



PEARLS OF LABORATORY MEDICINE

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TITLE: Sepsis and the Clinical Lab

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Hi, I'm Alison Woodworth. I am the medical director of the Core Clinical Laboratory and Point of Care Testing at the University of Kentucky Medical Center. Today I will tell you about the important role that the clinical laboratory plays in diagnosis and monitoring of sepsis.

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Sepsis is a debilitating disorder affecting over 751,000 Americans each year. Worldwide, the annual incidence of sepsis is >1.8 million cases and continues to rise. If left untreated, sepsis progresses rapidly to severe sepsis and septic shock—resulting in 200,000 deaths each year in the United States. Sepsis mortality increases with age and co-morbidities such as cancer; therefore the number of deaths due to sepsis is expected to rise significantly. US hospital costs for sepsis are >\$15 billion per year, with an uptrend of ~12% per year. The increasing costs are largely due to increasing prevalence of severe sepsis in the Intensive Care Units (ICUs) where septic patients are thought to make up >40% of the population. In fact, it is the leading cause of death in the medical, trauma and other non-cardiac ICUs. In order to understand why sepsis causes such significant morbidity and mortality, we must understand its pathobiology.

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Early sepsis is an insidious process that begins with a host's response to an infecting pathogen. Normally the host response involves localization and control of the bacterial invasion and then

initiation of repair of injured tissue through the activation of macrophages and release of both pro and anti-inflammatory mediators. If the mediators are in balance and the infecting agent is killed and phagocytosed, then homeostasis is restored. Sepsis begins when the host response process is no longer localized. In globalized inflammation or Systemic Inflammatory Response syndrome (SIRS) pro-inflammatory cytokines act directly or indirectly through secondary mediators to induce fever, leukocytosis and activation of endothelial cell function and the coagulation cascade. This leads to global cell damage, mitochondrial dysfunction and tissue injury – organ dysfunction. If not adequately treated, significant cellular damage and tissue hypoxia leads to organ failure and ultimately death.

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In 1992, the American College of Chest Pain Physicians and the Society of Critical Care Medicine got together to develop consensus guidelines for diagnosis and treatment of sepsis. This group later became known as the surviving sepsis campaign. The first step was to put forth definitions for SIRS and sepsis. SIRS-systemic inflammatory response syndrome was defined clinically. A patient met SIRS criteria when he or she had at least 2 out of the 4 of the following: A high or low body temperature, High or low white blood cell count, an elevated heart rate, and/or respiratory rate. They went on to define sepsis as the presence of SIRS in a patient with a documented infection. This was the “gold standard” for the diagnosis of sepsis. A uniform definition of sepsis led to significant improvement in quality of the research studies and in treatments, however it has several caveats. In particular, identification of pathogens is most commonly achieved by culture. Depending on the pathogen, cultures take a long time to grow and are subject to significant contamination, resulting in both false positive and false negative results. Therefore, updated guidelines include SIRS + a documented or suspected infection. The consensus guidelines also defined different severities of sepsis.

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Septic patients are classified into 3 categories of increasing severity depending on degree of organ dysfunction and hypotension. More severe forms of sepsis are associated with increased mortality rates. Sepsis without organ involvement is associated with a 15-20% mortality rate. Sepsis with organ dysfunction, confers a 25 – 30% mortality rate. Septic shock, sepsis with

organ dysfunction and hypotension is associated with up to 70% mortality. Numerous studies have looked at reducing sepsis related mortality.

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In this multicenter study of >2700 ICU patients with septic shock, the authors demonstrate that the earlier septic shock is identified and treated with antimicrobial therapy, the better the chance of survival. Septic shock was defined as time of hypotension onset. The X-axis shows increasing amount of time since with septic shock in hours. The red line represents the fraction of patients surviving to hospital discharge while the blue line represent the percentage of patients in whom antibiotic therapy was initiated with increasing time. Survival is significantly higher in those patients who had early initiation of antibiotics. Therefore rapid identification of sepsis early in its pathobiological process is critical.

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The sepsis definition has been continually refined since the original 1992, and with that came new recommendations for therapy targeted to specific signs/symptoms associate with the disease. In 2002, Sepsis 2 came out and along with it, the recommendation for early-targeted treatment of sepsis with antimicrobials and fluid resuscitation based on patient's laboratory values and Physical exam values. In 2004, the Surviving sepsis campaign (SSC) published its first recommendations for evidence based diagnosis and treatment of sepsis. Many trials and iterations of the sepsis definition and SSC goals led to complicated diagnostic criteria attempting to identify patients earlier in disease followed. However, in 2016 a new sepsis definition (Sepsis-3) was published in JAMA followed by a 2017 revision to the SSC recommendations for therapy. The new definition was quite different and did not focus on early disease, but instead more severe disease.

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Instead of a complicated diagnosis, they defined sepsis clinically and related it to outcomes. Sepsis is a "life-threatening organ dysfunction caused by a dysregulated host response to infection". They went on to clarify this definition to include a documented or suspected infection and a SOFA score >2. Sequential Organ Failure (SOFA) asses the degree of failure across several organ systems including liver, kidney, respiratory, cardiovascular, coagulation, lung, and

CNS. The Septic shock definition is similar in that it is a subset of septic patients with hypotension, cellular and metabolic abnormalities associated with a greater risk of mortality. Clinical parameters include patients who require vasopressor therapy to maintain arterial pressure and a lactate over 2 mmol/L. This definition is specific for inpatients, but in the ED, they found that in patients with a suspected infection a quick SOFA (qSOFA) score > 2 is associated with a poor outcome. QSOFA includes an elevated respiratory rate, altered mental status and/or low blood pressure. Despite the change in diagnostic criteria for sepsis, our goals remain the same: to identify and treat septic patients early and personalize the therapy for their stage of disease. In the laboratory we support these goals in several ways including: (1) reporting of accurate and timely test results; (2) educating clinicians on the clinical utility of relevant lab testing in sepsis; (3) helping clinicians to properly utilize and interpret lab testing; (4) and discovering new biomarkers. There are over 200 biomarkers identified in the literature as potentially useful in the diagnosis, prognosis and/or monitoring of sepsis, however only a handful are recommended for routine use in sepsis management.

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Lactate, which is an end product of anaerobic glycolysis, is increased in various clinical situations including in patients under excessive energy demands and those with depleted oxygen supply in blood or to the tissue (as in hypoperfusion associated with septic shock). Lactate is also increased in patients with impaired cell metabolism or gluconeogenesis. Patients with severe sepsis and septic shock typically have elevated blood lactate concentrations. Patients very early in the septic pathobiological process without organ dysfunction or hypotension typically do not have elevated lactate. Therefore, the clinical utility of lactate measurements is in the management of septic patients. In fact, the SSC guidelines suggest that lactate should be measured within 6 hours of presentation. An elevated lactate is an indicator of severe sepsis or septic shock, increased mortality and fluid resuscitation should be initiated. Lactate clearance- defined by the % decrease in lactate in 6 hours is associated with response to therapy and overall survival. If the initial lactate is elevated a second lactate measurement should be drawn within 6 hours of presentation. A clearance of >10% within 6 hours is associated with a better prognosis and response to therapy. New recommendations are to use lactate to guide therapy.

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The 2013 surviving sepsis campaign guidelines also mention two other biomarkers, Procalcitonin and C-reactive protein, which may be elevated in septic patients. Procalcitonin is the 116 amino acid pro-hormone of calcitonin. When synthesized in the thyroidal C-cells, the N-terminal signal sequence of procalcitonin (PCT) is proteolytically cleaved to form calcitonin. In non-thyroidal cells, inflammatory mediators like TNF- α upregulate PCT synthesis. Non-thyroidal cells lack enzymes to cleave its signal sequence, thus PCT is secreted unprocessed into circulation. PCT synthesis is inhibited by the Interferon- γ , and theoretically should not be present in virally induced sepsis. PCT concentrations are elevated in sepsis and the degree of elevation is associated with severity of disease. However, because PCT is upregulated by proinflammatory cytokines, it is also secreted in response to non-infectious inflammation.

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Numerous studies have investigated the clinical and diagnostic utility of PCT to predict early sepsis, prognosis and guide antimicrobial therapy. Unfortunately, PCT does not have ample diagnostic strength to differentiate early sepsis from non-infectious causes of SIRS. In a meta-analysis of >2000 ICU and ED patients with SIRS, PCT only showed 70% sensitivity and specificity to identify patients with an infection (Sepsis). When measured overtime changes in PCT concentrations may predict prognosis. In studies of critically ill patients patients, when PCT concentrations are low or decreasing over time the patient's chance of survival was significantly higher than if PCT concentrations were steady or increasing. Because PCT upregulation may be specific for bacterial sepsis, groups have investigated its ability to guide antibiotic therapy. Guidelines do not agree, but in general in adults, decreasing PCT concentrations along with other clinical and laboratory signs and symptoms may be used to direct antibiotic cessation, but high PCT concentrations should NOT be used to increase or change the antibiotic regiment. The FDA has recently approved PCT for this purpose. More data is needed to demonstrate the benefits of PCT guided antibiotic therapy in kids. Further, no studies have investigated whether the decreased antibiotic use has led to a decreased number of "superbugs".

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C-reactive protein (CRP) is an acute phase reactant that is upregulated in response to proinflammatory stimulus. CRP is a pentameric globular protein synthesized in the liver. It binds phosphatidylcholine, which is commonly present on the surface of microbial membranes as well as damaged host cells, and activates complement. For these reasons it has been touted as an ideal sepsis biomarker candidate. However, most studies show that like PCT, CRP is not useful in identifying infectious SIRS (sepsis). This is likely due to its long half-life and lack of specificity for bacterial sources of inflammation. CRP may have a role in predicting prognosis, particularly in patients already on antimicrobial therapy. In one study of septic patients, a low CRP after 2 days on antibiotics conferred a better chance of survival compared to a high CRP. There does not seem to be a role for CRP in monitoring antibiotic therapy over time because it has a long half-life and can stay elevated for over 72 hours after infectious insult. At this point, there is not a good tool for identifying sepsis early in the pathobiological process. Recent studies have focused on cytokines.

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As I mentioned early in the talk, synthesis of pro- and anti-inflammatory cytokines is up-regulated rapidly in response to insult by foreign pathogens or other inflammatory signals. The figure on the left shows the increase in plasma concentration of inflammatory cytokines, PCT and CRP in response to an inflammatory insult in otherwise healthy people. There is a rapid rise in cytokine concentrations which peak at about 2 hours after insult, and if the patient recovers, cytokines rapidly return to normal. PCT is detectable at 2-4 hours and a plateau is maintained for 8 to 24hr, CRP takes at least 6 hours to increase and an even longer time to normalize, which is not good for early identification or monitoring therapy. PCT takes a long time to increase, but does come down rapidly so it can be used to monitor therapy, but not early diagnosis.

Proinflammatory cytokines go up early and decline rapidly with recovery. In clinical trials cytokines have similar diagnostic strength to predict infectious sepsis among SIRS patients as PCT when measured alone. However, when cytokines are combined in a panel, they demonstrate superior diagnostic strength to identify sepsis. Concentrations of cytokines increase with increasing disease severity, and IL-6 elevations are an excellent predictor of mortality. Very few studies have looked at whether serial measurements of one or more cytokines may help monitor therapy.

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Let's take a moment to evaluate the clinical and diagnostic utilities of these sepsis biomarkers by looking at the most common utilities. As you recall the former "gold standard" for diagnosis of sepsis is at least 2 out of 4 SIRS criteria combined with documented or suspected infection. Cultures are subject to false positive and false negative results. Technologies for detecting infectious pathogens (i.e. Molecular detection or MALDI-TOF) are improving, but we still have to test for drug susceptibility using old fashioned methods. Biomarkers are an attractive and rapid alternative to the "gold standard". Lactate is part of most sepsis resuscitation bundles and is a good marker for prognosis and response to therapy in patients with severe sepsis and septic shock, but it lacks utility in patients early in the sepsis pathobiological process. Procalcitonin is elevated with increasing severity of sepsis, but is also elevated in non-infectious conditions and therefore is not ideal for identification of early sepsis. It does have utility in helping clinicians determine when to discontinue antibiotic therapy. CRP has some utility to predict prognosis especially in septic patients that are already on antibiotics, however its long half-life makes it impractical to monitor therapy. Like PCT and CRP, cytokines are upregulated in response to many inflammatory stimuli and are not specific for sepsis. Cytokines do have a role in predicting prognosis. Recent studies suggest that panels consisting of multiple biomarkers may identify infectious SIRS early in the process as well and predict prognosis. More studies are needed to determine the utility of multimarker panels to guide therapy. At this point only lactate is standard of care in most hospitals. PCT's use is increasing.

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Sepsis is among the leading causes of death in hospitalized patients, and its prevalence is rising. The pathobiology of sepsis is complex, but begins with a global inflammatory response to an infecting pathogen. Clinical signs and symptoms (fever, elevated respiratory or heart rate) are common across numerous inflammatory conditions and no single biomarker, to date, can accurately identify an infectious cause for systemic inflammation. Thus diagnosis of early sepsis is challenging. Lactate is a good predictor of patients with severe sepsis or septic shock as well as response to sepsis resuscitation therapy. Inflammatory markers like procalcitonin, CRP and cytokines can predict prognosis. Procalcitonin can also be used to guide cessation of

antibiotic therapy in adult septic patients. Newer studies demonstrate the superior diagnostic strength to identify early sepsis when biomarkers are combined.

Slide 16: References

Slide 17: Disclosures

Slide 18: Thank You from www.TraineeCouncil.org

Thank you for the opportunity to talk to you about the evolving field of sepsis diagnosis. I've listed a few key references for your review.

