State of Globe: Neutrophil CD64: Is It a Reliable Biomarker for Sepsis?

CD64, also known as Fcγ receptor I, is among the members of the immunoglobulin (Ig) supergene family. Fc receptors are found on leukocytes, where they function to integrate response involving both the innate and acquired immunity. CD64 is constitutively expressed on macrophages, monocytes, and eosinophils, where it binds with IgG-type antibodies with high affinity. Normally, CD64 is present on the surface of a few circulating polymorphonuclear leukocytes, but neutrophil CD64 (nCD64) expression rapidly increases as a physiological response to microbial wall components, complement split products, and proinflammatory cytokines to up to 10-fold higher levels within 4–6 h.[1] Systemic inflammatory response syndrome (SIRS) is essentially an overstimulation of the immune system, usually caused by infection, major surgery, severe trauma, or burns. In SIRS, the proinflammatory response precedes the anti-inflammatory reaction. When a patient acquires a bacterial infection, it may lead to SIRS, which can further progress to sepsis, severe sepsis, septic shock, and finally death. Despite advances in antibiotic treatment, the mortality of sepsis is still high, with reported rates being up to 50%.[2] A major reason for this high mortality is that treatment is often started at a time where irreversible damage has already occurred. Undoubtedly, early initiation of antibiotic therapy increases the chance of survival if sepsis is clinically suspected.[3] The gold standard for diagnosing sepsis is still a blood culture.[4] A serious disadvantage of this test is that it can take up to 2 days before the final result is available, and during this period, the condition of a septic patient can rapidly deteriorate. Therefore, it is common practice to start therapy with broad-spectrum antibiotics before the results of blood culture are known. However, giving antibiotics to patients who have no bacterial infection is unnecessary and expensive and can contribute to developing bacterial resistance to antibiotics. Clinicians are in need of biomarkers that can reliably detect sepsis or exclude infection so that timely decisions on starting or terminating antibiotic treatment can be made.[4]

nCD64 is one such biomarker. In a large study of 548 critically ill patients, Dimoula *et al*. found that nCD64 identified sepsis with a sensitivity of 89% (81%–94%) and specificity of 87% (83%–90%).[5] Septic patients receiving inappropriate empirical antibiotics had persistently elevated nCD64 expression, whereas expression decreased over time in patients receiving appropriate antibiotics. In nonseptic patients, an increase in nCD64 expression predicted intensive care unit (ICU)-acquired infection ($n = 29$) with a sensitivity of 88% and specificity of 65%. However, there are studies showing low sensitivity of nCD64 as well. In one such study by Gros *et al.*, nCD64 predicted bacterial infection with a sensitivity and specificity of 63% (55%–71%) and 89% (83%–94%).[6] A meta-analysis reported that the overall pooled sensitivity of nCD64 as a sepsis diagnostic biomarker was 79% and specificity was 91%.[7] However, the authors noted a high degree of variability in the literature and concluded that the methodological quality of the included studies was suboptimal. In 2006, Livaditi *et al*. prospectively enrolled adult ICU patients with sepsis and measured nCD64 levels within 24 h of the onset of sepsis.[8] They found that nCD64 expression was significantly increased when compared with healthy controls and that higher levels correlated with worsening severity of sepsis as determined by clinicians upon enrollment and through the Acute Physiology and Chronic Health Evaluation II scoring. Furthermore, 28-day mortality was significantly associated with increased CD64 expression. Although the literature on the prognostic utility of nCD64 is not extensive, CD64 remains a promising candidate, given its potential to serve both diagnostic and prognostic roles.

In the current issue of Journal of Global Infectious Diseases, *et al*. presented a study, where 109 patients in the emergency department with SIRS were included to evaluate the ability of nCD64 to differentiate between SIRS due to sepsis and noninfective causes.[9] Results show that diagnostic accuracy for nCD64 is 82% with a sensitivity of 85% and specificity of 75%. This study adds to the previous studies, making the overwhelming evidence that nCD64 is good biomarker for sepsis. A limitation of the current and the previous studies is that many septic SIRS patients can never be proven to have a bacterial infection by a microbiological culture due to various reasons such as previous use of antibiotics, delayed culture collection, and faulty collection technique. Hence, they have to be treated and classified by clinical suspicion.

nCD64 expression can be reported by various ways such as percentage of neutrophils expressing CD64 or by mean fluorescence intensity. It is a simple test with a short turnaround time (1–2 h) and has a cost comparable with C-reactive protein and procalcitonin. This test can be performed at any laboratory with flow cytometry facilities and does not need other special equipment or expertise. However, each laboratory would need to establish its own cutoff values. These characteristics make nCD64 an attractive test to incorporate into daily clinical practice.

Sajal Ajmani, Vikas Agarwal, Mohan Gurjar[1]

Departments of Clinical Immunology and [1]Critical Care Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address for correspondence: Dr. Mohan Gurjar, Department of Critical Care Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow - 226 014, Uttar Pradesh, India.
E-mail: m.gurjar@rediffmail.com

References

1. Qureshi SS, Lewis SM, Gant VA, Treacher D, Davis BH, Brown KA. Increased distribution and expression of CD64 on blood polymorphonuclear cells from patients with the systemic inflammatory response syndrome (SIRS). Clin Exp Immunol 2001;125:258-65.
2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. Crit Care Med 2007;35:1244-50.
3. 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;34:1589-96.
4. Chan T, Gu F. Early diagnosis of sepsis using serum biomarkers. Expert Rev Mol Diagn 2011;11:487-96.
5. Dimoula A, Pradier O, Kassengera Z, Dalcomune D, Turkan H, Vincent JL. Serial determinations of neutrophil CD64 expression for the diagnosis and monitoring of sepsis in critically ill patients. Clin Infect Dis 2014;58:820-9.
6. Gros A, Roussel M, Sauvadet E, Gacouin A, Marqué S, Chimot L, *et al*. The sensitivity of neutrophil CD64 expression as a biomarker of bacterial infection is low in critically ill patients. Intensive Care Med. 2012;38(3):445-52.
7. Cid J, Aguinaco R, Sánchez R, García-Pardo G, Llorente A. Neutrophil CD64 expression as marker of bacterial infection: A systematic review and meta-analysis. J Infect 2010;60:313-9.
8. Livaditi O, Kotanidou A, Psarra A, Dimopoulou I, Sotiropoulou C, Augustatou K, *et al.* Neutrophil CD64 expression and serum IL-8: Sensitive early markers of severity and outcome in sepsis. Cytokine 2006;36:283-90.
9. Dal Ponte ST, Alegretti AP, Pilger DA, Rezende GP, Andrioli G, Ludwig HC, *et al*. Diagnostic accuracy of CD64 for sepsis in emergency department. J Glob Infect Dis 2018;10:42-6.

Access this article online	
Quick Response Code:	Website: www.jgid.org
	DOI: 10.4103/jgid.jgid_95_17

How to cite this article: Ajmani S, Agarwal V, Gurjar M. State of globe: Neutrophil CD64: Is it a reliable biomarker for sepsis?. J Global Infect Dis 2018;10:33-4.