Situation

Procalcitonin (PCT) is a biomarker that can be used to help with the initiation and de-escalation of antibiotics. There are various practices regarding the use of PCT within Ascension Ministries. Due to the waviering practices and understanding of the utility of PCT, there is opportunity to provide guidance on the clinical scenarios that PCT can offer the biggest impact.

Background

Inappropriate antimicrobial usage has several negative consequences, including increasing antimicrobial resistance, secondary complications such as Clostridium difficile infection (CDI), and increased costs due to medication costs as well as increased length of stay. Health-care systems are constantly evaluating methods to reduce inappropriate antimicrobial use including the development of antimicrobial stewardship (AMS) committees, empiric antibiotic therapy guides, automatic antibiotic stop orders, implementation of antibiotic indication orders and developing standard antibiotic treatment pathways that are evidence-based.

PCT is a precursor of calcitonin that increases during most bacterial infections and can be used as a biomarker in patients to support a presumptive diagnosis of bacterial infections (1). PCT is released in multiple tissues due to direct stimulation from cytokines such as tumor necrosis factor and IL-6. The magnitude of the increase also correlates to the severity of infection. The levels of PCT in viral infections and other non-infectious conditions are typically low, although some exceptions have been identified, such as infection with H1N1 and H7N9 influenza strains. PCT becomes detectable in 2-6 hours after a triggering event and typically peaks at 12-24 hours. PCT has been evaluated in a number of clinical research studies and has been shown to be a more specific marker for bacterial infections compared with more traditional markers such as C-reactive protein and WBC. Not all bacterial infections, however, trigger significant PCT elevations. Several studies of atypical organisms have reported low or only mildly elevated PCT values (<0.25 ng/mL) compared to typical infections, which may be a confounding factor for clinical utilization of PCT.

The utility of PCT has been extensively evaluated as a serum marker with the majority of the data found in respiratory infections. There is also increasing body of literature supporting the use in sepsis however there are distinct differences in how the results are interpreted. The use of PCT has shown utility in various settings such as the emergency department, intensive care unit and general medical/surgical units. The interpretive threshold has varied within the literature with values less than 0.25mcg/L typically indicating the absence of a bacterial infection and an alternative diagnosis should be considered (Table 1).
The U.S. Food and Drug Administration (FDA) approved the expanded use of certain PCT assays to include use by health care providers to determine if antibiotic treatment should be started or stopped in patients with lower respiratory tract infections (LRTIs), and for antibiotic discontinuation in patients with sepsis. The clinical implication for use in LRTI will be discussed below.

Review of Literature

Respiratory Infections

PCT has the most evidence as a diagnostic biomarker in respiratory infections. These data show that PCT should not be used as a traditional diagnostic test because it does not clearly identify specific pathogens. Yet its impact may be more pronounced in identifying the higher likelihood of a relevant bacterial infection that increases with increasing PCT concentrations and, conversely, falls if the PCT level is low. Muller and colleagues evaluated PCT in 925 patients with community-acquired pneumonia (CAP). In this cohort, 7.9% of subjects had bacteremic CAP with typical pathogens, mostly *Streptococcus pneumoniae*. PCT was increased significantly in bacteremic patients compared with patients without an identified bacterial pathogen. Less than 1% of patients had a positive blood culture when their initial PCT level was 0.25 mg/L, which increased to 20% in patients with PCT 2.5 mg/L. Schuetz and colleagues evaluated the use of PCT in 1359 patients with lower respiratory tract infections, which the majority of patients had CAP and/or COPD, using the PCT algorithm in Figure 1 below. The mean duration of antibiotics exposure in the PCT vs control groups was lower in all patients, 5.7 vs 8.7 days. The authors concluded that in patients with LRTIs, a strategy of PCT guidance compared with standard guidelines resulted in similar rates of adverse outcomes, as well as lower rates of antibiotic exposure and antibiotic-associated adverse effects.
Schuetz and colleagues evaluated 14 RCT with a total of 4211 patients that used PCT protocols to initiate antibiotics, discontinue, or both in patients with ARI. PCT directed therapy was evaluated in multiple settings including primary care, emergency medicine, and intensive care. PCT was found to significantly reduce the overall patient exposure to antibiotics with the PCT group receiving 4 days vs 8 days median in the control group. Treatment failure was also reduced overall but was not significant in most trials with failures in 397/2072 in the PCT group and 466/2116 in the control. Length of stay also saw a significant decrease but was not found to be significant in most of the individual trials and varied significantly by setting. The authors concluded that PCT had no benefit in mortality or rates of treatment failure, but a significant decrease in antibiotic consumption was found in all settings in patients with ARI diagnoses.
Chronic obstructive pulmonary disease (COPD) is a common disease that is the fourth leading cause of death. Approximately 50% of COPD exacerbations are caused by infections, therefore antibiotics are commonly utilized. This has led to antibiotics being commonly used for treatment despite the cause of exacerbation not being infection related. Verduri et al. evaluated the use of PCT guided therapy on duration of therapy or patients with severe COPD. If the PCT value was less than 0.1 mcg/L or less than 0.25 mcg/L and clinical stable, antibiotics was discontinued at day 3. The rate of exacerbations at 6 months was not significantly different in the PCT-guided group when compared to standard of care. Stolz et al. also evaluated the utility of PCT-guided therapy for patients experiencing an acute COPD exacerbation using a PCT value of 0.1 mcg/L or less to determine if antibiotics were discouraged. The use of PCT-guided therapy reduced antibiotic utilization and exposure by 30% compared to standard of care. The reduction of antimicrobial use did not result in a decline in clinical improvement between the groups. To assess the cost-effectiveness of PCT-guided therapy, Van der Maas et al. evaluated the economic consequences of PCT-guided therapy on incremental cost per antibiotic day in the Netherlands, Germany and United Kingdom. The incremental cost savings per day on antibiotic therapy avoided were (in Euros) e90 in the Netherlands, e125 in Germany, and e52 in the United Kingdom. In their sensitivity analyses, the PCT biomarker strategy was superior to current practice.

When treating COPD exacerbations it is important to consider PCT is useful for alerting clinicians the presence of bacterial infections. Falsely et al. described a sensitivity of 96%, however only exhibited a specificity of 31%. PCT was not able to distinguish bacterial from viral and noninfectious causes of AECOPD. Low PCT values do not completely exclude bacterial causes of PCT and should always be correlated with the clinical presentation.

Most of the clinical trials evaluating PCT algorithms excluded patients with active IV drug use, severe immunosuppression (other than corticosteroid use), life-threatening medical comorbidities leading to possible imminent death, patients with HAP (pneumonia developing ≥48 hours after hospital admission or if the patient was hospitalized within 14 days before presentation), and patients with chronic infection necessitating antibiotic treatment.

Sepsis

The literature supporting the use of procalcitonin in sepsis is growing, primarily using serial testing as a method of guiding antimicrobial treatment. Schroeder et al. evaluated the utility of a procalcitonin algorithm to shorten the length of antibiotics. Antibiotic treatment was discontinued if clinical signs of infection improved and the PCT value was either <1 ng/ml or decreased to <35% of the initial concentration within three consecutive days. PCT guidance led to a significant reduction of antibiotic treatment from 6.6±1.1 days compared with 8.3±0.7 days in control patients (p<0.001) along with a reduction of antibiotic treatment costs of 17.8% (p<0.01) without any adverse effects on outcome. Monitoring of PCT is a helpful tool for guiding antibiotic treatment in surgical intensive care patients with severe sepsis. Shehabi and colleagues evaluated the effect of a low PCT cut-off on antibiotic prescription and to describe the relationships between PCT plasma concentration and sepsis severity and mortality. The protocol instructed for the cessation of antibiotics in the following scenarios: initial or any subsequent PCT is level is 0.10 ng/ml; initial or any subsequent PCT is level 0.10–0.25 ng/ml and infection is highly unlikely or subsequent PCT level declined more than 90% from baseline. The overall median number of antibiotic treatment days were 9 (6–21) versus 11 (6–22), P = 0.58; in patients with positive pulmonary culture, 11 (7–27) versus 15 (8–27), P = 0.33; and in patients with septic shock, 9 (6–22) versus 11 (6–24), P = 0.64. In critically ill adults with undifferentiated infections, a PCT algorithm including 0.1 ng/ml cut-off did not achieve 25% reduction in duration of antibiotic treatment; however there was a trend towards a reduction in antibiotic...
use with PCT. Georgopoulou and colleagues also demonstrated that when serial PCT measurements within the first 48 hours show an increase of PCT or decrease by less than 30%, the empirically prescribed antimicrobial therapy should be reviewed.

Limitations of PCT

Some observational studies have suggested that the elderly have elevated baseline PCT levels, particularly those with underlying chronic kidney disease. PCT levels may also be elevated by other noninfectious causes, such as acute myocardial infarction, non-septic shock, small cell lung carcinoma or fungal infections. When using a PCT-guided algorithm for initiating antibiotic therapy, there is concern for clinical usefulness and antibiotic overtreatment in these patient populations who may be thought to have a bacterial infection based solely on a PCT level. PCT levels may be falsely low in patients with a localized infection or antimicrobial pretreatment, so caution should be taken to assess for patients with loculated effusions or previous antibiotic use prior to presentation. The success of PCT, particularly in sepsis is based on the understanding and adoption of processes that promote the appropriate use and interpretation of PCT values. Chu et al demonstrated that when PCT is used with no understanding or consistent process, it will have no effect on antimicrobial therapy.

Assessment

Procalcitonin guided decision making is an innovative approach to managing patients with LRTIs. If used serially, procalcitonin has demonstrated prognostic value for lower respiratory tract infection. Unfortunately, procalcitonin has minimal utility as an indicator to initiate or discontinue antibiotic therapy for sepsis.

The appropriate utility of PCT is largely dependent on the comprehensive understanding of how to use and interpret PCT values, particularly serial values. In February 2017, the Food and Drug Administration has approved the use of PCT to help determine antibiotic use in patients with LRTI and sepsis. However, the literature in septic patients is evolving, and its clinical application in sepsis must be further delineated. To ensure successful utilization, education and a detailed process must be implemented.

The evidence suggests that using PCT for patients with respiratory infections can lead to more parsimonious antibiotic use and de-escalation, without safety concerns.

Recommendation (Adults Population)
Procalcitonin (PCT) levels may be used as part of the antimicrobial stewardship efforts to assist with de-escalation/discontinuation of respiratory antimicrobials as outlined below:

- PCT should only be used at your facility if it is being run in-house or within the same health system. PCT should NOT be used if it has to be a send-out test.
- PCT should be ordered as a one-time order by the provider or pharmacist within 24 hours of initiation of antibiotic therapy in patients with active order for a systemic antibiotic for the indication of community-acquired pneumonia.
- Upon review of results and assessment of patients’ clinical status, it is recommended that the antimicrobial stewardship team discuss the option of discontinuation of antibiotics with the ordering provider if the procalcitonin level is less than 0.25 ug/L.
- Serial (multiple) PCT levels should NOT be ordered for any infection source, including sepsis.
- PCT should NOT be ordered in patients with LRTIs in the following scenarios:
  - Patients with HAP
  - Active IV drug use
  - Severe immunosuppression (other than corticosteroid use)
  - Life-threatening medical comorbidities leading to possible imminent death
  - Recent antibiotic use or patients with a suspected or confirmed concomitant non-pulmonary infection in which antibiotics are indicated.

- Provide the above recommendations and education to ED physicians and pharmacists at sites that have PCT testing.
- The antimicrobial stewardship team shall evaluate on a consistent basis whether the test is having an impact in improving antimicrobial use across the organization. Steps shall be taken to reinforce education with providers if the test is not having an impact in improving appropriate antimicrobial use.

Software Updates:
- Update verbiage on procalcitonin results in EHR to include clinical applicability for LRTIs that is consistent with the FDA-approved labeling.
- Create Sentri7 rule to identify patients receiving antibiotics with a PCT level 0.25.
Ascension Lower Respiratory Tract Infection Procalcitonin Algorithm for Community Acquired Pneumonia

1. **≤ 0.25 μg/L**
   - Antibiotic Cessation Encouraged

2. **> 0.25 μg/L**
   - Antibiotic Cessation Discouraged

**Decisions on antibiotic use should not be based solely on procalcitonin levels.** The information is not meant to be applied rigidly and followed in all cases. Clinical judgment must remain central to application of this information and treatment decisions need to be re-assessed based on clinical condition and results of further testing.
References:

13. Chu DC, Mehta AB, Walkey AJ. Practice Patterns and Outcomes Associated with Procalcitonin Use in Critically Ill Patients with Sepsis. CID 2017;00(00):1–7.