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Sepsis

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Introduction

"One out of five people who come in with a heart attack don't die." – Dr. Donald Yealy

Severe sepsis and septic shock can be difficult to diagnosis as patients can present with atypical symptoms and presentation, therefore it is important to have a high index of suspicion and to understand the evaluation and reassessment of this disease process in our ED patients. Since sepsis, severe sepsis, and septic shock represent a continuum of disease, students should understand that patients without severe disease may evolve over time.

Objectives

- Develop an awareness of the high mortality of patients presenting with sepsis syndromes.
- Understand the role of early screening for sepsis in triage of at risk patients.
- Understand the evolution of sepsis management, from early goal directed therapy (EGDT) to lactate clearance to CMS based measures.

Background

While sepsis mortality remains high, it has been decreasing over the years. This likely relates to heightened awareness and early intervention, but the exact reasons are difficult to pinpoint. The estimated mortality varies depending on the definition of sepsis used in determining the incidence. Regardless of whether the Angus or Martin definition is used, both show decreases in annual mortality.

Initial Survey

The initial survey should be carried out during triage and repeated by the initial provider. Screening varies by institution, but typically involves an assessment of vital signs to identify the presence of systemic inflammatory response (SIRS) criteria. These criteria are well known to have poor sensitivity and specificity for the presence of sepsis syndromes.

Classic Presentation

The classic presentation is that of an elderly patient with multiple comorbidities who presents to the ED with fever, tachycardia, tachypnea, and/or hypotension with altered mental status coming in from a nursing home. A WBC may be elevated. The patient may have a pneumonia or UTI on CXR or UA. Many patient may present like this, but this should not be considered routine.

Often, patients will present with one or maybe no abnormal vitals signs. Symptoms may be nonspecific, such as malaise, fatigue, or weakness. Sometimes, patients will have only mild delirium, manifesting only with inattention. At other times, patients may appear well, but give history of fever, rigors, or confusion occurring earlier in the day. The astute student (and physician!) will carry a high level of suspicion and screen patients with point of care lactate measurements (see below) with the same level of vigilance as one screens chest pain patients with an ECG.

SIRS Criteria

The traditional definition of sepsis comprises many different categories. First, a patient should meet the SIRS criteria. As mentioned above, these have poor sensitivity and specificity.

- Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension (PaCO 2) of less than 32 mm Hg

- Abnormal white blood cell count (>12,000/μL or < 4,000/μL or >10% immature [band] forms)

Sepsis

Sepsis is defined as a patient who has a potential infectious cause for the SIRS response. These may be an obvious source (such as a pneumonia noted on history, physical or radiography) or suspected source (reported fever and abdominal pain).

Severe Sepsis

A patient is said to have severe sepsis if they meet the criteria for sepsis and have sepsis-induced organ dysfunction or tissue hypo perfusion. This could present as hypotension, kidney failure, altered mental status or an elevated lactate (traditionally greater than 4 mmol/L).

The Centers for Medicare and Medicaid Services (CMS) (https://cdemcurriculum.com/sepsis/cms.gov) define end-organ dysfunction by the following criteria.

- (SBP)<90 mm Hg or mean arterial pressure <70 mm Hg or a SBP decrease >40 mm Hg or <2 SD below normal for age or known baseline
- Creatinine > 2.0 mg/dl (176.8 mmol/L) or Urine Output < 0.5 ml/kg/hour for > 2 hours,
- Bilirubin > 2 mg/dl (34.2 mmol/L),
- Platelet count < 100,000,
- Coagulopathy (INR >1.5 or aPTT >60 secs),
- Lactate > 2 mmol/L (18.0 mg/dl)

Defining a patient with severe sepsis implies certain reporting requirements. See the section titled CMS Measure: SEP-1 below.

Septic Shock

Septic shock is defined as persistently low blood pressure despite the fluid administration. This is typically agreed to be 30 mL/kg.

Diagnostic Testing

Diagnostic testing for sepsis revolves around risk stratification and investigation of potential sources of infection.

Risk Stratification

- Lactate is the primary method of risk stratification for patients presenting with sepsis. Lactate is believed to be a marker of anaerobic glycolysis during periods of insufficient oxygen delivery. Low lactate levels correlate with low mortality; conversely, elevated lactate levels correlate with high mortality.
- Lactate measurements should be performed immediately after blood is drawn from the patient. Delays in measurement may lead to falsely elevated levels. i.e. EMS blood and other older samples should not be used to obtain lactate levels. Ideal testing involves use of point of care testing or an arterial blood gas machine based in the ED.

Investigation of potential sources of infection

- Most ED investigations will include the following: CBC with diff, CMP, PT/INR/PTT, blood cultures x 2, urinalysis with culture & sensitivity, CXR. Blood cultures should be obtained prior to antibiotic administration when feasible, though this should not delay antimicrobial administration.
- Optional investigations, depending on suspected sources of infection may include: third blood culture (endocarditis), cerebrospinal fluid (meningitis), arthrocentesis (septic arthritis), wound cultures, and other targeted investigations based on clinical suspicion.

Assessment of therapeutic interventions

- Reductions in lactate after therapy correlate with reduced mortality.

So how do you make the diagnosis?

The diagnosis is typically made based on clinician concern for infection combined with evidence of either hypoperfusion of end organs or hypotension. Hypoperfusion of end organs is typically defined as an elevated lactate ≥ 2 mmol/L. Other signs of end organ hypoperfusion include: creatinine 2.0 mg/dl, urine output < 0.5 ml/kg/hour, bilirubin > 2, platelets < 100,000, INR > 1.5, PTT > 60 secs. Hypotension is typically defined as SBP ≤ 90 mm Hg, MAP ≤ 70 mm Hg, or a drop in SBP by 40 mm Hg from baseline. (Baseline SBP can often be determined through modern electronic health records.)

Treatment

Antimicrobials

Most recommendations for early antimicrobial administration come from the Kumar data, which was a retrospective review of 14 ICUs from 11 hospitals. Time from first measured hypotension to administration of "effective" antibiotics was correlated with mortality. Effective antibiotics were defined by culture and sensitivity data, which are generally not available at presentation to the ED.

The EMSHOCKNET research network, found that among patients treated with a quantitated resuscitation protocol, hourly delays in antimicrobial administration did not affect mortality. One hour (OR 1.2, 0.6-2.5), 2 hours (OR 0.71, 0.4-1.3), 3 hours (OR 0.59, 0.3-1.3), and up to six hours from triage.

A retrospective review of 17,990 patients in the Surviving Sepsis Campaign's database showed little change in mortality between 0 and 5 hours time to antimicrobial administration.

So what do these somewhat conflicting antimicrobial studies mean? Administer antimicrobials at the earliest possible time, however it is appropriate to obtain necessary data (CXR, UA, etc.) to determine the most likely cause so that the most appropriate antimicrobials can be selected.

Treatment protocols

Treatment has traditionally focused on early, aggressive therapies. Early goal directed therapy (EGDT) initially showed great promise, with an absolute risk reduction in mortality of 16%! This involved placement of an arterial line and central venous catheter, titration of IV fluids to achieve a central venous pressure between 8-12 mm Hg, titration of vasopressors to achieve a MAP greater than 65, and measurements of central venous oxygen saturation. When low, blood transfusions and dobutamine were administered to raise this level.

Lactate clearance was proposed to be an alternative to EGDT, allowing for less invasive and more time efficient method to manage patients from a busy ED. Achieving a normal lactate ($\leq$ 2 mmol/L) or a reduction of 10% was found to be equivalent to achieving an Scvo2 $\geq$ 70%.

Three recent large trials, ProCESS, ARISE, and ProMISE, compared EGDT, standardized protocol of care, and routine care. They each separately found that there was no difference in mortality, resource utilization, and length of stay (LOS) between each treatment arm, suggesting that there was no longer a significant role of CVC and Scvo2 monitoring for most patients. Many clinicians have inferred that this highlights the importance of early screening of sepsis patients, however none of the trials actually compared patients with early versus delayed (or no) screening.

CMS Measure: SEP-1

SEP-1 is a publicly reported quality measure for hospitals that will eventually affect hospital reimbursement. SEP-1 is an all or nothing quality measure. Failure to perform or document one component leads to failure of the entire measure. CMS defines sepsis by the presence of ICD-10 codes at time of discharge. The time of onset (whether it occurred in the ED) is assumed to be ED arrival time unless there is documentation stating

otherwise: the earliest presence of SIRS criteria, physician suspicion of infection, and evidence of lactate elevation or hypotension. Documentation of the presence or lack of sepsis is a very important activity.

The following constitute component of the sepsis bundles and should be completed by the time specified:

Three Hour Bundle

- Lactate measurement
- Blood cultures obtained before antimicrobial administration
- Administration of broad spectrum antimicrobials.
- Administration of 30 ml/kg IV crystalloid for hypotension or lactate ≥ 4 mmol/L. (Despite this recommendation, providers should use caution in patients with end stage renal disease, congestive heart failure, and end stage liver disease where aggressive fluid resuscitation may prove to be deleterious.)

Six hour Bundle

- Administration of vasopressors for hypotension that does not respond to fluids in order to achieve a MAP ≥ 65 mm Hg
- Reassess and document volume status after fluid administration for patients with hypotension that does not respond to fluids or lactate ≥ 4 mmol/L
- Repeat lactate measurement for patients with initial lactate ≥ 4 mmol/L

Source Control

Potentially infected intravascular devices should be removed promptly when feasible.

Disposition

Nearly all patients with sepsis syndromes will require hospitalization. Patients with septic shock (either lactate ≥ 4 mmol/L or vasopressor dependent hypotension) should be admitted to an intensive care unit (ICU). For less severely ill patients, the specific level of care will be based on local facility capabilities and practice patterns. Community hospitals with lower levels of physician coverage after hours may prefer many of these patients be admitted to an ICU. Larger academic hospitals with greater physician coverage may be capable of managing these patients on step-down or regular nursing floors

In our hospital system, disposition is based on post-intervention lactate and blood pressure. Normotensive patients with lactate ≤ 2 mmol/L are generally considered safe for regular nursing floor. Normotensive patients with lactate between 2.0 – 3.5 mmol/L receive a consult from the medical ICU. Hypotensive patients and patients with lactate ≥ 3.5 mmol/L are routinely admitted to an ICU.

Pearls & Pitfalls

- Students should have a high suspicion for sepsis syndromes, especially in patients of advanced age, with significant comorbidity, and/or who appear to be clinically ill.
- Screen all suspected cases with a lactate obtained from a fresh blood sample. Lactate should be considered the ECG of sepsis. An elevated measurement is the STEMI that opens the cath lab for the patient.
- Utilize hospital screening tools and bundled order sets, whether on paper or within the EHR, to achieve desired consistency in process.
- Reassess patients frequently. Often, patients may become hypotensive 30-60 minutes after antibiotic administration.
- Hospital systems are under great pressure from CMS to implement very specific sepsis bundles, despite evidence showing lack of benefit. While this makes for great intellectual and political debate, students should follow hospital protocols.

Superstar Corner

Want more? Here's an intellectually stimulating link to EMCrit.org (https://cdemcurriculum.com/sepsis/emcrit.org) by Scott Weingart, written on June 11, 2015: We are Complicit – A glimpse into the current state of Severe Sepsis/Septic Shock Quality Measures (https://cdemcurriculum.com/sepsis/emcrit.org/blogpost/current-state-of-severe-sepsis-quality-measures/)

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