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Original Contribution

A prehospital screening tool utilizing end-tidal carbon dioxide predicts sepsis and severe sepsis

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ABSTRACT

Objective: To determine the utility of a prehospital sepsis screening protocol utilizing systemic inflammatory response syndrome (SIRS) criteria and end-tidal carbon dioxide ($ETCO_2$).
Methods: We conducted a prospective cohort study among sepsis alerts activated by emergency medical services during a 12 month period after the initiation of a new sepsis screening protocol utilizing ≥2 SIRS criteria and $ETCO_2$ levels of ≤25 mmHg in patients with suspected infection. The outcomes of those that met all criteria of the protocol were compared to those that did not. The main outcome was the diagnosis of sepsis and severe sepsis. Secondary outcomes included mortality and in-hospital lactate levels.
Results: Of 330 sepsis alerts activated, 183 met all protocol criteria and 147 did not. Sepsis alerts that followed the protocol were more frequently diagnosed with sepsis (78% vs 43%, $P < .001$) and severe sepsis (47% vs 7%, $P < .001$), and had a higher mortality (11% vs 5%, $P = .036$). Low $ETCO_2$ levels were the strongest predictor of sepsis (area under the ROC curve (AUC) of 0.99, 95% CI 0.99-1.00; $P < .001$), severe sepsis (AUC 0.80, 95% CI 0.73-0.86; $P < .001$), and mortality (AUC 0.70, 95% CI 0.57-0.83; $P = .005$) among all prehospital variables. Sepsis alerts that followed the protocol had a sensitivity of 90% (95% CI 81-95%), a specificity of 58% (95% CI 52-65%), and a negative predictive value of 93% (95% CI 87-97%) for severe sepsis. There were significant associations between prehospital $ETCO_2$ and serum bicarbonate levels ($r = 0.415$, $P < .001$), anion gap ($r = -0.322$, $P < .001$), and lactate ($r = -0.394$, $P < .001$).
Conclusion: A prehospital screening protocol utilizing SIRS criteria and $ETCO_2$ predicts sepsis and severe sepsis, which could potentially decrease time to therapeutic intervention.

1. Introduction

Severe sepsis caused by overwhelming infection is responsible for significant morbidity and mortality among hospitalized patients [1]. Early identification and aggressive treatment of this disorder has been shown to improve survival [2,3]. Clinical identification of sepsis includes 2 or more of the systemic inflammatory response syndrome (SIRS) criteria in the presence of a suspected infection [1–3]. A hallmark of severe sepsis is hypoperfusion leading to end-organ damage and cardiovascular collapse (septic shock) [1–3]. Objective measures for hypoperfusion allow for risk stratification along the continuum of this disease process.

Lactic acidosis is a well-accepted marker for hypoperfusion and disease severity in this population [2,4] and has been shown to predict mortality in emergency department (ED) patients with infection [5]. Additionally, low end-tidal carbon dioxide ($ETCO_2$) levels have been associated with lactic acidosis, organ dysfunction, and mortality in ED patients with suspected sepsis [6,7].

Prehospital identification and initiation of therapy for severe sepsis may expedite resuscitative efforts. Prior studies have shown that sepsis is common among patients transported by emergency medical services (EMS) [8–11], and that outcomes improve with appropriate prehospital care [8,12–14]. It is feasible to obtain serum lactate levels in the prehospital environment [15], and a recent study demonstrated that utilizing this marker of hypoperfusion might allow for recognition of severe sepsis and decrease in-hospital mortality [16].

While early identification and resuscitative efforts may improve outcomes in severe sepsis, obtaining lactate levels in the field can be difficult and expensive. However, prior studies have shown that prehospital providers can accurately obtain $ETCO_2$ levels simultaneously with traditional vital signs [17]. In the current study, we examined a prospective cohort of patients after initiating a new prehospital "sepsis alert" screening protocol utilizing $ETCO_2$ as an objective measure for hypoperfusion. We hypothesized that patients meeting all of the protocol criteria would be more likely to have a hospital diagnosis of sepsis and severe sepsis.

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The purpose of a **Sepsis Alert** is to provide pre-arrival Emergency Department notification in order to facilitate rapid assessment and treatment of a suspected severe sepsis patient. A **Sepsis Alert** will be instituted for patients meeting the following **3** criteria:

1. Suspected infection
2. Two or more of the following:
   - Temperature > 38° C (100.4° F) OR < 36° C (96.8° F)
   - Respiratory Rate > 20 breaths/min
   - Heart Rate > 90 beats/min
3. ETCO2 ≤ 25 mmHg

Fig. 1. Sepsis alert protocol.

2. Methods

2.1. Design and Setting

We conducted a prospective cohort study among patients transported by a single EMS system to several regional hospitals during a one-year period from July 2014 through June 2015 in Orange County, Florida. The institutional review board at the participating hospitals approved the study protocol.

Inclusion criteria consisted of any case where prehospital personnel activated a "sepsis alert". Per the Orange County EMS system protocols, a sepsis alert is called when an adult patient (≥18 years) has a suspected infection, two or more of the following SIRS criteria (temperature >38°C or <36°C, heart rate > 90 beats/min, or respiratory rate > 20 breaths/min) and an $ETCO_2$ level ≤25 mmHg (see Fig. 1). The protocol was established immediately prior to the study period, and during the roll-out time education was provided in the form of a short, on-line training module. Despite this, there were variations in protocol compliance. This was the basis for our comparison groups. Those patients whereby EMS personnel followed all diagnostic criteria of the protocol formed our "protocol compliant" cohort. In one hundred percent of these patients, EMS personnel suspected infection, patients had ≥2 of the above SIRS criteria, and initial $ETCO_2$ values were ≤25 mmHg. This was strictly a protocol driven process - EMS personnel activated sepsis alert notifications based on their determination that patients met all criteria (see Fig. 1). Those patients whereby EMS personnel activated a sepsis alert but did not follow all diagnostic criteria of the protocol defined our control or "protocol noncompliant" group. In the protocol noncompliant group, EMS personnel suspected infection in all patients, but they either did not have ≥2 SIRS criteria (5% of the cases), or $ETCO_2$ values were >25 mmHg (95% of the cases). This was a paramedic discretionary process, where sepsis alert notifications were activated despite the fact that not all protocol criteria were met.

Exclusion criteria included pediatric patients (< 18 years old), and patients without available hospital records. Orange County, Florida is an urban/suburban region with a population of approximately 1.2 million individuals. The Orange County EMS system consists of 8 Advanced Life Support EMS agencies utilizing the same medical protocols, providing over 100, 000 transports annually.

2.2. Data Collection

Initial out-of-hospital vital signs documented by first arriving EMS personnel including respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse (P), oxygen saturation (Spo_2), and $ETCO_2$ were obtained utilizing LIFEPAK ® 15 multi-parameter defibrillator/monitors. Prehospital measurement of $ETCO_2$ is a standard practice performed by paramedics in the Orange County EMS System. $ETCO_2$ was measured via Microstream capnography using LIFEPAK 15 devices (PhysioControl, Redmond, WA). Microstream capnography is an $ETCO_2$ sampling method using molecular correlation spectroscopy applicable to both intubated and non-intubated patients. $ETCO_2$ was recorded when capnographic wave peaks were at a constant end-tidal for 3 to 5 respirations as directed by protocol. All included patients were spontaneously breathing at the time of evaluation.

Patient age, gender, race, $ETCO_2$, RR, SBP, DBP, P, Spo_2, were obtained from prehospital run reports. Patient mortality, admission to hospital or intensive care unit (ICU), initial ED vital signs, pertinent past medical history, principle and admitting diagnoses defined by *International Classes of Disease, Ninth Edition* (*ICD-9*) codes, as well as serum bicarbonate (HCO_3), lactate, and calculated anion gap (when available) were obtained from the hospital chart. Records were linked by manual archiving of EMS and hospital data.

The primary outcome was diagnosis of sepsis and severe sepsis upon hospital admission. We also measured mortality, patient disposition described as discharge, hospital admission, or ICU admission, *ICD-9* codes, and the relationship between $ETCO_2$ and HCO_3, anion gap, and lactate levels.

2.3. Analysis

Data were described using means and proportions with 95% confidence intervals. Data were assessed for variance and distribution and comparisons between groups were performed using Fisher exact test and independent sample *t* tests with pooled or separate variance as appropriate. Receiver operating characteristic (ROC) curves were constructed to assess the performance of $ETCO_2$, and traditional vital signs for predicting sepsis, severe sepsis, and mortality. The correlation between levels of $ETCO_2$ and HCO_3, anion gap, and lactate were conducted using Spearman's correlation. Significance was set at .05. Data were analyzed using STATA (StataCorp, College Station, TX).

3. Results

There were 330 prehospital sepsis alerts activated over a one-year period. Of the 330 sepsis alerts, 183 (55%) were protocol compliant and 147 (45%) were protocol noncompliant. Complete hospital records were available for 298 patients. The mean age was 70 years (SD17), 169 (51%) were male, 286 (97%) were admitted to the hospital, 100 (34%) were admitted to the ICU, and 25 (8%) died during hospital admission (see Table 1). Among the patients with complete hospital records, 187 (63%) were diagnosed with sepsis and 87 (29%) were diagnosed with severe sepsis (see Table 2). The protocol compliant sepsis alerts were significantly older (72 vs 67 years old, $P = .014$) and more likely to be admitted to the hospital (99% vs 93%, $P = .014$) and to the ICU (41% vs 25%, $P = .006$, see Table 1). A significantly higher percentage of the protocol compliant sepsis alerts were diagnosed with sepsis (78% vs 43%, $P < .001$) and severe sepsis (47% vs 7%, $P < .001$), and these patients also had a higher mortality rate (11% vs 5%, $P = .036$, see Table 1).

In all patients, average temperature was 101.4°F (95% CI 101.1-101.6°F), P was 118 bpm (95% CI 115-120 bpm), RR was 30 bpm (95% CI 29-31 bpm), SBP was 128 mmHg (95% CI 125-131 mmHg), DBP was 78 mmHg (95% CI 72-85 mmHg), Spo_2 was 93% (95% CI 92%-93%) and $ETCO_2$ was 25 mmHg (95% CI 25-26 mmHg, see Table 2). There was no significant difference in mean DBP between the group that followed the protocol and those that did not. The overall mean level of $ETCO_2$ in protocol compliant sepsis alerts was 20 mmHg