Antimicrobial Stewardship News

Volume 10, Number 8

August 2022

Pondering Procalcitonin

Introduction

Procalcitonin is a precursor protein of the hormone calcitonin and is produced by thyroid C cells. Normally peripheral serum levels of the hormone are undetectable; however, it is an acute phase reactant rising during times of significant stress on the body similar to other biomarkers such as ferritin or CRP. Procalcitonin became of particular interest as a biomarker when it was discovered to be relatively specific for bacterial infection as opposed to viral infection or other forms of inflammation.[1,2] Other factors that raised interest in this biomarker include its kinetics (rises within 4 hours of systemic infection, peaks within 8-24 hours, a half-life of 24 hours), and the relatively low influence of steroids on its production.[3] These properties led to many studies evaluating the utility of procalcitonin as a clinical decision aid for antibiotic initiation and duration. The most robust data are in the cases of lower respiratory tract infection and duration of therapy for severe sepsis.[4] The COVID-19 pandemic has generated some renewed interest in procalcitonin, and this newsletter seeks to review the potential utility and limitations of procalcitonin for antibiotic stewardship in the ICU, and some considerations in the COVID era.

Procalcitonin Guided Antibiotic Cessation in Severe Sepsis

Time to antibiotic initiation is critical to reducing mortality in sepsis and procalcitonin is not recommended in decision making around the initiation of antibiotics for patients presenting with severe sepsis syndrome.[5] However, optimal duration of antimicrobial therapy in patients with sepsis syndrome can be difficult to establish. In fact, antimicrobial use is often excessive in this scenario risking increasing antimicrobial resistance, healthcare costs, and incidence of *Clostridium difficile* infections.[6] A key use for procalcitonin is to potentially aid in antibiotic de-escalation in the ICU. Three recent meta-analyses in 2018 and 2019 looked at the use of procalcitonin for antimicrobial de-escalation in sepsis.[7,8,9] Most of the RCTs included in these studies used protocols which recommended antibiotic discontinuation when procalcitonin levels dropped below a cutoff of 0.5ng/mL or when levels had decreased by 80-90% from their peak.

Iankova et al performed a meta-analysis of 10 RCTs with 3489 ICU patients, 8 of which were included in the analysis for antibiotic duration.[7] Across these studies they found patients who were randomized to the procalcitonin based discontinuation protocol received 7.35 days of antibiotics on average as opposed to 8.85 days in the control arm (mean difference -1.49, 95% CI -2.27 to -0.71, P<001). There was no difference in ICU length of stay or mortality across the two groups supporting the safety of this approach.

Wirz et al performed a unique type of meta-analysis by directly pulling individual patient data from 11 RCTs and repeating statistical analysis.[8] This method allowed them to better control for the subtle differences in definitions of sepsis and patient outcomes across the trials. They found a procalcitonin based discontinuation protocol reduced antibiotic duration by 1.19 days and interestingly had a signal for decreased mortality in the procalcitonin arm. This mortality difference led to the Pepper at al study which included 16 RCTs and 5158 patients which again showed a reduction in antibiotic duration (1.31 days on average), and a possible signal for reduced mortality in the procalcitonin arm (risk ratio for morality 0.89, 95% CU 0.83-0.97).[9] Authors emphasized that this mortality benefit occurred primarily in studies with low protocol adherences (providers overriding PCT guidance) and felt this finding came with a high risk of bias and a low certainty of evidence.

In light of these data, the 2021 surviving sepsis guidelines make a weak recommendation for the use of procalcitonin with clinical evaluation in deciding when to

discontinue antibiotics when optimal duration is unclear.[5]

It is worth noting that more "real-world" studies have shown less significant reductions in antimicrobial use attributed to low adherence to procalcitonin based de-escalation protocols.[1] Additionally, many of these studies reviewed are older and were performed before shorter antibiotic treatment courses became overall more common for many infections. For example, the magnitude of this effect is likely smaller if procalcitonin is implemented in a facility where 5-7 days is the usual duration for respiratory infections. Additionally, the success of these interventions has generally depended on continuing education for frontline providers and the involvement of an antimicrobial stewardship team.[10]

Limitations

Procalcitonin has a number of significant limitations, primarily in the large number of other conditions which can result in false positive elevations. Important confounders which can result in false elevations of procalcitonin levels include:

- Massive Stress:
  - Major surgery[11]
  - Severe trauma or burns[12]
  - Cardiogenic shock[13]
  - Post-partum state[12]
  - Severe pancreatitis[2]

- Specific host factors leading to elevated procalcitonin:
  - Acute kidney injury and CKD have higher baseline procalcitonin levels and different thresholds may be needed[14]
  - Severe immunocompromise including hematologic malignancy, transplant populations or paraneoplastic syndromes can cause false elevations in serum levels[2]
  - Medications which stimulate cytokines, such as immunotherapies also cause significant elevations in procalcitonin levels[2]

In patients with these comorbid conditions, continued procalcitonin elevation would not necessarily support continuation of antimicrobial therapy, and for this reason an elevated procalcitonin alone would not be evidence of treatment failure. These comorbid conditions are common in the ICU setting. However, while false positive tests are of primary concern, there are also a number of scenarios which can result in false negative testing:[2]

- Timing: Procalcitonin does not start to rise until 2-4 hours after onset of systemic infection
- Atypical bacterial infection: Patient with mycoplasma and chlamydophila infections have often have normal or decreased procalcitonin levels
- Contained infection: Localized infections such as intraabdominal abscess, or local wound infections can result in normal procalcitonin levels

Given the broad range of confounders with this test clinical judgement is always of primary importance with procalcitonin being just one additional piece of the puzzle.

Application in COVID-19

As with everything these days, COVID is adding another layer of complication. SARS-COV-2 lower respiratory tract infection is associated with a systemic hyperinflammatory response. In this setting procalcitonin also becomes elevated. In fact, some groups even sought to look at procalcitonin as a prognostic indicator for severity of disease, though its performance was not superior to other similar biomarkers.[15] This elevation persists even in the absence of a concomitant bacterial pneumonia and severe infection, which poses a challenge to the use of procalcitonin as a stewardship tool in the COVID era.[16] A recent multicenter retrospective analysis by Fabre et al looked at the added value of procalcitonin testing in patients with COVID and for whom there was concern for possible superimposed community acquired pneumonia.[17] They found no added benefit to procalcitonin testing when compared to clinical criteria

alone. In fact, in patients who did NOT meet criteria for possible CAP, elevated procalcitonin level was associated with an additional 1.8 days (95% CI 1.01 -2.75) of CAP therapy further limiting its utility in this clinical setting.

Conclusions

There is a wealth of research looking into the application of procalcitonin as a biomarker for a vast array of infectious syndromes. These data are mixed, and there are many pros and cons for a hospital to consider before investing in this test, or putting out guidance related to these results.

If your hospital chooses to utilize procalcitonin testing the antimicrobial stewardship application with the most robust data is in the context of antimicrobial de-escalation in patients with sepsis and we would emphasize the following points:

- Use of a procalcitonin guided de-escalation strategy may help in decreasing unnecessary antibiotic use in patients with sepsis without a known source of infection
- In cases of severe sepsis procalcitonin should not be used to guide initiation of antibiotics
- While more specific than other biomarkers, there are still a wide array of conditions common in the ICU which can lead to false positive values.
- Procalcitonin is not reliable in the population of patients with hematologic malignancies or immune compromise
- Procalcitonin is elevated by SARS-COV2 infection further complicating its use during the pandemic
- Successful interventions require ongoing education and close involvement of the antimicrobial stewardship team
- Please do not hesitate to reach out to your DASON Liaison as you consider procalcitonin

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