frontiers | Frontiers in Analytical Science

TYPE Mini Review
PUBLISHED 03 July 2023
DOI 10.3389/frans.2023.1229003

OPEN ACCESS

EDITED BY
Martina Zangheri,
University of Bologna, Italy

REVIEWED BY
Qingchun Lan,
Fudan University, China

*CORRESPONDENCE
Luke Valencia,
lvalencia2@kumc.edu

RECEIVED 25 May 2023
ACCEPTED 12 June 2023
PUBLISHED 03 July 2023

CITATION
Valencia L (2023), PCT testing in sepsis protocols.
Front. Anal. Sci. 3:1229003.
doi: 10.3389/frans.2023.1229003

PCT testing in sepsis protocols

Luke Valencia*

School of Health Professionals, University of Kansas Medical Center, Kansas City, KS, United States

Septicemia is a prominent disease with a mortality rate of over 20%, making it one of the most expensive illnesses for hospitals in the United States. Many cells throughout the body release procalcitonin (PCT) in response to severe bacterial infection. This literature review attempts to assess PCT testing as a potential addition to sepsis protocols and to identify recommendations when implementing PCT testing into sepsis workups. The incorporation of PCT testing could significantly reduce the financial burden, antibiotic usage, and mortality rates in sepsis cases.

KEYWORDS

procalcitonin, sepsis, septicemia, protocol, guidelines

Introduction

Sepsis accounts for one million hospitalizations yearly, has a mortality rate of over 20%, and causes re-hospitalization in up to 40% of cases (Prescott, 2016). Due to these factors, septicemia is one of the most costly illnesses for hospitals in the United States (Jones et al., 2016). A patient who becomes septic due to a hospital-acquired infection can ultimately cost the treating hospitals over $180,000 in related medical expenses. As yet, these consequences have not led hospital administrations to reevaluate their policies, largely because most sepsis protocols in common practice rely on relatively outdated testing procedures. The most commonly ordered panel of laboratory tests for sepsis includes two sets of blood cultures, a lactate, a C-reactive protein, a complete blood cell count, a coagulation panel, and a chemistry panel. A major issue hospital staff face with utilizing current protocols is the initiation and continuation of antibiotics. Blood culture bottles can take multiple days to become positive and additional days to isolate the organism with an antibiotic susceptibility panel. The CRP, a bio-inflammatory marker that is neither sensitive nor specific, offers minimal insights into the disease process in response to treatment. Innovations are available to combat sepsis events by helping clinicians make real-time decisions on antibiotic usage more effectively.

Procalcitonin is an inflammatory biomarker that can be readily tested for and is currently offered by many clinical laboratories. Commonly ordered as PCT, it was initially approved for use in the setting of acute bacterial infections in the United States by the FDA in 2017 for diagnosis of lower respiratory tract infections (Katz et al., 2019). PCT testing helps to determine the probability of a bacterial infection turning into a sepsis event and aids in the selection and cessation of antibiotics in these situations. Utilization of a PCT test can help to reduce the time to diagnose sepsis and ensure the administration of appropriate antibiotics. Ultimately, the use of this test could aid in the reduction of patient mortality and the incurred costs associated with a sepsis event, in addition to promoting good antibiotic stewardship. In reviewing the current literature, this study looks to address whether PCT testing would beneficially impact hospitals and clinicians if included in surveillance and sepsis protocols.

Methods

The literature search utilized journal search engines on PubMed Central. When searching on PubMed Central, the terms "sepsis," "sepsis protocol," "PCT," and "procalcitonin" were used to begin the search. English-speaking journal articles, peer-reviewed and published within the last 7 years, were selected for analysis. Publications released prior to 2016 were excluded from the search, as they would be obsolete and not correlate with the population of interest, adult patients in United States hospital systems after the FDA approved the use of PCT testing. Articles were screened to include information pertaining to PCTs and sepsis and exclude those involving localized bacterial infections and lower respiratory tract infections. Articles selected after the screening process were thoroughly reviewed for reasonable connection to the research question.

Results

The search resulted in the identification of several peer-reviewed articles outlining PCT usage in sepsis workups and antibiotic initiation or cessation. In general, the articles concluded that the PCT is a positive predictor for progression to sepsis, more specific than standard lactic acid or CRP tests included in current protocols. Publications reviewing the effectiveness of sepsis biomarkers also noted that early initiation of antibiotics in patients with an elevated PCT helped to reduce mortality and length of hospital stay (Hohn et al., 2018; Wirz et al., 2018; Chow et al., 2021; Niederman et al., 2021; De Oro et al., 2019).

A retrospective review, *Impact of a Procalcitonin-Based Protocol on Antibiotic Exposure and Costs in Critically Ill Patients*, validated that PCT-based protocols for evaluation and treatment of sepsis are associated with reduced antibiotic usage and significant cost savings, with no decrease in patient mortality (Chow et al., 2021). Another study, *Initial Antimicrobial Management of Sepsis*, demonstrated a statistically significant ($p < 0.001$) reduction in treatment times for sepsis patients from 10.4 days without intervention based on PCT testing to 9.3 days with PCT testing. The study also showed a significantly improved survival rate ($p < 0.5$; 0.89 odds ratio) with PCT-guided antibiotic treatments in ICU patients (Niederman et al., 2021).

The general guideline surrounding intervention based on PCT testing is that antibiotics should be initiated in patients with an elevated PCT and should be discontinued when values begin to decline or normalize (Bartoletti et al., 2018; Neeser et al., 2019; Schuetz et al., 2019; Gauer et al., 2020; Kyriazopoulou et al., 2021; Velissaris et al., 2021). The time frame to reevaluate PCT levels varied from 6 hours to every 24 or 48 h. The parameters required to discontinue antibiotics varied slightly on the accepted "normalized" PCT levels. Published normalizing values, indicating control of the infection, ranged from a halving over 24 h to a ≥80% reduction from peak values or any PCT ≤0.5 μg/L at day five or later during antibiotic therapy.

Even though the PCT is sensitive to sepsis, one article suggests PCT ranges for sepsis confirmation are impacted by the source of infection and comorbidities, with the clinical setting changing the standard of treatment (Mierzchała-Pasierb and Lipińska-Gediga, 2019). The authors of this article suggest several other markers that could be better for sepsis diagnosis and monitoring, including testican-1, kallistatin, presepsin, and the mid-regional fragment of pro-adrenomedullin. Although these alternatives may provide advantages over PCT usage, there is less documented evidence supporting their abilities to indicate sepsis than there is supporting PCT. They are also less available to clinical facilities, with very few having immediate access to use in real-time monitoring for patient diagnosis and treatment. Until more information and usage become available, the PCT is a superior biomarker to those in current sepsis protocols.

Another challenge PCT usage faces is private insurance and Centers for Medicare & Medicaid Services (CMS) reimbursement. Because it is not yet recognized as a necessary component of standard sepsis protocols, hospitals may see minimal reimbursement; however, with minimal reimbursement, this still makes PCTs more cost-effective than non-reimbursed alternative testing not approved by the FDA.

Discussion

Overall, the evidence found during this literature review demonstrated that PCT is a vital test that should be included in sepsis workups. Utilization of this inflammatory biomarker provides a variety of benefits, including improved antibiotic stewardship, better patient outcomes, and significant financial savings. Current literature demonstrates that incorporating this inflammatory biomarker during a sepsis case reduces the time to antibiotic initiation and cessation. PCT elevation helps to identify patients with suspected bacteremia and addresses risks associated with the likelihood of progression to sepsis. This information can be used by clinicians to decide on early antibiotic initiation prior to severe clinical symptom presentation and blood culture results. Once antibiotics are started, the peak PCT value can be recorded and compared against preceding results for the purpose of antibiotic discontinuation. Even though several reviewed articles noted similar procedures for PCT utilization in antibiotic cessation, further research is needed to determine best practices regarding antibiotic cessation based on sequential PCT results. Both the *Initial Antimicrobial Management of Sepsis* study and the *Impact of a Procalcitonin* retrospective review noted that hospitals incorporating PCT testing in their sepsis algorithms had a reduced length of stay, leading to significant cost savings without affecting the quality of patient care. Based on the material reviewed, patients with a PCT <0.1 μg/L are strongly discouraged from receiving antibiotics, and patients with a PCT level above 2.0 μg/L should be strongly considered for antibiotic therapy. The PCT should be evaluated every 12–48 h, depending on the severity of the patient's condition, and discontinued once the PCT levels fall below 80% of the peak value or are consistently <0.5 μg/L. PCT values between 0.5 μg/L and 2.0 μg/L should be monitored, and antibiotic treatment should be guided by patient presentation and other diagnostic testing, such as molecular testing or culture for pathogen identification.

Alternative markers, such as kallistatin, testican-1, the mid-regional fragment of pro-adrenomedullin, and presepsin, could rival PCT testing in addressing sepsis events. PCT testing, although

widely available, is limited by insurance and CMS reimbursement; however, utilization of alternative markers in the clinical setting is uncommon as most facilities do not routinely offer these on their test menu and usually receive no insurance reimbursement, thus proving more difficult to use as a rapid identifier of sepsis. PCT testing provides immediate benefits, and the use of alternative testing *in lieu* should be addressed when alternative methods become more widely available and cost-effective. This may occur as sepsis protocols are reevaluated, and more evidence of the benefit of these alternatives is documented.

Limitations

The literature used in this review was selected from published and peer-reviewed articles published prior to 2017 through PubMed. Solely utilizing PubMed could miss relevant literature not included in this database. Articles that included pediatrics and neonates and literature not in English were excluded. PCT testing may be used in the diagnosis and treatment of lower respiratory tract infections, LTRI. This subject was excluded from the literature search as the focus was on sepsis cases involving PCT. As such, sepsis cases secondary to LRTI need to be reviewed separately. The information provided in this review should only be applied to the study's population: adult patients experiencing a sepsis event within United States healthcare systems. I would also like to note that because PCT testing was only recently approved by the FDA, the current literature lacks longitudinal studies incorporating the biomarker in hospital algorithms.

Author contributions

The author confirms being the sole contributor to this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Bartoletti, M., Antonelli, M., Blasi, F., Casagranda, I., Chieregato, A., Fumagalli, R., et al. Procalcitonin-guided antibiotic therapy: An expert consensus. *Clin. Chem. Laboratory Med. (CCLM)* (2018) 56(8):1223–1229. doi:10.1515/cclm-2018-0259

Chow, J., Markossian, T. W., Albarillo, F. S., Donahey, E. E., and Bobay, K. L. Impact of a procalcitonin-based protocol on antibiotic exposure and costs in critically Ill patients. *Crit. Care Explor* (2021) 3(11):e0571. PMID: 34778793; PMCID: PMC8580196. doi:10.1097/CCE.0000000000000571

De Oro, Nathalia, Gauthreaux, Maria E., Lamoureux, Julie, and Scott, Joseph. The use of procalcitonin as a sepsis marker in a community hospital. *J. Appl. Laboratory Med.* (2019) 3(4):545–552. doi:10.1373/jalm.2018.026955

Gauer, R., Forbes, D., and Boyer, N. Sepsis: Diagnosis and management. *Am. Fam. Physician* (2020) 101(7):409–418. PMID: 32227831.

Hohn, A., Balfer, N., Heising, B., Hertel, S., Wiemer, J. C., Hochreiter, M., et al. Adherence to a procalcitonin-guided antibiotic treatment protocol in patients with severe sepsis and septic shock. *Ann. Intensive Care* (2018) 8:68. doi:10.1186/s13613-018-0415-5

Jones, S. L., Ashton, C. M., Kiehne, L. B., Nicolas, J. C., Rose, A. L., Shirkey, B. A., et al. Outcomes and resource use of sepsis-associated stays by presence on admission, severity, and hospital type. *Med. Care* (2016) 54(3):303–310. PMID: 26759980; PMCID: PMC4751740. doi:10.1097/MLR.0000000000000481

Katz, S. E., Sartori, L. F., and Williams, D. J. Clinical progress note: Procalcitonin in the management of pediatric lower respiratory tract infection. *J. Hosp. Med.* (2019) 14(11):688–690. Epub 2019 Sep 18. PMID: 31532736; PMCID: PMC6827540. doi:10.12788/jhm.3301

Kyriazopoulou, E., Liaskou-Antoniou, L., Adamis, G., Panagaki, A., Melachroinopoulos, N., Drakou, E., et al. Procalcitonin to reduce long-term infection-associated adverse events in sepsis. A randomized trial. *Am. J. Respir. Crit. Care Med.* (2021) 203(2):202–210. PMID: 32757963; PMCID: PMC7874409. doi:10.1164/rccm.202004-1201OC

Mierzchała-Pasierb, M., and Lipińska-Gediga, M. Sepsis diagnosis and monitoring – procalcitonin as standard, but what next? *Anaesthesiol. Intensive Ther.* (2019) 51(4):299–305. doi:10.5114/ait.2019.88104

Neeser, O., Branche, A., Mueller, B., and Schuetz, P. How to implement procalcitonin testing in my practice. *Clin. Microbiol. Infect.* (2019) 25(10):1226–1230. Epub 2019 Jan 4. PMID: 30616016. doi:10.1016/j.cmi.2018.12.028

Niederman, M. S., Baron, R. M., Bouadma, L., Calandra, T., Daneman, N., DeWaele, J., et al. Initial antimicrobial management of sepsis. *Crit. Care* (2021) 25(1):307. PMID: 34446092; PMCID: PMC8390082. doi:10.1186/s13054-021-03736-w

Prescott, H. What are septic shock and sepsis? The facts behind these deadly conditions is sepsis fatal? Septic shock treatment & diagnosis (2016). Available at: https://www.michiganmedicine.org/health-lab/what-are-septic-shock-and-sepsis-facts-behind-these-deadly-conditions (Accessed January 29, 2023).

Schuetz, P., Beishuizen, A., Broyles, M., Ferrer, R., Gavazzi, G., Gluck, E., et al. Procalcitonin (PCT)-guided antibiotic stewardship: An international experts consensus on optimized clinical use. *Clin. Chem. Laboratory Med. (CCLM)* (2019) 57(9):1308–1318. doi:10.1515/cclm-2018-1181

Velissaris, D., Zareifopoulos, N., Lagadinou, M., Platanaki, C., Tsiotsios, K., Stavridis, E. L., et al. Procalcitonin and sepsis in the emergency department: An update. *Eur. Rev. Med. Pharmacol. Sci.* (2021) 25(1):466–479. PMID: 33506938. doi:10.26355/eurrev_202101_24416

Wirz, Y., Meier, M. A., Bouadma, L., Luyt, C. E., Wolff, M., Chastre, J., et al. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: A patient-level meta-analysis of randomized trials. *Crit. Care* (2018) 22:191. doi:10.1186/s13054-018-2125-7