivity of the SIRS criteria to detect infection compared with that of both the clinical and microbiological criterion standards of infection detection was 69%, while the specificity compared with that of both criterion standards was 35% and 32%, respectively.[29] Likewise, in perhaps the best prospective study of sepsis detection and alert in the ICU setting, the PPV of the automated system in the randomized trial by Hooper et al[12] was 41%. If the accuracy of the sepsis sniffer were improved in a prospective study, more widespread implementation could be performed through existing electronic medical record (EMR) systems to test for improvement in hard outcomes, such as improved ICU LOS and decreased mortality. Despite these challenges, there has been a decrease in mortality in patients with severe sepsis enrolled in "usual care" arms of multicenter randomized trials for the past 15 years.[30,31] However, there is considerable variability among reports of the degree of decrease, which depends largely on the methodology used in individual studies.[32] Importantly, to further reduce mortality it will be necessary to combine novel pathobiological findings with increasingly sophisticated technology for a true clinical revolution in sepsis management.[33]

Recently, results of the ProCESS[6] and ARISE[7] trials were published. Both of these US and Australia/New Zealand multicenter trials, respectively, call into question the need for elements of EGDT and the SSC guidelines/bundles, such as CVP measurement. Because the current EGDT-based SSC guidelines and bundles have existed as the standard of care for septic shock for over a decade, it is too soon to know precisely how the results of these trials will alter future standards of care. For example, a recent

multicenter cross-sectional study found that 21.2% of clinicians were unaware of the presence or absence of central venous access (peripherally inserted central catheter or central venous catheter) in their patients.[34] Smaller studies also continue to document a correlation between CVP measurement and potential reduction in mortality.[35] Thus, the true value of central venous access and/or CVP measurement as a risk stratification tool in patients with sepsis remains to be determined. This is particularly the case in the setting of clinical decision making in the context of vasopressors and abnormal lactate values, which are other components of the sepsis surveillance algorithm used in this study.

There are several limitations to this study. Like all the other studies referenced in this article, our study was conducted at a single academic medical center, which limits the potential transferability of these results to other medical centers. The single-center study design can also introduce bias into the study outcomes. In addition, this was an observational diagnostic performance study. Although this design was also used by several cited studies (and independent derivation and validation cohorts were used in this study), the observational study design has the potential to introduce more error in clinical data availability compared with the prospective study design. Our study was conducted using only adult patients in the medical ICU of an academic medical center, and thus the delay in recognition and treatment of sepsis sniffer may not be generalizable to all septic patients, especially those outside the ICU setting such as hospital wards and EDs. Although current sepsis guidelines and clinical knowledge were used to design the sniffer, it is still possible there is room for additional improvement. For example, some of the clinical variables found to not improve the sniffer may in fact be valuable for severe sepsis diagnosis in the clinical setting. Alternatively, the inclusion of other variables not analyzed in this study because of electronic infrastructure limitations,

such as timely and appropriate antibiotic administration, must be examined. Thus, a prospective (and eventual multicenter) study is necessary to further validate the sniffer by examining hard clinical end points such as ICU LOS, hospital LOS, mortality, and long-term outcomes. The process described in defining delay in recognition and treatment has not been widely reported outside the surgical and nursing literature, where it is termed *failure to rescue*. Thus, the novel application of this concept to sepsis and the critical care setting requires further exploration by other research groups. More complex methods of recursive data portioning, such as continuous variable analysis and random forests, have the potential to improve algorithm accuracy but were not employed in our study because the relatively small size of our data set limits the interpretability of such approaches.

CONCLUSION

A severe sepsis sniffer was able to correctly identify delay in recognition and treatment, which is necessary for implementation into existing EMR systems. Likewise, an algorithm for delay in recognition and treatment of severe sepsis was successfully developed. This component of the sepsis sniffer is important to decrease information overload, human error, interruption, and alert fatigue in intelligent EMR alerting systems. Combined, such a sniffer has the potential for implementation in the ICU setting.

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POTENTIAL COMPETING INTERESTS

AWARE is patent pending (US 2010/0198622, 12/697861, PCT/US2010/022750). Sepsis sniffer is patent number 20110137852. Drs. Herasevich, Gajic, and Pickering and Mayo Clinic have a financial interest relating to licensed technology described in this article. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest Policies.

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CHAPTER 3

Methods of alert delivery to critical care providers in the ICU setting

This manuscript have been submitted as a student paper to the American Medical Informatics Association 39th Annual Symposium and is currently under review for both an oral presentation and publication in AMIA Annu Symp Proc as Harrison AM, Thongprayoon C, Aakre CA, Jeng J, Gajic O, Pickering BW, Herasevich V. Barriers to implementation of simulation and alert studies in the ICU setting.

ABSTRACT

The objective of this study was to determine the best method of alert delivery in the ICU setting for urgent and non-urgent alerts by delivering simulated sepsis notifications to critical care providers in the ICU setting, via text paging and an ICU-specific patient viewer/monitoring system, and by measuring participant satisfaction. Simulated alerts were delivered to 12 providers for 2 weeks. Outcomes were time to alert acknowledgement and a structured, mixed quantitative/qualitative survey.

INTRODUCTION

The ECRI Institute (Emergency Care Research Institute) ranked “alarm hazards” as the #1 health technology hazard in their 2014 Top 10 List of Health Technology Hazards (1). With the implementation of increasingly sophisticated electronic medical record (EMR) systems, interest in the development of novel automated detection and alert systems has also increased (2). However, investigation into the best method of alert notification (text paging, EMR systems, email, phone calls, and/or text messaging) for urgent and non-urgent alerts in the hospital setting is limited (3). Likewise, investigation into the most appropriate provider (attending physicians, fellows, residents, and/or nurse practitioners/physician assistants) for alert delivery is also limited (4, 5).

Monitoring and alert systems have been developed for patient use in the home setting (6, 7). However, there has been comparatively limited investigation into methods of alert and notification delivery to these patients' providers in the hospital setting (8). Interestingly, many of these studies have been performed in the geriatric patient population, but not in the intensive care unit (ICU) setting, where the average patient age is often 65 or older (9). Studies of methods of alert delivery for clinical information delivery and clinical trial enrollment have been performed outside of the critical care setting (10, 11). Thus, there is a specific need to perform systematic investigation of alert processes in the critical care/ICU setting.

Implementation of automated detection and alert systems without consideration of factors such as best method of alert notification and most appropriate provider has the potential to result in alert fatigue (12), interruption (13), human error (14), and information overload (15, 16). Thus, there is also a need for further systematic investigation into of the role of these factors in both the hospital and ICU-specific settings (17, 18).

The objective of this study was to determine the best method of alert delivery in the ICU setting for urgent and non-urgent alerts by delivering simulated sepsis notifications to critical care providers in the ICU setting, via text paging and an ICU-specific patient viewer/monitoring system, and by measuring participant satisfaction.

METHODS

Study design and setting

This simulated alert study was performed in the medical ICU at Mayo Clinic in Rochester, Minnesota. This medical ICU consists of 2 physically adjacent 12-bed units, in close proximity to a nearby 9-bed Respiratory Care Unit (RCU). On any given month, there are approximately 15 attending physicians, 6 fellows, 4 Postgraduate Year 3 (PGY-3) residents, 6 PGY-1 residents, and 9 dedicated medical ICU nurse practitioner/physician assistant (NP/PA) staff. There are 2 shifts: 6am to 6pm ("AM") and 6pm to 6am ("PM"). On any given day, the AM shift is further divided into 2 teams. Team 1 is assigned to the majority of patients across the 2 adjacent medical ICU units. Team 2 is assigned the remaining medical ICU patients, as well as the RCU, which is further staffed on any given day by a dedicated fellow and NP/PA from the same pool of approximately 40 clinicians on staff in the medical ICU that month. This ICU setting has been described previously (9, 19). This study had IRB approval.

Study participants

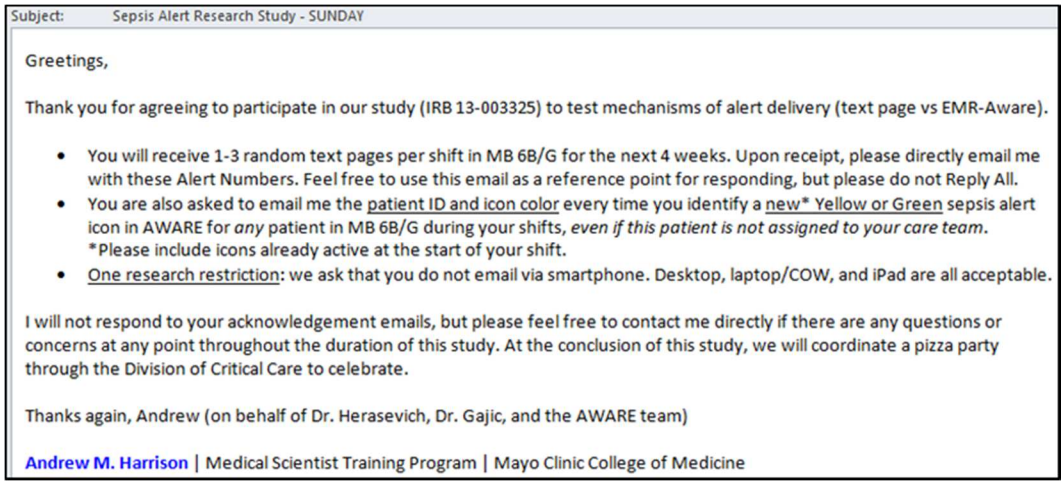
Multiple attempts to recruit participants by email and in-person resulted in enrollment of 32% of the medical ICU staff (13 out of 40). However, as this study was prematurely terminated after 2 weeks, it was necessary to exclude 1 NP/PA, recruited by subsequent email, due to unavailability in the medical ICU during the time period studied. Ultimately, 3 attending physicians (out of 15), 2 fellows (out of 6), 2 PGY-3s (out of 4), 0 PGY-1s (out of 6), and 5 NPs/PAs (out of 9) participated in this study. Of the 28 shifts that occurred during this 2-week study period (02/02/2015 "AM" through 02/15/2015 "PM"), 23 shifts (82.1%) were covered by at least 1 participant (Table 1).

Table 1: Number of shifts per participant and number of participants per shift

	Total AM Shifts	Total PM Shifts	Total Shifts	Shift, part 1	Number of Providers	Shift, part 2	Number of Providers
Attending 01	7	0	7	02/02 Mon AM	4	02/09 Mon AM	2
Attending 02	1	0	1	02/02 Mon PM	0	02/09 Mon PM	1
Attending 03	0	1	1	02/03 Tue AM	4	02/10 Tue AM	5
Fellow 01	7	2	9	02/03 Tue PM	1	02/10 Tue PM	0
Fellow 02	6	0	6	02/04 Wed AM	3	02/11 Wed AM	5
Resident 01	5	5	10	02/04 Wed PM	1	02/11 Wed PM	0
Resident 02	7	2	9	02/05 Thu AM	2	02/12 Thu AM	4
NP/PA 01	5	0	5	02/05 Thu PM	1	02/12 Thu PM	1
NP/PA 02	4	0	4	02/06 Fri AM	2	02/13 Fri AM	4
NP/PA 03	3	1	4	02/06 Fri PM	2	02/13 Fri PM	0
NP/PA 04	3	0	3	02/07 Sat AM	1	02/14 Sat AM	6
NP/PA 05	1	0	1	02/07 Sat PM	2	02/14 Sat PM	0
	49	**11**	**60**	02/08 Sun AM	3	02/15 Sun AM	4
				02/08 Sun PM	1	02/25 Sun PM	1
					27		**33**

Simulation study procedures

Participants agreed to participate in this study for the month of February 2015 (02/02 through 02/28). The evening before each subsequent “AM”/“PM” shift, participants for these upcoming shifts received a detailed email reminder with instructions (Figure 1). Briefly, participants randomly received up to 3 simulated sepsis alert text pages per shift. The timing of these sepsis alert text pages was also random. Participants were instructed to respond via email. The difference between the time to text page delivery time and the time to email response was defined as the time to alert acknowledgement.



Subject: Sepsis Alert Research Study - SUNDAY

Greetings,

Thank you for agreeing to participate in our study (IRB 13-003325) to test mechanisms of alert delivery (text page vs EMR-Aware).

- You will receive 1-3 random text pages per shift in MB 6B/G for the next 4 weeks. Upon receipt, please directly email me with these Alert Numbers. Feel free to use this email as a reference point for responding, but please do not Reply All.
- You are also asked to email me the patient ID and icon color every time you identify a new* Yellow or Green sepsis alert icon in AWARE for *any* patient in MB 6B/G during your shifts, *even if this patient is not assigned to your care team.*
  *Please include icons already active at the start of your shift.
- One research restriction: we ask that you do not email via smartphone. Desktop, laptop/COW, and iPad are all acceptable.

I will not respond to your acknowledgement emails, but please feel free to contact me directly if there are any questions or concerns at any point throughout the duration of this study. At the conclusion of this study, we will coordinate a pizza party through the Division of Critical Care to celebrate.

Thanks again, Andrew (on behalf of Dr. Herasevich, Dr. Gajic, and the AWARE team)

Andrew M. Harrison | Medical Scientist Training Program | Mayo Clinic College of Medicine

Figure 1: Detailed daily email reminder to participants with complete instructions

Participants were also instructed to respond via email whenever they noticed any new "yellow" or "green" sepsis alert icon (on either Team 1 or Team 2) in Ambient Warning and Response Evaluation (AWARE), an ICU-specific patient viewer/monitoring system, which was developed at Mayo Clinic (20). Briefly, AWARE has been demonstrated to improve provider task load, errors of cognition, and performance (21). It has been in routine use in clinical practice in the medical ICU at Mayo Clinic since July 2012 (2.5 years ago, as of the time of this study) (22). A sepsis detection and alert system has also been developed at Mayo Clinic and more recently (December 2014) implemented into AWARE (23). In this context, yellow alerts represent automatic (or manual) sepsis detection and green alerts represent automatic detection of completion of the 4 elements of the 3-hour Surviving Sepsis Campaign "bundle" (24). Once triggered, a yellow alert persists for at least 6 hours (Figure 2). Although these alerts can be silenced by provider acknowledgement during routine practice of care, frequent failure to do so often results in the persistence of these alerts (in the context of persistent sepsis) for many more hours or even days. Green alerts automatically revert to "no sepsis detected" after 3 hours, unless additional automatic (or manual) triggers occur. Over the course of this 2-week, 28-shift study, 28 patients triggered at least 1 yellow and/or green alert. Based on the 82.1% shift coverage achieved in this study (Study participants section above), it was possible for participants to acknowledge AWARE alerts for 23 of these 28 patients (82.1%). For reference, the median number of potential AWARE alert acknowledgements per shift was 2 (IQR 1 to 4). The minimum and maximum numbers were 0 and 5, respectively.

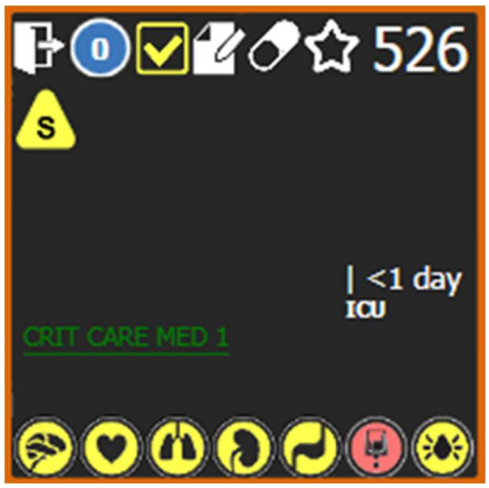


Figure 2: Yellow sepsis alert icon in upper left hand corner in sample patient display in AWARE

Based on the above randomization, the number of actual text page alerts and number of potential AWARE alert acknowledgements was roughly equal. Thus, the two comparison arms were sufficiently balanced to answer the objective of this simulation study (Figure 3). For both text pages and AWARE, participants were instructed to respond by email via any mechanism except smartphone. This was due to the potential for this specific method of alert response to unequally affect some measured outcomes in the quantitative portion of the structured, mixed quantitative/qualitative survey, such as difficulty of alert acknowledgement.

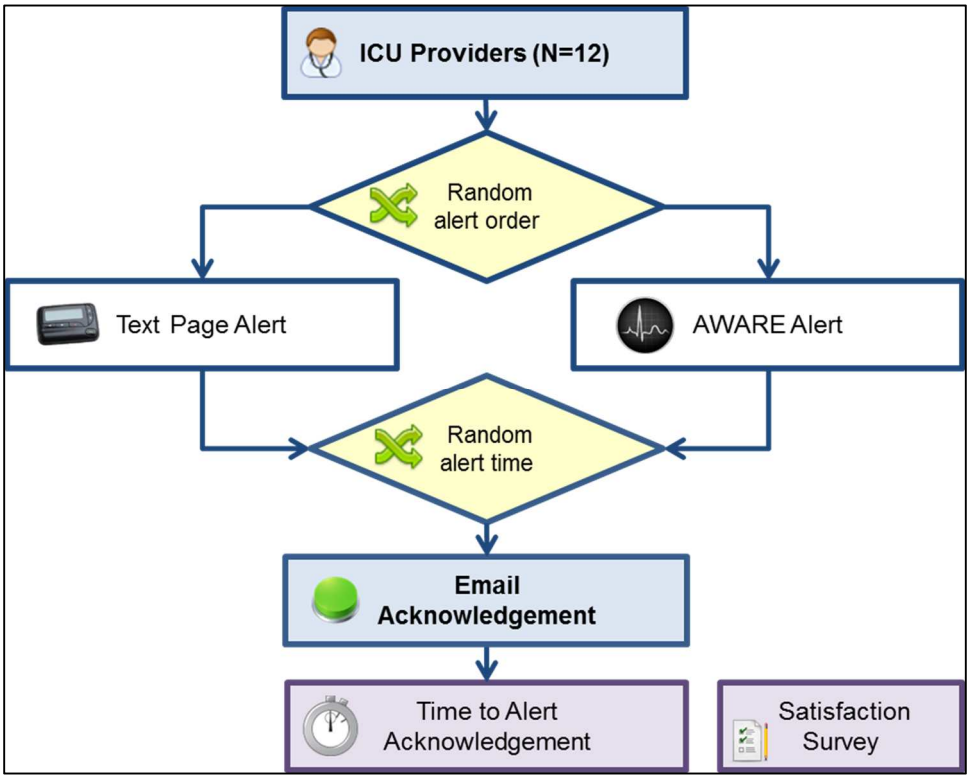


Figure 3: Schematic of the sepsis alert simulation study procedure

Survey design

At the conclusion of the sepsis alert simulation portion of this study, all 12 participants completed a structured, mixed quantitative/qualitative survey. This survey consisted of 5 demographic questions, 6 five-point Likert scale questions, 2 “select one or more” questions, and 2 free-text qualitative response questions (Figure 4 in the Results section). In part, these questions were designed based on published provider satisfaction surveys of alert methods for use in the hospital (10) and critical care (11) settings.

Outcomes

The difference between the time to text page delivery time and the time to email response was defined as the time to alert acknowledgement. The structured survey (described in the Survey design section above) consisted of mixed quantitative and qualitative questions. At the conclusion of both the sepsis alert simulation and survey portions of this study, an informal group interview in the format of a noon pizza party was conducted to both thank the participants and gather addition feedback on the barriers faced in both implementation of this simulation study and alert studies in general in the ICU setting. The group interview was attended by 4 of the 12 participants.

Statistical analysis

Data for the occurrence of sepsis alerts in AWARE was extracted directly from the AWARE middleware database and Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) Data Mart, a near-real time relational database of EMR data, which was developed at Mayo Clinic and has been described previously (25).

Data was queried using SQL scripts in JMP (Version 11 Pro, SAS Institute, Cary, NC), a statistical software package with Open Database Connectivity (ODBC) to function as an API for Database Management Systems (DBMSs). Specifically, JMP was used as a Relational Database Management System (RDBMS) to query METRIC Data Mart. JMP was also used for data collection. The statistical software features of JMP were used for all statistical analysis, including the two-sided Student's t-test and the Chi-squared test. For all analyses, a p-value of less than 0.05 was considered to be statistically significant. For all median values, interquartile range (IQR) is reported.

RESULTS

Prior to initiation of this study, a 1-day feasibility pilot was performed in January 2015 using 7 medical ICU providers recruited in person that day. Based on the result of this feasibility study (data not shown), it was determined that sufficient text page alert and AWARE sepsis alert acknowledgements could be obtained in the ICU setting to make this simulation study feasible. Based on the results of this feasibility pilot, participant instructions were also optimized.

Participants (N=12) were recruited for 1 month based on power calculations designed to discriminate between clinically significant differences in median time to alert acknowledgement between simulated sepsis text page alerts and real sepsis alerts in AWARE. However, after 2 weeks, with a text page response rate of 51.3% (N=156) and AWARE response rate of 3.4% (N=148), this study was prematurely terminated (Table 2). The primary outcome of this study, time to alert acknowledgement, was median 2 minutes for text page responses (N=80) and median 274 minutes for AWARE response rates (N=5). Although this result approached statistical significance (p-value 0.053), the

large difference between median acknowledgement times and low AWARE response rate confounds interpretation of statistical significance.

Table 2: Comparison of alert response rate and median time to alert acknowledgement between simulated sepsis text page alerts and real sepsis alerts in AWARE

	Text paging (N=156)	**AWARE (N=148)**	***p*-value**
Alert response rate (N)	51.3% (80)	3.4% (5)	0.001
Median time to alert acknowledgement (IQR)	2 mins (1 to 31.5)	274 mins (130 to 517)	0.053

At the conclusion of the sepsis alert simulation portion of this study, all 12 participants completed a structured, mixed quantitative/qualitative survey (Figure 3). For the quantitative portion of the survey, clinicians found notification by text paging to be slightly more disruptive than notification by AWARE (3 versus 2 on a 5-point Likert scale). Clinicians found acknowledgement of text paging and AWARE to be equally disruptive (scale 3). However, it is noteworthy that only 3 of the 12 participants (NP/PA 01, NP/PA 04, and NP/PA 05) acknowledged only 5 of 148 potential sepsis alerts in AWARE, while all 12 participants acknowledged at least 1 simulated sepsis text page. When text paging was compared directly to AWARE, there was a clear preference for text paging for both non-urgent (scale 2) and urgent (scale 1) alerts. When asked to “select one or more” (text paging, AWARE, email, phone call, text message, or other), the results for non-urgent alerts were mixed. However, when asked the same question for urgent alerts, the preference was once again clearly text paging.

For the qualitative portion of the survey, 11 out of 12 participants provided “at least one suggestion for improving alert/notification delivery” (Figure 5). Attending physicians, fellows, residents, and NPs/PAs acknowledged limited overall use of AWARE in the medical ICU setting, despite implementation 2.5 years earlier (July 2012). Beyond this,

suggestions varied greatly both by individual clinician and provider group. However, there was a general theme concerning new technology in the ICU setting and its potential impact on alert fatigue, interruption, human error, and information overload for both urgent and non-urgent alerts.

Age (years): **41.0 (29.3 to 43.5)**
Years in practice: **6.5 (2.3 to 14.8)**
Years, months, weeks, or days working with the Mayo Clinic EMR: **2.5 years (1.1 to 13.3)**
Years, months, weeks, or days working in the medical ICU: **1.1 years (0.7 to 2.8)**
Years, months, weeks, or days working with AWARE: **1.4 years (0.6 to 2.5)**

Please rate 1 through 5: 1 (Never), 2 (Rarely), 3 (Sometimes), 4 (Frequently), or 5 (Always)

- Was notification by paging disruptive? **3 (2 to 3)**
- Was notification by AWARE disruptive? **2 (1 to 2)**
- Was paging acknowledgment difficult? **3 (1 to 4)**
- Was AWARE acknowledgment difficult? **3 (1 to 4)**

Please rate 1 through 5: 1 (Always paging), 2 (Mostly paging), 3 (No preference), 4 (Mostly AWARE), 5 (Always AWARE)

- Which would be your preferred method of non-urgent alert/notification? **2 (1 to 5)**
- Which would be your preferred method of urgent alert/notification? **1 (1 to 2)**

For the questions below, if multiple options are preferred, please select more than one.

- The best method for non-urgent clinical alert/notification is (circle or **bold**)
  Paging **(6)** AWARE **(5)** Email **(3)** Phone call **(0)** Text message **(2)** Other: **none (1)**
- The best method for urgent clinical alert/notification is (circle or **bold**)
  Paging **(11)** AWARE **(1)** Email **(0)** Phone call **(2)** Text message **(1)** Other: **(0)**

Please provide at least one suggestion for improving alert/notification delivery:

11 out of 12 participant provided a response.

Please provide any additional comments you wish:

4 out of the 11 participants above also provided an additional comment.

Figure 4: Facsimile of the structured, mixed quantitative/qualitative survey provided to the participants with all quantitative results overlaid: median (IQR)

For the qualitative portion of the survey, only 4 out of 12 participants provided “any additional comments”. It is noteworthy that 3 of these 4 respondents were the same 3 NP/PA participants to acknowledge any sepsis alert in AWARE (NP/PA 01, NP/PA 04,

and NP/PA 05). Interestingly, 1 of these NP/PA participants commented that “I became more ‘aware’ of the critically ill patients by participating – not only on my team but my colleagues’ team as well. Became more mindful to offer assistance.” This is in reference to the fact that the medical ICU is divided into 2 teams (Team 1 and Team 2) during the “AM” shift.

The informal group interview (noon “pizza party”) to thank the participants and gather additional feedback on the barriers faced in both implementation of this simulation study and alert studies in general in the ICU setting was attended by the same 4 participants (1 attending physician and 3 NPs/PAs) who provided “any additional comments” on the structured, mixed quantitative/qualitative survey. Concerns were once again raised in acknowledgement of the limited overall use of AWARE in the medical ICU setting, despite longstanding implementation. Concerns were once again raised regarding alert fatigue, interruption, human error, and information overload. In addition to the comments reflected in the qualitative portion of the survey, one NP/PA admitted to not using AWARE. Another admitted to using it, but not acknowledging any sepsis alerts in AWARE due to difficulty of response in the ICU setting. The failure to recruit any of the 6 PGY-1 residents and only 2 of the 4 PGY-3 residents was also raised. Reasons cited for this failure included lack of resident interest in learning new tools not immediately applicable to their next (non-ICU) rotation and general lack of interest in participation in research studies in the various departments/divisions through which they rotate.

Please provide at least one suggestion for improving alert/notification delivery:
Attending 01: Having a nurse pay closer attention to the patient and be less involved in online shopping/facebook checking (something I see way too often) and not to hesitate to notify the clinician when something is not right. Sometimes when I pass by, there is no one around and patient is hypotensive and looks very ill, and no one is aware of it because nurse is on a break and the other nurse doesn't know the patient and is otherwise occupied.
Attending 02: Text page for urgent issues should work. For non-urgent issues, creating more "in-baskets" or messages will create fatigue
Attending 03: Text message to phone or pager (phone preferred). Alternative would be a notification to phone through Synthesis or whatever the future app EMR might hold. This would be the most preferred for those of us that don't live glued to scanning the AWARE home screen.
Fellow 01: When notifying with pager add patient details too like room number, clinic number etc
Fellow 02: Most of residents do not use AWARE regularly. AWARE compliance need to be improved if messages are to be delivered by AWARE
Resident 02: I prefer pages. I'm still not used to using AWARE. If there is a truly urgent matter, I prefer a phone call to the portable phone.
NP/PA 01: I like paging as I always have it with me. I don't always have AWARE even with my iPAD that I have to log in to every 5-10 minutes.
NP/PA 02: No E-mial
NP/PA 03: Please use the pager for all urgent clinical alerts. Providers do not always have their Ipads or access to a computer, particularly during when spending time in patient rooms and in discussion with families.
NP/PA 04: Paging is best as I do not always have up e-mail if with patients, etc.. Text pages worked well. Just for thought: what if page did not go through… should there be a second option in place? **Duplicate Page ** notification
NP/PA 05: It is more difficult to keep up in the notifications through AWARE, especially if you don't always use the aware program throughout the day. I feel that the paging system would make me more prone to look at aware for a sepsis alert, but I feel that it would become a bit much and put to the side if I received a page for every sepsis alert everyday shift, all day. A suggestion would be to page with red alerts only or if no one has "claimed" a sepsis warning patient to remind us.

Please provide any additional comments you wish:
Attending 03: Native AWARE app would be great, with swiping between screens to move from organ system to organ system for those of us that are not in love with big clunky iPads … yes, even the ipad mini is too big for my taste.
NP/PA 01: Paging will get me alerted to soonest.
NP/PA 04: None, I hope my participation helped with the survey. I became more "aware" of the critically ill patients by participating – not only on my team but my colleagues' team as well. Became more mindful to offer assistance.
NP/PA 05: Due to my schedule during the trial period, I only worked a couple of shifts, which may have altered my input as I did not get accustom to it or have a lot of time working with the paging system. Thanks.

Figure 5: All qualitative responses to the structured, mixed quantitative/qualitative survey reproduced in their entirety, including typographical errors

DISCUSSION

The objective of this simulated alert study, performed in the medical ICU setting, was to determine the best method of alert delivery in the ICU setting for urgent and non-urgent alerts by delivering simulated sepsis notifications to critical care providers in the ICU setting via text paging and AWARE (an ICU-specific patient viewer/monitoring system). After 2 weeks, with a text page response rate of 51.3% (N=156) and AWARE response rate of 3.4% (N=148), this study was prematurely terminated. The primary outcome of this study, time to alert acknowledgement, was median 2 minutes for text page responses (N=80) and median 274 minutes for AWARE response rates (N=5). The structured, mixed quantitative/qualitative survey portion of this study and group interview raised concerns regarding alert fatigue, interruption, human error, and information overload. Compared to other provider groups, especially PGY-1 residents, there was noteworthy participation, study compliance, and survey/interview feedback from NPs/PAs.

Successful automated detection and alert systems should reduce alert fatigue, interruption, human error, and information overload. It has been known since the 1990s that successful EMR-based notification delivery has the potential to reduce errors in the hospital setting (26-28). Recognition of the importance of alert fatigue in the hospital setting has increased significantly in recent years (29). However, implementation of an automated alert system generally must be performed in the context of information overload and complex task interruption (30, 31). Thus, a clinical alert system must be capable of more than generating clinically meaningful alerts to be useful. In the setting of complex tasks, even meaningful alerts pose the risk of interruption. It is also known that information overload can alter alert perception in the medical setting (32). This can cause clinicians to perceive alert systems negatively and deter future use (33). Thus, the

task of generating clinically meaningful alerts while concurrently minimizing information overload and task interruption is challenging.

An understanding of human cognition and user interfaces is required to address the challenge of improved alert perception and delivery (34, 35). However, perception of different methods of notification delivery is influenced by complex human cognition factors (4, 5). New methods of alert delivery have led to the development of technology to reduce errors in the hospital setting (36). However, the need for improved cognition-based development of clinician interfaces and system ergonomics has been recognized (37). This has led to systematic investigation into the relationship between computer technology, cognition, clinician behavior, and systems failure (38-40). Additionally, a framework has been proposed to address the subject of clinical information system design, implementation, and evaluation (41). In this context, a sepsis alert system for use in the critical care setting represents only one example of an EMR-based monitoring and alert system. However, the need for ICU-specific, intelligent patient monitoring systems remains longstanding (42) and faces many barriers, even at the level of implementation of simulation and alert studies.

Limitations

Beyond the barriers already outlined, this study has several limitations. (1) This is a single-center study. (2) This study was performed in a large, academic medical center. (3) The results of this study may not be applicable to areas of the hospital outside of the ICU setting. (4) Although sepsis alerts in AWARE were real, this was a simulation study. Thus, a multi-center, non-simulation study is ultimately required to address these limitations.

CONCLUSION

In this simulated alert study, performed in the medical ICU setting, response to simulated sepsis text pages was 51.3%, while response to sepsis alerts in ICU-specific patient viewer/monitoring system was 3.4% (p-value 0.001). However, determination of the primary outcome of interest, time to alert acknowledgement, was confounded by factors that a structured, mixed quantitative/qualitative survey subsequently revealed to include alert fatigue, interruption, human error, and information overload. These barriers require further study for successful implementation of simulation and alert studies in both the hospital and ICU settings.

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CHAPTER 4

Prospective implementation and testing of an improved sepsis alert system using the hospital EMR

This research study has been submitted as an abstract to the American Medical Informatics Association 39th Annual Symposium and is currently under review for a poster presentation as Harrison AM, Thongprayoon C, Park JG, Daniels CE, Clements CM, Goyal DG, Elmer JL, Gajic O, Pickering BW, Herasevich V. Before-after implementation of the sniffer for the detection of failure to recognize and treat severe sepsis.

ABSTRACT

The objective of this pilot study was to measure the impact of the automated, electronic sepsis sniffer on compliance with the 3-hour Surviving Sepsis Campaign (SSC) bundle elements. Preliminary results show that implementation of the sepsis sniffer improved overall 3-hour SSC bundle compliance with respect to percent completion, as well as average time to completion for some elements.

BACKGROUND

From 1979 to 2000, the incidence of sepsis in the U.S increased from 164,000 to 660,000 cases (1). This is an increase of 8.7% annually. Despite a decrease of total in-hospital mortality from 27.8% to 17.9% (1979-1984 versus 1995-2000), the total number of sepsis-related deaths has increased overall due to the significant increase in the incidence of sepsis. Thus, in 2002, the international Surviving Sepsis Campaign was formed and declared the goal to reduce the relative mortality of sepsis by 25% in five years (2). To date, this goal has not been achieved. However, early goal-directed therapy is known to improve outcomes in patients with severe sepsis and septic shock

(3). Furthermore, it is known that automated notification systems can prevent adverse occurrences in the hospital setting (4). Importantly, the diagnosis of sepsis and implementation of sepsis care bundles—the detailed sepsis response protocols—are complex tasks (5). Thus, successful implementation of an automated notification system to prevent severe sepsis onset will require the ability to detect failure to rescue following the diagnosis sepsis (6).

Existing sepsis detection and notification systems are not yet perfect. Early hospital detection and notification systems were developed primarily for clinical trial enrollment purposes (7-9). Although recent sepsis detection and notification systems have focused on clinical outcomes, these systems have failed to demonstrate improvement in clinically meaningful endpoints (10-13). Thus, an improved approach is necessary to develop and validate a clinically useful sepsis notification system, especially for implementation in the critical care setting.

A sniffer for the automatic screening and timely identification of patients with severe sepsis/septic shock has already been developed by Herasevich and colleagues at Mayo Clinic (9). This sniffer has been shown to improve the efficiency of patient enrollment into a time sensitive clinical study in the critical care setting (14). The development of this tool was made possible through the concurrent development of the METRIC Data Mart, a Microsoft SQL-based, research warehouse, which integrates clinical and administrative data from heterogeneous sources within the EMR to support research and practice improvement in the ICU setting (15). The objective of this study was to measure the impact of the automated, electronic sepsis sniffer on compliance with the 3-hour Surviving Sepsis Campaign bundle elements.

METHODS

Study design

Before-after study

Study setting and subjects

This study will be conducted in two adult medical ICUs and the Emergency Department (ED) at Mayo Clinic Rochester. Subjects will include all consecutive medical ICU patients who are age 18 or older with consent to participate in research studies.

Study procedures

Two medical ICUs and the ED will be studied during implementation of a severe sepsis notification system (Figure 1). The algorithm for this notification system is based on five clinical domains: (1) suspicion of infection; (2) systemic inflammatory response system; (3) organ hypoperfusion and/or dysfunction; (4) shock; and (5) failure to rescue following the diagnosis of severe sepsis and/or septic shock (16). This improved sepsis detection algorithm has been developed based on the algorithm validated in previous studies (9, 14).

Severe sepsis monitoring and notification will both occur through AWARE (Ambient Warning and Response Evaluation) (17). This rule-based patient viewer and electronic-environment enhancement program extracts and presents patient information that is relevant to the ICU setting from the standard EMR. In previous studies, AWARE has been validated and demonstrated to reduce task load and errors in a simulated clinical experiment (18). For this study, a severe sepsis alert icon was inserted into this patented clinical information delivery system (Figure 2) (19).

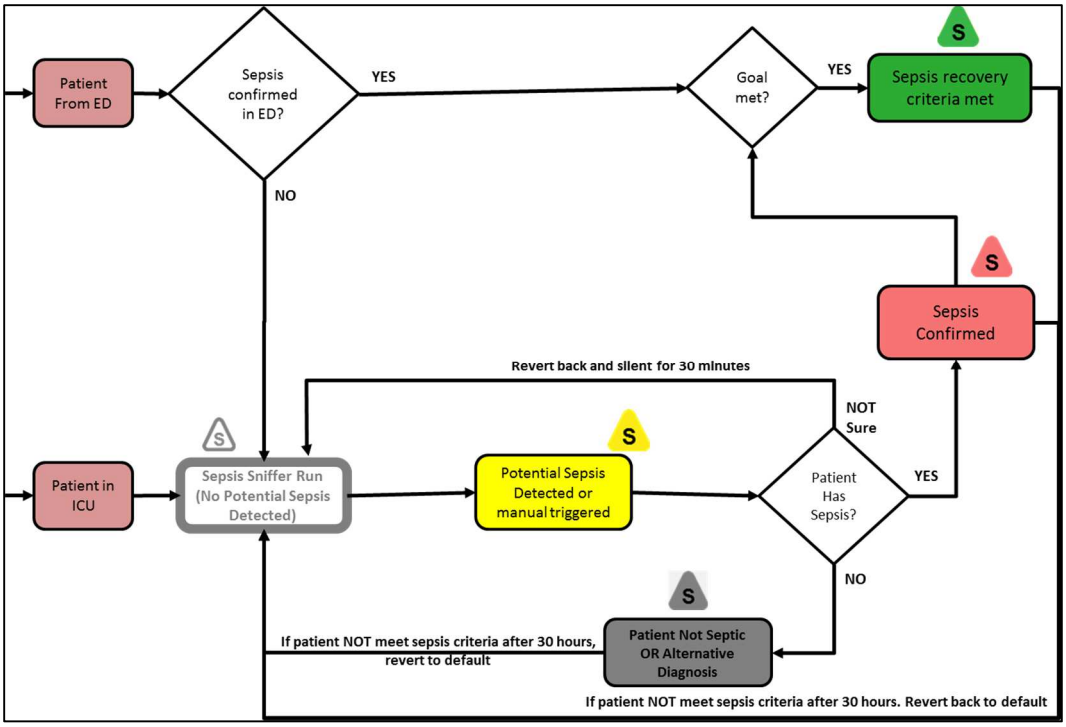

Figure 1: Sepsis Provider Workflow in the ICU and ED settings

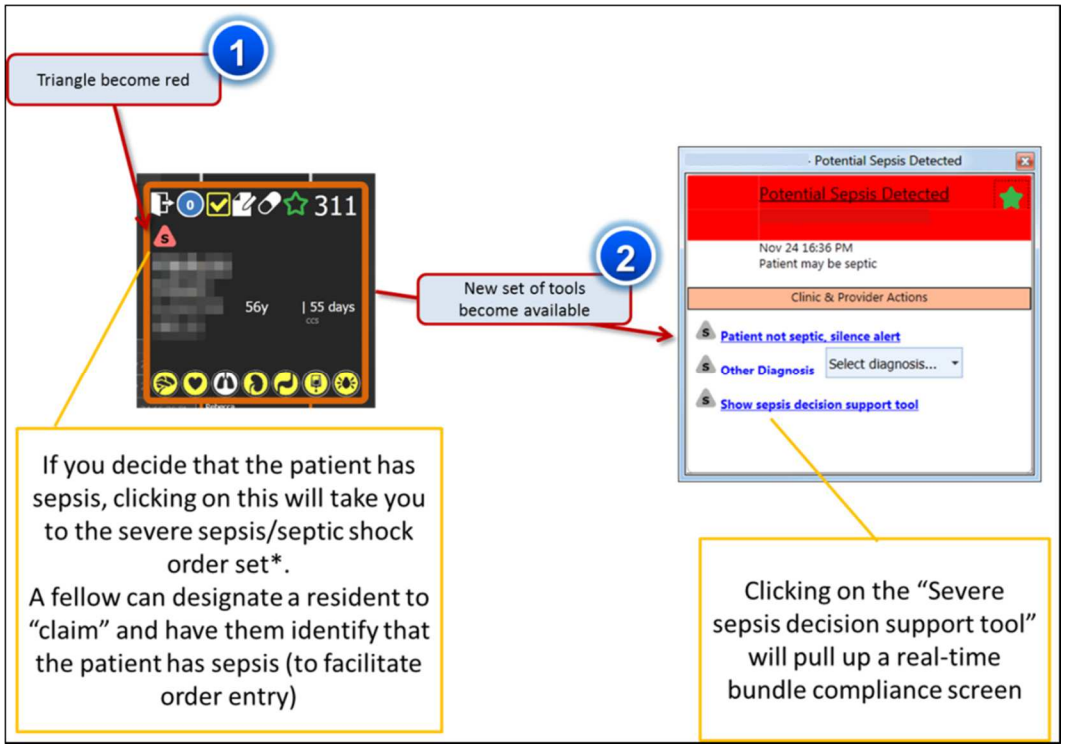

Figure 2: Severe sepsis alert icon in AWARE

Time to sepsis resuscitation in the before portion (standard of care) and after portion of this study will be measured. For both portions of this study, time to sepsis resuscitation will be measured in the presence of the severe sepsis notification system. AWARE is already in use as the standard of care at multiple ICUs throughout Mayo Clinic Rochester, including the two adult medical ICUs and the ED. Thus, alteration of workflow in the presence of this notification system will be minimal.

Data collection and measurements

For patients who develop severe sepsis while in the medical ICU or the ED, time to sepsis resuscitation will be calculated upon completion of this study. Time to sepsis resuscitation will be based on adherence to the sepsis resuscitation bundles, which have been described previously.(20) In addition to this primary outcome measurement, secondary outcomes measures that will be analyzed include average ICU length of stay, overall ICU mortality, and outcome of septic patients.

This study will use a before-after study design.(21) The study design has numerous advantages over other study designs, especially when a randomized controlled trial is not feasible. In this study, the before portion and after portion will occur in both medical ICUs and the ED.

RESULTS

Beginning 01/14/2015, the sepsis sniffer (suspicion of infection, Systemic Inflammatory Response Syndrome, and organ dysfunction components) was implemented in the medical ICU (MICU) at Mayo Clinic Rochester in AWARE—a patient-viewer and clinical decision support tool designed at Mayo Clinic to reduce risk of error and already in

routine use in the MICU—as well as in the ED. Implementation occurred after focused provider training and presentations. Using METRIC Data Mart, a relational database and near-real time duplicate of the complete hospital EMR at Mayo Clinic, data on 3-hour SSC bundle element compliance for patients before implementation of the sepsis sniffer in the MICU (January through March 2013, N=98) was compared to MICU and ED data after implementation of the sepsis sniffer (January 14th through March 2015, N=60). As some ED visits result in no hospital admission or no admission to the MICU, these outcomes are not present for all patients in the "after" cohort. Average time to completion was calculated as: "Time of bundle element completion" minus "Time of sepsis detection". Thus, negative results indicate compliance before detection. Overall percent completion of the 3-hour SSC bundle was increased after tool implementation (Table 1). Overall average time to bundle completion was reduced for all 4 elements.

Table 1: 3-hour SSC bundle compliance

	BEFORE (N = 98)	AFTER (N = 60)	*p*-value
Percent completion (%)			
3-hour SSC Bundle overall compliance	25	55	0.001
Measure lactate level	64	95	0.001
Obtain blood cultures	81	88	0.204
Administer antibiotics	61	93	0.001
Administer 30 mL/kg fluids	46	62	0.055
Average time to completion median value, mins (IRQ)			
3-hour SSC Bundle overall compliance	-4 (-137 to 148)	-126 (-159 to -18)	0.184
Measure lactate level	128 (0 to 374)	13 (-63 to 125)	0.002
Obtain blood cultures	416 (79 to 710)	153 (53 to 517)	0.019
Administer antibiotics	116 (8 to 398)	-31 (-84 to 85)	0.001
Administer 30 mL/kg fluids	-4 (-138 to 332)	-120 (-159 to 105)	0.380

DISCUSSION

Although automated notification systems have been developed for use in the clinical setting, recent attempts to develop a sepsis detection and notification system have failed to demonstrate improvement in clinically meaningful endpoints. To address this

knowledge gap, we seek to develop a new system in the specific context of failure to rescue following the diagnosis of sepsis. The expected overall impact of this research study is the integration of a sepsis notification system to reduce time to appropriate response after diagnosis of severe sepsis in the ICU and the ED settings. This knowledge will lay the foundation for the development of increasingly sophisticated automated detection systems to reduce patient mortality and enhance the ability of providers to improve patient outcomes.

CONCLUSION

Implementation of the sepsis sniffer improved overall 3-hour SSC bundle compliance with respect to percent completion, as well as average time to completion for some elements, in the ICU and the ED settings.

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CHAPTER 5

Discussion

An optimized detection algorithm to accurately identified patients with severe sepsis, which bedside clinicians failed to recognize and treat in a timely manner, was successfully developed (Chapter 2). This algorithm had a sensitivity of 80% and a specificity of 96% when applied to a validation cohort. Also, 68% of patients with severe sepsis were found to have delay in recognition and treatment, defined as no lactate and central venous pressure measurement within 2 hours of algorithm detection. This means our algorithm was able to achieve sufficient sensitivity and specificity to proceed to using this retrospectively developed algorithm for use in a prospective study in the medical ICU setting. Compared to other studies, we achieved similar sensitivities and specificities to other research groups. However, our algorithm was the first publication to successfully detect delay in failure treat severe sepsis.

The best method of alert delivery in the ICU setting for urgent and non-urgent alerts was studied by delivering simulated sepsis notifications to critical care providers in the ICU setting, via text paging and an ICU-specific patient viewer/monitoring system (AWARE), and by measuring participant satisfaction (Chapter 3). Response to simulated sepsis text pages was 51.3%, while response to sepsis alerts in AWARE was 3.4%. However, determination of the primary outcome of interest, time to alert acknowledgement, was confounded by factors that a structured, mixed quantitative/qualitative survey subsequently revealed to include alert fatigue, interruption, human error, and information overload. These barriers require further study for successful implementation of simulation and alert studies in both the hospital and ICU settings. This means significant implementation challenges provided us great insight into implementation barriers, but obscured a clear answer to the original research question of the best method of

notification delivery. However, we learned that significant clinician interest is required for any simulation study in the ICU setting. Comparison to other studies is difficult, as almost none have been performed, presumably for the reasons outlined here. However, I was able to contribute to a research project by one of my METRIC colleagues and collaborators on the effect of an electronic checklist within AWARE on critical care provider workload, errors, and performance (Appendix A). The results of this study provided me not only with insight into this subject, but the revelation that critical care providers are more likely to participate in simulation studies outside of the ICU setting.

A sepsis detection and alert system was successfully implemented in the ICU setting in AWARE (Chapter 4). A pilot study was also performed to measure the impact of this automated, electronic sepsis system on compliance with the 3-hour Surviving Sepsis Campaign (SSC) bundle elements. Preliminary results show that implementation of the sepsis sniffer improved overall 3-hour SSC bundle compliance with respect to percent completion, as well as average time to completion for some elements. This means that the sepsis detection and alert system appears to be improving sepsis management. However, it is not yet clear if these preliminary, short term outcomes will ultimately translate into long term outcomes such as hospital length of stay (LOS), ICU LOS, and mortality. Other studies suggest that even modest improvements in SSC bundle compliance leads to significant improvements in long term outcomes. However, as no academic medical institution has yet to “saturate” SSC bundle compliance, the maximum extent to which these observations can hold true is still unknown. The primary barrier to completion of this project was simply time. Originally designed as a before-after study (6 months each) in a single medical ICU in Mayo Clinic Rochester, a sudden and enormous investment of leadership scrutiny and involvement in the detailed workings of the sepsis detection algorithm—as a result of a Sepsis Management to Reimbursement Campaign

by Critical Care Medicine—resulted in logistical delays. These delays resulted from the need to include a new component for compliance with the 4 elements of the 3-hour Surviving Sepsis Campaign bundle into AWARE and launch AWARE within more ICUs at all three Mayo Clinic campuses. However, the implementation and launch of the sepsis detection and alert system in AWARE (the sepsis "sniffer") has already occurred.

Limitations: The unique barriers faced in developing the surveillance algorithm for detection of failure to recognize and treat severe sepsis (Chapter 2) were perhaps the least complex, interesting, and insightful (1). However, the unique barriers faced in testing methods of alert delivery to critical care providers (Chapter 3) and implementation of the sepsis alert system in the ICU setting (Chapter 4) were more complex and intertwined. The decision of Critical Care Medicine to launch the Sepsis Campaign was a logical choice (2), as the lethality and expense of sepsis in the in hospital setting is only further amplified in the ICU setting (3-6). Likewise, implementation of the sepsis detection and alert system in the ICU setting in AWARE was identified as a key component of this Campaign (7). However, a prospective, multi-center trial of both AWARE and the sepsis detection and alert system is ultimately required to eliminate site-specific bias and confounders, as well as to determine the generalizability to other patient populations and applicability to other academic (and non-academic) medical centers. However, even the best studies, designed in this context, will be subject to the Hawthorne effect: the recognition that the act of observation fundamentally influences the actions of the subjects under observation.

Future directions: The barriers to implementation of new technology in the technologically-sophisticated and data-rich ICU setting will eventually dissipate, in part through continued research, and in part through improvements in both informatics

infrastructure and EMR granularity, as a result of the basic passage of time. However, there will still be a need to develop other detection and alert systems for use in other syndromes of critical illness in the ICU setting. For example, starting in my first year of medical school, I validated an algorithm for computerized, automatic calculation of the Sequential Organ Failure Assessment (SOFA) score (Appendix B). The SOFA score is a longstanding and validated morbidity and mortality scoring system for use in the critical care setting. As my interest in morbidity and mortality scoring systems for use in the critical care setting never diminished (8, 9), I recently contributed to a research project to improve the accuracy of the cardiovascular component of the SOFA score with the same METRIC colleagues and collaborators (Appendix B). As another example, I was able to contribute to a research project by another METRIC colleague and collaborator on agreement between whole blood and plasma sodium measurements in profound hyponatremia (Appendix D). With this same colleague, I contributed to another project on sodium correction practice and clinical outcomes in profound hyponatremia (Appendix E). Beyond the results and conclusions described in both of these studies, profound hyponatremia was identified as a potentially important “next target” for automated, EMR-based detection and alert in a lengthy list of syndromes of critical illness (after sepsis). Another example, which is also an important component of severe sepsis management, is appropriate vasopressor use in the ICU setting. With the same METRIC colleague and collaborator referenced in Appendix A, I was able to contribute to a research project to study changing trends in the use of vasopressors in the ICU setting over a period of seven years (Appendix F).

In the future, the adoption of additional detection and alert systems in the ICU setting will allow for the adoption of this technology in other relevant settings, such as the ED, operating room, anesthesiology, and the hospital floors. As a final example with another

METRIC colleague and collaborator, I was able to contribute to a research project studying the effect of admission hyperuricemia on the risk of acute kidney injury (AKI) in hospitalized patients (Appendix G). Although frequently regarded as a syndrome of critical illness, such as sepsis or profound hyponatremia, this study was not restricted to the ICU setting. However, it is noteworthy that the profound hyponatremia studies (Appendix D and Appendix E) also included hospital floor patients and thus were not restricted to only the critical care/ICU setting either. Thus, a clear need for hospital-wide detection and alert systems is already present. As barriers dissipate with the basic passage of time (10), as well as continued research and improvements in both informatics infrastructure and EMR granularity, new technology will be implemented in the technologically-sophisticated and data-rich ICU setting. Increasingly complex mathematical modelling and/or machine learning techniques may also be adopted (11-14). However, all of the above must be carefully designed and implemented in the context of alert fatigue, interruption, human error, and information overload (15, 16). Lastly, I wish note the importance of substantial, multidisciplinary collaboration in successfully completing these studies and arriving at these conclusions.

CHAPTER 6

Conclusions

An optimized detection algorithm to accurately identified patients with severe sepsis, which bedside clinicians failed to recognize and treat in a timely manner, was successfully developed (Chapter 2). This algorithm had a sensitivity of 80% and a specificity of 96% when applied to a validation cohort. Also, 68% of patients with severe sepsis were found to have delay in recognition and treatment, defined as no lactate and central venous pressure measurement within 2 hours of algorithm detection. The best method of alert delivery in the ICU setting for urgent and non-urgent alerts was studied by delivering simulated sepsis notifications to critical care providers in the ICU setting, via text paging and an ICU-specific patient viewer/monitoring system (AWARE), and by measuring participant satisfaction (Chapter 3). Response to simulated sepsis text pages was 51.3%, while response to sepsis alerts in AWARE was 3.4%. However, determination of the primary outcome of interest, time to alert acknowledgement, was confounded by factors that a structured, mixed quantitative/qualitative survey subsequently revealed to include alert fatigue, interruption, human error, and information overload. These barriers require further study for successful implementation of simulation and alert studies in both the hospital and ICU settings. A sepsis detection and alert system was successfully implemented in the ICU setting in AWARE (Chapter 4). A pilot study was also performed to measure the impact of this automated, electronic sepsis system on compliance with the 3-hour Surviving Sepsis Campaign (SSC) bundle elements. Preliminary results show that implementation of the sepsis sniffer improved overall 3-hour SSC bundle compliance with respect to percent completion, as well as average time to completion for some elements.

CHAPTER 7

Summary

Chapter 1: Septic Shock Electronic Surveillance

- Increasingly complex mathematical modelling and/or machine learning techniques are being utilized to develop sepsis detection and alert systems
- Without consideration of alert fatigue, interruption, human error, and information overload, these system do not improve clinical outcomes in the ICU setting

Chapter 2: Developing the surveillance algorithm for detection of failure to recognize and treat severe sepsis (Aim 1)

- As sepsis is common in the ICU setting, detection and alert must target failure to recognize severe sepsis before progression to septic shock
- In addition to sepsis detection, failure to provide appropriate therapy in a timely manner is crucial to improve clinical outcomes in the ICU setting

Chapter 3: Methods of alert delivery to critical care providers in the ICU setting (Aim 2)

- In a simulation study, ICU providers were more likely to acknowledge sepsis alert via text paging versus an EMR-viewer system (AWARE)
- Whether provider preference for text paging for urgent alerts would produce the best clinical outcomes remains unknown

Chapter 4: Prospective implementation and testing of an improved sepsis alert system using the hospital EMR (Aim 3)

- With the support of the leadership of Critical Care Medicine, it was possible to successfully implement the sepsis alert system in the ICU setting
- Preliminary data from an ongoing pilot study suggests that this system has improved compliance with the Surviving Sepsis Campaign bundle

CHAPTER 8

Discussion References

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CHAPTER 9

Appendices

APPENDIX A

The Effect of an Electronic Checklist on Critical Care Provider Workload, Errors, and Performance

This manuscript has been published as Thongprayoon C, Harrison AM, Sevilla Berrios RA, O'Horo JC, Pickering BW, Herasevich, V. (2014). The effect of electronic checklist on intensive care provider workload, errors, and performance. J Intensive Care Med. PMID: 25392010.

ABSTRACT

Purpose: The strategy used to improve effective checklist use in intensive care unit (ICU) setting is essential for checklist success. This study aimed to test the hypothesis that an electronic checklist could reduce ICU provider workload, errors, and time to checklist completion, as compared to a paper checklist.

Methods: This was a simulation-based study conducted at an academic tertiary hospital. All participants completed checklists for 6 ICU patients: 3 using an electronic checklist and 3 using an identical paper checklist. In both scenarios, participants had full access to the existing electronic medical record system. The outcomes measured were workload (defined using the National Aeronautics and Space Association task load index [NASA-TLX]), the number of checklist errors, and time to checklist completion. Two independent clinician reviewers, blinded to participant results, served as the reference standard for checklist error calculation.

Results: Twenty-one ICU providers participated in this study. This resulted in the generation of 63 simulated electronic checklists and 63 simulated paper checklists. The

median NASA-TLX score was 39 for the electronic checklist and 50 for the paper checklist (P = .005). The median number of checklist errors for the electronic checklist was 5, while the median number of checklist errors for the paper checklist was 8 (P = .003). The time to checklist completion was not significantly different between the 2 checklist formats (P = .76).

Conclusion: The electronic checklist significantly reduced provider workload and errors without any measurable difference in the amount of time required for checklist completion. This demonstrates that electronic checklists are feasible and desirable in the ICU setting.

APPENDIX B

Improving the Accuracy of Cardiovascular Component of the Sequential Organ Failure Assessment Score

This manuscript has been published as Yadav H, Harrison AM, Hanson AC, Gajic O, Kor DJ, Cartin-Ceba R. (2015). Improving the Accuracy of Cardiovascular Component of the Sequential Organ Failure Assessment Score. Crit Care Med. PMID: 25785522.

ABSTRACT

Objectives: The Sequential Organ Failure Assessment score is an attractive risk prediction model because of its simplicity and graded assessment of morbidity and mortality. Due to changes in clinical practice over time, the cardiovascular component of the Sequential Organ Failure Assessment score no longer accurately reflects current clinical practice. To address this limitation, we developed and validated a modified cardiovascular component of the Sequential Organ Failure Assessment score that takes into account all vasoactive agents used in current clinical practice, uses shock index as a substitute for mean arterial pressure, and incorporates serum lactate as a biomarker for shock states.

Design: Retrospective cohort.

Setting: Mayo Clinic, Rochester, MN.

Patients: Adult patients admitted to one of six ICUs.

Interventions: None.

Measurements and Main Results: Score performance was assessed via area under the receiver operator characteristic curve. A total of 16,386 ICU admissions were included: 9,204 in the derivation cohort and 7,182 in the validation cohort. area under the receiver operator characteristic curve was significantly higher for modified cardiovascular component of the Sequential Organ Failure Assessment score than for cardiovascular

component of the Sequential Organ Failure Assessment for in-ICU mortality (0.801 vs 0.718; difference = 0.083; $p < 0.001$), in-hospital mortality (0.783 vs 0.651; difference = 0.132; $p < 0.001$), and 28-day mortality (0.737 vs 0.655; difference = 0.082; $p < 0.001$). When modified cardiovascular component of the Sequential Organ Failure Assessment score was added to the remaining Sequential Organ Failure Assessment components, the modified Sequential Organ Failure Assessment score again outperformed the existing Sequential Organ Failure Assessment score: in-ICU mortality (0.836 vs 0.822; difference = 0.014; $p < 0.001$), in-hospital mortality (0.799 vs 0.784; difference = 0.015; $p < 0.001$), and 28-day mortality (0.798 vs 0.783; difference = 0.015; $p < 0.001$). Similar results were seen in the validation cohort. Conclusions: The modified cardiovascular component of the Sequential Organ Failure Assessment score outperforms the existing cardiovascular component of the Sequential Organ Failure Assessment score in predicting patient outcomes and improves the overall performance of the Sequential Organ Failure Assessment model. This score is easily calculated, includes serum lactate as a biomarker for shock states, and incorporates all vasopressors used in current clinical practice.

APPENDIX C

Validation of computerized automatic calculation of the sequential organ failure assessment score

This manuscript has been published as Harrison AM, Yadav H, Pickering BW, Cartin-Ceba R, Herasevich V. (2013). Validation of computerized automatic calculation of the Sequential Organ Failure Assessment (SOFA) score. Crit Care Res Pract. PMCID: PMC3722890.

ABSTRACT

Purpose: To validate the use of a computer program for the automatic calculation of the sequential organ failure assessment (SOFA) score, as compared to the gold standard of manual chart review.

Materials and Methods: Adult admissions (age > 18 years) to the medical ICU with a length of stay greater than 24 hours were studied in the setting of an academic tertiary referral center. A retrospective cross-sectional analysis was performed using a derivation cohort to compare automatic calculation of the SOFA score to the gold standard of manual chart review. After critical appraisal of sources of disagreement, another analysis was performed using an independent validation cohort. Then, a prospective observational analysis was performed using an implementation of this computer program in AWARE Dashboard, which is an existing real-time patient EMR system for use in the ICU.

Results: Good agreement between the manual and automatic SOFA calculations was observed for both the derivation (N=94) and validation (N=268) cohorts: 0.02 ± 2.33 and 0.29 ± 1.75 points, respectively. These results were validated in AWARE (N=60). Conclusion: This EMR-based automatic tool accurately calculates SOFA scores and can

facilitate ICU decisions without the need for manual data collection. This tool can also be employed in a real-time electronic environment.

APPENDIX D

Agreement between whole blood and plasma sodium measurements in profound hyponatremia

This manuscript has been published as Geoghegan P, Koch CD, Wockenfus AM, Harrison AM, Dong Y, Kashani KB, Karon BS. (2015). Agreement between whole blood and plasma sodium measurements in profound hyponatremia. Clin Biochem. PMID: 25773258.

ABSTRACT

Introduction: We compared two different methods of whole blood sodium measurement to plasma sodium measurement using samples in the profoundly hyponatremic range (Na <120 mmol/L).

Materials and Methods: Whole blood pools with a range of low sodium values were generated using combinations and dilutions of pooled electrolyte-balanced lithium heparin samples submitted for arterial blood gas analysis. Each pool was analyzed five times on a Radiometer 827 blood gas analyzer and iSTAT analyzer. Pools were centrifuged to produce plasma, which was analyzed five times on a Roche Cobas c501 chemistry analyzer. An additional 40 fresh (analyzed on day of collection) excess lithium heparin arterial blood gas samples from 36 patients were analyzed on the Radiometer 827, iSTAT, and Cobas c501 as described above. The setting was a tertiary referral center. Blood samples were collected from a combination of patients in the intensive care unit, operating theaters and emergency room. Results: All methods demonstrated excellent precision, even in the profoundly hyponatremic measurement range (Na <120mmol/L using a plasma reference method). However, agreement between the methods varied with the degree of hyponatremia. In the profoundly hyponatremic range, Radiometer whole blood sodium values were nearly identical to plasma reference

sodium, while iSTAT whole blood sodium showed a consistent positive bias relative to plasma sodium in this range.

Conclusions: If whole blood, direct sodium measurements are compared to plasma sodium in profoundly hyponatremic patients, consideration should be given to using Radiometer blood gas analyzers over iSTAT, since the latter shows a positive bias relative to a plasma comparative method.

APPENDIX E

Sodium correction practice and clinical outcomes in profound hyponatremia

This manuscript is currently in revision for publication in Mayo Clin Proc as Geoghegan P, Harrison AM, Kashyap R, Ahmed A, Dong Y, Rabinstein AA, Kashani KB, Gajic O. Sodium correction practice and clinical outcomes in profound hyponatremia.

ABSTRACT

Objective: To assess the epidemiology of non-optimal hyponatremia correction and to identify associated morbidity or mortality.

Patients and Methods: Electronic medical record search identified all patients admitted with profound hyponatremia ([Na] <120mmol/L) between 1/1/2008 and 12/31/2012. Patients were classified as optimally or non-optimally corrected at 24 hours post admission. Optimal correction was defined as 5< sodium correction in 24 hours ≤ 10mmol/L. We investigated the relationship between sodium correction and demographic and outcome variables, including occurrence of osmotic demyelination syndrome (ODS). Baseline characteristics by correction outcome categories were compared using the Kruskal-Wallis test for continuous variables, and $\chi 2$ for categorical variables. Odds ratios for mortality between groups were assessed using logistic regression. Adjusted differences in hospital length of stay (LOS) and intensive care unit (ICU) LOS were assessed using Dunnett's two tailed t test.

Results: 412 patients satisfied inclusion criteria of whom 174 (42%) were admitted to the ICU. 211 (51%) were optimally corrected at 24 hours, 87 (21%) were under-corrected, and 114 (28%) were overcorrected. Both patient factors and treatment factors were associated with non-optimal correction. There was a single case of ODS. Overcorrection was not associated with in-hospital mortality or ICU LOS. When adjusted for patient

factors under-correction of profound hyponatremia was associated with an increase in hospital LOS (9.3 days, 95% CI [1.9 - 16.7]).

Conclusion: Non-optimal correction of profound hyponatremia is common. Non-optimal correction may be associated with poorer patient outcomes.

APPENDIX F

Changing Trends in the Use of Vasopressors in Intensive Care Unit: A 7 Year Study

This manuscript is currently under review for publication in Chest as Thongprayoon C, Cheungpasitporn W, Harrison AM, Srivali N, Erdogan A, Carrera P, Herasevich V, Kashani KB. Changing Trends in the Use of Vasopressors in Intensive Care Unit: A 7 Year Study.

ABSTRACT

Background: The choice of vasopressor use in the intensive care unit (ICU) depends primarily on provider preference. This study aims to describe the prevalence of vasopressor use and the trends in agent use in the ICU over the past 7 years.

Methods: All ICU admissions, including medical, cardiac, and surgical ICUs from January 2007 through December 2013 were included in this study. Vasopressor use was defined as the continuous intravenous administration of epinephrine, norepinephrine, phenylephrine, dopamine, or vasopressin within a given ICU day. The vasopressor utilization index (VUI) was defined as the proportion of ICU days on each vasoactive agent divided by the total ICU days with vasopressor usage.

Results: Over the course of this study (72,005 ICU admissions), 272,271 ICU days were generated. Vasopressors were used in 19,575 ICU admissions (27%) and on 59,811 ICU days (22%). Vasopressor use was 24,496 (41%) for vasopressin, 23,229 (39%) for epinephrine, 20,648 (34%) for norepinephrine, 9,449 (16%) for dopamine, and 7,508 (13%) for phenylephrine. There was an increasing trend in the use of norepinephrine and a decreasing trend in phenylephrine utilization. The VUI for norepinephrine increased from 0.24 in 2007 to 0.46 in 2013 and decreased for phenylephrine from 0.20 in 2007 to 0.08 in 2013. Epinephrine, dopamine, and vasopressin trends did not change.

Conclusions: Vasopressors were used in about one fourth of ICU admissions and about one fifth of ICU days. Although vasopressin is the most commonly used vasopressor, the use of norepinephrine found to have an increasing trajectory.

APPENDIX G

Admission Hyperuricemia Increases the Risk of Acute Kidney Injury in Hospitalized Patients

Portions of this manuscript are currently under review for publication in Nephrology as Cheungpasitporn W, Thongprayoon C, Harrison AM, Erickson SB. Admission Hyperuricemia Increases the Risk of Acute Kidney Injury in Hospitalized Patients.

ABSTRACT

Background and objectives: The association between elevated admission serum uric acid and risk of in-hospital acute kidney injury (AKI) is limited. The aim of this study was to assess the risk of developing AKI in all hospitalized patients with various admission serum uric acid (SUA) levels.

Design, setting, participants, & measurements: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission SUA available from January 2011 through December 2013 were analyzed in this study. Admission SUA was categorized based on its distribution into six groups (less than 3.4, 3.4 to 4.5, 4.5 to 5.8, 5.8 to 7.6, 7.6 to 9.4, and greater than 9.4 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of AKI of various admission SUA levels using SUA of 5.8 to 7.6 mg/dL as the reference group.

Results: Of 1,435 patients enrolled, AKI occurred in 263 patients (18%). The incidence of AKI and need for dialysis was increased in patients with higher admission SUA levels. After adjusting for potential confounders, SUA greater than 9.4 mg/dL was associated with an increased risk of developing AKI with odds ratios of 1.79 (95% CI 1.13-2.82). Conversely, admission SUA of less than 3.4 mg/dL and 3.4 to 4.5 mg/dL were

associated with decreased risk of developing AKI with odds ratios of 0.38 (95% CI 0.17-0.75) and of 0.50 (95% CI 0.28-0.87) respectively.

Conclusion: Elevated admission SUA was associated with an increased risk for in-hospital AKI.