EDITORIAL

Whetting the Rapid Diagnostic Tools for Sepsis

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Sepsis is a common clinical syndrome faced by physicians in the Emergency Department (ED) and intensive care units. It has been recognized by World Health Organization as a global health problem, with a reported incidence of 50 million cases and 11 million deaths in 2017.[1] Sepsis syndrome is a medical emergency and prompt diagnosis and treatment, including administration of antibiotics, within the first hour of arrival to the healthcare facility, has been shown to reduce morbidity and mortality.[2] The biggest challenge for physicians in the ED is the accurate diagnosis of sepsis in this critical period. An accurate diagnosis will decrease the indiscriminate administration of antibiotics and aid in decreasing the burden of antimicrobial resistance, and in proper triaging of the patients.

Blood culture is the gold standard test for the diagnosis of sepsis. But the increased turnaround time and low-test positivity pose a serious limitation for the utility of this test in the emergency department. The use of qSOFA (quick sequential organ failure assessment) score as a screening tool for sepsis has low sensitivity, and surviving sepsis guidelines no longer recommend its use as a single screening tool for sepsis.[3,4]

The use of biomarkers in the rapid and accurate diagnosis of sepsis has been researched extensively.[5] There are several biomarkers that are currently available as tests for rapid diagnosis of sepsis, but none of them have sufficient sensitivity and specificity to be employed in clinical practice. The extensively studied biomarkers, both in adult and neonatal sepsis are C-reactive protein (CRP), procalcitonin, and interleukin-6 (IL-6) which are produced in response to inflammation in the body. There are several newer biomarkers for the diagnosis of sepsis, to name a few are, soluble triggering receptors expressed on myeloid cells-1 (s-TREM-1), presepsin, CD64 and neutrophil to lymphocyte count ratio. No single biomarker has been found to have good clinical utility.

Neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin superfamily, is a large glycosylated protein molecule that is expressed by neutrophils, macrophages, hepatocytes, and renal tubular epithelial cells.[6] There is increased production of this protein during various pathological conditions. Studies have shown that serum and urine NGAL levels increase after renal injury and have good accuracy for predicting the development of acute kidney injury in both septic and non-septic patients.[7,8] The advantage of measuring NGAL levels is that it increases soon after renal insult, much earlier than creatinine levels.[9]

NGAL is also released by neutrophils at sites of inflammation and infection and exhibits innate immunity.[10] It has antibacterial action by scavenging bacterial siderophores and prevents bacteria from acquiring iron from the surroundings for bacterial growth. It was extrapolated that NGAL levels would increase in the setting of a bacterial infection and elevated values could be a marker of sepsis. The studies assessing the diagnostic utility of NGAL for sepsis, both in neonates and adults, have been limited to a few studies with small sample sizes.[11–13]

This study by Paul et al. evaluated the predictive value of NGAL for sepsis in the emergency department.[14] The findings suggest that NGAL is elevated in sepsis with a test sensitivity of 87% and specificity of 47% for sepsis, with a receiver operating curve (ROC) value of 0.69. There was no significant association between NGAL values to acute kidney injury in the study.

The more important point to be noted from the study is the development of a predictive model for sepsis from significant baseline characteristics, which included co-morbidities (diabetes), symptoms (rigors), qSOFA, and NGAL. The screening tool could not clearly differentiate between those with sepsis and without, and the authors concluded that a larger population is needed to test the efficacy of the tool.

It is clear from the evidence to date that, no single screening tool or test can accurately differentiate sepsis from systemic inflammatory response syndrome due to non-septic causes. Combination of biomarkers like procalcitonin, with NGAL, maybe more robust for both diagnosis and prognostication of sepsis.[12,15]

Bioscores for the diagnosis of sepsis has been proposed in the past, where a combination of qSOFA, procalcitonin, and CRP have been found to be useful in the diagnosis of sepsis at intensive care unit (ICU) admission.[16] The feasibility and availability of performing the tests in the ED, is a major limitation. The cut-off values for these tests across the studies have been variable and hence fixing a single diagnostic cut-off value is not possible, thereby limiting its applicability. The time taken for processing the laboratory samples for biomarkers can limit their use in the emergency department.

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Point-of-care testing for biomarkers will be the future for a diagnosis of sepsis in the ED, combined with clinical scoring systems. Point of care tests are available for lactates, CRP, procalcitonin, and NGAL. Large, multicenter studies are needed to develop the best bioscore with point of care tests, for rapid and accurate, diagnosis, prognostication, and triaging of patients with sepsis.

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References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: Analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200–211. DOI: 10.1016/S0140-6736(19)32989-7.
2. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34(6):1589–1596. DOI: 10.1097/01.CCM.0000217961.75225.E9.
3. Song JU, Sin CK, Park HK, Shim SR, Lee J. Performance of the quick sequential (sepsis-related) organ failure assessment score as a prognostic tool in infected patients outside the intensive care unit: A systematic review and meta-analysis. Crit Care 2018;22:1–3. DOI: 10.1186/s13054-018-1952-x.
4. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med 2021;47(11):1181–1247. DOI: 10.1097/CCM.0000000000005337.
5. Pierrakos C, Vincent JL. Sepsis biomarkers: A review. Critical Care 2010;14:1–8. DOI: https://doi.org/10.1186/cc8872.
6. Virzì GM, Clementi A, De Cal M, Cruz DN, Ronco C. Genomics and biological activity of neutrophil gelatinase-associated lipocalin in several clinical settings. Blood purif 2013;35(1–3):139–143. DOI: 10.1159/000346100.
7. Zhou H, Cui J, Lu Y, Sun J, Liu J. Meta-analysis of the diagnostic value of serum, plasma and urine neutrophil gelatinase-associated lipocalin for the detection of acute kidney injury in patients with sepsis. Exp Ther Med 2021;21(4):386. DOI: 10.3892/etm.2021.9817.
8. Pan HC, Yang SY, Chiou TT, Shiao CC, Wu CH, Huang CT, et al. Comparative accuracy of biomarkers for the prediction of hospital-acquired acute kidney injury: A systematic review and meta-analysis. Critical Care 2022;26(1):1–30. DOI: https://doi.org/10.1186/s13054-022-04223-6.
9. Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, et al. Association between increases in urinary neutrophil gelatinase–associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology 2006;105(3):485–491. DOI: 10.1097/00000542-200609000-00011.
10. Xu SY, Carlson M, Engström A, Garcia R, Peterson CG, Venge P. Purification and characterization of a human neutrophil lipocalin (HNL) from the secondary granules of human neutrophils. Scand J Clin Lab Invest 1994;54(5):365–376. DOI: 10.3109/00365519409088436.
11. Mårtensson J, Bell M, Oldner A, Xu S, Venge P, Martling CR. Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Med 2010;36:1333–1340. DOI: 10.1007/s00134-010-1887-4.
12. Wang M, Zhang Q, Zhao X, Dong G, Li C. Diagnostic and prognostic value of neutrophil gelatinase-associated lipocalin, matrix metalloproteinase-9, and tissue inhibitor of matrix metalloproteinases-1 for sepsis in the Emergency Department: An observational study. Crit Care 2014;18(6):634. DOI: 10.1186/s13054-014-0634-6.
13. Midan D, El-Gendy F, Abo ELAlla D, Kotb M. Clinical assessment of neutrophil gelatinase-associated lipocalin as a potential diagnostic marker for neonatal sepsis: A prospective cohort study. Ann Med 2022;54(1):1725–1731. DOI: 10.1007/s00134-010-1887-4.
14. Paul A, Newbigging NS, Lenin A, Gowri M, Varghese JS, Nell AJ, et al. Role of neutrophil gelatinase-associated lipocalin (NGAL) and other clinical parameters as predictors of bacterial sepsis in patients presenting to the emergency department with fever. Indian J Crit Care Med 2023;27(3):176–182.
15. Hur M, Kim H, Lee S, Cristofano F, Magrini L, Marino R, et al. Diagnostic and prognostic utilities of multimarkers approach using procalcitonin, B-type natriuretic peptide, and neutrophil gelatinase-associated lipocalin in critically ill patients with suspected sepsis. BMC Infect Dis 2014;14(1):1–8. DOI: 10.1186/1471-2334-14-224.
16. Yang Y, Xie J, Guo F, Longhini F, Gao Z, Huang Y, et al. Combination of C-reactive protein, procalcitonin and sepsis-related organ failure score for the diagnosis of sepsis in critical patients. Ann Intensive Care 2016;6:1–9. DOI: 10.1186/s13613-016-0153-5.