TITLE: Procalcitonin Testing and Antibiotic Stewardship

PRESENTER: Nadia Ayala-Lopez, PhD, MLS (ASCP)

Slide 1:

Hello, my name is Nadia Ayala-Lopez. I am a fellow in clinical chemistry at Vanderbilt University Medical Center. Welcome to this Pearl of Laboratory Medicine on "**Procalcitonin testing and Antibiotic Stewardship**."

Slide 2:

Over 2 million people in the United States are infected with antibiotic-resistant bacteria each year (CDC)[1]. One cause of antibiotic resistance is the over-prescribing of antibiotics. This occurs when antibiotics are prescribed in: viral infections, inflammatory conditions without infectious origin, and when continuing antibiotics after original infection has cleared. At least 30% of all antibiotics prescribed are unnecessary[2]. Unnecessary antibiotic use puts patients at a greater risk for antibiotic-related adverse drug events (ADEs)[1], which are reported to occur in 20% of patients and include emergence of resistance to antimicrobial drugs, selection of pathogens such as *Clostridioides difficle,* side effects and toxic effects due to the drugs themselves.

Slide 3:

The goal of antibiotic stewardship is monitor and improve the way antibiotics are prescribed and used. Antibiotic stewardship programs include strategies for early and accurate detection of pathogens, initiation of optimal therapy, ways to tailor therapy as new information is revealed, and ways to monitor doses and pharmacokinetics of the drug if necessary. Lastly, clinical and laboratory information are used to discontinue antibiotics and shorten therapy.

As you can see, antibiotic programs encompass many workflows within a healthcare institution. Therefore, a successful antibiotic stewardship program requires the collaboration between hospital departments, administrators, clinicians and laboratory professionals.

Slide 4:

One way that the laboratory has expanded its role in antimicrobial stewardship is by providing laboratory-assisted guidance of antimicrobial therapy through the measurement of procalcitonin. Procalcitonin is a serum biomarker used for bacterial infection. It is a 116 amino acid protein produced in most cells and tissues, which is cleaved from preprocalcitonin[3]. In thyroid cells, procalcitonin is a precursor of calcitonin.

Slide 5:

Procalcitonin is increased up to 1,000x in response to cytokines released during a bacterial infection[4]. Upon stimulation of the inflammatory host response to bacterial infection, transcription of calcitonin mRNA is stimulated and translated into the procalcitonin peptide. In adipocytes and other cells of the body, procalcitonin is constitutively expressed. In C-cells of the thyroid, endocrine stimulation causes procalcitonin to be produced and cleaved into calcitonin, which undergoes regulated secretion from secretory granules. Production of INF gamma due to a viral infection inhibits procalcitonin production.

Slide 6:

Procalcitonin levels rise within 4-6 hours after onset of infection and they peak at 15-24 hours and its half-life is 24 hours[3]. Procalcitonin decreases by half each day after the control of an infection and plateaus in the setting of ongoing inflammation. The kinetic profile of calcitonin is exploited in monitoring procalcitonin concentration to guide cessation of antibiotics. Procalcitonin has greater sensitivity and specificity in sepsis than other markers of inflammation, such as C-reactive peptide (CRP), lactate and interleukin-6.[5]

Slide 7:

Procalcitonin is used in antibiotic stewardship as a blood biomarker used to measure a patient's response to infection. It aids in risk assessment for critically ill patients upon intensive care unit admission for progression to severe sepsis or septic shock. It is also prognostic for mortality risk in severe sepsis or septic shock. Measuring procalcitonin can assist in antibiotic therapy decision making

for patients with suspected lower respiratory tract infection and as an aid in decision to discontinue antibiotics. Procalcitonin is not to be used as a sole marker to guide antibiotic therapy.

Slide 8:

As of September 2019, there are 30 FDA-cleared procalcitonin assays/platforms. They are based on the immunoassay principle and include electrochemiluminescence immunoassay (ECLIA), chemiluminescent microparticle immunoassay (CMIA), chemiluminescent enzyme immunoassay (CLEIA), latex particle enhanced immunoturbidimetry, immunofluorescent assay with Time-Resolved Amplified Cryptate Emission (TRACE ® on KRYPTOR ® analyzers) technology, enzyme-linked fluorescent assay (ELFA). The sample types that may be used are; heparin, or EDTA plasma, or serum tubes. The indications for which the assays are FDA approved for vary. Verify that the assay you choose fits your reporting needs.

Slide 9:

Various suggested reference intervals and algorithms exist to be used with the procalcitonin assay. The reference intervals and algorithms used may be condition specific (such as to be used with either suspected respiratory infections or sepsis), specific to severity of illness, and/or patient location (i.e. the emergency department or intensive care unit). An expert consensus published by Schuetz et al. proposed the use of three different algorithms depending on the severity of a patient's clinical condition (mild, moderate, or severe). In patients with mild and moderate illness outside of the ICU, a cutoff of 0.25 ug/L was proposed to distinguish whether a bacterial infection is likely in situations where bacterial infection is uncertain. In patients with severe illness in the ICU a cutoff of 0.5 ug/L was proposed. Discontinuation of antibiotics was proposed when a decrease in procalcitonin lower than the cutoff, or a drop of >80% from peak procalcitonin results is observed. Additionally, most algorithms incorporate guidelines for when to perform follow-up procalcitonin testing to monitor its rise and fall. Viewers are directed to the publication for the full algorithms, in addition to the definition of each category for patient acuity[6].

Slide 10:

Conditions that may elevate procalcitonin besides bacterial infection include certain cancers, severe burns, trauma, after prolonged resuscitation, myocardial infarction, rhabdomyolysis, newborns, some autoimmune disorders, organ transplantation, liver dysfunction or severe renal disease (especially with dialysis), cardiogenic shock, malaria, invasive fungal infections, multiple organ dysfunction

syndrome, systemic inflammatory response syndrome (SIRS), cytokine storm and/or antibody therapy[7].

Slide 11:

Considerations to keep in mind when using procalcitonin testing is that assay does not identify pathogen. Procalcitonin may be low early in infection and localized infections, and in some immunocompromised patients7,8. A low procalcitonin does not exclude bacteria as etiology of infection. A single procalcitonin measurement has limited value. Serial measurements are more useful in clinical decisionmaking than one absolute result.

Slide 12:

Caution should be applied when testing procalcitonin in patients with conditions known to affect procalcitonin, as well as in patients with chronic infections[6]. Retrospective studies examining the success of procalcitonin-guided antibiotic therapy have given positive and neutral results, which could be due to mixed adherence to protocol conditions[9]. Also, more studies are needed that evaluate the value of testing procalcitonin in infections other than respiratory infections and systemic infections. Evidence for procalcitonin use with children and neonates, patients with acute conditions, pregnant women, and patients with compromised immune systems are not discussed in this presentation. Lastly, procalcitonin assays are not harmonized across platforms. Thus, caution should be used when following procalcitonin results longitudinally in a patient if the procalcitonin assay was performed using different methods.

Slide 13:

In implementing procalcitonin-guided antibiotic therapy the American Society for Clinical Pathology suggests using an evidence-based utilization plan when performing procalcitonin testing[10]. It is recommended to identify major users of procalcitonin assay and establish guidelines that are appropriate for the institution, setting, and patient population. Consider the patient population (ED, ICU, outpatient vs. inpatient) and other co-morbidities patients may have. Furthermore, reference intervals need to be optimized for the patient population including acuity level, the clinical setting, and type of infection suspected (respiratory versus systemic). It is beneficial that the test be available around the clock and on weekends, so that the information from the result can be used to inform clinicians who can act quickly to tailor the antimicrobial therapy. Education and training in the implementation phase and after are crucial.

Slide 14:

In summary: Procalcitonin testing can be incorporated into an institution's antibiotic stewardship program. Facilities are encouraged to implement an evidence-based algorithm that is appropriate for the use of procalcitonin testing in their population. Providing information and education to providers is essential when introducing procalcitonin testing

Slide 15: References

1. US Department of Health and Human Services, Centers for Disease Control. About antimicrobial resistance.
https://www.cdc.gov/drugresistance/about.html. (Accessed September 2019)
2. US Department of Health and Human Services, Centers for Disease Control. Antibiotic use in the United States, 2018
Update: Progress and Opportunities. https://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report-
2018-508.pdf. (Accessed September 2019)
3. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. Intensive Care Med 1998; 24:888-92
4. Lincheid P, Seboek D, Nylen E, Langer I, Schlatter M, Becker K, Keller U. In vitro and in vivo Calcitonin I gene
expression in parenchymal cells: a novel product of human adipose tissue. Endocrinology 2003; 144: 5578-84.
5. Müller B, Becker KL, Schächinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R. Calcitonin precursors are
reliable markers of sepsis in a medical intensive care unit. Critical Care Med 2000; 26: 977-83.
6. Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, González Del Castillo J, Jensen JU, Kanizsai PL, Kwa ALH, Krueger S, Luyt CE, Oppert M, Plebani M, Shlyapnikov SA, Toccafondi G, Townsend J, Welte T, Saeed K. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med 2019; 57(9); 1308-187.
7. Meisner M. Update on procalcitonin measurements. Ann Lab Med 2014;34:263–73.

8. Svaldi M, Hirber J, Lanthaler AI, Mayr O, Faes S, Peer E, Mitterer M. Procalcitonin-reduced sensitivity and specificity in heavily leucopenic and immunosuppressed patients. Br J Haematol 2001;115(1):53-7.

9. Chambliss, AB. Embracing procalcitonin for antimicrobial stewardship. Journal of Applied Lab Med 2019; 712-5

10. American Society for Clinical Pathology. Thirty things physicians and patients should question. September 4, 2019release. http://www.choosingwisely.org/societies/american-society-for-clinical-pathology/ (Accessed September 2019)

Slide 16: Disclosures

I have no disclosures

Slide 17: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Procalcitonin and Antibiotic Stewardship**."