NEUTROPHIL CD64 – A POTENTIAL BIOMARKER IN PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTIONS? – A LITERATURE REVIEW

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Complicated intra-abdominal infections (cIaIs) respresent a serious cause of morbidity and mortality. Early diagnosis and well-timed treatment can improve patients' outcome, whereas the delay in management often result in rapid progression to circulatory collapse, multiple organ failure, and death. Neutrophil CD64 antigen expression has been studied for several years as infectious and sepsis biomarker and has several characteristics that make it good for clinical employment. It has been suggested to be predictive of positive bacterial cultures and a useful test for management of sepsis and other significant bacterial infections. Our review concluded that the neutrophil CD64 expression could be a promising and meaningful biomarker in patients with cIaIs. It shows good potential for evaluating the severity of the disease and could give information about the outcome. However, more large studies should be performed before using it in clinical practice.

Keywords: biomarkers, CD64, prognosis, complicated intra-abdominal infections, sepsis

Introduction

Complicated intra-abdominal infections (cIaIs) are associated with mortality rates of 25% [1]. At the beginning of the 21st century, cIaIs remain responsible for 20% of sepsis in intensive care units (ICUs). Thus, cIaIs represent the second common cause for infectious morbidity and mortality after pneumonia [2, 3].

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Intra-abdominal infections (IaI) are classified as uncomplicated or complicated according to the spread of infection. Uncomplicated infections involve inflammation of the gastrointestinal organs without anatomic disruption. Usually, there are no difficulties with their treatment; but when it is delayed or incorrect, or the infection is nosocomial, the risk of evolution into a complicated one becomes considerable [4, 5]. cIaIs extend beyond the source organ into the peritoneal cavity and cause localized or diffuse peritonitis [6]. They are usually accompanied with sepsis that can evolve into septic shock and eventually to multiple organ dysfunction syndrome and death.

Sepsis is a life-threatening organ dysfunction based on dysregulated host response to infection – sepsis 3 definitions [7]. Organ dysfunction is defined as an increase of two points or more in the sequential organ failure assessment (SOFA) Score (sepsis clinical criteria). For patients with infections, an increase of two SOFA points gives an overall mortality rate of 10%. Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can promptly be identified at the bedside with quick SOFA (qSOFA). qSOFA uses these 3 criteria (HAT):

Hypotension: systolic blood pressure less than or equal to 100 mmHg,

Altered mental status: (Glasgow Coma Scale less than 15 points),

Tachypnea: respiratory rate greater than or equal to 22 min.

Septic shock is the presence of sepsis with (despite adequate volume resuscitation) both the persistent hypotension-requiring vasopressors to maintain mean arterial pressure greater than or equal to 65 mm Hg and lactate greater than or equal to 2 mmol/L. With these criteria, hospital mortality is in excess of 40% [8].

cIaIs include a wide range of patient populations, which make it difficult to suggest a general treatment regimen and show the need of an individual approach to each patient. There are a lot of different factors influencing the prognosis of patients with cIaIs, including poor nutrition, preexisting diseases, advanced age, prolonged hospitalization before therapy, immunosuppression, diffuse peritonitis, septic shock, poor source control, organ failures, and presence of nosocomial agents [9]. Sepsis remains important and leading cause of morbidity and mortality in cIaIs [10]. Early diagnosis and well-timed treatment can improve patients' outcome [11, 12]; therefore, there is an instant need of exact methods that can diagnose sepsis in early stages, make early prognostic evaluation, and define the aggressiveness of conservative treatment and surgical management. Great hopes for dealing with these problems are focused on the group of biomarkers.

In 2010, Pierrakos and Vincent [13] established that nearly 180 different biomarkers for sepsis have been described in the literature to date. Nowadays, this number is surely larger. Some of them like white blood cell (WBC) count, erythrocyte sedimentation rate, C-reactive protein (CRP), and procalcitonine (PCT) are already used in clinical practice, but their efficacy is limited by the lack of sufficient sensitivity and specificity. At this moment, one thing is for sure,

there is no ideal sepsis biomarker and we are still looking for it. In our article, we reviewed various studies that show the neutrophil CD64 potential for the diagnosis, prognosis, and disease severity.

Neutrophil CD64

CD64 antigen expression on neutrophils has been under investigation for several years as a biomarker of infection and sepsis. It has several characteristics that make this marker well suited for clinical application: CD64 expression on resting neutrophils is low and after activation, it is significantly upregulated within few hours. Once the activation stimulus disappears, CD64 expression returns to its basal level in few days. Moreover, CD64 is relatively stable after blood collection and the assay is straightforward and requires only small sample volume. Last but not least, CD64 expression represents a physiological process, which plays a key role in the innate immune response: neutrophils acting as phagocytes [14].

CD64, a leukocyte surface antigen, is a high-affinity Fc receptor, which binds to monomeric IgG. The Fc receptors are involved with the innate and adaptive immune response, stimulating either phagocytosis or antibody-mediated cytotoxicity [15]. Neutrophil CD64 expression rapidly increases in the presence of microbial wall components, complement split products, and some proinflammatory cytokines, such as interferon gamma and granulocyte colony-stimulating factor [16]. CD64 is constitutively expressed on neutrophils at low levels during the absence of infection, but when activated by proinflammatory cytokines, it is rapidly upregulated up to tenfold higher levels [14]. The upregulation of CD64 on the polymorphonuclear (PMN) cell surface is considered to be an early step in the innate immune response to bacterial infection [17, 18]. CD64 expression increases hours after activation of innate immunity and therefore it can reflect at the very early stages of infection and can help make early diagnosis and prognosis. The CD64 index has been suggested to be predictive of positive bacterial cultures and a useful test for management of sepsis and other significant bacterial infections [19].

The most common method for neutrophil CD64 determination is flow cytometry. Unfortunately, this determination lacks standardization.

Diagnostic Value

First, in 2006, Davis et al. [17] in prospective analysis of 100 blood samples from the emergency department patients concluded that neutrophil CD64 expression quantitation provides improved diagnostic detection of infection/sepsis with sensitivity of 87.9% and specificity of 71.2% compared with the standard diagnostic tests used in current medical practice. In 2012, Gros et al. [20] in

their study including 293 patients with a Simplified Acute Physiology Score II of 45 (31–59) found bacterial infection in 148 patients and documented systemic inflammatory response syndrome or non-bacterial infection in 145 patients. A CD64 index >2.2 predicted bacterial infection with a specificity and sensitivity of 89% and 63%, respectively. The authors showed that because of its weak sensitivity for bacterial infection, CD64 index should be combined with other more sensitive biomarkers. Gibot et al. [21] in their study with 300 patients showed that serum concentrations of PMN CD64 index were higher in patients with sepsis compared with all others. The cut-off CD64 index was 1.62. A Brazilian study conducted in 2014 including 93 patients indicates that high expression of CD64 is an important indicator in the diagnosis of infection and sepsis [22]. In 2014, Righi et al. [23] evaluated 93 consecutive patients presented with infection signs on admission. CD64 neutrophil expression, CRP, and WBC count were investigated. CRP and CD64 showed a significant difference between septic and non-septic patients, respectively. Receiver operating characteristic (ROC) curves of CD64, CRP, and WBC count showed the superiority of CD64: considering a cut-off of 2000 antibody-binding capacity for infection, sensitivity was 90.2%, and specificity was 96.9% in comparison with CRP (85.2% sensitivity and 46.9% specificity for cut-off of 10 mg/L). CD64 neutrophil expression, but not CRP, was able to differentiate the septic stages ($p < 0.001$). Their conclusion is that neutrophil CD64 represents a sensitive and specific marker for the early diagnosis of systemic infections in adult patients admitted to ICU, superior to traditional hematological parameters and CRP. In 2014, prospective observational study with 468 patients, Dimoula et al. [24] showed that septic patients had higher nCD64 expression at admission than did non-septic patients. A cut-off nCD64 expression at admission of 230 median fluorescence intensity (MFI) identified sepsis with a sensitivity of 89% (81%–94%) and specificity of 87% (83%–90%). Septic patients receiving inappropriate empirical antibiotics had persistently elevated nCD64 expression, whereas expression decreased over time in patients receiving appropriate antibiotics. In non-septic patients, an increase in nCD64 expression ≥40 MFI predicted ICU-acquired infection ($n = 29$) with a sensitivity of 88% and specificity of 65%. Neutrophil CD64 expression was associated with the severity of sepsis. Patients with septic shock had significantly higher nCD64 expression than did other septic patients [median (lower–upper quartile) 413 (324–493) vs. 331 (268–395) MFI; $p < 0.001$]. Dimoula et al. concluded that measurement of nCD64 expression at ICU admission, especially when combined with CRP concentrations, is useful in diagnosing sepsis. Serial determinations of nCD64 could be used for monitoring purposes.

On the basis of 2013 meta-analysis with a total of 26 studies including 3,944 patients, neutrophil CD64 expression could be a promising and meaningful biomarker for diagnosing bacterial infection with sensitivity of 76% and

specificity of 85% [16]. Nevertheless, more large prospective studies should be carried out before the neutrophil CD64 test is used widely in the clinical setting because of the various cut-off values.

Meta-analysis from 2015 including a total of eight studies with 1,986 patients showed that nCD64 expression is a helpful marker for an early diagnosis of sepsis in critically ill patients with sensitivity and specificity 76% [95% confidence interval (CI): 73%–78%] and 85% (95% CI: 82%–87%), respectively [25]. The results of the test should not be used alone to diagnose sepsis, but instead should be interpreted in combination with medical history, physical examination, and other test results. The authors could not determine the ideal cut-off point for the nCD64 test, because there were several assay methods for nCD64 test and they did not have enough data.

However, all of these studies did not show which patients are from surgical department or have abdominal sepsis (except Dimoula et al.). Maybe, there will be a benefit for future meta-analysis including only surgical patients that could determine the diagnostic potential of nCD64 for cIaIs (Table I).

Disease Severity Value

Neutrophil CD64 expression is useful not only for the diagnosis of sepsis, but several authors have also reported its value as severity marker: patients with septic shock generally show higher CD64 values than patients with sepsis [14]. Livaditi et al. [26] studied several biomarkers that best evaluate the severity of sepsis [via Acute Physiology And Chronic Health Evaluation II Score (APACHE II)] – CD64, IL-8, and IL-6 ($p < 0.01$), and the severity of organ failure (via SOFA) – CD64 and IL-8. CD64 expression was associated with mortality within 28 days (OR = 1.3, $p = 0.01$) and ROC curve analysis showed high sensitivity and specificity for predicting sepsis stages and the 28-day mortality. The authors

Table I. Characteristics of the studies

Authors	Year	Type of study	Medical department	Number of patients	Cut-off value	Sensitivity (%)	Specificity (%)
Davis et al.	2006	Prospective	Emergency department	100	2000 MESF	87.9	71.2
Gros et al.	2012	Prospective	ICU	293	2.2 index	63	89
Gibot et al.	2012	Prospective	ICU	300	1.62 index	84.4	95.2
Farias et al.	2014	Prospective	ICU	93	1.51%	No data	No data
Righi et al.	2014	Prospective	ICU	93	2000 ABC	90.2	96.9
Dimoula et al.	2014	Prospective	ICU	468	230 MFI	89	87
Li et al.	2013	Meta-analysis	–	3,944	No cut-off	76	85
Wang et al.	2015	Meta-analysis	–	1,986	No cut-off	76	85

conclude that there is an early increase of neutrophil CD64 expression during sepsis. Based on this single measurement, it is possible to reliably assess the stage, detect the severity, and predict the 28-day mortality of sepsis. A prospective study of Hsu et al. [27] with 66 patients showed that CD64 expression and the ratio of CD64/CD16 significantly increased with the severity of sepsis. CD64, CD64/CD16, and PCT all significantly predicted sepsis, septic shock, and bacteremia. CD64 was associated with mortality and was better than PCT for identifying patients who required treatment with antibiotics. Icardi et al. [19] found in 109 patients over a 2-month period that a CD64 index of <1.19 was predictive of "no growth" blood culture results. An index of >1.19 was predictive of an ultimate clinical and/or culture diagnosis of infection with a sensitivity and specificity of 94.6% and 88.7%, respectively. Positive and negative predictive values were 89.8% and 94%, respectively. The CD64 index is a useful and inexpensive test for improving the diagnosis and management of hospital patients with bacterial infection. It can be readily performed by clinical laboratories and could result in considerable savings for the institution.

Prognostic Value

According to some authors, nCD64 contains prognostic significance as well. However, the available data are highly contradictory. Some publications demonstrated that survival could be predicted by a low expression of CD64 [14]. Fischer et al. [28] showed in their study that CD64 expression was greater in patients with septic shock than in patients without sepsis. Moreover, CD64 expression was only initially and transiently elevated in most survivors (9/10) and non-survivors (8/12) of septic shock. These authors concluded that decreased neutrophil CD64 expression in an acutely ill population with septic shock may reflect the development of a non-responsive state as well as the early downregulation of neutrophil activation prior to the resolution of an ongoing infection. Chen et al. [29] in their cohort consisting of 797 ICU patients found that CD64 had the greatest power for predicting ICU mortality other than APACHE II scores. They showed that CD64 provides superior capability to predict ICU mortality compared with CRP. In addition, the combined use of CD64 levels and APACHE II scores significantly improved the accuracy in predicting ICU mortality. CD64 index is higher in non-survivors (2.94 ± 1.86) than in survivors (1.62 ± 1.15). Overall, CD64 is a useful biomarker for assessing the health status of patients enrolled in the ICU.

Other authors indicated that high nCD64 could be a marker of favorable prognosis. Probably, the small patient groups and the study designs explain these conflicting findings. Danikas et al. [30] showed in their publication that

reduced phagocytic activity of neutrophils during the first 24 h after admission was a negative predictor for survival. Increased expression of CD64 antigen on PMN cells and monocytes was favorably correlated to the patients' survival. In multivariate analysis, the phagocytic activity of PMNs was the only independent predictor factor for survival. Patients with PMN phagocytic activity (37%) had higher expression of CD64 on monocytes and PMNs and better outcome. Reduced phagocytic activity of neutrophils may represent a state of neutrophil inactivation. Cid et al. [31] prospectively included 132 patients with fever $\geq$38 °C ($\geq$100.4 °F) during the last 24 h and measured CD64 expression on neutrophils the day after the admission at the emergency department. They followed the patients until full recovery or death. There were 115 (87%) patients with bacterial infection and 108 (94%) of them survived. There were 17 (13%) patients without bacterial infection and 12 (71%) of them survived. Patients with bacterial infection and patients who survived showed a CD64 index higher when compared with patients without bacterial infection and patients who died, respectively (3.7 ± 3.2 vs. 2.5 ± 2.3; $p = 0.03$ and 3.7 ± 3.1 vs. 1.7 ± 0.6; $p = 0.002$; Mann–Whitney U test). The ROC curve analysis for detecting bacterial infection and predicting survival with the CD64 index showed an area under curve of 0.66 (95% CI: 0.52–0.8; $p = 0.03$) and 0.71 (95% CI: 0.57–0.85; $p = 0.01$), respectively. Diagnostic accuracy and prognostic value of CD64 expression was good in adult patients with fever.

Conclusions

Because of the complexity of sepsis and sepsis pathophysiological mechanisms, probably in the near future, it will be very hard to find the ideal biomarker. However, we think that neutrophil CD64 deserves attention, because it demonstrates very good sensitivity and specificity as diagnostic marker for sepsis. Our opinion is that nCD64 could be a reliable diagnostic biomarker in patients with cIaIs. It also shows good potenitial for defining the disease severity, but there is contradictory data about its prognostic value. Of course, further large multicenter studies especially with more surgical patients should be performed, before using this biomarker in clinical practice.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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