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The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Assistant Dean for MSN and DNP Studies, on behalf of the program; we verify that this is the final, approved version of the student's DNP Project including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Amy P. Fisher, Student

Dr. Melanie G. Hardin-Pierce, Advisor

DNP Practice Inquiry Project Report

Screening for Sepsis: A Key Strategy for Early Identification and Management of Septic Patients

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University of Kentucky

College of Nursing

Fall 2014

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Dedication

This capstone project is dedicated to my family, whose love and support made my achievement of a Doctorate of Nursing Practice possible. To my amazing husband, Bruce, whose unwavering support, relentless optimism, and constant cheerleading kept me motivated to complete the program. To my parents, Ted and Pat Pedigo, whose guidance kept me grounded and focused when I was overwhelmed by the demands of school, work, and life. To my in-laws, John and Mary Lee Fisher, whose words of encouragement helped lighten some of my darkest days. To my stepdaughter, Alexis, whose quiet observation inspires me to be a positive role model and strengthened my drive to achieve my educational and professional goals. Thanks to all of you for helping me reach this important milestone.

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Introduction to DNP Practice Inquiry Project

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Sepsis, defined as a systemic inflammatory response to infection, is a life-threatening medical condition that rapidly progresses from severe sepsis (characterized by signs of organ dysfunction) to septic shock with fluid-refractory hypotension (Bone et al., 1992; Levy et al., 2003). It accounts for one of every 23 hospitalizations and affects an average of 4,600 new patients daily (Elixhauser, Friedman, & Stranges, 2011). Similar to other conditions, like acute myocardial infarction and ischemic stroke, treatment of sepsis is time-sensitive and patient outcomes depend on early aggressive intervention to restore adequate perfusion of organs (Dellinger et al., 2013). Half of all patients admitted for sepsis require admission to an intensive care unit (Angus et al., 2001; Martin, 2012) and more than 240,000 patients with sepsis die annually (Gaieski, Edwards, Kallan, & Carr, 2013). To put this in perspective, approximately one patient dies every two minutes as a consequence of sepsis.

Evidence-based guidelines for managing sepsis have existed for over a decade (Dellinger et al., 2004; Dellinger et al., 2008; Dellinger et al., 2013). The premise of the guidelines is that early goal-directed therapy improves patient outcomes; yet, sepsis-related mortality remains unacceptably high (Gaieski et al., 2013). The initial focus of this practice inquiry project was to determine if implementation of the guidelines affected patient outcomes as predicted. The first manuscript is a review of studies published between 2008 and 2014 that described the effects of implementing evidence-based sepsis protocols in U.S. hospitals on the delivery of diagnostic and therapeutic interventions and patient outcomes including mortality and hospital length of stay. During the review, delayed recognition of patients with sepsis was identified as one barrier to achieving the goals of therapy in a timely manner. Given that prompt recognition of sepsis is a prerequisite for implementing early goal-directed therapy, the purpose of the practice inquiry shifted to identifying effective strategies for screening patients for sepsis. The second

manuscript includes a review of studies relevant to sepsis screening practices that were published between 2004 and 2014. Findings from the review of literature related to sepsis screening suggested that an effective strategy involves monitoring for SIRS, assessing for a source of infection, and facilitating early goal-directed therapy for patients with a positive sepsis screen. The purpose of the final project was to determine if a sepsis screening protocol could facilitate earlier identification of patients with sepsis. The final manuscript consists of a description of an innovative approach to quantifying the potential impact a sepsis screening strategy could have on reducing the time to identification of sepsis at a 569-bed academic medical center in central Kentucky and the results of a simulation of screening using a retrospective medical record review.

Implementation of Sepsis Management Guidelines: A Review of the Literature

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Abstract

Sepsis is a significant health problem in the United States (U.S.) accounting for more than 1.6 million hospitalizations, \$20.3 billion in hospital costs, and more than 240,000 deaths annually. Evidence-based guidelines for the management of sepsis have been available for over a decade, yet adherence to the recommendations has not become routine practice. The purpose of this paper is to review studies published since the release of the 2008 guidelines that describe the effects of implementing evidence-based sepsis protocols in U.S. hospitals on the delivery of diagnostic and therapeutic interventions for the management of sepsis and patient outcomes including mortality and hospital length of stay. Twelve observational studies met inclusion criteria. Findings suggest that protocol-driven care may increase the frequency, timeliness, and appropriateness of diagnostic and therapeutic interventions and patients who receive care in accordance with the evidence-based guidelines will likely incur a survival benefit.

Keywords: sepsis, implementation, bundles, protocols, guidelines, sepsis campaign, patient outcomes, and mortality

Implementation of Sepsis Management Guidelines: A Review of the Literature

Sepsis is a significant health problem in the United States (U.S.) resulting in nearly 980,000 emergency department visits (Agency for Healthcare Research and Quality, 2014), more than 1.6 million hospitalizations (Elixhauser, Friedman, & Stranges, 2011), and over 240,000 deaths annually (Gaieski, Edwards, Kallan, & Carr, 2013). Although in-hospital mortality ranges from 15% to 30% (Gaieski et al., 2013), patients who survive sepsis to hospital discharge continue to be at increased risk of dying with fewer than half of them still alive one year post-discharge (Winters et al., 2010; Yende & Angus, 2007). Additionally, sepsis has been associated with development of at least one new physical limitation for survivors and a 3-fold risk for developing moderate to severe cognitive impairment (Iwashyna, Ely, Smith, & Langa, 2010), which may explain why more than one in three survivors are discharged to long-term care facilities (Elixhauser et al., 2011). Sepsis contributes \$20.3 billion in hospital costs to the annual economic burden of the national healthcare system (Torio & Andrews, 2013), but the long-term consequences of sepsis highlight the true magnitude of this public health problem.

In 2002, a collaborative effort among the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Sepsis Forum resulted in the creation of the Surviving Sepsis Campaign with the goal of reducing global mortality from sepsis (Society of Critical Care Medicine, 2014). To achieve that goal, a group of international critical care and infectious disease experts reviewed evidence to determine best practices for the management of sepsis and partnered with the Institute for Healthcare Improvement to develop two sepsis bundles (a 6-hour resuscitation bundle and a 24-hour management bundle) to facilitate implementation of their recommendations to improve the quality of care provided to patients with sepsis (Society of Critical Care Medicine, 2014). The first Surviving Sepsis Campaign

guidelines for the management of sepsis were published over a decade ago (Dellinger et al., 2004) and observational studies conducted after the initial guidelines were released showed that implementation of guideline-based sepsis protocols was associated with increased frequency and more timely administration of supportive and adjunctive therapy (Jones, Focht, Horton, & Kline, 2007; Kortgen, Niederprum, & Bauer, 2006; Micek et al., 2006; Nguyen et al., 2007; Shapiro et al., 2006) and a relative reduction in mortality by one-third to one-half (Gao, Melody, Daniels, Giles, & Fox, 2005; Jones et al., 2007; Kortgen et al., 2006; Micek et al., 2006; Nguyen et al., 2007).

The original guidelines have undergone two revisions with the most recent guidelines published in February 2013 (Dellinger et al., 2008; Dellinger et al., 2013), which further emphasize the importance of prompt treatment by establishing earlier time goals (3-hour bundle and 6-hour bundle) for achieving diagnostic and therapeutic interventions critical to the management of patients with sepsis. The 3-hour bundle includes measuring a serum lactate level, obtaining blood cultures prior to administration of antibiotics, administering broad-spectrum antibiotics, and administering 30 mL/kg of crystalloid solution to patients with hypotension or a lactate greater than or equal to 4 mmol/L (Dellinger et al., 2013). The 6-hour bundle includes initiating vasopressors for hypotension that does not respond to the initial fluid challenge to maintain a mean arterial pressure greater than or equal to 65 mm Hg, attaining a central venous pressure of greater than or equal to 8 mm Hg, achieving a central venous oxygen saturation of greater than or equal to 70%, and targeting normalization of serum lactate for those whose initial measurement was elevated (Dellinger et al., 2013).

Despite the availability of evidence-based guidelines for the management of sepsis and their association with improved patient outcomes, mortality remains high and implementation

and adherence to the guidelines has not yet become routine practice (Dellinger et al., 2013). The purpose of this paper is to review studies published since the release of the 2008 guidelines that described the effects of implementing evidence-based sepsis protocols in U.S. hospitals on the delivery of diagnostic and therapeutic interventions for the management of sepsis and patient outcomes including mortality and hospital length of stay.

Methods

Search Strategy

The Cumulative Index to Nursing and Allied Health Literature (CINAHL) and MEDLINE databases were searched using the keywords *sepsis, implementation, bundles, protocols, guidelines, sepsis campaign, patient outcomes, and mortality*. Inclusion criteria consisted of studies published between 2008 and 2014 that were conducted in the U.S. that evaluated the effect of implementing evidence-based sepsis protocols on care delivery and outcomes of adult patients (age 18 years and older) hospitalized for sepsis. Article titles and abstracts were reviewed to determine the relevance of individual studies to the purpose of this review. For studies whose relevance could not be determined by reviewing the title and abstract only, the full-text article was obtained and assessed for inclusion. Studies were excluded if the authors merely described the process of implementing a sepsis protocol without reporting its effect on patient care delivery, hospitalization, or mortality.

Search Results

Twelve studies met inclusion criteria. All twelve studies had an observational before-and-after design. Studies were conducted in academic medical centers (El Solh, Akinnusi, Alsawalha, & Pineda, 2008; Focht, Jones, & Lowe, 2009; Gurnani et al., 2010; Puskarich, Marchick, Kline, Steuerwald, & Jones, 2009; Thiel et al., 2009), community hospitals (Crowe,

Mistry, Rzechula, & Kulstad, 2010; Nguyen, Schiavoni, Scott, & Tanios, 2012; Patel, Roderman, Gehring, Saad, & Bartek, 2010; Soo Hoo, Muehlberg, Ferraro, & Jumaoas, 2009), and a comprehensive cancer center (Hanzelka et al., 2013). Only two studies involved multiple sites; Cannon et al. (2013) included eleven hospitals from nine different states and Miller et al. (2013) included eighteen intensive care units (ICUs) from eleven hospitals in two states. Sample sizes ranged from 96 to 675 patients in single-site studies (Nguyen et al., 2012; Soo Hoo et al., 2009) to 6,355 patients in a multicenter study (Cannon et al., 2013).

Researchers examined the impact of implementing sepsis protocols on the outcomes of adult patients with severe sepsis and/or septic shock in the emergency department (Crowe et al., 2010; El Solh et al., 2008; Focht et al., 2009; Hanzelka et al., 2013; Puskarich et al., 2009), intensive care unit (Miller et al., 2013; Nguyen et al., 2012; Patel et al., 2010), or hospital wide (Cannon et al., 2013; Gurnani et al., 2010; Soo Hoo et al., 2009; Thiel et al., 2009). Mortality and frequency and/or timeliness of interventions were the primary outcome measures for all studies reviewed. Other outcomes included: protocol adherence (Crowe et al., 2010; Miller et al., 2013), time to resolution of shock (Nguyen et al., 2012), ICU length of stay (El Solh et al., 2008; Focht et al., 2009; Gurnani et al., 2010; Hanzelka et al., 2013; Nguyen et al., 2012; Patel et al., 2010; Puskarich et al., 2009; Soo Hoo et al., 2009), hospital length of stay (Cannon et al., 2013; Focht et al., 2009; Hanzelka et al., 2013; Miller et al., 2013; Patel et al., 2010; Puskarich et al., 2009; Soo Hoo et al., 2009; Thiel et al. 2009), and hospital costs (Cannon et al., 2013; Soo Hoo et al., 2009). Key findings identified during this review of the literature fall into two categories: those relevant to the delivery of care and those relevant to patient outcomes. Key findings are discussed in the following section.

Key Findings

Care Delivery

Frequency and timeliness of interventions. Implementation of a sepsis protocol appears to facilitate the management of patients with severe sepsis and septic shock. Patients who received protocol-driven care versus those who received provider-driven care were given 1.5 liters (El Solh et al., 2008; Focht et al., 2009; Nguyen et al., 2012) to 3 liters (Puskarich et al., 2009) more intravenous fluids in the first six hours and nearly 5 liters more in the first 24 hours (Patel et al., 2010); had serum lactate measured 48% to 75% more often (El Solh et al., 2008; Patel et al., 2010); and were administered appropriate antibiotics 12.5% to 37% more frequently (El Solh et al., 2008; Gurnani et al., 2010; Thiel et al., 2009). Protocol-driven care was also associated with decreased time to diagnostic and therapeutic interventions. For example, Patel and colleagues (2010) demonstrated that implementation of a sepsis protocol was associated with significant reduction in times to blood culture collection (17.5 minutes, $p = .002$), first dose of antibiotics (73.5 minutes, $p = .001$), and transfer to the ICU (85 minutes, $p = .011$). Similarly, Cannon et al. (2013) found that as compared to patients who were treated for sepsis prior to implementation of a protocol, those treated for sepsis following the implementation of an evidence-based protocol received an intravenous fluid challenge and antibiotics more than one hour sooner and had their serum lactate measured three hours earlier.

Of particular interest is the study by Thiel et al. (2009), which revealed a 26% improvement in the time to appropriate antibiotic coverage from 16.6 hours to 12.3 hours ($p = .04$) after implementation of a hospital wide sepsis protocol. Considering that only 65.5% of patients in the post-protocol group received an appropriate first dose of antibiotic, this study highlights the importance of administering broad-spectrum antibiotics early to increase the

likelihood that the causative organism would be susceptible to the agents chosen. Although Focht et al. (2009) and Gurnani et al. (2010) found that protocol-driven care could facilitate earlier administration of antibiotics (by 72 and 96 minutes earlier, respectively), their findings did not reach statistical significance. Still, their findings have clinical significance given that among patients with sepsis each one-hour delay in administration of antibiotics is associated with a 7.6% decrease in survival for patients with sepsis (Kumar et al., 2006), delays greater than 4.5 hours are linked to a 2-fold increase in mortality (Gurnani et al., 2010), and receiving antibiotics after the development of shock is associated with a 2.4 increased risk for death (Puskarich et al., 2011).

Achievement of treatment goals. Not only have sepsis protocols been associated with improved delivery of interventions, but they have also been associated with significantly earlier achievement of targeted goals of therapy. For example, Cannon and colleagues (2013) observed that patients who received protocol-driven care attained a central venous pressure (CVP) of at least 8 mm Hg nearly three hours faster and a central venous oxygen saturation of at least 70% almost two hours sooner than patients whose care was provider-driven. Furthermore, Hanzelka et al. (2013) found that the proportion of patients who reached a mean arterial pressure of at least 65 mm Hg in the first 6 hours of treatment was 16% higher than those who received provider-driven care and that 17% more patients reached a goal urine output of at least 0.5 mL/kg/hour within 6 hours with protocol-driven care.

Protocol adherence. Only two studies measured protocol adherence. Crowe et al. (2010) implemented a sepsis protocol in the emergency department of a large, suburban community teaching hospital and discovered that adherence to key resuscitation measures such as infusing adequate intravenous fluids to meet central venous pressure goals, obtaining blood

cultures, measuring serum lactate, and administering antibiotics within the first six hours was greater than 90% two years after implementation. However, only 28.2% of patients had their central venous oxygen saturation measured and interventions to improve delivery of oxygen to the tissues such as administering dobutamine and transfusing red blood cells were performed even less frequently (3.7% and 19.4%, respectively). The authors speculated that chronic overcrowding in their emergency department might have contributed to the lower adherence to the more labor-intensive components of the protocol. This finding suggests that deficiencies in staffing and lack of time are barriers to protocol adherence and that facilitating transfer of patients from the emergency department to the ICU may be an important strategy for optimizing the outcomes of patients with sepsis.

Unlike Crowe et al. (2010) who assessed adherence to individual components of their sepsis protocol, Miller and colleagues (2013) utilized a more comprehensive strategy to measure compliance. They assessed compliance to eleven elements of a sepsis protocol that were divided into three bundles: a 3-hour bundle, a 6-hour bundle, and a 24-hour bundle. The 3-hour bundle targeted all patients with suspected sepsis and consisted of measuring serum lactate, obtaining blood cultures prior to antibiotics, and administering broad-spectrum antibiotics. The 6-hour bundle was used for patients with signs of hypoperfusion and shock and consisted of giving 20-40 mL/kg of fluid intravenously to patients with hypotension or an elevated lactate; starting a vasopressor infusion for patients with fluid-refractory hypotension; measuring CVP and central venous oxygen saturation at regular intervals for patients with an elevated serum lactate level; and starting an inotrope infusion or transfusing packed red blood cells for patients with a CVP less than 8 mm Hg and central venous oxygenation less than 70% after adequate fluid resuscitation. The 24-hour maintenance bundle consisted of achieving a mean glucose of less

than 180 mg/dL; administering glucocorticoids to patients with fluid- and single vasopressor-refractory hypotension; and utilizing lung-protective ventilation strategies for patients who required mechanical ventilation. Miller and colleagues further classified the components into an early bundle (consisting of the 3-hour bundle plus glucose control) and a later bundle (consisting of the 6-hour and 24-hour bundles). They hypothesized that adherence to the early bundle would mitigate the need for the later bundle interventions. Compliance was measured 24-hours from the time of emergency department admission using an all-or-none approach. Total bundle compliance improved from 5% at baseline to 73% after six years and the median number of non-adherent bundle elements declined by three-quarters. Perhaps more importantly, compliance with the 3-hour bundle was associated with a decrease in the number of patients who met criteria for the later bundles, which supports the idea that early recognition and prompt intervention can prevent the progression of sepsis to septic shock.

Patient Outcomes

Resolution of shock. Protocol-driven care has been associated with quicker resolution of shock states in patients with sepsis. Patients whose care was consistent with the recommendations of the Surviving Sepsis Campaign guidelines spent an average of 12 fewer hours in shock than patients whose care was not guided by the evidence-based recommendations (Nguyen et al., 2012). This finding is supported by El Solh et al. (2008) who showed that patients who received care after implementation of a sepsis protocol required a 50% lower vasopressor dose than those treated for sepsis prior to implementation of the protocol. Moreover, the post-implementation group required 4 fewer hours of vasopressor support (El Solh et al., 2008), which is consistent with Patel et al.'s (2010) and Gurnani et al.'s (2010) findings that demonstrated patients who received protocol-driven care had significantly shorter durations of

vasopressor infusion by one day and 2.4 days, respectively. Although Patel et al. (2010) demonstrated that implementation of a sepsis protocol was associated with a significant 20.3% reduction in the proportion of patients who required vasopressor support, Puskarich and colleagues' (2009) study did not support that finding by revealing a 38% increase in the proportion of patients who received vasopressors. Still, the bulk of the evidence seems to support that protocol-driven care may decrease a patient's time in shock.

Development of organ dysfunction. Severe sepsis is hallmarked by organ dysfunction induced by inadequate tissue perfusion (Bone et al., 1992; Levy et al., 2003). In a comparison of outcomes between patients who were treated for severe sepsis before and after implementation of a sepsis protocol, Cannon and colleagues (2013) demonstrated an absolute improvement of 34% in the Sequential Organ Failure Assessment (SOFA) scores ($p < .001$) and an absolute improvement of 27.4% in the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores ($p < .001$) of patients in the post-implementation group, which suggests that adherence to the sepsis guidelines impedes the progression of severe sepsis to septic shock and mitigates organ damage. Similarly, Thiel and colleagues (2009) found that 13% fewer patients had renal failure, 13.5% fewer patients had cardiovascular failure, and 15% fewer patients had respiratory failure after a sepsis protocol was implemented. The findings of Cannon et al. (2013), which reflected a 6.2% reduction ($p = .02$) in the use of mechanical ventilation, support Thiel and colleagues' conclusion that fewer patients had respiratory failure after implementation of a sepsis protocol. Although Patel et al. (2010) showed that the use of mechanical ventilation was reduced by 16.3% after a protocol was implemented, the finding was not statistically significant ($p = .08$).

To the contrary, Puskarich et al. (2009) and Focht et al. (2009) showed significant increases in the proportion of patients with endotracheal intubation (18% and 17%, respectively)

after a sepsis protocol was implemented. Focht and colleagues also found that following the implementation of a sepsis protocol, the duration of mechanical ventilation increased by one day however, mortality associated with acute respiratory distress syndrome was reduced by 30%. This finding suggests that greater use of lung-protective ventilation strategies (also recommended in the Surviving Sepsis Campaign guidelines) occurred after the sepsis protocol was implemented although the authors did not explicitly acknowledge this. Focht and colleagues' and Puskarich et al.'s findings of increased duration of mechanical ventilation in the post-implementation groups was not supported by Gurnani et al. (2010) whose data indicated that protocol-driven care was associated with a 6.4 day shorter duration of mechanical ventilation ($p < .001$), while two other groups of researchers were unable to demonstrate a statistically significant difference in duration of mechanical ventilation between groups, although the duration was shorter for patients who received protocol-driven care (El Solh et al., 2008; Nguyen et al., 2012).

Length of stay and hospital costs. The impact that the implementation of a sepsis protocol had on ICU length of stay was inconsistent. Gurnani et al. (2010) realized a substantial statistically significant reduction of 7.4 days in ICU length of stay compared to Soo Hoo et al.'s (2009) reduction of one day. While Hanzelka et al.'s (2013) reduction of 2.6 days was not statistically significant it likely had clinical relevance due to cost savings from the elimination of unnecessary ICU days. Conversely, Focht et al. (2009) found that patients who were treated for sepsis following the implementation of a sepsis management protocol stayed in the ICU 2 days longer than those who were treated before implementation of the protocol. Other researchers found no significant difference in ICU length of stay between groups of patient before and after implementation of a sepsis protocol (El Solh et al., 2008; Nguyen et al., 2012; Patel et al., 2010).

Similar to their findings regarding ICU length of stay, Focht et al. (2009) revealed that patients treated for sepsis after implementation of a sepsis protocol had a 2-day longer hospital length of stay ($p = .0499$). On the contrary, Cannon et al. (2013) and Thiel and colleagues (2009) demonstrated hospital lengths of stay that were significantly shorter (5.1 days and 6.3 days, respectively) for patients with sepsis after the implementation of a sepsis management protocol. Other researchers realized more modest reductions in hospital length of stay ranging from one to 2.2 days (Hanzelka et al., 2013; Miller et al., 2013; Soo Hoo et al., 2009).

Utilization of fewer resources (i.e., decreased ICU and hospital lengths of stay) is an important strategy for reducing hospital costs. For example, Cannon et al. (2013) witnessed a one-third reduction in per admission hospital charges after a sepsis protocol was implemented, which was likely primarily driven by a 5.1 days shorter hospital length of stay. Despite the costs of implementing the protocol, Cannon and colleagues reported a potential savings of over \$10 million. Likewise, Soo Hoo et al. (2009) found that shorter ICU and hospital lengths of stay reduced direct variable costs for patients with sepsis resulting in a cost savings of \$3,533 per case and a total savings of nearly \$1.9 million for the hospital.

Mortality. Implementation of a sepsis protocol was associated with an overall reduced mortality in all but one of the studies reviewed. Crowe et al. (2010) witnessed a 5.6% increase in mortality between patients in the pre-protocol and post-protocol groups. Upon further investigation, the researchers determined that unequal percentages of patients with septic shock in the pre-protocol and post-protocol groups (60% versus 85%) could explain the unexpected finding. A subgroup analysis comparing only patients with septic shock in each group showed that protocol-driven care was associated with an 8.7% reduction in mortality, although the value did not reach statistical significance. Data from two other studies (Focht et al., 2009; Gurnani et

al., 2010) also revealed an 8% non-statistically significant decrease in mortality in patients who received protocol-driven care. The remaining studies showed that implementation of a sepsis protocol was correlated with a statistically significant 12.1% to 41% reduction in in-hospital mortality (Cannon et al., 2013; Miller et al., 2013; Nguyen et al., 2012; Patel et al., 2010; Soo Hoo et al., 2009), a 16% to 18% decrease in 28-day mortality (El Solh et al., 2008; Hanzelka et al., 2013), and a 12% one-year survival benefit (Puskarich et al., 2009). Regardless of whether mortality reductions were statistically significant, the absolute reduction in mortality has clinical significance. For example, even a modest absolute risk reduction of 8% can be translated to one life saved for every 13 patients with sepsis whose care is managed in accordance with evidence-based guidelines.

Discussion

Implementation of a sepsis management protocol was associated with earlier and more frequent administration of diagnostic and therapeutic interventions to patients with sepsis and reduced mortality regardless of whether the management protocol was implemented in an emergency department, an ICU, or hospital wide. The effect of a sepsis protocol on facilitating care delivery for patients with sepsis was observed in both community hospitals and academic medical centers. Protocol adherence was only reported in two of the studies reviewed. Not surprisingly, adherence to early bundle components (lactate measurement, blood cultures, administration of antibiotics, and intravenous fluid bolus) was better than adherence to the more labor-intensive central venous saturation-monitoring component of the later bundle in an emergency department setting where stabilization of patients is the priority. This finding highlights the importance of moving a patient along the continuum of care to an intensive care

unit where there is adequate resources (staff and equipment) to support invasive monitoring and close observation of patients for subtle changes in condition and response to interventions.

The Surviving Sepsis Campaign guidelines were published to provide a standardized approach to managing patients with sepsis based on the best available evidence with the overall goals of improving patient outcomes and reducing sepsis-associated mortality (Dellinger et al., 2013). While observational studies cannot demonstrate cause and effect, the associations found between protocol-driven care and the frequency and timeliness of interventions support the use of sepsis protocols to improve the delivery of evidence-based care to patients with sepsis. Likewise, researchers demonstrated an association between protocol-driven care and reduced mortality, which further supports the use of sepsis protocols to improve a patient's chance for survival.

Limitations

This review has several limitations. All of the studies had an observational before-and-after design, which prevents the establishment of a causal relationship between implementation of a sepsis protocol and the frequency and timeliness of diagnostic and therapeutic interventions and patient outcomes such as mortality and hospital length. The observational design also weakens the strength of the evidence that seems to support the use of protocols to facilitate care and improve outcomes. Additionally, the observational design threatens the internal validity of the studies, particularly in relation to the potential for selection bias and comparison of heterogeneous groups within a single study. The before-and-after design of the studies may also subject the differences found between patients in the pre- and post-implementation groups to confounding factors that can occur with temporal changes. Furthermore, there were differences among the sepsis protocols used in the studies with regards to the time frame for achieving goals

of therapy (i.e., 3-hour bundle vs. 6-hour bundle) and the volume of fluid given for resuscitation (20-40 mL/kg). Some researchers did not report specific details about the protocol used, but simply referred to the use of an early goal-directed therapy bundle. This limits the equitable comparison of outcomes and may account for some of the differences in findings between studies. Finally, only studies conducted in U.S. hospitals were reviewed and the majority of studies were single-site studies, which limits the generalizability of the findings to other populations.

Implications for Practice

Collectively, data from the reviewed studies support the implementation of a sepsis protocol that is founded on the evidence-based recommendations of the Surviving Sepsis Campaign guidelines to facilitate the delivery of care to patients with sepsis and to improve patient outcomes. Implementation of a sepsis protocol may increase the frequency, timeliness, and appropriateness of diagnostic and therapeutic interventions. Patients with sepsis who have received protocol-driven care have benefitted from its association with an increased chance of survival. Quality improvement efforts that target the dissemination and adoption of the Surviving Sepsis Campaign guidelines among clinicians should continue.

Implications for Future Research

Evidence-based guidelines for the management of sepsis have been available for more than a decade; yet, the translation of research from bench to bedside has been slow and implementation of the guidelines has not become standard practice. Potential barriers to successful implementation and adherence to the sepsis guidelines reported in the reviewed studies include: lack of time, staffing, and specialized equipment (Crowe et al., 2010; Patel et al. 2010); deficient knowledge among clinicians regarding the definition of sepsis and inability to

recognize the signs and symptoms of sepsis (Cannon et al., 2013; El Solh et al, 2008; Focht et al., 2009; Hanzelka et al., 2013); unfamiliarity with the evidence-based guidelines for the treatment of sepsis (Soo Hoo et al., 2009); and lack of clinician engagement with quality improvement initiatives (Soo Hoo et al., 2009). More multicenter clinical trials are needed to strengthen the body of evidence that supports the implementation of the sepsis guidelines. In addition, further research is needed to identify evidence-based strategies effective for overcoming obstacles to the successful implementation of sepsis protocols and the barriers to recognizing patients with sepsis within specific care settings.

Conclusion

Researchers have shown that implementation of an evidence-based sepsis protocol is associated with better processes of care and improved patient outcomes. Studies reviewed in this paper, as a whole, have demonstrated that protocol-driven care is associated with increased frequency and volume of intravenous fluid given; more frequent and timely measurements of serum lactate; shorter time to administration of first dose of antibiotics; decreased hospital length of stay; and increased survival for patients with sepsis. Efforts to overcome barriers that have hindered the adoption and implementation of the sepsis management guidelines should continue if the Surviving Sepsis Campaign's goal to globally reduce sepsis-related mortality is to come to fruition.

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Sepsis Screening: An Integrative Review

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Abstract

Sepsis is a life-threatening medical condition associated with significant mortality. It is the single most expensive condition treated in United States' hospitals, and its incidence more than doubled between the years of 2000 and 2008. Evidence-based guidelines for the treatment of sepsis have existed since 2004, and research has shown early recognition and timely goal directed therapies improve patient outcomes. Yet, screening for sepsis in hospitalized adult patients has not become standard practice. The purpose of this integrative review is to discuss the state of the evidence for current practices related to sepsis screening for the adult hospitalized patient population. The specific aim is to identify effective screening strategies for the early identification of patients with sepsis. Studies included in the review targeted improving early recognition of sepsis and facilitating early goal directed therapy (EGDT) or sought to validate screening criteria. Findings reveal there is no single standardized approach to screening for sepsis. Screening criteria include variations of physiological parameters indicative of systemic inflammatory response syndrome (SIRS) and inadequate tissue perfusion. Tools used for sepsis screening include manual checklists and electronic surveillance. Evidence suggests effective screening is a process that includes: monitoring for systemic inflammatory response syndrome (SIRS), assessing for a source of infection, and activating a sepsis management protocol.

Keywords: sepsis, infection, screening, early recognition, early identification, early detection, and electronic surveillance

Sepsis Screening: An Integrative Review

Sepsis is a life-threatening medical condition characterized by an overwhelming systemic inflammatory response to infection (Bone et al., 1992; Levy et al., 2003). While sepsis can occur in anyone, there are some independent risk factors: advanced age, male gender, non-white race, and specific comorbidities including HIV infection, cancer, cirrhosis, alcohol dependence, and pressure ulcers (Angus et al., 2001; Foreman, Mannino, & Moss, 2003; Martin, Mannino, Eaton, & Moss, 2003; Martin, Mannino, & Moss, 2006; Melamed & Sorvillo, 2009; O'Brien et al., 2007; Williams et al., 2004). Additionally, advances in medical treatments including greater use of invasive procedures, immunosuppressive drugs, chemotherapy, and transplantation contribute to its growing incidence (Kumar et al., 2011).

Between the years of 2000 and 2008 in the United States (U.S.), hospitalizations for a principal diagnosis of sepsis or septicemia more than doubled, increasing from 11.6 to 24.0 per 10,000 population (326,000 cases in 2000 to 727,000 cases in 2008); and when patients with a secondary diagnosis of septicemia or sepsis were included, rates increased to 37.7 per 10,000 population or over 1.1 million cases (Hall, Williams, DeFrances, & Golosinskiy, 2011). Sepsis is associated with an average hospital length of stay that is 75% longer than other conditions (Hall et al., 2011) and approximately one-half of patients with sepsis require admission to an intensive care unit (ICU) (Angus et al., 2001; Martin, 2012). Recent data suggest that hospitalizations for sepsis have surpassed 1.6 million per year and that the average length of stay for a patient with sepsis is between eight and fifteen days with an average cost of 2,300 dollars per day (Elixhauser, Friedman, & Stranges, 2011). Sepsis is the single most expensive condition treated in U.S. hospitals, responsible for only 2.8% of all hospitalizations but 5.3% of all hospital costs, accounting for 20.3 billion dollars annually (Torio & Andrews, 2013). Additionally,

patients with sepsis are eight times more likely to die than patients hospitalized for other conditions (Elixhauser et al., 2011; Hall et al., 2011).

In 2002, the Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the International Sepsis Forum formed an alliance to create the Surviving Sepsis Campaign with the goal of reducing global sepsis-related mortality (Society of Critical Care Medicine, 2014). This group of international critical care and infectious disease experts reviewed evidence to determine best practices in the management of sepsis and published the first sepsis guidelines in March 2004 (Dellinger et al., 2004). To facilitate the use of the guidelines, the Surviving Sepsis Campaign partnered with the Institute of Healthcare Improvement to create a sepsis bundle, which incorporates a group of key elements that when implemented together have a high likelihood of reducing sepsis-related mortality (Levy et al., 2004). The premise of the Surviving Sepsis Campaign guidelines for the management of sepsis is that early goal-directed therapy (EGDT) improves patient outcomes (Dellinger et al., 2004; Dellinger et al., 2008; Dellinger et al., 2013). Early recognition of sepsis is essential for implementing the recommended time sensitive bundles of care. The recently revised sepsis guidelines emphasize the importance of early recognition with a new recommendation for routine screening of patients for sepsis (Dellinger et al., 2013).

Adherence to the sepsis guidelines has been associated with 2.6 to 7.4 fewer intensive care unit days (Castellanos-Ortega et al., 2010; Gurnani et al., 2010; Hanzelka et al., 2013; Zambon, Ceola, Almeida-de-Castro, Gullo, & Vincent, 2008), a hospital length of stay that is 2.2 to 6.3 days shorter (Cannon et al., 2013; Castellanos-Ortega et al., 2010; Hanzelka et al., 2013; Miller et al., 2013; Thiel et al., 2009), and a reduction in sepsis-related mortality ranging from 6.2% in an international multisite data analysis (Levy et al., 2010) to 41% in a community

hospital (Patel, Roderman, Gehring, Saad, & Bartek, 2010). Researchers at academic medical centers demonstrated adherence to the guidelines was associated with a 15.5% to 28% absolute reduction in mortality (Castellanos-Ortega et al., 2010; Gurnani et al., 2010; Nguyen et al., 2007; Thiel et al., 2009; Zambon et al., 2008). Yet, lack of adherence to these guidelines continues to be a problem. One reason for non-adherence is failure to recognize early signs of sepsis (Dellinger et al., 2013; Nguyen et al., 2010; Stoneking, Denninghoff, DeLuca, Keim, & Munger, 2011). Although the Surviving Sepsis Campaign guidelines recommend routine screening of patients for sepsis, no specific method for screening is described.

Therefore, the purpose of this integrative review is to discuss the state of the evidence for current practices related to sepsis screening for the adult hospitalized patient population. The specific aim is to identify effective screening strategies for the early identification of patients with sepsis. For this review, effective strategies will include those that have been associated with increased compliance with EGDT and improved patient outcomes, such as decreased hospital length of stay and reduced sepsis-related mortality. Screening criteria and strategies, the validity of screening protocols, and the effects of screening on facilitation of EGDT and patient clinical outcomes will be discussed.

Method

Search Strategy

The Cumulative Index to Nursing and Allied Health Literature (CINAHL) and MEDLINE databases were searched using the keywords *sepsis*, *infection*, *screening*, *early recognition*, *early identification*, *early detection*, and *electronic surveillance*. The following inclusion criteria were applied: published between 2004 and 2014; English language; human studies; peer reviewed; and adults age 18 years and older. Article titles and abstracts were

reviewed to determine applicability of the studies to the purpose of the review. For studies in which title and abstract information was insufficient to determine applicability, the full-text article was retrieved and appraised for inclusion. Consistent with the specific aim of this review, only studies designed to improve early recognition of sepsis and facilitate EGDT or to analyze the validity of screening criteria for the adult population (18 years of age and older) were included. Studies were excluded that targeted neonatal or pediatric populations or utilized serum biomarkers as indicators of sepsis. Serum biomarkers are more relevant to confirming the diagnosis of sepsis and to monitoring a patient's response to treatment than to screening and early recognition. After review, ten articles were deemed relevant. Ancestral searching resulted in one additional study that met inclusion criteria.

Search Results

A total of eleven studies were identified. Study designs, samples, and settings varied. Study designs included: five prospective observational studies (Croft et al., 2014; Kent & Fields, 2012; Nelson, Smith, Jared, & Younger, 2011; Sawyer et al., 2011; Westphal et al., 2011); five retrospective observational studies (Giuliano, 2007; McRee, Thanavaro, Moore, Goldsmith, & Pasvogel, 2014; Moore et al., 2009; Patocka, Turner, Xue, & Segal, 2014; Thiel et al., 2010); and one randomized controlled trial (Hooper et al., 2012). All but three studies were conducted in U.S. hospitals. One study was conducted in Brazil (Westphal et al., 2011), another in Canada (Patocka et al., 2014), and one study involved secondary analysis of patient data extracted from an international data set (Giuliano, 2007). Six studies were conducted in academic medical centers (Croft et al., 2014; Hooper et al., 2012; Moore et al., 2009; Nelson et al., 2011; Sawyer et al., 2011; Thiel et al., 2010). Sample populations included patients located in emergency departments (EDs; Kent & Fields, 2012; Nelson et al., 2011; Patocka et al., 2014), intensive care

units (ICUs; Croft et al., 2014; Giuliano, 2007; Hooper et al., 2012; Moore et al., 2009), and non-ICU medical wards (McRee et al., 2014; Sawyer et al., 2011; Thiel, et al., 2010). In one study, the sample population included patients in ED, ICU, and non-ICU wards (Westphal et al., 2011). The ICU sample populations included patients from surgical ICUs (Croft et al., 2014; Moore et al., 2009) and a medical ICU (Hooper et al., 2012). The variation in sample and setting provides a broad view of sepsis screening.

The purpose of each study selected for this review can be divided into two categories: those that aimed to determine the effectiveness of screening protocols for improving early recognition of sepsis and facilitating EGDT and those that sought to validate screening criteria. Researchers used various methods to screen for sepsis: manual screening utilizing checklists (Kent & Fields, 2012; Moore et al., 2009; Patocka et al., 2014; Westphal et al., 2011) and automated screening using computerized surveillance of electronic medical records (Hooper et al., 2012; McRee et al., 2014; Nelson et al., 2011; Sawyer et al., 2011). Croft et al. (2014) first implemented a paper checklist to screen for sepsis and subsequently converted it to a computerized version with automated summative scoring. Statistical regression models (Giuliano, 2007; Thiel et al., 2010) and simple 2 x 2 contingency tables (Moore et al., 2009) were used to determine the validity and reliability of screening criteria.

Key Findings

Screening Criteria and Strategies

Sepsis is defined as the presence of two or more indicators of systemic inflammatory response syndrome (SIRS) plus a known or suspected source of infection. SIRS criteria include: 1) temperature greater than 38 degrees Celsius or less than 36 degrees Celsius; 2) heart rate greater than 90 beats per minute; 3) respiratory rate greater than 20 breaths per minute or partial

pressure of arterial carbon dioxide (PaCO_2) less than 32 mm Hg; and 4) altered white blood cell (WBC) count: greater than $12,000/\text{mm}^3$, less than $4,000/\text{mm}^3$, or greater than 10 percent immature neutrophils (“bands”; Bone et al., 1992). Although these alterations in vital signs and basic laboratory values provided the foundation for screening in most of the studies reviewed, some researchers modified the criteria by adjusting threshold values, including additional clinical signs or hemodynamic values, or requiring a specific combination of SIRS criteria. For example, Hooper et al. (2012) required an abnormal temperature or WBC count as one of the two SIRS criteria needed to indicate a positive screen, whereas other researchers included hypotension (systolic blood pressure [SBP] less than 90 mm Hg or mean arterial pressure [MAP] less than 65 mm Hg) and other signs of inadequate perfusion (altered mental status or decreased urine output) in addition to SIRS criteria (Nelson et al., 2011; Westphal et al., 2011). Similarly, Patocka et al. (2014) required the presence of an abnormal temperature as the primary marker for a positive sepsis screen. Moore et al. (2009) based their screening tool on SIRS indicators but used a range of values for temperature, heart rate, respiratory rate, and WBC count adapted from a scoring system for severity of illness. They assigned numerical values to each category dependent on the level of derangement from normal to determine a SIRS score. Similarly, Croft et al. (2014) used a range of values for SIRS indicators but also included blood pressure and assessment of mental status to determine a total sepsis recognition score.

Though several variations of initial screening criteria were used, only two processes for screening were utilized: manual completion of a checklist (Croft et al., 2014; Kent & Fields, 2012; Moore et al., 2009; Patocka et al., 2014; Westphal et al., 2011) or automated continuous surveillance of an electronic medical record (Hooper et al., 2012; McRee et al., 2014; Nelson et al., 2011; Sawyer et al., 2011; Thiel et al., 2010). The checklist used for the manual screening

process varied from study to study. For example, Kent and Fields (2012) utilized a 4-step checklist in a community ED setting that was completed by a registered nurse and included recognizing SIRS criteria, determining a potential source of infection, assessing for signs of organ dysfunction, and communicating findings to a physician using the Situation, Background, Assessment, and Recommendation (SBAR) technique. Similarly, Moore et al. (2009) and Croft and colleagues (2014) evaluated a 3-step screening tool; however a hierarchy of clinicians completed the screening in surgical ICUs in academic medical centers. First, the bedside nurse assessed the patient for SIRS criteria and calculated a SIRS score. For a SIRS score greater than or equal to 4 (Moore et al., 2009) or a sepsis recognition score greater than or equal to 6 (Croft et al., 2014), the nurse contacted a nurse practitioner or resident physician to assess the patient for a possible source of infection. If infection was suspected, the surgical intensivist was required to evaluate the patient and confirm a diagnosis of sepsis and initiate a sepsis management protocol as needed. In contrast, Westphal et al. (2011) trained nursing care technicians to identify and report any abnormality of two or more screening criteria to the nurse who then assessed the patient's risk for infection and requested physician evaluation to confirm diagnosis of sepsis and initiate proper management. Westphal and colleagues' study population included patients in the EDs, ICUs, and hospital wards of two hospitals in southern Brazil.

Similar to the manual screening protocols, heterogeneous variables were used in the computerized algorithms ranging from simple SIRS criteria (Hooper et al., 2012; McRee et al., 2014; Nelson et al., 2011) to elaborate hemodynamic and laboratory values (Sawyer et al., 2011; Thiel et al., 2010). Despite the variation in criteria, the process for automated screening was similar between studies. Computerized algorithms were used to continuously survey electronic medical records to identify patients exhibiting early indicators of sepsis and to notify clinicians

via text alerts of a positive screen (Hooper et al., 2012; McRee et al., 2014; Nelson et al., 2011; Sawyer et al., 2011). Patients with a positive screen were assessed for a possible source of infection to confirm a diagnosis of sepsis and treatment was initiated as necessary. Although all four studies were conducted in academic medical centers, study populations were different for each study: medical ICU patients (Hooper et al., 2012); ED patients (Nelson et al., 2011); and medical non-ICU patients (McRee et al., 2014; Sawyer et al., 2011). Additionally, Nelson et al. (2011) included treatment recommendations as part of the alert notification, whereas the other groups of researchers did not.

Clearly, there is a variety of screening strategies being used in practice, which limits the comparative value of their outcomes and hinders the development of a strong recommendation for a specific screening strategy. Although all screening strategies were based on physiological parameters, there was no single standard approach. The only common factor was the necessity of a clinician to assess the patient for a potential source of infection due to the nonspecific nature of SIRS. The signs of SIRS are often the earliest indicators of sepsis, but SIRS is not specific to sepsis as it may have noninfectious causes such as pancreatitis, ischemia, trauma, and autoimmune disorders (Bone et al., 1992; Levy et al. 2003). The nonspecific nature of SIRS brings into question the validity and reliability of its use as the basis of most screening protocols.

Validity of Screening Protocols

Three studies specifically addressed the validity of screening criteria (Giuliano, 2007; Moore et al., 2009; Thiel et al., 2010). Statistical analysis of patient data and 2 x 2 contingency tables were used to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and odds ratios for various screening criteria. For example, Thiel et al. (2010) performed recursive partitioning and regression tree (RPART) analysis of

commonly monitored physiological parameters and laboratory values for septic patients. They compared patients with a diagnosis of sepsis who were transferred from a medical ward to the ICU with those who were not transferred to develop an algorithm of variables that could detect patients at risk for developing septic shock before they exhibited clinical signs of deterioration. A comparison of two different algorithms was performed: one that included arterial blood gas (ABG) results and one that did not. The researchers surmised that ABGs would not be routinely obtained from patients in a non-ICU setting, rather an ABG would only be obtained if a patient experienced signs of deterioration. Although the simpler model that excluded ABG results yielded lower sensitivity, it detected patients with impending sepsis five hours earlier than the model that included ABG results (Thiel et al., 2010). This finding supported the researchers' deduction that ABG samples are not collected from patients in a non-ICU setting until their condition begins to decline. Overall, the results suggest RPART analysis may be a useful tool for creating electronic data surveillance algorithms that can facilitate the identification of patients with sepsis before signs of hypoperfusion ensue, which may promote early intervention and improve patient outcomes.

Alternatively, Giuliano (2007) utilized an international data set to determine the value of common vital signs in predicting sepsis among critically ill patients. In a comparison of physiological parameters including heart rate, MAP, body temperature, and respiratory rate for patients in the first twenty-four hours of ICU admission, only low MAP and elevated temperature were found to be independently and significantly associated with sepsis. MAP of less than 70 mm Hg and fever of 38° C or greater were independently associated with a 4-fold and 2-fold increase in the odds of having sepsis, respectively. Additionally, nearly 80% of septic patients were correctly identified using blood pressure and temperature only. These findings

highlight the importance of recognizing fever and hypotension as indicators of sepsis; however, screening based on physiological criteria alone yielded a sensitivity of 78.9% and specificity of 45.1% (Giuliano, 2007). These findings indicate that more than one in five cases of sepsis would not be identified using vital signs alone and over half of patients without sepsis would have a positive screen. This supports the nonspecific nature of the early indicators of sepsis and implies that accurate early detection of sepsis depends on more than just altered vital signs.

Moore et al.'s (2009) primary purpose was to validate a 3-step screening tool that followed a tiered response involving clinician assessment and decision-making. Utilizing a simple 2 x 2 contingency table, they found their tool had a sensitivity of 96.5%, specificity of 96.7%, a PPV of 80.2 %, and a NPV of 99.5%. Their tool failed to identify sepsis in only 3.5% of patients with sepsis and only resulted in a false-positive result in 3.3% of patients without sepsis. The high sensitivity and specificity imply the screening tool is valid for identifying general surgical patients with early indicators of sepsis. The PPV and NPV indicate that the screening tool was reliable and valid for predicting sepsis among the general surgical population in that particular surgical ICU where the prevalence of sepsis was 12.2%. Because PPV and NPV are directly related to the prevalence of disease, the findings are not generalizable to other populations, which may have a different prevalence of sepsis. Despite this limitation, the validity of Moore et al.'s (2009) 3-step screening tool supports its use in a surgical ICU setting and provides a foundation for replication studies utilizing different patient populations.

Validity of screening tools (checklists and electronic surveillance algorithms) measured as sensitivity and specificity varied, which is not surprising considering the diversity of screening criteria used. Studies support that monitoring physiological parameters and laboratory values is an important component of screening for sepsis (Giuliano, 2007; Thiel et al., 2010); however,

monitoring these parameters in isolation is insufficient for determining the presence of sepsis. Aberrant vital signs should raise the clinician's index of suspicion for sepsis and prompt them to assess the patient for a source of infection and signs of organ dysfunction such as altered mental status or decreased urine output. The nonspecific nature of the earliest indicators of sepsis requires clinician confirmation of a potential source of infection to optimize early recognition of sepsis (Moore et al., 2009).

Effectiveness of Screening

Research suggests effective sepsis screening involves more than just monitoring vital signs and laboratory values. A screening process that included monitoring for SIRS, assessing for infection, and initiating EGDT was associated with a 23-hour earlier identification of sepsis (Westphal et al., 2011); a 12.2% increase in antibiotic escalation, 14.4% increase in intravenous fluid administration, and 11.9% increase in application of supplemental oxygen (Sawyer et al., 2011); a 3-fold increase in collection of blood cultures and administration of antibiotics (Nelson et al., 2011); a 76-minute decrease in time to administration of antibiotics (Patocka et al., 2014); and an 8.3% to 23.5% reduction in mortality (McRee et al., 2014; Moore et al., 2009; Westphal et al., 2011). Neither Hooper and colleagues (2012) nor Nelson and colleagues (2011) found an association between screening and improved time to key interventions of EGDT such as intravenous fluid resuscitation and antibiotic administration. In both studies, electronic screening with automated physician alerts for positive screens was utilized in clinical settings where index of suspicion for sepsis was high (medical ICU and ED, respectively). The authors reported that clinicians identified patients with sepsis and initiated treatment prior to receiving the automated alert. This implies that computerized systems dependent on data entry by nurses and other health care providers may deliver alert notifications too late to be helpful to clinicians

with a high index of suspicion as documentation may be delayed as nurses deliver care to high acuity patients. However, Croft et al. (2014) found a trend toward fewer cases of septic shock in a surgical ICU when a computerized checklist was used for screening compared to a paper checklist (42% versus 71%, respectively; $p = .07$). Although Croft and colleagues' findings did not reach statistical significance, the 29% decrease in occurrence of septic shock in a surgical ICU setting has clinical significance and implies that the use of a computerized screening strategy may facilitate earlier recognition and management of sepsis that might mitigate the progression of sepsis to septic shock.

The findings of Westphal et al. (2011) are of particular interest because after implementation of a screening checklist, there was no significant change in compliance with EGDT bundles, but the mean time to detection of sepsis decreased from 34 to 11 hours ($p < .001$) and mortality fell from 47% to 24.3% ($p < .001$). The significant reduction in both time to detection of sepsis and mortality, despite no improvement in compliance with EGDT, allow the authors to speculate that mortality may be more strongly correlated with the time it takes to recognize sepsis than with EGDT compliance. The strength of the findings should be interpreted with caution as the study was subject to bias due to a comparison of two distinct groups in a prospective before and after study potentially confounded by differences in participant inclusion and screening criteria, as well as temporal changes. The "before" period included only patients with a previous diagnosis of infection and surveillance for the development of sepsis was based on clinical signs of infection (CSI) such as SIRS criteria, hypotension, and headache with neck stiffness. The "after" period involved active surveillance of all hospitalized patients for expanded clinical signs of infection, which included the original CSI plus signs of organ dysfunction such as altered mental status, decreased urinary output, and need for supplemental

oxygenation. The approach to surveillance was dramatically different between the two periods. In the “before” period, the nursing staff was looking for signs of a systemic inflammatory response in patients with known infection, whereas in the “after” period, the nursing staff was looking for patients with SIRS and then assessing whether the systemic response was due to an infection. The improved time to identification of sepsis and the associated mortality reduction in the “after” period suggests it may be more advantageous to screen all patients for SIRS rather than limit surveillance to only patients with known infection. Overall, the findings highlight the importance of identifying patients with sepsis early and the potential impact early recognition can have on patients’ survival.

Discussion

Limitations

The studies analyzed for this review have several limitations. All but three of the studies reviewed were single site studies conducted in the U.S. Westphal and colleagues (2011) conducted their study using two hospitals in southern Brazil and Patocka et al. (2014) screened patients who presented to the ED of an urban teaching hospital in Canada. Giuliano (2007) conducted a secondary analysis of an international data set of ICU patients. This limits the generalizability of the studies’ findings. The variability in the methods and criteria used for screening makes it difficult to equitably compare the findings to derive a strong recommendation for a specific screening practice. The lack of randomized controlled trials also limits the strength of the findings. Observational studies may reveal an association between an intervention and a specific outcome, but they cannot establish causality. Finally, the use of hospital billing codes to confirm the presence of sepsis in the retrospective observational studies (Giuliano, 2007; Moore

et al., 2009; Thiel et al., 2010) may not have accurately reflected the patients' illness and may have led to misclassification bias.

Implications for Practice

The collective findings of the reviewed studies support the use of sepsis screening protocols. Evidence suggests that a tiered-response strategy may be the most effective method for screening patients for sepsis (Moore et al., 2009; Nelson et al., 2011; Sawyer et al., 2011; Westphal et al., 2011). The 3-step screening tool described by Moore et al. (2009) incorporates a multidisciplinary approach that facilitates the primary purpose of screening: to provide the patient with evidence-based early goal-directed interventions. The 3-step process—screen for SIRS, assess for infection, and activate a sepsis management protocol—could be expounded into a decision tree to guide providers' next actions. Additionally, utilizing the SBAR technique to inform the physician or advanced practice provider of a positive sepsis screen and to suggest activation of a sepsis management protocol may be an effective strategy for communicating with providers (Kent & Field, 2012).

Furthermore, continuous electronic surveillance of medical records for modified SIRS criteria offers a practical approach to achieve the first step of the screening process (Hooper et al., 2012; Nelson et al., 2011). Automation of the first step of the screening process ensures early indicators of sepsis are not overlooked as nurses manage multiple patient care tasks. The development of an electronic screening tool will require clinicians to collaborate with health information technology specialists and may exceed the available resources of some facilities, especially those that do not have integrated electronic medical records. Still, the use of a computer-generated alert to notify a provider that a patient has met screening criteria thresholds is an effective cue for transitioning to the next step of the screening process: assessing the patient

for signs of infection. Evaluating the patient for a possible source of infection and identifying signs of clinical deterioration is key to confirming a positive screen (Moore et al., 2009). Due to the significant mortality associated with sepsis, rapid implementation of EGDT is crucial to patients' survival and provides the rationale for the final step of the screening process: activation of a sepsis management protocol (Westphal et al., 2011).

A sepsis screening protocol may provide nurses with the support they need to identify patients with sepsis before severe sepsis and septic shock occurs. A key strategy for increasing nurse "buy-in" for a screening protocol is to use nurse champions to drive the change in practice (Kent & Fields, 2012; Westphal et al, 2011). Additionally, performance feedback and ongoing education are important to achieving early identification of patients with sepsis (Westphal et al., 2011).

Implications for Future Research

Multicenter studies that utilize a standardized approach to screening and use consistent outcome measurements are needed to adequately assess the effectiveness of screening for improving early recognition of sepsis and facilitating EGDT. Studies replicated among various patient populations could broaden the understanding of what screening criteria are most predictive of sepsis among different populations. Although randomized controlled trials are needed, pragmatic concerns should be considered when designing future studies. Well-designed prospective observational studies with carefully defined cohorts, screening criteria and strategies, and outcome measures can provide evidence for best practice.

Conclusion

Future research is imperative to determine the strength of the relationships between early recognition, timely diagnostic and therapeutic interventions, and sepsis-related mortality.

Findings from this review of the literature suggest that effective sepsis screening strategies include recognizing abnormal physiological parameters and laboratory values, assessing for a potential source of infection, and communicating the information to a physician or an advanced practice provider in a manner that facilitates therapeutic and diagnostic interventions aimed at preventing the progression of sepsis to septic shock. Computerized algorithms that generate an automated alert to notify providers when a patient exceeds SIRS criteria thresholds is a practical approach to the first step of screening but is not sufficient to determine a patient's clinical condition or to identify a potential source of infection. Clinicians are essential to the evaluation of a patient for clinical signs and symptoms of sepsis and are critical to achieving the Surviving Sepsis Campaign's goal of reducing sepsis-related mortality.

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Simulation of a Sepsis Screening Strategy Using Retrospective Medical Record Review

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Abstract

Purpose: To determine if a sepsis screening protocol could facilitate earlier identification of patients with sepsis

Methods: A retrospective medical record review was conducted for adult patients with a primary or secondary diagnosis of sepsis using ICD-9 codes 038.9 (unspecified septicemia), 995.91 (sepsis), 995.92 (severe sepsis), and 785.52 (septic shock). A sepsis screening strategy was applied retrospectively to simulate implementation of a screening protocol. Application of the screening strategy was performed to quantify the interval between when clinicians first recognized sepsis and when patients first exhibited signs of systemic inflammatory response syndrome (SIRS).

Results: The median interval of time between when a clinician recognized sepsis and when a patient first exhibited signs of sepsis was 222 minutes. A difference in time occurred in 22% of the cases. Duration of the interval was positively correlated with hospital length of stay ($r_s = .65$, $n = 17$, $p = .005$).

Conclusion: The interval between when patients with sepsis were first identified by a clinician (without screening) and when those patients could have been recognized utilizing a screening protocol was quantified. Results suggest that more than one in five patients would have been identified earlier using a screening protocol. A pilot study to further investigate the potential impact of sepsis screening on time to identification is warranted.

Simulation of a Sepsis Screening Strategy Using Retrospective Medical Record Review

Sepsis is a life-threatening medical condition characterized by an overwhelming systemic inflammatory response to infection (Bone et al., 1992; Levy et al., 2003) with an associated mortality of 15% to 30% (Gaieski, Edwards, Kallan, & Carr, 2013). In the United States, hospitalizations for a principal diagnosis of sepsis or septicemia more than doubled between 2000 and 2008 from 11.6 to 24.0 per 10,000 population (Hall, Williams, DeFrances, & Golosinskiy, 2011) and its incidence is increasing by 13% annually (Gaieski et al., 2013). Sepsis accounts for nearly 980,000 emergency department visits (Agency for Healthcare Research and Quality, 2014) and more than 1.6 million hospitalizations per year (Elixhauser, Friedman, & Stranges, 2011) per year. It is associated with an average hospital length of stay that is 75% longer than other conditions (Hall et al., 2011) and is the single most expensive condition treated in U.S. hospitals, responsible for only 2.8% of hospitalizations but 5.3% of all hospital costs, accounting for \$20.3 billion in annual hospital costs (Torio & Andrews, 2013). More than one in three patients hospitalized with a principal diagnosis of sepsis are discharged to a long-term care facility (Elixhauser et al., 2011) and 62.3% of patients with a principal diagnosis of sepsis are readmitted to the hospital within 30 days of discharge (Sutton & Friedman, 2013). Sepsis not only contributes a significant financial burden to the national healthcare system, but it also substantially increases the risk of mortality, as patients with sepsis are eight times more likely to die than patients hospitalized for other conditions (Elixhauser et al., 2011; Hall et al., 2011).

Background

In 2002, an international consortium known as the Surviving Sepsis Campaign was established to drive initiatives meant to increase awareness of sepsis and reduce global sepsis-related mortality (Society of Critical Care Medicine, 2014). This group of critical care and

infectious disease experts published the first Surviving Sepsis Campaign guidelines in March 2004 (Dellinger et al., 2004) and has continued to review evidence and revise the guidelines to maintain up-to-date recommendations for best practices in the management of sepsis. The most recent recommendations were released February 2013 (Dellinger et al., 2013).

The premise of the sepsis guidelines is that early goal-directed therapy improves patient outcomes (Dellinger et al., 2004; Dellinger et al., 2008; Dellinger et al., 2013). A prerequisite for achieving timely implementation of early goal-directed therapy is prompt recognition of sepsis, which has been highlighted in the recently revised guidelines with a new recommendation for routine screening of patients for sepsis (Dellinger et al., 2013). Early recognition paired with rapid treatment of patients with sepsis is imperative to mitigating the development of organ dysfunction, preventing the progression of sepsis to septic shock, and optimizing patient outcomes.

Adherence to the sepsis guidelines has been associated with 2.6 to 7.4 fewer intensive care unit (ICU) days (Castellanos-Ortega et al., 2010; Gurnani et al., 2010; Zambon, Ceola, Almeida-de-Castro, Gullo, & Vincent, 2008), a hospital length of stay that is 4.8 to 6.3 days shorter (Cannon et al., 2013; Castellanos-Ortega et al., 2010; Thiel et al., 2009), and a reduction in sepsis-related mortality ranging from 6.2% in an international multi-site data analysis (Levy et al., 2010) to 41% in a community hospital (Patel, Roderman, Gehring, Saad, & Bartek, 2010). Researchers at academic medical centers demonstrated adherence to the guidelines was correlated with a 16% to 25% reduction in mortality (Castellanos-Ortega et al., 2010; El Solh, Akinnusi, Alsawalha, & Pineda, 2008; Nguyen et al., 2007; Zambon et al., 2008). Yet, low adherence to the guidelines remains a problem (Durthaler, Ernst, & Johnston, 2009; Mikkelsen et al., 2010; Stoneking, Denninghoff, DeLuca, Keim, & Munger, 2011).

One reason for non-adherence is failure to recognize early signs of sepsis (Carlbom & Rubenfeld, 2007; Durthaler et al., 2009). Moore and colleagues (2009) reported that bedside nurses and other healthcare providers often miss the nonspecific early indicators of sepsis, as they focus on prioritizing multiple patient care needs and associated tasks. Additionally, the investigators found that nurses demonstrated a lack of awareness of standard definitions for sepsis, severe sepsis, and septic shock, as well as unfamiliarity with the components of early goal-directed therapy for sepsis (Moore et al., 2009).

Because early goal-directed therapy is dependent on timely recognition of patients with sepsis, it is imperative that routine screening be included as a key component of a comprehensive protocol for the early identification and management of patients with sepsis (Dellinger et al., 2013). The foundation of most screening strategies is monitoring for signs of systemic inflammatory response syndrome (SIRS) and assessing the patient for a known or potential source of infection (Croft et al., 2014; Hooper et al., 2012; McRee, Thanavaro, Moore, Goldsmith, & Pasvogel, 2014; Moore et al., 2009; Nelson, Smith, Jared, & Younger, 2011; Westphal et al., 2011). Signs of SIRS are often the earliest indicators of sepsis and include: temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F); heart rate greater than 90 beats/minute; respiratory rate greater than 20 breaths/minute; and/or white blood cell count greater than 12,000/mm³ or less than 4,000/mm³ (Bone et al., 1992). Although SIRS is not specific to sepsis as it may have noninfectious causes such as pancreatitis, ischemia, trauma, and autoimmune disorders (Bone et al., 1992; Levy et al., 2003), it provides a useful framework for the initial step of sepsis screening (Croft et al., 2014; Dellinger et al., 2013; McRee et al., 2014; Moore et al., 2009; Nelson et al., 2011; Westphal et al., 2011). Subsequent assessment of patients with two or more SIRS criteria by a clinician to determine the presence of a known or

potential source of infection appears to be critical to the sepsis screening strategy as it provides a specific clinical context for a clinician's observations of a patient's physiological response to illness or injury. Implementation of a screening protocol that includes monitoring for SIRS, assessing for a known or potential source of infection, and initiating a sepsis management protocol has been associated with a 23-hour earlier identification of sepsis (Westphal et al., 2011); a 3-fold increase in performance of chest radiograph, collection of blood cultures, and administration of antibiotics, and a 2-fold increase in measurement of serum lactate (Nelson et al., 2011). Additionally, screening for sepsis has been associated with a 76-minute decrease in time to administration of antibiotics (Patocka, Turner, Xue, & Segal, 2014) and an 8.3% to 23.5% reduction in mortality (McRee et al., 2014; Moore et al., 2009; Westphal et al., 2011).

Despite the availability of evidence-based guidelines for the management of patients with sepsis and the Surviving Sepsis Campaign's recent recommendation for routine sepsis screening (Dellinger et al., 2013), a gap existed between the evidence for best practice and usual clinical practice at a central Kentucky 569-bed academic medical center. Although the facility had implemented a protocol for the management of patients with sepsis, the protocol lacked a formal process for routine sepsis screening. As nurses are responsible for monitoring patient condition and spend time at the patient's bedside, they have the potential to significantly impact patient outcomes by identifying early signs and symptoms of sepsis and facilitating implementation of time-sensitive bundles of care before the patient's condition progresses to severe sepsis and septic shock. Implementation of an evidence-based screening protocol may empower nurses to recognize sepsis earlier, which is the first step to expediting appropriate care.

Purpose

The purpose of this study was to determine if a sepsis screening protocol could facilitate earlier identification of patients with sepsis. Three specific aims guided the study. The first aim was to describe general characteristics of the sample patients, including demographics (age, gender, and race); occurrence of individual components of SIRS criteria; occurrence of known or potential sources of infection (central vascular access, urinary catheter, artificial airway, pneumonia, altered skin integrity, or *Clostridium difficile* colitis); and patient outcomes (hospital length of stay and mortality). The second aim was to quantify the time in minutes between when clinicians first recognized sepsis in patients using methods of usual practice (no screening) and the time those patients would have screened positive for sepsis if a screening protocol was utilized. The third aim was to determine if the interval between when clinicians first recognized sepsis in patients and when patients would have first screened positive for sepsis (using SIRS criteria plus source of infection) correlated with patient outcomes (hospital length of stay and mortality).

Methods

Study Design and Sample

A retrospective medical record review was conducted for this descriptive study. One hundred fifty medical records, representing 10% of all adult patients (18 years of age and older) discharged from a central Kentucky academic medical center between July 1, 2013 and June 30, 2014 with a primary or secondary diagnosis of sepsis using International Classification of Diseases, Ninth Revision (ICD-9) codes 038.9 (unspecified septicemia), 995.91 (sepsis), 995.92 (severe sepsis), and 785.52 (septic shock), were randomly selected for review. Approval for the study was obtained from the facility's Nursing Research Council (Appendix A). Subsequently

an expedited review application, including waivers of informed consent and Health Insurance Portability and Accountability (HIPAA) authorization, was submitted to and approved by the hospital's Institutional Review Board (IRB), Appendix B.

Procedure

Following IRB approval, the principal investigator utilized the facility's Center for Clinical and Translational Science to obtain an electronic master list of 150 randomly selected medical record numbers paired with a unique identifier and an electronic file of de-identified demographic data extracted from each of the 150 electronic medical records. The de-identified demographic data was imported into an electronic spreadsheet that was used for data collection during the medical record review.

The primary outcome measure for this study was the duration of the interval in minutes between the time of recognition of sepsis by clinicians using methods of usual practice (no screening) and the time patients could have been recognized if a sepsis screening protocol was utilized. For this study, Time 1 (T_1) was defined as the time at which a clinician first recognized sepsis and Time 0 (T_0) was defined as the time at which a patient first met criteria indicative of a positive sepsis screen. Time 1 was identified by reviewing the electronic medical record of patients selected for this study for the presence of three specific types of physician or advanced practice provider prescriptions: fluid bolus; culture of blood, urine, sputum, or other fluid or tissue; and antibiotics. The time at which two or more of the three interventions was prescribed was considered T_1 (clinician recognition of sepsis).

Once T_1 was identified, a sepsis screening strategy was applied retrospectively twice daily (once per nursing shift at 0800 and 2000) working back in time from T_1 until screening criteria no longer indicated a positive sepsis screen (defined as documentation of two or more

SIRS criteria plus a known or potential source of infection) or until the time the patient was admitted. The screening strategy involved two steps: 1) assess for documentation of two or more SIRS criteria and 2) determine if the patient had a known or potential source of infection. Vital signs and white blood cell (WBC) count were evaluated at 0800 and 2000 daily, retrospectively starting at T_1 , to determine if criteria for SIRS were met. Vital signs documented nearest to 0800 and 2000 and the last documented WBC count for each screening interval was used for the SIRS screen. When two or more SIRS criteria were identified, the electronic medical record was surveyed for a known or potential source of infection. The point in time at which screening criteria first met conditions for a positive screen utilizing the twice-daily screening strategy was labeled T_0 .

The time at which a clinician first recognized a patient had sepsis (T_1) and the time at which the first positive sepsis screen occurred (T_0) was documented so that the difference between the two times could be measured in minutes. The interval was used to evaluate the time difference and determine whether routine screening could facilitate the identification of patients with sepsis at an earlier time. Occurrence of individual components of SIRS screening criteria and known or potential sources of infection were also documented to identify the most common SIRS criteria and sources of infection among the sample patients. Each SIRS criterion was categorized as a binary nominal variable (present or not present) for the retrospective application of the screening strategy, as well as a continuous variable with specific values for each of the SIRS criteria measured at T_1 and T_0 so that a range of values for each criterion could be generated, which could potentially be used to revise thresholds to improve sensitivity and specificity of the SIRS screening criteria.

Data related to acuity and patient location at T_1 and T_0 was collected to determine whether there was a transition to a higher level of care (e.g. transfer to ICU) and/or whether the patient was transferred to a different location within the hospital during the interval between T_0 and T_1 . Patient acuity at T_1 and T_0 was classified as an ordinal variable: acute care/telemetry (low acuity), progressive care (intermediate acuity), or intensive care (high acuity). Patient location was categorized as an acute care/telemetry unit, progressive care unit, intensive care unit, or transitional unit (emergency department, post-anesthesia care unit, or clinical decision unit). Additionally, demographic (age, gender, and race) as well as patient outcome data (hospital length of stay and mortality) were collected to describe the general characteristics of the sample and to determine whether the interval between clinician identification of sepsis (T_1) and first positive sepsis screen (T_0) correlated with patient outcomes.

Data Analysis

This study was dependent on two conditions: the presence of adequate documentation to identify T_1 and the occurrence of criteria consistent with a positive sepsis screen at T_1 . Because T_0 was defined as the time at which the first positive screen occurred and the screening strategy was applied working back in time starting at T_1 , the absence of either of the two previously described conditions would result in the inability to identify T_0 . A total of 150 medical records were reviewed for this study. Seventy-three records were ineligible for final analysis due to the absence of provider prescriptions necessary to identify T_1 or the occurrence of a negative sepsis screen at T_1 (less than two SIRS criteria or no identifiable potential source of infection documented). The remaining 77 records met criteria for identification of T_1 and T_0 and were considered to be eligible cases for the purpose of this study. To ensure the cohort of eligible patients was representative of the entire sample of patients, demographic data for the eligible

patients was compared with that of the ineligible patients. There were no significant differences in age, gender, race, or mortality between the eligible and ineligible groups (Table 1). However, the median length of stay was significantly shorter for the ineligible group compared to the eligible group ($p < .05$). Further analysis did not reveal a statistically significant difference in the acuity of patients between the two groups; however, the sample size of each group was small and may have prevented a difference from reaching statistical significance. Alternatively, the occurrence of comorbid conditions might have contributed to the difference in hospital length of stay between the two groups, but any difference that may have existed between the two groups could not be assessed as comorbid conditions was not a variable for which data was collected during this study.

Statistical analysis was performed utilizing SPSS version 22.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to describe the sample. Chi-square test for independence, independent-samples t-test, and Mann-Whitney U test were used to assess for differences between groups as appropriate. The Spearman rank order correlation was used to test for associations between duration of time between the first positive sepsis screen (T_0) and provider identification of sepsis (T_1) and patient outcomes (hospital length of stay and mortality). A $p < .05$ was considered statistically significant.

Results

Sample Description, SIRS Criteria, and Sources of Infection

Nearly 52% of the eligible cases were female and more than 93% were Caucasian. The patients had an average age of 56 years and a median hospital length of stay of eight days, with a mortality of 14.3%. The most frequently occurring indicators of sepsis were tachycardia (heart rate greater than 90 beats/min) and leukocytosis (WBC count greater than 12,000/mm³).

Tachycardia was documented in 85.7% of the cases and leukocytosis was documented in 58.4% of the cases. The most frequently documented sources of infection were chest radiograph suggestive of pneumonia (48.1%), urinary catheter (41.6%), and altered skin integrity (39%). Further details about the frequency of SIRS criteria and sources of infection are provided in Table 2. The range of values for each SIRS criterion was broad, but the median scores for all criteria except temperature were consistent with the thresholds established for a positive sepsis screen (Table 3). The mean and median values for temperature were above the lower threshold (96.8°F) but below the upper threshold (100.4°F).

Interval Between Clinician Identification of Sepsis (T_1) and First Positive Sepsis Screen (T_0)

Twenty-two percent (17/77) of eligible cases demonstrated a difference in time between when a clinician recognized the patient had sepsis and when the first positive sepsis screen occurred as identified by application of the screening strategy. For those 17 cases, the interval between T_1 and T_0 had considerable heterogeneity and measured 12 minutes to 1213 minutes (Figure 1). The median interval was 222 minutes.

More than 58% of eligible cases were located in the emergency department at T_1 (Figure 2). Half of all eligible cases were considered to have a low level of acuity as indicated by a bed request for an acute care bed (Figure 3). Only three patients were transferred to a different location during the interval between T_1 and T_0 and none of those patients had a change in their bed request status indicating a need for a higher level of care.

Correlations Between Time Interval and Patient Outcomes

No significant correlation was found between the duration of the interval between T_1 and T_0 and hospital length of stay or mortality when all eligible cases were included in the analysis. However, when cases with no difference between T_1 and T_0 were excluded, a strong positive

correlation between the duration of the interval between T_1 and T_0 and hospital length of stay was discovered ($r_s = .65$, $n = 17$, $p = .005$), Table 4.

Discussion

The goals of therapy in the management of patients with sepsis are time-sensitive and the effectiveness of treatment is dependent on early recognition of patients with this life-threatening medical condition. Therefore, prompt identification of patients with sepsis is imperative to improving their clinical outcomes. Previous studies have demonstrated that routine screening of patients was associated with earlier identification of sepsis (Croft et al., 2014; Westphal et al., 2011), more timely delivery of antibiotics (a key component of early goal-directed therapy; Patocka et al., 2014), and reduced mortality (Moore et al., 2009; Westphal et al., 2011).

Only one previously published study was designed to quantify early identification of sepsis. Westphal and colleagues (2011) conducted a 2-phase study in which they compared the mean time elapsed between identification of the first signs of sepsis risk (positive screen) and the detection of sepsis (confirmed diagnosis) utilizing two different screening strategies. In the first phase, only patients with a diagnosed infection were screened for signs of SIRS. In the second phase, all hospitalized patients were routinely assessed for signs of sepsis utilizing a more comprehensive screening strategy that included SIRS criteria plus signs of organ dysfunction. The more robust screening strategy utilized in the second phase of the study was associated with a significantly shorter duration of time to identification of patients with sepsis compared to the simple strategy utilized in the first phase (11 hr vs. 34 hr; $p < .001$).

Similarly, the present study was designed to quantify the interval between when clinicians first recognized sepsis and when patients first exhibited signs of SIRS. However, an innovative approach was used to simulate implementation of a sepsis screening strategy. The

electronic medical records of patients diagnosed with sepsis (ICD-9 codes 038.9, 995.91, 995.92, and 785.52) were retrospectively reviewed to identify T_1 (clinician recognition of sepsis) and T_0 (first positive screen) so that the interval could be measured. The screening strategy was purposively designed to be simple so that it would be easy for a bedside nurse to remember and unobtrusive to established workflows. The screening criteria were restricted to the four indicators of SIRS and the potential sources of infection were narrowly defined as objective observable conditions (i.e., presence of a urinary catheter: yes or no) and were aligned with the hospital's emphasis on nurse sensitive indicators (Appendix C).

In the present study, 77 of 150 cases were eligible. This suggests that the screening criteria used for this retrospective simulation may not have been comprehensive enough to effectively reflect the clinical condition of patients with sepsis, which likely contributed to the exclusion of nearly half of the cases reviewed. Although SIRS is a useful concept for developing a screening strategy, an expanded list of criteria that includes early signs of organ dysfunction such as altered mental status, oliguria (urine output of less than 0.5 mL/kg/hr), and a need for supplemental oxygen, may have more accurately reflected a patient's "real-world" clinical response to infection (Dellinger et al., 2013; Levy et al., 2003) and may have resulted in a larger number of eligible cases for this study. Use of less restrictive definitions for possible sources of infection may also have increased the number of eligible cases, which may have yielded different results.

Of the eligible patients, 17 had an interval of greater than zero minutes between clinician recognition of sepsis and the first positive sepsis screen. This finding has clinical significance as more than one in five eligible cases were identified earlier than T_1 with simulation of a screening protocol and suggests that implementation of a screening strategy might facilitate earlier

identification of patients with sepsis. Interestingly, two-thirds of the eligible cases that had no difference between T_1 and T_0 were identified in the emergency department and an additional 10% of them were identified in an ICU. This observation suggests that a screening protocol may be less effective at decreasing the time to recognition of sepsis for patients in units where the index of suspicion is high, which is consistent with findings of previously published studies (Hooper et al., 2012; Nelson et al., 2011). It also implies that the majority of patients included in this study may have had sepsis present on admission. Given that this study was conducted at an academic medical center, which serves as a tertiary care center for rural Kentucky, it is reasonable to expect that a considerable proportion of patients with sepsis had the condition on arrival. It is likely that the interval between T_1 and T_0 may have been different if only patients with hospital-acquired sepsis had been included in the study.

Additionally, although the sample of eligible patients was small, a strong positive correlation between the duration of the interval between T_1 and T_0 and hospital length of stay was demonstrated for the cohort of patients whose interval was greater than zero. This indicates that as the duration of the interval between onset of SIRS and clinician recognition increased so did the number of days a patient was hospitalized. This suggests that efforts to reduce delays in identification of sepsis, such as routine screening, may also lessen the financial burden of sepsis on the healthcare system.

Interestingly, less than one third of patients exceeded the SIRS criteria threshold for fever. Although fever has been demonstrated to be an independent predictor of sepsis in critically ill patients (Giuliano, 2007), it was not a frequent indicator of sepsis among patients in the present study. One possible explanation for this discrepancy is that temperature was not documented in 9.1% of the cases.

Limitations

This study had several important limitations. First, the screening strategy was applied retrospectively, which threatened the validity of the data as the principal investigator could only collect data for variables that were actually documented in the medical record and nearly half of the records had incomplete documentation for the variables of interest, which resulted in a small sample size. Additionally, vital sign data may have been incorrectly entered at the point of care and may not have accurately reflected the health status of individual patients. Second, only the principal investigator was authorized to review the medical records for data collection, which precluded the establishment of inter-rater reliability and potentially introduced misclassification bias to the findings. Furthermore, misclassification bias could have occurred at the time of medical record selection due to inaccurate billing codes, which may have contributed to the number of ineligible records excluded from the statistical analysis. Third, although the data obtained from the medical record review was used to describe a sample of adult patients with documented sepsis at a particular central Kentucky academic medical center and to perform a gap analysis for time to identification of patients with sepsis between current practice (no sepsis screening) and proposed future practice (routine sepsis screening), the impact of screening on patient outcomes could not be measured nor could the findings be used to inform decisions about the effectiveness of the strategy to correctly identify patients with sepsis among a general patient population. Finally, the findings may not be generalizable to other facilities or populations as the study was conducted at only one hospital and only patients with documented sepsis were included.

Implications for Practice

This innovative approach to quantifying the interval between the time a clinician first recognized a patient had sepsis and the time a patient first exhibited signs of SIRS in the context of a suspected infection has a few important practical implications. First, the findings of this study suggest that screening for sepsis may not make a difference in the time sepsis is identified for patients who present to units where the index of suspicion is high. Efforts to implement a screening strategy at the facility should focus on the acute care units where staff may not be as familiar with the early signs of sepsis or aware of the tenets of the Surviving Sepsis Campaign's guidelines for the management of sepsis. Second, the sepsis screening strategy utilized in this simulation will likely need to be revised before it is implemented into practice. Expanding the initial screening criteria to include early indicators of organ dysfunction, such as confusion or lethargy, and a more inclusive list of potential sources of infection might provide a better framework for identifying patients with sepsis.

Implications for Future Research

Future research should include implementation of a pilot study to assess the effects of screening on time to identification of sepsis, achievement of early goal-directed therapy targets, and patient outcomes. The current study could be replicated for patients who had documented hospital-acquired sepsis to see if the screening strategy would yield different results from those of the current study. Alternatively, the current study could be replicated using a different screening strategy that includes an expanded list of SIRS criteria and a more inclusive list of potential sources of infection for a sample of patients that includes an equal number of patients from each of two categories: those with sepsis present on admission and those with hospital-acquired sepsis, to determine if the duration of the interval between clinician recognition and the

first positive sepsis screen differs between the two groups. Additionally, studies designed to measure the sensitivity and specificity of screening criteria are needed to determine the validity of specific screening strategies. Finally, replication studies utilizing a standard screening strategy conducted at multiple sites utilizing different populations are needed to establish the reliability of a specific screening strategy.

Conclusion

This study aimed to determine if a sepsis screening protocol could facilitate earlier identification of patients with sepsis. The interval between when patients with sepsis were first identified by a clinician (without screening) and when those patients could have been recognized utilizing a screening protocol was quantified. Results suggest that more than one in five eligible patients would have been identified earlier using a screening protocol. With consideration of the entire 150 patients whose medical records were reviewed, if the group of ineligible cases were added to the group of eligible cases whose interval was equal to zero (no difference between T_1 and T_0), the findings still suggest that more than one in ten patients (11.3%) could have been identified earlier utilizing the screening protocol. The clinical significance of this finding for a hospital with approximately 1500 cases of sepsis per year is that implementation of a sepsis screening protocol has the potential to facilitate earlier identification of sepsis for nearly 170 patients per year. A pilot study to further investigate the potential impact of sepsis screening on time to identification of sepsis is warranted.

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Figure 1.

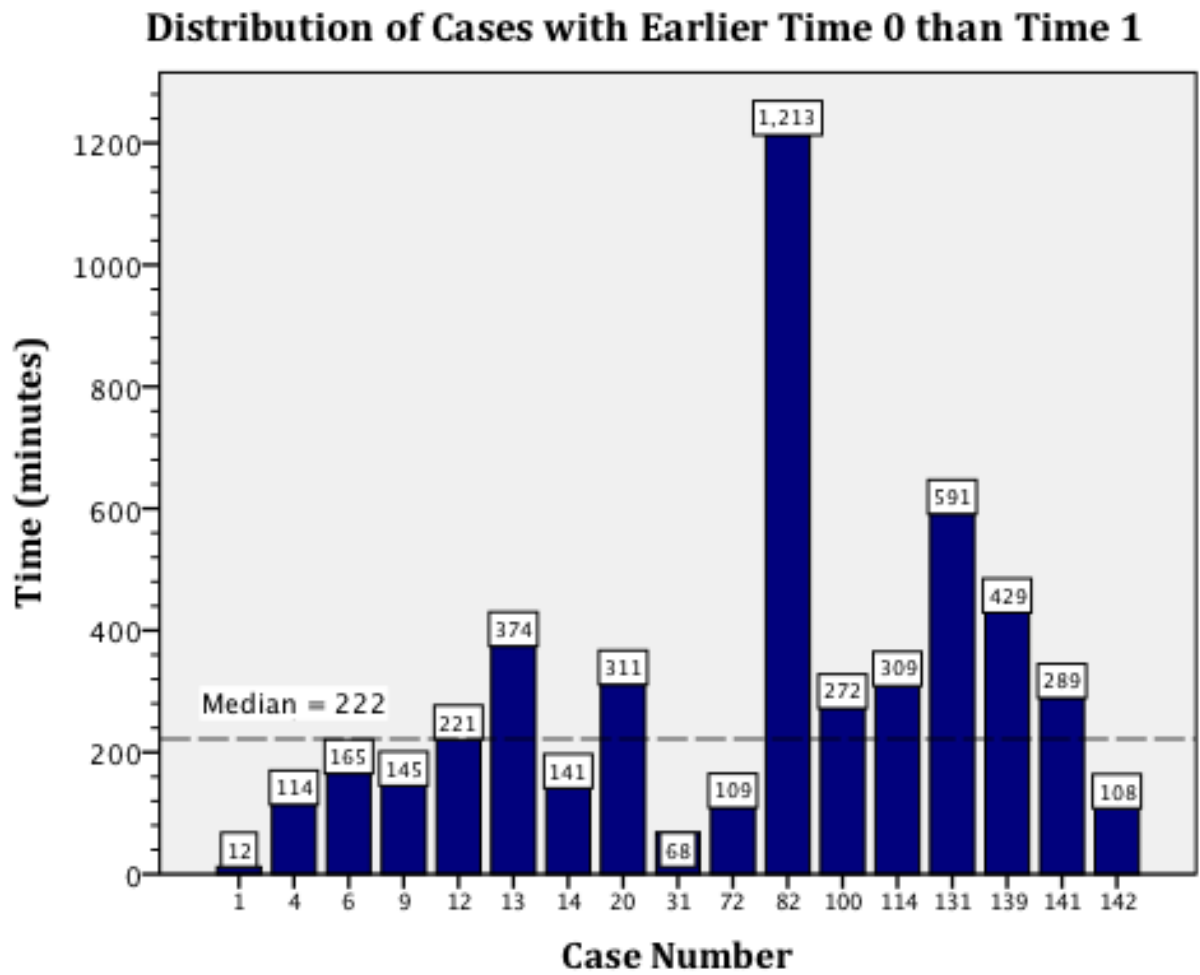


Figure 2.

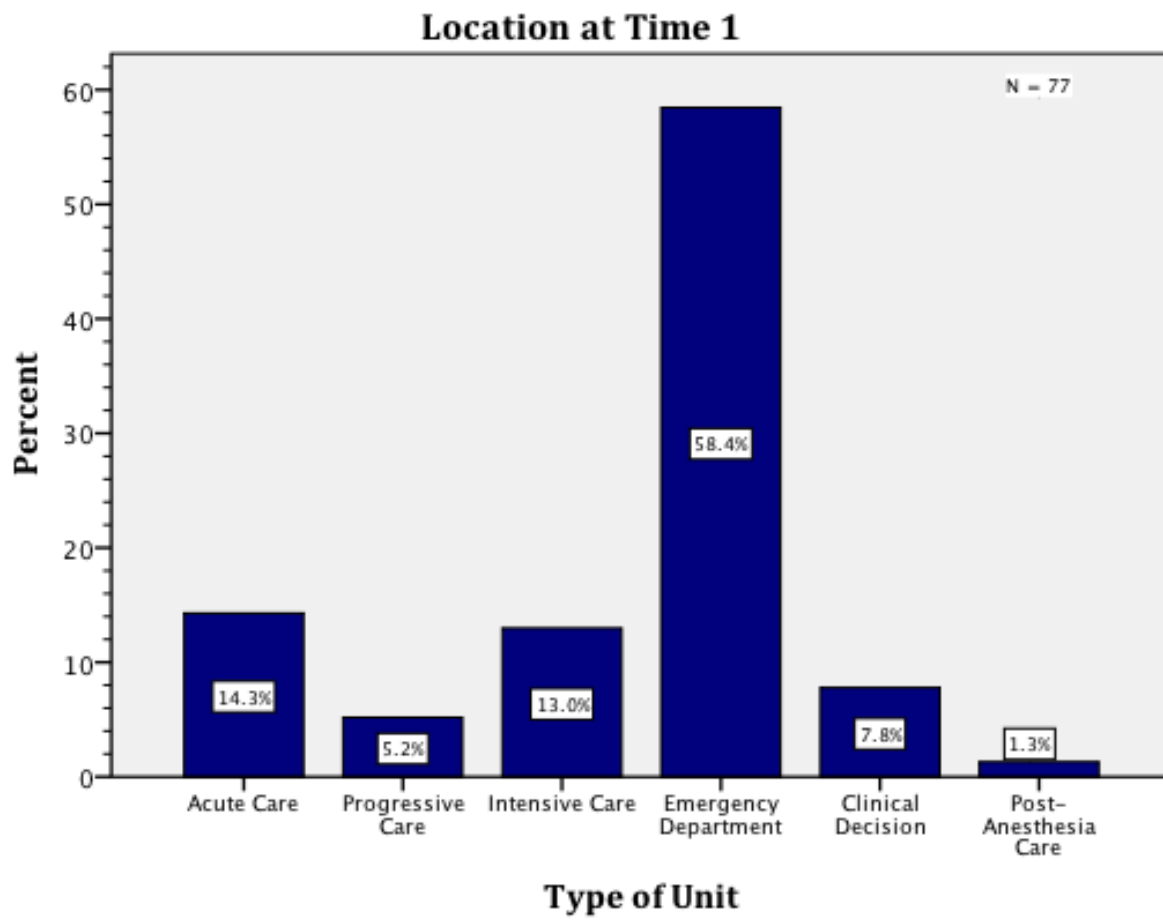


Figure 3.

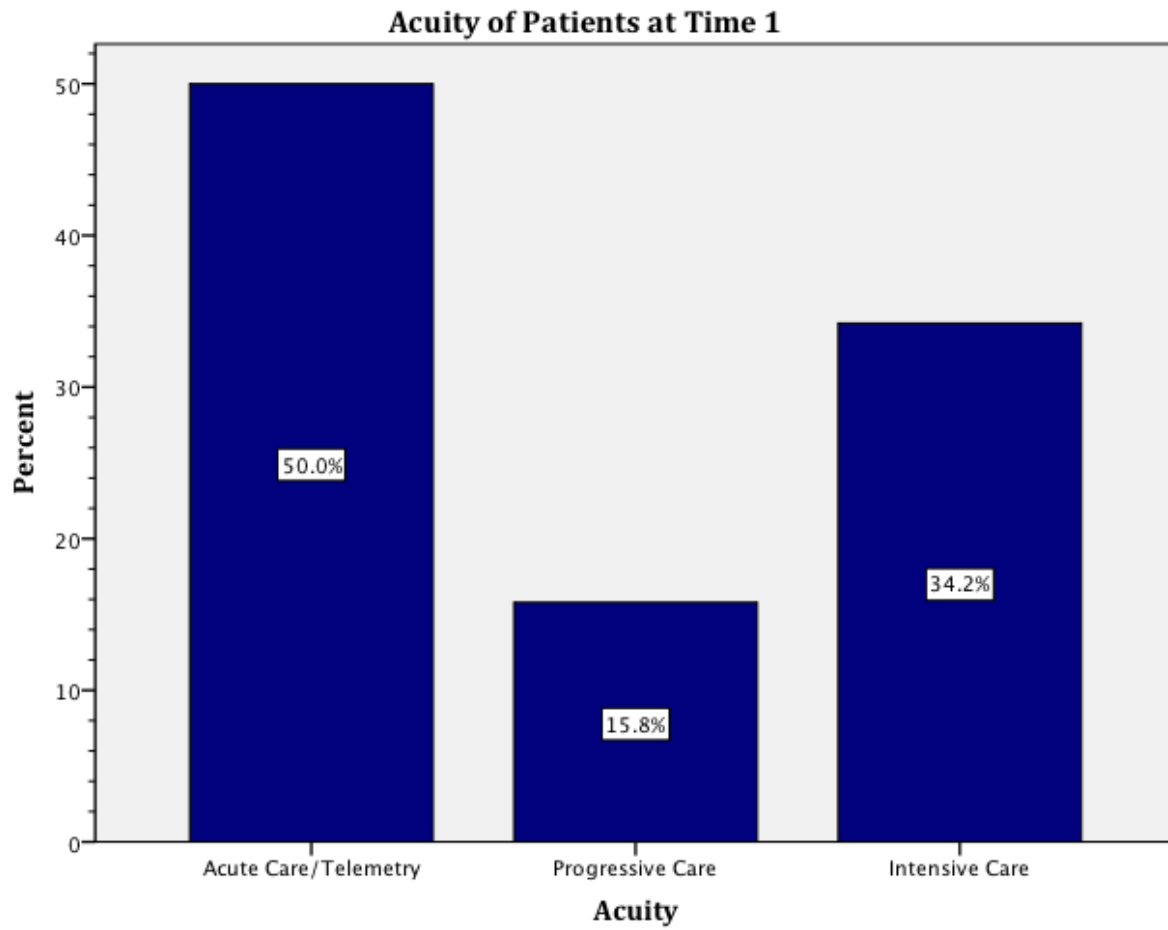


Table 1
Patient Characteristics (N = 150)

	Eligible Cohort (n = 77)	Ineligible Cohort (n = 73)
Age in years, mean (SD)	56.2 (16.9)	57.9 (15.6)
Gender, n (%)		
Male	37 (48.1)	35 (47.9)
Female	40 (51.9)	38 (52.1)
Race, n (%)		
Caucasian	73 (93.5)	65 (89.0)
African American	4 (5.2)	6 (8.2)
Spanish American	0	1 (1.4)
American Indian	0	1 (1.4)
Unreported	1 (1.3)	0
Length of stay in days, median*	8	5
Mortality, n (%)		
Survived to discharge	66 (85.7)	64 (87.7)
Died	11 (14.3)	9 (12.3)

* $p < .05$

Table 2
Frequency of SIRS Criteria and Potential Source of Infection (N = 77)

SIRS Criteria	n (%)
Temperature	
< 98.6°F	3 (3.9)
> 100.4°F	22 (28.6)
Heart rate > 90 beats/min	66 (85.7)
Respiratory rate > 20 breaths/min	40 (51.9)
White blood cell count	
< 4,000/mm ³	6 (7.8)
> 12,000/mm ³	45 (58.4)
Potential Source of Infection	
Central venous catheter	21 (27.3)
Urinary catheter	32 (41.6)
Artificial airway	12 (15.6)
Pneumonia	37 (48.1)
Altered skin integrity	30 (39.0)
Bowel infection	9 (11.7)

Table 3
SIRS Criteria Values

	Range	<i>M (SD)</i>	<i>Mdn</i>
Temperature, °F	86.8 – 104.0	99.2 (2.7)	99.3
Heart rate, beats/min	59 – 248	110 (26)	104
Respiratory rate, breaths/min	11 – 44	22 (6)	21
White blood cell count, thousands per mm ³	0.5 – 199.8	20.3 (26.4)	15.8

Table 4
*Relationship Between Sepsis Identification Interval
and Patient Outcomes*

	<i>r_s (p)</i>
Hospital length of stay	
T ₁ – T ₀ interval ≥ 0, <i>N</i> = 77	-.009 (.983)
T ₁ – T ₀ interval > 0, <i>n</i> = 17	.652 (.005)
Mortality	
T ₁ – T ₀ interval ≥ 0, <i>N</i> = 77	.066 (.571)
T ₁ – T ₀ interval > 0, <i>n</i> = 17	.477 (.072)

Appendix A

Letter of Approval from the Nursing Research Council



7/14/2014

Dear Amy Fisher

Your proposal entitled *Retrospective Simulation of a Sepsis Screening Strategy* was reviewed during the July 2nd, 2014 meeting of the Nursing Research Council at the University of Kentucky Medical Center, and we are happy to report that your proposal has been approved. If you have not yet obtained approval for your research through the University of Kentucky Institutional Review Board (IRB), you must complete this process as well.

The Nursing Research Council reviews all proposals to conduct scientific inquiry that involve UK nursing staff in an effort to assess for a number of indicators: to determine the feasibility of conducting the proposed research, to establish the level of support from nursing management or administration to conduct the research, to determine the applicability to nursing, to evaluate protection of human subjects, and to assess the completeness of the proposal. If your proposal is amended in any way such that the methods or procedures are modified significantly, your proposal must be re-submitted for review by this Council.

Please contact me if you need further assistance, have questions, or wish to discuss anything.

Sincerely,

A handwritten signature in black ink, appearing to read 'RS', is written over a horizontal line.

Rob Sutter, BSN, MPA

Chair, Nursing Research Council

Office of the Executive Vice President for Health Affairs

University of Kentucky • 317 Wethington Building • 900 South Limestone • Lexington, Kentucky 40536-0200
Phone: (859) 323-5126 • Fax: (859) 323-1918 • www.ukhealthcare.uky.edu

Appendix B

Letter of Approval from the Institutional Review Board



Expedited Initial Review

Approval Ends
September 14, 2015

IRB Number
14-0625-P6H

Office of Research Integrity
IRB, IACUC, RDRC
315 Kinkead Hall
Lexington, KY 40506-0057
859 257-9428
fax 859 257-8995
www.research.uky.edu/ori/

TO: Amy Fisher, BSN, RN
College of Nursing
208 Payne's Landing Blvd.
Georgetown, Kentucky 40324
PI phone #: (859)323-4272

FROM: Chairperson/Vice Chairperson
Medical Institutional Review Board (IRB)

SUBJECT: Approval of Protocol Number 14-0625-P6H

DATE: September 17, 2014

On September 15, 2014, the Medical Institutional Review Board approved your protocol entitled:

Retrospective Simulation of a Sepsis Screening Strategy

Approval is effective from September 15, 2014 until September 14, 2015 and extends to any consent/assent form, cover letter, and/or phone script. If applicable, attached is the IRB approved consent/assent document(s) to be used when enrolling subjects. [Note, subjects can only be enrolled using consent/assent forms which have a valid "IRB Approval" stamp unless special waiver has been obtained from the IRB.] Prior to the end of this period, you will be sent a Continuation Review Report Form which must be completed and returned to the Office of Research Integrity so that the protocol can be reviewed and approved for the next period.

In implementing the research activities, you are responsible for complying with IRB decisions, conditions and requirements. The research procedures should be implemented as approved in the IRB protocol. It is the principal investigators responsibility to ensure any changes planned for the research are submitted for review and approval by the IRB prior to implementation. Protocol changes made without prior IRB approval to eliminate apparent hazards to the subject(s) should be reported in writing immediately to the IRB. Furthermore, discontinuing a study or completion of a study is considered a change in the protocol's status and therefore the IRB should be promptly notified in writing.

For information describing investigator responsibilities after obtaining IRB approval, download and read the document "PI Guidance to Responsibilities, Qualifications, Records and Documentation of Human Subjects Research" from the Office of Research Integrity's IRB Survival Handbook web page [<http://www.research.uky.edu/ori/IRB-Survival-Handbook.html#PIresponsibilities>]. Additional information regarding IRB review, federal regulations, and institutional policies may be found through ORI's web site [<http://www.research.uky.edu/ori/>]. If you have questions, need additional information, or would like a paper copy of the above mentioned document, contact the Office of Research Integrity at (859) 257-9428.

Ellen Halpin RN, PhD/hg
Chairperson/Vice Chairperson

Appendix C

Sepsis Screening Instrument

Date/Time	0800	Date/Time	0800
Step 1: SIRS Screening (Check all that apply) <input type="checkbox"/> Temperature > 38C (100.4F) <input type="checkbox"/> Temperature > 36C (96.8F) <input type="checkbox"/> HR > 90 beats per min <input type="checkbox"/> Respiratory rate > 20 breaths per min <input type="checkbox"/> WBC > 12,000 <input type="checkbox"/> WBC < 4,000 If ≥ 2 SIRS criteria are present, go to step 2		Step 1: SIRS Screening (Check all that apply) <input type="checkbox"/> Temperature > 38C (100.4F) <input type="checkbox"/> Temperature > 36C (96.8F) <input type="checkbox"/> HR > 90 beats per min <input type="checkbox"/> Respiratory rate > 20 breaths per min <input type="checkbox"/> WBC > 12,000 <input type="checkbox"/> WBC < 4,000 If ≥ 2 SIRS criteria are present, go to step 2	
Step 2: Potential Source of Infection (PSOI) (Check all that apply) <input type="checkbox"/> Urinary Catheter (CAUTI) <input type="checkbox"/> Central Venous Catheter (CLABSI) <input type="checkbox"/> Artificial Airway (VAP) <input type="checkbox"/> Pneumonia <input type="checkbox"/> Altered Skin Integrity <input type="checkbox"/> Bowel Infection (C-diff)		Step 2: Potential Source of Infection (PSOI) (Check all that apply) <input type="checkbox"/> Urinary Catheter (CAUTI) <input type="checkbox"/> Central Venous Catheter (CLABSI) <input type="checkbox"/> Artificial Airway (VAP) <input type="checkbox"/> Pneumonia <input type="checkbox"/> Altered Skin Integrity <input type="checkbox"/> Bowel Infection (C-diff)	
Date/Time	2000	Date/Time	2000
Step 1: SIRS Screening (Check all that apply) <input type="checkbox"/> Temperature > 38C (100.4F) <input type="checkbox"/> Temp > 36C (96.8F) <input type="checkbox"/> HR > 90 beats per min <input type="checkbox"/> Respiratory rate > 20 breaths per min <input type="checkbox"/> WBC > 12,000 <input type="checkbox"/> WBC < 4,000 If ≥ 2 SIRS criteria are present, go to step 2		Step 1: SIRS Screening (Check all that apply) <input type="checkbox"/> Temperature > 38C (100.4F) <input type="checkbox"/> Temperature > 36C (96.8F) <input type="checkbox"/> HR > 90 beats per min <input type="checkbox"/> Respiratory rate > 20 breaths per min <input type="checkbox"/> WBC > 12,000 <input type="checkbox"/> WBC < 4,000 If ≥ 2 SIRS criteria are present, go to step 2	
Step 2: Potential Source of Infection (PSOI) (Check all that apply) <input type="checkbox"/> Urinary Catheter (CAUTI) <input type="checkbox"/> Central Venous Catheter (CLABSI) <input type="checkbox"/> Artificial Airway (VAP) <input type="checkbox"/> Pneumonia <input type="checkbox"/> Altered Skin Integrity <input type="checkbox"/> Bowel Infection (C-diff)		Step 2: Potential Source of Infection (PSOI) (Check all that apply) <input type="checkbox"/> Urinary Catheter (CAUTI) <input type="checkbox"/> Central Venous Catheter (CLABSI) <input type="checkbox"/> Artificial Airway (VAP) <input type="checkbox"/> Pneumonia <input type="checkbox"/> Altered Skin Integrity <input type="checkbox"/> Bowel Infection (C-diff)	

CAUTI (Catheter Associated Urinary Tract Infection); CLABSI (Central Line Associated Bloodstream Infection); VAP (Ventilator Associated Pneumonia)

POSITIVE SEPSIS SCREEN = ≥ 2 SIRS criteria + ≥ 1 PSOI

(P. Branson, personal communication, May 19, 2014)

Practice Inquiry Project Conclusion

Amy P. Fisher, RN, CCRN

University of Kentucky

The Surviving Sepsis Campaign is an international collaboration of critical care and infectious disease experts whose aim is to reduce sepsis-related mortality worldwide. They published the first evidence-based guidelines for the management of sepsis in 2004, which emphasized that the outcomes of patients with sepsis are optimized when time-sensitive interventions are delivered early. In manuscript one, the impact of adherence to the guidelines on processes of care and patient outcomes was discussed. Though protocol-driven care was associated with increased frequency and timeliness of diagnostic and therapeutic interventions and increased survival, delayed recognition of patients with sepsis was identified as a barrier to initiating the protocol. Manuscript two was a review of literature relevant to sepsis screening practices. Findings suggested that an effective screening strategy includes monitoring for signs of SIRS, assessing for a source of infection, and communicating the occurrence of a positive sepsis screen in a manner that facilitates activation of a sepsis management protocol. Finally, manuscript three consisted of a description of an innovative strategy for quantifying the potential effect sepsis screening could have on reducing the time to identification of sepsis. A screening strategy was applied retrospectively using documentation from a medical record review. Results suggested that the screening strategy could facilitate earlier identification of patients with sepsis. The findings of this practice inquiry project support the use of a comprehensive protocol to facilitate early identification and timely management of patients with sepsis. A pilot study is warranted to assess the impact of sepsis screening on time to identification, adherence to management guidelines, and patient outcomes.

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