

Eosinopenia as predictor of infection in patients admitted to an internal medicine ward: a cross-sectional study

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Abstract

Background: The identification of infection in an internal medicine ward is crucial but not always straightforward. Eosinopenia has been proposed as a marker of infection, but specific cutoffs for prediction are not established yet. We aim to assess whether there is difference in eosinophil count between infected and noninfected patients and, if so, the best cutoffs to differentiate them.

Methods: Cross-sectional, observational study with analysis of all patients admitted to an Internal Medicine Department during 2 consecutive months. Clinical, laboratory and imaging data were analyzed. Infection at hospital admission was defined in the presence of either a microbiological isolation or suggestive clinical, laboratory, and/or imaging findings. Use of antibiotics in the 8 days before hospital admission, presence of immunosuppression, hematologic neoplasms, parasite, or fungal infections were exclusion criteria. In case of multiple hospital admissions, only the first admission was considered.

Sensitivity and specificity values for eosinophils, leukocytes, neutrophils, and C-reactive protein were determined by receiver operating characteristic curve. Statistical analysis was performed with IBM SPSS Statistics[®] v25 and MedCalc Statistical Software[®] v19.2.3.

Results: A total of 323 hospitalization episodes were evaluated, each corresponding to a different patient. One hundred fifteen patients were excluded. A total of 208 patients were included, 62.0% (n = 129) of them infected at admission. Ten patients had multiple infections.

Infected patients had fewer eosinophils than uninfected patients (15.8 ± 42 vs 71.1 ± 159 cell/mm³; $P < .001$). An eosinophil count at admission ≤ 69 cell/mm³ had a sensitivity of 89.1% and specificity of 54.4% (area under the curve 0.752; 95% confidence interval 0.682–0.822) for the presence of infection. Eosinophil count of >77 cells/mm³ had a negative likelihood ratio of 0.16.

Conclusions: Eosinophil count was significantly lower in infected than in uninfected patients. The cutoff 69 cells/mm³ was the most accurate in predicting infection. Eosinophil count >77 cells/mm³ was a good predictor of absence of infection.

Keywords: C-reactive protein, eosinopenia, eosinophil count, infection, leukogram

Introduction

The diagnosis of infection in the internal medicine ward is critical but sometimes difficult. Laboratory biomarkers are usually helpful. Leukocytosis and neutrophilia had traditionally been

associated with bacterial infection. The C-reactive protein (CRP) and procalcitonin are more recent and the most commonly used biomarkers used in clinical practice with this purpose.^{1–3} Eosinopenia was proposed a long time ago as a marker of infection, but is not commonly used in clinical practice.⁴

Eosinophils are responsible for 1% to 3% of peripheral blood leukocytes.⁵ They play an important role in the immune response to infection,^{6–8} namely in host defense against parasites and fungi and these patients have higher eosinophils counts.^{9,10} Besides their immunological functions, they are important in tissue development, repair, support, and maintenance of tissue integrity.¹¹ Despite these important roles, there is evidence in animal models and humans that the lack of eosinophils is not associated with an increased risk of disease.¹²

Eosinopenia was first described as a predictor of bacterial infection in 1893 by Zappert, and was used with this purpose during the first quarter of the 20th century.¹³ Under normal situations, eosinophils remain briefly in the peripheral blood until they migrate to the thymus or the gastrointestinal tract.⁹ Under physiological stress (including infection), eosinopenia results from an increased marginalization to infected tissues¹⁴ due to cortisol-dependent¹⁵ and cortisol-independent factors.^{14,16,17} More recently, a new mechanism for eosinopenia was proposed: marginalization into nonphysiological homing tissues due to

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immune stimulation by T lymphocytes, mast cells, IL-2, IL-5, complement factors (C3a and C5a), eotaxin and anaphylatoxin.¹¹ The exact mechanisms of eosinopenia are, however, still debated.⁴

Recently, interest of eosinopenia as an infection marker has resurfaced. Analysis of eosinophils is a cheap, easy to obtain, and reliable parameter,³ particularly relevant in countries in which new biomarkers are not readily available.¹³ To date, some different eosinophil cutoffs predicting infection have been proposed,^{18–21} depending on specific diseases and different ages.^{22,23}

We aim to assess if there is a difference in eosinophil count between infected patients and non-infected patients and, if so, the best cutoffs to differentiate between infected and uninfected patients.

Methods

A cross-sectional, observational study was performed. All patients aged 18 years or older, admitted in the Internal Medicine Department between January 1, 2020 and February 29, 2020 were enrolled in this study. In case of multiple hospital admissions during the time of the study, only the first admission was considered.

Presence of infection was determined when a causative agent (bacterial, virus, fungus, or parasite) was identified (in blood, urine, ascitic liquid, liquor, catheter culture, or respiratory secretions) by direct observation, culture, polymerase chain reaction, or serology. When there was no microbiological isolation, the diagnosis was based on clinical, biochemical, cytologic, and radiologic data consistent with infection. Respiratory infection was defined in the presence of respiratory symptoms (cough, sputum, dyspnea), associated with suggestive alterations on chest roentgenography or chest computed tomography scan (infiltrates, consolidation, or cavitation) with or without isolation of microorganisms in bronchial secretions or hemocultures. Urinary infection was defined by the presence of dysuria, urinary frequency, urgency, and/or suprapubic pain, with associated leukocyturia (defined as >20 leukocytes in urine sediment) and/or positive nitrites and/or pH alteration in urine II analysis, with or without agent isolation in urine culture. Gastrointestinal infection was defined by the presence of nausea, vomiting, diarrhea with documented fever, and elevation of inflammatory parameters, with or without identification of the causative agent in blood culture or feces. Central nervous system infection was defined by the presence of organism identified in culture- or nonculture-based microbiologic testing, presence of abscess, or the presence of 2 or more of the symptoms/signs: headache or fever (defined as tympanic temperature >37.9°C), meningeal signs or cranial nerve signs plus one of the following: >4 cells/mm³ in cerebrospinal fluid; protein dosage >45 mg/dL; glucose <45 mg/dL; presence of atypical cells with identification of agent in gram stain, culture, or polymerase chain reaction.

Cardiovascular infection was defined in the identification of organism in pericardial tissue or fluid or the presence of fever (defined as tympanic temperature >37.9°C), chest pain, paradoxical pulse, or increased heart size with at least one of the following criteria: abnormal electrocardiogram consistent with myocarditis or pericarditis; pericardial effusion identified by echocardiogram, computed tomography scan, magnetic resonance imaging, or angiography. Endocarditis diagnosis was done by the modified Duke criteria.²⁴ We considered the patient as

infected when criteria for one or more system infections were present.

Mortality was defined as death occurring during hospital stay in the evaluated time.

The use of antibiotics in the 8 days before the admission, infection by parasites and fungus, presence of immunosuppression (innate or acquired, including immunosuppressive drugs such as chemotherapy and corticosteroids, irrespective of administration route, and dose), or presence of ongoing hematologic neoplasms were considered exclusion criteria. The use of antibiotics may diminish the infectious stimulus and result in higher eosinophil counts, as described by Davido et al.²⁵ Infections by parasites and fungus are usually associated with higher eosinophil counts.¹¹ The presence of immunosuppression and hematological neoplasm may act as a bias as it increases the susceptibility to infection²⁶ and may alter eosinophil counts.²⁷

The following data were collected from each patient who was hospitalized: demographic and epidemiologic data, blood count (hemogram and leukogram), and CRP at hospital admission, as well as clinical reference to the presence of infection on hospital admission. Microbiological studies of ascites, urine, catheter, and other samples for microbiological analysis were considered when collected on the first 2 days of hospitalization. We defined a positive blood culture in the presence of at least 1 positive blood culture bottle. We considered hemoculture contamination in the presence of common skin contaminants (as negative-coagulase staphylococci; *Staphylococcus warneri*; *S hominis* spp; *S capitis*) or mixed skin flora isolated in one or more blood culture samples from the same patient without evidence of cutaneous lesion (infection, ulceration, or trauma).

A urine culture was considered contaminated in the presence of mixed flora or the presence of *Candida* species in the absence of fungemia.

Medical history and prescriptions (including antibiotics) were collected as well. Leukogram differential cell count was obtained by flow cytometry, using Beckman Coulter UniCel DxH 800®. CRP dosing was obtained by immunoturbidimetry, using Roche Cobas 8000®. Leukocyte subset count was obtained by multiplying the total leukocyte count by the leukocyte subset-specific percentage. The lower limit of detection was 0 cells/mm³. A leukocyte count of 10,000 cells/mm³, neutrophil count of 8000 cells/mm³, and CRP value of 0.5 mg/dL are the upper limit value of the utilized laboratory tests and considered criterion standard to which sensitivity, specificity, and likelihood ratios were compared.

Statistical analysis was performed with IBM SPSS Statistics Subscription® version 25.0 and MedCalc Statistical Software version® 19.2.3. Qualitative variables are described according to their frequencies. Quantitative variables are described as mean and standard deviation (or median and interquartile if the variables do not have a normal distribution). The comparison between groups with qualitative variables was made using the χ^2 test. The comparison between quantitative and qualitative variables was made by nonparametric tests (Mann-Whitney *U* test). Sensitivity and specificity for eosinophil count, and for leukocyte, neutrophil, and CRP for comparison were determined with receiver operating characteristic (ROC) curve. Comparison between ROC curves was done using the method described by DeLong et al.²⁸

The most accurate cutoff for eosinophil count was determined using Youden index.²⁹ Statistical significance was considered when $P < .05$. Ethical and legal principles were followed

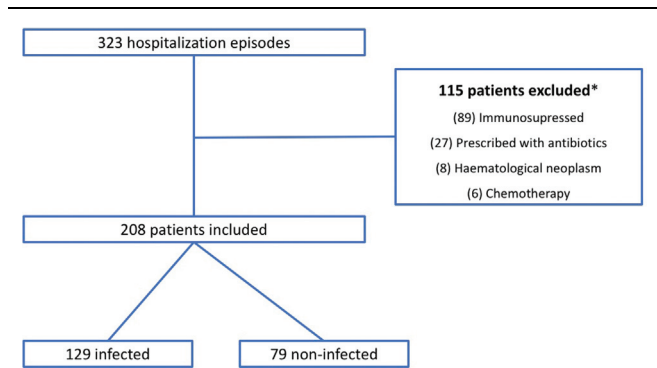


Figure 1. Study flow diagram. * 14 had 2 or more exclusion criteria.

according to the Declaration of Helsinki and the study obtained a favorable opinion from the local Ethics Committee.

Results

A total of 323 hospital stay were evaluated, each corresponding to a different patient (n=323 patients). A total of 115 patients were not considered in the analysis due to the following exclusion criteria: 89 were immunosuppressed; 27 had antibiotic therapy in the 8 days preceding the admission; 8 had ongoing hematologic neoplasm; 6 were under chemotherapy. No patient had documented or suspected parasitic or fungal infections. Fourteen patients had multiple exclusion criteria.

A total of 208 hospital admission episodes were included in the study, corresponding to 208 individual patients. Female patients accounted for the majority of admissions (54.3%; n=113/208).

Most admitted patients (62.0%; n=129/208) were infected at admission entry. The majority of infected patients were women (59.7%, n=77/129). Although the median length of hospital stay was similar in the infected and noninfected group (9 vs 8 days; P=.814), the hospital mortality of infected patients was significantly higher (16.3% vs 5.1%; P=.016). We present the study flow in Figure 1. The characterization of the population is presented in Table 1.

Among the 129 infected patients, a total of 139 infections were documented. Ten patients presented 2 infections at admission. The most common infections were respiratory tract infections (75.5%; n=105/139), urinary tract infections (16.5%; n=23/139), and gastrointestinal infections (7.2%; n=10/139) as presented in Table 2. In SDC Tables 1, <http://links.lww.com/PBJ/A3> and 2, <http://links.lww.com/PBJ/A4> we present the results of cultural tests of the infected patients.

Table 2
Infections by site

Site of infection	n* (%)
Respiratory tract	105 (75.5)
Urinary tract	23 (16.5)
Gastrointestinal tract	10 (7.2)
Cardiovascular system	1 (0.7)
Central nervous system	0 (0.0)

* n=10 patients had multiple infections.

Median eosinophil count was lower in patients infected at hospital admission, compared with noninfected patients (15.8 vs 71.1 cell/mm³; P<.001) (Table 3 and Fig. 2). The occurrence of undetectable eosinophils was more common among infected patients (33.3%; n=43/129) than among noninfected patients (10.1%; n=8/79) (P<.001). We also observed that leukocyte count, neutrophil count, and CRP were significantly higher among infected patients (Table 3).

An ROC was performed for eosinophil count and other traditional biomarkers of infection (total leukocyte, neutrophil, and CRP) (Table 4). A cutoff of 69 eosinophils/mm³ (determined by Youden index) had the best accuracy for predicting infection, with a sensitivity of 89.1%, specificity of 54.4%, and a positive likelihood ratio of 1.95. A cutoff of 77 cells/mm³ had a negative likelihood ratio of 0.16.

The upper limit of leukocytes (10,000 leukocytes/mm³) had a sensitivity of 55.8% and a specificity of 78.5% for predicting infection. The upper limit of neutrophil count (8000 neutrophils/mm³) had a sensitivity of 57.4% and a specificity of 79.7%. Regarding the CRP, the traditional cutoff of 0.5 mg/dL had a sensitivity of 96.9% and specificity of 29.1%. No differences were observed between the area under the curve of eosinophil count and area under the curve of CRP (P=.073), leukocytes count (P=.448), and neutrophils (P=.857) (Table 4).

Discussion

In this study, we observed that patients infected at hospital admission had significantly lower eosinophil counts than noninfected patients. The cutoff of 69 eosinophils/mm³ was a more sensitive predictor for infection when compared with the traditional neutrophil and leukocyte cutoffs, although less sensitive than the upper limit of normal for CRP.

We also found that an eosinophil count >77 eosinophil/mm³ was a good predictor of absence of infection. It performed better at excluding infection than the traditional cutoffs for leukocytes and neutrophils, but not as well as serum values of

Table 1
Population characteristics

	All (n=208)	Infected (n=129)	Noninfected (n=79)	P value (infected vs noninfected)
Age - median ± IQR	83.5 ± 15.0	86 ± 11.0	79.0 ± 17.0	<.001
Sex—n (%)				
Female	113 (54.3)	77 (59.7)	36 (45.6)	.047
Hospital stay (days)*—median ± IQR	9 ± 7	9 ± 6	8 ± 11	.814
Death—n (%)	25 (12.0)	21 (16.3)	4 (5.1)	.016

IQR=interquartile range, SD=standard deviation.

* Twenty patients have not been discharged on February 29, 2020.

Table 3

Comparison of eosinophil count, leukocyte count, neutrophil count, and C-reactive protein at admission between infected and noninfected patients

	All (n=208)	Infected (n=129)	Noninfected (n=79)	P
Eosinophils (cell/mm ³)—median ± IQR	25.7 ± 68	15.8 ± 42	71.1 ± 159	<.001
Leukocytes (cell/mm ³)—median ± IQR	9400 ± 5985	10,900 ± 7000	7500 ± 3500	<.001
Neutrophils (cell/mm ³)—median ± IQR	7483 ± 5793	8704.8 ± 6352	4867 ± 3613	<.001
CRP (mg/dL)—median ± IQR	6.67 ± 16.78	12.8 ± 15.04	1.22 ± 2.97	<.001

Median comparison was obtained by Mann-Whitney *U* test.
CRP = C-reactive protein; IQR = interquartile range.

CRP <0.5 mg/dL. In this sample, with patients with bacterial and viral infections, the higher the eosinophil count, the lower the probability of infection.

There is no universal cutoff to define the grade of eosinopenia²⁵ suggesting presence of infection. Gil et al³⁰ conducted a prospective study that included patients with inflammatory syndrome (defined by values of CRP >20 mg/L) and compared the eosinophil count of patients with documented infection to those without infection. In this work, a value of 40 eosinophils/mm³ was a good predictor of infection. Later, the same value was adopted by Efstathiou et al³¹ to define eosinopenia, and used to compare sensitivity and specificity between infected and noninfected groups. Karakonstantis et al¹⁹ conducted a study with 271 patients admitted in a medicine ward with fever (>38°C) or inflammatory syndrome (defined as leukocyte count >12,000 cells/mm³ or CRP >5 mg/dL). In this work, significant eosinopenia (defined as <10 cells/mm³) was highly specific (90%) for the diagnosis of infection, whereas higher values of eosinophil counts (>400 cells/mm³) suggested absence of infection.

More recently, Hirose et al³² retrospectively reviewed the processes of 189 patients admitted in a medicine ward with blood culture results. The authors determined that eosinophil count <24.3 cells/mm³ was a good predictor of presence of positive blood culture, better than quick sequential organ failure assessment score and the presence of chills.

Abidi et al¹³ conducted a study with 177 patients admitted in an intensive care ward with or without documented infection at admission. The authors found that <50 eosinophils/mm³ was a specific predictor for differentiating patients with sepsis versus systemic inflammatory response syndrome by other causes.

The eosinophil count of 69 cell/mm³ for the presence of infection is slightly higher than the proposed by other authors.

This difference is explained by the different patients included in each study and the method adopted by each author to define the best cutoff. In the presented studies, Abidi et al¹³ determined the cutoff value using the Youden Index. The obtained value using this statistical method has the best relation between sensitivity (probability that a test result will be positive when the disease is present) and specificity (probability that a test result will be negative when the disease is not present).

In the present case, we found that the capability to exclude infection (as documented by negative likelihood ratio, which is the ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease) is more relevant than sensitivity or specificity values. So, for values >77 eosinophils/mm³, the probability of infection is low.

Although we made our best effort to minimize possible bias, some may remain. The eosinophil count was obtained by automatic fluorometric technique, which has already been documented as being potentially imprecise at lower counts.³³ Some comorbidities are, per se, associated to eosinopenia and could impair interpretation. To minimize this possible limitation, we excluded patients under chemotherapy, with hematologic pathologies or otherwise treated with corticosteroids. Nevertheless, some other unrecognized causes of eosinopenia may have persisted. Another possible bias is the interval between the beginning of the infectious insult and the time the blood sample was collected. In animal models, eosinopenia develops in the first minutes after the insult and remains as long as there is noxious stimulus from the insulting agent.¹⁴ In humans, the interval between the initial insult and establishment of eosinopenia in humans is not known, and blood could therefore have been drawn too soon after development of infection. Infected patients were older than noninfected patients, probably with more comorbidities for which eosinopenia is not well established, and can bias the obtained results. We highlight the fact that there were no patients with documented or suspected infections by fungus or parasites in this population. Therefore, our conclusions are not applicable to infections due to those agents.

We believe that this eosinophil may have a major interest not as an individual predictor of infection by itself, but rather as a complement to other clinical and laboratory predictors already used in clinical practice. Further studies are necessary to confirm our findings and explore other possible eosinophil-based cutoffs.

We propose the inclusion of eosinophil count as a potential new predictor for further scores used to evaluate the risk of infection in patients admitted to a medicine ward. To achieve this objective, a higher patient sample must be included to perform a logistic regression that includes confounding factors.

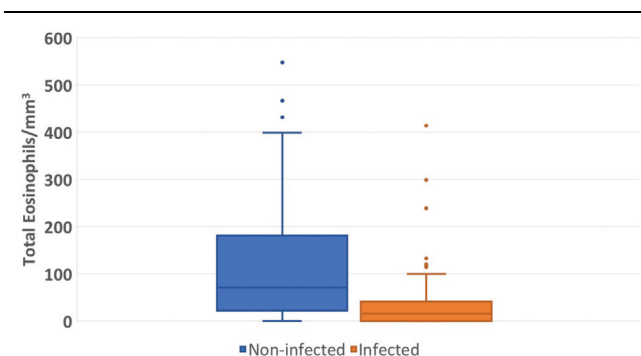


Figure 2. Box plot presentation of absolute eosinophil count in noninfected and infected patients.

Table 4
Diagnostic characteristics of leukocyte, neutrophil, eosinophil count, and C-reactive protein in different cutoff values

	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Eosinophil count (cutoff values; cell/mm ³)*				
<10	38.8	84.8	2.55	0.72
<40	74.4	62	1.96	0.41
<50	81.4	59.5	2.01	0.31
<69 [†]	89.1	54.4	1.95	0.20
<77	92.2	50.6	1.82	0.16
<300	99.2	7.6	1.07	0.11
Leukocyte count (cutoff values; cell/mm ³) [‡]				
>10,000	55.8	78.5	2.59	0.56
Neutrophil count (cutoff values; cell/mm ³) [§]				
>8000	57.4	79.7	2.83	0.53
CRP (cutoff values; mg/dL)				
>0.5	96.9	29.1	1.37	0.11

The values in bold are the normal upper limit for the technique.

CRP = C-reactive protein.

* Area under the curve (AUC) 0.752 (95% CI 0.682–0.822).

[†] The cutoff value obtained using Youden index.

[‡] AUC: 0.713 (95% CI 0.640–0.786).

[§] AUC: 0.744 (95% CI 0.672–0.815).

^{||} AUC 0.833 (95% CI 0.770–0.896).

In conclusion, eosinophil count was significantly lower in infected patients at admission than in noninfected patients. Eosinophil counts <69 eosinophils/mm³ are a sensitive predictor of infection. A cutoff value of 77 eosinophils/mm³ is better at predicting the absence of infection than the laboratory cutoff values of neutrophil and leukocyte counts. Further studies are encouraged.

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Conflicts of interest

The authors declare no conflicts of interest.

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