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Original Research

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Factors Associated With Nonadherence to Early Goal-Directed Therapy in the ED

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Background: **Protocol-driven early goal-directed therapy (EGDT) has been shown to reduce mortality in patients with severe sepsis and septic shock in the ED. EGDT appears to be underused, even in centers with formalized protocols. The aim of our study was to identify factors associated with not initiating EGDT in the ED.**

Methods: **This was a cohort study of 340 EGDT-eligible patients presenting to a single center ED from 2005 to 2007. EGDT eligibility was defined as a serum lactate ≥ 4 mmol/L or systolic BP < 90 mm Hg after volume resuscitation. EGDT initiation was defined as the measurement of central venous oxygen saturation via central venous catheter. Multivariable logistic regression was used to adjust for potential confounding.**

Results: **EGDT was not initiated in 142 eligible patients (42%). EGDT was not completed in 43% of patients in whom EGDT was initiated. Compliance with the protocol varied significantly at the physician level, ranging from 0% to 100%. Four risk factors were found to be associated independently with decreased odds of initiating EGDT: female sex of the patient (*P* = .001), female sex of the clinician (*P* = .041), serum lactate (rather than hemodynamic) criterion for EGDT (*P* = .018), and nonconsultation to the Severe Sepsis Service (*P* < .001).**

Conclusions: **Despite a formalized protocol, we found that EGDT was underused. We identified potential barriers to the effective implementation of EGDT at the patient, clinician, and organizational level. The use of a consultation service to facilitate the implementation of EGDT may be an effective strategy to improve protocol adherence.** ***CHEST 2010; 138(3):551–558***

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CVC = central venous catheter; CVP = central venous pressure; EGDT = early goal-directed therapy; EMR = electronic medical record; MAP = mean arterial pressure; OR = odds ratio; $Scvo_2$ = central venous oxygen saturation

Severe sepsis and septic shock are associated with significant morbidity and mortality.[1] Early goal-directed therapy (EGDT), a strategy of early hemodynamic optimization that targets central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation ($Scvo_2$) goals, reduced mortality when implemented in the ED of a single center.[2] Several observational studies have

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validated the effectiveness of protocol-directed resuscitation[3-8] and its use has been advocated in practice-based guidelines for sepsis management.[9]

The failure to translate evidence into practice has been identified as one of the great challenges of modern medicine.[10] Despite advances in the care of critically ill patients, evidence-based interventions remain underused.[11-15] To date, few institutions have adopted a formal protocol for the delivery of EGDT.[16-19] In institutions that have adopted protocol-based resuscitation, compliance ranges from 50% to 60%.[20,21] Despite evidence that the introduction of an EGDT protocol at our institution was associated with lower mortality compared with historical controls,[4] we recently reported that EGDT was underused in patients with severe sepsis and septic shock at our institution for unclear reasons.[22] Because mortality exceeded 35% in these patients, it is important to understand why a potentially life-saving intervention like EGDT was not implemented.[22]

Why EGDT is underused in centers that have adopted an EGDT protocol has not been studied. The primary goal of this study was to identify potential barriers to the implementation of EGDT in the ED. We hypothesized that patient, clinician, and organizational factors would be associated with the noninitiation of EGDT.

Materials and Methods

The Institutional Review Board of the University of Pennsylvania approved the study with an informed consent waiver. This was a retrospective cohort study of EGDT-eligible patients admitted through the University of Pennsylvania ED between 2005 and 2007. In late 2004, our ED institutionalized a Severe Sepsis protocol to identify and treat all EGDT-eligible patients. EGDT eligibility was defined as a serum lactate ≥ 4 mmol/L in hemodynamically stable patients (occult shock) or systolic BP < 90 mm Hg after volume resuscitation (1,500 mL).[2-5,8,20,23,24] A Severe Sepsis Consultation Service was available to facilitate the effective implementation of EGDT. The Sepsis Service was staffed by one of two attending ED physicians continuously.

EGDT-eligible patients were identified within our ED severe sepsis cohort.[22] Admitted patients were screened for inclusion if serum lactate was measured in the ED or a physician documented any of the following in the ED electronic medical record (EMR): sepsis, severe sepsis, cryptic septic shock, septic shock, or EGDT. The EMR of these patients was then evaluated for evidence of severe sepsis in the ED. Sepsis, severe sepsis, and septic shock were defined according to the International Sepsis Definitions Conference criteria.[23,24] Subjects were excluded if criteria for severe sepsis were not met, if serum lactate was not measured ($< 2\%$ of exclusions), or if the placement of a central venous catheter (CVC) was refused by the patient or their proxy ($n = 15$). Subjects with a do-not-resuscitate order were not excluded. The details of our ED severe sepsis cohort have been previously published.[22]

Data Collection and Exposures

Candidate risk factors hypothesized to be associated with the noninitiation of EGDT were categorized into patient, clinician, and organizational factors (Table 1). Candidate risk factors were selected based on previous literature,[11,13-15,25-28] biologic plausibility, and/or consensus opinion of the investigators based on their clinical experience. Candidate risk factors were not meant to be exhaustive; to minimize potential type 1 error, patient factors were limited to sociodemographic factors and factors that could alter the perceived risk-to-benefit ratio of initiating EGDT (eg, less severely ill patients may not have EGDT initiated). Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated based on initial variables obtained in the ED.[27] Consistent with the APACHE methods,[27] organ dysfunction was categorized as absent if unmeasured. Our assessment of clinician factors was limited to the attending physician.[28]

Using a predrafted case report form, three trained investigators recorded the relevant patient, clinician, and organizational data from the EMR. ED therapies, including EGDT interventions and resuscitation end points (eg, $ScvO_2$), were also recorded, as was mortality. Each case was assessed by a second investigator for completeness and accuracy.

Outcomes

The primary outcome was the noninitiation of EGDT. EGDT initiation was defined as the measurement of $ScvO_2$ via CVC in the ED. $ScvO_2$ was the resuscitation end point that distinguished the EGDT group in the trial by Rivers et al[2] and its measurement has been used to define EGDT initiation previously.[20] EGDT was categorized as initiated in 13 patients in whom $ScvO_2$ was measured via preexisting CVC (eg, peripherally inserted central catheter). The secondary outcome was EGDT completion. EGDT was completed if the following targets were achieved in the ED: CVP ≥ 8 mm Hg, MAP ≥ 65 mm Hg, and $ScvO_2 \geq 70\%$.[2,9,20]

Statistical Analysis

Comparisons between patients in whom EGDT was and was not initiated were tested using the Student t test or Wilcoxon rank-sum test for continuous variables or the χ^2 statistic or Fisher exact test for categorical variables. We used the nonparametric test for trends across ordered groups and the Mantel-Haenszel statistic for stratified analyses.

Multivariable logistic regression was used to adjust for potential confounding and the results are presented as adjusted odds ratios (OR) with 95% CI. Separate models were created for patient and organizational factors. Candidate risk factors for the noninitiation of EGDT were included in the models if the P value was $< .20$ in univariate analyses. Potential confounders, including attending information, were added one at a time to the model and maintained if the point estimate for the OR of any of the candidate risk factors was altered by $> 10\%$.[29] Nonnormally distributed continuous variables were categorized. Multicollinearity, assessed using variance inflation factors,[30] was detected between APACHE II score and age, MAP, and hematocrit; these variables were not included in the model separately. Finally, patient, clinician, and organizational risk factors found to be significantly associated with the noninitiation of EGDT at the ≤ 0.05 level were included in a model simultaneously. Statistical significance was defined as a P value of ≤ 0.05. Analyses were conducted using Stata 10.1 software (Stata Datacorp; College Station, TX).

Results

Baseline Characteristics

The EGDT-eligible cohort included 340 adults (Fig 1). The age range of the cohort was 18 to 101 years and 54% were men. Septic shock was the criterion

Table 1—*Candidate Risk Factors For Noninitiation of Early Goal-Directed Therapy in Eligible Septic Patients*

Patient-Specific Factors	Organizational Factors
Age	Criteria for EGDT[a]
Sex	Admitting service[b]
Severity of illness	Time and day of presentation
Comorbidities[c]	ED census (occupancy)[d]
Organ dysfunction[c]	Activation of Severe Sepsis Consultation Service
Do-not-attempt resuscitation	Attending of record
Cause of severe sepsis	

EGDT = early goal-directed therapy.

[a]EGDT initiation would be less likely in patients fulfilling the serum lactate rather than the hemodynamic criterion; as such, eligibility criteria could affect protocol implementation. Serum lactate and hemodynamic data were analyzed in the patient factor model.

[b]The initiation of EGDT may be influenced by the service admitting the septic patient, as nonmedical services can assume primary care for the patient in the ED. All patients admitted to nonmedical services (surgery, obstetrics and gynecology, neurology, and neurosurgery) fulfilled criteria for sepsis and EGDT in the ED.

[c]EGDT initiation would be less likely in patients with certain comorbidities (congestive heart failure, end-stage renal disease, or chronic liver failure) and characteristics (ie, increased bleeding risk secondary to coagulopathy, thrombocytopenia).

[d]Occupancy, the percentage of ED beds filled at the time of patient triage, was used to measure ED crowding.[25]

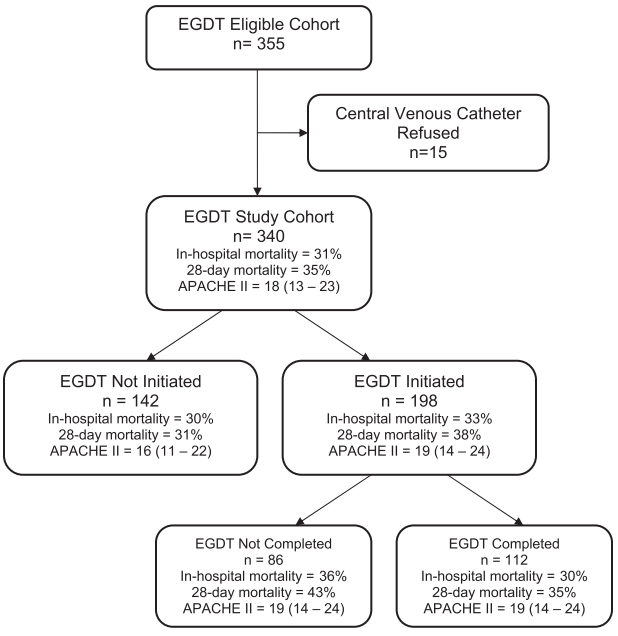

FIGURE 1. Patients meeting criteria for EGDT, EGDT compliance, and severity of illness measures and outcomes by subgroup. The primary comparison was between the EGDT-initiated and noninitiated subgroups. APACHE = Acute Physiology and Chronic Health Evaluation; EGDT = early goal-directed therapy.

for EGDT in 183 patients (54%); 157 (46%) fulfilled occult shock criteria.

EGDT was not initiated in 142 patients (42%). The EGDT group (n = 198) received more IV fluids ($P < .001$), vasoactive agents ($P < .001$), and central venous catheterizations ($P < .001$) (Table 2). The inhospital mortality rate was 33% in the EGDT-initiated group and 30% in the EGDT noninitiated group ($P = .52$). The odds of inhospital death, adjusted for each patient, clinician, and organizational factor found to be associated independently with the noninitiation of EGDT in separate multivariable models, was not significantly different in the EGDT-initiated group (adjusted OR = 0.95; 95% CI: 0.52, 1.75; $P = .87$).

EGDT was not completed in 86 of 198 (43%) patients in whom EGDT was initiated. The inhospital mortality rate was 36% in the 86 patients in whom EGDT was initiated but not completed, compared with 30% in those in whom EGDT was completed ($P = .40$). The CVP target was not achieved in 43 patients, the MAP target was not achieved in 18 patients, and the $ScvO_2$ target was not achieved in 44 patients. EGDT was completed in 33% of the overall cohort. The rate of EGDT completion significantly decreased over the 2-year observational period ($P = .003$); by 6-month interval, rate of completion decreased from 48% to 35% to 25% to 22%.

The patients were managed by 33 physicians (Table 3). Compliance with EGDT (initiation and completion) varied significantly by attending, ranging from 0% to 100%. EGDT was less likely to be initiated by physicians who were female ($P = .017$) and in practice for more years ($P = .026$). The use of the Sepsis Service also differed significantly by attending, ranging from 0% to 100%. The Sepsis Service was less likely to be activated by physicians who were women ($P = .017$), older ($P = .028$) and in practice for more years ($P = .002$).

We identified nine patient-specific factors that were associated with the noninitiation of EGDT in unadjusted analyses (Table 4). EGDT was less likely to be initiated in women ($P = .001$). This association was independent of the sex of the physician; female subjects were less likely to have EGDT initiated whether the attending was a woman (OR = 0.29; 95% CI: 0.13, 0.65) or a man (OR = 0.54; 95% CI: 0.32, 0.92; $P < .001$). EGDT initiation was less likely in patients who were younger ($P = .043$) and less severely ill, as measured by higher initial MAP ($P = .002$), lower lactate levels ($P = .014$), lower APACHE II scores ($P = .001$), and less coagulation dysfunction. Finally, patients with a preexisting CVC ($P = .013$) and patients with bacteremia as the cause of sepsis ($P = .02$) were less likely to have EGDT initiated.

We identified three organizational factors that were associated with the noninitiation of EGDT in unadjusted analyses (Table 5). First, EGDT was less likely to be initiated when the Sepsis Service was not consulted ($P < .001$). Second, EGDT was less likely to be initiated in occult shock patients, compared with patients fulfilling the hemodynamic criterion (50% vs 65%, $P = .006$). Follow-up lactate levels

Table 2—*Interventions Received and Measurements Obtained in the ED by Whether EGDT Was Initiated*

ED Interventions	EGDT Not Initiated (n = 142)	EGDT Initiated (n = 198)	*P* Value
IV fluids (mL)	2,675 (2,000-4,000)	3,750 (2,605-4,975)	< .001
Vasoactive agents	13, 9.2%	61, 30.8%	< .001
Blood transfusion	13, 9.2%	25, 12.6%	.32
Central venous catheterization	31, 21.8%[a]	185, 93.4%[b]	< .001

Continuous measures are presented as medians with interquartile ranges (25th, 75th percentile). Categorical variables are presented as counts and percents. CVC = central venous catheter. See Table 1 for expansion of other abbreviation.

[a]Of the 31 patients in whom EGDT was not initiated, 16 received femoral central venous catheterization, seven received EGDT upon arrival to the ICU, six received central venous catheterization for inadequate peripheral venous access, and three for central venous pressure measurement only.

[b]Thirteen patients had EGDT initiated via preexisting CVC.

were decreasing in 98% (60/61) of the occult shock patients who did not receive EGDT; levels remained ≥ 4 mmol/L in 25% (15/61) of cases. Finally, EGDT was less likely to be initiated in patients admitted to nonmedical services ($P = .049$). The rate of EGDT initiation did not significantly decline over the 2-year period of observation ($P = .22$); by 6-month interval, use was 61%, 60%, 59%, and 51%. The use of the Sepsis Service declined over the 2-year interval ($P = .005$); use decreased from 61% to 48% to 40% in the last two epochs. The association between consultation to the Sepsis Service and EGDT initiation was observed within each 6-month interval ($P < .001$ in each epoch). In patients in whom EGDT was initiated, EGDT was less likely to be completed when the Sepsis Service was not consulted (44% vs 62%, $P = .02$).

Independent patient-specific risk factors associated with decreased odds of initiating EGDT included: female sex ($P = .002$), lower severity of illness, as measured by the ED APACHE II score ($P = .013$), and the absence of coagulopathy ($P = .007$) (Table 6). Organizational factors associated with the noninitiation of EGDT included: serum lactate (rather than hemodynamic) criterion for EGDT eligibility ($P = .024$), admission to a nonmedical service ($P = .021$), and failure to consult the Sepsis Service ($P < .001$). The six risk factors identified remained statistically significant when attending demographics were included in each model.

When patient, clinician, and organizational risk factors were included simultaneously in a separate multivariable logistic regression model, four risk factors were found to be associated independently with decreased odds of initiating EGDT: female sex of the patient ($P = .001$), female sex of the clinician ($P = .041$), lactate (rather than hemodynamic) criterion for EGDT ($P = .018$), and failure to consult the Sepsis Service ($P < .001$). Severity of illness, as measured by higher APACHE II score and the presence of coagulation dysfunction, was not associated independently with EGDT initiation in the complete model, nor was admission to a nonmedical service (Table 6).

Discussion

In this single-center cohort study, we found that EGDT was not initiated in 42% of eligible patients and was incomplete in 43% of patients in whom EGDT was initiated. We identified potential barriers to the initiation of EGDT at the patient, clinician, and organizational level. At the patient level, sex and severity of illness appeared to influence the decision to initiate EGDT. We found that the rate of EGDT use varied widely at the physician level and the sex of the physician appeared to influence whether EGDT was initiated; at the organizational level, we found that when the Severe Sepsis Service was not activated, EGDT was significantly less likely to be initiated and less likely to be completed in those in whom EGDT was initiated.

Our findings demonstrate the challenges that exist in translating evidence into clinical practice effectively. Despite evidence that adoption of EGDT led to improved outcomes at our institution,[4] EGDT was underused. Even when EGDT was initiated, CVP and $ScvO_2$ targets were not achieved in > 20% of cases. Prior studies[2-8,31-35] suggest that the observed mortality in the cohort would have been lower had EGDT been implemented effectively and these benefits appear to last beyond the initial hospitalization.[36] Despite significantly higher APACHE II scores in the EGDT-initiated group, their observed mortality was comparable to the EGDT non-initiated group, suggesting both a benefit

Table 3—*Characteristics of the ED Attending Physicians and Association With the Initiation of EGDT*

Attending Characteristics	Attending Physicians (n = 33)	EGDT Initiated, %	*P* Value
Age category, y			.078
31-40	13, 39.4%	61.3	
41-50	13, 39.4%	60.0	
51-70	7, 21.2%	43.2	
Sex			.017
Female	12, 36.4%	48.5	
Male	21, 63.6%	62.4	
Years in practice since residency			.026
0-5	14, 42.4%	63.6	
6-10	2, 6.1%	66.7	
11-15	10, 30.3%	55.7	
> 15	7, 21.2%	46.2	

Categorical data presented as counts and percents. Nonparametric test for trend across ordered groups was used to test for association between categorized demographics and the initiation of EGDT. See Table 1 for expansion of abbreviation.

Table 4—*Univariate Comparisons of Patient-Specific Factors and the Initiation of EGDT*

Patient-Specific Factors	EGDT Not Initiated (n = 142)	EGDT Initiated (n = 198)	*P* Value
Demographics			
Age, y	56 (44-71)	59 (50-71)	.16
Age, y, categorized			.043
< 47 (lowest quartile)	42, 29.6%	38, 19.2%	
47-70	61, 43.0%	109, 55.0%	
> 70 (highest quartile)	39, 27.4%	51, 25.8%	
Sex, female	81 (57.0%)	76 (38.4%)	.001
Race[a]			.56
White	70, 51.5%	87, 45.3%	
Black	62, 45.6%	99, 51.6%	
Other	4, 2.9%	6, 3.1%	
Initial ED vital signs			
Temperature	37 (36.5-38.3)	36.9 (36.2-38.3)	.43
Heart rate	116 (92-130)	114 (98-132)	.40
Respiratory rate	20 (16-24)	20 (18-25)	.94
Mean arterial pressure	81 (68-96)	74 (60-89)	.002
Baseline ED laboratory values			
WBC count	12.3 (7.0-19.3)	12.9 (8.3-18.9)	.55
Hematocrit	36 (31-40)	34 (27-40)	.12
Platelet count	216 (149-295)	217 (139-304)	.85
Thrombocytopenic (< 100)	21, 14.8%	34, 17.2%	.56
Creatinine, mg/dL	1.3 (1.0-2.5)	1.6 (1.1-2.4)	.074
Glucose, mg/dL	122 (94-178)	124 (96-189)	.64
Total bilirubin,[b] mg/dL	0.8 (0.4-1.6)	0.9 (0.5-2.6)	.14
Hepatic failure[b]	13, 9.2%	26, 13.1%	.26
PT, s[b]	14.1 (12.7-15.8)	15.1 (13.4-18.9)	.004
Coagulopathic[b]	17, 12.0%	48, 24.2%	.005
Lactate, mmol/L	4.4 (2.9-5.9)	5.1 (3.9-6.8)	.014
Hypoperfusion, lactate ≥ 4 mmol/L	95, 66.9%	145, 73.2%	.21
Severity of illness			
APACHE II (baseline)	16 (11-22)	19 (14-24)	.001
Comorbidities[a]			
Coronary artery disease	10, 7.0%	24, 12.1%	.12
Chronic renal insufficiency	18, 12.7%	28, 14.1%	.70
Congestive heart failure	16, 11.3%	26, 13.1%	.61
COPD	8, 6.2%	16, 8.8%	.31
Diabetes mellitus	34, 23.9%	56, 28.4%	.24
End-stage renal disease	11, 7.5%	8, 4.1%	.16
HIV	7, 4.9%	14, 7.1%	.41
Hypertension	54, 38.0%	84, 42.4%	.42
Chronic liver failure	11, 7.8%	24, 12.1%	.19
Oncology	52, 36.6%	61, 31.0%	.28
Transplant	14, 9.9%	17, 8.6%	.70
Do-not-resuscitate	12, 8.4%	10, 5.0%	.21
Preexisting central venous access	37, 26.1%	30, 15.2%	.013
Etiology of sepsis			
Bacteremia	25, 17.6%	18, 9.1%	.02
Respiratory	39, 27.5%	49, 24.8%	.57
Urosepsis	24, 16.9%	43, 21.7%	.27
Gastrointestinal	25, 17.6%	32, 16.2%	.72
Soft-tissue infection	7, 4.9%	14, 7.1%	.42
Surgical-site related	1, 0.7%	4, 2.0%	.40
Central nervous system	5, 3.5%	5, 2.5%	.75

Continuous data presented as medians with interquartile ranges. Categorical data presented as counts and percents. APACHE = Acute Physiology and Chronic Health Evaluation; INR = international normalized ratio; PT = protime; PTT = partial thromboplastin time. See Table 1 for expansion of other abbreviation.

[a]Comorbidities and race not reported in all patients (< 5% missing).

[b]Reported in those in whom a measurement was obtained. Coagulopathy defined as an INR > 1.5 or PTT (s) > 60. Hepatic failure defined as a total bilirubin > 4 mg/dL.

for initiating and completing EGDT in patients who are more severely ill and potential harm when EGDT is not initiated or not completed. Given recent evidence that failure to achieve target $Scvo_2$ within the first 6 h is associated with increased mortality,[37] it would be reasonable to focus future efforts on achieving goal $Scvo_2$ to improve outcomes.

Our observed compliance rates are consistent with those reported previously.[19-21] Nguyen and colleagues[20] reported 51% compliance with EGDT initiation at the inception of their EGDT protocol, which increased to 83% after 2 years; similarly, the rate of EGDT completion increased from 8% to 54%. More recently, Ferrer et al[35] reported that despite a nationwide education effort to improve compliance with processes of care for patients with severe sepsis, EGDT was initiated in < 40% of eligible patients and < 10% had EGDT completed.

We did not observe an increase in the rate of EGDT initiation at our institution; however, we did observe a significant decline in the rate of EGDT completion. Importantly, we did not use a formal feedback mechanism to providers as others have implemented successfully.[20,38] In lieu of a formal feedback mechanism, we developed a consultation service to facilitate the implementation of EGDT. The use of the consultation service was strongly associated with EGDT initiation and EGDT completion; however, the service was underused at the inception of the protocol and its use decreased over time, a finding that may explain the decline in EGDT completion rate. Potential reasons that the service was used less over time include physician fatigue with the service, physician dissatisfaction with the services provided, and the perception that consultation, over time, was no longer necessary to implement the protocol effectively. Furthermore, the use of the service, and EGDT itself, varied significantly at the practitioner level, which serves to highlight the fact that some physicians will adopt protocols more readily, whereas the inertia of previous practice

Table 5—*Univariate Comparisons of Organizational Factors and the Initiation of EGDT*

Organizational Factors	EGDT Not Initiated (n = 142)	EGDT Initiated (n = 198)	*P* Value
Criterion for EGDT protocol eligibility			.006
Serum lactate (occult shock)	78, 54.9%	79, 39.9%	
Hemodynamic (shock)	64, 45.1%	119, 60.1%	
Admitting service			.049
Medical	120, 84.5%	181, 91.4%	
Nonmedical[a]	22, 15.5%	17, 8.6%	
Time of presentation			.43
7:00 AM-11:59 AM	24, 16.9%	45, 22.7%	
12:00 PM-6:59 PM	63, 44.4%	89, 45.0%	
7:00 PM-11:59 PM	34, 23.9%	36, 18.2%	
12:00 AM-6:59 AM	21, 14.8%	28, 14.1%	
Day of presentation			.84
Weekend (Saturday or Sunday)	38, 26.8%	51, 25.8%	
Weekday (Monday to Friday)	104, 73.2%	147, 74.2%	
Protocol duration			.22
First 6 mo of protocol	31, 23.3%	49, 24.8%	
Second 6 mo of protocol	43, 29.5%	65, 32.8%	
Third 6 mo of protocol	36, 24.7%	51, 25.8%	
Fourth 6 mo of protocol	32, 22.6%	33, 16.7%	
ED occupancy[b]	73 (60-83)	70 (53-85)	.37
Activation of the Severe Sepsis Consultation Service	21, 14.8%	141, 71.2%	< .001

Continuous data presented as medians with interquartile ranges. Categorical data presented as counts and percents. See Table 1 for expansion of definition.

[a]Surgery, obstetrics and gynecology, neurology and neurosurgery.

[b]Percentage of ED beds filled at time of ED triage at the patient level.

Table 6—*Multivariable Logistic Regression Models Demonstrating Adjusted Odds Ratio for Initiating EGDT*

Model (N = 340)	Adjusted OR (95% CI)	*P* Value
Patient factor model		
Sex, female	0.48 (0.30-0.75)	.002
Coagulopathic	2.57 (1.30-5.06)	.007
APACHE II (baseline)[a]	1.05 (1.01-1.09)	.013
Serum lactate[a]	0.98 (0.91-1.06)	.60
Serum creatinine[a]	1.04 (0.90-1.21)	.56
Chronic liver failure	1.03 (0.44-2.40)	.95
End-stage renal disease	0.44 (0.14-1.38)	.16
Preexisting central catheter	0.71 (0.38-1.33)	.28
Bacteremia as cause of sepsis	0.57 (0.27-1.22)	.15
Organizational factor model		
Eligibility criterion (serum lactate inclusion criterion)	0.54 (0.32-0.92)	.024
Admitting service (nonmedical[b])	0.37 (0.16-0.86)	.021
Activation of the Severe Sepsis Consultation Service	14.85 (8.37-26.35)	< .001
Complete model		
Sex, female	0.38 (0.22-0.68)	.001
Coagulopathic	1.94 (0.90-4.18)	.089
APACHE II (baseline)[a]	1.04 (1.00-1.08)	.064
Eligibility criterion (serum lactate inclusion criterion)	0.50 (0.28-0.89)	.018
Admitting service (nonmedical[b])	0.42 (0.17-1.05)	.065
Activation of the Severe Sepsis Consultation Service	13.38 (7.36-24.36)	< .001
Attending sex, female	0.50 (0.26-0.97)	.041
Attending experience, years in practice		
0-5	Referent	Referent
6-10	3.74 (0.78-18.04)	.10
11-15	0.86 (0.46-1.60)	.63
> 15	0.73 (0.31-1.70)	.47

An adjusted OR < 1 indicates that the factor is associated with lower odds of EGDT being initiated. OR = odds ratio. See Tables 1 and 4 for expansion of other abbreviations.

[a]OR for each 1-unit increase in baseline APACHE II score, serum lactate, or serum creatinine.

[b]Surgery, obstetrics and gynecology, neurology, and neurosurgery.

may prove to be a barrier to protocol adherence for others.[11] We are directing our current efforts to understand provider-specific reasons for not using the consultation service, as the service appears to be an effective strategy to improve protocol adherence.

We identified several potential barriers to the effective implementation of EGDT, in addition to nonconsultation to the Sepsis Service. First, sex appears to influence the decision of whether to initiate EGDT. EGDT was less likely to be initiated in women. Sex-based differences in care have been observed in cardiovascular medicine[26] and, more recently, in critical care medicine.[39,40] Females are less likely to be admitted to an ICU and to receive invasive procedures and these findings may adversely affect outcomes.[39,40] Sex-based disparities may reflect differences in patient preferences or they may reflect preferences perceived by the patient's proxy or physician.[40] Alternatively, as seen in the critically ill elderly patient,[41] physicians may underestimate female patients' desire for aggressive care and, as a result, may withhold EGDT. Interestingly, we found that the sex of the physician may also influence EGDT use, as female physicians were less likely to initiate EGDT. Our finding that sex-based differences exist in the delivery of protocol-based resuscitation warrants further investigation.

Finally, patients experiencing occult shock were less likely to have EGDT initiated than patients fulfilling the hemodynamic EGDT criterion. Occult shock accounted for 46% of eligible patients; EGDT was not initiated in 50% of these patients. Although follow-up lactate measurements were decreasing in 98% of these patients, 25% remained eligible for EGDT and yet EGDT was still not initiated. Previous research suggests that patients with occult shock may derive an even greater mortality benefit from EGDT,[42] yet serum lactate measurements remain underused.[19] Within our observational study, it is impossible to determine how outcomes were affected by the failure

to initiate and/or complete EGDT and it is unclear why EGDT was less likely to be initiated in occult shock patients. Admittedly, this observation may reflect how patient-specific disease severity influences the use of EGDT. Regardless, the potential impact of underusing EGDT in patients with occult shock warrants further investigation.

It is unclear how the factors we identified influenced the decision of whether to initiate EGDT. EGDT may not have been initiated because of barriers related to physician knowledge or attitudes regarding EGDT.[11] For example, it is possible that physicians failed to recognize that patients were eligible for EGDT (eg, less ill, occult shock). Alternatively, physicians may have decided to implement EGDT in the most severely ill patients only, or to modify or not use EGDT in others based on objective data or inherent biases. As is the case for translating evidence into practice in general,[14-17,26] disease severity likely affects the timely recognition of eligible patients as well as the decision to apply EGDT to a given patient.

There are several important limitations to our study. First, we acknowledge that relevant information pertaining to the complex decision to use EGDT may not have been identified, and a cause-and-effect relationship cannot be determined, through our observational study design. Furthermore, we are unable to comment on other important processes of care (eg, early and appropriate antibiotics) that affect the outcomes of septic patients. We are also unable to determine how outcomes were affected by underusing EGDT; confounding by indication impairs our ability to compare the observed mortality between the EGDT-initiated and EGDT noninitiated groups. Second, our study is subject to type 1 error given the multiple comparisons used. Although we adjusted for potential confounding and limited our hypotheses, our findings are hypothesis-generating and warrant confirmation. Third, we acknowledge the potential for misclassification bias based on our definition of EGDT initiation. Because EGDT resuscitation end points (eg, $Scvo_2$) can be measured and fluids administered via preexisting CVCs, we categorized such patients as having EGDT initiated. Importantly, only 13 patients had EGDT initiated through a preexisting CVC. A fourth limitation is the generalizability of our study; other centers may experience significantly different rates of EGDT use. Nevertheless, the barriers that we identified are likely to be experienced at other institutions. Finally, our use of the APACHE II score to assess severity of illness was not used as originally described;[27] nevertheless, its use in the ED has construct and content validity and, given its association with mortality, criterion validity (data not shown).

In conclusion, our study revealed that EGDT was underused and we identified potential barriers to the effective implementation of EGDT. We found that a consultation service to facilitate the implementation of EGDT may be an effective strategy to improve protocol adherence. Whether EGDT underuse is due to underrecognition, disagreement with its use for specific patients, organizational barriers, or a combination thereof, is unknown and requires further investigation.

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