EDUCATIONAL COMMENTARY – SEPSIS: DIAGNOSIS AND MANAGEMENT WITH LABORATORY TESTING

Educational commentary is provided through our affiliation with the American Society for Clinical Pathology (ASCP). To obtain FREE CME/CMLE credits click on Earn CE Credits under Continuing Education on the left side of the screen.

Learning Outcomes

On completion of this exercise, the participant should be able to
- describe sepsis;
- discuss the laboratory tests that are important in the diagnosis and management of sepsis;
- discuss the role of lactic acid in the assessment of outcomes for a patient with sepsis; and
- describe the Surviving Sepsis Campaign’s history and its recommendations related to sepsis.

Case History

An elderly woman was brought to the emergency department by her daughter, who reported that the woman had fainted at home and had been confused recently. The patient reported that she had lower back pain and was feeling dizzy and chilled. She had a history of frequent bladder infections but denied any urinary symptoms. Physical examination by the emergency department physician revealed tachycardia, low blood pressure, and fever (temperature, 100° F [37.8°C]). The emergency department physician ordered laboratory studies.

Laboratory studies revealed:
- an elevated white blood cell count of 14,000/µL (reference range, 4,500-11,000; to convert to 10⁹/L, multiply by 0.001)
- more than 10% band neutrophils (reference range, 0-5%; to convert to proportion of 1.0, multiply by 0.01)
- leukocytes and blood in the urine
- C-reactive protein (CRP) of 7.0 mg/dL (reference range, 0.08-3.1; to convert to mmol/L, multiply by 9.524)
- creatinine of 2.5 mg/dL (reference range, 0.6-1.2; to convert to µmol/L, multiply by 88.4)
- lactic acid concentration of 3.0 mmol/L, demonstrates hyperlactatemia (reference range, 0.6 -1.7)

Blood cultures were drawn and the patient was admitted to the intensive care unit, where intravenous (IV) antibiotics were initiated. She was treated for sepsis and other complications of bacteremia, which was confirmed by the blood cultures.
Introduction

According to the 2008 National Hospital Discharge Survey conducted by the Centers for Disease Control and Prevention (CDC) / National Center for Health Statistics, more than one million Americans were hospitalized with septicemia or sepsis in 2008. The average length of inpatient stay was 8.4 days, 75% longer than for any other hospitalization diagnosis. The calculated treatment cost of septicemia and the complications associated with the disease was $14.6 billion. With two-thirds of these patients aged 65 years or older, there is a huge financial impact for health care facilities to recognize and manage sepsis as quickly as possible to not only use resources effectively, but also save lives.1

Sepsis is the leading cause of death in noncoronary intensive care units and the tenth leading cause of death in the United States overall.2 The mortality rate for patients with complications from sepsis is estimated to be between 28% and 50%. Annually, sepsis causes more deaths than prostate cancer, breast cancer, and AIDS combined.3 In 2002, a joint project of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine set out to reduce mortality from severe sepsis and septic shock worldwide. They initiated the Surviving Sepsis Campaign, which established evidence-based guidelines, implemented a performance-improvement program, and compiled and published analysis and data from thousands of cases of sepsis from health care institutions worldwide. The third edition of the Surviving Sepsis Guidelines was published in 2012.4

Etiology of Sepsis

Sepsis is the systemic response to an infectious agent, which can be bacterial, fungal, or viral. The body mounts a nonspecific inflammatory response termed systemic inflammatory response syndrome (SIRS). The diagnosis of sepsis is made by the presence of infection, confirmed or presumed, as well as the presence of SIRS. The diagnosis of SIRS is made when two of the following four signs are present:

- Body temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
- Pulse rate of more than 90/min
- Respiratory rate of more than 20/min OR arterial carbon dioxide tension (PaCO₂) of less than 32 mmHg
- Abnormal white blood cell count (>12,000/µL OR < 4000/µL OR >10% immature [band] forms)2

Systemic inflammatory response syndrome can develop in response to any stimulus that elicits an acute inflammatory response, such as burns, trauma, critical illnesses such as myocardial or pulmonary infarcts, or pancreatitis. The inflammatory cascade is a complex process involving humoral and cellular
EDUCATIONAL COMMENTARY – SEPSIS: DIAGNOSIS AND MANAGEMENT WITH LABORATORY TESTING (cont.)

responses, complement, and cytokine cascades. When SIRS is initiated in response to an infectious agent, an endotoxin or exotoxin is usually the trigger for the release of a host of cytokines from the reticuloendothelial system, the blood, and lymphatic cells. In turn those cytokines, such as tumor necrosis factor (TNF) and interleukin 1 (IL-1), initiate and mediate a wide range of responses by the complement system and the coagulation system, and the release of more cytokines and acute-phase reactants such as CRP and procalcitonin. If left untreated the body is soon overwhelmed by the inflammatory process, causing regulatory system failure and organ dysfunction, leading to severe sepsis and increased risk for mortality.5

Laboratory findings that are significant in the diagnosis and management of sepsis are listed in the Table below.6

**Table.** Significant findings in sepsis diagnosis and management.

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Finding</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count</td>
<td>&lt;4000/μl OR &gt;12,000/ μl &gt;10% band neutrophils</td>
<td>Exposure of endotoxin stimulus</td>
</tr>
<tr>
<td>C-Reactive protein</td>
<td>&gt;2 SD above normal</td>
<td>Acute phase response</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>&gt;2 SD above normal</td>
<td>Differentiates infectious SIRS from noninfectious SIRS</td>
</tr>
<tr>
<td><strong>Organ dysfunction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>Increase &gt;0.5 mmol/L over baseline</td>
<td>Acute renal injury</td>
</tr>
<tr>
<td>Coagulation tests</td>
<td>protein C deficiency</td>
<td>Onset of organ failure/DIC</td>
</tr>
<tr>
<td></td>
<td>antithrombin deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>elevated D-dimer level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prolonged PT and PTT</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;100 ×10^3/μL</td>
<td>DIC</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&gt;4.0 mg/dL</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Tissue perfusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic acid</td>
<td>&gt;4 mmol/L</td>
<td>Tissue hypoxia</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood cultures</td>
<td>Positive</td>
<td>Septicemia</td>
</tr>
</tbody>
</table>

Abbreviations: SIRS, systemic inflammatory response syndrome; SD, standard deviation; DIC, disseminated intravascular coagulopathy; PT, prothrombin time; and PTT, partial thromboplastin time.
EDUCATIONAL COMMENTARY – SEPSIS: DIAGNOSIS AND MANAGEMENT WITH LABORATORY TESTING (cont.)

Surviving Sepsis Campaign

The Surviving Sepsis Campaign focuses on two primary treatment bundles. Defined in the Surviving Sepsis Guidelines, a *bundle* is “a selected set of elements of care that, when implemented as a group, have an effect on outcomes beyond implementing the individual elements alone”. The initial rapid diagnosis and treatment of severe sepsis within 3 hours and aggressive management within 6 hours of patient presentation are the primary focus of the sepsis bundles.

Evaluation and treatment to be completed within 3 hours of patient presentation is targeted at the isolation and management of infection by immediate imaging studies as well as drawing a lactic acid level and blood cultures prior to starting empiric IV antibiotics. If lactate levels are ≥ 4.0 mmol/L, a crystalloid for hypotension is administered.

Secondly, initiation of IV fluid therapy, vasopressor treatment, and oxygen therapy to promote tissue perfusion within 6 hours is key to patient survival. Reassessment of volume status and tissue perfusion is done in response to persistent hypotension and the initial increased lactate level. Subsequent inpatient care such as providing intensive monitoring and support of organ function, avoidance of complications, and de-escalation of care when appropriate, focuses on supportive therapy, which may include blood product administration to treat active bleeding, mechanical ventilation in cases of acute respiratory distress, glycemic control, and nutritive therapy. Redirected antibiotic therapy is essential when definitive identification of the causative agent has been obtained.

Role of Lactic Acid

The Surviving Sepsis Campaign has identified lactic acid (lactate) as an important analyte in the assessment of risk for mortality in sepsis patients. Studies have shown that managing lactic acid clearance to levels less than 1.8 mmol/L within 24 hours of admission greatly reduces the risk for death in patients diagnosed as having severe sepsis. Lactic acid is an important marker in the assessment of tissue perfusion. Tissue hypoperfusion is defined by treatment-persistent hypotension after initiating IV fluids or a lactic acid concentration of greater than 4.0 mmol/L. Tissue hypoxia in sepsis can be termed *septic shock*.

Lactate is formed by an anaerobic pathway in the breakdown of glucose. Lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactate, as it converts NADH to NAD⁺ in a

<table>
<thead>
<tr>
<th>O</th>
<th>NADH</th>
<th>NAD⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂⁻</td>
<td>pyruvate</td>
<td>H⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OH⁻</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO₂⁻</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lactate</td>
</tr>
</tbody>
</table>

*Figure: Pyruvate + NADH + H⁺ = lactate + NAD⁺*
Although all tissues produce lactate, primary production occurs in the skeletal muscle, brain, red blood cells, and kidneys. The body clears it rapidly under normal conditions by liver metabolism or conversion of lactate back to pyruvate, to keep blood levels below 1.0 mmol/L. Hyperlactatemia occurs when lactate levels reach 2.0 to 4.0 mmol/L and persist as the body maintains pH balance by metabolic compensation through renal reabsorption of bicarbonate ($\text{HCO}_3^-$) or respiratory compensation through hyperventilation with a relative reduction in carbon dioxide ($\text{PaCO}_2$). Lactic acidosis occurs when blood lactate levels increase to greater than 5.0 mmol/L and the body is no longer able to regulate pH balance, resulting in a decreased pH (acidosis) from an increase in hydrogen ions ($\text{H}^+$) or from a reduction in $\text{HCO}_3^-$ concentrations.

Lactate accumulation can be caused by mechanisms that are hypoxic or non-hypoxic in nature. Hypoxia occurs when the body’s oxygen delivery is compromised, as in shock, severe anemia, cardiac arrest, respiratory failure, severe asthma, chronic obstructive pulmonary disease (COPD), and regional hypoperfusion. Non-hypoxic pathophysiologic states are the result of the body’s inability to clear lactate due to organ dysfunction such as renal or hepatic dysfunction, or compromised metabolic pathways present in pyruvate dehydrogenase dysfunction, sepsis, thiamine deficiency, alcoholic and diabetic ketoacidosis, accelerated aerobic glycolysis, and other processes. The metabolism of certain drugs and other chemicals, such as salicylate, cyanide, methanol, ethylene glycol, valproic acid, and certain antiviral agents, can also cause lactate overload.

In cases of trauma and stress such as sepsis, poor tissue perfusion (inadequate oxygen delivery) strains the cellular metabolism to cause lactic acid to accumulate in the blood. Therapy is directed at increasing tissue oxygenation through mechanical ventilation and IV fluids to increase blood pressure. Optimizing the delivery of oxygen to distressed organs is primary in the treatment of severe sepsis. Within the first 6 hours of a patient’s presentation, the use of early goal-directed therapy (EGDT) to achieve a central venous oxygen saturation of 70% or greater has been shown to significantly reduce mortality and further complications associated with sepsis. To assess response to oxygen therapy, serial lactate measurements are often drawn. It is important to consider that the half-life of lactate is around 20 minutes. If the lactate concentration does not decrease over time, it is not due to poor clearance, but to poor response to oxygen therapy, indicating that the primary source of lactatemia is anaerobic metabolism.
Conclusion

Sepsis is a complicated syndrome that physicians have struggled to manage for centuries. Laboratory tests play a key role in the diagnosis of sepsis and treatment of the patient with sepsis. The initial assessment of tissue perfusion by the measurement of lactic acid has been shown to significantly reduce mortality with prompt treatment with oxygen therapy to reverse anaerobic metabolism, support oxygen saturation, and ultimately cellular metabolism. The Surviving Sepsis Campaign, formed in 2002, has made great strides in the reduction of sepsis complications and mortality related to severe sepsis. The goal to implement bundles of care in the diagnosis and management of sepsis that are consistent across health care organizations and to model best practices using evidence-based medicine will ultimately lead to efficient use of health care resources and improve patient outcomes.

References


