Eosinopenia as a Diagnostic and Prognostic Marker in Sepsis

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ABSTRACT

Introduction: Sepsis is one of the most common causes of morbidity and mortality in the intensive care unit (ICU). An early diagnosis of sepsis using a sensitive and specific marker would facilitate prompt antibiotic therapy and reduce patient mortality. Eosinopenia typically accompanies acute response to infection and eosinophil count is a rapid and inexpensive test which could be used to differentiate between infective and other causes of the systemic inflammatory response syndrome (SIRS) in critically ill patients.

Material and Methods: A prospective study of patients admitted to the medical ICU was conducted and eosinophil counts measured at admission. Eosinophil count <50cells/cu.mm was considered as eosinopenia. Patients were followed up for a diagnosis and outcome.

Results: 146 participants were enrolled in the study out of which 112 were found to have sepsis or a sepsis related condition. 98.5% of patients who had eosinopenia, had sepsis and 74% of patients with eosinophil counts>100cell/cu.mm had no sepsis (P<0.0001). Sensitivity of eosinopenia in the diagnosis of sepsis was 65% and specificity, 97%. As 76.9% of patients who expired had AEC<50cells/cu.mm, it suggests that eosinopenia may be useful in predicting outcomes in critically ill patients.

Conclusion: Eosinopenia, as a rapid and inexpensive indicator of sepsis on admission in addition to its prognostic value, may be a useful tool in guiding physicians in the management of critically ill patients.

Keywords: SIRS, Infection, Critically Ill, Procalcitonin

INTRODUCTION

Sepsis is one of the most common causes of morbidity and mortality in the intensive care unit (ICU).[1] It is characterized by clinical and laboratory parameters that are not specific and can be misleading because these parameters often change in critically ill patients with systemic inflammatory response syndrome (SIRS).[2]

An early diagnosis of sepsis before receiving the results of microbial culture would certainly facilitate the choice of antibiotic therapy and reduce patient mortality. An ideal marker of infection would be highly specific, highly sensitive, easy to measure, rapid, inexpensive and, correlated with the severity and prognosis of infection.

Recent studies have suggested an important role of procalcitonin plasma concentration monitoring[3], and more recently the triggering receptor expressed on myeloid cells-1[4], in the clinical diagnosis of sepsis, because they differentiate sepsis from non-infectious causes of SIRS. However, in developing countries such as ours, these remain expensive and inaccessible to most patients.

Eosinopenia and neutrophilia typically accompany the responses to acute stress or acute infection.[5]

Eosinophil production is regulated by interleukin-3 (IL-3), interleukin-5 (IL-5) and, granulocyte macrophage colony stimulating factor (GM-CSF) which are not significantly activated in sepsis thus causing eosinopenia.[6] Also, the initial eosinopenic response to acute infections may be the result of a rapid peripheral sequestration of circulating eosinophils into the inflammatory site itself by chemotactic substances released during acute inflammation.[7,8]

Study aimed to assess the value of eosinopenia in differentiating sepsis-related conditions (sepsis, severe sepsis, septic shock) from other non-sepsis conditions including SIRS in critically ill patients, to compare eosinopenia with C-reactive protein (CRP) and leukocytosis, both proven markers of sepsis and to assess the correlation between eosinopenia and prognosis of sepsis related conditions.

MATERIAL AND METHODS

Patients fulfilling the inclusion criteria admitted to Kasturba Hospital, Manipal Medical ICUs during October 2009 to June 2011 were included in the study. The target sample size was 129 however, 146 patients were included. Patients with immunocompromised states, concomitant parasitic infestations and allergic disorders were excluded from the study. The participants were subjected to a detailed clinical examination by a predesigned proforma along with the relevant investigations as per the history and were then followed up till the time of discharge (to look for improvementor death). Blood samples were collected in microtubes containing ethylenediaminetetraacetic acid anticoagulant. The white blood cell count and the eosinophil cell count were performed by the Coulter hematology analyzer.

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Definitions[9,10,11]

- Eosinopenia: AEC <50cells/cu.mm
- SIRS: 2 or more of the following criteria:
  - Body temperature >38°C or <36°C
  - Heart rate >90 beats/min
  - Respiratory rate >20/min or PaCO2 < 32 Torr
  - White blood cell (WBC) count >12,000 cells/mm3, <4,000 cells/mm3, or >10% immature forms
- Sepsis: SIRS associated with the presence of an infectious process.
- Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension (systolic blood pressure <90 mmHg or a reduction ≥ 40 mmHg from baseline).
- Septic shock: A subset of severe sepsis and is defined as a persisting sepsis-induced hypotension despite adequate fluid resuscitation.
- Diagnosis of infection
  1. Culture/microscopy of a pathogen from a clinical focus.
  2. Clinical lower respiratory tract symptoms and radiographic pulmonary abnormalities that are at least segmental and not due to pre-existing or other known causes.
  3. Infection documented with another imaging technique.
  4. Lumbar puncture when meningitis was suspected.
  5. Obvious clinical infection (erysipelas).
  6. Identification of a pathogen by serology or by PCR.

STATISTICAL ANALYSIS

- Analysis of data was done using SPSS 16.0
- A *P* value of <0.005 was regarded as statistically significant.

RESULTS

Population profile

A total of 146 patients were included the study out of which 34 were classified as having 'no sepsis' and the remaining as having a 'sepsis related condition' which included sepsis, severe sepsis and septic shock (Fig. 1). Patients classified as having no sepsis included non-infectious causes of SIRS such as pancreatitis, drug overdose and poisoning.

Patient Characteristics

68.5% of patients included in the study were male. The mean age was 53.3 years. 50% of patients had a premorbid illness which included diabetes mellitus, hypertension, ischaemic heart disease (IHD), chronic liver disease (CLD), chronic renal failure (CRF and), chronic obstructive pulmonary disease (COPD)

Diagnosis of infection

The diagnosis of infection to classify a patient with SIRS as having sepsis was based on the following criteria- i)Positivity of blood culture or culture/microscopy of urine, sputum/ respiratory secretions, cerebrospinal/ascitic/pleural fluid, pus and wound swabs; ii) Serology such as Leptospira IgM, Scrub typhus IgM, Weil-Felix or Widal tests; iii) Imaging including radiographic pulmonary abnormalities that are

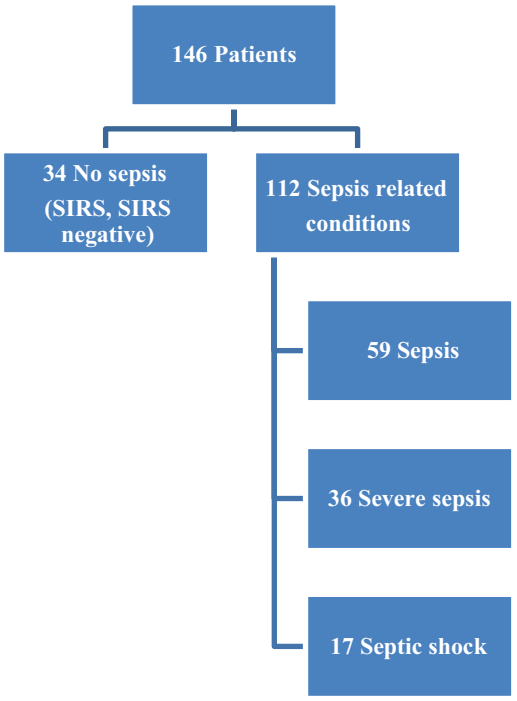


Figure-1: Population profile

Investigation	No. of Patients	Percent
Blood culture	22	15.07%
Other culture/microscopy	50	34.25%
Serology	14	9.59%
Imaging	56	38.36%
Clinical	4	2.74%

Table-1: Diagnosis of infection

No. of SIRS Criteria	No. of Patients	Percent
<2	16	10.96%
2	73	50%
>2	57	39.04%

Table-2: SIRS criteria

	No. of Patients	Percent
No sepsis	34	23.29%
Sepsis	59	40.41%
Severe sepsis	36	24.66%
Septic shock	17	11.64%

Table-3: Severity of sepsis

AEC	No. of Patients	Percent
<50	74	50.68%
50-100	29	19.86%
>100	43	29.45%

Table-4: AEC

	Sensitivity	Specificity
Eosinopenia	65%	97%
CRP	92%	9%
Leukocytosis	62%	53%

Table-5: Sensitivity and specificity

at least segmental, ultrasound or computed tomography findings of an abscess and iv) Obvious clinical infection such as erysipelas (Refer Table 1)

In the majority of cases, a diagnosis of infection was made by an imaging technique or culture/microscopy of specimens other than blood.

SIRS Criteria

All patients were classified as SIRS positive or negative based on the criteria defined above (Refer Table 2)

10.96% of patients did not satisfy criteria for SIRS and were hence, automatically included in the 'no sepsis' group.

Severity of sepsis

Patients were divided into those with no sepsis, sepsis, severe sepsis and septic shock as defined above (Refer Table 3)

Absolute eosinophil count (AEC)

Absolute esosinophil count of <50cells/cu.mm was defined as eosinopenia. As the Coulter analyzer could not measure eosinophil count <10cells/cu.mm, AEC was defined as a categorical variable and divided into 3 categories of AEC<50, 50-100 and >100cell/cu.mm (Refer Table 4).

50% of the patients were found to have an absolute eosinophil count less than 50cells/cu.mm.

Outcome

Patients were followed up to look for improvement or death. 52 (35.62%) patients included in the study expired after admission to ICU.

Analysis

Eosinopenia and differentiation of sepsis from non-sepsis (*P = <0.001*)

AEC was calculated for patients in both sepsis and non-sepsis groups (Refer Graph 1).

98.65% of patients with eosinopenia (AEC less than 50cells/cu.mm) had sepsis. 74.42% of patients with AEC>100cell/cu.mm were found to have no sepsis. Data was found to be statistically significant with a p value of <0.0001.

Eosinopenia and Severity of sepsis

AEC values did not help to differentiate between sepsis related conditions (Refer Graph 2)

The above graph reflects the utility of eosinopenia in differentiating sepsis related conditions from non-sepsis but that it is not very useful in predicting the severity of sepsis.

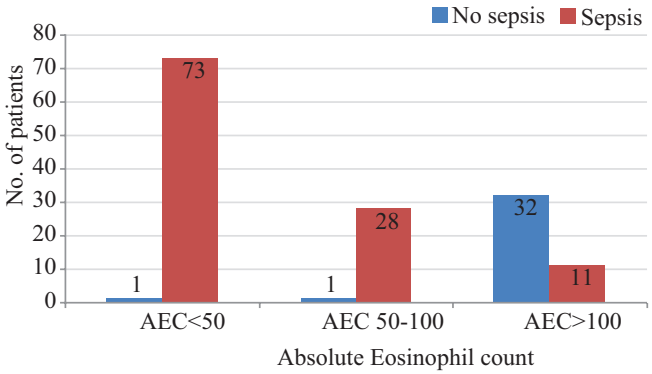
Sensitivity and Specificity of Eosinopenia, CRP and Leukocytois in the diagnosis of Sepsis

The sensitivity and specificity of Eosinopenia, CRP and Leukocytosis (WBC count > 12,000 cells/cu.mm) in the diagnosis of sepsis were compared (Refer Table 5).

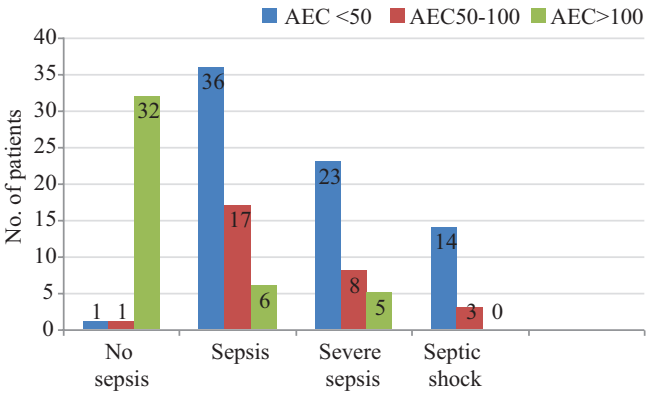
Sensitivity of eosinopenia in the diagnosis of sepsis was 65% and specificity, 97%.CRP was more sensitive but not as specific. Leukocytosis was comparable to eosinopenia in sensitivity but not in specificity.

AEC and CRP (*P = <0.001*)

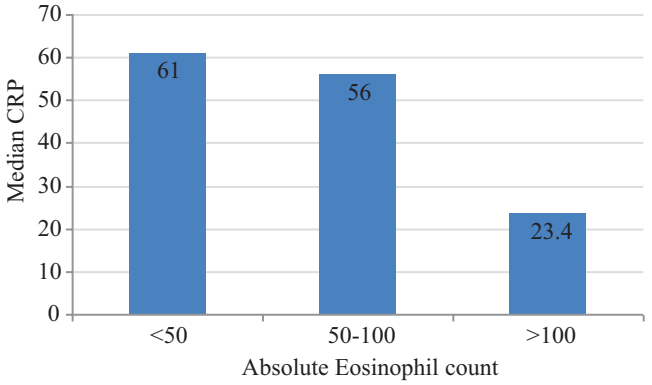
Median value of CRP in each AEC group was calculated. Median CRP was used instead of mean as CRP values did not follow a normal distribution. (Refer Graph 3)



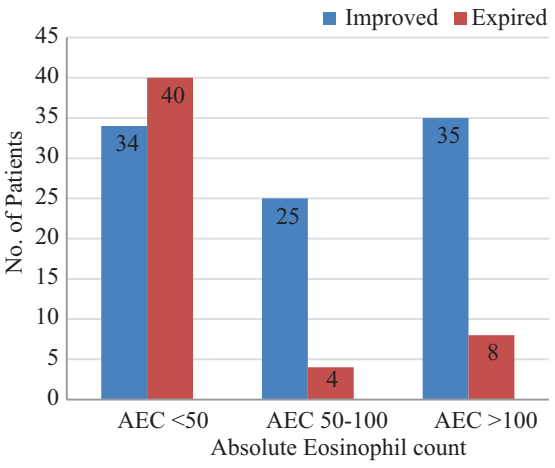
Graph-1: Eosinopenia and sepsis



Graph-2: AEC and severity of sepsis



Graph-3: AEC and CRP



Graph-4: AEC and outcome

Median CRP was highest among patients with AEC<50, less in patients with AEC 50-100 (not significant) and least in patients with AEC>100 (Statistically significant).(p=<0.001)

AEC and Outcome (*P = <0.001*)

The outcome of patients in each group of AEC was compared to find a correlation between eosinopenia and prognosis (Graph 4).

76.9% of patients who expired had AEC<50cells/cu.mm.

DISCUSSION

Eosinopenia occurs in response to acute infection because cytokines regulating production of eosinophils are not significantly activated in sepsis.[5] Our study aimed to assess the utility of eosinopenia as a screening tool to diagnose sepsis in critically ill patients. A total of 146 patients were enrolled.

Eosinopenia proved to be a useful marker in identifying sepsis in the present study. 98.65% of patients with AEC <50cells/cu.mm were diagnosed as having a sepsis related condition (p=0.001). Eosinophils at <50cells/cu.mm yielded a sensitivity of 65% and a specificity of 97% in identifying sepsis. In a study by Abidi et al, sensitivity was 80% and specificity 91%.[9] In a study by Shabaan et al, the reverse was reported. Eosinophils at<50 cells/cu.mm yielded a sensitivity of 81% and specificity of 65%.[12] Wibrow et al reported a sensitivity of 47% and a specificity of 79% for eosinophils at <10cells/cu.mm in detecting bloodstream infections.[13] In study conducted in Kerala by Joy et al, AEC< 50cells/cu.mm yielded a sensitivity of 20.8% and specificity of 95.65%.[14] The optimal eosinophil cutoff values have not yet been established and may differ depending on the clinical setting and the site and the etiology of infection.

The lack of differences in eosinophil count between sepsis, severe sepsis and septic shock groups, however, may be explained by the low rate of eosinophil count (near zero) in all the infection groups.

Elevated CRP and neutrophilia are proven markers of infection and part of the aim of the study was to compare their utility to AEC. Elevated CRP was found to be highly sensitive (92%) but poorly specific (9%) for the diagnosis of sepsis. In addition, eosinopenia correlated well with CRP with the highest median CRP being in the group with AEC <50cells/cu.mm. In a study by Povoa et al, a CRP concentration of >8.7 mg/dL was associated with infection, with a sensitivity of 93.4% and a specificity of 86.1%.[15]

Sensitivity and specificity of elevated WBC counts (>12000cells/cu.mm) in the present study was 62% and 53% respectively hence proving eosinopenia to be a more useful marker for sepsis. In a study by Muliyani et al, leukocytosis/ leucopenia had a sensitivity of 27.6% and specificity of 85.7% in the diagnosis of neonatal sepsis.[16]

Few studies have reported the utility of eosinopenia as a prognostic marker. Holland et al examined the usefulness of eosinopenia (≤40cells/cu.mm), for predicting the severity of exacerbations of COPD using inpatient mortality and length of stay as markers of severity. They noted significant differences in mortality (4/23 (17.4%) vs 1/42 (2.4%), $P = 0.049$) and length of stay (8 vs 5 days, $P = 0.005$) in the eosinopenia group compared with those with normal eosinophils.[17] In the present study, 36% of patients expired after admission to ICU. 76.9% of patients who expired had AEC<50cells/cu.mm. Further, eosinopenia correlated well with the APACHE II scoring system where median APACHE II score was highest among patients with AEC<50cells/ cu.mm. These observations suggest that eosinopenia may be useful in predicting outcomes in critically ill patients.

The mortality rate in our study seems high (35.6%) and is essentially related to infection. This can be explained as follows. First, infection is a common cause of admission to our medical ICU which may be due to the lack of a specific unit for infectious diseases in our hospital, delayed presentation of severely sick patients to the ICU, financial constraints and lack of medical insurance for all patients or a high prevalence of hospital-acquired infection in our hospital. Second, our results show that mortality among the infected group was 42%; this rate appears to be high but is comparable with the study by Abidi et al in which mortality among the infected group was also 42%.[9] Other studies reported ICU mortality related to sepsis conditions varying between 28% and 54%.[18,19]

The limitations of this study were as follows. The eosinophil count and the CRP value were collected only on the day of ICU admission and not daily during the entire ICU stay. No surgical patients were enrolled because of the specificity of our medical ICU.

CONCLUSION

The present study has a considerable implication for physicians in the Indian scenario. The on going battle with antimicrobial resistance added to financial constraints poses a dilemma in the ideal management of sepsis. Eosinopenia, as a rapid and inexpensive indicator of sepsis on admission in addition to its prognostic value, may be a useful tool in guiding physicians in the management of critically ill patients.

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