ONLINE EXCLUSIVE

Consider this tool to reduce antibiotic-associated adverse events in patients with sepsis

Predictive biomarker procalcitonin can aid clinical decision-making on continued antibiotic treatment in this patient population.

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PRACTICE CHANGER

For patients hospitalized with sepsis, consider procalcitonin (PCT)-guided early discontinuation of antibiotic therapy for fewer infection-associated adverse events (AEs).

STRENGTH OF RECOMMENDATION

B: Based on a single randomized clinical trial.[1]

Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, et al. Procalcitonin to reduce long-term infection-associated adverse events in sepsis. A randomized trial. *Am J Respir Crit Care Med.* 2021;203:202-210. doi: 10.1164/rccm.202004-1201OC

ILLUSTRATIVE CASE

A 52-year-old woman presents to the emergency department complaining of dysuria and a fever. Her work-up yields a diagnosis of sepsis secondary to pyelonephritis and bacteremia. She is admitted and started on broad-spectrum antimicrobial therapy. The patient's symptoms improve significantly over the next 48 hours of treatment. When should antibiotic therapy be discontinued to reduce the patient's risk for antibiotic-associated AEs and to optimize antimicrobial stewardship?

Antimicrobial resistance is a growing public health risk associated with considerable morbidity and mortality, extended hospitalization, and increased medical expenditures.[2-4] Antibiotic stewardship is vital in curbing antimicrobial resistance. The predictive biomarker PCT has emerged as both a diagnostic and prognostic agent for numerous infectious diseases. It has recently received much attention as an adjunct to clinical judgment for discontinuation of antibiotic therapy in hospitalized patients with lower respiratory tract infections and/or sepsis.[5-11] Indeed, use of PCT guidance in these patients has resulted in decreased AEs, as well as an enhanced survival benefit.[5-15]

The utility of PCT-guided early discontinuation of antibiotics had yet to be studied in an expanded population of hospitalized patients with sepsis—especially with regard to AEs associated with multidrug-resistant organisms (MDROs) and *Clostridioides difficile* (formerly *Clostridium difficile*). The Surviving Sepsis Campaign's 2021 international guidelines support the use of PCT in conjunction with clinical evaluation for shortening the duration of antibiotic therapy ("weak recommendation, low quality of evidence").[16] They also suggest daily reassessment for de-escalation of antibiotic use ("weak recommendation, very low quality of evidence") as a possible way to decrease MDROs and AEs but state that more and better trials are needed.[15]

STUDY SUMMARY

PCT-guided intervention reduced infection-associated AEs

This pragmatic, real-world, multicenter, randomized clinical trial evaluated the use

This trial demonstrated the benefit of PCT-guided antimicrobial therapy in reducing infection-associated AEs, length of antibiotic treatment, and 28-day mortality for patients with sepsis.

of PCT-guided early discontinuation of antibiotic therapy in patients with sepsis, in hopes of decreasing infection-associated AEs related to prolonged antibiotic exposure.[1] The trial took place in 7 hospitals in Athens, Greece, with 266 patients randomized to the PCT-guided intervention or the standard of care (SOC)—the 2016 international guidelines for the management of sepsis and septic shock from the Surviving Sepsis campaign.[17] Study participants had sepsis, as defined by a sequential organ failure assessment (SOFA) score ≥ 2, and infections that included pneumonia, pyelonephritis, or bacteremia.[16] Pregnancy, lactation, HIV infection with a low CD4 count, neutropenia, cystic fibrosis, and viral, parasitic, or tuberculosis infections were exclusion criteria. Of note, all patients were managed on general medical wards and not in intensive care units.

Serum PCT samples were collected at baseline and then at Day 5 of therapy. Discontinuation of antibiotic therapy in the PCT trial arm occurred once PCT levels were ≤ 0.5 mcg/L or were reduced by at least 80%. If PCT levels did not meet one of these criteria, the lab test would be repeated daily and antibiotic therapy would continue until the rule was met. Neither patients nor investigators were blinded to the treatment assignments, but investigators in the SOC arm were kept unaware of Day 5 PCT results. In the PCT arm, 71% of participants met Day 5 criteria for stopping antibiotics, and a retrospective analysis indicated that a near-identical 70% in the SOC arm also would have met the same criteria.

The assessment of stool colonization with either *C difficile* or MDROs was done by stool cultures at baseline and on Days 7, 28, and 180.

The primary outcome of infection-associated AEs, which was evaluated at 180 days, was defined as new cases of *C difficile* or MDRO infection, or death associated with baseline infection with either *C difficile* or an MDRO. Of the 133 participants allocated to each trial arm, 8 patients in the intervention group and 2 in the SOC group withdrew consent prior to treatment in the intervention group, with the remaining 125 and 131 participants, respectively, completing the interventions and not lost to follow-up.

In an intention-to-treat analysis, 9 participants (7.2%; 95% CI, 3.8%-13.1%) in the PCT group compared with 20 participants (15.3%; 95% CI, 10.1%-22.4%) in the SOC group experienced the primary outcome of an antibiotic-associated AE at 180 days, resulting in a hazard ratio (HR) of 0.45 (95% CI, 0.2-0.98).

Secondary outcomes also favored the PCT arm regarding 28-day mortality (19 vs 37 patients; HR = 0.51; 95% CI, 0.29-0.89), median length of antibiotic treatment (5 days in the PCT group and 10 days in the SOC group; $P < .001$), and median hospitalization cost (24% greater in the SOC group; $P = .05$). Results for 180-day mortality were 30.4% in the PCT arm and 38.2% in the SOC arm (HR = 0.71; 95% CI, 0.42-1.19), thereby not achieving statistical significance.

WHAT'S NEW

An effective tool in reducing AEs in patients with sepsis

In this multicenter trial, PCT proved successful as a clinical decision tool for discontinuing antibiotic therapy and decreasing infection-associated AEs in patients with sepsis.

CAVEATS

A promising approach but its superiority is uncertain

The confidence interval for the AE hazard ratio was very wide, but significant, suggesting greater uncertainty and less precision in the chance of obtaining improved outcomes with PCT-guided intervention. However, these data also clarify that outcomes should (at least) not be worse with PCT-directed therapy.

CHALLENGES TO IMPLEMENTATION

Assay limitations and potential resistance to a new decision tool

The primary challenge to implementation is likely the availability of the PCT assay and the immediacy of turnaround time to enable physicians to make daily decisions regarding antibiotic therapy de-escalation. Addition-

ally, as with any new knowledge, local culture and physician buy-in may limit implementation of this ever-more-valuable patient care tool. **JFP**

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