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The Changing Paradigm of Sepsis: Early Diagnosis, Early Antibiotics, Early Pressors, and Early Adjuvant Treatment*

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The global burden of sepsis is substantial with an estimated 32 million cases and 5.3 million deaths per year (1). In 2013, over 1.3 million patients were hospitalized in the United States with a diagnosis of sepsis of whom over 300,000 died (2). In addition to short-term mortality, septic patients suffer from numerous long-term complications with a reduced quality of life. The early detection and timely administration of appropriate antibiotics are likely the most important factors in improving the outcome of patients with sepsis. However, the initial signs and symptoms of sepsis are frequently nonspecific, leading to a delay in diagnosis. In this issue of *Critical Care Medicine*, Filbin et al (3) report that over a one third of patients with septic shock presented to the emergency department (ED) with vague symptoms that were not specific for infection. The diagnosis of sepsis and the administration of antibiotics were delayed in these patients. Most importantly, patients presenting with vague symptoms were twice as likely to die. The most common vague symptoms included malaise, fatigue, shortness of breath, and altered mental status. As sepsis is largely a disease of the elderly (age, > 60 yr), clinicians should have a high degree of suspicion of sepsis in elderly patients presenting to the ED with these vague symptoms. A blood count with differential, chest radiograph, and urinalysis are essential in these patients. Early signs of sepsis may include tachycardia, hypotension, abnormal temperature, tachypnea with a respiratory alkalosis, abnormal leukocyte count (with left shift), bandemia, thrombocytopenia, or elevated lactate level (4). An elevated procalcitonin would further support the diagnosis of sepsis (5). In addition, the trajectory of the procalcitonin level is useful in monitoring the response to treatment and in decisions regarding stopping antibiotics (6).

The timely diagnosis of sepsis is critical particularly once hypotension develops. The delayed administration of antibiotics in hypotensive patients is associated with an increased risk of death (7). However, we do not agree with enforcing

*See also p. 1592.

Key Words: fever; sepsis; septic shock; vasopressors

Dr. Marik disclosed off-label product use of vitamin C for sepsis. Dr. Farkas has disclosed that he does not have any potential conflicts of interest.

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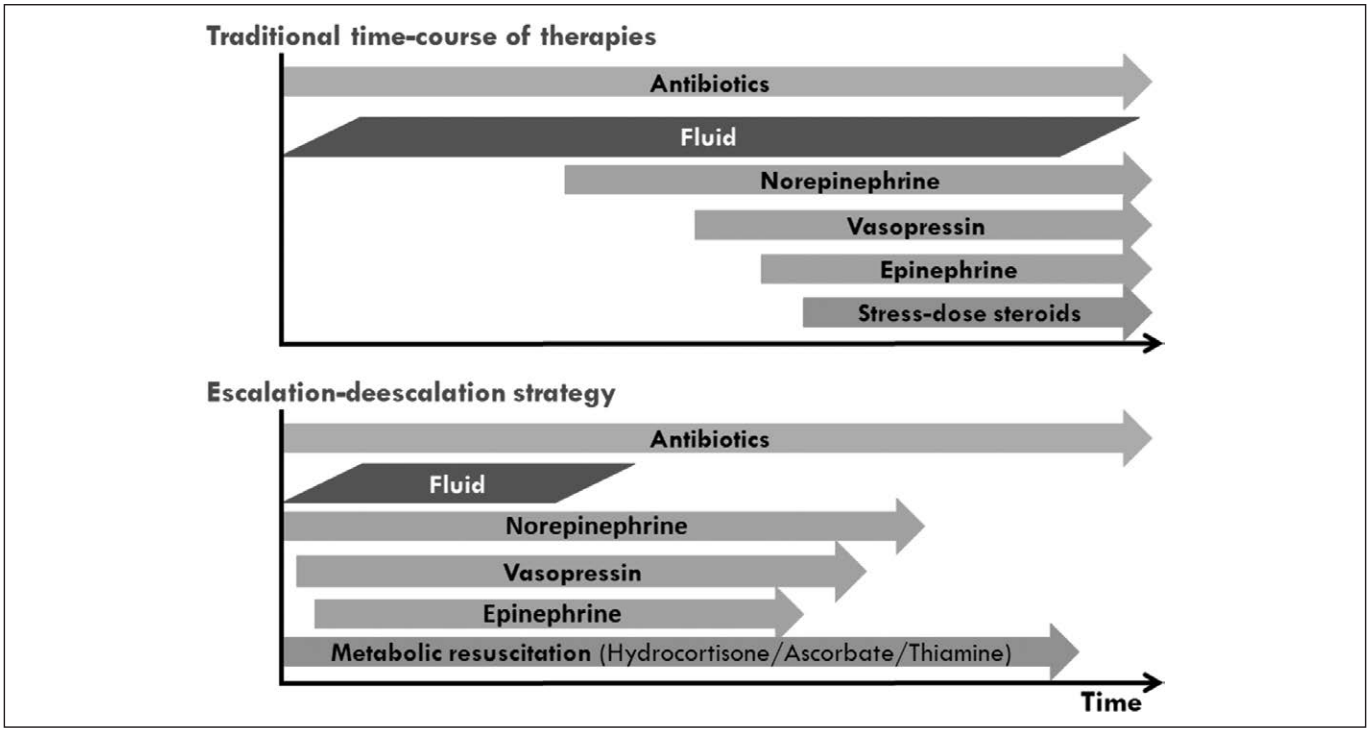

Figure 1. Paradigm change in the management of sepsis and septic shock.

an aggressive, fixed time period "from the time of recognition" to the administration of antibiotics because this may lead to unintended consequences (8). We endorse the concept that "For patients with presumed sepsis or septic shock, the administration of each antibiotic ordered should be initiated promptly, with healthcare systems working to reduce that time to as short a duration as feasible" (9). Furthermore, we do not support the concept of that aggressive fluid resuscitation is crucial for stabilization of sepsis-induced tissue hypoperfusion or septic shock (10). Although having a minimal effect on blood pressure (11), fluid boluses may cause a fall in effective arterial elastance potentiating arterial vasodilatation and the hyperdynamic state characteristic of septic shock (12, 13). Large volume fluid administration is likely to cause severe organ edema (14) and "delayed" hemodynamic compromise (15); the early initiation of norepinephrine is therefore recommended (14). Indeed, in patients with septic shock, Bai et al (16) demonstrated an increasing risk of death with each hour delay in the initiation of norepinephrine. In addition, it is likely that adjuvant treatment with corticosteroids alone (17) or in combination with IV vitamin C and thiamine will improve the outcome of patients with septic shock (18). The benefits of such adjuvant therapy are also likely time dependent. We are suggesting a paradigm change in the management of sepsis that is dependent on the early recognition and management of sepsis. Historically, sepsis therapy would start with antibiotics and fluids. After giving a lot of fluid (customarily 4 L), the need for vasopressor would be grudgingly acknowledged. A couple hours delay would ensue to allow for placement of a central line and x-ray confirmation. Later on, if the vasopressors were not working, steroid might be added on. This process of treatment escalation might take 12 hours or more. A better approach to septic shock is illustrated in **Figure 1**. Antibiotic, fluid, and peripheral vasopressor are all started immediately. Additional vasopressors are added within minutes if needed. Metabolic resuscitation with hydrocortisone, ascorbate, and thiamine are started immediately. As patients improve, vasopressors and metabolic therapy are weaned off. Rapid escalation stabilizes the patient faster, which overall reduces the ICU length of stay and likely reduces organ failure and death.

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Fluid, Fluid Everywhere, and All the Organs Did Not Shrink; Fluid, Fluid Everywhere, Administered Without a Think*

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Much, if not all, of critical care is a J-(or U-) shaped curve. On the left side of the *x*-axis, the inadequate provision of a particular therapy is associated with an increase in complications, demonstrated on the *y*-axis. On the right side of the *x*-axis, an overabundance of the same therapy will also increase complications and worsen outcome. The main objective of training in Critical Care Medicine is to, therefore, provide the clinician with the necessary skills to treat patients at the bottom of the curve, where the complication rate is at its lowest. In essence, our goal in caring for the critically ill should be to attain Goldilocks status. Outcomes are therefore optimized by "just right" therapy, which can change based on timing, severity, and an individual patient's response, followed in a short-loop feedback fashion. Goldilocks would be a fantastic intensivist.

It is with that analogy in mind that we can think of fluid resuscitation. Spanning several eras gone by, the benefits of fluids have been demonstrated in patients with: 1) cholera and hypovolemia, 2) extracellular ("third space") fluid loss, 3) underresuscitated cryptic shock, and 4) supranormal resuscitation targets (1–4). Decades ago, a greater concern was that critically ill patients were too frequently on the left side of the *x*-axis, with commensurate complications related to underresuscitation. So a prevailing dogma stated that critically ill and injured patients should receive large volumes of fluid, with little consideration of any objective, individualized data. Not surprisingly, this will violate the Goldilocks principle, and a significant amount of outcomes data now demonstrate the dangers of overresuscitation and positive fluid balance (5, 6). We now seem to be operating on the right side of the *x*-axis all too frequently with respect to fluid administration.

It is under this backdrop that Silversides et al (7), in their article published in this issue of *Critical Care Medicine*, conducted a multicenter cohort study on mechanically ventilated patients to describe fluid administration practice and to assess the impact of fluid balance and deresuscitation measures (i.e., fluid removal with furosemide or renal replacement therapy) on clinical outcomes. A convenience sample of 400 patients from 10 ICUs in Canada and the United Kingdom comprised the cohort. Multiple regression models and sensitivity analyses were employed to adjust for potential confounding related to illness severity, comorbid conditions, and fluid balance.

Some of the descriptive data have been described before and are expected: higher fluid balance was observed in nonsurvivors. Yet some are unique and thought-provoking, including that over 60% of fluid input during the first 3 days was from medications and maintenance IV fluids, whereas only 24.4% of volume was accounted for by fluid boluses. There was also marked variability in practice regarding both dose and sources of fluid between sites and with the use of deresuscitation measures. There was a mortality association with greater fluid

***See also p. 1600.**

Key Words: deresuscitation; fluids; outcomes

This work was performed at Washington University School of Medicine in St. Louis, St. Louis, MO.

The title of this editorial was adapted from passages from "The Rime of the Ancient Mariner" by Samuel Taylor Coleridge.

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Presenting Symptoms Independently Predict Mortality in Septic Shock: Importance of a Previously Unmeasured Confounder*

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Objectives: Presenting symptoms in patients with sepsis may influence rapidity of diagnosis, time-to-antibiotics, and outcome. We tested the hypothesis that vague presenting symptoms are associated with delayed antibiotics and increased mortality. We further characterized individual presenting symptoms and their association with mortality.

Design: Retrospective cohort study.

Setting: Emergency department of large, urban, academic U.S. hospital.

Patients: All adult patients with septic shock treated in the emergency department between April 2014 and March 2016.

Interventions: None.

Measurements and Main Results: Of 654 septic shock cases, 245 (37%) presented with vague symptoms. Time-to-antibiotics from first hypotension or elevated lactate was significantly longer for those with vague symptoms versus those with explicit symptoms of infection (1.6 vs 0.8 hr; $p < 0.01$), and in-hospital mortality was also substantially higher (34% vs 16%; $p < 0.01$). Patients with vague symptoms were older and sicker as evidenced by triage hypotension, Sequential Organ Failure Assessment score, initial serum lactate, and need for intubation. In multivariate analysis, vague symptoms were independently associated with mortality (adjusted odds ratio, 2.12; 95% CI, 1.32–3.40; $p < 0.01$), whereas time-to-antibiotics was not associated with mortality (adjusted odds ratio, 1.01; 95% CI, 0.94–1.08; $p = 0.78$). Of individual symptoms, only the absence of fever, chills, or rigors (odds ratio, 2.70; 95% CI, 1.63–4.47; $p < 0.01$) and presence of shortness of breath (odds ratio, 1.97; 95% CI, 1.23–3.15; $p < 0.01$) were independently associated with mortality.

Conclusions: More than one third of patients with septic shock presented to the emergency department with vague symptoms that were not specific to infection. These patients had delayed antibiotic administration and higher risk of mortality even after controlling for demographics, illness acuity, and time-to-antibiotics in multivariate analysis. These findings suggest that the nature of presenting symptoms is an important component of sepsis clinical phenotyping and may be an important confounder in sepsis epidemiologic studies. (*Crit Care Med* 2018; 46:1592–1599)

Key Words: diagnosis; emergency department; presenting symptoms; septic shock; time-to-antibiotics; unmeasured confounding

*See also p. 1690.

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Sepsis leads to high morbidity and mortality (1). Although numerous studies have explored the relationship between various patient characteristics and mortality, presenting

symptoms outside of fever have received comparatively little consideration. Presenting symptoms may be important to consider for several reasons: 1) they may influence initial sepsis recognition and timing of antibiotic administration and other important therapies; 2) they may represent underlying variation in disease pathophysiology; and 3) they may have associations with outcome as a result of one or both of these reasons.

To address the significance of presenting symptoms in sepsis, we studied two cohorts of patients presenting to our emergency department (ED) with septic shock: those with "explicit" infectious symptoms and those with "vague" symptoms. We hypothesized that patients with vague symptoms of infection would have higher in-hospital mortality. We postulated a mechanism whereby vague symptoms lead to delayed recognition, delayed antibiotic administration, and therefore increased mortality. We also explored the prevalence of individual symptoms and their relationship to mortality.

METHODS

Study Design

We conducted a retrospective cohort study of all adult (age, ≥ 18 yr old) ED patients at a large, urban academic hospital over a 2-year period from April 1, 2014, to March 31, 2016. The study protocol was approved by our Institutional Review Board with a waiver of informed consent.

Inclusion and Exclusion Criteria

We included patients for analysis who met the following definition for septic shock, adapted from the current Centers for Medicare and Medicaid Services (CMS) Severe Sepsis/Septic Shock Early Management Bundle (SEP-1) definition (2): 1) a hospital *International Classification of Diseases,* 9th Edition, diagnosis code for sepsis, and confirmed source of infection or high suspicion for infection upon hospital admission based on chart review of ED and hospital admission notes; 2) presence of two or more systemic inflammatory response syndrome criteria while in the ED; and 3) persistent hypotension in the ED (systolic blood pressure [SBP], < 90 mm Hg on at least two measurements), elevated lactate greater than 4.0 mmol/dL, or initiation of vasopressor infusion while in the ED. We excluded patients transferred from an outside facility after having received fluid or vasopressor resuscitation or broad-spectrum antibiotics, and those deemed not eligible for aggressive care.

Data Collection and Definition of Covariates

Data were abstracted from the electronic medical record system via both electronic query and chart review. Time-to-appropriate antibiotic was defined as time elapsed from hypoperfusion, defined as first hypotension recorded (SBP, < 90 mm Hg) or high lactate resulted (> 2.0 mmol/dL) to administration of broad-spectrum antibiotics (2). Broad-spectrum antibiotics were defined as per CMS guidelines (i.e., a single broad-spectrum agent, or both antibiotics from an approved combination therapy regimen) (2). Additionally, a "nonapproved" antibiotic was considered appropriate if it was indicated for a specific known organism at the time of administration. We also reported time-to-antibiotics from triage.

The initial Sequential Organ Failure Assessment (SOFA) score (3) was calculated using component inputs documented during the patient's ED stay. We also calculated the weighted Charlson Comorbidity Score (4). Triage location was dichotomized into acute versus nonacute areas, where the acute area of the ED has the highest level of resources. The "Sepsis Flag" is part of a protocol introduced before the period of study whereby ED providers trigger a color-coded warning on the electronic track board indicating suspicion for possible sepsis. The protocol included trigger criteria (possible infection, risk factors, and SBP < 100 or shock index ≥ 1) and was linked to prioritizing care, obtaining diagnostics, and considering antibiotics and fluid bolus within 1 hour (5).

Explicit and Vague Presenting Symptoms

Presenting symptoms were abstracted from nursing triage, ED physician, resident, and/or physician assistant's notes. We developed an a priori definition of explicit presenting symptoms, as those we thought would immediately lead the clinician to consider infection, for example, apparent enough to trigger the sepsis alert (5). Symptoms were considered explicit if they included fever, chills, or rigors, cough with productive sputum, dysuria, reported skin redness or concern for soft-tissue infection, or referral for specific infection diagnosis. Additionally, measured temperature greater than or equal to 100.4°F at triage was included as explicit given its likely influence on the treating clinician to immediately consider infection. Presenting symptoms were defined as vague if they did not include any of the explicit symptoms listed above, thus making infection less apparent. For example, presenting symptoms of fatigue, weakness, and abdominal pain without fever were considered vague. Vague presenting symptom complex was the primary predictor of interest.

Primary Outcome

The primary outcome was in-hospital mortality.

Data Analysis

Summary statistics, including in-hospital mortality, were calculated for all subjects during the 2-year study period and reported by vague versus explicit symptom cohorts.

Multivariate logistic regression was used to determine the adjusted association between vague symptoms and in-hospital mortality. With in-hospital mortality as the dependent variable, we included the primary exposure and all potential confounders, based on a priori knowledge, into a forward-selection logistic regression model (for all candidate covariates included, see the **online supplement**, **Supplemental Digital Content 1**, http://links.lww.com/CCM/D751). We set the covariate stay criteria to p less than or equal to 0.10 for significance. We forced the term time-to-appropriate antibiotic from first documented hypoperfusion into the model, given our particular interest in its confounding effect on the relationship between vague symptoms and mortality. We examined the univariate effect of time-to-antibiotics on mortality and its effect in multivariate modeling with and without vague symptoms. Lactate value was dichotomized using a cut-off of 4.0 mmol/dL. We calculated the *C*-statistic to evaluate model fit.

Next, we constructed a forward-selection multivariate model using delayed first appropriate antibiotic as the dependent variable, and vague symptom complex as the primary predictor of interest. We chose a threshold for delayed antibiotic administration as greater than 1 hour after first SBP less than 90 mm Hg or lactate greater than 2.0 mmol/dL, according to Surviving Sepsis Campaign treatment recommendations (6). Candidate covariates were the same as in the first model.

Finally, we constructed a model using in-hospital mortality as the dependent variable, including the individual symptom covariates that had univariate association with mortality. These symptom variables were forced into the model, given that they were of primary interest as exposure variables. We also forced Sao_2/Fio_2 (S/F) ratio and Glasgow Coma Scale (GCS) less than 15 because of their potential confounding effects on the presenting symptoms shortness of breath and altered mental status.

We used SAS version 9.4 (SAS Institute, Cary, NC) and R.3.4.4 (R Foundation, Vienna, Austria; https://R-project.org) for all analyses. A two-tailed *p* value of less than or equal to 0.05 was used as the cut-off for all tests of statistical significance. Odds ratios (ORs) are reported with 95% CIs and *p* values.

RESULTS

During the 2-year study period, 654 patients met criteria for septic shock, 245 (37%) of whom presented with vague

TABLE 1. Patient Characteristics by Vague Versus Explicit Symptoms

Total, *n* = 654	Vague *n* = 245 (37%)	Explicit *n* = 409 (63%)	*p*
Demographics			
Age, median year (IQR)	68.0 (57–79)	65.0 (52–75)	< 0.01[a]
Male, *n* (%)	152 (62)	235 (58)	0.28
White, *n* (%)	192 (78)	324 (79)	0.87
Triage information			
Temperature ≥ 100.4 at triage, *n* (%)	0 (0)	117 (29)	< 0.01[a]
Heart rate, mean (SD)	101 (29)	111 (25)	< 0.01[a]
Hypotension at triage (systolic blood pressure < 90 mm Hg), *n* (%)	66 (27)	83 (20)	0.06
Initial Glasgow Coma Scale < 15, *n* (%)	68 (31)	89 (22)	0.03[a]
qSOFA met on presentation, *n* (%)	62 (25)	94 (23)	0.50
Charlson score, median (IQR)	3 (1–5)	2 (1–4)	0.25
Triage location, acute care area, *n* (%)	204 (83)	288 (70)	< 0.01[a]
ED course			
Temperature ≥ 100.4°F at any point during ED stay, *n* (%)	43 (18)	238 (58)	< 0.01[a]
Temperature ≤ 96.8°F at any point during ED stay, *n* (%)	127 (52)	102 (25)	< 0.01[a]
qSOFA met in the ED, *n* (%)	202 (82)	327 (80)	0.49
Sequential Organ Failure Assessment score, mean (SD)	7.5 (3.7)	6.6 (3.6)	< 0.01[a]
Initial WBC count, median (IQR)	14.0 (8.3–20.2)	12.8 (6.6–18.2)	0.04[a]
Bandemia ≥ 10%, *n* (%)	27 (11)	61 (15)	0.18
Elevated initial serum lactate ≥ 4.0 mmol/dL, *n* (%)	141 (58)	159 (39)	< 0.01[a]
Identified infectious source, *n* (%)			
Pulmonary/pneumonia	73 (30)	96 (24)	0.09
Abdominal	56 (23)	90 (22)	0.88
Urinary tract	38 (16)	87 (21)	0.09
Wound/soft tissue/skin	6 (2)	34 (8)	< 0.01[a]
Unclear source	68 (28)	101 (25)	0.44
Other source	12 (5)	19 (5)	1.00

(*Continued*)

TABLE 1. (*Continued*). Patient Characteristics by Vague Versus Explicit Symptoms

Total, *n* = 654	Vague *n* = 245 (37%)	Explicit *n* = 409 (63%)	*p*
ED treatments			
Sepsis flag set on electronic track board, *n* (%)	135 (55)	304 (74)	< 0.01[a]
Time-to-appropriate antibiotic, median hours (IQR)			
From triage	2.8 (1.5–6.0)	2.1 (0.9–3.9)	< 0.01[a]
From first hypotension or high lactate[b]	1.6 (0.6–3.3)	0.8 (0.2–2.0)	< 0.01[a]
Appropriate antibiotic not received, *n* (%)	28 (11)	22 (5)	< 0.01[a]
Volume IV fluid received in the ED (L), mean (SD)	2,699 (1,679)	3,414 (1,824)	< 0.01[a]
Intubated in the ED, *n* (%)	63 (26)	49 (12)	< 0.01[a]
Vasopressors started in the ED, *n* (%)	123 (50)	194 (47)	0.55
Outcomes			
In-hospital mortality, *n* (%)	84 (34)	65 (16)	< 0.01[a]
Admission to the ICU within 48 hr, *n* (%)	178 (73)	269 (66)	0.08
First ICU length of stay, median hours (IQR)	73 (40–155)	76 (45–151)	0.69
Vasopressors started within 48 hr of ED triage, *n* (%)	157 (64)	234 (57)	0.10
Positive blood culture,[c] *n* (%)	44 (19)	144 (36)	< 0.01[a]

ED = emergency department, IQR = interquartile range, qSOFA, quick Sequential Organ Failure Assessment.
[a]Highlighting significant *p* values ≤ 0.05.
[b]Time 0 is first systolic blood pressure < 90 mm Hg or lactate > 2.0 mmol/dL.
[c]Appendix (Table A1) shows breakdown of cultured pathogens by symptom group.

symptoms of infection (**Table 1**). The in-hospital mortality rates of those with vague versus explicit symptoms of infection were 34% and 16% ($p < 0.01$), respectively. On multivariate analysis, the adjusted OR of vague presenting symptoms for mortality was 2.12 (95% CI, 1.32–3.40) (**Table 2**). Of note, only eight patients (2%) included in the explicit cohort met the explicit criteria based on measured triage fever alone.

Patients who presented with vague symptoms were older (median age, 68 vs 65 yr; $p < 0.01$) and sicker compared with those presenting with explicit symptoms (Table 1), as evidenced by hypotension (SBP, < 90 mm Hg) at triage (27% vs 20%; $p = 0.06$), mean SOFA score (7.5 vs 6.6; $p < 0.01$), initial serum lactate greater than 4.0 mmol/L (58% vs 39%; $p < 0.01$), and intubation in the ED (26% vs 12%; $p < 0.01$). Patients with vague symptoms were more frequently triaged to acute (83% vs 70%; $p < 0.01$). Despite triage recognition of acuity, acknowledgement of possible sepsis was lower for those with vague symptoms (55% vs 74% having the Sepsis Flag set in ED by provider; $p < 0.01$). Patients with vague symptoms also received antibiotics later after onset of hypoperfusion (hypotension or elevated lactate) (1.6 vs 0.8 hr; $p < 0.01$).

In multivariate analysis, vague symptoms were independently associated with delays in antibiotic administration by greater than 1 hour after documented hypoperfusion (adjusted OR, 2.03; 95% CI, 1.41–2.93). Despite a univariate association with mortality (OR, 1.06; 95% CI, 1.00–1.12; $p = 0.04$), time-to-appropriate antibiotic was not significantly associated with mortality in multivariate analysis that included vague symptoms (adjusted OR, 1.01; 95% CI, 0.94–1.08; $p = 0.78$). Removing vague symptoms from the mortality model, the magnitude of the effect size of time-to-antibiotics increased (adjusted OR, 1.04; 95% CI, 0.97–1.11; $p = 0.27$) but remained insignificant. The rate of positive blood cultures was greater in patients with explicit symptoms compared with vague symptoms (Table 1); the isolated pathogens are listed in the Appendix (**Table A1**). Presence of positive blood culture was not significantly associated with mortality in multivariate analysis. Table 2 reports all covariates that were independently associated with mortality.

Separating explicit and vague symptom complexes into their component elements, the symptom fever/chills/rigors was a qualifying symptom in 326 patients (80%) of the explicit cohort. The following individual symptoms all had univariate associations with mortality: fever/chills/rigors, altered mental status, shortness of breath, and headache (**Table 3**). Fever/chills/rigors was the only symptom that had a univariate association with antibiotic delay greater than 1 hour (OR, 0.41; 95% CI, 0.29–0.57; $p < 0.01$). Only absence of fever/chills/rigors (adjusted OR, 2.70; 95% CI, 1.63–4.47) and presence of shortness of breath (adjusted OR, 1.97; 95% CI, 1.23–3.15) were independently associated with mortality (**Table 4**). The effect of fever/chills/rigors symptom on mortality was independent of measured fever in the ED, and of larger magnitude.

TABLE 2. Univariate Screen and Multivariable Model Investigating the Adjusted Association of Vague Symptoms With In-Hospital Mortality

Characteristics	Univariate OR (95% CI)	*p*	Multivariable OR (95% CI)[a]	*p*
Primary exposure				
Vague presenting symptoms	2.76 (1.90–4.01)	< 0.01	2.12 (1.32–3.40)	< 0.01
Time-to-antibiotic				
From first hypotension or high lactate in hours[b]	1.06 (1.00–1.12)	0.04	1.01 (0.94–1.08)	0.78
Confounders selected for final model				
Age by decade	1.16 (1.03–1.31)	0.01	1.32 (1.12–1.55)	< 0.01
White race	0.48 (0.32–0.72)	< 0.01	0.32 (0.19–0.54)	< 0.01
Active cancer diagnosis	1.49 (0.99–2.23)	0.05	2.03 (1.24–3.34)	< 0.01
Severe liver disease, cirrhosis	3.15 (1.76–5.60)	< 0.01	2.60 (1.23–5.50)	0.01
Abdominal source of infection	1.20 (0.78–1.84)	0.40	1.90 (1.07–3.36)	0.03
Unknown source of infection	2.09 (1.41–3.09)	< 0.01	1.79 (1.05–3.06)	0.03
No documented fever ≥ 100.4 in ED after triage	3.70 (2.43–5.78)	< 0.01	2.37 (1.30–4.29)	< 0.01
Sequential Organ Failure Assessment score in ED	1.28 (1.21–1.36)	< 0.01	1.24 (1.16–1.33)	< 0.01
Intubation in the ED	3.28 (2.13–5.05)	< 0.01	2.20 (1.25–3.89)	0.01

ED = emergency department, OR = odds ratio.

[a]*C*-statistic for model fit is 0.82.

[b]Substituting term time-to-antibiotics from triage yields adjusted OR 1.00; 95% CI, 0.93–1.07; $p = 0.94$.

DISCUSSION

Consistent with our hypothesis, we found differences in mortality, 34% versus 16%, for septic patients who presented to the ED with vague versus explicit symptoms of infection, respectively. The presence of vague symptoms upon hospital presentation was independently associated with higher mortality when adjusted for commonly reported confounders. Although vague presenting symptoms were associated with both delayed antibiotic administration and in-hospital mortality, our data did not support the corollary to our hypothesis that antibiotic delay was a primary driver of mortality. Furthermore, we found that absence of fever, chills, or rigors was the primary driver of the mortality association. Additionally, shortness of breath was independently associated with mortality even after adjusting for measured S/F ratio in the ED and other important confounders.

The observation that patients with vague symptoms had longer time-to-antibiotics warrants consideration. Patients with vague symptoms were generally identified as being seriously ill at triage, as evidenced by the higher rate of triage to the acute area of the ED. Yet the treating team did not recognize infection as often, based on the electronic Sepsis Flag being set less frequently. This highlights an interesting disconnect between recognition of "acuity" versus recognition of "infection." Both cohorts had similar rates of meeting quick SOFA (qSOFA) criteria within the ED, with equally low sensitivities at triage. Assuming early recognition is important, these findings suggest that better education or clinical decision rules are needed to help clinicians identify sepsis on presentation, and that vague symptoms are a risk factor for diagnostic delay.

However, the substantial difference in mortality between the two cohorts appears to be due to factors beyond just sepsis recognition and antibiotic delay. Time-to-antibiotics was not a significant predictor of mortality in multivariate analysis, although this study was not powered to show effect sizes associated with hourly delays that have been previously published (7–12). Septic patients with explicit symptoms may tend to receive earlier antibiotics and also have higher survival, but not necessarily due to earlier antibiotic administration. The strong mortality association with vague symptoms persisted even after adjusting for common predictors of mortality in sepsis. This suggests that there could be value of including presenting symptoms into sepsis risk prediction rules. Other clinical decision tools (e.g., thrombosis in myocardial infarction risk score or pulmonary embolism rule out criteria rule) have incorporated presenting symptoms (13, 14); however, this has not been explored in depth in sepsis.

Our findings that septic patients with vague symptoms have an elevated risk of mortality upon presentation, and are also prone to treatment delays, suggest that the presenting symptom complex may be an unmeasured confounder in epidemiologic studies that report associations between early sepsis treatments and mortality. The largest study to date by Seymour et al (9) reported an OR for death of 1.04 for each hour of antibiotic delay, but did not adjust for presenting symptoms. In univariate analysis, we found an OR for death of 1.06 for each hour of antibiotic delay, which was statistically significant. In multivariate analysis, including symptom complex, the OR was 1.01 and no longer significant (removing symptom complex from the model, the OR for each hour of antibiotic delay was

TABLE 3. All Individual Presenting Symptoms With Frequency and Univariate Odds Ratios for In-Hospital Mortality

Characteristics	Frequency, *n* (%)	Univariate OR (95% CI)	*p*
Symptoms that comprise explicit definition			
Fever, chills, rigors	326 (49.8)	0.25 (0.16–0.37)	< 0.01[a]
Referred for infection diagnosis	76 (11.6)	1.06 (0.59–1.83)	0.84
Cough, productive	65 (9.9)	0.92 (0.48–1.67)	0.80
Cutaneous symptom (erythema, abscess)	59 (9)	1.56 (0.85–2.76)	0.14
Dysuria	24 (3.7)	0.30 (0.05–1.03)	0.10
All other presenting symptoms			
Fatigue, malaise, weakness, lethargy	330 (50.5)	0.96 (0.67–1.38)	0.83
Altered mental status, confusion, somnolence	235 (35.9)	1.83 (1.26–2.65)	< 0.01[a]
Nausea or vomiting	231 (35.3)	0.90 (0.61–1.32)	0.61
Shortness of breath	207 (31.7)	1.77 (1.21–2.58)	< 0.01[a]
Abdominal pain	194 (29.7)	0.77 (0.50–1.15)	0.21
Diarrhea	130 (19.9)	0.72 (0.44–1.16)	0.19
Cough, dry	79 (12.1)	0.92 (0.51–1.60)	0.78
Chest pain	55 (8.4)	0.84 (0.40–1.61)	0.61
Body aches, myalgias	46 (7)	0.70 (0.30–1.46)	0.37
Headache	45 (6.9)	0.07 (0.00–0.33)	0.01[a]
Back pain	45 (6.9)	0.72 (0.30–1.50)	0.41
Upper respiratory (sore throat, congestion, etc.)	41 (6.3)	1.26 (0.59–2.51)	0.52
Extremity pain	41 (6.3)	1.10 (0.50–2.23)	0.80
Focal neurologic symptoms	30 (4.6)	1.25 (0.51–2.75)	0.60
Abnormal urine (bloody or cloudy)	18 (2.8)	0.67 (0.15–2.07)	0.53
Flank pain	17 (2.6)	0.21 (0.01–1.02)	0.13
Genital pain	5 (0.8)	2.28 (0.30–13.86)	0.37

OR = odds ratio.

[a]Highlighting symptoms with univariate ORs that met statistical significance.

1.04, also insignificant albeit in a much smaller study population than that of Seymour et al [9]). Our findings suggest that adjusting for presenting symptoms may attenuate the effect of antibiotic delays that have been previously reported.

We found that the presenting symptom of fever/chills/rigors was the primary driver of the observed mortality effect in our a priori definition of explicit symptoms. This finding is consistent with those of Henning et al (15), who identified the association of fever and mortality in sepsis in a smaller patient sample (14). However, Henning et al (15) did not distinguish between symptom of fever and measured fever in the ED. Our findings suggest that each of these sources of information about fever is independently associated with mortality. Other studies have reported the association between measured fever and mortality (15–21).

The observed association between fever/chills/rigors and mortality supports the concept of differing underlying patient phenotypes at play in sepsis populations (22, 23). Prior investigators have explored immunologic differences between septic patients with and without fever. Marik and Zaloga (16) found that a febrile response was not associated with higher levels of circulating proinflammatory cytokines and suggested that "the hypothermia of sepsis may be due to hypothalamic dysfunction with alternation in the thermal set-point..." It is also possible that virulence factors of the inciting pathogen may contribute to the presence or absence of febrile symptoms: we found that afebrile patients were significantly less likely to have positive blood cultures. However, positive blood cultures were not independently associated with mortality, consistent with Kethireddy et al (8) who report that culture-positive and culture-negative septic patients have similar outcomes. We examined blood culture pathogen counts and found no one species was disproportionate between groups.

TABLE 4. Multivariate Model for In-Hospital Mortality Evaluating Four Individual Symptoms That Had Univariate Associations With Mortality

Characteristics	Multivariate OR (95% CI)[a]	*p*
Presenting symptoms, those with univariate association with mortality		
Absence of fever, chills, or rigors	2.70 (1.63–4.47)	< 0.01
Shortness of breath symptom	1.97 (1.23–3.15)	< 0.01
Altered mental status	1.27 (0.77–2.08)	0.35
Headache	0.11 (0.01–0.96)	0.05
Organ dysfunction terms represented within Sequential Organ Failure Assessment score		
Sao_2/Fio_2 ratio < 300 during ED stay	1.41 (0.88–2.25)	0.15
Glasgow Coma Scale < 15 documented in ED	1.25 (0.75–2.08)	0.40
Vasopressor in ED	1.98 (1.26–3.12)	< 0.01
Intubation in ED	2.09 (1.20–3.66)	0.01
Measured fever in ED		
Absence of documented temperature ≥ 100.4 in ED	2.33 (1.37–3.98)	< 0.01
Remaining significant confounders selected for final model		
Age in decades	1.29 (1.11–1.51)	< 0.01
White race	0.31 (0.18–0.52)	< 0.01
Active cancer diagnosis	2.49 (1.50–4.00)	< 0.01
Severe liver disease, cirrhosis	4.83 (2.37–9.85)	< 0.01
Pulmonary source of infection	0.48 (0.28–0.80)	0.01

ED = emergency department, OR = odds ratio.
[a]C-statistic for model fit is 0.82.

Shortness of breath emerged as an independent predictor of mortality in our cohort. The Sepsis-3 consensus definition and qSOFA derivation address the importance of respiratory abnormality in identifying high-mortality septic patients (24, 25). However, S/F ratio measured in the ED and respiratory rate measured at triage had lower predictive value than the shortness of breath symptom. This has clinical implications, as reliable measurement of respiratory rate can be difficult. Although respiratory infections can contribute to patients developing the sensation of shortness of breath, this symptom might indicate decompensation from an underlying sepsis-related etiology. Therefore, shortness of breath warrants consideration in risk stratification upon presentation and in adjusted analyses of mortality.

The effect of the symptom altered mental status, which had a significant univariate association with mortality, was attenuated when analyzed in a model with documented GCS in the ED. This argues that the reported symptoms altered mental status and GCS measurement in the ED are similar, and distinguishing the two has no additive value. This does not, however, diminish the importance of mental status assessment upon hospital presentation.

This analysis has several limitations. First, this was a single-center study in a large, urban academic medical center; therefore, local patient mix, practice patterns, and mortality variation may exist that are not representative of the general population or patient cohorts at other hospitals. Second, this was a retrospective study that relied on chart review to obtain patient history components. Third, a clinician may not obtain (or document) as detailed a history on a patient who is extremely ill or in extremis, leading to ascertainment bias for those classified with vague symptoms. Fourth, patients with vague symptoms were older and sicker, and this may have had an influence on mortality above what we were able to adjust for. Finally, as with any observational study, there may still exist unmeasured bias that we did not account for.

CONCLUSIONS

More than one third of patients admitted with septic shock present to the ED with vague symptoms that are not specific to infection. These patients have significantly higher mortality than those with explicit infectious symptoms that is independent of demographics, illness acuity, and time-to-antibiotics. These findings suggest that the nature of presenting symptoms may play an important role in sepsis clinical phenotyping and may be an important confounder in sepsis epidemiologic studies.

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TABLE A1. MOST COMMON PATHOGENS BY SYMPTOM COMPLEX

	Vague ($n = 245$)	Explicit ($n = 409$)
Pathogen	**Positive Cultures 44 (18%)**	**Positive Cultures 145 (35%)**
Gram negative, *n* (%)	23 (52)	96 (66)
Escherichia coli	17 (39)	48 (33)
Klebsiella species	4 (9)	19 (13)
Proteus mirabilis	0 (0)	9 (6)
Pseudomonas species	0 (0)	8 (6)
Other	2 (5)	17 (12)
Gram positive, *n* (%)	22(50)	62 (43)
Staphylococcus aureus	8 (18)	20 (14)
Streptococcus species	4 (9)	17 (12)
Streptococcus pneumoniae	1 (2)	8 (6)
Enterococcus species	2 (5)	7 (5)
Clostridium species	4 (9)	3 (2)
Other	7 (16)	6 (4)