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Cumulative Organ Dysfunction in the ED as a Predictor of Mortality in Patients with Severe Sepsis

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Cumulative Organ Dysfunction in the ED as a Predictor of Mortality in Patients with Severe Sepsis

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Abstract

HYPOTHESIS AND SPECIFIC AIMS OF STUDY: The primary aim of this study is to evaluate the hypothesis that increasing cumulative organ dysfunction in patients presenting to the Emergency Department (ED) with severe sepsis or septic shock correlates with 28-day and total in-hospital mortality, mechanical ventilation requirement and vasopressor use within 72 hours of presentation. This investigation also aims to elucidate differences in patients with high cumulative organ dysfunction scores (≥5) and low cumulative organ dysfunction scores (<5), as well as externally validate the Mortality in Emergency Department Sepsis (MEDS) score.

METHODS: This study is a retrospective chart review of patients at Yale – New Haven Hospital who presented to the ED with severe sepsis or septic shock. Included patients were at least 18 years of age, met at least two of four criteria for Systemic Inflammatory Response Syndrome (SIRS), had a documented suspicion of clinical infection, as well as manifested acute organ injury. Patients were stratified according to the number of cumulative organ failures. The principle outcome measure in this study was in-hospital mortality. Secondary outcomes include vasopressor use within 72 hours and mechanical ventilation rates, as well as MEDS scores.

RESULTS: Of the 521 patients who met criteria for enrollment in our study, 83.5% (n=435) were classified as severe sepsis patients and 16.5% (n=86) as septic shock patients. The overall in-hospital mortality rate in this study was 15.2% (n=79). Septic shock patients experienced higher mortality (33.7%, n=29) than patients diagnosed with severe sepsis (11.5%, n=50).

The five or more organ injury group had more males (59.5%) than females (40.5%), likely due to a higher number of baseline co-morbidities among males in that group, more liver

disease and congestive heart failure and had fewer residents presenting from extended care facilities.

Organ failure groups had mortality rates as follows: one or two organ failures, 8.7%; three or four, 13.8%; five or six, 19.5%; and seven or more, 55.9% ($p<0.05$ when comparing the one or two organ dysfunction group to the highest two groups (five or six and seven or more organ dysfunctions). Fifty-four patients (48.6%) in the higher cumulative organ failures group were mechanically ventilated compared to 99 (24.1%) in the fewer cumulative organ failures group ($p<0.0001$). Nearly 56% (n=56) in the higher dysfunctional group versus 17% (n=70) in the lower dysfunctional group received vasopressor support within 72 hours ($p<0.0001$).

Patients with fewer than five organ failures had a mean MEDS score of 10.7 ± 4.5, as compared to the other group with mean MEDS score of 12.5 ± 4.9 ($p=0.0002$). When the experimental groups are further stratified, the MEDS scores neither trended with cumulative organ failure, nor with the three study end-points, including mortality, vasopressor and mechanical ventilation rates.

CONCLUSION: This study demonstrated that the Emergency Department assessment of cumulative organ dysfunction is a promising measurement of disease severity in patients who present with severe sepsis and septic shock because it correlates with in-hospital mortality, early vasopressor and mechanical ventilation rates. The MEDS scoring system was not externally validated by this study.

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Introduction

The following literature review will explore several key clinical and physiological aspects of severe sepsis in order to emphasize the relevance of this critical illness as it pertains to emergency physicians today. First, the epidemiologic impact of severe sepsis on patients and the health care system at large is explored. Next, we highlight key definitions used to standardized clinical diagnoses of sepsis and research inclusion criteria. A brief discussion of the pathophysiology of sepsis syndrome is included to provide background for current diagnostic criteria, monitoring protocols and treatment standards.

Given that early identification has proven chiefly important in reducing sepsis-related mortality, a synopsis of the clinical and laboratory data recommended for diagnosis, predictors of mortality and markers of illness severity, such as organ dysfunction, is presented as fundamental criteria on which the risk stratification of patients with severe sepsis is based. Similarly, the strengths and limitations of global scoring systems for mortality risk assessment frequently applied to septic populations are included, given that they integrate knowledge about critical illness into a clinically predictive tool for mortality.

Finally, current treatment recommendations are emphasized as the mechanisms by which mortality is ultimately reduced. Presentation of all of these elements of sepsis syndrome provide an necessary context within which to understand the motivation for this research, import of the clinical question addressed, rationale for the parameters evaluated and data collected and current clinical limitations in improving survival among patients with severe sepsis and septic shock.

Epidemiology

According to a recent National Vital Statistics Report based on 2006 data from the National Center for Health Statistics, septicemia is the 10th leading cause of death in the United States (1), affecting 750,000 hospitalized patients and resulting in 215,000 deaths each year (2). It is estimated that approximately two-thirds, or 571,000, of these patients present to the Emergency Department (ED) annually, a potential underestimate given that this figure does not include patients in whom the illness is detected later in the hospitalization (2, 3).

Records from 2006 also demonstrate that sepsis is the 6th most expensive disease managed by hospitals in this country, with costs reaching $30.3 billion or 3.2% of the total healthcare bill, up from $24.8 billion or 2.8% the previous year. Furthermore, sepsis ranks 3rd most expensive disease for Medicare and Medicaid payers (4, 5). National costs will likely rise in the setting of a growing elderly population susceptible to sepsis. For example, individual patient costs rose $8,800 largely due to increased ICU length of stays after an integrated sepsis protocol was instituted at Beth Israel Deaconess Medical Center (6). At the same time, life expectancy and quality-adjusted life years were higher, making interventions cost-effective despite increasing expenditure.

Demographically, patients with sepsis are more like to be elderly (3, 7, 8). A 2003 study of national epidemiological data spanning from 1979 through 2000 noted that the mean age of patients during that period increased from 57.4 to 60.8 years (7). However, sepsis tended to develop later in life for women (mean age 62.1 years) than men (mean age 56.9 years). Although men accounted for 48% of the patients with sepsis, they were more likely to have sepsis than women when adjusted for sex in the population. A later review of the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 2001-2004 observed that the gender

distribution had shifted to 54% of patients suspected of having severe sepsis being female. Finally, approximately 17% of all patients reside in nursing homes (3).

Nguyen and others compiled data regarding community- and hospital-acquired infections from 16 studies conducted between 1963 and 1998 to conclude that the distribution of the sites of infection in patients with severe sepsis and septic shock are pulmonary (35%), intra-abdominal (21%), genitourinary (13%), skin and soft tissue (7%) and other (8%) (9). More recent data show a slightly different distribution with pneumonia suspected in 32-45% of cases, urinary system in 27-28%, skin and soft tissue in 9-20%, abdomen in 1-18% and blood or central line sources in 3-6% (10-12). In patients over 65 years of age, urinary sources are the most common site (13). Furthermore, gram positive bacteria are the predominant pathogens causing severe sepsis and septic shock, accounting for 52.1% compared to 37.6% for gram-negative bacteria, 4.7% polymicrobial infections, 1.0% anaerobes and 4.6% fungi (7).

Regarding mortality in sepsis, Shapiro and colleagues found in a prospective investigation that 28-day in-hospital mortality for sepsis syndrome prior to the implementation of early goal-directed therapy (EGDT) was 4.1% overall, while 1-year mortality was 22% (14). When stratified according to illness severity, in-hospital mortality rates for sepsis were 1.3%, severe sepsis 9.2% and septic shock 28%. Other estimates of mortality derived from data from eight countries approximate that mortality could be as high as 53.6% in patients with hospital-acquired infections prior to the implementation invasive protocolized hemodynamic optimization therapies (15). A potentially critical factor in rising mortality rates is that the proportion of patients with severe sepsis or septic shock who have any organ failure has increased over time for unclear reasons, from 19.1% in the early 1980s to 33.6% at the turn of the century.

Given these dynamics, early detection and management of sepsis in the Emergency Department is critically linked to outcomes. Despite existing advancements in management, further reduction in mortality is needed. A necessary area of future research addresses ED risk stratification of patients presenting with sepsis syndrome, which will enhance early identification of septic patients, enable early therapeutic interventions and allow for appropriate and timely disposition from crowded Emergency Departments. Each of these areas is of vital concern in the movement to improve sepsis outcomes as promulgated by the Surviving Sepsis Campaign (16, 17) and endorsed by numerous medical societies and quality improvement initiatives.

Definitions

In a 1992 statement of a consensus conference from the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM), Bone et al. first familiarized the medical community with a description of the Systemic Inflammatory Response Syndrome (SIRS) (18). SIRS is defined by two or more of the following clinical findings: (a) body temperature >38^{o}C or <36^{o}C; (b) heart rate >90 min^{-1}; (c) respiratory rate >20 min^{-1} or $PaCO_2$ <32 mmHg; and (d) white blood cell count of >12,000 cells μL^{-1} or <4,000 μL^{-1} or >10% immature neutrophils (bands). The statement also defines “sepsis” as SIRS plus infection (18). Of note, signs of SIRS do occur in the absence of infection, such as with burns, pancreatitis and trauma (19, 20).

Increasing in severity, “severe sepsis” is classified as sepsis plus organ dysfunction, hypoperfusion or hypotension, while “septic shock” is described as sepsis with hypotension refractory to adequate fluid resuscitation (18) or a state of acute circulatory failure (21). Therefore, by definition, septic shock is the most perilous subset of severe sepsis (20). Finally,

"hypotension" is defined by systolic blood pressure below 90 mmHg, a mean arterial pressure (MAP) <60 or a reduction in systolic blood pressure greater than 40 mmHg from baseline (19).

Definitions of severe sepsis and septic shock include a component in the progression of the illness known as multiple organ dysfunction. Reports of multiple organ failure, as it was then called, first emerged in 1969 (22). Later, a conceptual framework was introduced in 1992 by the ACCP/SCCM Consensus Conference Committee, which defined Multiple Organ Dysfunction Syndrome (MODS) as "the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention" (18). It results directly from injury (primary MODS) or from the host's response to injury (secondary MODS). Furthermore, MODS represents a continuum of inter-related dysfunctions in organs that could be either reversible or irreversible. Therefore, evaluation of organ function over time is viewed as an essential element in prognostication. (18).

These definitions were reinforced at the International Sepsis Definitions Conference in 2001 (19). Despite efforts to bridge the gap in clinical understanding by refining definitions of sepsis syndrome further, participants in the conference determined that there was not sufficient evidence to support the use of biomarkers in diagnosing sepsis at that time. Additionally, the cohort concluded that despite the usefulness of the SIRS concept, it is still too nonspecific, thus elucidating the need for continued review and potential for future revisions of the current definitions. Despite ongoing debate concerning SIRS, numerous clinical trials evaluating treatments for sepsis syndrome have utilized them as enrollment criteria (23-26). Finally, conference participants highlighted the limitation of current definitions in staging or prognosticating the patient's response to the disease, thus supporting our research interest, specifically risk stratification of septic patients, as an area where further investigation and developments are needed (19).

Pathophysiology

The host's response to infection is a delicate balance between pro- and anti-inflammatory components of the immune system, as well as apoptotic mediators (27). Proinflammatory cytokines such as tumor necrosis factor and interleukins, as well as other plasma substances, such as nitric oxide, are mobilized (9, 28, 29), while complement and the clotting cascade are activated causing natural anticoagulation responses to be suppressed (30). The vascular endothelium is the primary site of these various interactions, leading to microvascular injury, thrombosis and capillary leak which cause tissue ischemia. Diffuse endothelial damage is the common pathway of the various classifications of organ dysfunction from global tissue hypoxia that characterize severe sepsis and septic shock (9) *(see Figure 1).*

Global tissue hypoxia occurs when oxygen delivery cannot meet elemental oxygen requirements, a relationship that is quantified by mixed venous oxygen saturation (SvO_2) or central venous oxygen saturation ($ScvO_2$), which are considered physiologic equivalents (9, 27). Critical determinants of $ScvO_2$ are cardiac output (CO), oxygen consumption (VO_2), hemoglobin concentration (Hgb) and arterial oxygen saturation (SaO_2). Thus, changes in $ScvO_2$ are directly proportional to CO, Hgb, and SaO_2, while inversely proportional to VO_2 (i.e. $ScvO_2 = (CO / Vo_2) \times Hgb \times SaO_2$). In sepsis syndrome, oxygen extraction by tissue increases as cardiac output is decreased, by falling preload for example, causing ScvO2 to diminish. This mismatch in oxygen delivery and consumption represents an important transition from sepsis to severe sepsis (27).

While the treatment goals of early interventions and evaluation of the clinical progression of disease include indices of macrocirculatory perfusion such as cardiac filling pressure, mean arterial pressure, cardiac output or mixed/central venous oxygen saturation, all of which have been independently associated with mortality (31, 32), studies have shown that the chief regulators of oxygen delivery in the effort to meet cellular demand are the <100 µm in

diameter network of blood vessels that make up the microcirculation (33). Vasoactive mediators of sepsis exert their vasodilatory effects at the arterioles causing low systemic vascular resistance leading to hypotension, while at the level of the capillaries, endothelial damage and persistent capillary leakage also manifests clinically as hypotension (34).

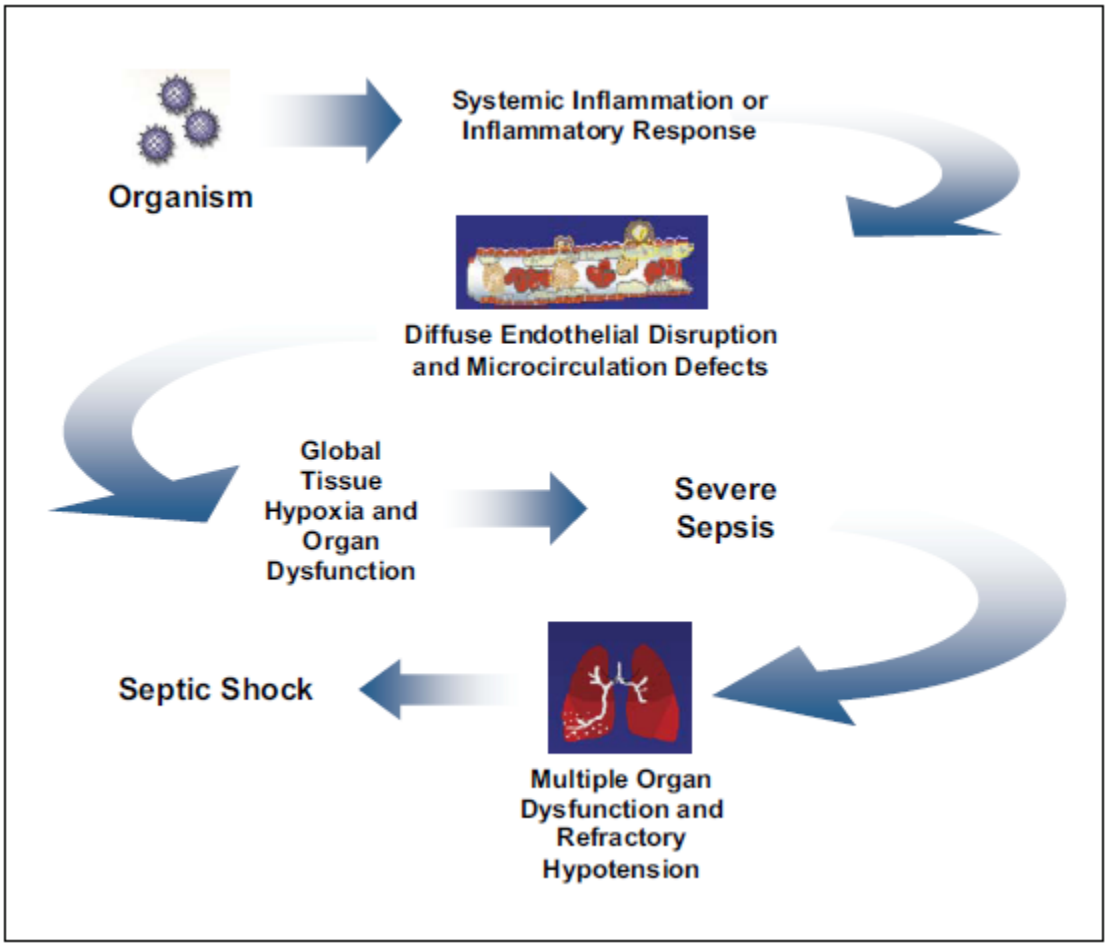

Figure 1. Pathogenic mechanisms from infection to septic shock.
The initial response to an infecting organism is a systemic response, with release of inflammatory mediators and activation of the coagulation cascade. Microvascular injury, thrombosis, and diffuse endothelial disruption follow, resulting in imbalance between oxygen delivery and oxygen consumption. Global tissue hypoxia and cytopathic (cellular) hypoxia develop, leading to multiple organ dysfunction and irreversible shock.
Reprinted from Nguyen et al. 2006. Severe sepsis and septic shock: review of the literature and Emergency Department management guidelines (9).

Moreover, studies have determined that the severity of derangements in microcirculatory homeostasis correlates with mortality (35-37). In like manner, Trzeciak et al.

demonstrates that improvements in microcirculatory flow during resuscitation reduce organ failure at 24 hours independent of global (i.e. macrocirculatory) hemodynamics as indicated clinically by arterial blood pressure (33). Toward this end, nitroglycerin and dobutamine have been associated with increases in microcirculatory flow, as well as tissue perfusion and cardiac output (38-41) and dobutamine is currently recommended in the Early-Goal Directed Therapy protocol (24).

Early Identification and Risk Stratification

Because it is believed that the physiological determinants of outcomes are manifested early in the continuum of illness in critically ill patients, medical practitioners are compelled toward early recognition and treatment of sepsis syndrome to achieve optimal results. However, the cryptic nature of the disease and a broad diagnostic approach contrast the timely detection of other fatal illnesses that require early interventions such as myocardial infarction, which have specific methods of risk stratification (i.e. ECG), leading to delays in the care of septic patients or inappropriate treatment. Given this, the propensity toward better means of identification and systems of risk stratification in patients with sepsis syndrome has been the subject of recent research.

Vital Signs

Originally, easily measurable bedside parameters known as the 10 signs of vitality were utilized for the diagnosis of sepsis syndrome. These include temperature, pulse, pain, as well the following vital signs that could indicate a perfusion deficit: blood pressure, arterial oxygen saturation, respiratory rate, level of consciousness, capillary refill, urinary output and $ScvO_2$/base deficit (42). Data show that patients whose blood pressure decreases below 80

mmHg carry three times the risk of death when compared with patients who maintain blood pressures greater than or equal to 80 mmHg (16% versus 5% mortality rate, respectively) (43).

While sustained hypotension indicates the transition from severe sepsis to septic shock, a recently published study from Marchick, Kline and Jones determined that even non-sustained hypotension is associated with a threefold increased risk in mortality over no hypotension (43). However, there remains a significant subset of patients who can initially present with normal vital signs, and then progress to rapid cardiopulmonary collapse (44), thus making reliance on vital signs an inadequate mode of disease detection.

Laboratory Results

More recently, recognition of sepsis syndrome has conventionally been linked to its defining criteria (42), as well as enrollment criteria in clinical trials. Among many laboratory data, clinicians use white blood cell count, particularly leukocytosis and bandemia, as an indication of the presence of a bacterial infection, though leukopenia and neutropenia have also been predictive of outcomes in severe sepsis (20). Extreme abnormalities in these values have been associated with mortality, yet they have minor predictive value when compared to other prognostic indicators and have poor accuracy in including or excluding bacterial infection (45-50).

Initially, hemoglobin and hematocrit values may be elevated, indicating hemoconcentration due to severe hypovolemia (20). These measurements will likely trend down with fluid resuscitation. Conversely, thrombocytopenia, which is a harbinger of disseminated intravascular coagulation (DIC), is independently predictive of poor outcomes (51). Furthermore, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study detected a prolonged prothrombin time and elevated D-dimer in 93.4% and 99.7% of patients with severe sepsis, respectively (23, 52). Given this, it is recommended

that clinicians obtain a platelet count and prothrombin time in patients suspected of severe sepsis, adding further coagulation factor studies, such as D-dimer, activated partial thromboplastin time, fibrinogen and fibrin degradation products, when suspicious of DIC (20).

Lactic acidosis, or high serum lactate levels with metabolic acidosis, in the ED, as well as upward trending lactate levels, have also been predictive of poor outcomes and may be followed serially to evaluate response to therapy (53-58). Elevations in lactate have several etiologies including acute tissue hypoperfusion and anaerobic metabolism (59), augmentation of lactate production by pathways involving catecholamines (60-62), derangements in pyruvate-dehydrogenase enzyme activity (63) and reduction in lactate clearance due to hepatic dysfunction (64, 65).

Evaluating lactate clearance as a predictor of mortality, Nguyen et al. revealed an 11% decreased likelihood of mortality for each 10% increase in lactate clearance in an ED sepsis study. In other words, at least a 10% lactate clearance during the first six hours in the ED correlates with better survival outcomes. Arnold and others observed a 60% mortality rate in patients with severe sepsis who did not clear lactate during protocol-guided quantitative resuscitation as compared to 19% in patient who did clear lactate, indicating that lactate clearance is an independent predictor of death (66). Howell and colleagues further concluded that lactate is a significant predictor of 28-day mortality independent of blood pressure and provides prognostic information superior to that conveyed by hemodynamic status and co-morbidities (58).

Finally, the acquisition of blood cultures before antibiotic administration to optimize pathogen isolation is also a recommended practice when sepsis is suspected, as they will guide antimicrobial therapy. Although cultures will only be positive in approximately 50% of patients with severe sepsis/septic shock (67), it is a necessary diagnostic test which should be performed

on all patients. Other laboratory results may illuminate specific organ dysfunctions and are highlighted in the section below.

Assessment of Organ Dysfunction

Multiple organ dysfunction caused by circulatory derangements is a harbinger of mortality in patients with severe sepsis and septic shock. Currently, it is recommended that clinicians perform organ failure assessments on patients, as prior literature evaluating the Multiple Organ Dysfunction Score (MODS) and Sequential Organ Failure Assessment (SOFA) score correlates severity of ICU organ dysfunction with outcome (19, 68, 69). In 1995, originators of the MODS reviewed literature from 1969 to 1993 to derive this severity of illness scoring system that was found to correlate in a graded fashion with ICU mortality rate. With a maximum score of 24, patients with MODS of 9 to 12 points had an approximately 25% ICU mortality rate, 50% at 13 to 16 points, 75% at 17 to 20 points and 100% at greater than 20 points (68).

The MODS study goes on to describe the various organ dysfunctions identified in the foundational literature. Respiratory dysfunction is identified by variables signifying impaired oxygen exchange, such as Po_2/Fio_2 ratio, and those necessitating mechanical ventilation or positive end-expiratory pressure (PEEP). Of the two, the Po_2/Fio_2 ratio emerged as the optimal descriptor, limited by oscillations in this parameter with interventions (68).

Acute respiratory distress syndrome (ARDS), a syndrome of diffuse lung parenchyma injury causing noncardiogenic pulmonary edema, occurs with high frequency in septic patients and results in hypoxic respiratory failure (70). ARDS is a clinical diagnosis defined by the American-European Consensus Conference (71). Criteria include acute onset, Pao_2/Fio_2 <200 regardless of PEEP, bilateral infiltrates and pulmonary capillary wedge pressure (PCWP) <18 mm Hg (71).

Renal dysfunction, or acute kidney injury, is defined as reduced urine output or the need for dialysis to maintain homeostasis of fluid, electrolytes or acid-base parameters, as well as by increasing serum creatinine, with the latter being a sufficient indicator. Hepatic dysfunction is indicated by jaundice, hyperbilirubinemia, decreased albumin or elevations in transaminases, alkaline phosphatase or lactate dehydrogenase. Despite the fact that none of these emerged singly or in combination as a superior variable, the study relied on hyperbilirubinemia as an indicator of organ failure, even though its presence may denote other disease processes (i.e. cholangitis, hemolysis, etc.) as opposed to primary liver dysfunction (68).

Indicators of cardiovascular dysfunction vary considerably and include hypotension, need for inotropic support, increased left- or right-sided filling pressures, dysrhythmias, serum biomarker elevations and cardiac arrest. Minimum systolic blood pressure (SBP) <80 mmHg demonstrated the highest correlation with ICU mortality rate (as high as 58% mortality when SBP <50 mmHg). However, SBP is very susceptible to transient fluctuations with therapy and is non-specific for intrinsic cardiovascular dysfunction (a concern that is now offset by the common use of cardiac enzymes such as troponin). Thrombocytopenia was the most frequent marker of hematologic dysfunction likely due to disseminated intravascular coagulation (DIC). But studies have also reported leukopenia or leukocytosis, anemia, increased prothrombin time (PT) or partial thromboplastin time (PTT), disseminated intravascular coagulation (DIC) or fibrin degradation products as signs of hematologic failure(68).

In defining neurologic dysfunction, many authors employed subjective criteria, including confusion, psychosis, coma and decreased responsiveness, as well as the Glasgow Coma Scale (GCS) and presence of meningitis or intracerebral hemorrhage. The MODS is generated using the GCS values. Finally, even though gastrointestinal dysfunction was included in many of the clinical investigations, it was omitted from the MODS because of difficulties in isolating a reliable

descriptor. Some contenders include stress bleeding, which is now less common in the ICU, as well diarrhea, enteral feeding intolerance, volume of nasogastric drainage, pancreatitis, acalculous cholecystitis, bowel perforation and necrotizing enterocolitis. Endocrine and immunologic dysfunctions were also omitted due to infrequent citation in the literature (68).

In like manner, the SOFA score, also developed as a mortality predictive tool for critically ill patients, incorporated Pa_{O_2}/Fi_{O_2} ratio (respiratory variable), platelet count (coagulation variable), bilirubin (hepatic variable), hypotension (cardiovascular variable), Glasgow Coma Score (neurologic variable) and creatinine or urine output (renal variable) (69). Initial, peak and mean SOFA scores (measured zero through 24) calculated upon ICU admission and every 48 hours thereafter, correlated well with mortality. For example, initial and peak scores of more than 11 or mean scores more than five correlated with >80% mortality rates. Moreover, the score was better at discriminating mortality rates within the first 48 hours of ICU stay. Jones, Trzeciak and Kline recently determined that the change in SOFA score from time zero (calculated at ED recognition of illness) and 72 hours after intensive care admission also had a positive correlation with mortality (72).

Beyond scores incorporating organ failure into survival prediction models, no study had directly evaluated the relationship between end-organ damage and critically ill septic patients in the Emergency Department until the 2006 secondary analysis of an observational cohort by Shapiro et al. (14). They affirmed that the mortality rate increased with the number of organ dysfunctions noted in the ED as follows: no organ dysfunction (1.0% mortality), one organ dysfunction (5.9% mortality), two (12.5% mortality), three (25.9% mortality), and four or more (53.3% mortality). Of importance, this study only evaluated dysfunctions of six organ systems including renal, cardiovascular, respiratory, central nervous, hematological and metabolic.

Additionally, these results reflect fatal outcomes prior to the implementation of current therapeutic standards (i.e. early goal-directed therapy).

In short, the MODS study identified fundamental criteria to define organ failure in severe sepsis. Furthermore, both the MODS and SOFA score solidified the relationship between organ dysfunction mortality. Despite this significant contribution, the MODS and SOFA score were derived from ICU data in critically ill patients, not in septic patients presenting to the Emergency Department, as a means of evaluating severity of illness. Shapiro and colleagues recognized this limitation and conducted a study that confirmed a positive correlation between cumulative organ failure and mortality. However, to our knowledge, this study is the only one of its kind. Additionally, despite the overwhelming evidence linking organ dysfunction and mortality, a formal assessment of dysfunction in each of the organ systems in a patient suspected of severe sepsis is not uniformly performed in the ED. Therefore, continued research with the aim of translating this knowledge to clinical practice is much needed.

Global Scoring Systems

While the MODS and SOFA score both employ organ failure as the sole variable in predicting outcomes, several ICU-derived models have been developed that also integrate other parameters such as laboratory data, age and past medical history. As such, the Acute Physiology and Chronic Health Evaluation (APACHE) II classification is most often utilized scoring system for critically ill patients in studies published over the last decade. It is a point system that relies on 12 physiologic variables including, temperature, mean arterial pressure (MAP), respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, white blood count and Glasgow Coma Scale (73). By design, the APACHE II score is utilized 72 hours into the hospitalization to predict outcome.

Only limited studies have evaluated the influence of APACHE II scores in the ED, as the APACHE II assessment typically requires information that is not readily available in a patient's first hours of presentation. One such small sepsis study from Nguyen and others demonstrated that higher APACHE II scores measured at the time of ED admission were associated with nonsurvivors, but the APACHE II score predicted mortality approached actual in-hospital mortality at 12 hours after ED admission. Additionally, hourly decreases in the score were significantly greater in the ED than at any other time during the hospital stay in surviving group (74). While these data support early, ED-based interventions in septic patients, sufficient information to conclude that APACHE II is a generalizable technique to risk stratify and delineate specified treatment regimens for septic Emergency Department patients does not exist. Thus, it is not current standard of practice to clinically estimate the APACHE II score in ED patients.

Another system in the theoretical stage of development is the *P*redisposition, *I*nfection, *R*esponse and *O*rgan dysfunction (PIRO) sepsis staging classification introduced at the 2001 International Sepsis Definition Conference (19). This conceptual system models the TMN approach to cancer with the understanding that a useful staging system takes into account a patient's baseline characteristics, as well as the potential to respond to therapy (19).

Predisposition concerns the co-morbidities that modify both the disease process and the approach to therapy, thus having a considerable effect on outcomes. Previous studies have found an association between specific co-morbid conditions, including cancer, cirrhosis, congestive heart failure and HIV infection, and poorer outcomes in sepsis (75, 76). For example, one study observed a two-fold increase in the risk of death in sepsis patients with cancer compared to those without cancer, a risk that is also seen in septic patients with HIV (76). Other factors affecting approach to therapy would be cultural and religious beliefs and norms of

the patient and his/her family, which are often very difficult to quantify in an effort to translate these factors to clinical use.

Within the PIRO system, *infection* takes into account recent data that suggest that pneumonia and intra-abdominal infections have higher rates of mortality than other sources, as well as the discovery that secondary nosocomial bacteremia may be more lethal than primary or catheter-related bacteremia (77). Similarly, there is evidence proposing that there are differences in the endogenous host response to gram-positive microbes as compared to gram-negative organisms (78). Regarding the host's *response*, which has been difficult to characterize, current therapies such as hemodynamic optimization, steroids and drotrecogin alfa (activated) generally target this factor (19). Finally, *organ dysfunction* in septic patients parallels the presence of metastatic disease in cancer patients within the TMN system.

In response to the need for an easily applicable, Emergency Department-derived scoring system, Shapiro and colleagues developed the Mortality in Emergency Department Sepsis (MEDS) score, which is organized according to the PIRO framework (50). In this derivation and validation study, nine variables independently associated with outcome, defined as 28-day mortality, were identified. The MEDS score utilizes clinical variables that are readily available to ED physicians such as terminal illness, tachypnea or hypoxia, septic shock, platelet count, band proportion >5%, age >65, lower respiratory infection, nursing home residence and altered mental status *(see Table 1).* Once the MEDS score parameters were determined, the clinical prediction rule stratified patients into five mortality risk groups indicating severity of illness: very low (MEDS 0-4), 1.1%; low (MEDS 5-7), 4.4%; moderate (MEDS 8-12), 9.3%; high (MEDS 12-15), 16%; and very high (MEDS >15), 39%, in the validation set.

Table 1. Mortality in Emergency Department Sepsis (MEDS) Score

	Points
Rapidly terminal co-morbid illness*	6
Age > 65 years	3
Bands > 5%	3
Tachypnea or hypoxemia	3
Septic shock	3
Platelet count <150,000 mm^3	3
Altered mental status	2
Nursing home resident	2
Lower respiratory infection	2

*Terminal illness is defined as metastatic cancer or a disease condition with a >50% likelihood of predicted fatality within 30 days.

The MEDS score was later externally validated by several small studies. One study stratified patients into high-risk (MEDS 12-27) or low-risk (MEDS <12) and discovered that high-risk patients had a significantly higher 28-day mortality of 48.9% versus 17.5%, which was a substantially better discriminatory tool than the APACHE II score (79). Another study showed that the MEDS score has superior prognostic test performance compared to the Confusion Urea Nitrogen Respiratory Rate Blood Pressure 65 Years or Older (CURB-65) score and the Rapid Emergency Medicine Score (REMS) (80).

In a small investigation comparing the MEDS score to biomarkers C-reactive protein (CRP) and procalcitonin (PCT), MEDS score had better prognostic accuracy than either in predicting short-term (5-day) mortality, as well as identifying those at risk for late (6-30 day) mortality (81). However, MEDS score was more specific and less sensitive than PCT for early and late mortality. Finally, a four-hospital prospective external validation of the MEDS score showed mortality rates stratified similarly to the Shapiro et al. study, ranging from 0.6% to 40% in increasing progression (82).

Despite these affirmative results, the MEDS score performed poorly in one prospective study of EGDT (83). The most notable insufficiency occurred in the moderate ranges (5-15) of the MEDS score, where mortality was consistently underestimated. This study may have been limited by several factors including size and the post hoc nature of the application of the score. As a secondary analysis that included only 143 patients, the study may be insufficiently powered to demonstrate with accuracy the predictive value of the MEDS score. Furthermore, had it been employed prospectively in critical decision-making such as disposition from the ED, the MEDS score might have performed better.

Though further validation is needed, the MEDS score is largely considered the most promising Emergency Department-derived scoring system specifically for patients with sepsis syndrome. While this risk stratification method has performed well overall in clinical trials to determine illness severity, the MEDS score has not yet translated to the bedside. Therefore, continued progress toward a projection tool for septic patients in the ED to aid in critical clinical decisions, such as disposition and use of risky treatments, is necessary.

Treatment Recommendations

Early Antibiotics

The Surviving Sepsis Campaign recommendations state that "intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis," though in practice administration of antibiotics takes several hours (16). This standard was established based on data from a retrospective investigation of 2731 patients with septic shock that determined that survival was inversely proportional to time of administration of antibiotics, with an approximately 8% per hour absolute decline (84). Furthermore, time to initiation of antibiotic therapy was the superior marker for outcomes.

As equally important to the timing of antibiotics is the appropriate selection of empiric therapy. In one study, appropriate antibiotics started empirically to cover potential pathogens reduced mortality from 34% to 20% in bacteremic patients. The odds ratio for fatality with inappropriate coverage was 1.6 (85). Despite limited availability of some key factors informing which antimicrobial to administer in the ED setting, ED practitioners have the supremely important responsibility of dispensing appropriate and timely antibiotic treatments to reduce sepsis-related mortality.

Source Control

In addition to the timely and accurate usage of antibiotics, elimination of infectious foci limits host exposure to the pathogen. Some bacteria evade antimicrobial eradication by adhering to synthetic medical devices in protective biofilms (86). Infectious sites are usually identified through history, physical exam and imaging studies and should be removed in the ED when possible and safe for the patient; however, source control may necessitate invasive measures such as abscess drainage or open procedures in the operating room (70).

Early Goal-Directed Therapy

The concept of quantitative resuscitation, or hemodynamic optimization, as a treatment strategy to improve outcomes in critically ill patients was first introduced by Shoemaker et al. in a 1988 study of high risk surgical patients. In a later meta-analysis of hemodynamic optimization trials, Kern and Shoemaker determined that early, rather than later, therapeutic hemodynamic interventions improve outcome by significantly reducing short-term mortality (87). Based upon these studies and other observations from goal-directed therapy trials performed on ICU patients, early goal-directed therapy (EGDT) in the ED setting was evaluated

in 2001 by Rivers and colleagues and served as the stimulus for a new generation of evidence-based clinical treatments for sepsis syndrome (24).

In contrast to previous trials enrolling patients later in the course of hospitalization, and in concordance with the results from the Kern systematic review, early goal-directed therapy aims to optimize physiologic endpoints in the proximal stage of disease. This study initiated therapies in the ED in a protocol that was executed for up to 6 hours prior to ICU admission. Early goal-directed therapy "involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand" (24).

Two hundred and thirty-six patients were randomized to the therapeutic or standard arms of the study. The protocol under investigation was as follows:

> "A 500-ml bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg. If the mean arterial pressure was less than 65 mm Hg, vasopressors were given to maintain a mean arterial pressure of at least 65 mm Hg. If the mean arterial pressure was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70 percent, red cells were transfused to achieve a hematocrit of at least 30 percent. After the central venous pressure, mean arterial pressure, and hematocrit were thus optimized, if the central venous oxygen saturation was less than 70 percent, dobutamine administration was started at a dose of 2.5 µg per kilogram of body weight per minute, a dose that was increased by 2.5 µg per kilogram per minute every 30 minutes until the central venous oxygen saturation was 70 percent or higher or until a maximal dose of 20 µg per kilogram per minute was given. Dobutamine was decreased in dose or discontinued if the mean arterial pressure was less than 65 mm Hg or if the heart rate was above 120 beats per minute. To decrease oxygen consumption, patients in whom hemodynamic optimization could not be achieved received mechanical ventilation and sedatives" (24) *(see Figure 2).*

As stated, the protocol involved continuous invasive monitoring of various hemodynamic parameters including CVP, $ScvO_2$, and MAP. Outcomes measured by in-hospital, 28-day and 60-day mortality, were much improved, with rates of 30.5%, 33.3% and 44.3% respectively, versus 46.5%, 49.2% and 56.9% in the standard therapy group (24).

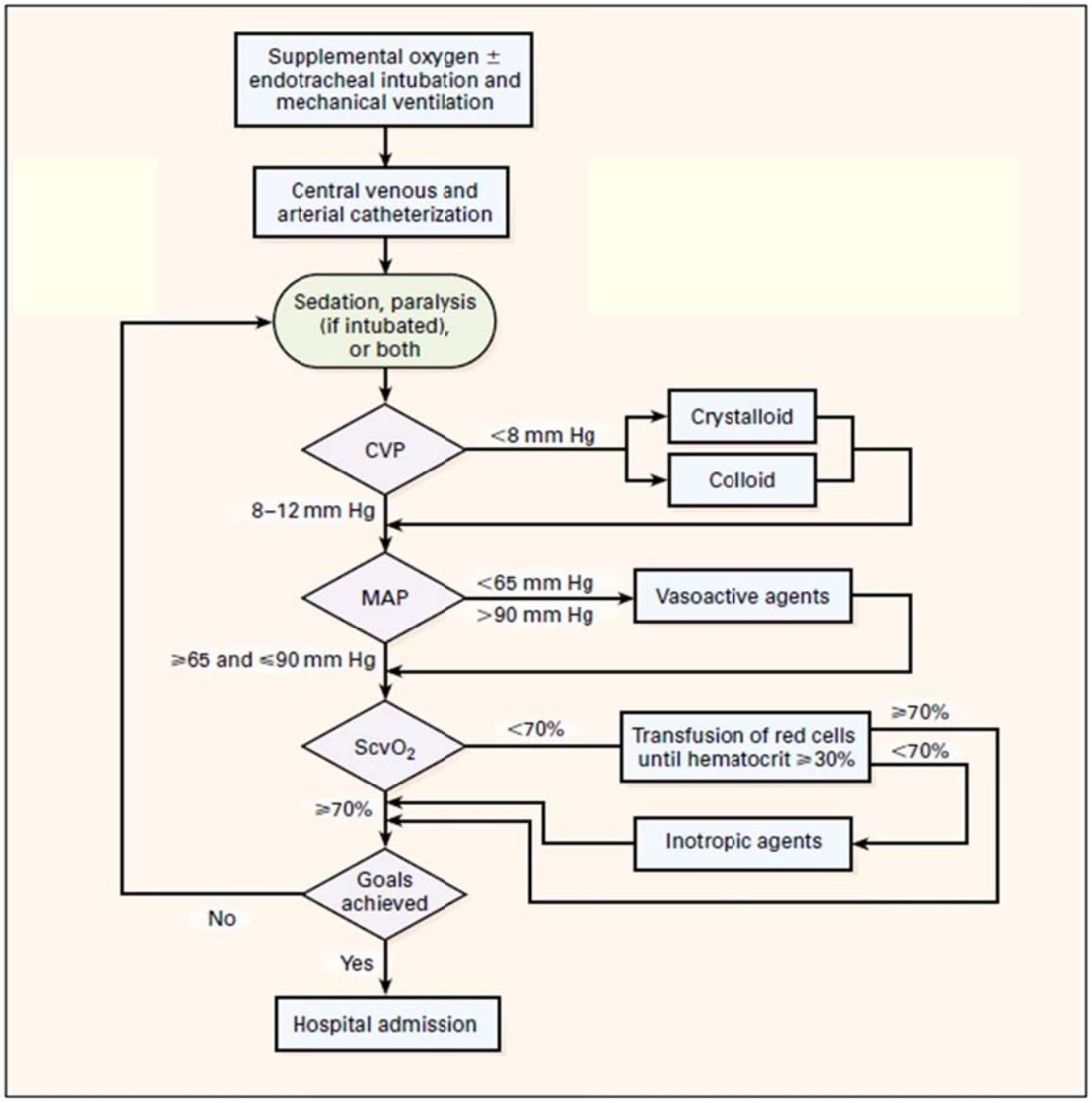

Figure 2. Protocol for Early Goal-Directed Therapy. .
CVP denotes central venous pressure, MAP mean arterial pressure, and $ScvO_2$ central venous oxygen saturation.
Reprinted from Rivers et al. 2001. Early goal-directed therapy in the treatment of severe sepsis and septic shock (24)**.**

The findings in the Rivers et al. early goal-directed therapy trial were determined to be reproducible, generalizable and externally validated (10, 88). Moreover, a comparison of eleven peer-reviewed articles and 28 abstracts involving EGDT in septic patients in the ED produced superior results to the original study, with relative and absolute risk reductions of 46% and

20.3%, respectively (89). Similarly, a meta-analysis from Jones and others also demonstrated a decrease in mortality with EGDT (90), as well as numerous other studies that evaluated mortality after implementation of EGDT in conjunction with other therapies in septic patients as far as 1-year out and in generalizable ED settings (11, 91). Despite these data, concerns remain regarding the effectiveness of individual interventions that were bundled in the EGDT protocol (92). Therefore, further validation of the EGDT protocol is planned through the multi-center, randomized, National Institutes of Health (NIH) – funded Protocolized Care of Early Septic Shock (PROCESS) trial (20).

Activated Protein C

Activated protein C is a powerful anticoagulant, pro-fibrinolytic, anti-inflammatory and anti-apoptotic enzyme that is down-regulated in sepsis (20). Given this, the PROWESS trial was designed to investigate the utility of drotrecogin alfa (activated) in reducing 28-day sepsis-related mortality (23). Investigators discovered that mortality rates were lowered from 30.8% in the placebo group to 24.7% in the treatment group, with a relative reduction in mortality rate of 19.8%. Most notably, the drug was found to reduce absolute mortality by 13% in septic patients with greater than or equal to two illness-related organ dysfunctions or APACHE II scores greater than or equal to 25 (23).

The Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial revealed that less acute patients with single-organ dysfunction or an APACHE II score below 25 did not benefit from drotrecogin alfa (activated) (93). Furthermore, the ADDRESS study also discovered that patients who had surgery within 30 days and single organ dysfunction who received drotrecogin alfa (activated) had higher 28-day mortality compared with the placebo group. Other investigations suggest a modest benefit in mortality when drotrecogin alfa (activated) is administered early in septic patients (94-96).

Furthermore, there are several absolute contraindications to the use of drotrecogin alfa (activated) including: active internal bleeding, hemorrhagic stroke within three months, recent intracranial or intraspinal surgery, severe head trauma within two months, trauma with an increased risk of life-threatening bleeding, presence of an epidural catheter, intracranial neoplasm or mass lesion, evidence of cerebral herniation or known hypersensitivity to drotrecogin alfa (activated) (20). However, it is still utilized in select patients with high severity of illness scores who are not at risk for coagulopathic complications.

Mechanical Ventilation

Studies from the 1990s demonstrate that mechanical ventilation with lower tidal volumes reduces mortality in patients with ARDS (97, 98). Later, the ARDSNET study enrolled over 800 patients in a prospective multicenter design to compare ventilation with tidal volumes of 6 cc/kg and 12 cc/kg of ideal body weight, where "permissive hypercapnea," or a controlled hypoventilation and mild respiratory acidosis (pH 7.30-7.45), was tolerated in the reduced tidal volume group (99). The study demonstrated a 9% absolute reduction in mortality in the reduced tidal volume group when the plateau pressure was maintained below 30 cm H_2O. This was the largest and most successful trial to investigate lung-protective ventilation in critically ill patients and implementation of low tidal-volume ventilation strategies is promulgated by sepsis treatment guidelines (70). A subsequent study of the clinical translation of the ARDSnet protocol discovered that there is much room for improvement in implementing this measure at the bedside (100).

Tight Glucose Control

A prospective, randomized, controlled trial of patients in a surgical ICU demonstrated that tight glucose control (i.e. maintaining blood glucose levels between 80 and 100 mg/dL)

compared with conventional treatment reduced mortality by one-third, particularly with respect to deaths due to multiple organ failures (26). However, a more recent study of medical ICU patients from the same lead author revealed no difference in mortality rates between intensive and standard insulin therapy, though tight glucose control did reduce morbidity due to prevention of acute kidney injury, accelerated weaning off ventilators and faster ICU and hospital discharges (101). On the other hand, many other studies have reported high incidence of hypoglycemia with tight glycemic control, a potentially lethal adverse consequence in critically ill populations (102).

Intensive insulin therapy is not a standard intervention not only because of the conflicting data, but also because none of these studies have been conducted specifically on patients with severe sepsis/septic shock (20). To aid in the debate, Wiener, Wiener and Larson conducted a meta-analysis of the randomized controlled trials that investigated glycemic control in critically ill patients, as well as conducted subgroup analyses of both glucose goals (≤110 mg/dL or <150 mg/dL) and ICU settings (surgical, medical or all critically ill patients) (102). Within the 29 randomized controlled trials including a total of 8,432 patients, hospital mortality rates did not differ between tight glucose control and standard groups. Furthermore, there was no significant mortality difference when patients were stratified by glucose goal or intensive care setting. The study also determined that tight glucose control was associated with diminished risk of septicemia and a higher risk of hypoglycemia (102). Thus, further investigation in this area is necessary before practice guidelines can be established.

Steroids

Part of the physiologic response to sepsis is a surge in stress hormones such as cortisol. However, high levels of cytokines in septic patients can inhibit cortisol synthesis and induce corticosteroid resistance in tissues (103-105). Septic patients can have poor responses when

challenged with adrenocorticotropic hormone (ACTH) or corticotrophin-releasing hormone in the setting of deficient adrenal reserve. Relative adrenal insufficiency is defined as an increase in serum cortisol of less than or equal to 9 mg/dL one hour after administration of 250mg of ACTH (20).

Poor adrenal reserve has been linked to higher mortality rates and protracted vasopressors requirements (106). Prior to the 2002 study from Annane et al. (25), investigations did not demonstrate a beneficial effect of pharmaceutical grade corticosteroids in patients with septic shock (107-109). However, Annane and colleagues found a relative reduction in 28-day mortality rate of 16% (63% in the placebo group as compared to 53% in the treatment group) in severely ill patients with septic shock and inadequate adrenal reserve with administration of corticosteroids. Time on vasopressors was also reduced when treated with low-dose corticosteroids.

On the contrary, patients with adrenal responsiveness had a non-statistical increase in mortality rates when treated with corticosteroids, a factor that may prove problematic with this treatment option (25). Given that the majority of ED patients maintain appropriate adrenal function, the use of corticosteroids is not recommended unless frank adrenal insufficiency is suspected (20). Recently, the European-based multicenter Corticosteroid Therapy of Septic Shock (CORTICUS) trial did not validate the efficacy to low-dose corticosteroid use in septic patients and even showed that the incidence of superinfection may increase with steroid therapy (110). Therefore, in the ED setting, corticosteroids should only be utilized when there is a high suspicion of adrenal insufficiency in combination with vasopressor dependence (17).

Summary

Severe sepsis is a critical illness with a vital impact on affected patients, Emergency Departments and the health care system as a whole. It is a disease of our nation's fastest

growing population, the elderly, affecting both men and women nearly equally. Due to the cryptic nature of the illness and lack of definitive biomarkers, definitions of sepsis syndrome are derived from consensus conferences. These definitions reflect some of the key pathophysiological processes in the progress of illness leading to global tissue hypoxia and end-organ failure.

Because the physiologic determinants of health outcomes are likely established early in the course of severe sepsis and septic shock, advancements in the two phases of management, early identification and early intervention, in Emergency Department settings are critical factors in reducing mortality. An accurate method of risk stratifying patients with severe sepsis and septic shock will optimize the selection of critical ED interventions and ICU resources in high-risk patients (111).

Toward this end, continued ED-based investigation of early predictors of poor outcomes in patients with sepsis syndrome is essential. One very important candidate for inclusion in risk stratification schemes is cumulative organ dysfunction. While organ injury is a long established cause of death in septic patients, studies evaluating cumulative organ dysfunction upon presentation to the ED as a predictor of mortality are extremely limited. Moreover, no clinical investigation assessing the predictive value of cumulative organ injury in patients receiving currently recommended treatments such as early-goal directed therapy, vasopressors and mechanical ventilation exists, thus providing an opportunity for future research.

Hypothesis and Aims of Research

Hypothesis

Increasing cumulative organ dysfunction in patients presenting to the Emergency Department with severe sepsis and septic shock correlate with post-Emergency Department deterioration as defined by in-hospital mortality, mechanical ventilation requirement and vasopressor use within 72 hours of presentation.

Aims of Research

The primary aim of this study is to:

1. Evaluate cumulative organ dysfunction as a predictor of short term (28-day) and total in-hospital mortality.

Secondary aims of the study are to:

1. Evaluate cumulative organ dysfunction as a predictor of short-term vasopressor dependence within 72 hours of presentation to the Emergency Department;
2. Evaluate cumulative organ dysfunction as a predictor of mechanical ventilation during hospitalization;
3. Elucidate differences in patients with high cumulative organ dysfunction scores (≥5) and low cumulative organ dysfunction scores (<5); and
4. Externally validate the Mortality in Emergency Department Sepsis (MEDS) score.

Methods

Involvement

This study is a continuation of a project originally designed by the Principal Investigator (PI), Charles R. Wira, III. It has been approved by the Department of Emergency Medicine Research Committee at Yale School of Medicine, as well as the Human Investigation Committee (HIC). An amendment was made in 2009 to the original 2007 HIC project proposal to add this author, Martina Sanders-Spight, as a clinical investigator on the project. Two other students, Melissa Wollan and Sundeep Bhat, worked with the severe sepsis registry containing the data used in this project in preceding years. Additionally, residents in the Department of Emergency Medicine have also contributed data to the severe sepsis registry. However, the research question under investigation by this author is original and independent of those asked by the previous student clinical investigators.

The PI has been responsible for the long-term management of the registry, facilitating approval of the project by the HIC and Department of Emergency Medicine Research Committee, guiding the data analysis and contributing greatly to the substance of the research and scientific thought. This author is responsible for data abstraction and data entry, as well as calculating the Mortality in Emergency Department Sepsis (MEDS) scores for the last 109 patients added to the registry. This author also conducted statistical analyses under the supervision of the PI using statistical calculators ("GraphPad Quick Calcs" software) and generated all tables and figures in this report, unless otherwise cited.

Subjects

This study is a retrospective chart review of patients selected from an interdisciplinary severe sepsis registry comprised of patients at Yale – New Haven Hospital in New Haven, CT and

the satellite site in Guilford, CT, who presented to the Emergency Department (ED) with severe sepsis and septic shock between July 1, 2005 and September 5, 2009. The main ED in New Haven serves an urban, academic hospital and treats approximately 75,000 patients per year. The principal investigator used clinical suspicion, not otherwise specified, to select patients who were suspected of meeting criteria for severe sepsis or septic shock at the time of presentation to the Emergency Department. This author performed an in-depth review of each patient's medical records to determine eligibility in this study.

Inclusion Criteria

All patients included in this study are at least 18 years of age, meet at least two of four criteria for Systemic Inflammatory Response Syndrome (SIRS), have a documented suspicion of a source of clinical infection, as well as at least one newly diagnosed organ dysfunction in the Emergency Department *(see Table 2).*

Exclusion Criteria

Patients were excluded from the study if there were less than 18 years old, did not meet criteria for severe sepsis or septic shock, were discharged to home directly from the Emergency Department or had documentation of comfort measures only.

Data Collection

Patient identification numbers were assigned by the principal investigator prior to chart review. Data were extracted from patient medical records using a standardized data collection form designed by the principal investigator and previous student clinical investigators (see Appendix). Under the faculty PI's supervision, the entire patient record in either electronic or paper form chronicling the visit included in the study was used for abstraction. Electronic

medical records were obtained via "Chart View," "Lynx Medical Systems" and "Sunrise Clinical Manager."

Table 2. Inclusion Criteria.*

1. At least 18 years of age
2. Meets criteria for severe sepsis as follows:
   a. Two or more criteria for the Systemic Inflammatory Response Syndrome (SIRS), including:
      - Body temperature >100.4°F or <96.8°F
      - Heart rate >90 min^{-1}
      - Respiratory rate >20 min^{-1} or a PaCO2 of <32 mm Hg
      - White blood cell count of >12,000 cells μL^{-1} or <4,000 cells μL^{-1} or > 10% immature neutrophils
   b. Documented suspicion of a source of infection, including any one of the following:
      - White blood cell count of >10,000 cells μL^{-1} or <4,000 μL^{-1} or > 10% immature neutrophils
      - Body temperature >100.4°F or <96.8°F
      - Blood cultures drawn in the Emergency Department
      - Antibiotics administered in the Emergency Department
      - Documentation of presumed source of infection in the Emergency Department
   c. A least one newly diagnosed organ dysfunction in the Emergency Department, including:
      - Transient systolic BP <90 mmHg that responds to fluid resuscitation
      - Lactate level > 2mmol/mL
      - Unexplained acidosis (pH < 7.35) or a serum bicarbonate < 21
      - Altered mental status (change from baseline)
      - Platelets <150,000mm^3 (no history of thrombocytopenia)
      - Elevation of bilirubin above normal or either direct or indirect bilirubin > than baseline
      - High coagulation factors (any elevation in absence of heparin or Coumadin use)
      - Acute Renal Failure (Cr >0.5 from baseline, or abnormal if no baseline available)
      - Hypoxemia (oxygen saturation less than 90% or change in oxygen requirement)
      - Troponin elevation above baseline

*Adapted for the 2001 Sepsis Definitions Conference (19).

After review of medical records, data were first recorded on the data collection form, then transferred by this author into a Microsoft Excel database previously used by student clinical investigators, adding to the severe sepsis registry. As required by the Yale HIC, all protected identifying health information was kept separately from the data collection forms in a password-protected spreadsheet accessible to only this author, other clinical investigators and the principal investigator. Data collection forms were kept in a locked cabinet by the faculty PI. Prior students collected 514 overlapping data points on patients with 95% precision,

demonstrating a reliable method of data extraction and entry from the source patient's medical records.

Elements of medical records that were reviewed include all available Emergency Department documents, hospital laboratory data, clinician admission and progress notes, nursing flow sheets and discharge summaries. Abstracted data included demographic information about patients such as age, gender and residence in a nursing home or extended care/group living facility. Vital signs during Emergency Department stay, including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, oxygen saturation and oxygen requirement were also recorded. Heart rate, systolic blood pressure and diastolic blood pressure were recorded until discharge or the start of vasopressors. Vital signs recorded after the initiation of vasopressors in the Emergency Department were not included in the database, nor were they used for calculations in this study.

Other clinical data gathered from the Emergency Department stay included the Glasgow Coma Scale, ED arrival and departure times, calculated total ED length of stay, amount of fluids and time to administration, type of antibiotics and time to administration, source of microbial cultures, appropriateness of antibiotics based on microbial culture susceptibilities, past medical history and documentation of early goal-directed therapy in the ED. Documentation of early goal-directed therapy included the presence of a central line and time initiated, central venous pressure initial value and time plus peak measurement and central mixed venous oxygen saturation initial value and time, as well as recordings during the first 24 hours of hospitalization.

Laboratory data included final microbial culture results, including blood, urine and other cultures taken, white blood cell count, percentage bands, hematocrit, platelets, serum sodium, serum chloride, serum potassium, serum bicarbonate, blood urea nitrogen, serum creatinine,

cardiac troponins, direct and indirect bilirubin, international normalized ration (INR), prothrombin time (PT) and partial prothrombin time (PTT) measured initially in the ED. Additionally, initial and peak lactate levels in the Emergency Department and upon admission to the floors, as well as arterial blood gas results in the Emergency Department were recorded. Lab values were considered abnormal if they exceeded previously established normal values at Yale-New Haven Hospital.

Use of vasopressors and timing of administration, specifically less than or greater than 72 hours after presentation, were determined from the ED and intensive care unit (ICU) nursing flow sheets and discharge summaries. Vasopressors included in this study were norepinephrine, dopamine, vasopressin, epinephrine and phenylephrine. Inotropes such as dobutatmine and digoxin were also recorded. Other therapies and interventions used and location administered, such as corticosteroids, source control, mechanical ventilation, tight glucose control, blood products and activated protein C, were also recorded. Vasopressor, inotrope and mechanical ventilator use were used as direct outcomes measures for this analysis.

Finally, disposition from the ED, diagnoses of attending emergency physician, final diagnosis upon discharge from the hospital, initial and total ICU length of stay, total hospital length of stay, initial and total time intubated, were documented. Of note, the ICU and hospital length of stay and mechanical ventilation length data were recorded for the last 109 patients only, which this author collected.

Assessment of Severe Sepsis and Septic Shock

Each patient included in this study had at least two of four SIRS criteria and evidence of a suspected infection based on presence of at least one of the following: white blood cell count greater than 10,000 cells μL^{-1}, temperature >100.4^{o}F or <96.4^{o}F, blood cultures obtained in ED, antibiotics administered in ED or suspected source of infection based on clinical exam or

imaging results *(see Table 2).* Additionally, all patients had evidence of at least one end-organ dysfunction. Patients with no organ dysfunction, by definition having only sepsis (as opposed to severe sepsis or septic shock), were not included in this study because they were excluded from the registry since its inception.

Any patient who presented with or developed septic shock during their ED stay was also included. Septic shock is defined as severe sepsis and a systolic blood pressure <90 mmHg that is unresponsive to intravenous fluids. Patients in extremis (defined as an initial systolic blood pressure <80 mmHg and/or requiring vasopressors within 15 minutes of presentation to ED) were also included in this study.

Statistical Analysis

Previous thesis research from Yale Medical Student Melissa Wollan revealed a statistically significant difference in mortality between patients with fewer than five and five or more organ injuries (112). Based on this information, our experimental groups reflect this finding and are delineated by five organ failures. Furthermore, in the evaluation of the MEDS score, we employ a similar mortality risk grouping to that determined by the original derivation study: very low (0-4), low (5-7), moderate (8-12), high (12-15) and very high (≥16) risk (50). The one exception is that the very low and low risk groups are combined in our study to create a zero to seven (0-7) MEDS score group, as the difference in their mortality rates (0.9% versus 2.0%) was not statistically significant in the original study. Finally, alpha is set to 0.05.

Results

Of the 640 charts reviewed for inclusion in the severe sepsis registry, 521 patients (81%) met criteria for enrollment in our study. Included patients were divided into two experimental groups, fewer than five organ dysfunctions (n=410 or 79%) and greater than or equal to five organ dysfunctions (n=111 or 21%).

The 119 patients excluded from this study had a mean age of 63.9 years, with approximately half (n=60) being male. None of the excluded patients were less than 18 years of age, 12 (10%) had documented comfort measures only in the Emergency Department, 74 (62%) met fewer than two SIRS criteria, 25 (21%) had sepsis only (meaning patients met criteria for SIRS but had no documented end-organ failure) and 18 (15%) were discharge to home directly from the ED.

Patient Baseline Characteristics

Demographic information and co-morbidities for all patients included in this study can be found in *Table 3.* Overall, 256 (49.1%) of patients were male and 265 (50.9%) were female. A statistically significant higher percentage of men than women had greater than or equal to five organ failures (59.5% versus 40.5%, respectively; p=0.02). The mean age at presentation was 63.1 ± 18.1 years, with a similar distribution in both the fewer than five and greater than five organ injuries groups.

Of the 16 co-morbid conditions reviewed in this study, only three demonstrated differences between patients with either fewer than five or greater than/equal to five organ dysfunctions, including residence in an extended care facility prior to admission (33.4% vs. 19.8%, respectively; p=0.005) and past medical history of liver disease (7.1% vs. 15.3%, respectively; p=0.01) and congestive heart failure (20.7% vs. 31.5%, respectively; p=0.02). The

rates of the remaining co-morbidities, consisting of coronary artery disease, hypertension, chronic obstructive pulmonary disease, asthma, end-stage renal disease, diabetes mellitus, alcohol abuse, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunodeficiency not otherwise specified (NOS), cancer, cancer with chemotherapy, cerebral vascular accident (CVA)/transient ischemic attack (TIA) and chronic altered mental status, were not different between the two groups.

Table 3. **Demographics and co-morbidities.**

	All patients (n=521)	**<5 organ dysfunctions (n=410)**	**≥5 organ dysfunctions (n=111)**	**p-value***
Demographics				
Age, *mean years ± SD*	63.1 ± 18.1	63.1 ± 18.1	63.1 ± 18.2	0.99
Sex, *n (%)*				**0.02**
Male	256 (49.1)	190 (46.3)	66 (59.5)	
Female	265 (50.9)	220 (53.7)	45 (40.5)	
Co-morbidities, n (%)				
Nursing home resident**	159 (30.5)	137 (33.4)	22 (19.8)	**0.005**
Liver disease	46 (8.8)	29 (7.1)	17 (15.3)	**0.01**
Congestive heart failure	120 (23.0)	85 (20.7)	35 (31.5)	**0.02**
Coronary artery disease	120 (23.0)	87 (21.2)	33 (29.7)	0.07
Hypertension	282 (54.1)	226 (55.1)	56 (50.5)	0.39
COPD	97 (18.6)	82 (20.0)	15 (13.5)	0.13
Asthma	31 (6.0)	26 (6.3)	5 (4.5)	0.65
End-stage renal disease	60 (11.5)	50 (12.2)	10 (9.0)	0.41
Diabetes mellitus	173 (33.2)	133 (32.4)	40 (36.0)	0.5
Alcohol abuse	49 (9.4)	33 (8.0)	16 (14.4)	0.06
HIV/AIDS	33 (6.3)	25 (6.1)	8 (7.2)	0.66
Immunodeficiency NOS	46 (8.8)	39 (9.5)	7 (6.3)	0.35
Cancer	95 (18.2)	75 (18.3)	20 (18.0)	1.0
Cancer with chemotherapy	47 (9.0)	34 (8.3)	13 (11.7)	0.27
CVA/TIA	78 (15.0)	63 (15.4)	15 (13.5)	0.76
Chronic altered mental status	62 (11.9)	50 (12.2)	12 (10.8)	0.87

SD, standard deviation; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; NOS, not otherwise specified; CVA, cerebral vascular accident; TIA, transient ischemic attack

*Bolded p-values are <0.05 and considered statistically significant.

**Includes any variation of extended care facility or group home living.

Disease severity classifications and cumulative organ dysfunction characteristics are detailed in *Table 4.* Four hundred and thirty five cases or 83.5% were classified as severe sepsis and 86 or 16.5% as septic shock. The mean number of cumulative dysfunctional organ systems for all patients was 3.2 ± 1.8, with survivors having 2.9 ± 1.6 versus 4.5 ± 2.3 mean organ failures in nonsurvivors (p<0.0001). Stratified further, 229 (44.0%) patients had one or two dysfunctional organ systems, 181 (34.7%) had three or four, 77 (14.8%) had five or six and 34 (6.5%) had greater than or equal to seven organ injuries.

Table 4. Disease severity classification and cumulative organ dysfunction.

	All patients (n=521)	<5 organ dysfunctions (n=410)	≥5 organ dysfunctions (n=111)	p-value*
Disease severity classification, n (%)				
Severe sepsis	435 (83.5)	366 (89.3)	69 (62.2)	**<0.0001**
Septic shock	86 (16.5)	44 (10.7)	42 (37.8)	**<0.0001**
Cumulative organ dysfunction, mean ± SD	3.2 ± 1.8			
Survivors**	2.9 ± 1.6			**<0.0001**
Nonsurvivors**	4.5 ± 2.3			
Number of end-organ dysfunctions, n (%)				
1 or 2	229 (44.0)			
3 or 4	181 (34.7)			
5 or 6	77 (14.8)			
7 or more	34 (6.5)			
Specific end-organ dysfunctions, n (%)				
Transient hypotension	194 (37.2)	117 (28.5)	77 (69.4)	**<0.0001**
Elevated lactate	238 (45.7)	151 (36.8)	87 (78.4)	**<0.0001**
Unexplained acidosis	230 (44.1)	141 (26.1)	89 (80.2)	**<0.0001**
Altered mental status	164 (31.5)	107 (26.1)	57 (51.4)	**<0.0001**
Thrombocytopenia	78 (15.0)	35 (8.5)	43 (38.7)	**<0.0001**
Hyperbilirubinemia	186 (35.7)	106 (25.9)	80 (72.1)	**<0.0001**
Abnormal coagulation studies	74 (14.2)	26 (6.3)	48 (43.2)	**<0.0001**
Acute renal failure	208 (39.9)	116 (28.3)	92 (82.9)	**<0.0001**
Hypoxemia	158 (30.3)	115 (28.0)	43 (38.7)	**0.04**
Troponin elevation	120 (23.0)	64 (15.6)	56 (50.5)	**<0.0001**

SD, standard deviation
*Bolded p-values are <0.05 and statistically significant; **p<0.0001 when comparing mean number of cumulative organ dysfunctions among survivors and nonsurvivors.

All specific organ systems had statistically significant differences in incidence between the two experimental groups.

Features of the Disease

Data regarding SIRS criteria, suspected source of infection and presumed site of infection are included in *Table 5.* All parameters of both SIRS criteria and suspected source of infection were equivalent, except white blood cell (WBC) count. Seventy-seven percent (77%) of patients with higher cumulative organ dysfunction compared with 66.1% of patients in the other group had elevated WBC counts meeting SIRS criteria (p=0.04).

Table 5. SIRS criteria and suspected source of infection.

	All patients (n=521)	<5 organ dysfunctions (n=410)	≥5 organ dysfunctions (n=111)	p-value*
SIRS criteria, n (%)				
Temperature	282 (54.1)	219 (53.4)	63 (56.8)	0.59
Heart rate	447 (85.8)	349 (85.1)	98 (88.3)	0.45
Respiratory rate	410 (78.7)	320 (78.0)	90 (81.1)	0.52
White blood cell count**	356 (68.3)	271 (66.1)	85 (76.6)	**0.04**
Suspected source of infection, n (%)				
White blood cell count***	401 (77.0)	304 (74.1)	97 (87.4)	**0.003**
Temperature	282 (54.1)	219 (53.4)	63 (56.8)	0.59
Blood cultures drawn in ED	475 (91.2)	371 (90.5)	104 (93.7)	0.35
Antibiotics administered	466 (89.4)	363 (88.5)	103 (92.8)	0.23
Presumed site of infection	331 (63.5)	262 (63.9)	69 (62.2)	0.74
Presumed site of infection, n (%)				
Pulmonary	158 (30.3)	130 (31.7)	28 (25.2)	0.20
Genitourinary	82 (15.7)	64 (15.6)	18 (16.20	0.88
Abdominal	55 (10.6)	39 (9.5)	16 (14.4)	0.16
Soft tissue	34 (6.5)	31 (7.6)	3 (2.7)	0.08
Other	41 (7.9)	28 (6.8)	13 (11.7)	0.11

SIRS, systemic inflammatory response syndrome; ED, emergency department
*Bolded p-values are <0.05 and considered statistically significant.
**White blood cell count >12,000 cells μL^{-1} or <4,000 cells μL^{-1} or > 10% immature neutrophils.
*** White blood cell count >10,000 cells μL^{-1} or <4,000 cells μL^{-1} or > 10% immature neutrophils.

Similarly, 87.4% versus 74.1% of patients in the greater than/equal to five and fewer than five organ failures groups, respectively, had elevated WBC counts as a measure for suspected infection (p=0.003). Of note, the two criteria differ in that SIRS requires a WBC count is >12,000 cells μL^{-1}, while the suspected source of infection requirement is WBC count >10,000 cells μL^{-1}. Finally, both groups were comparable in the distribution of presumed sites of infection.

Information regarding initial laboratory findings and vital signs is documented in *Table 6.* Despite disparities in the rates of elevated WBC counts, mean white blood cell counts and serum sodium concentrations were comparable between the two groups. On the contrary, the fewer than five and greater than or equal to five organ injuries groups diverge when evaluating mean hematocrit (37.2% vs. 35.5%, respectively; p=0.03), bicarbonate (22.0 vs. 18.0, respectively; p<0.0001), creatinine (2.0 vs. 3.0, respectively; p<0.0001) and elevated troponin (0.35 vs. 0.81, respectively; p=0.02). Lactate levels also distinguish the groups with the fewer than five organ failures group having an mean initial ED and floor lactate of 2.3 and 1.8, respectively, compared to the greater than or equal to five organ failures group, which had mean initial ED and floor lactates of 4.0 and 3.2, respectively (p<0.0001 in for both ED and floor values).

Both groups had similar percentages of total cultures sent, as well as blood and urine cultures specifically. There was a difference in the number of other cultures sent, which include sites like wound or central line, with 40.5% of the highly organ dysfunctional group compared to 29.3% of more mildly organ dysfunctional group (p=0.03). However, this did not have an impact on the distribution of positive cultures. The more severely organ dysfunctional group had more (57.4%) positive blood cultures of any kind compared to 43.8% in the other group (p=0.007). Most of this difference is accounted for with positive blood cultures, as 18.1% of those sent

from the fewer than five organ injuries group were positive versus 38.1% of the greater than/equal to five organ injuries group (p<0.0001).

Table 6. Initial laboratory and vital signs data.

	All patients (n=521)	<5 organ dysfunctions (n=410)	≥5 organ dysfunctions (n=111)	p-value*
Initial laboratory values, mean ± SD				
White blood cell count	14.8 ± 12.5	14.4 ± 9.1	16.2 ± 20.6	0.19
Hematocrit	36.8 ± 7.0	37.2 ± 6.5	35.5 ± 8.5	**0.03**
Sodium	135.4 ± 6.2	135.7 ± 5.7	134.6 ± 7.5	0.12
Bicarbonate	21.1 ± 5.4	22.0 ± 5.0	18.0 ± 5.7	**<0.0001**
Creatinine	2.2 ± 2.0	2.0 ± 1.9	3.0 ± 2.0	**<0.0001**
Elevated troponin	0.57 ± 1.06	0.35 ± 0.50	0.81 ± 1.4	**0.02**
Initial ED lactate	2.7 ± 2.2	2.3 ± 1.6	4.0 ± 3.3	**<0.0001**
Initial floor lactate	2.2 ± 2.3	1.8 ± 1.7	3.2 ± 3.2	**<0.0001**
Cultures, n (%)				
Total cultures sent	496 (95.2)	388 (94.6)	108 (97.3)	0.32
Blood	480 (92.1)	375 (91.5)	105 (94.6)	0.33
Urine	350 (67.2)	267 (65.1)	83 (74.8)	0.07
Other	165 (31.7)	120 (29.3)	45 (40.5)	**0.03**
Total positive cultures**	232 (46.8)	170 (43.8)	62 (57.4)	**0.007**
Blood	108 (22.5)	68 (18.1)	40 (38.1)	**<0.0001**
Urine	94 (26.9)	75 (28.1)	19 (22.9)	0.4
Other	88 (53.3)	64 (53.3)	26 (57.8)	0.73
Vital signs, mean ±SD				
Lowest SBP	94.2 ± 23.1	98.0 ± 23.2	80.6 ± 16.7	**<0.0001**
Lowest MAP	62.7 ± 16.5	65.5 ± 16.4	52.4 ± 12.4	**<0.0001**

SD, standard deviation; ED, emergency department; SBP, systolic blood pressure; MAP, mean arterial pressure
*Bolded p-values are <0.05 and considered statistically significant.
**Coagulase negative staphylococcus, corynebacterium and mixed flora were all treated as contaminants in accordance with hospital microbial patterns and were not considered positive results.

Key vital signs including systolic blood pressure (SBP) and mean arterial pressure (MAP) also varied among the experimental groups. The mean SBP and MAP for the fewer than five organ failures group were 98.0 and 65.5, respectively, compared to 80.6 and 52.4 in the greater than or equal to five organ failures group (p<0.0001 for both).

Therapies

Statistics concerning early goal-directed therapy and other interventions are detailed in *Table 7.* Patients with a greater number of organ dysfunctions received corticosteroids (36.9%), blood products (16.2%) and activated protein C (3.6%) more frequently than patients with fewer organ dysfunctions (26.1%, p=0.03; 3.7%, p<0.0001; and 0.2%, p=0.008; respectively). Notably, the overall rates of activated protein C were extremely low (n=5 or 1%). Source control, tight glucose control and antibiotic rates were similar among both groups, as well as time to antibiotics and rates of appropriate microbial coverage.

Table 7. Early goal-directed therapy and other interventions

	All patients (n=521)	<5 organ dysfunctions (n=410)	≥5 organ dysfunctions (n=111)	p-value*
Therapies, n (%)				
Antibiotics	469 (90.0)	366 (89.3)	103 (92.8)	0.37
Time to antibiotics, *mean h:m ± SD*	2:39 ± 2:18	2:23 ± 1:41	2:44 ± 2:27	0.17
Appropriate microbial coverage**	277 (92.9)	208 (92.0)	69 (95.8)	0.07
Corticosteroids	148 (28.4)	107 (26.1)	41 (36.9)	**0.03**
Source control	90 (17.3)	74 (18.0)	16 (14.4)	0.4
Blood products	33 (6.3)	15 (3.7)	18 (16.2)	**<0.0001**
Tight glucose control	34 (6.5)	28 (6.8)	6 (5.4)	0.67
Activated protein C	5 (1.0)	1 (0.2)	4 (3.6)	**0.008**
Early goal-directed therapy, n (%)				
Documented EGDT	72 (13.8)	48 (11.7)	24 (21.6)	**0.01**
Intravenous fluids, *mean liters ± SD*	2.8 ± 2.1	2.6 ± 1.8	4.1 ± 2.6	**<0.0001**
Central line	161 (30.9)	103 (25.1)	59 (53.2)	**<0.0001**
CVP	94 (18.0)	62 (15.1)	32 (28.8)	**0.001**
Initial CVP, *mean ± SD*	9.2 ± 5.4	9.5 ± 5.6	8.7 ± 5.1	0.5
$ScvO_2$	102 (19.6)	69 (16.8)	33 (29.7)	**0.004**
Initial $ScvO_2$, *mean ± SD*	69.4 ± 13.1	69.6 ± 12.5	69.2 ± 14.3	0.88

h:m, hours:minutes; SD, standard deviation; EGDT, early goal-directed therapy; CVP, central venous pressure; $ScvO_2$, central venous oxygen saturation
*Bolded p-values are <0.05 and considered statistically significant.
**Applicable to patients in whom both antibiotics were administered in the Emergency Department and at least one microbe with antibiotic susceptibilities was identified through cultures with susceptibilities, variables on which the clinical evaluation of appropriate microbial coverage is based. Therefore, the total number of cases include for this data set is 298, with 226 in the <5 organ dysfunctions group and 72 in the ≥5 organ dysfunctions group.

Individual interventions included in the early goal-directed therapy protocol were all employed more frequently in the five or more failures group. Specifically, EGDT was documented in 21.6% of the patients in the high number of organ failures group compared to 11.7% (p=0.01) in the other group. Additionally, central lines (53.2%) were placed more frequently and CVPs (28.8%) and $ScvO_2$s (29.7%) were drawn more often in the higher organ injuries group versus 25.1% (p<0.0001), 15.1% (p=0.001) and 16.8% (p=0.004), respectively, in the fewer cumulative organ injuries group, though the mean values for both CVP and $ScvO_2$ were comparable. Finally, patients with more organ dysfunctions received a larger amount of IV fluids, a mean of 4.1 ± 2.6 L versus 2.6 ± 1.8 L (p<0.0001).

Outcomes

Table 8 outlines data regarding disposition, length of stay, mortality, vasopressor requirement, inotrope use, mechanical ventilation, as well as Mortality in Emergency Department Sepsis score outcomes. Disposition locations from the Emergency Department had extremely significant differences between both experimental groups. As such, 99 patients (89.2%) with greater than or equal to five organ dysfunctions were admitted to acute or subacute units (i.e. intensive care unit (ICU), stepdown unit, operating room (OR) or morgue), while 12 (10.8%) of these patients went to regular floor bed. On the other hand, patients with fewer than five organ dysfunctions were distributed more equitably upon admission with 186 (45.4%) going to the floor and 224 (54.6%) to an acute or subacute bed. The variation between the two groups had p-values <0.0001 for both floor and escalated care units.

Admission rate to the intensive care unit specifically was 83.8% in the group with more organ failures and 48.3% in the group with fewer failures (p<0.0001), and was also significant for differences in patients going to the morgue (two or 1.5% in the higher injury group versus zero

in the other group, p=0.04). The stepdown unit and operating room had similar admission rates between groups.

Table 8. Disposition and Outcomes

	All patients (n=521)	<5 organ dysfunctions (n=410)	≥5 organ dysfunctions (n=111)	p-value*
Disposition from the ED, n (%)				
Floor	198 (38.7)	186 (45.4)	12 (10.8)	**<0.0001**
Acute/subacute unit	323 (63.3)	224 (54.6)	99 (89.2)	**<0.0001**
Step down unit	20 (3.8)	18 (4.4)	2 (1.8)	0.27
Intensive care unit	291 (55.9)	198 (48.3)	93 (83.8)	**<0.0001**
Operating room	10 (1.9)	8 (2.0)	2 (1.8)	1.0
Morgue	2 (0.4)	0 (0)	2 (1.8)	**0.04**
Length of stay, mean ± SD				
Emergency department, *hours:mins*	6:36 ± 4:04	6:35 ± 3:55	6:42 ± 4:36	0.78
Intensive care unit, *days***	4.2 ± 6.2	3.2 ± 5.9	7.0 ± 6.6	**0.02**
Total hospital, *days***	11.4 ± 11.0	10.2 ± 9.7	15.3 ± 13.9	0.07
Ventilator, *days****	6.8 ± 8.0	7.1 ± 9.8	6.6 ± 5.5	0.17
Study end-points, n (%)				
Mechanical ventilation	153 (29.4)	99 (24.1)	54 (48.6)	**<0.0001**
ED	77 (14.8)	47 (11.5)	30 (27.0)	**<0.0001**
ICU/OR	76 (14.6)	52 (12.7)	24 (21.6)	**0.02**
Vasopressors	147 (28.2)	85 (20.7)	62 (55.9)	**<0.0001**
ED	79 (15.2)	40 (9.8)	39 (35.1)	**<0.0001**
< 72 hours	126 (24.2)	70 (17.1)	56 (50.5)	**<0.0001**
Inotropes	37 (7.1)	22 (5.4)	15 (13.5)	**0.006**
Total in-hospital mortality	79 (15.2)	45 (11.0)	34 (30.6)	**<0.0001**
Septic shock patients****	29 (33.7)	10 (22.7)	19 (45.2)	**0.04**
Severe sepsis****	50 (11.5)	35 (9.6)	15 (21.7)	**0.007**
In-hospital <28 day mortality	67 (12.9)	35 (8.5)	32 (28.8)	**<0.0001**
Septic shock patients****	25 (29.1)	7 (15.9)	18 (42.9)	**0.009**
Severe sepsis patients****	42 (9.6)	28 (7.7)	14 (20.3)	**0.003**
MEDS Score, mean ± SD	11.1 ± 4.6	10.7 ± 4.5	12.5 ± 4.9	**0.0002**

ED, emergency department; hours:mins, hours:minutes; SD, standard deviation; ICU, intensive care unit; OR, operating room

*Bolded p-values are <0.05 and considered statistically significant.

**Value computed from last 109 cases reviewed, as this is a new data point in the registry and has not yet been updated for the remaining patients.

***Value computed from last 109 cases reviewed that were also mechanically ventilated (n=25), as this is a new data point in the registry and has not yet been updated for the remaining patients.

****Severe sepsis and septic shock here refer to diagnoses in the ED based on study inclusion criteria.

Mean emergency department and total hospital lengths of stay, as well as ventilator days, were equivalent between both groups (note that total hospital length of stay and ventilator days were only recorded for the last 109 patients included in the registry). However, mean intensive care unit lengths of stay were significantly increased for the higher organ failures group (7.0 days ± 6.6) over the lesser organ failures group (3.2 days ± 5.9; p=0.02) (also computed based on the last 109 patients of severe sepsis registry).

Mechanical Ventilation

Figure 3 presents mechanical ventilation rates according to narrowly stratified groups of cumulative organ failure. Seventy-seven patients (14.8%) were mechanically ventilated in the ED and another 76 (14.6%) in the ICU or operating room for a total of 153 patients (29.4%). When classified according to cumulative organ dysfunction, there was a statistically significant difference in the rates of mechanical ventilation between both experimental groups. Twenty-seven percent of patients in the higher cumulative organ injuries group were intubated in the ED, while 11.5% in the fewer cumulative organ injuries group received mechanical ventilation in the same location ($p<0.0001$). Intubation rates were similarly distributed in the ICU and OR, with 21.6% of highly organ dysfunctional compared to 12.7% of minimally organ dysfunctional patients (p=0.02).

Vasopressors and Inotropes

Figure 4 presents vasopressor and inotrope rates according to narrowly stratified groups of cumulative organ failures. Of the 147 patients (28.2%) who received vasopressors, 79 (15.2%) received them in the ED and a total of 126 patients (24.2%) went on to receive vasopressors at some point within the first 72 hours of their hospitalization. Variations among the two levels of organ failure were extremely statistically significant for all vasopressor time points.

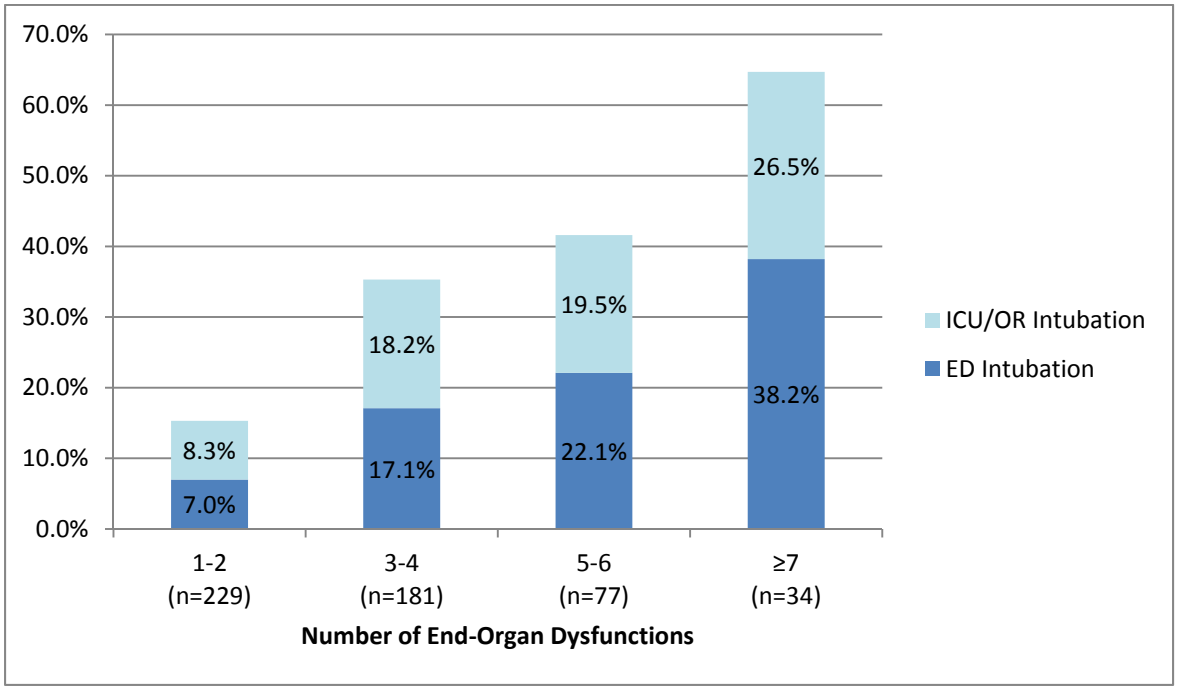

Figure 3. **Mechanical ventilation rates by location and cumulative end-organ dysfunction.**

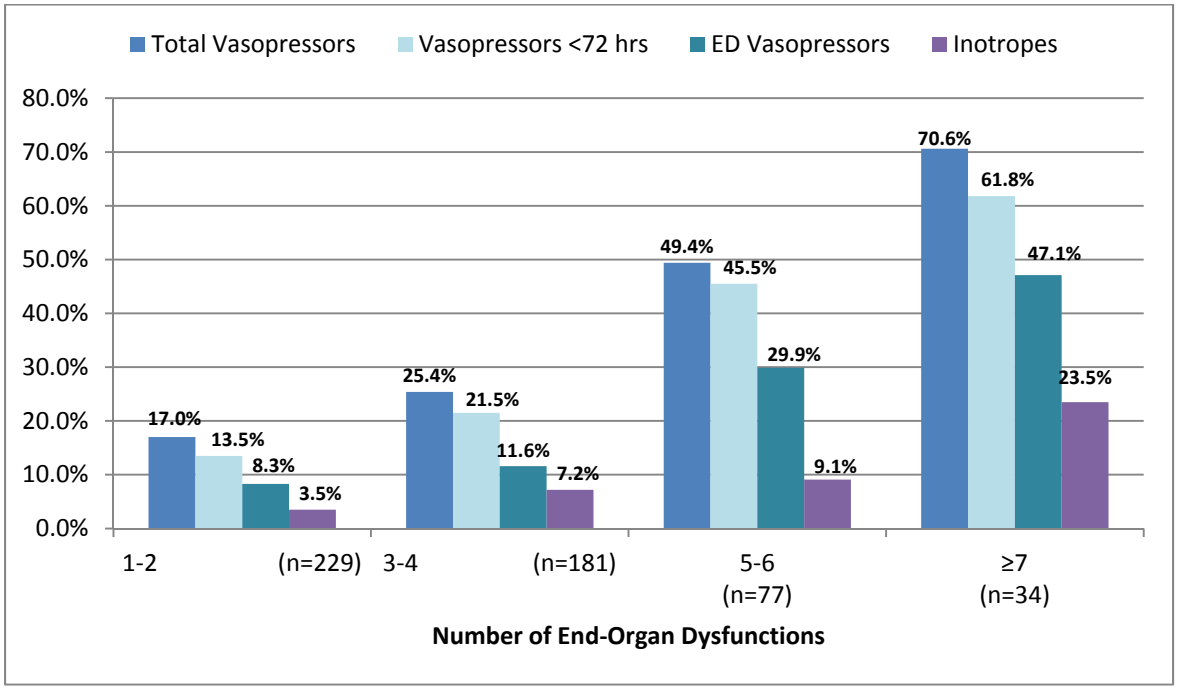

Figure 4. **Vasopressor and inotrope rates and cumulative end-organ dysfunction.**

As such, 55.9% of patients with greater than or equal to five organ failures received vasopressors at any point during the hospitalization compared to 20.7% in the other group ($p<0.0001$). Of those, 50.5% in the higher dysfunctional group versus 17.1% in the lower dysfunctional group received this form of hemodynamic support within 72 hours ($p<0.0001$). The rates of inotrope use paralleled that of vasopressors, with rates equaling 13.5% of the greater than or equal to five organ injuries patients compared to 5.4% in the other group ($p=0.006$).

Mortality

Figure 5 presents mortality rates according to narrowly stratified groups of cumulative end-organ failure. Similarly, *Figure 6* further details the relationship between specific organ injuries and mortality. The overall in-hospital mortality rate in this study was 15.2% (n=79). Septic shock patients experienced a higher mortality rate of 33.7% (n=29) than patients diagnosed with severe sepsis (11.5%, n=50). As such, there were significant variations between in-hospital mortality rates of the groups representing the two levels of organ dysfunction, both at 28-days and total hospital length of stay. Among patients with fewer than five organ failures, 8.5% died within 28 days, while 28.8% of the greater than or equal to five organ failures group died during that same time period ($p<0.0001$).

A statistically significant difference also existed among disease severity subgroups, with 42.9% of the higher number for organ dysfunctions group and 15.9% of the lower number of organ failures group having a fatal outcome among septic shock patients ($p=0.009$). Similarly, 20.3% of patients with severe sepsis and high cumulative organ injuries died compared to 7.7% in the less dysfunctional group ($p=0.003$).

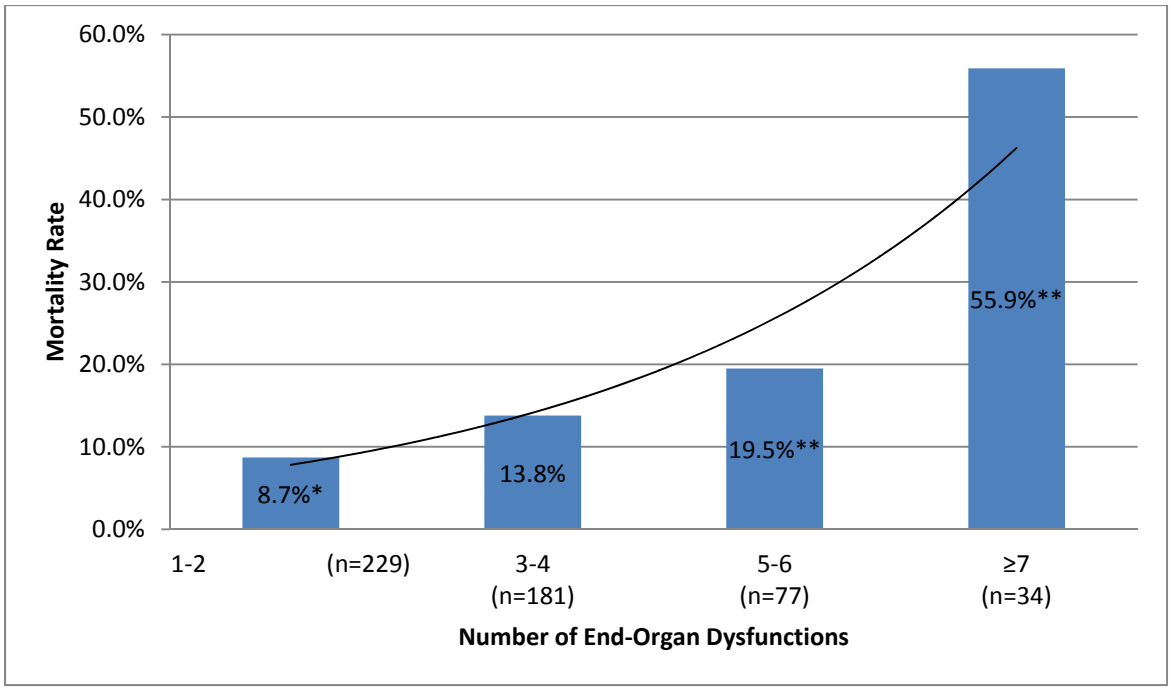

Figure 5. **Total in-hospital mortality rate and total number of end-organ dysfunctions.**
p<0.05 when comparing high organ failure groups** to the low organ failure group*.

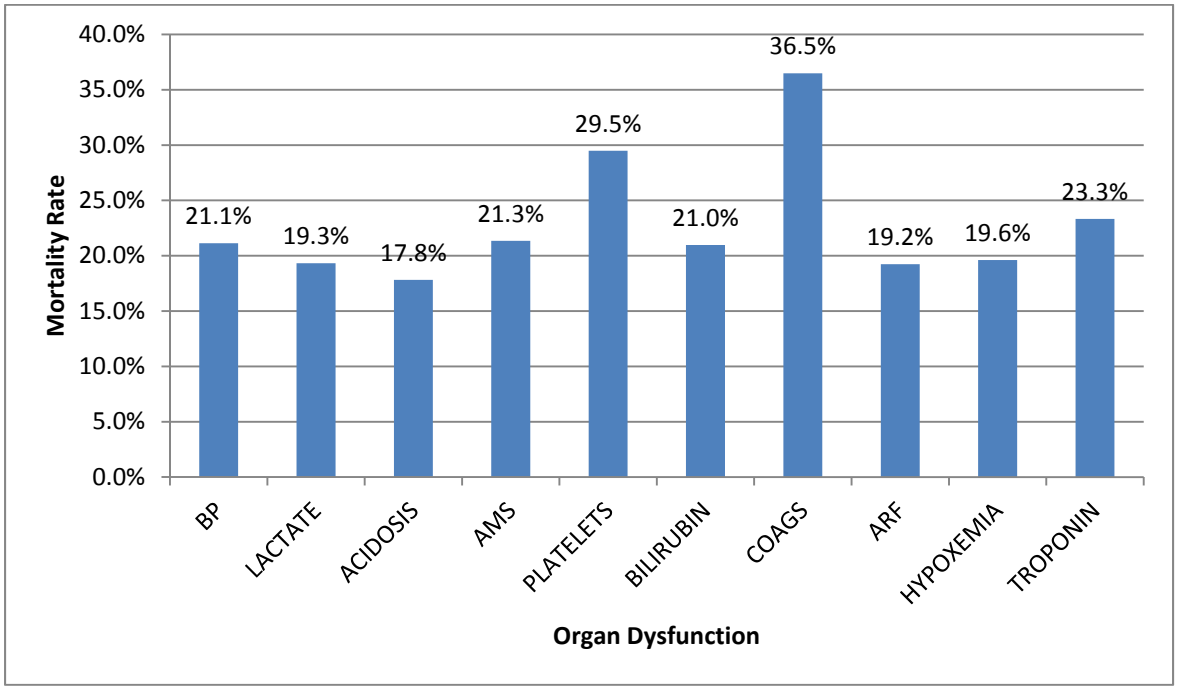

Figure 6. **Mortality rate and specific organ dysfunction.**

Mortality in Emergency Department Sepsis (MEDS) Score

The two experimental groups had a statistically significant difference in mean MEDS scores. Patients with fewer than five organ failures had a mean MEDS score of 10.7 ± 4.5, as compared to the other group with mean MEDS score of 12.5 ± 4.9 (p=0.0002). When the experimental groups are further stratified, the MEDS scores did not trend with cumulative organ failure *(see Figure 7).* One or two, three or four and seven or more end-organ dysfunctions groups all have the 8-11 MEDS score as the highest frequency group (32.8%, 32.6% and 35.3%, respectively), while a majority (33.8%) of the five or six organ failures group had MEDS scores of 12-15. None of the differences between the two extremes of organ injuries groups (one or two and seven or more) in the MEDS score subgroups were statistically significant.

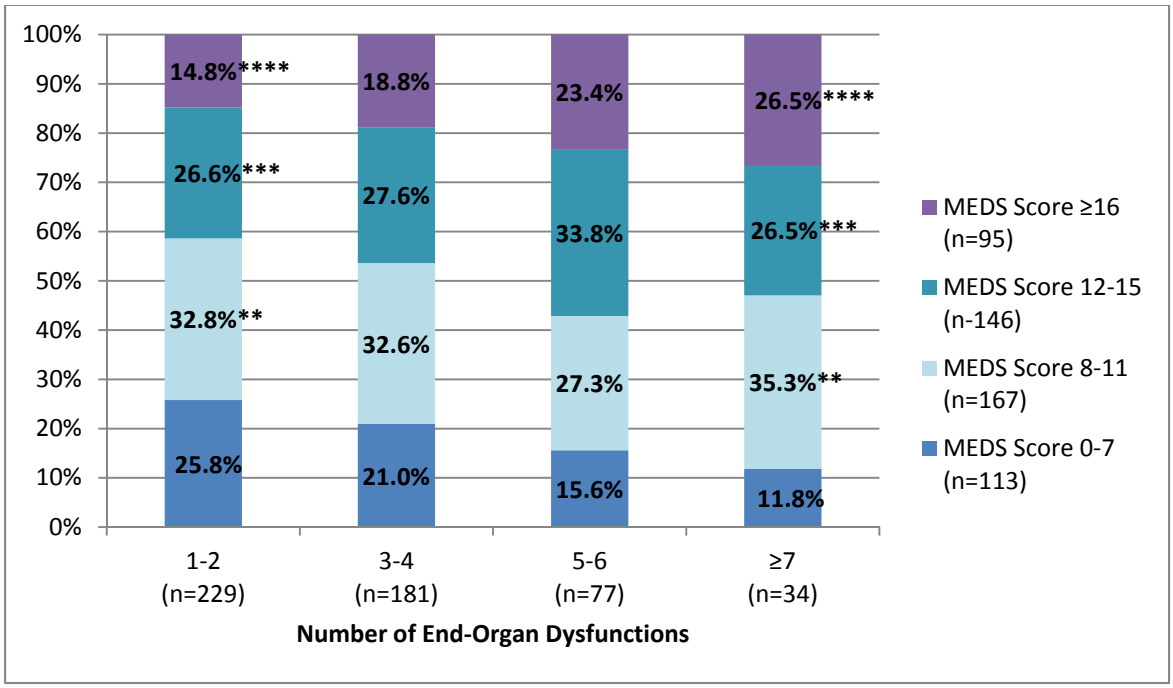

Figure 7. Number of end-organ dysfunctions compared to MEDS score.

Furthermore, the highest percentage (25.8%) of patients with MEDS scores zero to seven (0-7) emerge within the one or two organ dysfunctions group, as the rates descend with

increasing cumulative organ dysfunction within this MEDS score group. Likewise, the highest percentage (26.5%) of patients with MEDS scores ≥16 fall within the greater than or equal to seven organ failures group, with descending rates as the number of cumulative organ failures decrease.

Finally, when comparing MEDS scores to the three study end-points, mortality, vasopressor and mechanical ventilation rates, no clear relationship emerged *(see Figure 8)*. Vasopressor rates were nearly stable across the four MEDS score groups, with 21.2%, 24.6%, 26.0% and 24.2% of patients with MEDS scores in ascending order receiving this support. On the other hand, intubation and mortality rates peaked among the 8-11 MEDS score group, at 41.9% and 17.4%, respectively. Otherwise, mortality rates remained steady across all groups, while rates of mechanical ventilation decreased from the 8-11 to the ≥16 MEDS score groups.

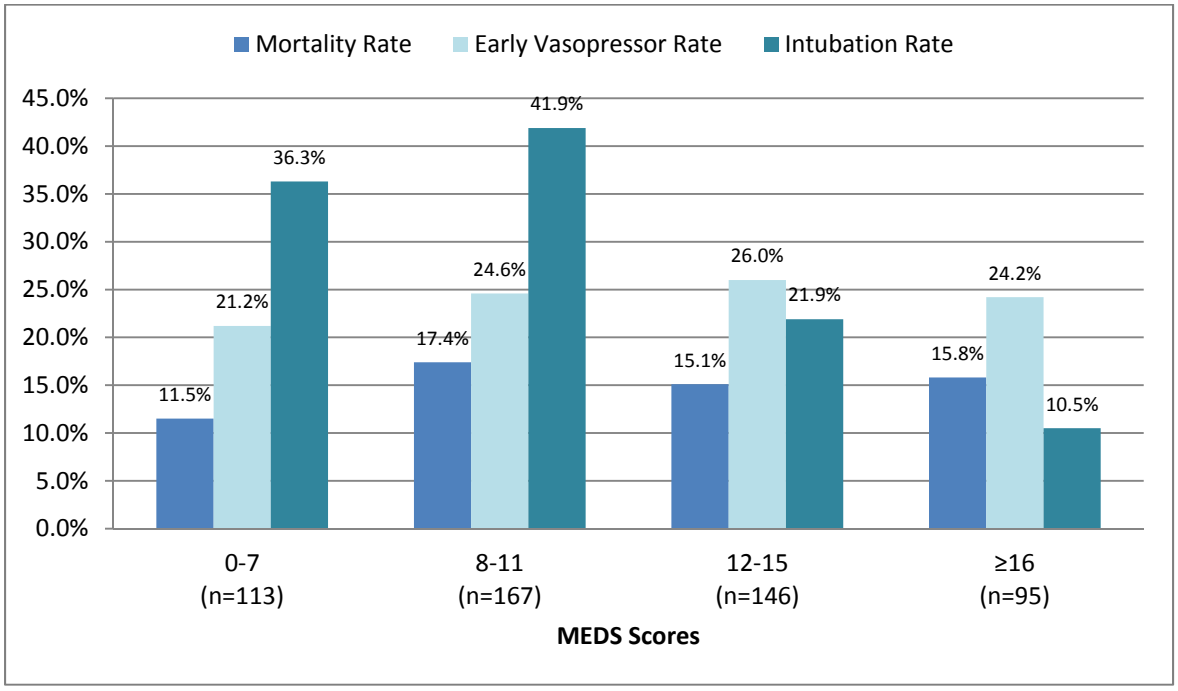

Figure 8. MEDS scores and mortality, early (<72 hour) vasopressor and mechanical ventilations rates.

Discussion

The primary aim of this study was to determine if cumulative organ dysfunction in patients presenting to the Emergency Department with severe sepsis and septic shock is a predictor of mortality. Toward this goal, we found that mortality rates increased as patients amassed more organ dysfunctions. These findings complement and enhance the existing literature by demonstrating that cumulative organ dysfunction identified in an ED, rather than the ICU setting, can be predictive of outcome. We also discovered that cumulative organ failure was associated in a linear fashion with pre-fatal indicators of deterioration, including mechanical ventilation, vasopressor and inotrope rates.

Additionally, this is the only study to our knowledge that specifically evaluates the relationship between organ dysfunction and mortality in patients receiving currently recommended therapies such as EGDT, corticosteroids, vasopressors and mechanical ventilation in an ED. Despite a higher frequency of critical interventions in patients with five or more organ failures, mortality rates still reached approximately 56% in patients with seven or more dysfunctions, underscoring the role of cumulative organ dysfunction as a lethal component of severe sepsis.

Our study also contrasts the investigations of the ICU-based MODS and SOFA score, as well as the ED study from Shapiro and others, which demonstrated that much higher rates of mortality prior to the advent of EDGT in septic patients. For instance, Shapiro et al. revealed the following mortality rates: no organ dysfunction (1.0% mortality), one organ dysfunction (5.9% mortality), two (12.5% mortality), three (25.9% mortality), and four or more (53.3% mortality), which are substantially higher than our mortality rates of 8.7% (one or two organ failures), 13.8% (three or four organ failures), 19.5% (five or six organ failures) and 55.9% (seven or more)

(14). This supports the notion that early and appropriate administration of current therapies is successful in reducing death due to sepsis-related to organ injury.

However, when comparing these studies, it is important to recognize that there are several key differences in the methodology, including definitions of organ injury, as well as the population studied. Generally, sepsis research definitions of specific organ failures range from more to less strict criteria (see *Figure 9*). Our study utilizes less stringent organ dysfunction definitions, while the Shapiro et al. study criteria are slightly more stringent, thus investigating outcomes in a potentially sicker population. What's more is that the Shapiro et al. study likely missed a population of patients who had significant organ failure, as it only evaluated six organ systems, while our study evaluated ten, including elevated lactate which is a previously demonstrated independent predictor of mortality, thus potentially underestimating mortality rates prior to the institution critical treatments in the ED (i.e. overall 28-day in-hospital mortality was 12.9% in this study compared to 4.1% in the Shapiro et al. study).

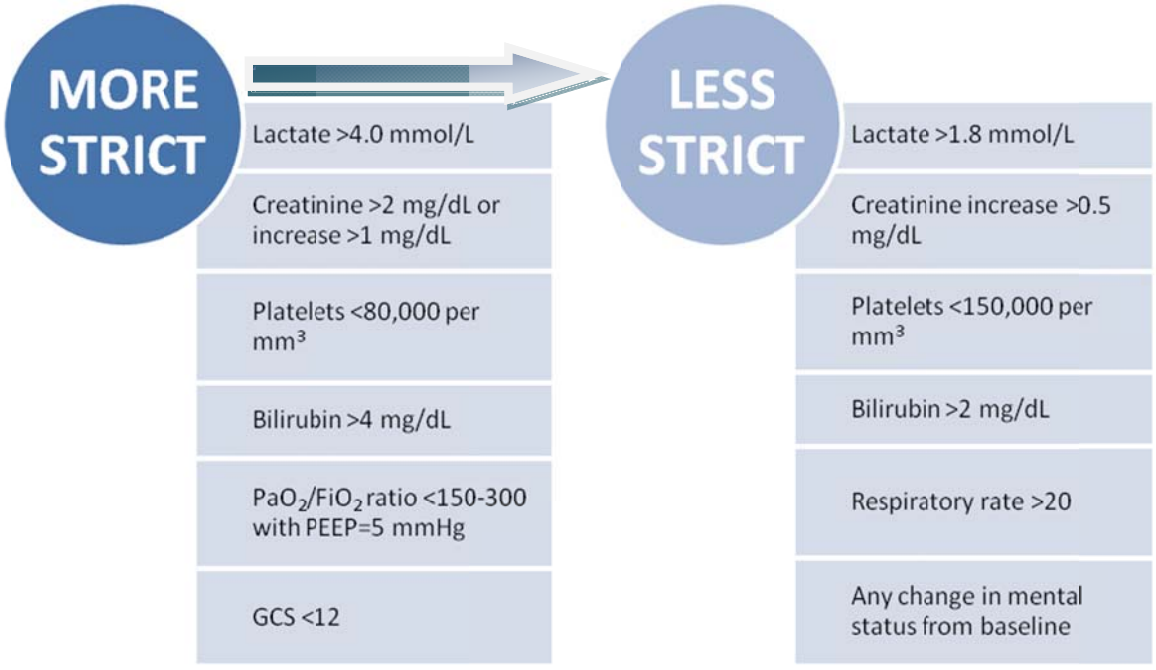

Figure 9. Examples of the spectrum of organ failure definitions (113).

Despite the intuitive nature of the premise examined in this study, that cumulative organ dysfunction correlates with mortality, Yale-New Haven hospital did not have an ED sepsis order set to monitor organ dysfunction up until approximately one and a half years ago. Furthermore, Yale medical student Sundeep Bhat had to exclude a significant proportion (approximately 25%) of patients from his lactate clearance thesis project using this same severe sepsis registry because they did not have lactates drawn in the ED (113).

Presumably, there are many EDs that treat critically ill septic patients that still do not draw comprehensive labs for the appropriate evaluation of organ injury, decreasing the likelihood that cumulative organ dysfunction monitoring is a standard of care, as clinicians are not likely to consciously incorporate cumulative organ failure into crucial decision-making without such data. Therefore, this study could help mold sepsis-related medical practices by encouraging the implementation of a comprehensive, ED-based protocol to evaluate laboratory and clinical evidence of end-organ dysfunction.

We also discovered that cumulative organ injury was associated in a linear fashion with pre-fatal indicators of deterioration, including mechanical ventilation, vasopressor and inotrope rates. Interestingly, inotrope rates for the more severe organ dysfunction group parallels that of the original EDGT trial (13.5% versus 13.7%, respectively) which recommended the use of dobutamine in its protocol (24). Given that these interventions are most safely employed in acute post-ED settings such as the ICU, these results support the role of cumulative organ dysfunction in disposition assessments.

Interestingly, 186 (45.4%) patients with fewer than five organ failures (which had a total in-hospital mortality rate of 11% overall) were sent to regular medical or surgical floor beds upon discharge from the ED. There were 11 fatalities (5.9%) among this subgroup of patients.

While this value is lower than the overall mortality for this group of patients, it is still higher than the Yale-New Haven Hospital mortality rates for STEMI alerts, modified traumas and acute stroke patients (113). Therefore, one could argue that all patients with severe sepsis or sepsis shock, regardless of modifiers of disease severity, should be admitted to acute care units initially from the ED.

Despite these optimistic findings relating organ dysfunction with mortality, mechanical ventilation and vasopressor rates, neither cumulative organ injury nor mortality correlated with the previously externally validated and deemed generalizable Mortality in Emergency Department Sepsis (MEDS) score. This null association may be a flaw of the study design, as this was a retrospective chart review which relied solely on documentation of clinical data that is designed to be prospectively determined in the MEDS score. While the data in the one study that failed to associate MEDS score with mortality were derived prospectively, it was also applied post hoc, similar to our retrospective application of the MEDS score (83). Furthermore, like this other study with a null finding, the poor correlation between MEDS scores and mortality was found predominantly in the moderate ranging MEDS scores (i.e. 5-15 MEDS score group in the other study compared with the 8-15 group in this study).

One such difficult parameter to assess retrospectively from limited charted information was the determination of terminal illness. Shapiro el al. defined terminal illness as “metastatic cancer or a disease condition with a >50% likelihood of predicted fatality within 30 days” in the original study to derive the MEDS score (50). Given that such a determination of fatality within 30 days is heavily dependent on other details of a patient’s medical history that was not likely outlined in the specific visit medical records used in this study, we relied on the presence of cancer or cancer with chemotherapy as an indicator of the presence of terminal illness.

With 21st century advancements in the treatment of cancer, the mere presence of cancerous cells does not denote terminal illness. This simplification likely severely skewed the MEDS score values given that terminal illness receives the greatest number of points (six) given to any parameter in the calculation, even despite the fact that the prevalence of cancer with or without chemotherapy had similar rates among both experimental groups. Therefore, to evaluate the effect of this generalization, a modified MEDS (MOD MEDS) score was computed for every patient, eliminating terminal illness as a component. The scores were then compared to the primary study end-point, mortality.

Figure 11 represents the association between the modified MEDS score and mortality. As expected, there is a linear relationship between this risk stratification model and death in patients with severe sepsis and septic shock, however, it is only statistically significant between the lowest MOD MEDS score group (0-7) and the other three groups (8-11, p=0.03; 12-15, p=0.004; and 16 or more groups, p=0.02). Despite this, the mortality rate progression with increasing MOD MEDS scores (MOD MEDS 0-7, 10.0%; MOD MEDS 8-11, 17.4%; MOD MEDS 12-15, 25.4%; MOD MEDS ≥16, 36.4%) is more similar to the original MEDS study mortality rates (MEDS 0-4, 1.1%; MEDS 5-7, 4.4%; MEDS 8-12, 9.3%; MEDS 12-15, 16%; and MEDS >15, 39%, in the validation set) than our MEDS score data including terminal illness.

It is reasonable that this ambiguity within the higher values categories in the terminal illness correction is a result of the fact the MOD MEDS score subgrouping remains the same (i.e. 0-7, 8-11, 12-15 and ≥16) as the MEDS score categories which included terminal illness in this study, despite significant reductions in total possible points. Because of this, the two modified MEDS score groups at the highest extremes of the population have very few numbers from which to evaluate the relationship. Thus, the statistical relationship between the prediction

score groups and mortality may be underestimated due to the likely suboptimal grouping of modified MEDS score classifications.

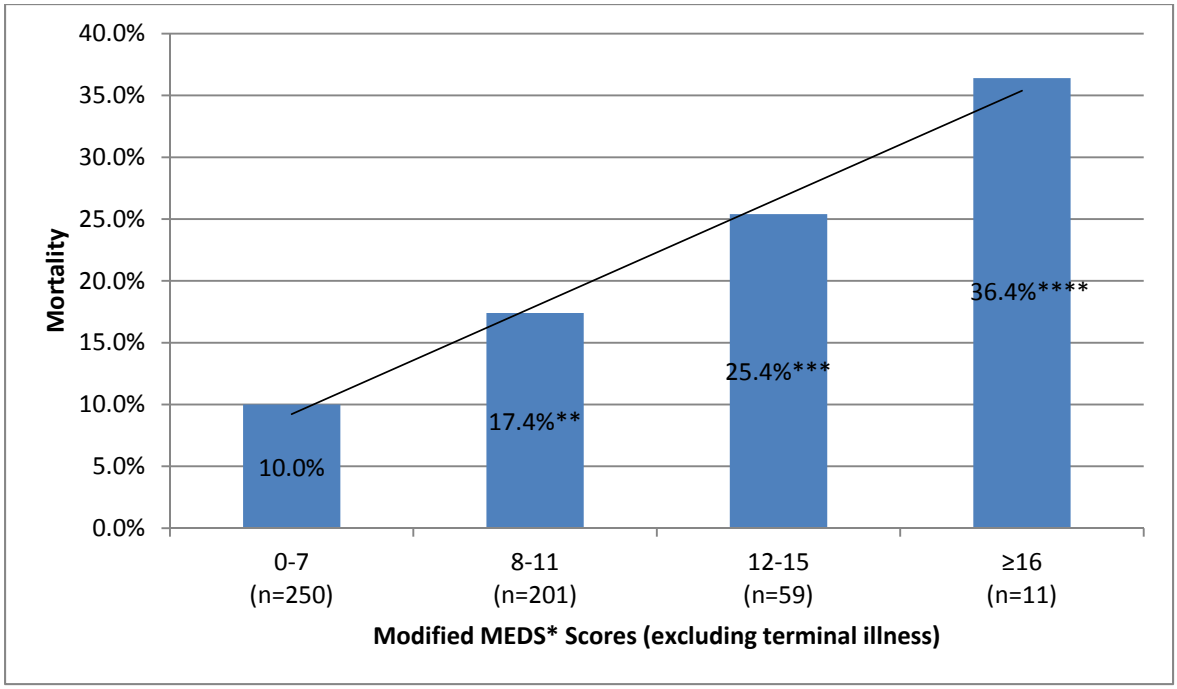

Figure 10. Modified MEDS Score (excluding terminal illness) and mortality rates.
*MOD MEDS score, Modified Mortality in Emergency Department Sepsis score.
**p=0.03 between the MOD MEDS score 0-7 and 8-11.
***p=0.004 between MOD MEDS score 0-7 and 12-15.
****p=0.02 between MOD MEDS 0-7 and ≥16.

Another plausible cause for the failed association between mortality and the Shapiro et al. MEDS score is that it does not include lactic acidosis or acute renal failure as derivatives. *Table 3* demonstrates that the most frequently occurring organ dysfunctions in this sample population were elevated lactate (45.7%), acidosis (44.1%) and renal failure (39.9%). While adding a point value for each specific organ failure to a risk stratification tool would render it unnecessarily cumbersome and time consuming, it may be tremendously beneficial to replace one of the current parameters (i.e. hypoxia/tachypnea, which is likely already represented by

the presence of lower respiratory infection) with lactic acidosis, which was not evaluated in the original study and has been demonstrated to be an independent predictor of mortality (53-58).

While comparing the two experimental groups, some distinctions in baseline characteristics emerged. First, there was a higher preponderance of male patients (59.5%) in the more severely organ dysfunctional group versus female (40.5%). It stands to reason that this difference might be attributed to either age or number of baseline co-morbidities. As such, the mean age of men in each group was comparable to the group mean and to each other. However, men had a statistically significant greater number of co-morbidities compared to women, with means of 3.2 and 2.8, respectively ($p=0.005$) in the five or more organ failures group.

Likewise, there were variations in the distribution of some key co-morbidities. For instance, there was actually an inverse relationship between residence in an extended care facility and organ dysfunction, with more patients (33.4%) in the fewer than five organ injuries group and fewer (19.8%) patients in the five or more organ injuries group. Perhaps this can be attributed to level of surveillance patients receive in group living facilities that facilitate the early detection of sepsis syndrome, hence earlier presentation to the ED before disease progression to fulminate end-organ damage. Another plausible explanation is that patients who were more severely ill and likely to fall in the high organ dysfunction category may have had code status documentation of comfort measures only that precluded inclusion in this study.

Liver disease and congestive heart failure (CHF) were also disproportionate among the two groups. Perhaps liver disease as a predisposing factor was more prevalent among the five or more organ failures group because of its relationship to many of the end-organ injuries measured in this study, including coagulopathy given that the liver is the site of production of coagulation factors, hyperbilirubinemia, altered mental status through hyperammonemia,

creatinine by way of hepato-renal syndrome and thrombocytopenia through splenic platelet sequestration, relatively decreased thrombopoietin synthesis and immune complex-associated platelet clearance (114). In like manner, CHF is also a formidable disease that complicates treatment of sepsis syndrome by tempering a fundamental intervention, intravenous fluid. Furthermore, it was determined to be a predictor of death in the MEDS score study and may be associated with a sicker population overall.

Statistically significant elevations of troponin, lactate and creatinine, as well as lower bicarbonate which is associated with renal function, in the five or more organ dysfunctions groups is intuitive given that these are markers of the cardiac, hemodynamic and renal failures. However, the explanation of differences in hematocrit is less obvious. One could expect the hematocrit of the more severe organ injury group to be higher in the case of predominance of hemoconcentration due to poorer volume status. However, the inverse was found in this study, with the mean hematocrit being 37.2 g/dL in the fewer than five versus 35.5 g/dL in the five or more organ failures group. This disparity may be a reflection of the larger volume of intravenous fluids administered to the higher organ dysfunction group before labs were drawn or be an indicator of decreased red blood cell synthesis or increased destruction in more critically ill patients. Nevertheless, while the difference in hematocrit was statistically significant between experimental groups, it is unlikely to be clinically significant.

The increased yield of positive blood cultures with increasing cumulative organ injury may be an indicator of a higher bacterial load in that group, given that blood cultures were drawn at the same rate. In like manner, the very low mean systolic blood pressure and mean arterial pressure values for the five or more organ failures group likely corresponds with the preponderance for septic shock patients in this group and subsequent mortality.

Finally, patterns across both groups concerning therapies and interventions reflect expected effects. The null difference between antibiotic administration, timing and appropriateness, as well as source control, is a reflection of the standardization of these practices. On the contrary, less proven treatments such as corticosteroids and activated protein C were used more often in the higher severity organ failure group given that these patients had more indicators of poor outcomes and likely required more aggressive interventions. Finally, the previously mentioned difference in hematocrit may account for the increased blood products given to the five or more organ dysfunctions group.

There was poor documentation overall of the implementation of the EGDT protocol by clinicians in this study (13.8%), though many employed multiple aspects of the protocol independent of formal documentation. As a consequence of disease severity, clinicians were more likely to document that they followed the protocolized form of EGDT, administering a higher volume of intravenous fluid, while placing more central lines leading to more CVP and $ScvO_2$ draws, in the high organ injuries group.

However, it is curious that there were no differences in the mean initial values for CVP and $ScvO_2$ among the two experimental groups. This may in part be attributed to a phenomenon known as "venous superoxia." As disease progression in severe sepsis and septic shock leads to greater tissue damage, oxygen extraction by the tissues plummets. This critical consequence causes shunting of oxygen from the arterial supply to venous vasculature triggering central venous oxygen saturation to rise as opposed to decrease as expected with oxygen delivery-consumption mismatch that typically occurs in the more proximal stages of the illness.

Another major concern for clinicians treating septic patients in the Emergency Department is appropriate disposition to hospital units based on acuity. While the patients with

greater organ failures were more likely to go to acute units with critical monitoring and treatment capabilities, 10.8% of potentially very ill patients went to a regular floor bed despite having five or greater organ injuries. This disparity could potentially be reduced if cumulative organ failure was a component of disposition algorithms.

As a consequence of more frequent ICU disposition, of the 109 patients for which this parameter was reviewed, those with five or more organ failures had significantly increased ICU length of stays. Interestingly, despite significant differences in mechanical ventilation rates, there is no difference in mean ventilator days between both groups. This may reflect the fact that a significant portion of patients are likely intubated early for non-disease or protocol-related reasons such as airway protection. Furthermore, since only a small percentage of the patients in the registry had this factor included, the numbers may not be sufficiently large enough to power an appropriate evaluation.

Limitations

General limitations in this study arise from its retrospective methodology. Interpretation of historical data included in medical records may differ from investigator to investigator, as multiple investigators contributed to the severe sepsis registry. To mitigate this, over 500 overlapping data points were collected by clinical investigators Sundeep Bhat and Melissa Wollan with 95% precision. Similarly, standards of documenting such information on data collection forms may vary leading to extraction error. Omitted or incorrectly or illegibly recorded information also jeopardizes the accuracy of the data collection.

Another major limitation of the retrospective design of this study is detection bias leading to underreporting of organ failures because the necessary laboratory tests were not assessed in the ED, a problem that would be avoided in a prospective study following a strict protocol. For example, only 60.8% of patients had a troponin value measured. Similarly, 78.1%

had a bilirubin value, 84.8% lactate, 87.5% prothrombin time, 91.9% partial thromboplastin time and 93.3% of patients had an international normalized ratio, as compared to nearly 100% of patients with both complete blood counts and electrolyte values, including creatinine. Furthermore, even among those laboratory data that were sent, several results returned insufficient quantity or invalid due to hemolysis and were not repeated in the ED for evaluation of cumulative organ injury. A similar argument can be made for other components of the study, such as the poor documentation of EGDT and calculation of Glasgow Coma Scores, which were derived from physical exams if not explicitly noted. Finally, differences in cultures sent could also contribute to the biased detection of microbes and thus suboptimal evaluation of antibiotic appropriateness.

This study is also limited by the sample population derived from a single institution. Furthermore, patients chosen for the database were selected based on a level of awareness of the principal investigator of their clinical condition and not a pre-determined standardized clinical variable, such as blood cultures drawn or antibiotic administration, a design characteristic that may produce sample selection bias toward patients known to fit inclusion criteria. Moreover, because multiple clinicians are not involved in the identification of potential patients for the registry, many patients meeting inclusion criteria for the severe sepsis registry are missed. Furthermore, patients with shorter ED lengths of stay may not have been identified, exposing the study to lead time bias. Finally, the study data were not adjusted for confounding variables.

Future Directions

Future research to expound upon the data presented here could include a logistic regression model to identify which specific organ dysfunctions have higher associations with mortality. Additionally, continued investigation of the lack of congruency between the MEDS

score and mortality in this study is needed, particularly with regard to the potential inclusion of lactic acidosis and the exclusion/clarification of terminal illness. Likewise, a prospective study comparing cumulative organ dysfunction with the MEDS score as predictions tools for mortality would likely contribute significantly toward the goal of reliable, ED-based risk stratification of septic patients.

Furthermore, hospital, ICU and ventilator days should be computed for the remaining patients in the severe sepsis registry in order to extrapolate this information more accurately and potentially complete a cost-benefit analysis. Finally, we suspect that mortality rates at this institution have improved significant over time and an evaluation of this trend would likely support the continued use of currently employed treatments.

Conclusion

Despite current standards to identify and treat severe sepsis and septic shock early in the disease progression, patients with sepsis syndrome can experience delays in care or inappropriate treatments due to the cryptic nature of the illness' presentation. While a multitude of data exist upon which to risk stratify patients presenting to the Emergency Department, there is still a critical need for a simplified, easily manipulated means to ensure maximum treatment to reduce mortality from sepsis syndrome. Therefore, in order to arrive at this tool, continued exploration of the key factors in predicting mortality is paramount.

This study demonstrated that the Emergency Department assessment of cumulative organ dysfunction is a promising measurement of disease severity in patients who present to the Emergency Department with severe sepsis and septic shock and may be implemented in existing ED-based risk stratification models to produce better outcomes. Cumulative organ dysfunction could even be a superior predictor to existing and more complicated prediction scores. Not only does cumulative organ dysfunction correlate with mortality, it is also

associated with pre-fatal escalations of care such as early vasopressor and mechanical ventilation use. All of these relationships are useful for the safe and appropriate disposition of patients from the ED in an effort to reduce sepsis-related mortality.

References

1. Huron, M., Hoyert, D., Murphy, S.L., Xu, J., Kochanek, K.D., and Tejada-Vera, B. 2009. Deaths: Final Data for 2006. In *National Vital Statistics Reports*. 1-136.

2. Angus, D., Linde-Zwirble, W., Lidicker, J., Clermont, G., Carcillo, J., and Pinsky, M. 2001. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29:1303-1310.

3. Wang, H.E., Shapiro, N.I., Angus, D.C., and Yealy, D.M. 2007. National estimates of severe sepsis in United States emergency departments. *Crit Care Med* 35:1928-1936.

4. Andrews, R. 2008. The National Hospital Bill: The Most Expensive Conditions by Payer, 2006. In *HCUP Statistical Brief #59*. Rockville, MD: Agency for Healthcare Research and Quality.

5. Andrews, R., and Elixhauser, A. 2007. The National Hospital Bill: Growth Trends and 2005 Update on the Most Expensive Conditions by Payer. In *HCUP Statistical Brief #42*. Rockville, MD: Agency for Healthcare Research and Quality.

6. Talmor, D., Greenberg, D., Howell, M.D., Lisbon, A., Novack, V., and Shapiro, N. 2008. The costs and cost-effectiveness of an integrated sepsis treatment protocol. *Crit Care Med* 36:1168-1174.

7. Martin, G., Mannino, D., Eaton, S., and Moss, M. 2003. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 348:1546-1554.

8. Strehlow, M.C., Emond, S.D., Shapiro, N.I., Pelletier, A.J., and Camargo, C.A., Jr. 2006. National study of emergency department visits for sepsis, 1992 to 2001. *Ann Emerg Med* 48:326-331, 331 e321-323.

9. Nguyen, H.B., Rivers, E.P., Abrahamian, F.M., Moran, G.J., Abraham, E., Trzeciak, S., Huang, D.T., Osborn, T., Stevens, D., and Talan, D.A. 2006. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. *Ann Emerg Med* 48:28-54.

10. Jones, A.E., Focht, A., Horton, J.M., and Kline, J.A. 2007. Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. *Chest* 132:425-432.

11. Puskarich, M.A., Marchick, M.R., Kline, J.A., Steuerwald, M.T., and Jones, A.E. 2009. One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: a before and after study. *Crit Care* 13:R167.

12. Shapiro, N., Howell, M., Talmor, D., Lahey, D., Ngo, L., Buras, J., Wolfe, R., Weiss, J., and Lisbon, A. 2006. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med* 34:1025-1032.

13. Mylotte, J., Tayara, A., and Goodnough, S. 2002. Epidemiology of bloodstream infection in nursing home residents: evaluation in a large cohort from multiple homes. *Clin Infect Dis* 35:1484-1490.

14. Shapiro, N., Howell, M.D., Bates, D.W., Angus, D.C., Ngo, L., and Talmor, D. 2006. The association of sepsis syndrome and organ dysfunction with mortality in emergency department patients with suspected infection. *Ann Emerg Med* 48:583-590, 590 e581.

15. Alberti, C., Brun-Buisson, C., Burchardi, H., Martin, C., Goodman, S., Artigas, A., Sicignano, A., Palazzo, M., Moreno, R., Boulmé, R., et al. 2002. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 28:108-121.

16. Dellinger, R., Carlet, J., Masur, H., Gerlach, H., Calandra, T., Cohen, J., Gea-Banacloche, J., Keh, D., Marshall, J., Parker, M., et al. 2004. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 32:858-873.

17. Dellinger, R., Levy, M., Carlet, J., Bion, J., Parker, M., Jaeschke, R., Reinhart, K., Angus, D., Brun-Buisson, C., Beale, R., et al. 2008. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 36:296-327.

18. Bone, R., Balk, R., Cerra, F., Dellinger, R., Fein, A., Knaus, W., Schein, R., and Sibbald, W. 1992. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 101:1644-1655.

19. Levy, M., Fink, M., Marshall, J., Abraham, E., Angus, D., Cook, D., Cohen, J., Opal, S., Vincent, J., and Ramsay, G. 2003. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31:1250-1256.

20. Talan, D.A., Moran, G.J., and Abrahamian, F.M. 2008. Severe sepsis and septic shock in the emergency department. *Infect Dis Clin North Am* 22:1-31, v.

21. Nguyen, H.B., and Smith, D. 2007. Sepsis in the 21st century: recent definitions and therapeutic advances. *Am J Emerg Med* 25:564-571.

22. Carrico, C.J., Meakins, J.L., Marshall, J.C., Fry, D., and Maier, R.V. 1986. Multiple-organ-failure syndrome. *Arch Surg* 121:196-208.

23. Bernard, G., Vincent, J., Laterre, P., LaRosa, S., Dhainaut, J., Lopez-Rodriguez, A., Steingrub, J., Garber, G., Helterbrand, J., Ely, E., et al. 2001. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 344:699-709.

24. Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., and Tomlanovich, M. 2001. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368-1377.

25. Annane, D., Sebille, V., Charpentier, C., Bollaert, P.E., Francois, B., Korach, J.M., Capellier, G., Cohen, Y., Azoulay, E., Troche, G., et al. 2002. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 288:862-871.

26. Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P., and Bouillon, R. 2001. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345:1359-1367.

27. Otero, R.M., Nguyen, H.B., Huang, D.T., Gaieski, D.F., Goyal, M., Gunnerson, K.J., Trzeciak, S., Sherwin, R., Holthaus, C.V., Osborn, T., et al. 2006. Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. *Chest* 130:1579-1595.

28. Wang, H., and Ma, S. 2008. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. *Am J Emerg Med* 26:711-715.

29. Sama, A.E., D'Amore, J., Ward, M.F., Chen, G., and Wang, H. 2004. Bench to bedside: HMGB1-a novel proinflammatory cytokine and potential therapeutic target for septic patients in the emergency department. *Academic Emergency Medicine* 11:867-873.

30. Aird, W. 2003. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood* 101:3765-3777.

31. Varpula, M., Tallgren, M., Saukkonen, K., Voipio-Pulkki, L.M., and Pettila, V. 2005. Hemodynamic variables related to outcome in septic shock. *Intensive Care Med* 31:1066-1071.

32. Pope, J.V., Jones, A.E., Gaieski, D.F., Arnold, R.C., Trzeciak, S., and Shapiro, N.I. 2009. Multicenter Study of Central Venous Oxygen Saturation (ScvO(2)) as a Predictor of Mortality in Patients With Sepsis. *Ann Emerg Med*.

33. Trzeciak, S., McCoy, J.V., Phillip Dellinger, R., Arnold, R.C., Rizzuto, M., Abate, N.L., Shapiro, N.I., Parrillo, J.E., and Hollenberg, S.M. 2008. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. *Intensive Care Med* 34:2210-2217.

34. Trzeciak, S., and Rivers, E. 2005. Clinical manifestations of disordered microcirculatory perfusion in severe sepsis. *Crit Care* 9 Suppl 4:S20-26.

35. Trzeciak, S., Dellinger, R.P., Parrillo, J.E., Guglielmi, M., Bajaj, J., Abate, N.L., Arnold, R.C., Colilla, S., Zanotti, S., Hollenberg, S.M., et al. 2007. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Annals of Emergency Medicine* 49:88-98.

36. Sakr, Y., Dubois, M.J., De Backer, D., Creteur, J., and Vincent, J.L. 2004. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 32:1825-1831.

37. De Backer, D., Creteur, J., Preiser, J., Dubois, M., and Vincent, J. 2002. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 166:98-104.

38. Duranteau, J., Sitbon, P., Teboul, J., Vicaut, E., Anguel, N., Richard, C., and Samii, K. 1999. Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. *Crit Care Med* 27:893-900.

39. Spronk, P., Ince, C., Gardien, M., Mathura, K., Oudemans-van Straaten, H., and Zandstra, D. 2002. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 360:1395-1396.

40. Shoemaker, W., Appel, P., and Kram, H. 1986. Hemodynamic and oxygen transport effects of dobutamine in critically ill general surgical patients. *Crit Care Med* 14:1032-1037.

41. Secchi, A., Wellmann, R., Martin, E., and Schmidt, H. 1997. Dobutamine maintains intestinal villus blood flow during normotensive endotoxemia: an intravital microscopic study in the rat. *J Crit Care* 12:137-141.

42. Funk, D., Sebat, F., and Kumar, A. 2009. A systems approach to the early recognition and rapid administration of best practice therapy in sepsis and septic shock. *Curr Opin Crit Care* 15:301-307.

43. Marchick, M.R., Kline, J.A., and Jones, A.E. 2009. The significance of non-sustained hypotension in emergency department patients with sepsis. *Intensive Care Med* 35:1261-1264.

44. Donnino, M.W., Nguyen, B., Jacobsen, G., Tomlanovich, M., and Rivers, E. 2003. Cryptic Septic Shock: A Sub-analysis of Early Goal-Directed Therapy [abstract]. In *Chest Supplement*. 90S.

45. Cornbleet, P. 2002. Clinical utility of the band count. *Clin Lab Med* 22:101-136.

46. Novak, R. 1993. The beleaguered band count. *Clin Lab Med* 13:895-903.

47. Wenz, B., Gennis, P., Canova, C., and Burns, E. 1986. The clinical utility of the leukocyte differential in emergency medicine. *Am J Clin Pathol* 86:298-303.

48. Ardron, M., Westengard, J., and Dutcher, T. 1994. Band neutrophil counts are unnecessary for the diagnosis of infection in patients with normal total leukocyte counts. *Am J Clin Pathol* 102:646-649.

49. Callaham, M. 1986. Inaccuracy and expense of the leukocyte count in making urgent clinical decisions. *Ann Emerg Med* 15:774-781.

50. Shapiro, N.I., Wolfe, R.E., Moore, R.B., Smith, E., Burdick, E., and Bates, D.W. 2003. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med* 31:670-675.

51. Vanderschueren, S., De Weerdt, A., Malbrain, M., Vankersschaever, D., Frans, E., Wilmer, A., and Bobbaers, H. 2000. Thrombocytopenia and prognosis in intensive care. *Crit Care Med* 28:1871-1876.

52. Kinasewitz, G.T., Yan, S.B., Basson, B., Comp, P., Russell, J.A., Cariou, A., Um, S.L., Utterback, B., Laterre, P.F., and Dhainaut, J.F. 2004. Universal changes in biomarkers of coagulation and inflammation occur in patients with severe sepsis, regardless of causative micro-organism [ISRCTN74215569]. *Crit Care* 8:R82-90.

53. Abramson, D., Scalea, T., Hitchcock, R., Trooskin, S., Henry, S., and Greenspan, J. 1993. Lactate clearance and survival following injury. *J Trauma* 35:584-588; discussion 588-589.

54. Bakker, J., Gris, P., Coffernils, M., Kahn, R., and Vincent, J. 1996. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 171:221-226.

55. Shapiro, N., Howell, M., Talmor, D., Nathanson, L., Lisbon, A., Wolfe, R., and Weiss, J. 2005. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 45:524-528.

56. Nguyen, H.B., Rivers, E.P., Knoblich, B.P., Jacobsen, G., Muzzin, A., Ressler, J.A., and Tomlanovich, M.C. 2004. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 32:1637-1642.

57. Lee, S.W., Hong, Y.S., Park, D.W., Choi, S.H., Moon, S.W., Park, J.S., Kim, J.Y., and Baek, K.J. 2008. Lactic acidosis not hyperlactatemia as a predictor of in hospital mortality in septic emergency patients. *Emerg Med J* 25:659-665.

58. Howell, M.D., Donnino, M., Clardy, P., Talmor, D., and Shapiro, N.I. 2007. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Medicine* 33:1892-1899.

59. Hurtado, F., Gutierrez, A., Silva, N., Fernandez, E., Khan, A., and Gutierrez, G. 1992. Role of tissue hypoxia as the mechanism of lactic acidosis during E. coli endotoxemia. *J Appl Physiol* 72:1895-1901.

60. James, J., Luchette, F., McCarter, F., and Fischer, J. 1999. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet* 354:505-508.

61. McCarter, F., Nierman, S., James, J., Wang, L., King, J., Friend, L., and Fischer, J. 2002. Role of skeletal muscle Na+-K+ ATPase activity in increased lactate production in sub-acute sepsis. *Life Sci* 70:1875-1888.

62. Luchette, F., Jenkins, W., Friend, L., Su, C., Fischer, J., and James, J. 2002. Hypoxia is not the sole cause of lactate production during shock. *J Trauma* 52:415-419.

63. Vary, T. 1996. Sepsis-induced alterations in pyruvate dehydrogenase complex activity in rat skeletal muscle: effects on plasma lactate. *Shock* 6:89-94.

64. Levraut, J., Ciebiera, J., Chave, S., Rabary, O., Jambou, P., Carles, M., and Grimaud, D. 1998. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med* 157:1021-1026.

65. Pastor, C., Billiar, T., Losser, M., and Payen, D. 1995. Liver injury during sepsis. *J Crit Care* 10:183-197.

66. Arnold, R.C., Shapiro, N.I., Jones, A.E., Schorr, C., Pope, J., Casner, E., Parrillo, J.E., Dellinger, R.P., and Trzeciak, S. 2009. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock* 32:35-39.

67. Brun-Buisson, C., Doyon, F., Carlet, J., Dellamonica, P., Gouin, F., Lepoutre, A., Mercier, J., Offenstadt, G., and Régnier, B. 1995. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. *JAMA* 274:968-974.

68. Marshall, J.C., Cook, D.J., Christou, N.V., Bernard, G.R., Sprung, C.L., and Sibbald, W.J. 1995. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 23:1638-1652.

69. Ferreira, F.L., Bota, D.P., Bross, A., Melot, C., and Vincent, J.L. 2001. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 286:1754-1758.

70. Catenacci, M.H., and King, K. 2008. Severe sepsis and septic shock: improving outcomes in the emergency department. *Emerg Med Clin North Am* 26:603-623, vii.

71. Bernard, G.R., Artigas, A., Brigham, K.L., Carlet, J., Falke, K., Hudson, L., Lamy, M., Legall, J.R., Morris, A., and Spragg, R. 1994. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 149:818-824.

72. Jones, A.E., Trzeciak, S., and Kline, J.A. 2009. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Crit Care Med* 37:1649-1654.

73. Knaus, W.A., Draper, E.A., Wagner, D.P., and Zimmerman, J.E. 1985. APACHE II: a severity of disease classification system. *Crit Care Med* 13:818-829.

74. Nguyen, H., Rivers, E., Havstad, S., Knoblich, B., Ressler, J., Muzzin, A., and Tomlanovich, M. 2000. Critical care in the emergency department: A physiologic assessment and outcome evaluation. *Acad Emerg Med* 7:1354-1361.

75. Alberti, C., Brun-Buisson, C., Chevret, S., Antonelli, M., Goodman, S., Martin, C., Moreno, R., Ochagavia, A., Palazzo, M., Werdan, K., et al. 2005. Systemic inflammatory response and progression to severe sepsis in critically ill infected patients. *Am J Respir Crit Care Med* 171:461-468.

76. Danai, P., Moss, M., Mannino, D., and Martin, G. 2006. The epidemiology of sepsis in patients with malignancy. *Chest* 129:1432-1440.

77. Renaud, B., and Brun-Buisson, C. 2001. Outcomes of primary and catheter-related bacteremia. A cohort and case-control study in critically ill patients. *Am J Respir Crit Care Med* 163:1584-1590.

78. Opal, S., and Cohen, J. 1999. Clinical gram-positive sepsis: does it fundamentally differ from gram-negative bacterial sepsis? *Crit Care Med* 27:1608-1616.

79. Chen, C.C., Chong, C.F., Liu, Y.L., Chen, K.C., and Wang, T.L. 2006. Risk stratification of severe sepsis patients in the emergency department. *Emergency Medicine Journal* 23:281-285.

80. Howell, M.D., Donnino, M.W., Talmor, D., Clardy, P., Ngo, L., and Shapiro, N.I. 2007. Performance of severity of illness scoring systems in emergency department patients with infection. *Acad Emerg Med* 14:709-714.

81. Lee, C.C., Chen, S.Y., Tsai, C.L., Wu, S.C., Chiang, W.C., Wang, J.L., Sun, H.Y., Chen, S.C., Chen, W.J., and Hsueh, P.R. 2008. Prognostic value of mortality in emergency department sepsis score, procalcitonin, and C-reactive protein in patients with sepsis at the emergency department. *Shock* 29:322-327.

82. Sankoff, J.D., Goyal, M., Gaieski, D.F., Deitch, K., Davis, C.B., Sabel, A.L., and Haukoos, J.S. 2008. Validation of the Mortality in Emergency Department Sepsis (MEDS) score in patients with the systemic inflammatory response syndrome (SIRS). *Crit Care Med* 36:421-426.

83. Jones, A.E., Saak, K., and Kline, J.A. 2008. Performance of the Mortality in Emergency Department Sepsis score for predicting hospital mortality among patients with severe sepsis and septic shock. *Am J Emerg Med* 26:689-692.

84. Kumar, A., Roberts, D., Wood, K., Light, B., Parrillo, J., Sharma, S., Suppes, R., Feinstein, D., Zanotti, S., Taiberg, L., et al. 2006. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 34:1589-1596.

85. Leibovici, L., Shraga, I., Drucker, M., Konigsberger, H., Samra, Z., and Pitlik, S.D. 1998. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 244:379-386.

86. Costerton, J.W., Stewart, P.S., and Greenberg, E.P. 1999. Bacterial biofilms: a common cause of persistent infections. *Science* 284:1318-1322.

87. Kern, J.W., and Shoemaker, W.C. 2002. Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med* 30:1686-1692.

88. Nguyen, H.B., Corbett, S.W., Steele, R., Banta, J., Clark, R.T., Hayes, S.R., Edwards, J., Cho, T.W., and Wittlake, W.A. 2007. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 35:1105-1112.

89. Rivers, E.P., Coba, V., Visbal, A., Whitmill, M., and Amponsah, D. 2008. Management of sepsis: early resuscitation. *Clin Chest Med* 29:689-704, ix-x.

90. Jones, A.E., Brown, M.D., Trzeciak, S., Shapiro, N.I., Garrett, J.S., Heffner, A.C., and Kline, J.A. 2008. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med* 36:2734-2739.

91. Trzeciak, S., Dellinger, R., Abate, N., Cowan, R., Stauss, M., Kilgannon, J., Zanotti, S., and Parrillo, J. 2006. Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest* 129:225-232.

92. Marik, P., and Varon, J. 2002. Goal-directed therapy for severe sepsis. *N Engl J Med* 346:1025-1026; author reply 1025-1026.

93. Abraham, E., Laterre, P., Garg, R., Levy, H., Talwar, D., Trzaskoma, B., François, B., Guy, J., Brückmann, M., Rea-Neto, A., et al. 2005. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 353:1332-1341.

94. Vincent, J., Bernard, G., Beale, R., Doig, C., Putensen, C., Dhainaut, J., Artigas, A., Fumagalli, R., Macias, W., Wright, T., et al. 2005. Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. *Crit Care Med* 33:2266-2277.

95. Vincent, J.-L., O'Brien, J., Jr., Wheeler, A., Wittebole, X., Garg, R., Trzaskoma, B.L., and Sundin, D.P. 2006. Use of an integrated clinical trial database to evaluate the effect of timing of drotrecogin alfa (activated) treatment in severe sepsis. *Critical Care (London, England)* 10:R74.

96. Dhainaut, J.F., Yan, S.B., and Claessens, Y.E. 2004. Protein C/activated protein C pathway: overview of clinical trial results in severe sepsis. *Crit Care Med* 32:S194-201.

97. Hickling, K.G., Henderson, S.J., and Jackson, R. 1990. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 16:372-377.

98. Hickling, K.G., Walsh, J., Henderson, S., and Jackson, R. 1994. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 22:1568-1578.

99. 2000. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 342:1301-1308.

100. Young, M.P., Manning, H.L., Wilson, D.L., Mette, S.A., Riker, R.R., Leiter, J.C., Liu, S.K., Bates, J.T., and Parsons, P.E. 2004. Ventilation of patients with acute lung injury and acute respiratory distress syndrome: has new evidence changed clinical practice? *Crit Care Med* 32:1260-1265.

101. Van den Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., Wouters, P., Milants, I., Van Wijngaerden, E., Bobbaers, H., and Bouillon, R. 2006. Intensive insulin therapy in the medical ICU. *N Engl J Med* 354:449-461.

102. Wiener, R.S., Wiener, D.C., and Larson, R.J. 2008. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 300:933-944.

103. Cooper, M., and Stewart, P. 2003. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 348:727-734.

104. Catalano, R., Parameswaran, V., Ramachandran, J., and Trunkey, D. 1984. Mechanisms of adrenocortical depression during Escherichia coli shock. *Arch Surg* 119:145-150.

105. Hammond, G., Smith, C., Paterson, N., and Sibbald, W. 1990. A role for corticosteroid-binding globulin in delivery of cortisol to activated neutrophils. *J Clin Endocrinol Metab* 71:34-39.

106. Lamberts, S., Bruining, H., and de Jong, F. 1997. Corticosteroid therapy in severe illness. *N Engl J Med* 337:1285-1292.

107. 1987. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. The Veterans Administration Systemic Sepsis Cooperative Study Group. *N Engl J Med* 317:659-665.

108. Sprung, C., Caralis, P., Marcial, E., Pierce, M., Gelbard, M., Long, W., Duncan, R., Tendler, M., and Karpf, M. 1984. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *N Engl J Med* 311:1137-1143.

109. Bone, R., Fisher, C.J., Clemmer, T., Slotman, G., Metz, C., and Balk, R. 1987. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 317:653-658.

110. Sprung, C.L., Annane, D., Keh, D., Moreno, R., Singer, M., Freivogel, K., Weiss, Y.G., Benbenishty, J., Kalenka, A., Forst, H., et al. 2008. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 358:111-124.

111. Shapiro, N.I., Howell, M.D., Talmor, D., Donnino, M., Ngo, L., and Bates, D.W. 2007. Mortality in Emergency Department Sepsis (MEDS) score predicts 1-year mortality. *Crit Care Med* 35:192-198.

112. Wollan, M. 2008. Shock Index as a Predictor of Vasopressor Use in Severe Sepsis Patients in the Emergency Department. In *Unpublished Doctorate of Medicine Thesis*. New Haven, CT: Yale School of Medicine, Section of Emergency Medicine. 53.

113. Wira, C.R. 2010. Member of Yale-New Haven Hospital Sepsis Committee and Member of the Yale-New Haven Hospital, Greenwich Hospital and Bridgeport Hospital Sepsis Collaborative. New Haven, CT: Personal correspondence.

114. Giannini, E.G., and Savarino, V. 2008. Thrombocytopenia in liver disease. *Curr Opin Hematol* 15:473-480.

Appendix

Sex: ☐ **Male** ☐ **Female** **Age**_____

1. EXCLUSION CRITERIA

- ☐ Age <18
- ☐ Pt with documented comfort measures prior to, or during stay in ED
- ☐ Sepsis (2 SIRS + Source and without organ failure)
- ☐ Discharged to home

2. SIRS (at least two of the following):

- ☐ Temperature > 100.4 or < 96.8 degrees Fahrenheit
- ☐ Heart Rate > 90 beats per minute
- ☐ Respiratory Rate > 20 breaths per minute or PCO_2 less than 32 mm Hg
- ☐ White blood cell count > $12x10^3$ or < $4x10^3$ or > 10% immature neutrophils

3. SOURCES (any one of the following):

- ☐ WBC >10,000 or <4000 or >10% bands
- ☐ Temp > 100.4 or < 96.8
- ☐ Blood cultures drawn in ED
- ☐ Antibiotics administered in ED
- ☐ Documentation of presumed source of infection in ED- LOCATION:
  - ☐ PNA – upper or lower respiratory by physical exam or chest x-ray
  - ☐ Genitourinary – by urinalysis, physical exam or diagnostic study
  - ☐ Intra-abdominal – peritonitis, abscess, or other suspected source
  - ☐ Soft Tissue – cellulitis, necrotizing fasciitis, abscess, or ulceration of skin
  - ☐ Other – (Ex—CNS, line, etc.) List: _____

4. END-ORGAN DYSFUNCTION (any one of the following):

- ☐ Transient systolic BP <90 that responds to fluid resuscitation
- ☐ Lactate level > 2mmol/mL
- ☐ Unexplained acidosis (pH < 7.35) or a serum bicarbonate < 21
- ☐ Altered mental status (change from baseline)
- ☐ Platelets <150,000 mm^3 (no hx thrombocytopenia)
- ☐ Elevation of bilirubin above normal or (direct or indirect) > than baseline
- ☐ High coagulation factors (any elevation in absence of heparin or coumadin use)
- ☐ Acute Renal Failure (Cr >0.5 from baseline, or abnormal if no baseline available)
- ☐ Hypoxemia (oxygen saturation less than 90% or change in oxygen requirement)
- ☐ Troponin elevation above baseline
- ☐ Other – please list: _____

5. CLASSIFICATION (Highest classification at any point in ED)

- ☐ Severe Sepsis (2 SIRS + Source+ Organ Failure)
- ☐ Septic Shock (SBP < 90mmHg after IVF)

6. Inclusion in Study:

- ☐ **Yes** – meets all inclusion criteria and does not meet any exclusion criteria
- ☐ **No** – does NOT meet all Inclusion Criteria, or meets any Exclusion Criteria

7. Extremis:

- ☐ Pt in extremis SBP< 80 and/or started on Vasopressors <15mins of arrival to ED

1. TIME (24:00): ED Presentation: Triage VS (T0)

ED Discharge: Last RN note or VS (Tf) __ __ : __ __

2. VITAL SIGNS (Initial to Discharge from ED or start of Vasopressor)

	TIME	SBP	DBP	HR	Temp	Pox	RA, NC
Initial							
Final						**N/A**	**N/A**

	TIME	SBP	DBP	HR		TIME	SBP	DBP	HR
1					**9**				
2					**10**				
3					**11**				
4					**12**				
5					**13**				
6					**14**				
7					**15**				
8					**16**				

3. OTHER VITALS: (IN ED)

Lowest SBP _____ Lowest DBP _____ Highest Temp: _____

Highest RR: _____ breaths/minute Lowest SaO_2: _____ *on: _____

4. GCS (Triage or scored from neuro exam) _____

5. FLUIDS (in ED) TIME START __ __ : __ __

TRIAGE:_____ mL + ED _____ mL = **TOTAL _____ mL**

6. ANTIBIOTICS ☐ NO ☐ YES TIME STARTED __ __: __ __

☐ Vancomycin ☐ Zosyn ☐ Ciprofloxacin ☐ Flagyl ☐ Unasyn

☐ Ceftriaxone ☐ Gentamycin ☐ Doxycycline

☐ Other(s) _____

7. CULTURES/SENSITIVITIES ☐ Appropriate ED ABX Coverage ☐ Inappropriate

BLOOD ☐ NO ☐ YES-TIME __ __: __ __

RESULTS: ☐ n/a ☐ No Growth ☐_____DATE: __ __ / __ __ / __ __

URINE ☐ NO ☐ YES-TIME __ __: __ __

RESULTS: ☐ n/a ☐ No Growth ☐_____DATE: __ __ / __ __ / __ __

OTHER ☐ NO ☐ YES-TIME __ __: __ __

RESULTS: ☐ n/a ☐ No Growth ☐_____DATE: __ __ / __ __ / __ __

8. PAST MEDICAL HISTORY (from ED notes or discharge Summary)

Nursing Home Residence ☐ NO ☐ YES

☐ Liver Disease ☐ CHF - ☐ EF_____ ☐ No Echo ☐ CAD ☐ HTN

☐ COPD ☐ Asthma ☐ ESRD ☐ DM ☐ ETOH

☐ Immunocompromised (NOS) ☐ HIV/AIDS ☐ Cancer ☐ Cancer w/ chemo

☐ CVA/TIA ☐ Alzheimers/Dementia/MR/Chronic AMS at baseline

☐ Other Significant _____

9. LABORATORY DATA (Initial)

WBC	_____	Bands	_____%	Hct	_____	Plt	_____
Na	_____	Cl	_____	BUN	_____		
K	_____	HCO_3	_____	Cr	_____	Baseline Cr	_____
Bt	_____	Bd	_____	Trop	_____		
PT	_____	INR	_____	PTT	_____		

10. LACTATE (Value/Time and Date)

1st ED____/____ ED Peak____/____ 1st Floor ____/____ Floor Peak____/____

11. ABG's – INITIAL _____/ _____/ _____ / _____ Time __ __ : __ __

Lowest pH _____ Other PO_2_____

12. Early Goal Directed Therapy: Documented in Note ☐ NO ☐ YES

a. Central Line Placed	☐ NO	☐ YES	TIME __ __: __ __
b. Initial ED CVP____ Peak ____	☐ NO	☐ YES	TIME __ __: __ __
c. $ScvO_2$ (VBG) _____	☐ NO	☐ YES	TIME __ __: __ __
1st 24 hours _____ _____ _____ _____ _____ _____ _____			
d. Vasopressors in ED	☐ NO	☐ YES	TIME __ __: __ __
Vasopressors in Hospital	☐ NO	☐ YES	☐ <72h ☐ >72h

☐ Norepinephrine ☐ Dopamine ☐ Other_____

e. Inotropes in ED	☐ Dobutamine	☐ Digoxin
Inotropes in ICU	☐ Dobutamine	☐ Digoxin

13. OTHER TREATMENTS:

a. Corticosteroids	☐ NO	☐ YES	☐ IN ED	☐ IN Floor
b. Source Control	☐ NO	☐ YES	☐ IN ED	☐ IN Floor
Type: ☐ Line pulled ☐ abscess drained ☐ to OR ☐ Other:_____				
c. Mechanical Ventilation	☐ NO	☐ YES	☐ IN ED	☐ IN ICU
d. Tight Glucose Control	☐ NO	☐ YES	☐ IN ED	
e. Blood Products in ED	☐ NO	☐ YES	Type _____	
f. Activated protein C (Xigris)	☐ NO	☐ YES	☐ IN ED	☐ IN ICU

14. DISPOSITION from ED

☐ Admitted ☐ ICU ☐ STEP DOWN ☐ FLOOR ☐ OR

☐ Morgue ☐ Other _____

15. OUTCOME ☐ Survived hospital discharge
☐ Died In Hospital ☐ Died in Hospital < 28 days

16. ED Attending DIAGNOSES

1) _____ 2) _____ 3) _____

17. FINAL HOSPITAL DIAGNOSES on DISCHARGE SUMMARY

1) _____ 2) _____ 3) _____ 4) _____

18. RAPID SEQUENCE INTUBATION INFORMATION (ED, floor, or OR):

Induction agent:

☐ Etomidate ☐ Fentanyl ☐ Propofol ☐ Midazolam ☐ Ketamine

☐ Thiopental ☐ Other: (List) _____

☐ No induction medications

Intubated in OR: ☐ Yes ☐ No

19. SEPSIS MIMIC ☐ No ☐ Yes

20. EMCCM PT ☐ No ☐ Yes

21. Patient on beta-blocker prior to presentation: ☐ No ☐ Yes

Hospitalization Information (length of stay = LOS):

Initial ICU LOS (days): _____

Total ICU LOS (days): _____

Hospital LOS (days): _____

Initial ventilator days: _____

Total ventilator days: _____