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Evaluation Of A 5-Group Classification System For Severe Sepsis By Ed Vasopressor Use And Initial Serum Lactate

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Abstract

HYPOTHESIS AND SPECIFIC AIMS: The aim of this study is to characterize the incidence and outcomes of various groups within a novel classification system of severe sepsis and septic shock, for the purpose of informing more accurate risk prediction in the proximal phases of care. Our primary hypothesis is that an early classification system of septic patients categorized by organ dysfunction, initial emergency department (ED) serum lactate, and ED vasopressor utilization will offer accurate mortality prognostication in patients with severe sepsis and septic shock.

METHODS: We performed a retrospective analysis of a prospectively-gathered registry of severe sepsis and septic shock patients presenting to a dual-site academic emergency department (ED). In the primary analysis, registry subjects were categorized into five groups by initial ED serum lactate level and vasopressor requirement in the ED: dysoxic shock (vasopressor use + lactate >4 mmol/L), vasoplegic shock (vasopressor use + lactate ≤4 mmol/L), cryptic shock major (no vasopressor use + lactate >4 mmol/L), cryptic shock minor (no vasopressor use + lactate >2 and ≤4 mmol/L), and severe sepsis without lactate elevation (no vasopressor use + lactate ≤2 mmol/L + evidence of ≥1 organ dysfunction). For each group, the 28-day mortality rate was evaluated by logistic regression controlling for specific factors associated with sepsis severity.

RESULTS: Of 521 registry subjects, 85.6% (n=446) met inclusion criteria. 4.9% (n=22) subjects presented in dysoxic shock, 11.7% (n=52) in vasoplegic shock,

12.1% (n=54) in cryptic shock major, 30.9% (n=138) in cryptic shock minor, and 40.4% (n=180) in severe sepsis without lactate elevation. The 28-day mortality rates for these groups were 50.0%, 21.1%, 18.5%, 12.3%, and 7.2%, respectively; this stepwise trend was paralleled by metrics of critical care utilization such as ICU admission, mechanical ventilation, and vasopressor use within 72 hours of admission. After controlling for known risk factors for sepsis severity, the odds ratios for death before 28 days were 15.06 for dysoxic shock, 3.61 for vasoplegic shock, 3.77 for cryptic shock major, and 1.93 for cryptic shock minor, as compared to severe sepsis without lactate elevation.

CONCLUSION: This study suggests that high-risk subgroups of severe sepsis and septic shock patients can be identified at presentation and during the emergency department stay. We show that in severe sepsis and septic shock, a proximal-phase classification system based on vasopressor requirement in the ED and initial ED lactate level predicts 28-day in-hospital mortality and may inform prognostication, triage decisions and future sepsis clinical trial design.

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Introduction

Sepsis is a clinical syndrome of immense complexity, an understanding of which is essential for clinicians and researchers who hope to improve sepsis care. The following literature review explores the key epidemiologic and clinical aspects of sepsis that informed the current research project. After a review of the epidemiology and pathophysiology of sepsis, we summarize the current widely-utilized system for classifying sepsis. This is followed by an appraisal of the literature on sepsis severity, evidencing the need for both simpler and more accurate sepsis classification systems. We conclude with a summary of various alternative classification systems for severe sepsis and septic shock, to which our system, described in this thesis, can be compared.

Epidemiology

The clinical entity of sepsis, a systemic inflammatory response to infection, is one of the greatest causes of morbidity and mortality in the United States. Sepsis is the 6th most common admitting diagnosis in the US [1]. In 2009, 836,000 hospital stays were attributed to a principal diagnosis of sepsis, with another 829,500 having a secondary diagnosis of sepsis during the course of hospitalization; when combined, sepsis is implicated in 4.2% of all hospitalizations [1]. In addition, the incidence of sepsis has been trending upward. Hospital stays with a principal diagnosis of sepsis increased by 153% between 1993 and 2009: a six percent increase in hospitalizations due to sepsis every year [1]. This trend is likely due to an aging

population, increasing burden of other health conditions, a higher proportion of immunocompromised patients from any cause, and perhaps an increased awareness and documentation of sepsis by providers. Sepsis is also extremely costly, in terms of lives as well as care delivered. The mortality rate of all patients with a diagnosis of sepsis in the US was around 16% in 2009: eight times higher than the average mortality rate of all other hospital stays [1]. Sepsis remains the most expensive reason for hospitalization in the US, with estimates of $15.4 billion in aggregate hospital costs per year, representing 4.0% of all hospital costs [1].

Sepsis may also be increasing in severity. The incidence of severe sepsis (defined as sepsis-induced organ dysfunction, hypoperfusion or hypotension) is reportedly between 256,000-700,000 per year [2-4], with an increase of around 13% per year [5]: far faster than the rate of increase of all sepsis diagnoses. One study documented that the percentage of sepsis presentations qualifying as severe sepsis increased from 26% to 44% between 1993 and 2003 [2]. Severe sepsis accounts for between 6 and 15% of all intensive care unit (ICU) admissions, and is estimated to consume up to half of ICU resources [3]. Many of these sicker patients will present through the emergency department (ED); severe sepsis is the suspected diagnosis in 571,000 ED visits annually [6]. Thus, the majority of patients in severe sepsis will be hospitalized through the ED.

Fortunately, in-hospital mortality from sepsis may be decreasing. In a recent multicenter observational study involving over 100,000 ICU patients with severe sepsis, the mortality rate decreased between 2000 and 2012, from 35% to 18.4% [7]. This dramatic drop in mortality has been mirrored in other studies, both

observationally after implementation of protocol-based care [8, 9] and in the control groups of recent randomized trials [10, 11]. It is unknown whether the decreasing mortality rates seen in these trials represent an improvement in sepsis interventions or an increased recognition of sepsis in infected patients. Nevertheless, given the increasing incidence of sepsis as discussed previously, the absolute number of deaths due to sepsis is likely still on the rise. By some estimates, severe sepsis accounts for around 220,000 deaths per year, making it the 3rd most common cause of death in the US, after heart disease and malignancy [1].

Although the trend towards improved immediate mortality is heartening, less is known about the long-term prognosis of sepsis survivors. In a recent meta-analysis, a discharge diagnosis of sepsis carried an increased risk of recurrent sepsis as well as death after hospital discharge, with a mortality rate between 7 and 43% at one year [12]. Sepsis survivors were more likely to be discharged to acute or long-term care facilities than other discharged patients of similar illness severity; furthermore, they suffered a pronounced decrease in quality of life when matched against their own pre-sepsis condition, as well as compared to other patients recovering from critical illness [13, 14].

Pathophysiology

The inflammatory response and microvascular dysfunction

A basic understanding of the pathophysiology of sepsis is germane to both its clinical consequences and management. The presence of infection, usually by bacterial or fungal organisms, triggers an initial immune response via pattern-recognition receptors in the cells of the innate immune system. Occasionally, and

for reasons not well understood, local infection will trigger a systemic response heralding the onset of sepsis. This host response involves both pro- and anti-inflammatory pathways, and imbalances in these pathways, both in time and in scale, can be damaging to the host. In general, the pro-inflammatory pathways activate earlier in the course of sepsis and are involved in controlling and clearing the infectious organism; these pathways are mostly implicated in the collateral damage to host organs in severe sepsis and septic shock [15]. The anti-inflammatory pathways are generally associated with repairing tissue damage and may peak later in the course of sepsis. In a weakened host, dampening the immune response can increase the risk of secondary and opportunistic infections [15].

Pro-inflammatory processes conspire to orchestrate the dysfunctional and self-perpetuating tissue damage that underlies severe sepsis. Activated via innate responses to pathogen motifs, leukocytes infiltrate both infected and non-infected tissues, activating complement and releasing damaging substrates such as proteases and reactive oxygen species. When misdirected, these attacks cause damage to normally-functioning host cells. The pro-inflammatory milieu is also responsible for coagulation abnormalities via the intermediary protease-activated receptors (PARs) [15]. Increased tissue factor from damaged endothelial cells, the down-regulation of normal anticoagulant mechanisms (protein C, S, and antithrombin), and depression of natural fibrinolysis all contribute to clot formation; the ultimate result is disseminated intravascular coagulation (DIC) [16]. The downstream effect of these pathways, especially in the presence of hypoperfusion, is damage to collateral tissues and organ dysfunction. Furthermore, necrotic cell death releases damage-

associated molecular pattern (DAMP) molecules, leading to a vicious cycle of immune activation and tissue destruction [15].

The key intermediary between the damage described above and global tissue underperfusion is the vascular endothelium; microvascular dysfunction lies at the basis of severe sepsis and septic shock. The microvascular circulation is the main controller of end-organ perfusion [17]. In severe sepsis, the diffuse endothelial damage, hypercoagulability, and loss of vascular barrier function impair oxygen delivery and cause third-spacing of fluids into tissues. The resulting tissue hypoperfusion leads to abnormal systemic vasodilation and a decrease in systemic vascular resistance, likely via uninhibited release of vasoactive mediators such as nitric oxide and prostacyclin. When not corrected, these hypovolemic and distributive mechanisms contribute to hypoperfusion, organ dysfunction, and the shock state.

Organ-specific dysfunction

At the level of individual organs, direct tissue damage and hypoperfusion-related anoxic injury is initially reversible; however, if not corrected these insults can lead to irreversible loss of function and ultimately to organ failure. The mechanisms and clinical manifestations of failure in each organ are distinct. Acute kidney injury is common, either as a consequence of decreased perfusion or direct vascular injury; tubular necrosis and resultant chronic kidney disease can occur if the insults are not adequately reversed [18]. Similarly, hypoperfusion and damage to the blood-brain barrier can cause acute central nervous system (CNS) disturbances, most commonly encephalopathy. Splanchnic hypoperfusion can lead to gut translocation of bacteria

and bacterial toxins, the systemic effects of which are multiplied if hypoperfusion of the liver decreases first-pass metabolism [19].

Microvascular damage to the pulmonary circulation can impair barrier function of alveolar capillaries, leading to interstitial and alveolar edema. The clinical effect is ventilation/perfusion mismatching, causing hypoxemia: if severe enough, the acute respiratory distress syndrome (ARDS) develops, as evidenced by a PaO_2/FiO_2 ratio of less than 300 [20]. Sepsis-induced ARDS seems to be much more common in chronic alcoholics [21]. Sepsis-induced cardiomyopathy is another well-recognized clinical entity. The mechanism is not entirely elucidated, but certainly involves myocardial depression by inflammatory cytokines; in shock states, cardiac muscle hypoperfusion likely contributes [22]. In one study of 108 severe sepsis and septic shock patients, 64% had evidence of myocardial dysfunction, whether via left ventricular systolic, diastolic, or right ventricular failure [23]. The development of cardiomyopathy also contributes to poor tissue oxygenation and has implications for treatment strategies.

Evidence of systemic hypoperfusion

At the global level, impairment in microvascular circulation and hypotension leads to an imbalance between oxygen delivery and oxygen requirements: a critical juncture on the path to tissue hypoxia, irreversible tissue damage, organ failure, and death. The relationship between global oxygen consumption and its determinants is summarized in the following equation:

(Equation 1) $VO_2 = CO \times Hb \times 1.34 \times (SaO_2 - Sv0_2)$

(VO_2: oxygen consumption, CO: cardiac output, Hb: hemoglobin concentration, SaO_2: oxygen saturation of arterial blood, SvO_2: oxygen saturation of mixed venous blood)

When oxygen demand (DO_2) outstrips supply, a DO_2/VO_2 mismatch develops, and the body attempts to respond to global tissue hypoxia by optimizing certain variables in the equation above [24]. Regulation of some of these variables occurs directly: in brief, cardiac output is regulated by autonomic nervous activity and catecholaminergic stimuli, SaO_2 by changes in ventilator drive, and hemoglobin levels (slowly) by EPO secretion and subsequent RBC production. In contrast, there does not appear to be any direct process by which the body regulates SvO_2 [24]. Therefore, changes in SvO_2 are most truly representative of a growing gap between oxygen consumption and oxygen demand by tissues: the DO_2/VO_2 mismatch. $ScvO_2$, the saturation of venous blood at the level of the entrance to the right atrium, is considered a surrogate for SvO_2; it is usually 3-5mmHg higher than SvO_2 [24]. As will be discussed in a later section, $ScvO_2$ is often measured in clinical situations and utilized as a surrogate for the adequacy of oxygen delivery in severe sepsis.

Another physiologic marker of tissue hypoxia is the serum lactate level. Under hypoxic conditions, lactate is a byproduct of cellular glycolysis to regenerate much-needed reducing power (in the form of NAD+). Lactate excreted from the cell into the bloodstream can either be metabolized directly by certain tissues (such as the heart) or converted into glucose via gluconeogenesis in the Cori cycle, mostly in the liver but to a smaller extent in the kidneys [25]. This production of lactate often parallels the increased production and release of protons by metabolically-active,

hypoxic cells (a result of a shift in the ratio of ATP to ADP/AMP) [25]. Thus, the serum lactate has traditionally served as a marker for the presence of tissue hypoxia, whether at the local level (in acute mesenteric ischemia) or globally (in various forms of shock). Lactate production could also occur via anaerobic metabolism in the absence of hypoxia, as seen with mitochondrial dysfunction states.

More recently, the accuracy of using lactate levels as an indicator of anaerobic states has been questioned, and alternative hypotheses have been proposed. Lactate may be a byproduct of stress-induced muscle metabolism, a hypermetabolic response to the catecholaminergic surge commonly seen in severe sepsis. Alternatively, a decrease in lactate clearance by the liver or kidneys may be responsible for lactate elevation in a subset of septic patients [25]. Some studies even suggest that elevated lactate may play a protective role in sepsis as an alternative metabolic fuel for the heart and brain [26]. Although uncertainty exists regarding its true nature, the serum lactate level continues to be utilized in clinical situations as a surrogate for tissue hypoxia and as a prognostic indicator in sepsis.

Classification

Given the incredible variability of physiologic derangements in sepsis, an inclusive and accurate classification system is essential for aiding clinical diagnosis and treatment decisions, as well as for informing study design. For many years, the medical field lacked definitive criteria for making the diagnosis of sepsis and documenting its severity. In 1992, the American College of Chest Physicians (ACCP) and the Society for Critical Care Medicine (SCCM) jointly developed a classification

system for sepsis in order to standardize diagnosis and to categorize cases along a spectrum of disease severity [27].

The classification system included various definitions for sepsis syndromes. It first defined the systemic inflammatory response syndrome (SIRS), composed of four criteria: fever (>38°C) or hypothermia (<36°C), tachycardia (>90 beats/min), tachypnea (>30 breaths/min) or PaCO2 <32 mmHg, and an abnormal WBC (>12,000, <4,000, or >10% bands). The diagnosis of SIRS requires fulfilling at least 2 of the 4 above criteria [27], shown in Table 1.

Table 1. **Criteria for the Systemic Inflammatory Response Syndrome (SIRS)***

(1) temperature > 38°C or < 36°C

(2) heart rate > 90 beats per minute

(3) respiratory rate > 20 breaths per minute or $PaCO_2$ < 32mmHg

(4) white blood cell count > 12,000/mm^3, < 4,000/mm^3, or > 10% immature (band) forms

* Adapted from ACCP/SCCM Consensus Conference [27].

Using the above criteria for the system inflammatory response, the consensus defined sepsis as the presence of SIRS with a documented or probable infectious source. Severe sepsis was defined as sepsis with organ dysfunction, hypoperfusion, or hypotension; sepsis-induced hypotension is a subset of severe sepsis defined by a systolic blood pressure (SBP) less than 90 mmHg, a mean arterial pressure (MAP) less than 65 mmHg, or a decrease in SBP greater than 40 mmHg from baseline. The most severe form of sepsis is septic shock, defined as

sepsis with persistent hypotension or hyperlactatemia (above 4.0 mmol/L) despite adequate fluid resuscitation. These definitions have been shown to correlate stepwise with mortality: in one large series, patients with SIRS, sepsis, severe sepsis and septic shock had hospital mortality rates of 7%, 16%, 20%, and 46%, respectively [28].

The consensus document also categorized the multiple organ dysfunction syndrome (MODS), a severe and deadly consequence of sepsis related to hypoperfusion and endothelial damage. Multiple organ failure in response to acute insult had already been recognized for many years, but the focus of the consensus document on organ dysfunction, before the presence of overt failure, was original. The document defined MODS as "the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention," and subclassified MODS into primary and secondary etiologies [27]. Primary MODS can be considered a direct reaction to the initial insult; secondary MODS is a consequence of the host response to the original injury. Either type can lead to progressive organ failure and death, sometimes far removed in time and severity from the initial presentation [27]. Although no universally-accepted criteria exist for the diagnosis of MODS, it logically requires the continued presence of multiple measures of organ dysfunction.

In 2001, the ACCP/SCCM revisited their consensus document and altered some of their previous definitions, most importantly on the concept of SIRS [29]. Although characteristic of sepsis, the presence of SIRS is also common in other conditions, including trauma, pancreatitis, and burns. However, these criteria are

Table 2. **Sepsis definitions, International Sepsis Definitions Conference.***

Infection, documented or suspected, and some of the following:

General variables
- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min^{-1} or >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
- Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables
- Leukocytosis (WBC count >12,000 μL^{-1})
- Leukopenia (WBC count <4000 μL^{-1})
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

Hemodynamic variables
- Arterial hypotension (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
- SvO_2 >70%
- Cardiac index >3.5 $L/min/M^{-23}$

Organ dysfunction variables
- Arterial hypoxemia (PaO_2/FIO_2 <300)
- Acute oliguria (urine output <0.5 mL/kg/hr or 45 mmol/L for at least 2 hours)
- Creatinine increase >0.5 mg/dL
- Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000 μL^{-1})
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)

Tissue perfusion variables
- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling

* Adapted from 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [29]. WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; SvO_2, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

not exclusive to these disease states but are in fact present in many hospitalized patients; in one recent study of over 100,000 ED encounters, the presence of SIRS correlated with infection in only 26% of cases, whereas 56% of patients with SIRS did not fit into disease states normally associated with these criteria [30]. Given the

increased scrutiny surrounding the tenuous ability of the SIRS criteria to delineate the host response to infection, the ACCP/SCCM redefined sepsis as the presence of documented or probable infection in association with clinical signs/symptoms suggestive of a broader inflammatory response [29]; these consist of clinical and laboratory variables as displayed in Table 2. This definition suspended the explicit need for 2 of 4 SIRS criteria to be met. However, despite their removal from current sepsis guidelines, SIRS criteria are still widely used as convenient objective measures of sepsis in observational trials, in accordance with the original 1992 consensus.

Indicators of sepsis severity

Despite its utility, our current classification system for sepsis belies an incredibly diverse patient population; many factors influence the severity of the illness and alter the prognosis of the individual patient. Recognizing the incredible heterogeneity in sepsis and the many factors affecting outcomes, the 2001 International Sepsis Definitions Conference conceptualized a new system for categorizing sepsis [29]. The PIRO system (which stands for Predisposition, Infection, Response and Organ dysfunction) is loosely designed around known and suspected prognostic factors, and offers a template by which clinicians can conceptualize the severity of an individual patient's septic presentation. The following sections will discuss known risk factors in each component of the PIRO system. Therapeutic factors also influence outcomes in sepsis, as will be discussed in a later section.

Predisposing characteristics of the host

Well-known risk factors for developing sepsis include age, certain demographic factors, and comorbidities. Elderly age is a strong predictor of developing sepsis, with a stepwise increase in risk: in a longitudinal survey of over 30,000 adults, the hazard ratios for developing sepsis in adults between the ages of 55-64, 65-74, and ≥75 were 1.44, 2.29, and 3.87 respectively when compared to an age range of 45-54 [31]. In the same study, the frequency of sepsis episodes also correlated significantly with tobacco use, alcohol use, lower education, and lower income. Women who develop sepsis are generally older and less likely to have severe sepsis than their male counterparts, but are possibly at increased risk of death in the ICU [32, 33]. Chronic comorbid conditions which increase the likelihood of developing sepsis include a history of chronic lung disease, peripheral artery disease, chronic kidney disease, myocardial infarction and diabetes, among others; the presence of multiple comorbidities has an additive effect on the risk of developing sepsis [31]. Lastly, there is likely a large genetic component involving innate and adaptive immunity that exacerbates or mitigates the risk of sepsis [34].

Furthermore, the severity and prognosis of a sepsis episode is influenced by underlying comorbidities. Age above 40 years is a stepwise negative prognostic factor, and the effect of increasing age is most pronounced in the absence of comorbidities [3]. Mortality from sepsis seems to be lowest in previously healthy young adults: in a large retrospective analysis, adults younger than 45 without comorbidities who developed severe sepsis had a mortality rate of less than 5% [7]. Immunocompromised states such as AIDS [35], solid or hematologic malignancy

[36], neutropenia [36], chronic liver disease [3], chronic renal disease [3], and asplenia [37] worsen prognosis to varying degrees in severe sepsis. Alcohol dependence is independently associated with higher mortality in critically-ill patients with severe sepsis and septic shock [38].

Characteristics of infection

The prognosis in sepsis is also predicated on the characteristics of the underlying infection. The type of organism responsible may influence outcomes. The largest observational trial of sepsis to date showed that Gram-positive organisms account for the majority (52.1%) of sepsis cases with a documented culture, as compared to gram-negative organisms (37.6%), polymicrobial infections (4.7%), fungal infections (4.6%), and anaerobes (1.0%) [4]. Other studies have shown that Gram-negative sepsis cases may predominate in the ICU setting [39, 40]. The most common Gram-positive organisms are Staphylococcus aureas and Streptococcus pneumonia, whereas Gram-negative organisms are usually E. coli, Pseudomonas and Klebsiella subspecies [41]. Although the presence of bacteremia positively predicts the development of SIRS [42], bacteremia itself does not appear to be associated with mortality in sepsis [43]. Bloodstream infections carry a worse prognosis if they are caused by nosocomial pathogens, such as MRSA (OR 2.7), fungal infections (OR 2.32-2.66) or pseudomonas (OR 1.6) [44]. However, only one third to one half of septic patients have positive blood cultures [45, 46], and up to 30% of patients have negative cultures from all sites [40]. In some cases, blood cultures may be incorrectly negative due to previous use of antibiotics or the incorrect collection of blood cultures [47].

The source of infection in sepsis likewise influences severity. Respiratory infections are the most common source (35-44%), followed by urinary (9-37%), occult bacteremia (12-17%), abdominal (8-19%), wound/soft tissue (5-7%), device-related (2-6%), and other sources (including endocarditis, CNS, bone and joint infections) [3, 45, 48]. Sepsis develops commonly in the setting of pneumonia; in an observational study of 1,339 patients admitted with community-acquired pneumonia (CAP), severe sepsis developed in 48% [49].

Sepsis from a genitourinary source (urosepsis) is generally considered to have a better prognosis than other causes of sepsis, especially pneumonia [3, 50]. In a study cohort of almost 200,000 patients in the United States, Angus et al. found that patients who developed severe sepsis from a lung infection had a mortality of 32.9%, whereas the mortality of urosepsis was 16.1% [3]. In a more recent, large-scale cohort from Australia, the mortality from urosepsis in 2012 was 6.7% compared to 17.0% in sepsis from a non-urinary source [7]. The range of prognosis in sepsis from abdominal sources seems to be wider; although one study showed a mortality rate of 55% in septic patients with abdominal foci, larger studies quote mortality rates closer to urosepsis [3]. This may be due to differences in severity between sources within the abdomen. In one study of around 8,000 patients with septic shock, mortality rates depended on the underlying diagnosis including ischemic bowel (77.9%), spontaneous bacterial peritonitis (76.4%), perforated viscus (55.6%), pancreatitis (50.0%), cholecystitis/cholangitis (38.3%), and enterocolitis/diverticulitis (28.0%) [51]; these rates roughly reflect the clinical severity of the underlying disease process. In the same study, mortality from skin,

soft-tissue and bone infections was high (42.0-52.5%). Furthermore, the presence of multiple sources of infection seems to portend a poor prognosis [52]. However, distinctions in mortality between different infectious sources are not universally demonstrable [43].

Features of the host response

Many clinicians are intuitively aware that a formidable host response to infection, as exhibited by abnormalities in multiple SIRS criteria, is clinically relevant and has prognostic information. In one study of the SIRS criteria, in-hospital mortality increased steadily, from 14% with 2 criteria, 26% with 3 criteria, and 36% with 4 SIRS criteria met [42]. In keeping with this data, most of our current therapies seek to counteract the excessive host response to infection that occurs in sepsis. However, comparatively little is known about the specific pathways of host response that correlate with severity in sepsis. Biomarkers of immune activation may hold promise as risk stratifiers, and over 150 have been proposed. C-reactive protein is the most widely available marker of the inflammatory response; it is released by hepatocytes after stimulation from cytokines including IL-6 as part of the acute phase response. However, given its frequent elevation in non-septic conditions, its specificity is too poor to be of use as a prognostic indicator.

Procalcitonin is one of the best markers, not only for its high negative predictive value in ruling out infection but also as a prognosticator of severity [53]. Although not specifically performed in sepsis, one study of 472 critically-ill patients demonstrated an increased risk of death with an initial elevated procalcitonin level or an increase over 24 hours [54]. The ability of other biomarkers, including IL-6

and sTREM-1, to risk-stratify sepsis patients remains undefined. It is likely that, given the complexity of the host immune response, combinations of biomarkers will allow for better risk stratification than any single marker alone. However, there is as yet no evidence that incorporation of sepsis biomarkers, including procalcitonin, into sepsis alerts has improved outcomes.

Impairment in certain host endocrine pathways may exacerbate hypoperfusion in sepsis by augmenting systemic vasodilatation. A relative deficiency of endogenous cortisol, called critical illness-related corticosteroid insufficiency (CIRCI), is commonly seen in sepsis; this syndrome is likely an effect of inflammatory mediators on both suppression of the hypothalamic-pituitary-adrenal axis and peripheral tissue corticosteroid resistance [55]. The prevalence of CIRCI may be as high as 60% in patients with septic shock [56]. A relative deficiency in vasopressin in septic shock patients may also contribute to hypotension [57].

Organ dysfunction

As was discussed in the previous section, severe sepsis (which by definition involves sepsis-induced organ dysfunction) carries a worse prognosis than the sepsis syndrome. However, the type of organ or organ system involved also seems to affect outcomes. In a retrospective analysis of over 3,000 patients presenting to an emergency department with sepsis, Shapiro et al. found higher odds ratios for mortality in patients with hematologic (OR 4.5), cardiovascular (3.6), or respiratory (3.6) dysfunction [58]. In particular, coagulation dysfunction is considered one of the worst organ dysfunctions in severe sepsis; the presence of DIC is an independent predictor of organ failure and mortality, with a rate of up to 77% in

one study [16]. Higher DIC scores also correlate directly with mortality [59]. Even before overt DIC has developed, abnormal coagulation tests including thrombocytopenia and elevated INR predict increased mortality in infected patients presenting to the ED [60].

The number of dysfunctional organs is also a strong predictor of increased risk. In the same study by Shapiro et al., increasing number of organ dysfunctions was correlated stepwise with increased mortality: 1.0% with no organ dysfunction, 5.9% with 1 organ dysfunction, 12.5% with 2, 25.9% with 3, and 53.3% with 4 or more [58]. Similar, though lower, mortality rates were seen in a previous analysis of the registry used in this study; specifically, the mortality rate of 5-6 organ dysfunctions was only 17.7%, whereas 7 or more was 55.9% [61]. These discrepancies may be a result of differences in how one defines organ dysfunction. Although the 2003 Surviving Sepsis Campaign guidelines describe a strict set of definitions for organ dysfunction based on objective criteria, these thresholds clearly exist on a spectrum of organ health from normal functioning to complete failure. Furthermore, they are not inconclusive of all categories of organ dysfunction induced by sepsis, including altered mental status and cardiac dysfunction. For example, neurologic dysfunction can variably be defined with a specific threshold Glasgow Coma Scale <12 or, alternatively, any change from baseline mental status. Many studies both before and after 2003 have incorporated their own unique measures of organ dysfunction, and these discrepancies in definition by different investigators limit the comparability of various study populations.

Risk scoring systems

Given the massive heterogeneity of the patient population in sepsis, and the presence of many known and presumed prognostic influences, much research has been focused on finding a more universal system of prognostication. One method is to create objective scores to signify increased risk of a poor outcome. Some scoring systems, such as the Pneumonia Severity Index (PSI) or CURB-65 for pneumonia, are limited to a single type of presentation and are not generalizable. The APACHE II score was originally formulated to be used 72 hours into admission for critically-ill patients, and incorporates 12 physiologic variables [62]. In a study of fewer than 100 critically-ill patients presenting to the ED, Nguyen et al. found that the initial APACHE II predicted mortality at 12 hours, and that the largest changes in the score over hospitalization occurred in the first few hours within the emergency department [63]. However, these data are not exclusive to septic patients, and the score is too cumbersome to be utilized clinically in the emergency department.

Scores dedicated to assessing organ dysfunction in sepsis are widespread in the research literature. Two of the most prominent are the Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA). MODS was developed in 1995, after an extensive search of the previous sepsis literature to identify the most optimal descriptors of organ failure [64]. The MODS included six components of organ dysfunction: respiratory (PaO_2/FiO_2), renal (creatinine level), hepatic (bilirubin levels), hematologic (platelet count), CNS (Glasgow Coma Scale), and cardiovascular (pressure-adjusted heart rate, a unique variable devised for the score). Each dysfunction was scored from 0 to 4, for a total

MODS score out of 24 points. In the validation cohort, the MODS score was predictive of ICU mortality in a graded fashion: mortality was 25% with scores of 9-12, 50% with scores of 13-16, 75% with scores of 17-20, and 100% with scores greater than 20 [64].

The SOFA score is another method of characterizing organ dysfunction. Similarly to the MODS, the SOFA score incorporates assessments of respiratory (PaO2/FiO2), hepatic (bilirubin level), renal (creatinine level or urine output), neurologic (Glasgow Coma Score), cardiovascular (hypotension) and hematologic (platelet count) function. In the ICU setting, the initial, peak and mean SOFA scores all correlate well with mortality [65]. In a population of 248 emergency department patients with severe sepsis and evidence of hypoperfusion, the initial SOFA score was found to be moderately effective at predicting in-hospital mortality [66].

However, risk in sepsis depends on more than merely the presence of organ dysfunction, as the PIRO model shows. Howell et al. developed a scoring system based on the full extent of risk variables involved in sepsis severity; their PIRO score incorporated predisposing traits (age, COPD, liver disease, malignancy, and nursing home residency), infection characteristics (pneumonia, cellulitis, or other), host response criteria (tachypnea, tachycardia, and bandemia) and various objective measures of organ dysfunction [67]. In the derivation cohort as well as in two validation cohorts, the PIRO score had a high degree of accuracy in predicting sepsis mortality [67]. Because it incorporates known risk factors from each component of the PIRO system, the PIRO score is intuitively attractive as a prognostic tool; however, its complexity may make it unwieldy in the emergency department.

Responding to the need for a PIRO-based, prognostic tool for sepsis patients in the emergency setting, Shapiro et al. developed the Mortality in Emergency Department Sepsis (MEDS) score. As shown in Table 3, the MEDS score incorporates nine clinical variables that are immediately available from the patient history, physical exam, and early laboratory results. In the validation set of the initial study, the MEDS score correlated impressively with in-hospital mortality, in a graded fashion: 1.1% with MEDS 0-4, 4.4% with MEDS 5-7, 9.3% with MEDS 8-12, 16% with MEDS 12-15, and 39% with MEDS >15 [68]. The score and its stepwise correlation with 28-day mortality has been externally validated by other investigators [69], it performs similarly to the more complex PIRO score, and it may outperform organ dysfunction scores (such as SOFA) originally formulated for

Table 3. **Mortality in Emergency Department Sepsis (MEDS) Score.**

Criterion	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 mm3	3
Altered mental status	2
Nursing home resident	2
Lower respiratory infection	2

Adapted from Shapiro et al. [68].
* Terminal illness is defined as metastatic cancer or a disease condition with a >50% likelihood of predicted fatality within 30 days.

hospitalized patients [70]. One potential problem with the MEDS score exists in the intermediate range (scores 5-15) where MEDS may underestimate mortality [71]. Another criticism of MEDS is that it places a great deal of weight (6 points) on the assessment of a terminal chronic condition, which is somewhat subjective and often outweighs other components of the score.

Serum lactate as prognostic measure

The best prognostication tool would ideally be an objective measure, readily available and easily interpretable upon patient presentation. One such measure is the lactate level. As described in a previous section, the serum lactate level may represent tissue hypoperfusion, a hypermetabolic state with activation of skeletal muscle, mitochondrial dysfunction, decreased clearance by the liver or kidneys, or a combination of these mechanisms. An elevated lactate is also not specific for severe sepsis and occurs in many other disease states, such as in other forms of shock, liver failure, drugs and toxins (especially when interfering with mitochondrial activity), diabetic ketoacidosis, and regional forms of ischemia [25]. However, regardless of etiology, the serum lactate has been used for decades as a marker of poor prognosis and mortality in sepsis [72, 73]. In 2005, Shapiro et al. reported a study of 1,278 patients presenting to an emergency department with an infection-related diagnosis; 28-day mortality rates for normal (<2.5 mmol/L), intermediate (2.5-4 mmol/L) and high (>4 mmol/L) lactate levels were 4.9%, 9.0% and 28.4% respectively. Furthermore, the specificity of a high lactate for death within 3 days was 91%, although the sensitivity was poor [74].

Many other studies have supported these findings [75-77]. In one series of over 800 patients presenting to the emergency department, both intermediate (2-4 mmol/L) and high (>4 mmol/L) lactate levels correlated with 28-day mortality; these associations persisted in both shock and non-shock groups after controlling for the severity of other organ dysfunction [75]. Howell et al. found that in severe sepsis, an initial lactate level greater than 2.5 mmol/L was associated with an odds ratio for hospital mortality of 7.1 compared to a lactate less than 2.5 mmol/L [78]. After admission, sustained elevations in lactate is a poor prognostic sign: time-weighted lactate levels >2 mmol/L, also known as the "lac-time" [79], is associated with an in-hospital mortality OR of 4.8 [76]. Even lactate levels within the normal range (defined in one study as <2.3 mmol/L) are predictive of organ dysfunction and mortality in septic shock [77].

Given its very clear prognostic value, some clinicians have considered entirely replacing the more difficult and invasive measurements of hypoperfusion (such as $ScvO_2$) with serial lactate measurements. One possible goal is lactate clearance, defined as a decrease in the serum lactate level during sepsis resuscitation. Nguyen et al. calculated 6-hour lactate clearance in 111 septic patients presenting to an emergency department and found that a low lactate clearance (<10% decrease or any increase from initial lactate level) had a 67.6% accuracy of predicting in-hospital mortality [80]. The specificity of this cutoff was 84%, although the sensitivity was very low. Furthermore, the authors estimated that the risk of death decreased by around 11% for each 10% increase in lactate clearance at 6 hours. Arnold et al. published a similar trial showing that lactate non-

clearance was associated with a mortality rate of 60% vs. 19% with clearance. Interestingly, in this trial, 79% of patients with lactate non-clearance had met an $ScvO_2$ goal of ≥70% [81]. These data have spurred the use of lactate clearance as a goal for directing sepsis resuscitation in the proximal phases of care. In one trial to test the role of lactate compared to ScvO2 in goal-directed resuscitation of early sepsis, Jones et al. found that lactate clearance was non-inferior to $ScvO_2$ optimization in predicting hospital mortality [82].

Management

The proper management of sepsis relies on early identification of patients, prompt treatment with antibiotics and infectious source control, and appropriate hemodynamic resuscitation governed by perfusion assessments. These priorities are detailed in the Surviving Sepsis Campaign (SSC), originally formulated in 2004 and most recently updated in 2012 [83-85].

Early identification

The management of sepsis relies first and foremost on the recognizing the initial clinical signs and physiologic derangements that occur in patients with early sepsis. Similar to the concept of the "golden hour" in other life-threatening conditions such as trauma, myocardial infarction and stroke, early recognition allows sepsis-specific therapies to be quickly implemented and may decrease the likelihood of progressing to a more severe septic state. The key ingredients for early identification of sepsis include a high clinical suspicion for infection, the identification of a physiologic response indicative to systemic inflammation, and subsequent screening for

associated hypoperfusion or organ dysfunction. However, the often-cryptic presentation of early sepsis requires a much higher degree of clinical suspicion and a more thorough screening assessment than may be necessary in other conditions.

One screening method involves assessment of the "10 vital signs" of sepsis: changes in the five traditional vital signs (hypothermia, tachycardia, tachypnea/bradypnea, hypotension, and new onset of pain) and five other criteria assessing perfusion: oxygen saturation <90%, a decreased level of consciousness, capillary refill >3 seconds, urinary output <30ml/hr over 5 hours, and a base deficit or low $ScvO_2$. Nine of these vital signs can usually be assessed or estimated within minutes; the last requires an arterial or central blood gas measurement. Especially important is the presence of hypotension; even when non-sustained, low blood pressure is a sensitive risk marker for poor outcomes and should not be dismissed [86].

Sepsis alert systems are becoming increasingly common in both emergency departments and on hospital wards. A high clinical suspicion for early sepsis and effective screening measures is important for detecting patients in time for early, outcome-modifying treatments [87]. Screening tools in the ED setting, such as the MEWS (modified early warning system), can improve sepsis identification and have prognostic utility for making triage decisions [88]. Emergency medical services (EMS) involvement also appears to improve care in sepsis; patients with severe sepsis or septic shock who present via EMS transport or receive care by EMS prior to arrival tend to have better in-hospital outcomes, although no mortality benefit has been shown [89]. One concern with sepsis alert systems is their accuracy; as a

screening mechanism, a high sensitivity is desirable, but this often translates into a low specificity and many false positive alerts. For example, in a recent study implementing a severe sepsis alert and rapid response team system, 50% of sepsis alerts were triggered on non-septic patients, and 90% of the remaining alerts involved patients already diagnosed with sepsis [90]. This study found an increase in ICU admissions but no change in mortality after implementation. Still, it seems that current sepsis alert systems will tolerate a high false positive rate of alerts (more than 50%) in order to avoid missing potential sepsis cases.

Early recognition and screening is necessary but not sufficient for improving care in sepsis; there must also be a dedicated pathway for receiving essential early treatment. To this end, many institutions have built systems-based approaches triggered by early recognition, including a rapid response system (RRS) or dedicated medical emergency teams (METs) to respond to potential sepsis patients upon identification. In one of the largest trials of a sepsis alert system, Sebat et al. compared septic shock morbidity and mortality both before and after the implementation of several interventions (increased sepsis education, automatic electronic alerts, and a medical emergency team). They found that times to effective interventions and mortality decreased substantially over the 5 years of follow-up; the sepsis-specific mortality also dropped from 50% to 10% [91]. This study is rare in the literature for having such a dramatic effect, possibly due to its emphasis on multiple interventions and long follow-up.

Early antibiotics

Early antimicrobial therapy is essential in sepsis; delaying the treatment of the inciting infection increases the risk of organ dysfunction, shock and death. Kumar et al. described a series of 2,154 septic patients who received antibiotic therapy after the onset of hypotension, and found that mortality increased by 7.6% for each hour's delay in receiving antibiotics. In their cohort, the time to antibiotics was the strongest predictor of risk: stronger even than measures of disease severity such as the APACHE II score [92]. The importance of early antibiotics on improving outcomes has been established in community-acquired, hospital-acquired, and ICU-acquired sepsis [43]. Furthermore, empiric antibiotic therapy should have broad coverage, dictated by the characteristics of the host (such as neutropenia or risk factors for drug-resistant pathogens), likely source of infection, and local resistance patterns; inadequate initial antibiotic coverage is associated with a 2-fold increase in hospital mortality [93]. Blood cultures should ideally be drawn before initiation of antibiotic coverage, although not if this will inappropriately delay antibiotic administration. The SSC guidelines recommend daily reassessment of the empiric antibiotic regimen and de-escalation as tolerable, in order to minimize adverse effects and the emergence of resistance [83].

Source identification and control

In septic patients, it is important to adequately assess for any continuing focus of infection. This assessment will obviously be tailored to the individual's clinical presentation; sources to consider include pneumonia, urinary tract infection/pyelonephritis, intra-abdominal sources, skin and soft tissue infections,

septic arthritis, osteomyelitis, meningitis, endocarditis, and abscesses from any location, among others. The diagnostic workup must include imaging to assess for infectious foci, and directed cultures (blood, CSF, sputum, urine, wound) should be performed in order to properly identify the causative organism and permit de-escalation of antibiotic coverage. Certain sources require specific management, including drainage of an abscess, removal of potentially infected devices/lines, and debridement of necrotic tissue; if source control requires a procedure, it should be performed within the shortest amount of time as long as the patient is stable (preferably within 12 hours of presentation). For the most part, the least invasive method of source control is preferable in the septic patient, such as percutaneous rather than surgical abscess drainage [83].

Fluid resuscitation

Fluid therapy remains the focus of early resuscitation in sepsis. Septic patients often become hypovolemic, resulting from decreased intake, increased insensible fluid losses (fever, elevated respiratory rate), and third-spacing of fluids into tissue as a result of vascular endothelial dysfunction. Furthermore, septic shock is a form of distributive hypotension, which may respond to fluid therapy in its early stages. The SSC guidelines recommend an initial fluid challenge of at least 30ml/kg; crystalloids are considered the first line fluid, although colloids including albumin can be considered as part of this initial fluid bolus [83]. In the SAFE trial, Finfer et al. found no difference in mortality between albumin and crystalloids when used as the primary resuscitation fluid [94]. In ALBIOS, a more recent trial of albumin supplementing crystolloid resuscitation vs. crystalloid alone, there was no

difference between the two strategies in terms of mortality or any of the secondary outcomes [95]. The SSC guidelines state that albumin can be considered in patients who are likely to receive a large amount of crystalloids, in order to minimize the risk of fluid overload. Other colloids such as hydroxyethylstarch (HES) are discouraged due to an increase in mortality and need for renal replacement therapy [83].

Adequate volume resuscitation is a cornerstone of management in early sepsis. However, an inappropriate amount of fluid resuscitation can be detrimental, causing fluid overload leading to pulmonary edema and rarely to abdominal compartment syndrome. Over-resuscitation with normal saline has also been associated with hyperchloremic metabolic acidosis, an increased risk of acute kidney injury, and a worsening of underlying lung injury in the setting of ARDS [96, 97]. The SSC recommends continuing fluid resuscitation as long as there is continued improvement in hemodynamic variables, whether static (heart rate, blood pressure) or dynamic (pulse pressure variation, stroke volume variation) [83]. Pulse pressure variation is heralded as an accurate measure of fluid responsiveness; however, its assessment is only relevant in intubated patients who are not taking spontaneous breaths [98]. In the spontaneously-breathing patient, a simple passive leg raise may mimic the effect of an additional fluid bolus and thus predict the patient's responsiveness to further fluid. Bedside ultrasonography of the inferior vena cava also allows ultrasound-proficient clinicians to assess fluid responsiveness.

Vasopressors

In septic shock, adequate fluid resuscitation may not be sufficient to provide sufficient blood flow to critical organs, such as the brain. Vasopressor therapy is then recommended to target a MAP of 65mmHg, a blood pressure approaching the lower borderline of cerebral autoregulation. Norepinephrine is the first-line vasopressor agent of choice for patients in septic shock. Vasopressin is frequently used as an add-on agent (at a dose of 0.03U/min) to augment norepinephrine or to allow for a decrease in norepinephrine dosing [83]. In one trial, vasopressin infusion was non-inferior to norepinephrine as a first-line agent [99]; however, low-dose vasopressin in isolation is not advocated by the SSC. Phenylephrine is generally considered only as a third-line agent, in patients with normal cardiac function and after other vasopressors fail to control blood pressure. The use of dopamine as a first-line agent has declined since it was associated with higher rates of dysrhythmias [100] and is generally not recommended by the SSC guidelines [83]; however, it may be safer than norepinephrine as a peripheral agent if the patient lacks central access.

Marked delays in administering vasopressor support are associated with a large increase in mortality [101]. Even shorter delays may carry a worse prognosis; in a situation reminiscent of antibiotic therapy, one study on vasopressor timing showed an increase in mortality of 5.3% for every extra hour in which vasopressors were delayed in septic shock [102]. Higher doses of vasopressors may be associated with poorer outcomes [103], and high doses or multiple vasopressors may be futile in patients who already have developed multiple organ failure [104].

Inotropes

In patients with measured or perceived low cardiac output or in patients who remain hypotensive despite adequate fluid resuscitation and vasopressor use, other agents should be considered. An inotrope is usually recommended in order to augment cardiac output in patients with underlying cardiac dysfunction, or if there are signs to suggest sepsis-induced cardiomyopathy such as an elevated troponin or ultrasonographic signs of ventricular dysfunction [83]. Inotrope therapy should also be considered empirically if the goal $ScvO_2$ is not reached despite adequate fluid resuscitation and vasopressor use. Dobutamine is the first-line choice for inotropic therapy in septic shock. Little data is available to assess the individual effect of additional therapy on outcomes; however, the goal of supplementing cardiac output to supranormal levels is no longer considered desirable in sepsis [105].

Corticosteroids

In the absence of a history of adrenal insufficiency, the administration of corticosteroids in septic shock is contentious. A proportion of sepsis patients suffer from critical illness-related corticosteroid insufficiency (CIRCI), a form of inadequate stress response likely related to cytokine-mediated endocrine dysfunction that may cause vasopressor-refractory shock. Since CIRCI is a type of relative rather than absolute adrenal insufficiency, random cortisol levels are not diagnostic, and therefore ACTH stimulation test is preferable [55]. In a randomized trial of vasopressor-unresponsive septic shock, Annane et al. showed that corticosteroids improved mortality in ACTH non-responders (53% mortality in the

corticosteroid group vs. 63% in the control) [106]. In the larger CORTICUS trial, all patients with septic shock were included; mortality was not affected by corticosteroid therapy, even in patients with a negative response to ACTH stimulation [107]. However, in patients whose shock was reversed, corticosteroid therapy hastened that reversal. In clinical practice, an ACTH stimulation test is usually unfeasible and rarely warranted in the presence of septic shock, and so it is difficult to make a definitive diagnosis of CIRCI. The SSC guidelines suggest that if hemodynamic stability is not achievable with adequate fluid resuscitation and vasopressor therapy, intravenous hydrocortisone (at 200mg/day) can be given as a continuous infusion [83].

Mechanical ventilation

Patients with severe sepsis and septic shock often require intubation and mechanical ventilation. The oxygen demand involved in the work of breathing may be increased up to 40% of total demand in septic patients compared to 5% at baseline, due to interstitial/alveolar edema [87]; furthermore, total oxygen demand may be increased in the septic state as a result of fever, tachycardia, and acidosis. Mechanical ventilation can radically decrease the extra work of breathing and also improve central oxygenation if necessary. In patients with severe sepsis or septic shock who require intubation, a lung-protective strategy of mechanical ventilation is recommended even in the absence of ARDS. Lung protective ventilation incorporates low tidal volumes (6ml/kg of ideal body weight), low plateau pressures (<30cm H_20) and the application of positive end-expiratory pressure (PEEP) to avoid alveolar collapse; in the ARDSnet trial, a lung-protective ventilation

strategy was associated with an absolute reduction in mortality of 8.8% [108]. If ARDS develops, further treatment should involve minimizing fluid therapy, a short course of neuromuscular blockade, continuing lung protective ventilation, and considering prone positioning for patients with severe ARDS [83].

Additional therapies

Other supportive treatments for sepsis are described in the Surviving Sepsis Guidelines; a specific few will be discussed here. Red blood cell transfusions were originally considered at a hemoglobin threshold of 10 g/dL [109]; however, multiple trials in different patient populations, including one in septic shock patients specifically, have shown that a restrictive approach (>7 g/dL) is non-inferior to a liberal one (>9 g/dL) in terms of survival [110]. Likewise, fresh frozen plasma and platelets should be transfused according to standard indications for all patients, including bleeding or planned procedures. Bicarbonate therapy is not recommended to improve lactic acidosis or the efficacy of vasopressors, unless the patient's arterial pH is below 7.15 [83]. If renal replacement therapy is required in patients with septic shock, continuous therapies are preferred over intermittent hemodialysis in order to preserve hemodynamic stability. Glucose control in septic patients is similar to other critically-ill patients; insulin infusion protocols are recommended to target a glucose level of <180 mg/dL, based on the results of the NICE-SUGAR trial [111].

Lastly, a host of specific therapies targeting both inflammatory pathways and coagulation pathways have shown no benefit in sepsis trials, leading to sepsis being described as a "pharmaceutical graveyard." The most hopeful agent, recombinant

activated protein C, was initially found to improve mortality in severe sepsis and septic shock; however, after another trial showed no benefit to its administration in this population, it was withdrawn from the market [83]. More research is urgently needed to understand which patients may benefit from targeted immunomodulatory agents.

Early goal-directed therapy

In 2001, Rivers et al. instituted the first protocolized care algorithm for septic shock patients in the emergency department setting [109]. Their trial protocol called for optimization of certain hemodynamic variables (seen in Figure 1), including central venous pressure (CVP 8-12mmHg), mean arterial pressure (MAP >65mmHg) and central venous oxygenation saturation ($ScvO_2$ >70%). Fluid boluses of 500mL were given to improve CVP, and vasopressors were utilized to control MAP. If both of these variables were optimized and $ScvO_2$ remained below goal, dobutamine and red cell transfusions (to target of hematocrit >30%) were given to optimize oxygen delivery.

Early goal-directed therapy (EGDT) demonstrated a dramatic improvement in the hospital mortality rate compared to the control group: 30.5% vs. 46.5% respectively; these differences were maintained in the 28- and 60-day mortality rates as well [109]. Since its publication, numerous groups have replicated these findings in observational studies of sepsis care, pre- and post-EGDT-implementation [112, 113]. A meta-analysis of nine trials by Jones et al. showed that on average, the mortality rate fell by 20.3% after implementation of an EGDT-based protocol for severe sepsis and septic shock patients [114]. Another by Wira et al. included 25

trials and found a similar improvement in mortality with implementation of EGDT protocols, from 41.6% to 25.8% [8].

Despite the strong foundation of observational data favoring EGDT, two large randomized control trials have tempered enthusiasm for early-goal directed therapy. In the ProCESS trial, a total of 1,342 patients patients presenting to the ED

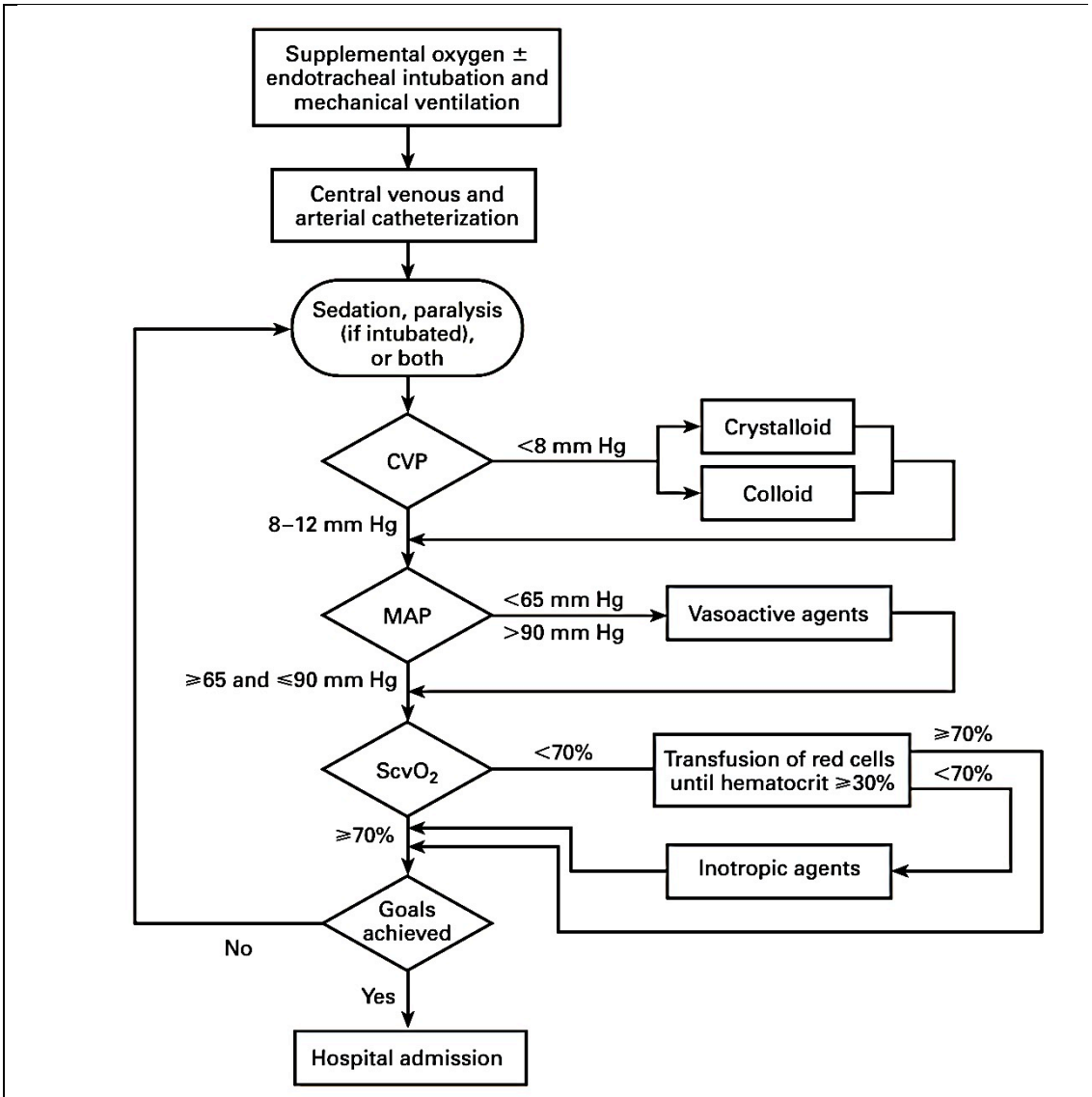

Figure 1. Protocol for early goal-directed therapy (EGDT).
Reprinted from Rivers et al. [109]. CVP: ventral venous pressure, MAP: mean arterial pressure, $ScvO_2$: central venous oxygen saturation.

in septic shock were assigned to one of three groups: EGDT protocol-based care, standard therapy protocol-based care, and usual care. EGDT-based care showed no advantage in 60-day mortality (21.0%) over either standard protocol-based care (18.2%) or the "usual care" group (18.9%) [10]. There were also no significant differences in any of the secondary outcomes, including 90-day mortality, 1-year mortality, or need for organ support. Recently, another randomized control trial of EGDT has corroborated the ProCESS results; in the ARISE trial, the EGDT care group had the same 90-day mortality (18.2%) as the "usual care" group (18.6%) [11].

Importantly, the "usual care" groups of both trials had almost universal antibiotic coverage by 6 hours, appropriate fluid management, and rates of vasopressor use and central line placement greatly exceeding those of the original EGDT trial; the rates of vasopressor requirement in the ProCESS and ARISE trials were 50.3% and 62.2%, respectively, compared to 44.1% in Rivers et al. Expeditious delivery of life-saving interventions likely contributed to the comparatively low mortality rate of the "usual care" groups in both ProCESS and ARISE. Still, both trials showed no benefit of EGDT over modern "usual care" for septic shock. Although another large randomized trial of EGDT will soon be published (ProMISe), it is unlikely to alter the conclusion that EGDT may not be effective in its current form for all patients in septic shock.

Protocolized care and sepsis bundles

After septic patients have been correctly identified, protocolized management ensures that they receive prompt and effective treatments based on their severity. For severe sepsis and septic shock, the Surviving Sepsis Campaign has formulated

sepsis care bundles, and these have been distributed widely in both the inpatient and emergency department settings. The SSC sepsis bundles are separated into components to be completed at 3-hour and 6-hour deadlines (Table 4) [83]. The 3-hour bundle includes obtaining blood cultures prior to antibiotic use, drawing a lactate level, administering broad-spectrum antibiotics, and administering an appropriate fluid challenge if the patient is hypotensive or hyperlactatemic. The 6-hour bundle consists of applying vasopressors for a MAP <65mmHg, remeasuring lactate if the initial lactate was elevated, and employing invasive hemodynamic monitoring (targeting goals for $ScvO_2$ and CVP) if hypotension or hyperlactatemia is refractory to adequate volume resuscitation; these bundles are modeled after the

Table 4. Surviving Sepsis Campaign Bundles.*

To be completed within 3 hours:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad-spectrum antibiotics
4) Administer 30mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

To be completed within 6 hours:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)$^{\Delta}$
   - Measure central venous oxygen saturation ($ScvO_2$)$^{\Delta}$
7) Remeasure lactate if initial lactate was elevated*

$^{\Delta}$ Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mmHg, $ScvO_2$ of ≥ 70%, and normalization of lactate.

*Adapted from Surviving Sepsis Campaign, International Guidelines for Management of Severe Sepsis and Septic Shock, 2012.

original EGDT trial [109, 115]. As mentioned previously, lactate clearance has been put forward as a possible replacement of the more invasive $ScvO_2$ targeting, and clearly is reasonable as a goal in patients without central access.

Observational data of bundled sepsis care has been favorable. To determine the relationship between bundle compliance and outcomes, Levy et al. analyzed data from 29,470 patients in the Surviving Sepsis Campaign database [116]. There was a significant mortality difference between those sites with high bundle compliance (29.0%) and those with low compliance (38.6%); this translated into a 25% relative risk reduction with high bundle compliance. Although this observational data favors protocolized care, the results of randomized control trials have not been as encouraging. For example, the ProCESS trial failed to show any survival benefit between protocolized and usual care [10]. This lack of benefit was surprising, but likely a result of the high level of "usual care" providers' awareness and competence in treating sepsis according to evidence-based guidelines, a major goal of the Surviving Sepsis Campaign.

Alternative classification systems

Given the wide range of mortality seen in sepsis studies, the poor clinical utility of complex scoring systems, and the recent negative results of large controlled trials using goal-directed resuscitation, it is clear that we need a new approach to classifying severity in sepsis. The current system seems inadequate to the task of indicating sepsis severity, prognosticating outcomes, and directing evidence-based management, especially in the proximal phases of care. A better classification schema could improve decisions on disposition as well as triage important

therapeutic maneuvers, such as central line placement, to the patients most likely to benefit. Furthermore, investigating subcategories of the traditional diagnoses of severe sepsis and septic shock could help us to identify patient populations who may benefit from early goal-directed interventions in future trials.

Cryptic shock

Cryptic shock, also known as cryptic septic shock, is defined as normotension or fluid-responsive hypotension with high serum lactate levels (>4.0 mmol/L) and is widely accepted as having a prognosis similar to overt septic shock. As was discussed in detail in a previous section, an elevated lactate is a strong prognostic factor for both the development of organ dysfunction and early mortality, especially in the high range above 4 mmol/L, and this correlation exists independently of refractory hypotension [75]. In a post-hoc analysis of cryptic shock patients in the original EGDT trial, the mortality rate of cryptic shock patients in the control group was an astonishing 60.9%, compared to 20% in the treated group [117]. Other studies have shown that mortality in cryptic shock is substantially higher than in other groups of severe sepsis, and approaches the mortality rate seen in overt septic shock [75, 76, 118].

Because of the high mortality in this patient population with occult hypoperfusion, the Surviving Sepsis Campaign guidelines recommend that these patients receive protocolized, quantitative resuscitation similar to patients with overt septic shock, with a goal of normalizing lactate. However, in practice, it is unlikely that cryptic shock patients receive the same level of clinical attention by emergency providers, and therefore appropriate resuscitation may be inadequate or

delayed [119]. Some patients in cryptic shock will ultimately progress to overt shock; in one study, the mortality rate of these cryptic-to-overt shock patients was indistinguishable from patients presenting with overt shock [120]. Lastly, there is considerable evidence that patients with even slightly elevated lactate levels have an increased risk of death over other patients with severe sepsis [77, 121]; one group has termed this patient subgroup "pre-shock" [122]. Some evidence suggests that in-hospital mortality rates are higher for cryptic-to-overt shock patients than for patients presenting to the ED in septic shock [123], suggesting that developing prediction tools for decompensation in cryptic shock is an imperative for improving the proximal phases of care.

Vasoplegic shock and tissue-dysoxic shock

The serum lactate level may also risk-stratify patients with septic shock; multiple studies have shown that initial lactate predicts mortality in shock patients [75, 124-126]. Some investigators have created new terms for subsets of septic shock based on lactate levels: "tissue-dysoxic" shock for patients with elevated lactate, and "vasoplegic" shock for patients with normal or mildly elevated lactate. In one study, Sterling et al. used a lactate cutoff of 2 mmol/L to divide 247 ED septic shock patients into vasoplegic and dysoxic categories; mortality was 9% in the vasoplegic group and 26% in the dysoxic group [126]. Similar numbers were published by Hernandez et al. in their prospective study of "persistent sepsis-induced hypotension without hyperlactatemia" (defined as hypotension requiring vasopressor use and a lactate <2.5); mortality rates were 7.9% and 20% for lactates <2.5 and >2.5, respectively [127]. The distinction between dysoxic and vasoplegic

shock may in fact have a physiologic basis; Hernandez et al. found that vasoplegic shock patients seem to have better microcirculatory function (as evidenced by percentage of perfused vessels and microcirculatory flow on sublingual videomicroscopy). Patients without hyperlactatemia also had lower rates of mechanical ventilation and lower disease severity scores. [127].

One large retrospective study has attempted to utilize this diversity in sepsis presentations to create a new prognostic schema for severe sepsis and septic shock [128]. Of 1,948 patients analyzed, 52% were diagnosed with severe sepsis, 8% with cryptic shock, 28% with vasoplegic shock, and 12% with dysoxic shock. Mortality was highest among the dysoxic shock patients at 60.3%, and lowest among patients with severe sepsis at 16.8%. The mortality rates for patients with vasoplegic shock and cryptic shock were 48.1% and 35.2%, although the difference was not statistically significant. The study also showed that mortality rates begin to rise as the lactate increases above 2 mmol/L, consistent with findings of other groups. However, the investigators lacked the ability to compare these lactate values to more standard hemodynamic variables of hypoperfusion, such as $ScvO_2$.

Other subsets of septic shock

Beyond initial lactate levels, there are likely other early predictors of risk in severe sepsis and septic shock. One such predictor is vasopressor dependence. Vasopressor use is commonly used as a surrogate for septic shock, since guidelines recommend vasopressor use for persistent hypotension (MAP <65 mmHg) despite adequate volume resuscitation. In practice, however, some patients with septic shock may only require a short course of vasopressors, whereas others require

prolonged use with increasing doses and additional agents. It is known that prolonged vasopressor use beyond 3 days in the ICU is associated with increased mortality [129]; less is known about shorter vasopressor requirements, such as within the hours of the emergency department stay. However, it is intuitive that patients requiring prolonged vasopressor support will have worse outcomes than those who are quickly weaned.

Another similar question revolves around the risk associated with increasing doses or added vasopressor agents. Severe septic shock has been previously defined as septic shock requiring high-dose vasopressor therapy (such as norepinephrine above 15μg/min [99]); however, based on the SSC guidelines, if a patient continues to be hypotensive despite low-dose therapy with one agent, additional vasopressors are often added rather than increasing the dose of the initial agent [83]. Although it has been shown that an ICU requirement for multiple vasopressors predicts a very poor outcome [130], little is known about multiple vasopressor requirements in the ED setting. Lastly, it is unknown if septic patients who initially present to the emergency department with very low blood pressures (which we define as presenting "in hemodynamic extremis") are at higher risk than those who develop hypotension after presentation. In a series of patients in the emergency department with undifferentiated hypotension, the lowest systolic blood pressure (SBP) correlated inversely with in-hospital mortality; however, the patients were not stratified by initial SBP, and the cause of the hypotension was not specified [131]. Further characterization of septic patients presenting "in extremis" is warranted.

Hypothesis and Aims of Research

Hypothesis

In a novel 5-group classification system for severe sepsis and septic shock, we hypothesize that high initial serum lactate levels and Emergency Department vasopressor dependence will be independently predictive of increased 28-day in-hospital mortality.

Aims of Research

Primary aim: To evaluate 28-day in-hospital mortality rates within a 5-group classification system; groups include dysoxic shock (vasopressor use + lactate >4 mmol/L), vasoplegic shock (vasopressor use + lactate ≤4 mmol/L), cryptic shock major (no vasopressor use + lactate >4 mmol/L), cryptic shock minor (no vasopressor use + lactate 2-4 mmol/L), and severe sepsis w/o lactate elevation (no vasopressor use + lactate ≤2 mmol/L + evidence of organ dysfunction).

Secondary aims:

1. To determine the incidence of each group within the classification system.
2. To evaluate the utilization of key critical care resources (i.e. mechanical ventilation, ICU admission, and ICU vasopressor utilization) during the course of hospitalization between groups in the classification system.
3. To evaluate severity of illness scoring systems within the classification system, including the cumulative number of organ dysfunctions, APACHE II score, and MEDS score.
4. To evaluate 28-day mortality, utilization of critical care resources, and severity of illness scoring for exploratory high-risk groups in the hyperacute phase of presentation: hemodynamic extremis (initial systolic blood pressure < 70 mmHg), and severe shock (requirement of multiple vasopressors in ED).

Methods

Study setting and design

The setting of our study is a dual-site emergency department of a major teaching hospital, which sees greater than 120,000 patient visits per year; the two sites were the adult section of the Yale-New Haven Hospital ED and the Shoreline Medical Center ED in Guilford, CT. This retrospective study was performed on a prospectively-identified population of patients in the Yale Emergency Medicine Sepsis Registry with severe sepsis or septic shock presenting to both emergency departments. Our registry and the study were reviewed and approved by the Yale Human Investigation Committee (HIC), which oversees research on patient medical records at Yale-New Haven Hospital. The registry was formulated by Dr. Charles Wira, III, and three previous medical students have performed investigations using this registry for their medical theses. This author was added to the list of HIC-certified investigators in 2013, and the independent research here presented was approved by the Emergency Medicine Research Committee in the same year.

Study population and inclusion/exclusion criteria

Between July 1st, 2005 and September 5, 2009, patients presenting to both emergency departments were screened, and 521 patients with severe sepsis or septic shock were included in the registry. Screening was performed by Dr. Wira according to clinical suspicion of sepsis; screened patients who met the inclusion and lacked exclusion criteria were entered into the registry.

Inclusion criteria for this study are shown in Table 5. All included patients were 18 years of age or older, met 2 or more criteria for the Systemic Inflammatory Response Syndrome (SIRS), had a presumed or documented source of infection, and had at least one organ dysfunction newly-diagnosed during their stay in the Emergency Department. Exclusion criteria included an age less than 18, lack of criteria for meeting the diagnosis of severe sepsis or septic shock (as described in Table 5), a discharge directly from the emergency department, or documentation of a pre-existing advance directive for implementing comfort care only. End-organ dysfunction was defined as in section C of Table 5. Patients were required to have at

Table 5: **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 $PaCO_2$ < 32 mmHg
      - White blood cell count > 12,000 μL^{-1}, <4,000 μL^{-1}, or >10% immature (band) forms
   b. Documented suspicion of a source of infection, including any one of the following:
      - White blood cell count > 12,000 μL^{-1}, <4,000 μL^{-1}, or >10% immature (band) forms
      - Body temperature > 100.4°F or < 96.8°F
      - Antibiotics administered in the Emergency Department
      - Documentation of presumed source of infection in the Emergency Department
   c. At least one newly diagnosed organ dysfunction in the Emergency Department, including:
      - Transient systolic BP < 90mmHg that responds to fluid resuscitation
      - Lactate level > 2 mmol/L
      - Unexplained acidosis (pH < 7.35) or serum bicarbonate < 21
      - Altered mental status (change from baseline)
      - Platelets < 150,000 μL^{-1} without a history of thrombocytopenia
      - Elevation of bilirubin above normal or either direct or indirect bilirubin > baseline
      - High coagulation factors (any elevation in absence of heparin or warfarin 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 from the 2001 Sepsis Definitions Conference [29].

least one of the following new organ dysfunctions in the ED: transient hypotension, hyperlactatemia, unexplained acidemia, new neurologic dysfunction, thrombocytopenia, hyperbilirubinemia, coagulation abnormalities, acute kidney injury, hypoxemia, or an elevated troponin measurement.

Data extraction

After screening, subsequent data extraction from medical charts was performed by medical students and residents, under the supervision of the faculty supervisor Dr. Wira; comparison of a subset of over 500 data points extracted in parallel by two previous investigators showed >95% concurrence, demonstrating the accuracy of the chart extraction process. The entire medical chart, from emergency department presentation to hospital discharge, was reviewed during extraction; electronic medical records included "ChartView," "Lynx Medical Systems," and "Sunrise Clinical Manager."

Customized data collection forms and a glossary of terms were used to record pre-defined data points, as detailed below; the data collection form is included in the Appendix. Patients were assigned a study identifier (ID) at time of data extraction, and the collection forms with included patient-identifying data were secured in a locked file cabinet in the Department of Emergency Medicine during and after the extraction process. The collected, hard-copy data was transcribed by Dr. Wira to a password-protected, customized Microsoft Excel database (Redmond, WA, USA), accessible only by Dr. Wira. De-identification occurred through the creation of a copy Excel database incorporating only study ID and lacking patient identifiers such as name, medical record number and admission date.

The data points extracted from the chart were pre-determined by Dr. Wira and other investigators, and included demographics, vital signs and other clinical data from the ED, laboratory data, and specifics of the clinical course during hospitalization. The collected demographic data included patient age, gender, previous medical history, and residence in an extended care facility. In general, all vital signs were collected for the entirety of the ED stay; in patients requiring vasopressor therapy in the ED, the heart rate and systolic/diastolic blood pressures were recorded only until the initiation of vasopressors. Extracted laboratory data included initial serum electrolytes, blood urea nitrogen (BUN), creatinine, cardiac troponins, direct and indirect bilirubin levels, international normalized ration (INR), prothrombin time (PT), partial prothrombin time (PTT), white blood cell count, percentage bands, hematocrit, platelet count, and final microbial culture results from blood, urine, and other sources. Arterial blood gas results were recorded if drawn. Initial and peak lactate levels during the ED stay were recorded, as well as the first repeated lactate level after admission.

Other clinical data recorded from the ED stay included arrival and departure times, length of stay, type of cultures drawn, presence and time to administration of various therapies (antibiotics, fluid repletion, central line placement), and specific measurements of CVP and $ScvO_2$ if available. Every patient was assessed for whether early goal-directed therapy was implemented; documentation of EGDT required the presence of a central line placed during the ED stay as well as CVP and $SCVO_2$ measurements continued throughout the first 24 hours of hospital stay. Specifically, the presence of vasopressor therapy, time to initiation of vasopressor,

and types of vasopressor agents (norepinephrine, dopamine, vasopressin, epinephrine and/or phenylephrine) were recorded for the ED stay. Other therapies, such as dobutamine, corticosteroids, and intubation in the ED, were recorded if implemented. APACHE II and MEDS scores were calculated from the relevant data obtained in the ED. Finally, specifics of the hospital stay included admission location (ICU, step-down unit, or floor), use of mechanical ventilation, vasopressor use within 72 hours of presentation, and vasopressor use after 72 hours.

Study protocol and classification system

As described previously, all subjects included in the study met criteria for severe sepsis or septic shock, shown in Table 5 in accordance with the original 1992 ACCP/SCCM definitions [27]. The subgroup of septic shock subjects were subsequently defined by the presence of severe sepsis and a systolic blood pressure less than 90mmHg that was unresponsive to adequate fluid resuscitation, in accordance with both 1992 and 2001 ACCP/SCCM guidelines. [27, 29]

In the primary analysis, initial lactate levels and vasopressor requirements in the ED were used to categorize subjects; these definitions are listed in Table 6. Subjects who did not have a serum lactate level drawn in the ED were excluded from this analysis. Those subjects who received vasopressors in the ED were classified into two groups: dysoxic shock (initial lactate >4.0mmol/L) or vasoplegic shock (initial lactate ≤4.0 mmol/L). Subjects who did not receive vasopressors in the ED were classified into three groups: cryptic shock major (initial lactate >4.0 mmol/L),

Table 6. **Definitions of classification system.**

Group	Definition
Dysoxic shock*	Vasopressor use in ED + initial lactate > 4 mmol/L
Vasoplegic shock*	Vasopressor use in ED + initial lactate ≤ 4 mmol/L
Cryptic shock major†	No vasopressor use in ED + initial lactate > 4 mmol/L
Cryptic shock minor	No vasopressor use in ED + initial lactate between 2-4 mmol/L
Severe sepsis without lactate elevation	No vasopressor use in ED + initial lactate ≤ 2 mmol/L
Severe shock	Multiple vasopressors in the ED
Hemodynamic extremis	Initial systolic blood pressure < 70 mmHg

* Variously defined in the literature [125-128].
† Originally defined as "cryptic shock" by Donnino et al. [117].

cryptic shock minor (initial lactate ≥2.0 and <4.0 mmol/L) and severe sepsis without lactate elevation (initial lactate ≤2.0). Other analyses involved separate subgroups of the registry; severe shock was defined by the use of more than one vasopressor agent in the ED, and hemodynamic extremis was defined by an initial blood pressure <70mmHg at presentation.

Statistical analysis

The primary outcome for our study was 28-day mortality. Secondary outcomes included ED LOS, severity of illness variables (such as rates of individual and cumulative organ dysfunction, MEDS and APACHE II scores, intubation rates, vasopressor use within 72 hours), and treatment or intervention variables (such as time to antibiotics, mean crystalloid volume, documented source control, and components and documentation of EGDT). Categorical data, such as 28-day mortality, were reported as a percentage, and these percentages were compared

using the 2-tailed Fisher's exact test. Continuous data were reported as mean ± standard deviation, and the 2-tailed, unpaired Student t-test was used to compare means of these data. The alpha value was set at 0.05 for all comparisons, so that statistical significance required a p value less than 0.05. All outcomes, both primary and secondary, were analyzed by univariate analysis; univariate statistical analysis of the data was performed by this author, using Graph Pad Quick Calcs, GraphPad Software (San Diego, CA, USA: www.graphpad.com) for Fisher's exact and Student t-tests, or MedCalc (MedCalc Software BVBA, Ostend, Belgium: www.medcalc.org) for odds ratio analyses.

Multivariate analysis using logistic regression modeling was performed by a faculty member and statistician of the Department of Medicine, who utilized SAS 9.3 software, SAS Institute Inc., (Cary, NC, USA). Our primary outcome and the dependent variable for the multivariate analysis was 28-day mortality. We adjusted for potential clinical confounders known to correlate with sepsis severity: age, source of infection (including pulmonary, genitourinary, abdominal and skin/soft tissue), and certain comorbidities (liver disease, ESRD, alcohol abuse, cancer, HIV/AIDS, diabetes mellitus, and other immunocompromised states not otherwise specified). Gender was included as a variable in the multivariate analysis as it is a common confounder, although with no specific correlation to sepsis severity. The group of subjects in severe sepsis without lactate elevation was used primarily as the reference group when calculating odds ratios via logistic regression analysis.

Results

Characteristics of included patients

In total, 521 subjects in severe sepsis or septic shock were included in the registry. Of these, 75 subjects were excluded from the classification system because no initial serum lactates were drawn in the ED; the remainder (446, or 85.6% of all registry subjects) was included in the primary analysis. These subjects were then categorized by initial lactates and vasopressor use in the ED, as described by the study protocol in Figure 2; the definitions for each group are documented in Table 6.

The mean age of all 446 included subjects was 63.7 ± 17.5 years, and the gender distribution was nearly equal with 53% of subjects being men. 65.7% of subjects presented with severe sepsis, whereas 34.3% were in septic shock. A detailed account of the various frequencies of comorbid conditions is found in Table 7. The most common comorbidities included hypertension (54.7%), diabetes (33.2%), congestive heart failure (23.5%) and coronary artery disease (24.2%). Additionally, many subjects had risk factors for an immunosuppressed state: 27.8% with a history of cancer (of whom a third had received chemotherapy), 6.1% with a diagnosis of HIV infection or AIDS, 8.7% with liver disease, 11.7% with end-stage renal disease, and 8.7% with immunosuppression not otherwise specified. Almost a third of subjects resided in an extended care facility.

On presentation to the ED, all subjects met at least 2 SIRS criteria by definition, and the mean number of positive SIRS criteria was 2.89 ± 0.76. The most common source of infection was pulmonary in 29.8% of subjects; the other common

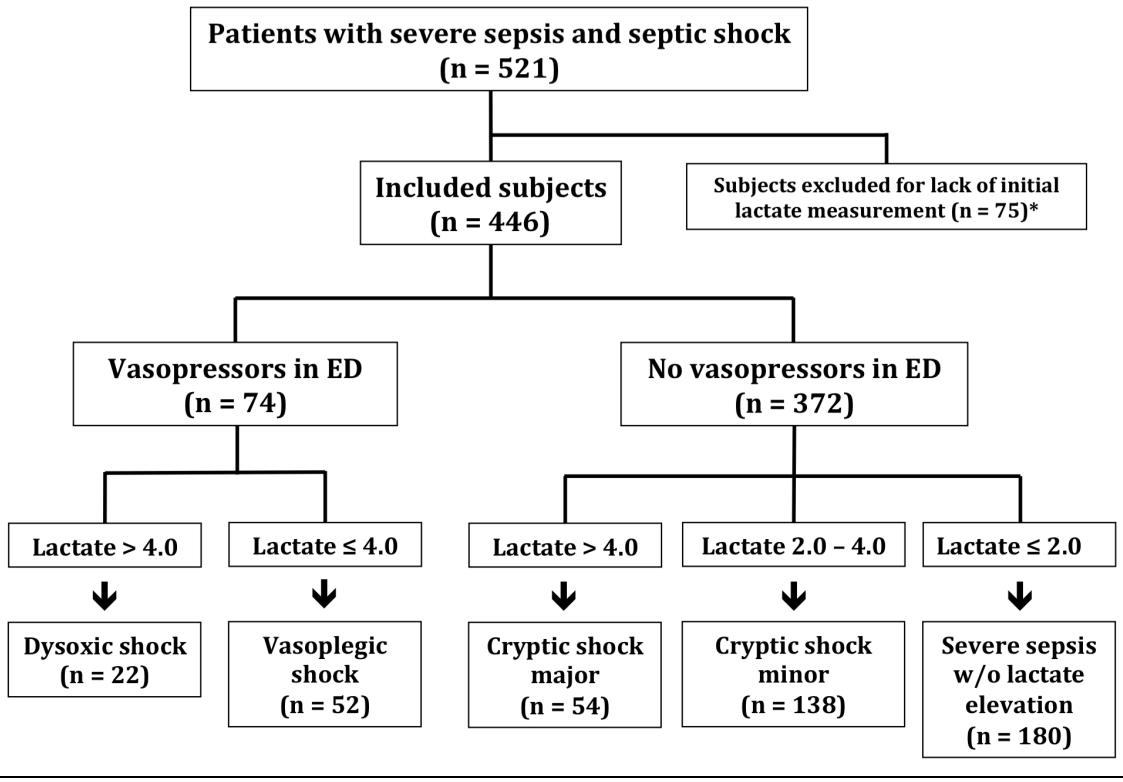

Figure 2. **Flow diagram of classification system.**

* Subjects without initial lactate level measured constituted 14.4% of the total registry.

sources included genitourinary (16.1%), abdominal (11.2%), and skin and soft tissue infections (6.3%). The primary infectious source was unknown in 28.8% of all subjects. Given the definitions of inclusion, the presence of organ dysfunction was universal. Hyperlactatemia (defined as a serum level ≥2 mmol/L) was common, occurring in 54.3% of subjects. Unexplained acidosis (44.6%), transient hypotension (38.6%), acute kidney injury (41.7%), hyperbilirubinemia (36.5%), hypoxemia (31.6%), and altered mental status from baseline (32.3%) were among the most common types of organ dysfunction. Almost a quarter of patients (24.4%) had elevations in their troponin levels. A minority of patients had a coagulopathy or thrombocytopenia (15% each). Finally, the mean MEDS score for all included

Table 7. **Subject characteristics** (n = 446).

Male gender	110 (53.1%)
Mean age ± SD (years)	63.7 ± 17.5
Diagnosis	
Severe sepsis	367 (65.7%)
Septic shock	71 (34.3%)
Diagnostic criteria	
Mean number of SIRS criteria ± SD[Δ]	2.89 ± 0.76
Documented source of infection	
Genito-urinary	72 (16.1%)
Intra-abdominal	50 (11.2%)
Pneumonia	133 (29.8%)
Soft Tissue	28 (6.3%)
Other[†]	35 (7.8%)
Mean number of organ dysfunctions ± SD	3.3 ± 1.9
Transient hypotension	170 (38.1%)
Hyperlactatemia	242 (54.3%)
Unexplained acidosis	199 (44.6%)
Altered mental status	144 (32.3%)
Thrombocytopenia	67 (15.0%)
Hyperbilirubinemia	163 (36.5%)
Coagulopathy (without prior anticoagulation)	67 (15.0%)
Acute kidney injury	186 (41.7%)
Hypoxemia	141 (31.6%)
Troponin elevation	109 (24.4%)
Past medical history	
Alcohol abuse	45 (10.1%)
Asthma	29 (6.5%)
Cancer	83 (18.6%)
Cancer with chemotherapy	41 (9.2%)
Congestive heart failure	105 (23.5%)
Coronary artery disease	108 (24.2%)
Chronic altered mental status	58 (13.0%)
Chronic obstructive pulmonary disease	83 (18.6%)
CVA / TIA	70 (15.7%)
Diabetes	148 (33.2%)
End stage renal disease	52 (11.7%)
HIV or HIV/AIDS	27 (6.1%)
Hypertension	244 (54.7%)
Immunosuppression	39 (8.7%)
Liver disease	39 (8.7%)
Residing in extended care facility (ECF)	142 (31.8%)
Mean MEDS score ± SD	11.3 ± 4.7
Mean APACHE II score ± SD	18.7 ± 7.2

SD = standard deviation, CVA = cerebrovascular accident, TIA = transient ischemic attack, HIV = human immunodeficiency virus, AIDS = acquired immune deficiency syndrome, MEDS = Mortality in Emergency Department Sepsis.

[†] e.g., central nervous system infection or line infection, [Δ] includes hyperlactatemia.

subjects was 11.3 ± 4.7, and the mean APACHE II score was 18.7 ± 7.2.

The treatments and interventions received by included subjects, as well as hospital outcomes, are summarized in Table 8. Overall, 92.6% of subjects received antimicrobial therapy during their ED stay; the most common antimicrobial agents included piperacillin/tazobactam, vancomycin, ceftriaxone, and ciprofloxacin. The mean time to antibiotics was 2 hours and 34 minutes, with a standard deviation of 2 hours and 12 minutes. Cultures were drawn in almost all patients, with blood cultures the most frequent (95.5%); only 52.9% of patients had a positive result on any culture. The frequency of hospital vasopressor use within 72 hours of admission was 27.6%, and only 2.2% were started on vasopressors more than 72 hours after admission. The most frequently used vasopressor agent was norepinephrine (used in 95.3% of vasopressor-dependent subjects), followed by vasopressin (31.6%), dopamine (29.3%), phenylephrine (18.1%), and epinephrine (6.8%). 49.6% (n=66) hospital vasopressor-dependent subjects were treated with multiple vasopressor agents. Corticosteroids were given in 29.1% of cases, dobutamine was used in 5.2%, and 31.2% of patients required mechanical ventilation at some point in their hospital course. Source control was achieved in 18.6% of subjects. Finally, the overall 28-day mortality for all included subjects was 13.9%; subjects presenting in severe sepsis had a mortality rate of 10.6%, whereas those presenting in in septic shock had a mortality rate of 29.1%.

Table 8. **Interventions, treatments and outcomes** (n = 446).	
Mean length of ED stay ± SD (hours)	6.80 ± 4.15
Mean intravenous fluid amount ± SD (L)	2.88 ± 2.16
Antimicrobial Treatment	
Received	413 (92.6%)
Mean time ± SD (hours)	2.57 ± 2.20
Type of Antimicrobial[†]	
Acyclovir	6 (1.3%)
Ampicillin	7 (1.6%)
Ceftazadime	21 (4.7%)
Ceftriaxone	94 (21.1%)
Ciprofloxacin	92 (20.6%)
Doxycycline	73 (16.4%)
Metronidazole	42 (9.4%)
Gentamicin	16 (3.6%)
Ampicillin/Sulbactam	24 (5.4%)
Vancomycin	245 (54.9%)
Piperacillin/Tazobactam	226 (50.7%)
Other[§]	29 (6.5%)
Cultures	
Blood culture drawn	426 (95.5%)
Urine culture drawn	308 (69.1%)
Other culture drawn[‡]	147 (33.0%)
Any culture positive[Δ]	236 (52.9%)
Hospital vasopressors	
Less than 72 hours after admission	123 (27.6%)
Greater than 72 hours after admission	10 (2.2%)
Hospital use of dobutamine	23 (5.2%)
Hospital use of corticosteroids	130 (29.1%)
Source control[ψ]	83 (18.6%)
Hospital use of mechanical ventilation	139 (31.2%)
28-day mortality	62 (13.9%)

SD = standard deviation.
[†] N = 413 (total subjects receiving antimicrobials).
[§] amoxicillin, clindamycin, meropenem, moxifloxacin, trimethoprim-sulfamethoxazole.
[‡] e.g., sputum, wound, or cerebrospinal fluid cultures.
[Δ] N = 435 (total subjects with at least 1 culture drawn).
[ψ] abscess drained, line pulled, endoscopic or operative management.

Frequencies of presentation and baseline characteristics

Included patients of the registry were stratified by initial serum lactate levels and vasopressor requirement, and then assigned to one of five groups, described in

Table 6. 16.6% (n=74) of the whole registry required vasopressors in the ED; 4.9% (n=22) were in dysoxic shock, whereas 11.7% (n=52) were in vasoplegic shock. 83.4% (n=372) subjects did not require vasopressors in the ED: 54 (12.1%) presented in cryptic shock major, 138 (30.9%) in cryptic shock minor, and 180 (40.4%) in severe sepsis without an elevated lactate level.

Table 9 lists the baseline characteristics of each group. The mean age of subjects was between 60-65 years for all groups: dysoxic shock (60.9±16.8), vasoplegic shock (64.9 ±15.4), cryptic shock major (63.0±17.1), cryptic shock minor (64.4±17.9), and severe sepsis without lactate elevation (63.4±18.2). Although the gender distribution of the registry was slightly weighted towards men (53.1% of total subjects), there was variability in the percentage of male subjects between groups: 54.5% in dysoxic shock, 42.3% in vasoplegic shock, 61.1% in cryptic shock minor, 60.1% in cryptic shock minor, and 42.2% in severe sepsis without lactate elevation. Subjects in cryptic shock major and cryptic shock minor were statistically more likely to be male than subjects in severe sepsis without hyperlactatemia ($p = 0.019$ and 0.002, respectively).

There were no major variations between the groups in terms of the frequencies of various comorbidities known to affect sepsis severity: alcohol abuse, cancer, and HIV/AIDS or other immunosuppressed states (including end-stage renal disease and diabetes). The frequency of liver disease in the dysoxic shock group was 22.7%, whereas the range for the other groups was 7.2-9.6%; liver disease was

Table 9. **Baseline patient characteristics by sub-group.**

Variable	Dysoxic shock (n = 22)	Vasoplegic shock (n = 52)	Cryptic shock major (n = 54)	Cryptic shock minor (n = 138)	Severe sepsis w/o lactate elev. (n = 180)
Age (years)	60.9 ± 16.8	64.9 ± 15.4	63.0 ± 17.1	64.4 ± 17.9	63.4 ± 18.2
Male gender	12 (54.5%)	22 (42.3%)	33 (61.1%)	83 (60.1%)	76 (42.2%)
Past Medical History					
Alcohol abuse	4 (18.2%)	5 (9.6%)	9 (16.7%)	14 (10.1%)	13 (7.2%)
Asthma	0 (0%)	4 (7.7%)	2 (3.7%)	5 (3.6%)	18 (10.0%)
Cancer	5 (22.7%)	6 (11.5%)	9 (16.7%)	27 (20.0%)	36 (20.0%)
Cancer with chemotherapy	3 (13.6%)	7 (13.5%)	4 (7.4%)	11 (8.0%)	16 (8.9%)
Congestive heart failure	4 (18.2%)	18 (34.6%)	9 (16.7%)	27 (20.0%)	47 (26.1%)
Coronary artery disease	0 (0%)*	14 (26.9%)	11 (20.4%)	40 (29.0%)	43 (23.9%)
Chronic altered mental status	2 (9.1%)	6 (11.5%)	6 (11.1%)	23 (16.7%)	21 (11.7%)
COPD	2 (9.1%)	13 (25.0%)	2 (3.7%)	22 (16.0%)	44 (24.4%)
CVA/TIA	4 (18.2%)	7 (13.5%)	7 (13.0%)	23 (16.7%)	29 (16.1%)
Diabetes	6 (27.3%)	21 (40.4%)	22 (40.7%)	50 (36.2%)	49 (27.2%)
End-stage renal disease	1 (4.5%)	10 (19.2%)	7 (13.0%)	15 (10.9%)	19 (10.6%)
HIV or HIV/AIDS	2 (9.1%)	6 (11.5%)	1 (2.0%)	9 (6.5%)	9 (5.0%)
Hypertension	6 (27.3%)	33 (63.5%)	27 (50.0%)	82 (59.4%)	96 (53.3%)
Immunosuppression	2 (9.1%)	4 (7.7%)	3 (5.6%)	10 (7.2%)	20 (11.1%)
Liver disease	5 (22.7%)	5 (9.6%)	5 (9.3%)	10 (7.2%)	14 (7.8%)
Residing in ECF	4 (18.2%)	16 (30.8%)	14 (26.0%)	45 (32.6%)	63 (35.0%)
Documented source of infection					
Genito-urinary	2 (9.1%)	6 (11.5%)	9 (16.7%)	25 (18.1%)	30 (16.7%)
Intra-abdominal	4 (18.2%)	8 (15.4%)	12 (22.2%)	15 (10.9%)	11 (6.1%)
Pneumonia	4 (18.2%)	13 (25%)	7 (13.0%)	43 (31.2%)	66 (36.7%)
Soft tissue	0 (0%)	4 (7.7%)	1 (2.0%)	12 (8.7%)	11 (6.1%)
Other†	1 (4.5%)	7 (13.5%)	4 (7.4%)	11 (8.0%)	12 (6.7%)
Unknown	11 (50.0%)	14 (27.0%)	21 (38.9%)	32 (23.2%)	50 (27.8%)

SD = standard deviation, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, TIA = transient ischemic attack, HIV = human immunodeficiency virus, AIDS = acquired immune deficiency syndrome, ECF = extended care facility, † e.g., line infection or central nervous system infection.
* $p < 0.05$ compared to values from all other groups.

more common in dysoxic shock subjects than in subjects with cryptic shock minor (7.2%, $p = 0.037$) and with severe sepsis without lactate elevation (7.8%, $p = 0.04$). In general, the frequencies of other comorbidities listed in Table 9 were similar between the groups, with the exceptions of coronary artery disease in dysoxic shock subjects (0.0%) and COPD in cryptic shock major (3.7%).

A genito-urinary source of infection was found in 9.1% of dysoxic shock, 11.5% in vasoplegic shock, 16.7% in cryptic shock major, 18.1% in cryptic shock minor, and 16.7% in severe sepsis subjects without lactate elevation. The rates of pneumonia as a source were 18.2%, 25.0%, 13.0%, 31.2%, and 36.7% respectively. Abdominal sources were found in 18.2%, 15.4%, 22.2%, 10.9%, and 6.1% of subjects, respectively. Soft tissue sources were rare (0-8.7%). The frequency of unknown sources of infection was 50.0% for dysoxic shock, 27.0% for vasoplegic shock, 38.9% for cryptic shock major, 23.2% for cryptic shock minor, and 27.8% for severe sepsis without lactate elevation.

Clinical features

Table 10 lists the clinical characteristics of subjects in each of the 5 classification groups. The mean number of positive SIRS criteria was similar for all groups, and the frequencies of various components of the SIRS criteria stayed roughly equal. Fever on presentation was seen in 42.6% of cryptic shock major subjects, compared to 53.8-72.7% for all other groups (all $p < 0.04$). Tachycardia was the most common positive SIRS criterion in all groups. Subjects requiring vasopressors presented with lower initial systolic, diastolic and mean arterial blood pressures than those not requiring vasopressors (all $p < 0.05$). The mean shock index (SI) of dysoxic shock subjects was 1.4±0.41 beats/min×mmHg, higher than other groups (all $p < 0.0001$). There was no difference in mean SI between vasoplegic shock and cryptic shock major groups (1.09±0.35 vs. 1.12±0.38 beats/min×mmHg, $p = 0.39$), an effect of a higher initial heart rate in cryptic shock major subjects compared to vasoplegic shock subjects (112.9±20.0 vs. 97.0±21.1 beats/min, $p = 0.0001$); these mean shock

indices were statistically different from those of cryptic shock minor and severe sepsis subjects (0.91±0.28 and 0.90±0.27 respectively, all $p < 0.001$).

There were differences in in both frequency and intensity of organ dysfunction across the classification system. The mean number of organ dysfunctions was 4.64±2.40 in dysoxic shock, 3.53±1.87 in vasoplegic shock, 3.09±1.95 in cryptic shock major, 2.46±1.77 in cryptic shock minor, and 2.49±1.27 in severe sepsis without lactate elevation. Due to the use of serum lactate as a discriminating variable between groups, hyperlactatemia was excluded as a type of organ dysfunction from these calculations. These differences were all statistically different when compared pairwise (all $p < 0.05$), with the exception of the following direct comparisons: cryptic shock major to vasoplegic shock ($p = 0.24$) and cryptic shock minor to severe sepsis without lactate elevation ($p = 0.86$). A similar trend persisted on comparison of individual types of organ dysfunction, especially among the most common such as altered mental status (AMS) and acute kidney injury (AKI). The dysoxic shock group had the highest proportion of subjects with AMS (72.3%) compared to all other groups, including vasoplegic shock subjects (40.4%, $p = 0.021$). AKI was common, occurring in 81.8% of dysoxic shock subjects, 48.1% of vasoplegic shock subjects, and 59.3% of cryptic shock major subjects. These rates of AKI were higher than those seen in cryptic shock minor and severe shock without lactate elevation (41.3%, all $p < 0.036$ and 30.0%, all $p < 0.0002$, respectively). The prevalence of acidosis, thrombocytopenia and coagulation abnormalities also followed a similar trend.

Table 10. **Clinical characteristics by sub-group.**

Variable	Dysoxic shock (n = 22)	Vasoplegic shock (n = 52)	Cryptic shock major (n = 54)	Cryptic shock minor (n = 138)	Severe sepsis w/o lactate elev. (n = 180)
SIRS criteria					
Number of positive SIRS criteria	3.00 ± 0.87	2.88 ± 0.78	2.89 ± 0.74	2.93 ± 0.78	2.86 ± 0.73
Fever	16 (72.7%)	28 (53.8%)	23 (42.6%)	85 (61.6%)	98 (54.4%)
Tachycardia	19 (86.4%)	45 (86.5%)	47 (87.0%)	122 (88.4%)	146 (81.1%)
Tachypnea	15 (68.2%)	43 (82.7%)	43 (79.6%)	107 (77.5%)	146 (81.1%)
Abnormal WBC count	16 (72.7%)	34 (65.4%)	43 (79.6%)	90 (65.2%)	121 (67.2%)
Initial vital signs					
Systolic blood pressure (SBP)	88.2 ± 24.7	93.5 ± 22.2	108.5 ± 29.4	122.2 ± 29.0	119.5 ± 27.3
Diastolic blood pressure (DBP)	47.3 ± 17.4	53.8 ± 18.6	65.4 ± 22.0	69.6 ± 18.1	65.8 ± 17.2
Mean arterial pressure (MAP)	60.9 ± 17.6	67.1 ± 18.0	79.8 ± 23.2	87.2 ± 20.2	83.7 ± 18.8
Heart rate (HR)	119.1 ± 40.5	97.0 ± 21.1	112.9 ± 20.0	105.6 ± 20.8	103.1 ± 23.4
Shock Index (HR/SBP)	1.40 ± 0.41*	1.09 ± 0.35	1.12 ± 0.38	0.91 ± 0.28	0.90 ± 0.27
Glasgow Coma Scale score[ψ]	11.68 ± 4.52	13.13 ± 3.46	13.60 ± 2.75	13.95 ± 2.45	14.05 ± 2.13
Number of organ dysfunctions[Φ]	4.64 ± 2.40*	3.53 ± 1.87	3.09 ± 1.95	2.46 ± 1.77	2.49 ± 1.27
Type of organ dysfunction					
Transient hypotension	13 (59.1%)	28 (53.8%)	20 (37.0%)	41 (29.7%)	68 (37.8%)
Hyperlactatemia	22 (100%)	28 (53.8%)	54 (100%)	138 (100%)	0 (0%)
Acidosis	15 (68.2%)	27 (51.9%)	27 (50.0%)	52 (37.7%)	78 (43.3%)
Altered mental status	16 (72.3%)*	21 (40.4%)	16 (29.6%)	38 (27.5%)	53 (29.4%)
Thrombocytopenia	7 (31.8%)	13 (25.0%)	8 (14.8%)	17 (12.3%)	22 (12.2%)
Hyperbilirubinemia	13 (59.1%)	24 (46.2%)	21 (38.9%)	50 (36.2%)	55 (30.6%)
Coagulopathy	8 (36.4%)	10 (19.2%)	13 (24.1%)	19 (13.8%)	17 (9.4%)
Acute kidney injury	18 (81.8%)	25 (48.1%)	32 (59.3%)	57 (41.3%)	54 (30.0%)*
Hypoxemia	8 (36.4%)	21 (40.4%)	9 (16.7%)	37 (26.8%)	66 (36.7%)
Troponin elevation	5 (22.7%)	16 (30.8%)	22 (40.7%)	32 (23.2%)	34 (18.9%)
MEDS score	14.05 ± 5.18	13.48 ± 4.65	10.48 ± 4.21	10.75 ± 4.55	10.89 ± 4.58
APACHE II score	26.95 ± 7.23*	21.71 ± 6.54	20.85 ± 6.89	16.89 ± 7.00	17.57 ± 6.45
Initial laboratory values					
WBC (1000 per mm^3)	10.96 ± 8.83	14.84 ± 11.51	16.78 ± 12.58	16.23 ± 18.86	13.53 ± 7.39[†]
Platelets (1000 per mm^3)[†]	189.9 ± 123.8	225.1 ± 131.9	288.1 ± 151.7	259.6 ± 120.4	276.7 ± 149.0[†]
Serum creatinine (mg/dL)	2.77 ± 1.61	2.88 ± 2.37	2.50 ± 1.96	2.22 ± 2.19	1.95 ± 1.65[‡]
Serum INR[Δ]	2.18 ± 2.46	1.76 ± 1.32	2.17 ± 3.71	1.58 ± 2.15	1.51 ± 1.35
Arterial blood gas pH[§]	7.17 ± 0.20*	7.30 ± 0.13	7.34 ± 0.18	7.40 ± 0.08	7.34 ± 0.11
Serum lactate (mmol/L)	7.82 ± 3.98*	2.08 ± 0.83*	5.99 ± 2.31*	2.79 ± 0.53*	1.22 ± 0.40*

SD = standard deviation, SIRS = systemic inflammatory response syndrome, WBC = white blood cell, INR = international normalized ratio.
* $p < 0.05$ compared to values from all other groups.

[ψ] N = 22, 52, 54, 135, 175 resp.
[†] N = 178.
[‡] N = 179.
[Δ] N = 22, 49, 52, 133, 171 resp.
[§] N = 14, 25, 21, 52, 65 resp.
[Φ] excludes hyperlactatemia, as serum lactate levels determined group placement.

Considering laboratory tests, the mean arterial pH was lower in the dysoxic shock group (7.17±0.20) compared to all others (7.30-7.40, all $p < 0.02$; see sample sizes within legend of Table 10). Mean platelet levels were low in the dysoxic shock group (189.9±123.8) in comparison to the three groups not on vasopressors (all $p < 0.02$). All groups had an elevated mean initial serum creatinine. The initial WBC counts and serum INR did not differ substantially between the groups. Finally, the mean serum lactates were 7.82±3.98 for dysoxic shock, 2.08±0.83 for vasoplegic shock, 5.99±2.31 for cryptic shock major, 2.79±0.53 for cryptic shock minor, and 1.22±0.40 for severe sepsis without lactate elevation.

Mean MEDS and APACHE II scores varied across the groups. The mean MEDS scores were 14.05±5.18 for dysoxic shock, 13.48±4.65 for vasoplegic shock, 10.48±4.21 for cryptic shock major, 10.75±4.55 for cryptic shock minor, and 10.89±4.58 for severe sepsis without lactate elevation. The mean APACHE II scores were 26.95±7.23 for dysoxic shock, 21.71±6.54 for vasoplegic shock, 20.85±6.89 for cryptic shock major, 16.89±7.00 for cryptic shock minor, and 17.57±6.45 for severe sepsis without lactate elevation.

Treatments

The frequencies of various treatments and interventions received by each group during the course of their ED stay are displayed in Table 11. Blood cultures were drawn greater than 90% of the time in all groups. Antibiotics were given in 81.8% of cases of dysoxic shock, compared to 98.1% in vasoplegic shock subjects ($p = 0.252$); all other groups had a rate above 90%. The mean time elapsed from ED

Table 11. **Emergency Department treatment characteristics by sub-group.**

Variable	Dysoxic shock (n = 22)	Vasoplegic shock (n = 52)	Cryptic shock major (n = 54)	Cryptic shock minor (n = 138)	Severe sepsis w/o lactate elev. (n = 180)
Blood cultures drawn	20 (91.0%)	51 (98.1%)	49 (90.7%)	131 (95.0%)	172 (95.6%)
Antibiotics given	18 (81.8%)	51 (98.1%)	49 (90.7%)	126 (91.3%)	166 (92.2%)
Time to antibiotics (hours)[ψ§]	1.67 ± 1.05	2.43 ± 1.86	2.34 ± 1.49	2.51 ± 1.55	3.10 ± 3.19
Total fluid volume received (L)	5.45 ± 3.73	4.31 ± 2.40	3.00 ± 1.64	2.64 ± 1.84	2.31 ± 1.78
Central line placed	20 (91.0%)	49 (94.2%)	15 (27.8%)	27 (19.6%)	39 (21.7%)
CVP measured	10 (45.5%)	31 (59.6%)	8 (14.8%)	17 (12.3%)	24 (13.3%)
Initial CVP (cmH_20)	8.0 ± 5.9	11.4 ± 5.9	6.9 ± 2.9	9.9 ± 4.5	7.0 ± 4.9
$ScvO_2$ measured	11 (50.0%)	29 (55.8%)	13 (24.1%)	19 (13.8%)	27 (15.0%)
Initial $ScvO_2$ (%)	74.6 ± 14.2	69.8 ± 13.5	67.1 ± 16.2	70.5 ± 10.8	67.2 ± 12.1
EGDT documented	5 (22.7%)	20 (38.4%)	7 (13.0%)	14 (10.1%)	23 (12.8%)
Vasopressors received	22 (100%)	52 (100%)	n/a	n/a	n/a
Number of vasopressor agents	2.3 ± 1.2	1.8 ± 0.9	n/a	n/a	n/a
Corticosteroids received[ψ]	11 (50.0%)	29 (55.8%)	11 (20.4%)	25 (18.1%)	54 (30.0%)
Dobutamine received[ψ]	4 (18.2%)	7 (13.5%)	5 (9.3%)	4 (2.9%)	3 (1.7%)
Source control obtained[ψ]	2 (9.1%)	10 (19.2%)	10 (18.5%)	30 (21.7%)	31 (17.2%)
Intubated	12 (54.5%)	17 (32.7%)	8 (14.8%)	17 (12.3%)	18 (10.0%)
ED length of stay (hours)	6.62 ± 5.27	6.79 ± 4.23	5.96 ± 3.42	6.93 ± 3.86	6.98 ± 4.38

[ψ] Includes hospital stay.
[Δ] abscess drained, line pulled, endoscopic or operative management.
[§] N = 18, 51, 49, 126, 167 resp.

presentation to receiving antibiotic therapy was shortest in the dysoxic shock group and longest in the subjects in severe sepsis without lactate elevation (1.67±1.05 vs. 3.10±3.19 hours, p = 0.0384); the other groups fell between 2-3 hours. The mean crystalloid volume received in the ED by both the dysoxic shock group (5.45±3.73 L) and vasoplegic shock group (4.31±2.40 L) was larger than the groups not on vasopressors (all $p < 0.002$). The cryptic shock major group also received a larger crystalloid volume than subjects in severe sepsis without lactate elevation (3.00±1.64 L vs. 2.31±1.78 L, p = 0.0117). The proportion of subjects whose care involved infectious source control (including drainage of abscesses, pulling infected lines, or obtaining endoscopic or operative control of infectious sources) was below

25% in all subject groups without differences between groups. The mean length of stay in the ED was 5.96-6.98 hours for all groups, and no differences were found between the mean lengths of stay.

Central venous catheters were placed in many patients in order to provide therapies (fluids, vasopressors) as well as monitor the hemodynamic status of the subjects. Almost all of the subjects presenting in vasopressor-dependent shock (91% of dysoxic shock subjects and 94.2% of vasoplegic shock subjects) had a central line placed in the ED: more frequently than the subjects in cryptic shock major, cryptic shock minor and severe sepsis without lactate elevation (27.8%, 19.6%, and 21.7% respectively, all $p < 0.0001$). The 5 patients in vasopressor-dependent shock who did not have a central line placed received vasopressors via a peripheral line.

Using the mention of early goal-directed therapy (EGDT) in charted documentation as evidence of the intention to follow an EGDT-based protocol, we found that among the groups on vasopressors, 22.7% of dysoxic shock subjects and 38.4% of vasoplegic shock groups had EGDT documentation. When combined, the rate of EGDT documentation was higher in the vasopressor-dependent shock subjects compared to the cryptic shock major group (33.8% vs. 13.0%, $p = 0.0076$). Of those subjects who had central venous catheters in the ED, more than half had both CVP and $ScvO_2$ measured at least once. However, there were no differences between groups in terms of whether CVP or $ScvO_2$ was measured, as well as no differences between the mean initial CVP or $ScvO_2$ values. The dysoxic shock group had a mean initial $ScvO_2$ of 74.6±14.2 ($n = 11$), and the vasoplegic shock group had a

mean of 69.8±13.5 (n = 29, p = 0.33); however, the proportion of patients initially below the ScvO2 goal of 70% in each group (45.4% and 54.8%, respectively, p = 0.73) was roughly equal. Subjects in the cryptic shock major group whose $Scv0_2$ was measured were very likely to be below goal $ScvO_2$ (69.2%, n = 13) and averaged a low initial $ScvO_2$ mean (mean saturation of 67.1%).

By definition, 100% of the dysoxic and vasoplegic shock groups received vasopressor therapy in the ED, whereas none of the other subjects did. 16 of 22 (73%) subjects in the dysoxic shock group and 26 of 52 (50%) of the vasoplegic group were on multiple vasopressor agents during their hospital stay (p = 0.08). The mean number of vasopressor agents used in the dysoxic shock group was 2.3±1.2, compared to 1.8±0.9 in the vasoplegic group (p = 0.052). Rates of intubation in the ED were higher in the dysoxic shock (54.5%) and vasoplegic shock (32.7%) groups than in the groups not on vasopressors (all p < 0.04), all of which had an intubation rate less than 15%.

Corticosteroids were commonly administered in both dysoxic shock (50%) and vasoplegic shock (55.8%) and were more likely to be administered to these subjects compared to those not requiring vasopressors (p < 0.0001); a minority of subjects not requiring vasopressors still received corticosteroids (18.1-30%). The prevalence of dobutamine administration in both the dysoxic shock (18.2%) and vasoplegic shock groups (13.5%) was higher than in the cryptic shock minor and severe sepsis without lactate elevation groups (p < 0.003), but not statistically different from its prevalence in the treatment of cryptic shock major (9.3%).

Hospital outcomes

The clinical outcomes of the classification groups are displayed in Table 12. All subjects were admitted to the hospital, as this was an inclusion criterion for the registry. The majority of subjects in all groups were admitted to acute or subacute care units (ICU, step-down unit, or operating room) from the ED. All dysoxic shock and vasoplegic shock subjects were admitted to an ICU, although two dysoxic shock subjects died before transfer to the ICU; 83.3% of cryptic shock major subjects were admitted to the ICU. In contrast, only 47.1% of cryptic shock minor subjects and 45.6% of severe sepsis subjects without lactate elevation were admitted to an ICU. Compared to the group in severe sepsis without lactate elevation, the odds ratios

Table 12. **Mortality and hospital outcomes by sub-group.**

Variable	Dysoxic shock (n = 22)	Vasoplegic shock (n = 52)	Cryptic shock major (n = 54)	Cryptic shock minor (n = 138)	Severe sepsis w/o lactate elev. (n = 180)
Hospitalization outcomes					
Disposition from ED					
ICU	20 (90.9%)[Δ]	52 (100%)	45 (83.3%)	65 (47.1%)	82 (45.6%)
Step-down unit	0 (0%)	0 (0%)	2 (3.7%)	9 (6.5%)	8 (4.4%)
Floor	0 (0%)	0 (0%)	6 (11.1%)	59 (42.8%)	87 (48.3%)
OR	0 (0%)	0 (0%)	1 (1.9%)	5 (3.6%)	3 (1.7%)
On mechanical ventilation	14 (63.6%)	27 (51.9%)	22 (40.7%)	36 (26.1%)	40 (22.2%)
Vasopressor use	22 (100%)	52 (100%)	16 (29.6%)	24 (17.4%)	19 (10.6%)
Early (within 72 hours)	22 (100%)	52 (100%)	16 (29.6%)*	17 (12.3%)	16 (8.9%)
Delayed (after 72 hours)	0 (0%)	0 (0%)	0 (0%)	7 (5.1%)	3 (1.7%)
Mortality					
28-day mortality	11 (50.0%)*	11 (21.1%)	10 (18.5%)	17 (12.3%)	13 (7.2%)

[Δ]2 patients died before transfer to ICU.
* $p < 0.05$ compared to values from all other groups.

for admission to an acute or subacute care unit was 42.1 (2.5-704.8, $p < 0.0001$) for the dysoxic shock group, 98.3 (6.0-1616.3, $p < 0.0001$) for the vasoplegic shock group, and 7.5 (3.0-18.4 $p < 0.0001$) for the cryptic shock major group. The rate of admission to acute/subacute care did not differ between cryptic shock minor and severe sepsis without lactate elevation.

The use of mechanical ventilation during the hospital course was very common among all groups, and followed a stepwise trend: 63.6% in dysoxic shock, 51.9% in vasoplegic shock, 40.7% in cryptic shock major, 26.1% in cryptic shock minor, and 22.2% severe sepsis without lactate elevation. Compared to severe sepsis without lactate elevation, the odds ratios for requiring mechanical ventilation were 6.1 (2.4-15.6, $p = 0.0001$) for dysoxic shock, 3.8 (2.0-7.2, $p < 0.0001$) for vasoplegic shock, 2.4 (1.3-4.6, $p = 0.0087$) for cryptic shock major, and 1.2 (0.7-2.1, $p = 0.43$) for cryptic shock minor. All subjects in the dysoxic and vasoplegic shock group continued on vasopressors at least during the proximal phase of their admission to the hospital. Additionally, 29.6% of cryptic shock major subjects required vasopressor therapy during the first 72 hours of their hospitalization, compared to 12.3% in cryptic shock minor (OR 3.0 (1.4-6.5), $p = 0.0095$) and 8.9% in severe sepsis without lactate elevation (OR 4.3 (2.0-9.4), $p = 0.0008$). Of the 133 subjects on vasopressor therapy during their hospital stay, 10 (7.5%) were started on vasopressors more than 72 hours after admission, and these subjects were exclusively found in the categories of cryptic shock minor and severe sepsis without lactate elevation.

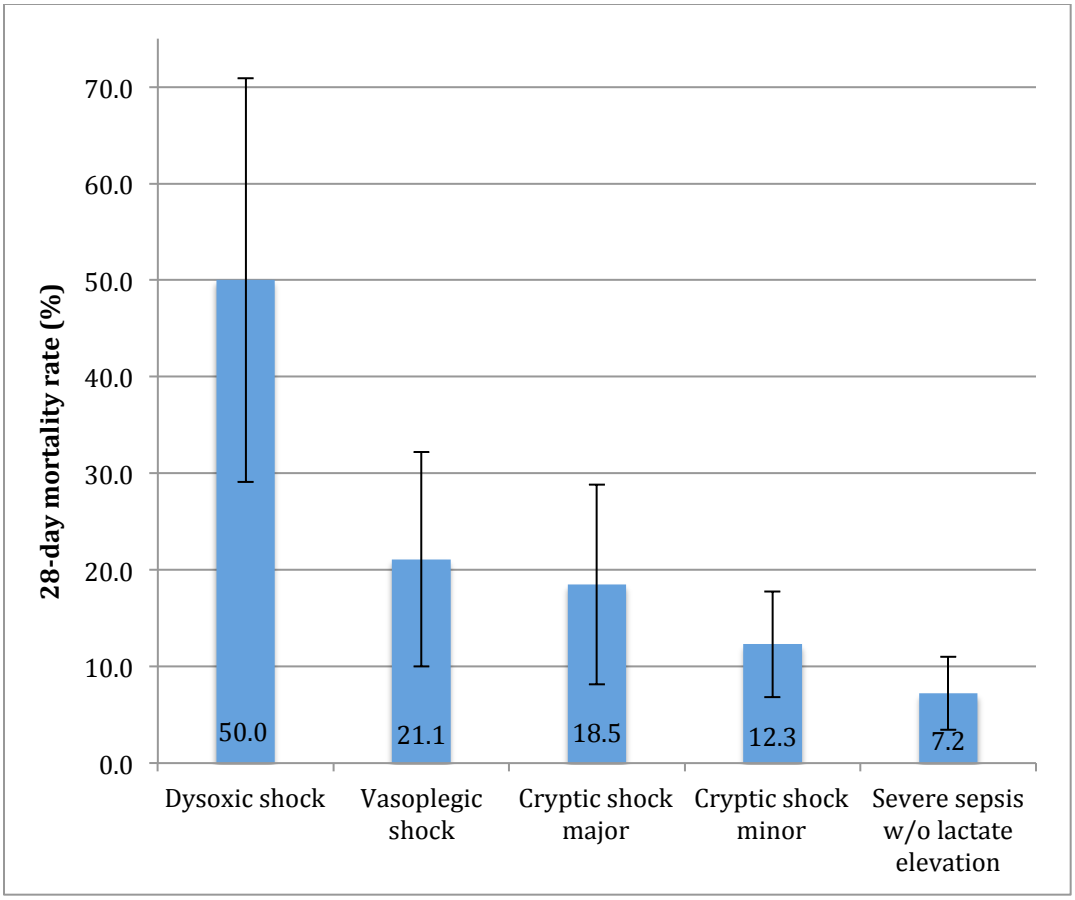

Figure 3. **Mortality rate at 28 days.**
Error bars represent 95% confidence intervals.

In the univariate analysis, the 28-day in-hospital mortality rates decreased in a stepwise fashion: 50.0% in dysoxic shock, 21.1% in vasoplegic shock, 18.5% in cryptic shock major, 12.3% in cryptic shock minor, and 7.2% in severe sepsis without lactate elevation. 28-day mortality was predicted by both ED vasopressor use (OR 3.5 (1.9-6.4), $p < 0.0001$) and an initial lactate greater than 4 mmol/L (OR 3.1 (1.7-5.6), $p = 0.0003$). On comparing groups pairwise, mortality in the dysoxic shock group was higher compared to groups in vasoplegic shock (OR 3.7, 1.3-10.9, $p = 0.0243$), cryptic shock major (OR 4.4, 1.5-13.0, $p = 0.0098$), cryptic shock minor (OR 7.1, 2.7-18.9, $p = 0.0001$), and severe sepsis without lactate elevation (12.9, 4.7-

35.2, p < 0.0001). The mortality rates in vasoplegic shock and cryptic shock major subjects were higher than those in severe sepsis without lactate elevation, with odds ratios of 3.5 (1.4-8.3, p = 0.0078) and 2.9 (1.2-7.1, p = 0.0201) respectively. However, despite a downward trend in mortality rates, no conclusive differences in these rates were found between vasoplegic shock and cryptic shock major (p = 0.81), between cryptic shock major and minor (p = 0.3551), and between cryptic shock minor and severe sepsis without lactate elevation (p = 0.1746).

Multivariate analysis was performed using a logistic regression model that controlled for known clinical correlates of increased sepsis severity. The dependent variable was 28-day mortality, the primary outcome of this study. Results of this analysis are shown in Table 13. Compared against the group in severe sepsis without lactate elevation, the odds ratios (ORs) for death before 28 days were 15.055 (4.997 - 45.354, p = < 0.0001) for dysoxic shock, 3.606 (1.435 - 9.063, p = 0.0064) for vasoplegic shock, 3.771 (1.458 – 9.756, p = 0.0062) for cryptic shock major, and 1.929 (0.875 - 4.255, p = 0.1035) for cryptic shock minor. When compared directly against the vasoplegic shock group, the dysoxic shock group had a 28-day mortality OR of 4.175 (1.291 – 13.508, p = 0.0002). Two covariates were predictive of increased risk of death before 28 days: every additional year of age demonstrated an increased OR of 1.021 (1.001 – 1.041, p = 0.0394), and a previous diagnosis of cancer carried an OR of 2.467 (1.316 – 4.627, p = 0.0049). A single covariate, genitourinary source of infection, was predictive of decreased risk of death before 28 days (OR 0.329, 0.117-0.921, p = 0.0343).

Table 13. **Multivariate analysis of 28-day mortality.**

	Odds Ratio (OR)	OR Confidence Intervals	p value
Comparison of groups			
Dysoxic shock	15.055*	4.997 - 45.354	< 0.0001
Vasoplegic shock	3.606*	1.435 - 9.063	0.0064
Cryptic shock major	3.771*	1.458 – 9.756	0.0062
Cryptic shock minor	1.929	0.875 - 4.255	0.1035
Parameters			
Female gender	0.996	0.544 - 1.824	0.9896
Age	1.021*	1.001 - 1.041	0.0394
Source of infection			
Pneumonia	0.981	0.493 - 1.952	0.9558
Genitourinary	0.329*	0.117 - 0.921	0.0343
Abdominal	0.503	0.182 - 1.39	0.1855
Skin/soft tissue	0.559	0.12 - 2.6	0.4585
Comorbid conditions			
Liver disease	1.187	0.417 – 3.381	0.7483
End-stage renal disease	1.009	0.374 – 2.726	0.9854
Alcohol abuse	0.579	0.175 – 1.916	0.3709
Diabetes mellitus	0.878	0.458 – 1.684	0.696
HIV/AIDS	2.923	0.888 – 9.2622	0.0776
Cancer	2.467*	1.316 – 4.627	0.0049
Immunocompromised (NOS)	0.971	0.308 – 3.06	0.9602

Reference group: "Severe sepsis without lactate elevation."
* Significant at $p < 0.05$.
NOS = Not otherwise specified.

Outcomes for exploratory groups

In addition to the primary analyses described above, we undertook an exploratory analysis of other sepsis groups who we believed were likely to be at high risk of poor outcomes. The first group was those subjects requiring more than one vasopressor agent within the ED, which we categorized as "severe shock;" this included 42 subjects from both the dysoxic and vasoplegic shock groups. The 28-day mortality of the severe shock group was 33.3%, compared to 25.0% in subjects who required a single vasopressor agent ($p = 0.61$). The severe shock subjects had a

mean number of organ dysfunctions of 4.98±2.25 (including hyperlactatemia), the mean MEDS score was 24.43±6.70, and the mean APACHE II score was 13.19±4.93. 64.3% of severe shock subjects were mechanically ventilated during their hospital stay. 59.5% (n=25) of severe shock subjects had an initial lactate >4.0 mmol/L, whereas 40.5% (n=17) had lactates ≤4.0 mmol/L.

We also analyzed the outcomes of subjects presenting in "hemodynamic extremis," i.e. with an initial systolic blood pressure in the ED of less than 70 mmHg. There were 23 subjects who presented in hemodynamic extremis; the mean presenting systolic blood pressure was 61.9±7.0 mmHg. The mean initial lactate was 4.46±3.76 mmol/L; 11 (47.8%) had an initial lactate >4 mmol/L, whereas the remaining 12 (52.2%) were initially ≤4 mmol/L. The mean APACHE II and MEDS scores for these subjects were 23.39±5.88 and 12.04±4.25, respectively, and the mean number of organ dysfunctions was 4.13±2.07 (including hyperlactatemia) Of these 23 subjects, 11 (47.8%) required vasopressors in the ED, and 15 (65.2%) received vasopressors within the first 72 hours of admission. The rate of intubation in the ED was 21.7%, and 43.5% required mechanical ventilation during their hospital stay. 17 (81.0%) subjects were admitted to an ICU. Lastly, the 28-day mortality rate for subjects presenting in hemodynamic extremis was 21.7%.

Discussion

To our knowledge, this is the first study to evaluate a novel classification scheme across the entire spectrum of severe sepsis and septic shock. To this end, we utilized two simple and readily-available measures, initial lactate level on ED presentation and ED vasopressor utilization, to risk-stratify patients at the hyperacute phase of care. Our aims were to describe the incidence and outcomes for the these classification groups, as well as other novel exploratory subgroups, with the intent of improving the ability of proximal phase providers to identify illness severity and risk-stratify patients.

In our primary analysis, we found that 28-day mortality differed substantially between groups; the differences persisted after adjusting for known covariates of sepsis severity, driven by strong independent yet additive risks associated with both elevated initial lactates and ED-based vasopressor utilization. Related and significant differences in other outcome measures between these groups, such as measures of critical care utilization, corroborated the primary outcome. Where our results overlap with previous studies, our data generally support current understanding of the heterogeneity of outcomes within the traditional sepsis classification system.

Our proposed classification system offers benefits to the emergency provider in that it utilizes simple metrics, generally available within the first two hours after presentation, to prognosticate in-hospital mortality in patients with severe sepsis or septic shock. Our system could aid these providers in making important triage and

disposition decisions, such as implementation of early goal-directed therapy. This is a timely result given the recent publication of randomized control trials of protocolized and early goal-directed therapy [10, 11]. Despite demonstrating a lack of superiority for protocolized and EGDT-based care over usual care in severe sepsis and septic shock, these trials nevertheless leave open the question of whether certain subgroups could potentially benefit from an early hemodynamic monitoring and optimization approach. Without a firm answer to this question, clinicians who are wary of employing EGDT indiscriminately will be searching for a method to judiciously choose patients for these protocols. The classification system evaluated in this study may help to categorize patients for whom invasive monitoring should be considered, and could inform the design of future trials of EGDT.

Table 14. **Key outcomes by group.**

Variable	Severe shock (n = 42)	Hemo-dynamic extremis (n = 23)	Dysoxic shock (n = 22)	Vasoplegic shock (n = 52)	Cryptic shock major (n = 54)	Cryptic shock minor (n = 138)	Severe sepsis w/o lactate elev. (n = 180)
Incidence (% of full registry)							
	9.4%	5.2%	4.9%	11.7%	12.1%	30.9%	40.4%
Primary outcome							
28-day mortality	14 (33.3%)	5 (21.7%)	11 (50.0%)	11 (21.1%)	10 (18.5%)	17 (12.3%)	13 (7.2%)
Secondary outcomes							
Mechanical ventilation	27 (64.3%)	10 (43.5%)	14 (63.6%)	27 (51.9%)	22 (40.7%)	36 (26.1%)	40 (22.2%)
Hospital vasopressor use	42 (100%) ϕ	15 (65.2%)	22 (100%) ϕ	52 (100%) ϕ	16 (29.6%)	24 (17.4%)	19 (10.6%)
ICU admission	40 (95.2%)Δ	17 (81.0%)	20 (90.9%)Δ	52 (100%)	45 (83.3%)	65 (47.1%)	82 (45.6%)
Number of organ dysfunctions*	4.17 ± 2.12	3.30 ± 2.08	4.64 ± 2.40	3.53 ± 1.87	3.09 ± 1.95	2.46 ± 1.77	2.49 ± 1.27
Mean APACHE II score	24.43 ± 6.70	23.39 ± 5.88	26.95 ± 7.23	21.71 ± 6.54	20.85 ± 6.89	16.89 ± 7.00	17.57 ± 6.45
Mean MEDS score	13.19 ± 4.93	12.04 ± 4.25	14.05 ± 5.18	13.48 ± 4.65	10.48 ± 4.21	10.75 ± 4.55	10.89 ± 4.58

Δ 2 patients died before transfer to ICU, ϕ Required by group definition, * Excludes hyperlactatemia.

The primary outcome of our study was 28-day mortality. In the univariate analysis, there was a dramatic and stepwise decrease in mortality over the classification system: 50% in dysoxic shock, 21.1% in vasoplegic shock, 18% in the cryptic shock major, 12.3% in cryptic shock minor, and 7.2% in severe sepsis without hyperlactatemia. When controlled for age, source of infection, and certain comorbidities in the multivariate analysis, the calculated odd ratios for 28-day mortality were 15.055 (4.997-45.354) for dysoxic shock, 3.606 (1.435-9.063) for vasoplegic shock, 3.771 (1.458–9.756) for cryptic shock major, and 1.929 (0.875-4.255) for cryptic shock minor. The group in severe sepsis without lactate elevation was used as the reference group for these calculations. The multivariate results reinforce the mortality trend seen in the univariate analysis and underscore the strength of both early vasopressor use and high lactate levels as risk factors in this patient population. There was also a trend towards an increased risk in cryptic shock minor over severe sepsis without lactate elevation, although this did not reach significance ($p = 0.1035$).

The trends in other severity indices, such as mean number of organ dysfunctions, the mean APACHE II score, and the rates of mechanical ventilation, roughly tracked with the 28-day mortality rates seen in the groups. By contrast, the only significant differences in mean MEDS scores occurred between vasopressor-dependent subjects and normotensive subjects. Most likely, this is purely a result of the MEDS score criterion "septic shock," which confers an additional 3 points to the score of each subject in the vasoplegic and dysoxic shock groups.

There was a significant difference in gender distribution between the groups; men formed 54.5% of vasoplegic shock, 42.3% of vasoplegic shock, 61.1% of cryptic shock major, 60.1% of cryptic shock minor, and 42.2% of severe sepsis subjects without lactate elevation. As these results show, the groups with hyperlactatemia have a higher proportion of men. In our registry, men also had a slightly higher mean initial lactate level than women (2.94±2.30 vs 2.48±2.22, p = 0.0315), although gender was not found to be significantly associated with 28-day mortality rates in the multivariate analysis. It is possible that men present with a worse degree of tissue hypoperfusion, produce more lactate constitutively (perhaps because of greater muscle mass) or fail to metabolize lactate as efficiently. However, another trial of 1,814 hospitalized patients, looking at disparities between sepsis treatment between men and women, found no differences in serum lactate measurements between men and women [132]. The possibility of a gender disparity in lactate production or clearance warrants further study.

A few differences were apparent in source of infection between groups on univariate analysis. Subjects in severe sepsis without lactate elevation were less likely to have an abdominal source of infection than the rest of included subjects (6.1% vs. 14.7%, p = 0.006), possibly since certain intra-abdominal sources are associated with poorer outcomes [51]. Pneumonia as a septic source was less common in cryptic shock major than cryptic shock minor (13.0% vs 31.2%, p = 0.01) or severe sepsis without lactate elevation (13.0% vs 36.7%, p = 0.001); given that pulmonary sources often increase risk of sepsis severity, this is a surprising

finding that merits scrutiny. Pneumonia as a source of infection was not found to be associated with increased mortality risk in our logistic regression analysis.

However, three other covariates of the multivariate analysis were found to be significantly associated with outcomes. Two were correlated with increased risk of death before 28 days: increasing age (with an OR of 1.021 per extra year), and previous history of cancer (OR of 2.467). Both of these results conform to the known risks of advanced age and underlying cancer diagnosis on sepsis severity [3, 31, 36]. The only covariate which correlated with a decreased risk of death before 28 days was the presence of a genitourinary source of infection (OR 0.329); this is in keeping with literature showing that urosepsis is less deadly than other forms of sepsis [50].

Comparing dysoxic and vasoplegic shock

In our study, the differences between the two categories of vasopressor-dependent septic shock (dysoxic shock and vasoplegic shock) were particularly striking. Vasoplegic shock was more common than dysoxic shock in our study subjects (52 vs. 22, an incidence ratio of 2.4 to 1). In the univariate analysis, 28-day mortality was much higher in dysoxic shock than in vasoplegic shock (50% vs. 21%, $p = 0.0243$), and this difference was maintained in the multivariate analysis (OR 4.175, 1.291-13.508, $p = 0.0002$). The difference in severity was also apparent when comparing other markers of increased risk; the dysoxic shock subjects had a higher shock index (1.4 ± 0.41 vs. 1.09 ± 0.35, $p < 0.0001$), mean number of organ dysfunctions (4.64 ± 2.40 vs. 3.53 ± 1.87, $p = 0.0357$), and mean APACHE II scores (26.95 ± 7.23 vs. 21.71 ± 6.54, $p = 0.0032$) at first presentation. The rates of

intubation in the ED and mechanical ventilation in the hospital were also higher in the dysoxic shock group, although these differences did not reach statistical significance. On the other hand, the initial mean MEDS scores were roughly the same between the two groups.

Interestingly, there is some discrepancy between the use of vasopressors in dysoxic and vasoplegic shock. Dysoxic shock patients showed a trend towards requiring more vasopressor therapy in the ED; they had a higher mean number of agents started (2.3±1.2 vs. 1.8±0.9, p = 0.0524) and were more likely than vasoplegic shock patients to be on multiple vasopressors (72.7% vs. 48.1%, p = 0.0734), although these trends were not significant. These data support the notion that dysoxic shock patients are less likely to have their blood pressure controlled with one vasopressor agent; ED clinicians may need to have a low threshold for adding a second agent in shock patients with high lactates, if MAP does not quickly improve after the start of the first agent.

Our results concerning disease severity are in line with other studies that have compared septic shock patients with high and low lactates; however, some of the thresholds of lactate used in these studies differed. Dugas et al. divided 123 vasopressor-dependent septic shock patients into three categories: non-lactate expressors (initial lactate <2.5 mmol/L), low lactate expressors (2.5-4.0) and high lactate expressors (>4.0) [133]. The first two categories, when combined, are consistent with our vasoplegic shock group, whereas the last is synonymous with our dysoxic shock group. The mortality rates for non-lactate, low lactate, and high lactate expressors were 20%, 29% and 43%, respectively, although the differences

were not significant. Similarly, in their shock subgroup of 196 subjects, Mikkelsen et al. found that a high lactate level (>4.0 mmol/L) and an intermediate lactate level (2.0-4.0 mmol/L) both correlated with mortality (OR 4.87 and 3.27, respectively) when compared to overt septic shock patients with lactate levels below 2 mmol/L [75]. Supporting these observed trends, a much larger study by Howell et al. classifying 1,200 hospitalized septic patients by initial lactate (<2.5, 2.5-4.0, and >4.0 mmol/L) found that lactate levels continued to predict 28-day mortality even after stratification by initial blood pressures [124].

Other studies have used lower lactate thresholds to subdivide vasoplegic from dysoxic shock patients. Sterling et al. stratified overt shock patients in the ED by a threshold lactate level of 2.0 mmol/L; in-hospital mortality in their "tissue dysoxic shock" was significantly higher than in their "vasoplegic shock" group (26% vs. 9%, respectively) [126]. As a result of using a lower lactate threshold, their "tissue dysoxic shock" group substantially outnumbered their "vasoplegic shock" group (157 vs. 90 patients, respectively). Likewise, in two back-to-back studies, Hernandez et al. similarly compared ICU overt shock patients with pre-ICU low and high initial lactates, using the lactate threshold of 2.5 mmol/L [125, 127]. The mortality rates of their 2011 and 2012 cohorts of "overt shock without hyperlactatemia" were remarkably consistent (7.7% vs. 7.9%, respectively); however, the mortality rates for the cohorts of "overt shock with hyperlactatemia" differed substantially (42.9% vs. 20.9%, respectively). It is apparent that as a result of choosing a much lower threshold for lactate levels, "dysoxic shock" in these studies was both more common and less deadly than in our dysoxic shock group;

the reverse trends are true when comparing their "vasoplegic shock" cohorts with our vasoplegic shock group. Furthermore, these three studies did not use vasopressor dependence as a criterion for shock.

In sum, while definitions of lactate categories (high, intermediate, low) and the presenting disposition (hospitalized vs. emergency department) differ somewhat between studies, it seems that there is a consistent and reproducible trend between high lactates and mortality in overt septic shock patients. The most appropriate threshold for the initial lactate for risk-stratification purposes remains unknown. In practice, stratification of patients into dysoxic and vasoplegic shock will not change treatment patterns or disposition decisions, as all overt shock patients should and will receive aggressive therapy to maintain blood pressure and will all be admitted to an intensive care unit. However, an understanding of the increased severity of dysoxic shock could help to inform prognostic discussions with family members and decisions regarding goals of care. Furthermore, the dramatic severity of dysoxic shock at initial presentation begs the question of whether this subgroup could conceivably benefit from early, invasive hemodynamic monitoring and optimization along the lines of EGDT. Although this question would be best answered through a randomized clinical trial, post-hoc subgroup analyses of the ProCESS and ARISE trials, based on the definitions of vasoplegic and dysoxic shock, could conceivably yield interesting results.

Comparing cryptic shock to vasopressor-dependent shock

There were 54 subjects defined as having cryptic shock, a similar number to the vasoplegic shock group (52 subjects) and more than twice the number of the

dysoxic shock group (22 subjects). Of the entire registry, the cryptic shock major group made up 12.1%. This incidence is consistent with other studies looking at cryptic shock major. In a post-hoc analysis of the original EGDT trial in 2001, there were 48 subjects classified as being in "cryptic shock" (severe sepsis with normotension and a lactate > 4mmol/L) of a total population of 263 (18.3%) [117]. Similarly, in a study incorporating hospital and ED-based patients in severe sepsis and septic shock, Ranzani et al. found a cryptic shock prevalence of 12% [128]. It seems from our data and others' that cryptic shock is only slightly less common than overt septic shock but far less common than other types of severe sepsis with a normal blood pressure. In a large database of over 15,000 patients in severe sepsis and septic shock, created by the Surviving Sepsis Campaign, cryptic shock patients made up just 5.4% of patients, compared vasopressor-dependent patients with lactate less than 4.0 mmol/L (49.5%) and with lactate greater than 4.0 mmol/L (16.6%) [116]. It is important to note, however, that these data should not be taken as accurate measurements of incidence; the database was open to submission from over 100 centers and was significantly weighted towards vasopressor-dependent patients (making up 71.5% of the database subjects).

The mortality rate of cryptic shock major in our study was 18.5%, considerably lower than in the dysoxic shock group (50%, $p = 0.0098$) but not statistically different from the vasoplegic shock mortality (21.1%, $p = 0.81$); these differences persisted when controlling for other severity predictors in the multivariate analysis. Among the secondary outcomes, the similarity in outcomes between vasoplegic shock and cryptic shock major is striking; these two groups had

roughly comparable mean number of organ dysfunctions (3.53±1.87 vs. 3.09±1.95, p = 0.24), mean APACHE II scores (21.71±6.54 vs. 20.85±6.89, p = 0.51), and the need for mechanical ventilation (51.9% vs. 40.7%, p = 0.33). However, the rate of ED intubation was higher in vasoplegic shock than cryptic shock major (32.7% vs. 14.8%, p = 0.0396). The mean MEDS scores were also significantly different (13.48±4.65 vs. 10.48±4.21, p = 0.0007), but this is clearly a result of a single criterion difference (3 points for "septic shock") that discriminates between the groups by definition. It is interesting to note that of the 54 subjects who presented in cryptic shock major, 16 (or 29.6%) required vasopressors during the first 72 hours of hospitalization; the mortality rate of these subjects was 43.8%, whereas the mortality rate in those not treated with in-hospital vasopressor therapy was 5.6% (p = 0.0016). No cryptic shock major subjects began vasopressors after 72 hours of hospitalization. These data support the notion that patients in cryptic shock major should be admitted to a high level of care, as indeed were most of our subjects (83.3% to ICU care).

These data are consistent with other studies that have compared cryptic shock to overt septic shock. In the large database described above, Levy et al. found that cryptic shock major had a mortality rate of 29.9%, comparable to the mortality rate of vasopressor-dependent patients with lactates below 4 mmol/L (36.7%) and slightly lower than vasopressor-dependent patients with lactates greater than 4mmol/L (46.1%) [116]. Puskarich et al. treated 300 cryptic shock and overt shock patients presenting to the ED with protocol-based sepsis resuscitation [118]. The in-hospital mortality of the cryptic shock group was 20% and the mortality of the

overt shock group was 19%; the mean lactate level of the overt shock group was 2.6 mmol/L, suggesting that most of these patients would have been categorized as "vasoplegic shock" in our classification scheme.

In a more recent study, Hwang et al. compared outcomes in patients presenting to an ED with cryptic shock, overt shock (define by persistent hypotension despite fluid resuscitation), and cryptic-to-overt shock (cryptic shock which progressed to overt shock within 72 hours) [120]. There were 187, 247, and 157 patients in these groups, respectively; their database contained a high proportion of patients presenting initially in cryptic shock compared to overt shock (58% vs. 42%). 80% of the subjects in the cryptic-to-overt shock group required vasopressors within the first 24 hours, and the mortality rates for cryptic shock, overt shock, and cryptic-to-overt shock were 7.0%, 21.9%, and 27.4%, respectively.

Table 15. **Existing studies on cryptic shock major and minor.**

	Author	Size of study	Incidence	Mortality rate
Cryptic shock major				
	Current study	54 subjects	12.1%	18.5%
	Donnino et al.	48 subjects	18.3%	39.6%
	Ranzani et al.	162 subjects	8.3%	35.2%
	Levy et al.	811 subjects	5.4%	29.9%
	Puskarich et al. *	53 subjects	17.7%	20.0%
	Huang et al. *	344 subjects	58.2%	16.3%
Cryptic shock minor				
	Current study	138 subjects	30.9%	12.3%
	Tang et al.	535 subjects	n/a$^{\Delta}$	1.1%
	Song et al.	474 subjects	n/a$^{\Delta}$	10.1%

* Studies only included septic shock and cryptic shock subjects.
$^{\Delta}$ Studies did not include other types of shock.

These results are in keeping with our data, demonstrating that cryptic shock patients represent a subgroup not only with similarly poor outcomes as overt shock, but also with high potential for developing overt shock in the early stages of hospitalization.

Despite the similarities in outcomes between cryptic shock major and types of overt shock, our data hint at differences in treatment. Cryptic shock major subjects were much less likely than vasoplegic shock patients to receive a central line placement (27.8% vs. 94.2%, $p < 0.0001$) or have EGDT documented in their chart (13.4% vs. 38.0%, $p = 0.0035$). In keeping with these results, Mikkelsen et al. similarly found that subjects meeting the lactate criterion rather than the hemodynamic criterion for EGDT resuscitation were much less likely to receive EGDT management [119]. Cryptic shock major subjects received a lower volume of crystalloid during their ED stay, which is to be expected given their stable hemodynamics (3.0±1.64L vs. 4.3±2.40L, $p = 0.0014$). The mean time to antibiotics and mean ED length-of-stay were not statistically different.

However, while every single vasoplegic shock patient was admitted to the ICU, only 83.3% of cryptic shock major patients were directly admitted to the ICU; 11.1% were sent to a floor bed from the ED. These data suggest that patients presenting in cryptic shock major are not considered by ED clinicians to be as sick as patients with refractory hypotension requiring vasopressors, despite similarly poor outcomes over the hospital stay. Given the relationships between dysoxic, vasoplegic, and cryptic shock major groups in terms of 28-day mortality, it is imperative for ED clinicians to consider both vasopressor dependence and initial

lactate greater than 4 mmol/L as equivalent risk factors for a poor outcome in the hospital.

Comparing non-vasopressor dependent subjects

We subdivided non-vasopressor-dependent subjects into three groups: cryptic shock major (lactate >4mmol/L), cryptic shock minor (lactate 2-4 mmol/L), and severe sepsis without lactate elevation (lactate <2mmol/L). Cryptic shock major was much less common than cryptic shock minor and severe sepsis without lactate elevation (54 vs. 138 vs. 180 subjects, respectively). The mortality rates of these three groups were 18.5%, 12.3%, and 7.2%; while demonstrating a clear trend, the difference was statistically significant only between cryptic shock major subjects and severe sepsis subjects without lactate elevation ($p = 0.02$). Of 372 non-vasopressor dependent subjects, 49 (13.2%) were started on vasopressors within 72 hours, and only 10 (2.7%) were started on vasopressors after 72 hours of admission. These data support the use of the 72-hour threshold used by other investigators [120, 122, 134] to capture the majority of hemodynamically-stable septic patients who decompensate during their hospital stay.

Comparing cryptic shock major to cryptic shock minor revealed significant differences in secondary outcomes. Cryptic shock major subjects were much more likely than cryptic shock minor subjects to be admitted to the ICU (83.3% vs. 47.1%, $p < 0.0001$), as well as having a higher mean number of organ dysfunctions (3.09±1.95 vs. 2.46±1.77, $p = 0.0325$), a higher rate of AKI (59.3% vs. 41.3%, $p = 0.0359$), a higher rate of troponin elevation (40.7% vs. 23.2%, $p = 0.0201$), and a higher mean APACHE II score (20.85±6.89 vs. 16.89±7.00, $p = 0.0005$). However,

mean MEDS scores were not different between the two groups (10.48±4.21 vs. 10.75±4.55, p = 0.71). In terms of critical care utilization, cryptic shock major subjects were more likely to receive vasopressors within 72 hours (29.6% vs. 12.3%, p = 0.0095) and trended towards a higher rate of mechanical ventilation during the hospital stay (40.7% vs. 26.1%, p = 0.0553) than their counterparts in cryptic shock minor.

The differences between cryptic shock major and severe sepsis without lactate elevation were even starker. The 28-day mortality rate was significantly higher in cryptic shock major than in severe sepsis without lactate elevation (18.5% vs. 7.2%, p = 0.0201); the cryptic shock major group also had a higher mean number of organ dysfunctions (3.09±1.95 vs. 2.49±1.27, p < 0.0001), rate of AKI (59.3% vs. 30.0%, p = 0.0002), mean APACHE II score (20.85±6.89 vs. 17.57±6.45, p = 0.0014), rate of ICU admission (83.3% vs. 45.6%, p < 0.0001), rate of vasopressor use within 72 hours (29.6% vs. 8.9%, p = 0.0008), and rate of mechanical ventilation (40.7% vs. 22.2%, p = 0.0087). Cryptic shock major subjects received more fluid resuscitation in the ED (3.00±1.64L vs. 2.31±1.78L, p = 0.0117) and were more likely to receive dobutamine (9.3% vs. 1.7%, p = 0.0176) than subjects in severe sepsis without lactate elevation.

Interestingly, there were even differences in initial vital signs between cryptic shock major subjects and the other non-vasopressor dependent groups. Cryptic shock major subjects had a lower initial SBP (108.5±29.4 vs. 122.2±29.0, p = 0.0038), higher initial HR (112.9±20.0 vs. 105.6±20.8, p = 0.0283), and higher shock index (SI, 1.12±0.38 vs. 0.91±0.28, p <0.0001) than cryptic shock minor subjects.

These same vital signs were significantly different when compared between cryptic shock major and severe sepsis without lactate elevation: SBP (108.5±29.4 vs. 119.5±27.3, p = 0.0114), HR (112.9±20.0 vs. 103.1 ± 23.4, p = 0.0058), and SI (1.12±0.38 vs. 0.90±0.27, p <0.0001). These findings further implicate an elevated lactate as a possible sign of impending hemodynamic instability, and support the shock index as a marker of poor perfusion and potential for hemodynamic collapse.

On the contrary, the groups with cryptic shock minor and severe sepsis without lactate elevation did not appear to have different outcomes. While the absolute rates of mechanical ventilation (26.1% vs. 22.2%, p = 0.43), vasopressor therapy (12.3% vs. 8.9%, p = 0.36), and 28-day mortality (12.3% vs. 7.2%, p = 0.175) appeared higher in cryptic shock minor subjects compared to severe sepsis without lactate elevation, none of these differences approached statistical significance. Mean APACHE II scores (16.89±7.00 vs. 17.57±6.45, p = 0.37), mean MEDS scores (10.75±4.55 vs. 10.89±4.58, p = 0.79), and mean number of organ dysfunctions (2.46±1.77 vs. 2.49±1.27, p = 0.86) were likewise comparable. The only statistically-significant difference between these groups was found in the prevalence of AKI (41.3% vs. 30.0%, p = 0.0436). Despite relatively high mortality rates compared to other conditions presenting through the ED, patients with cryptic shock minor and severe sepsis without lactate elevation are very frequently admitted to floor beds (42.8% and 48.3%, respectively). Taken together, these data suggest that in our population of patients in severe sepsis, hyperlactatemia is equivalent to other types of organ dysfunction in terms of severity.

Our results are interesting in light of the increasing attention being paid the patient group characterized by normotension and a serum lactate level above normal but below the threshold for cryptic shock (>4.0 mmol/L); this group, termed "cryptic shock minor" in our study, is also referred to as "preshock" by other groups. Howell et al. reported a mortality odds ratio of 2.2 for normotensive septic patients with lactates between 2.5-4.0 when compared to patients with lactates <2.5mmol/L [124]; this is similar to the odds ratio of 2.0 found by Mikkelsen et al. in their non-shock subgroup analysis [75]. In an observational study of 535 "preshock" patients, Tang et al. noted an in-hospital mortality rate of only 1.1% but high rates of vasopressor use (12.9%) and mechanical ventilation (13.3%) during the hospital stay [135]. In another study of similar size, Song et al. studied hospital outcomes for 474 ED patients presenting in "preshock;" their mortality rate was 10.1%, similar to our 28-day mortality rate of 12.3% [121]. Furthermore, 15.4% of these patients were given vasopressors during their hospital stay, which is comparable to the rate of in-hospital vasopressor usage in our cryptic shock minor population (17.4%).

Thus, whereas there were few significant differences in outcomes between our cryptic shock minor group and the group in severe sepsis without lactate elevation, we do observe trends toward increased severity, and these trends are in keeping with the literature. Cryptic shock minor or "preshock" likely represents an at-risk population with the potential for progression to either cryptic shock or vasopressor-dependent shock early in the hospital stay, and so it will be important to discover features of these patients that are markers for this risk. The current literature suggests that such features may include altered mental status,

hypotension, tachypnea, elevated BUN, and high organ dysfunction scores [121, 135].

Comparison with a similar classification schema

In contrast to many of the previously-described studies recorded in the literature, which focused primarily on one or two of subclassifications of severe sepsis or septic shock individually, we incorporated the full spectrum of severe sepsis and septic shock patients in our analysis. The advantage to this approach is that it offers a more universal risk stratification system for severe sepsis and septic shock patients. To our knowledge, only one other study has attempted to create a similar comprehensive classification system by combining initial lactate levels with an assessment of hemodynamic stability [128]. In a multicenter Brazilian study published after the initiation of our study, Ranzani et al. categorized 1,948 ED and hospitalized patients with severe sepsis and septic shock by lactate measurements and the presence of persistent hypotension despite adequate volume resuscitation. After categorization, there were 219 (12%) in dysoxic shock, 549 (28%) in vasoplegic shock, 162 (12%) in cryptic shock, and 1,018 (52%) in severe sepsis without hyperlactatemia. Their classification system utilized a high lactate threshold of >4 mmol/L for their dysoxic and cryptic shock groups and did not include a cryptic shock minor category. The hospital mortality rates of each group were 60.3%, 48.1%, 35.2% and 16.8%, respectively, a mortality trend roughly comparable with our results. Additionally, the incidence of dysoxic (12%) compared to vasoplegic shock (28%) in this study was similar to our data.

However, there are several key differences between this study and our own. The study by Ranzani et al. did not perform a multivariate analysis, so it is difficult to determine if clinical confounders may have been partly responsible for their results. Their study also used the presence or absence of persistent hypotension as a criterion for classification, but it is unclear how exactly this definition was instituted. For example, only 93% of their "vasoplegic shock" and 98% of their "dysoxic shock" groups received "adequate volume expansion and vasopressor if necessary," and the rate of vasopressor use was not mentioned for these groups. We chose to use a more definitive criterion (vasopressor use in the ED) to separate severe sepsis from septic shock patients, bearing in mind that our vasopressor-dependent patients likely represent a sicker subset of the total septic shock group. This difference in definition may partly explain why a lower percentage of our registry subjects were classified as having overt septic shock (16.6% vs. 39.4%). Another possibility is that their patients presented later or were diagnosed with sepsis at a later stage, leading to higher rates of septic shock.

Furthermore, Ranzani et al. included patients presenting from inpatient units (both wards and ICUs) as well as from the emergency department; ED patients made up less than half of their total patient population. It is unclear from their study whether the incidence and mortality rate of various subgroups is affected by the location of diagnosis (ICU, ward or ED). By contrast, our classification system is the first to focus exclusively on septic patients diagnosed and managed in the emergency department. Lastly, although the mortality trends were similar across groups between our two populations, their mortality rates are significantly higher

when directly compared to our corresponding group. This may be a result of a different septic patient population, a delayed time-to-diagnosis of sepsis, or differences in care in the hospitals from which their population was drawn.

Other high-risk groups

As an exploratory analysis of other septic patients considered at high risk, we evaluated incidence and outcomes for two other groups: subjects in severe shock (defined as requiring two or more vasopressor agents in the ED) and subjects presenting in hemodynamic extremis (initial SBP lower than 70mmHg). The presentation of severe shock was frequently seen; in fact, the majority of vasopressor-dependent shock subjects were treated with two or more vasopressors (42 of 74, or 57%), suggesting that one vasopressor agent was not effective in controlling blood pressure for the majority of vasopressor-dependent patients. The 28-day mortality rate for severe shock was 33.3%; in comparing this with the 50% mortality rate of the dysoxic shock group, it is surprising to note that an initial lactate >4.0 mmol/L seems to confer a higher risk for death than the requirement for multiple vasopressors. In a further sub-analysis, the 16 subjects in severe dysoxic shock showed a trend toward higher 28-day mortality than the 26 subjects in severe vasoplegic shock (50.0% vs. 23.1%, $p = 0.098$). These data suggest that even among the most hemodynamically-unstable patients requiring multiple vasopressors, the initial lactate level may be used as a further risk stratifier. However, further comparisons between these groups were limited by the low sample sizes.

23 subjects presented in hemodynamic extremis, representing just 5.2% of all subjects. The initial lactate level in 11 (47.8%) of subjects was >4.0 mmol/L, suggesting that a substantial minority of these patients have objective evidence of prolonged tissue hypoxia at presentation. A different set of 11 (47.8%) subjects required vasopressor therapy in the ED, and even more of these patients (65.2%) required vasopressor support early in the hospital course; this shows that initial resuscitation with fluids is commonly inadequate for hemodynamic stabilization in these patients. In fact, the 28-day mortality in this group (21.7%) seems equivalent to vasoplegic shock (21.1%) or cryptic shock major (18.5%), two groups for whom EGDT has been advocated; conceivably, patients presenting in hemodynamic extremis could also benefit from similar protocolized optimization of their hemodynamic status. To our knowledge, this is the first study to evaluate outcomes in this subgroup of sepsis patients; more research is certainly needed to better characterize this presentation of severe sepsis.

Limitations

Subjects in the registry were prospectively evaluated by multiple clinicians during pre-defined time periods; however, most ED clinicians working at the two sites were not affiliated with the registry, and thus the included patients represent a small subset of all septic patient seen at these two centers over the documented time period. Additionally, included patients were required to meet the 1992 clinical definition for sepsis (at least 2 of 4 SIRS criteria), a more stringent screening method than using the 2001 definition for sepsis (which allows for the presence of other clinical signs without positive SIRS). The chart extraction process was

performed retrospectively by multiple investigators, opening the possibility for errors in chart extraction because of individual variation in data interpretation. However, comparison of over 500 overlapping data points showed greater than 95% concordance between two separate investigators. Certain data points, such as arterial blood gas and CVP/$ScvO_2$ measurements, were not performed in all patients as care decisions were left to the treating providers; the lack of these data for certain subjects make the interpretation of patterns between groups difficult.

In order to categorize patients appropriately by initial lactate level, we were forced to exclude 75 registry patients with no initial lactate drawn in the emergency department, and the exclusion of these patients could conceivably have biased the data. However, the mortality rate of the excluded group was comparable to severe sepsis without lactate elevation (6.7% vs. 7.2%, p = 1.00). Although sepsis guidelines would advocate checking an initial lactate on presentation in these patients, it is likely that they represent a low-risk group whose inclusion in the classification would not have significantly altered the findings of our analysis.

We chose to include all severe sepsis and septic shock subjects enrolled during the time period, in order to accurately estimate the relative incidences of our groups; however, this created large disparities in group size. There were very few subjects in the most severe subject groups (dysoxic shock and vasoplegic shock), and so stochastic events would have been more likely to influence results, especially if the results had no biological explanation (such as the low frequency of coronary artery disease in dysoxic shock subjects). Furthermore, it is likely that our study registry was underpowered to detect small mortality differences between the larger

groups (cryptic shock minor and severe sepsis without lactate elevation, for example); other studies with similar outcome rates and larger sample sizes have found significant differences between these groups. Beyond the primary outcome of this study, the results of our comparisons are mainly hypothesis-generating; therefore we statistically compared all results at a constant alpha level of 0.05, and no correction was made for multiple comparisons.

In the multivariate analysis, we chose to exclude certain variables known to influence severity, such as certain treatment characteristics (time-to-antibiotics, appropriate antibiotics, and timely use of vasopressors) as well as markers of severity such as number of organ dysfunctions or MEDS scores. In discussing whether to include treatment decisions, we reasoned that treatment decisions would mostly be influenced by severity of presentation; sicker patients would be more likely to receive timely and correct sepsis management, and this would bias the results in favor of a positive result (a type I error). Second, we decided not include other severity markers (such as the MEDS score or mean number of organ dysfunctions) in our multivariate analysis. Our reasoning was that we considered our classification system to be a simpler alternative rather than complimentary method to MEDS or APACHE II scoring for risk prediction. Furthermore, one of the criteria for the MEDS score (septic shock) was definitional to our classification system, and we accounted for two of the other MEDS criteria within the multivariate analysis (age and pulmonary source of infection). Nevertheless, the exclusion of these known severity indicators in the multivariate analysis may have biased our

results. Lastly, the secondary outcomes were all assessed by univariate analysis, which increases the probability of confounding biases.

Future Directions

Future research in the realm of predicting severity in sepsis is urgently needed, with the objective of improving both prognostication and ultimately treatment decisions for the proximal phase provider. As we have shown, initial serum lactate levels confer a heterogeneity of outcomes on current definitions of vasopressor-dependent shock and severe sepsis; it would be fruitful to perform subgroup analyses of previous observational and randomized control trials in order to determine possible subgroups (such as dysoxic shock or cryptic shock minor) who may have benefitted from a protocolized care or EGDT-based strategy. Future trials could also use initial lactate levels and ED vasopressor use to inform the formation of a priori subgroups for the same purpose of defining treatment benefits.

In this study, we employed a snapshot of the patient at time of presentation in order to evaluate distant hospital outcomes. However, as sepsis is a progressive process, it would be useful to examine these subgroups longitudinally through their hospital stay to determine the progression of disease. Further longitudinal analyses could include time to vasopressors, length-of-stay in the ICU and hospital, serum lactate trends, the rate of individual and cumulative organ failures (via daily SOFA scores), and a Kaplan-Meier assessment of survival. It would be especially interesting to follow the clinical trajectories of the cryptic shock minor category, since a large percentage of these subjects may progress to either cryptic shock or vasopressor-dependent shock. A determination of clinical or laboratory criteria that

could predict risk of hemodynamic decompensation or death in the cryptic shock major and minor categories could also prove useful for risk stratification within this moderate-risk group. Lastly, there is still much to be done to understand the clinical history as well as evaluate the laboratory characteristics and outcomes of patients presenting in hemodynamic extremis.

Conclusion

Despite a wealth of knowledge on the determinants of severity in sepsis, a simple and accurate method of predicting risk in sepsis patients at time of presentation remains elusive. This study demonstrates that risk stratification can be performed in the hyperacute phase of care via categorizing septic patients by initial lactate levels, vasopressor use and organ dysfunction in the ED; this prognostication ability is maintained after controlling for major determinants of sepsis severity.

Even among vasopressor-dependent patients, presenting lactate levels can risk-stratify patients; dysoxic shock exemplifies a more deadly presentation of septic shock that certainly warrants increased awareness and further study. Remarkably, vasoplegic shock is similar in both incidence and severity to cryptic shock major despite the former group's dependence on early vasopressors. It appears that ED vasopressor use and initially high serum lactate levels confer roughly equal and additive risk of poor outcomes during the hospital stay. Lastly, patients presenting in cryptic shock minor seem to represent an intermediate-risk group between cryptic shock major and other severe sepsis patients; this group presents a unique opportunity to study sepsis progression and evaluate future treatment strategies.

Our classification system for severe sepsis and septic shock may help to inform the design of future trials in the field of early sepsis management. An assessment of incidence for different presentations within severe sepsis and septic shock, as we performed in this study, will assist in determining the subgroup sizes necessary to answer questions of efficacy and power. Furthermore, stratification of future treatment trials by initial lactate levels and early vasopressor use could aid in discovering subsets of patients that may benefit from goal-oriented resuscitative strategies. It is our hope that early and accurate prognostication in severe sepsis and septic shock will advance the cause of improving sepsis care in the future.

References

1. Elixhauser, A., B. Friedman, and E. Stranges, *Septicemia in U.S. Hospitals, 2009: Statistical Brief #122*, in *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. 2006, Agency for Health Care Policy and Research (US): Rockville (MD).

2. Dombrovskiy, V.Y., et al., *Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003.* Crit Care Med, 2007. **35**(5): p. 1244-50.

3. Angus, D.C., et al., *Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care.* Crit Care Med, 2001. **29**(7): p. 1303-10.

4. Martin, G.S., et al., *The epidemiology of sepsis in the United States from 1979 through 2000.* N Engl J Med, 2003. **348**(16): p. 1546-54.

5. Gaieski, D.F., et al., *Benchmarking the incidence and mortality of severe sepsis in the United States.* Crit Care Med, 2013. **41**(5): p. 1167-74.

6. Wang, H.E., et al., *National estimates of severe sepsis in United States emergency departments.* Crit Care Med, 2007. **35**(8): p. 1928-36.

7. Kaukonen, K.M., et al., *Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012.* Jama, 2014. **311**(13): p. 1308-16.

8. Wira, C.R., et al., *Meta-analysis of Protocolized Goal-Directed Hemodynamic Optimization for the Management of Severe Sepsis and Septic Shock in the Emergency Department.* West J Emerg Med, 2014. **15**(1): p. 51-9.

9. Gu, W.J., et al., *The effect of goal-directed therapy on mortality in patients with sepsis - earlier is better: a meta-analysis of randomized controlled trials.* Crit Care, 2014. **18**(5): p. 570.

10. Yealy, D.M., et al., *A randomized trial of protocol-based care for early septic shock.* N Engl J Med, 2014. **370**(18): p. 1683-93.

11. Peake, S.L., et al., *Goal-directed resuscitation for patients with early septic shock.* N Engl J Med, 2014. **371**(16): p. 1496-506.

12. Winters, B.D., et al., *Long-term mortality and quality of life in sepsis: a systematic review.* Crit Care Med, 2010. **38**(5): p. 1276-83.

13. Karlsson, S., et al., *Long-term outcome and quality-adjusted life years after severe sepsis.* Crit Care Med, 2009. **37**(4): p. 1268-74.

14. Iwashyna, T.J., et al., *Long-term cognitive impairment and functional disability among survivors of severe sepsis.* Jama, 2010. **304**(16): p. 1787-94.

15. Angus, D.C. and T. van der Poll, *Severe sepsis and septic shock.* N Engl J Med, 2013. **369**(9): p. 840-51.

16. Fourrier, F., et al., *Septic shock, multiple organ failure, and disseminated intravascular coagulation. Compared patterns of antithrombin III, protein C, and protein S deficiencies.* Chest, 1992. **101**(3): p. 816-23.

17. Trzeciak, S., et al., *Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival.* Ann Emerg Med, 2007. **49**(1): p. 88-98, 98.e1-2.

18. Gomez, H., et al., *A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury.* Shock, 2014. **41**(1): p. 3-11.

19. Moore, F.A., *The role of the gastrointestinal tract in postinjury multiple organ failure.* Am J Surg, 1999. **178**(6): p. 449-53.

20. Ranieri, V.M., et al., *Acute respiratory distress syndrome: the Berlin Definition.* Jama, 2012. **307**(23): p. 2526-33.

21. Moss, M., et al., *Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock.* Crit Care Med, 2003. **31**(3): p. 869-77.

22. Zanotti-Cavazzoni, S.L. and S.M. Hollenberg, *Cardiac dysfunction in severe sepsis and septic shock.* Curr Opin Crit Care, 2009. **15**(5): p. 392-7.

23. Pulido, J.N., et al., *Clinical spectrum, frequency, and significance of myocardial dysfunction in severe sepsis and septic shock.* Mayo Clin Proc, 2012. **87**(7): p. 620-8.

24. Squara, P., *Central venous oxygenation: when physiology explains apparent discrepancies.* Crit Care, 2014. **18**(6): p. 579.

25. Andersen, L.W., et al., *Etiology and therapeutic approach to elevated lactate levels.* Mayo Clin Proc, 2013. **88**(10): p. 1127-40.

26. Wutrich, Y., et al., *Early increase in arterial lactate concentration under epinephrine infusion is associated with a better prognosis during shock.* Shock, 2010. **34**(1): p. 4-9.

27. Bone, R.C., et al., *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, 1992. **101**(6): p. 1644-55.

28. Rangel-Frausto, M.S., et al., *The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study.* Jama, 1995. **273**(2): p. 117-23.

29. Levy, M.M., et al., *2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.* Crit Care Med, 2003. **31**(4): p. 1250-6.

30. Horeczko, T., J.P. Green, and E.A. Panacek, *Epidemiology of the Systemic Inflammatory Response Syndrome (SIRS) in the Emergency Department.* West J Emerg Med, 2014. **15**(3): p. 329-36.

31. Wang, H.E., et al., *Chronic medical conditions and risk of sepsis.* PLoS One, 2012. **7**(10): p. e48307.

32. Martin, G.S., D.M. Mannino, and M. Moss, *The effect of age on the development and outcome of adult sepsis.* Crit Care Med, 2006. **34**(1): p. 15-21.

33. Sakr, Y., et al., *The influence of gender on the epidemiology of and outcome from severe sepsis.* Crit Care, 2013. **17**(2): p. R50.

34. Netea, M.G. and J.W. van der Meer, *Immunodeficiency and genetic defects of pattern-recognition receptors.* N Engl J Med, 2011. **364**(1): p. 60-70.

35. Poutsiaka, D.D., et al., *Risk factors for death after sepsis in patients immunosuppressed before the onset of sepsis.* Scand J Infect Dis, 2009. **41**(6-7): p. 469-79.

36. Tolsma, V., et al., *Sepsis severe or septic shock: outcome according to immune status and immunodeficiency profile.* Chest, 2014. **146**(5): p. 1205-13.

37. Styrt, B., *Infection associated with asplenia: risks, mechanisms, and prevention.* Am J Med, 1990. **88**(5n): p. 33n-42n.

38. O'Brien, J.M., Jr., et al., *Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients.* Crit Care Med, 2007. **35**(2): p. 345-50.

39. Labelle, A., et al., *The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment*.* Crit Care Med, 2012. **40**(7): p. 2016-21.

40. Vincent, J.L., et al., *International study of the prevalence and outcomes of infection in intensive care units.* Jama, 2009. **302**(21): p. 2323-9.

41. Opal, S.M., et al., *Systemic host responses in severe sepsis analyzed by causative microorganism and treatment effects of drotrecogin alfa (activated).* Clin Infect Dis, 2003. **37**(1): p. 50-8.

42. Jones, G.R. and J.A. Lowes, *The systemic inflammatory response syndrome as a predictor of bacteraemia and outcome from sepsis.* Qjm, 1996. **89**(7): p. 515-22.

43. Zahar, J.R., et al., *Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality.* Crit Care Med, 2011. **39**(8): p. 1886-95.

44. Shorr, A.F., et al., *Healthcare-associated bloodstream infection: A distinct entity? Insights from a large U.S. database.* Crit Care Med, 2006. **34**(10): p. 2588-95.

45. Sands, K.E., et al., *Epidemiology of sepsis syndrome in 8 academic medical centers.* Jama, 1997. **278**(3): p. 234-40.

46. Nguyen, H.B., et al., *Severe sepsis and septic shock: review of the literature and emergency department management guidelines.* Ann Emerg Med, 2006. **48**(1): p. 28-54.

47. Donnino, M.W., et al., *Inadequate blood volume collected for culture: a survey of health care professionals.* Mayo Clin Proc, 2007. **82**(9): p. 1069-72.

48. Lagu, T., et al., *Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007.* Crit Care Med, 2012. **40**(3): p. 754-61.

49. Dremsizov, T., et al., *Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course?* Chest, 2006. **129**(4): p. 968-78.

50. Knaus, W.A., et al., *Evaluation of definitions for sepsis.* Chest, 1992. **101**(6): p. 1656-62.

51. Leligdowicz, A., et al., *Association between source of infection and hospital mortality in patients who have septic shock.* Am J Respir Crit Care Med, 2014. **189**(10): p. 1204-13.

52. Brun-Buisson, C., et al., *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, 1995. **274**(12): p. 968-74.

53. Ugarte, H., et al., *Procalcitonin used as a marker of infection in the intensive care unit.* Crit Care Med, 1999. **27**(3): p. 498-504.

54. Jensen, J.U., et al., *Procalcitonin increase in early identification of critically ill patients at high risk of mortality.* Crit Care Med, 2006. **34**(10): p. 2596-602.

55. Marik, P.E., *Critical illness-related corticosteroid insufficiency.* Chest, 2009. **135**(1): p. 181-93.

56. Annane, D., et al., *A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin.* Jama, 2000. **283**(8): p. 1038-45.

57. Landry, D.W., et al., *Vasopressin deficiency contributes to the vasodilation of septic shock.* Circulation, 1997. **95**(5): p. 1122-5.

58. Shapiro, N., et al., *The association of sepsis syndrome and organ dysfunction with mortality in emergency department patients with suspected infection.* Ann Emerg Med, 2006. **48**(5): p. 583-90, 590.e1.

59. Toh, C.H. and W.K. Hoots, *The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview.* J Thromb Haemost, 2007. **5**(3): p. 604-6.

60. Fischer, C.M., et al., *Abnormal coagulation tests obtained in the emergency department are associated with mortality in patients with suspected infection.* J Emerg Med, 2012. **42**(2): p. 127-32.

61. Sanders-Spight, M. and C.R. Wira, *Cumulative Organ Dysfunction in the ED as a Predictor of Mortality in Patients with Severe Sepsis*, in *Department of Emergency Medicine*. 2010, Yale University, School of Medicine: New Haven, CT.

62. Knaus, W.A., et al., *APACHE II: a severity of disease classification system.* Crit Care Med, 1985. **13**(10): p. 818-29.

63. Nguyen, H.B., et al., *Critical care in the emergency department: A physiologic assessment and outcome evaluation.* Acad Emerg Med, 2000. **7**(12): p. 1354-61.

64. Marshall, J.C., et al., *Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome.* Crit Care Med, 1995. **23**(10): p. 1638-52.

65. Ferreira, F.L., et al., *Serial evaluation of the SOFA score to predict outcome in critically ill patients.* Jama, 2001. **286**(14): p. 1754-8.

66. Jones, A.E., S. Trzeciak, and J.A. Kline, *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, 2009. **37**(5): p. 1649-54.

67. Howell, M.D., et al., *Proof of principle: the predisposition, infection, response, organ failure sepsis staging system.* Crit Care Med, 2011. **39**(2): p. 322-7.

68. Shapiro, N.I., et al., *Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule.* Crit Care Med, 2003. **31**(3): p. 670-5.

69. Sankoff, J.D., et al., *Validation of the Mortality in Emergency Department Sepsis (MEDS) score in patients with the systemic inflammatory response syndrome (SIRS).* Crit Care Med, 2008. **36**(2): p. 421-6.

70. Macdonald, S.P., et al., *Comparison of PIRO, SOFA, and MEDS Scores for Predicting Mortality in Emergency Department Patients With Severe Sepsis and Septic Shock.* Acad Emerg Med, 2014. **21**(11): p. 1257-1263.

71. Jones, A.E., K. Saak, and J.A. Kline, *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, 2008. **26**(6): p. 689-92.

72. Bernardin, G., et al., *Blood pressure and arterial lactate level are early indicators of short-term survival in human septic shock.* Intensive Care Med, 1996. **22**(1): p. 17-25.

73. Aduen, J., et al., *The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations.* Jama, 1994. **272**(21): p. 1678-85.

74. Shapiro, N.I., et al., *Serum lactate as a predictor of mortality in emergency department patients with infection.* Ann Emerg Med, 2005. **45**(5): p. 524-8.

75. Mikkelsen, M.E., et al., *Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock.* Crit Care Med, 2009. **37**(5): p. 1670-7.

76. Nichol, A.D., et al., *Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study.* Crit Care, 2010. **14**(1): p. R25.

77. Wacharasint, P., et al., *Normal-range blood lactate concentration in septic shock is prognostic and predictive.* Shock, 2012. **38**(1): p. 4-10.

78. Howell, M.D., et al., *Performance of severity of illness scoring systems in emergency department patients with infection.* Acad Emerg Med, 2007. **14**(8): p. 709-14.

79. Bakker, J., et al., *Serial blood lactate levels can predict the development of multiple organ failure following septic shock.* Am J Surg, 1996. **171**(2): p. 221-6.

80. Nguyen, H.B., et al., *Early lactate clearance is associated with improved outcome in severe sepsis and septic shock.* Crit Care Med, 2004. **32**(8): p. 1637-42.

81. Arnold, R.C., et al., *Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis.* Shock, 2009. **32**(1): p. 35-9.

82. Jones, A.E., et al., *Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial.* Jama, 2010. **303**(8): p. 739-46.

83. Dellinger, R.P., et al., *Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012.* Intensive Care Med, 2013. **39**(2): p. 165-228.

84. Dellinger, R.P., et al., *Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.* Crit Care Med, 2004. **32**(3): p. 858-73.

85. Dellinger, R.P., et al., *Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008.* Crit Care Med, 2008. **36**(1): p. 296-327.

86. Marchick, M.R., J.A. Kline, and A.E. Jones, *The significance of non-sustained hypotension in emergency department patients with sepsis.* Intensive Care Med, 2009. **35**(7): p. 1261-4.

87. Funk, D., F. Sebat, and A. Kumar, *A systems approach to the early recognition and rapid administration of best practice therapy in sepsis and septic shock.* Curr Opin Crit Care, 2009. **15**(4): p. 301-7.

88. Burch, V.C., G. Tarr, and C. Morroni, *Modified early warning score predicts the need for hospital admission and inhospital mortality.* Emerg Med J, 2008. **25**(10): p. 674-8.

89. Band, R.A., et al., *Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock.* Acad Emerg Med, 2011. **18**(9): p. 934-40.

90. Umscheid, C.A., et al., *Development, implementation, and impact of an automated early warning and response system for sepsis.* J Hosp Med, 2014.

91. Sebat, F., et al., *Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years.* Crit Care Med, 2007. **35**(11): p. 2568-75.

92. Kumar, A., et al., *Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.* Crit Care Med, 2006. **34**(6): p. 1589-96.

93. Ibrahim, E.H., et al., *The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting.* Chest, 2000. **118**(1): p. 146-55.

94. Finfer, S., et al., *A comparison of albumin and saline for fluid resuscitation in the intensive care unit.* N Engl J Med, 2004. **350**(22): p. 2247-56.

95. Caironi, P., et al., *Albumin replacement in patients with severe sepsis or septic shock.* N Engl J Med, 2014. **370**(15): p. 1412-21.

96. van der Heijden, M., et al., *Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia.* Crit Care Med, 2009. **37**(4): p. 1275-81.

97. Lira, A. and M.R. Pinsky, *Choices in fluid type and volume during resuscitation: impact on patient outcomes.* Ann Intensive Care, 2014. **4**: p. 38.

98. Marik, P.E., et al., *Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature.* Crit Care Med, 2009. **37**(9): p. 2642-7.

99. Russell, J.A., et al., *Vasopressin versus norepinephrine infusion in patients with septic shock.* N Engl J Med, 2008. **358**(9): p. 877-87.

100. Patel, G.P., et al., *Efficacy and safety of dopamine versus norepinephrine in the management of septic shock.* Shock, 2010. **33**(4): p. 375-80.

101. Beck, V., et al., *Timing of vasopressor initiation and mortality in septic shock: a cohort study.* Crit Care, 2014. **18**(3): p. R97.

102. Bai, X., et al., *Early versus delayed administration of norepinephrine in patients with septic shock.* Crit Care, 2014. **18**(5): p. 532.

103. Brown, S.M., et al., *Survival after shock requiring high-dose vasopressor therapy.* Chest, 2013. **143**(3): p. 664-71.

104. Abid, O., et al., *Strong vasopressor support may be futile in the intensive care unit patient with multiple organ failure.* Crit Care Med, 2000. **28**(4): p. 947-9.

105. Hayes, M.A., et al., *Elevation of systemic oxygen delivery in the treatment of critically ill patients.* N Engl J Med, 1994. **330**(24): p. 1717-22.

106. Annane, D., et al., *Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock.* Jama, 2002. **288**(7): p. 862-71.

107. Sprung, C.L., et al., *Hydrocortisone therapy for patients with septic shock.* N Engl J Med, 2008. **358**(2): p. 111-24.

108. *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, 2000. **342**(18): p. 1301-8.

109. Rivers, E., et al., *Early goal-directed therapy in the treatment of severe sepsis and septic shock.* N Engl J Med, 2001. **345**(19): p. 1368-77.

110. Holst, L.B., et al., *Lower versus higher hemoglobin threshold for transfusion in septic shock.* N Engl J Med, 2014. **371**(15): p. 1381-91.

111. Finfer, S., et al., *Intensive versus conventional glucose control in critically ill patients.* N Engl J Med, 2009. **360**(13): p. 1283-97.

112. Puskarich, M.A., et al., *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, 2009. **13**(5): p. R167.

113. Trzeciak, S., et al., *Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department.* Chest, 2006. **129**(2): p. 225-32.

114. Jones, A.E., et al., *The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis.* Crit Care Med, 2008. **36**(10): p. 2734-9.

115. Keegan, J. and C.R. Wira, 3rd, *Early identification and management of patients with severe sepsis and septic shock in the emergency department.* Emerg Med Clin North Am, 2014. **32**(4): p. 759-76.

116. Levy, M.M., et al., *The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis.* Intensive Care Med, 2010. **36**(2): p. 222-31.

117. Donnino, M.W., et al., *Cryptic septic shock: A sub-analysis of early, goal-directed therapy.* Chest, 2003. **124**(4_MeetingAbstracts): p. 90S-b-90S.

118. Puskarich, M.A., et al., *Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock.* Resuscitation, 2011. **82**(10): p. 1289-93.

119. Mikkelsen, M.E., et al., *Factors associated with nonadherence to early goal-directed therapy in the ED.* Chest, 2010. **138**(3): p. 551-8.

120. Hwang, S.Y., et al., *Association between hemodynamic presentation and outcome in sepsis patients.* Shock, 2014. **42**(3): p. 205-10.

121. Song, Y.H., et al., *Predicting factors associated with clinical deterioration of sepsis patients with intermediate levels of serum lactate.* Shock, 2012. **38**(3): p. 249-54.

122. Arnold, R.C., et al., *Multicenter observational study of the development of progressive organ dysfunction and therapeutic interventions in normotensive sepsis patients in the emergency department.* Acad Emerg Med, 2013. **20**(5): p. 433-40.

123. Sakr, Y., et al., *Early- versus late-onset shock in European intensive care units.* Shock, 2007. **28**(6): p. 636-643.

124. Howell, M.D., et al., *Occult hypoperfusion and mortality in patients with suspected infection.* Intensive Care Med, 2007. **33**(11): p. 1892-9.

125. Hernandez, G., et al., *Persistent sepsis-induced hypotension without hyperlactatemia: is it really septic shock?* J Crit Care, 2011. **26**(4): p. 435.e9-14.

126. Sterling, S.A., et al., *Characteristics and outcomes of patients with vasoplegic versus tissue dysoxic septic shock.* Shock, 2013. **40**(1): p. 11-4.

127. Hernandez, G., et al., *Persistent Sepsis-Induced Hypotension without Hyperlactatemia: A Distinct Clinical and Physiological Profile within the Spectrum of Septic Shock.* Crit Care Res Pract, 2012. **2012**: p. 536852.

128. Ranzani, O.T., et al., *Reclassifying the spectrum of septic patients using lactate: severe sepsis, cryptic shock, vasoplegic shock and dysoxic shock.* Rev Bras Ter Intensiva, 2013. **25**(4): p. 270-8.

129. Friedrich, J.O., G. Wilson, and C. Chant, *Long-term outcomes and clinical predictors of hospital mortality in very long stay intensive care unit patients: a cohort study.* Crit Care, 2006. **10**(2): p. R59.

130. Prys-Picard, C.O., et al., *Outcomes of patients on multiple vasoactive drugs for shock.* J Intensive Care Med, 2013. **28**(4): p. 237-40.

131. Jones, A.E., L.S. Aborn, and J.A. Kline, *Severity of emergency department hypotension predicts adverse hospital outcome.* Shock, 2004. **22**(5): p. 410-4.

132. Madsen, T.E., et al., *The DISPARITY Study: do gender differences exist in Surviving Sepsis Campaign resuscitation bundle completion, completion of individual bundle elements, or sepsis mortality?* J Crit Care, 2014. **29**(3): p. 473.e7-11.

133. Dugas, A.F., et al., *Prevalence and characteristics of nonlactate and lactate expressors in septic shock.* J Crit Care, 2012. **27**(4): p. 344-50.

134. Wira, C.R., S.R. Bhat, and M. Wollan, *The Shock Index as a Predictor of Vasopressor Dependance in Patients With Severe Sepsis.* Acad Emerg Med, 2010. **17**(5): p. S133.

135. Tang, Y., et al., *Clinical predictors of adverse outcome in severe sepsis patients with lactate 2-4 mM admitted to the hospital.* Qjm, 2014.

Appendix: Data Collection Form

SHOCK INDEX IN SEVERE SEPSIS

HIC # 0707002865 PT ID #_____

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 Celsius
☐ Heart Rate > 90 beats per minute
☐ Respiratory Rate > 20 breaths per minute or PCo2 less than 32 mm Hg
☐ White Blood cell count > 12x10 or < 4x10 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 Xray
  ☐ 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 <150,000mm^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%)
☐ 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

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 _____ Lowest MAP _____

Highest Temp: _____degrees C or F Highest RR: _____ breaths/minute

Lowest SaO2: _____ *on: _____ liters O2 by _____

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

☐ 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	_____	HCO3	_____	Cr	_____	Baseline Cr	_____
Bt	_____	Bd	_____	Trop	_____	Albumin	_____
PT	_____	INR	_____	PTT	_____		

10. LACTATE (Value/Time)

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

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

Lowest pH _____ Other P02_____

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. ScVo2 (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. Dobutamine in ED ☐ NO ☐ YES- TIME __ __: __ __

Dobutamine in Hospital ☐ NO ☐ YES - ☐ <72h ☐ >72h

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. Mech. Vent ☐ NO ☐ YES- ☐ IN ED ☐ IN ICU

d. Tight Glu Contr. ☐ NO ☐ YES ☐ IN ED

e. Blood Prod in ED ☐ NO ☐ YES- Type _____

f. 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. SEPSIS MIMIC ☐ No ☐ Yes

19. EMCCM PT ☐ No ☐ Yes

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