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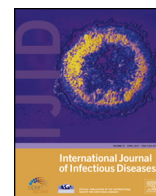
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Changes in eosinophil count during bacterial infection: revisiting an old marker to assess the efficacy of antimicrobial therapy[☆]



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ABSTRACT

Introduction: Eosinopenia as a criterion of sepsis has been the subject of debate for decades. Different authors have proposed different cut-off values.

Methods: A prospective study was conducted from February to August 2016. Hospitalized adults suffering from a bacterial infection with eosinopenia, defined as an eosinophil count $<100/\text{mm}^3$, were included. Patients were divided into two groups according to the first day of effective antimicrobial therapy. They were observed for 5 days in order to evaluate whether recovery from eosinopenia was predictive of an appropriate antibiotic regimen.

Results: One hundred and twenty-two patients were screened and 96 were included. Group 1 patients ($n=70$) received effective antimicrobial therapy from day 0. Their eosinophil count increased significantly between day 0 and day 1 ($p < 0.0001$). Group 2 patients ($n=26$) received delayed effective antimicrobial therapy, and there was no significant difference in eosinophil count between day 0 and day 1 ($p=0.55$). Moreover, eosinophil counts normalized on day 5 in both groups. The mean duration of antimicrobial therapy was comparable in the two groups (7.7 ± 1.16 days). The antibiotics most often prescribed in both groups were intravenous cephalosporins. During follow-up, all patients were considered to be cured after day 30.

Conclusions: The eosinophil count appears to normalize faster than C-reactive protein (CRP) and polymorphonuclear neutrophils in eosinopenic patients on appropriate antimicrobial therapy. This simple test is easy to perform as part of a regular complete blood count, with no additional costs as required for CRP or procalcitonin.

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Introduction

Eosinopenia as a response to infection was first described in Zappert (1893). The pathophysiology of eosinopenia is related to the migration of eosinophils to the inflammatory site, presumably as a result of chemotactic substances secreted during the acute phase of inflammation (Bass et al., 1980).

C-reactive protein (CRP) was discovered in the 1960s and is considered a marker for the diagnosis of bacterial infection.

Nevertheless, several studies performed during the last decades have shown that CRP, and more recently procalcitonin (PCT) (Le Bel et al., 2015), are not specific for sepsis but rather are markers of systemic inflammatory response syndrome (SIRS), as defined previously by the consensus conference for sepsis (American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, 1992). Furthermore, PCT has been demonstrated to be useful in the intensive care unit (ICU) to shorten the duration of treatment (de Jong et al., 2016), particularly in pneumonia (Schuetz et al., 2012; Kook et al., 2012). However, adding a PCT-guided protocol does not reduce the use of antibiotics in febrile neutropenia (Lima et al., 2016).

Numerous studies have shown that PCT testing in the first days after admission to the ICU is associated with a significantly reduced length of stay, as well as reduced overall cost of care (Balk et al.,

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2016; Harrison and Collins, 2015). Nevertheless, the use of routine PCT testing is associated with additional costs. Biological markers to reduce antibiotic consumption are very much appreciated in the context of high costs due to antibiotic resistance (Chandy et al., 2014).

The eosinophil count has been revisited in recent decades, especially eosinopenia, which some authors consider a criterion of SIRS. There is no precise cut-off value in the literature to define eosinopenia, with different authors reporting values ranging from $<40/\text{mm}^3$ (Gil et al., 2003) to $<50/\text{mm}^3$ (Abidi et al., 2008). Meanwhile some authors argue that eosinopenia should be defined as an eosinophil count $<1\%$ of the total leukocytes (Rothenberg, 1998), implying that eosinopenia should be defined by a value $<100/\text{mm}^3$.

Recently, a study conducted in an ICU concluded that eosinopenia is a very sensitive but not specific marker of sepsis, and can be useful to guide physicians in their diagnosis (Shaaban et al., 2010). More recently, a study performed in an emergency department demonstrated that profound eosinopenia is very specific for sepsis, and it was suggested that it may become a helpful tool in daily practice (Lavoignet et al., 2016), as described previously by Simon (1922). Furthermore, eosinopenia has the advantage of not requiring further investigations, because it can be obtained easily from a simple complete blood count (CBC). Thus, it was hypothesized that recovery from eosinopenia during the treatment of bacterial infection may be a marker to evaluate whether a patient is receiving the appropriate antibiotic regimen.

Methods

Study design

Data were collected prospectively from adults hospitalized in the Infectious Diseases Department of Raymond Poincaré Teaching Hospital in Garches, France. This observational study was conducted between February and September 2016 during routine medical practice.

Data collection and definitions

Patients were included on the basis of a bacterial infection, defined either microbiologically (blood culture, urinary culture, microbiological specimen, urinary antigen test, or nasopharyngeal swab for RT-PCR), radiologically (typical illustration), or through clinical documentation (especially for skin and soft tissue infection). All patients were included on the basis of an uncomplicated infection without sepsis, as per the new 'SEPSIS-3' definitions (Singer et al., 2016), associated with the presence of eosinopenia on CBC. The absence of sepsis was assessed using the new bedside clinical score quickSOFA (qSOFA) (Singer et al., 2016); this was confirmed by the SOFA score if necessary.

Eosinopenia was defined as an eosinophil count $<100/\text{mm}^3$, in accordance with the literature (Rothenberg, 1998). The eosinophil count was obtained from the CBC, acquired using a Coulter LH780 Hematology Analyzer (Beckman Coulter Inc., Nyon, France).

Exclusion criteria were: (1) immunosuppression (HIV with CD4 $<200/\text{mm}^3$, corticosteroids $>60\text{ mg/day}$, chemotherapy, immunosuppressive therapy); (2) autoimmune disease; (3) haematological malignancy; (4) documented viral infection.

For each patient admitted, their age, sex, principal diagnosis, and biology were recorded. Day 0 was considered the first day of care admission, including emergency room.

As a first step, patients were divided into two groups according to the first day of effective antimicrobial therapy. Group 1 was composed of patients on effective antimicrobial therapy from day 0, i.e., started within 12 h of the initial CBC. Antibiotic regimens

were provided at standard doses in accordance with guidelines and in respect to kidney function. Group 2 was composed of patients who received delayed effective antimicrobial therapy (after day 1), either because of delayed microbiological documentation or because of initial ineffective antimicrobial therapy.

As a second step, the course of antibiotics, CRP, leukocyte count (including polymorphonuclear neutrophil (PMN) and eosinophil counts), and temperature on days 1, 3, and 5 of hospitalization were analysed.

Finally, patients attended a follow-up consultation after 1 month as part of routine practice in the department.

Statistical analysis

The Student *t*-test was used to analyze continuous data in GraphPad Prism v.6.0d (GraphPad Software Inc., La Jolla, CA, USA). Statistical significance was defined as $p < 0.05$.

Ethical approval

All procedures in the study were performed as part as routine care and in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki.

Results

One-hundred and twenty-two patients were screened during the study period (Figure 1). Six patients were excluded because they were not infected. Eleven further patients were excluded because they presented an infection with an eosinophil count $>100/\text{mm}^3$. In addition, nine patients were excluded because they had a viral syndrome.

A total of 96 infected patients were included. Seventy were assigned to group 1 with effective antimicrobial therapy from day 0, and 26 patients were assigned to group 2 because of delayed effective antimicrobial therapy (after day 1). Patient characteristics were comparable and are detailed in Table 1.

For all patients, the qSOFA score calculated was <2 ; therefore they were not investigated further with the SOFA score and were considered to have uncomplicated infections. Moreover, the qSOFA scores were comparable between groups (median 0, range 0–1).

The parameters studied (temperature, PMN and eosinophil counts) were also comparable on day 0 before monitoring and the

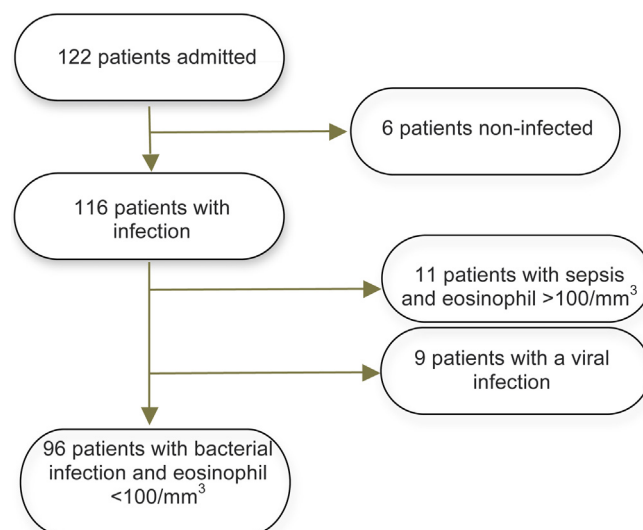


Figure 1. Flow chart of the study population at admission.

Table 1

Baseline characteristics of the study patients, diagnoses on admission, and eosinophil count. Tools used for the diagnosis of bacterial sepsis. Negative RT-PCR swabs for the detection of respiratory viruses were considered as in favour of bacterial infection. Specimens include sputum culture, aspiration, or other positive growth culture.

Parameter	Group 1 (n = 70) n (%)	Group 2 (n = 26) n (%)	p-Value
Age, years, mean ± SD	63 ± 22	67 ± 19	0.41
Sex, male	42 (60.0)	14 (53.8)	0.64
Type of infection			NA
Urinary tract	34 (48.6)	12 (46.1)	0.99
Respiratory tract	22 (31.4)	10 (38.4)	0.63
Isolated bloodstream	8 (11.4)	2 (7.7)	0.72
Skin and soft tissue	3 (4.3)	1 (3.9)	0.99
Digestive tract and liver	3 (4.3)	1 (3.9)	0.99
Microbiological data supporting infection	54 (77.1)	18 (60.0)	0.09
Blood culture	8 (14.8)	2 (11.1)	0.99
Urinary culture	34 (62.9)	12 (66.7)	0.99
Specimens	2 (3.7)	0 (0)	0.99
Urinary antigen test	5 (9.3)	2 (11.1)	0.99
RT-PCR swab	5 (9.3)	2 (11.1)	0.99
Radiological data supporting infection	29 (41.4)	12 (46.1)	0.81
Clinical diagnosis of infection	13 (18.6)	4 (15.4)	0.99

SD, standard deviation; NA, not applicable.

commencement of treatment, with the exception of CRP (see **Supplementary Material**, Table S1 in the online version at DOI: [10.1016/j.ijid.2017.06.005](https://doi.org/10.1016/j.ijid.2017.06.005)).

In group 2, the mean delay before receiving effective antimicrobial therapy was 1.23 ± 0.43 days. The mean duration of effective antimicrobial therapy was similar in group 1 (7.8 ± 1.1 days) and group 2 (7.5 ± 1.27 days) ($p = 0.26$). The initial antibiotics most often prescribed in group 1 were intravenous cephalosporins ($n = 38$, 54.3%), amoxicillin–clavulanate ($n = 16$, 22.8%), and ofloxacin ($n = 8$, 11.4%). The most frequently prescribed antibiotics in group 2 were intravenous cephalosporins ($n = 8$, 30.8%), piperacillin–tazobactam ($n = 6$, 23.1%), and trimethoprim–sulfamethoxazole (TMP–SMX) ($n = 5$, 19.2%). Ineffective or delayed antimicrobial therapies prescribed in group 2 are detailed in **Table 2**.

In group 1, the eosinophil count increased significantly between day 0 and day 1 after the commencement of effective antimicrobial therapy ($p < 0.0001$). Meanwhile, no parameter (PMN and eosinophil counts, temperature, CRP) changed significantly in group 2 (**Figure 2**).

It should be noted that eosinophil counts over time were not comparable in the two groups (see **Supplementary Material**, Table S1 in the online version at DOI: [10.1016/j.ijid.2017.06.005](https://doi.org/10.1016/j.ijid.2017.06.005)), implying that the two groups did not share the same changes over time, as previously shown in **Figure 2**. In addition, a ROC curve was plotted for day 1 to estimate a cut-off value for the eosinophil count to confirm the effectiveness of antimicrobial therapy between groups. An eosinophil count above $25/\text{mm}^3$ resulted in the best likelihood ratio (LR = 26) to predict that the patient was receiving an appropriate antibiotic regimen (group 1), with a sensitivity of 100% (95% confidence interval 94.8–100%) and a specificity of 96.1% (95% confidence interval 80.4–99.9%) (**Figure 3**).

All parameters changed significantly between day 1 and day 3, except temperature in group 2. Finally, between day 3 and day 5, the eosinophil count was significantly higher in group 1 ($p < 0.0001$), but did not change significantly in group 2. However, the eosinophil count normalized in both groups ($>100/\text{mm}^3$) with a significantly lowered CRP.

Table 2

Table linking clinical disease with the microorganism found and antibiotic given when patients were assigned to group 2, considered as 'delayed or ineffective antimicrobial therapy'.

Parameter	Group 2, n (%)	Antibiotic regimen on day 0	Antibiotic regimen after day 1
Type of infection	26 (100)		
Urinary tract (UTI)	12 (46.1)	–	–
Respiratory tract	10 (38.4)	–	–
Isolated bloodstream	2 (7.7)	–	–
Skin and soft tissue	1 (3.9)	–	–
Digestive tract and liver	1 (3.9)	–	–
Microbiological and clinical data			
ESBL <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> (UTI)	10 (38.4)	Cefotaxime (n = 5) TMP–CTX (n = 3) None (n = 2)	Cefoxitin (n = 6) Piperacillin–tazobactam (n = 4)
AmpC beta-lactamases	2 (7.7)	Amoxicillin–clavulanate	Cefepime
<i>Mycoplasma pneumoniae</i> or <i>Legionella pneumophila</i>	4 (15.4)	Cefotaxime (n = 2) TMP–SMX (n = 1) None (n = 1)	Macrolides
Nosocomial aspiration pneumonia	4 (15.4)	Amoxicillin–clavulanate	Piperacillin–tazobactam (n = 2) Ceftazidime–metronidazole (n = 2)
Penicillin-intermediate <i>Streptococcus pneumoniae</i> (PISP)	2 (7.7)	Amoxicillin–clavulanate	Cefotaxime or pristinamycin
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) bacteraemia	2 (7.7)	Cloxacillin or cefazolin	Daptomycin
Pressure sore infected by MRSA	1 (3.9)	None	TMP–SMX
<i>Clostridium difficile</i> diarrhoea	1 (3.9)	Ciprofloxacin	Fidaxomicin

UTI, urinary tract infection; ESBL, extended-spectrum beta-lactamase; TMP/SMX, trimethoprim/sulfamethoxazole.

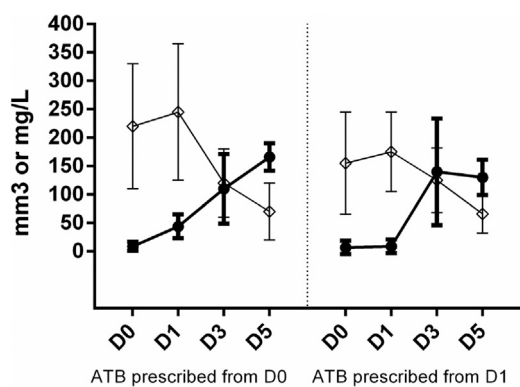


Figure 2. Comparison of changes in C-reactive protein (CRP) and eosinophil count over time. The means are plotted with standard deviation error bars. The eosinophil count is represented by black circles and CRP with white diamonds. ATB: antibiotics.

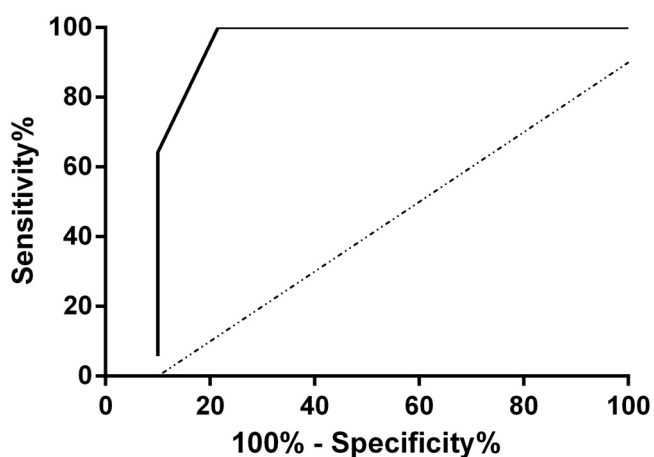


Figure 3. Receiver operating characteristics (ROC) curve considering the best cut-off value for the eosinophil count on day 1 of $>25/\text{mm}^3$ as a diagnostic tool to reassure the physician that the patient is on an appropriate antimicrobial regimen. Sensitivity 100% (95% confidence interval 94.8–100%) and specificity 96.1% (95% confidence interval 80.4–99.9%).

Clinical outcomes were favourable in both groups after the commencement of an effective antibiotic regimen, without any relapse after 30 days of follow-up.

Discussion

The results of this study revealed that eosinopenic patients receiving effective antimicrobial therapy during bacterial infection recovered from eosinopenia within 24 h, considering results in group 1. Conversely, PMN, CRP, and temperature only began to normalize after 3 days.

On day 0, CRP was not comparable between the groups, which could be interpreted as a bias. However, it is believed that this simply reflects a slightly better physical condition of patients in group 2, explaining why the physician decided to delay antimicrobial treatment for some of them. Indeed, the CRP value has no discriminative property for the determination of the severity of sepsis (Jekar et al., 2015). Between day 1 and day 3, the decrease in CRP and other inflammatory parameters confirmed that the patients were receiving an appropriate regimen in both groups.

In addition, the results of this study showed that the mean eosinophil count on day 3 was above normal ($100/\text{mm}^3$) in both groups, tending to demonstrate that this marker could be an

indicator of an appropriate regimen from day 3. Therefore, it is believed that the changes in eosinophil count can be considered an early marker of the response to treatment, unlike CRP which usually increases within 6 h of infection and has a longer half-life of 19 h (Coventry et al., 2009).

Unlike other markers or molecular diagnosis, the eosinophil count can be obtained easily from the CBC results without additional cost, blood sample, or extra time.

Furthermore, on day 3, the physician can be reassured not to broaden the antibiotic spectrum when a return of the eosinophil count to normal is observed. In addition, in the case of a hospitalized patient receiving ongoing antibiotics with a persistent fever or elevation of CRP, a favourable change in the eosinophil count can help to determine that such parameters are related to the ongoing infection (i.e. lymphangitis, thromboembolic event). Conversely, if a patient remains eosinopenic, the antimicrobial therapy should be re-assessed, in line with antibiotic stewardship practices.

PCT has also proved to be a marker of a favourable course under adequate antimicrobial therapy while reducing costs (de Jong et al., 2016; Harrison and Collins, 2015; Chandy et al., 2014). However, the routine use of changes in the eosinophil count results in cost savings. Indeed, the absence of any extra cost in comparison to the usual biological markers or other complementary tests must be emphasized.

Nevertheless, this study has some limitations. First, despite best efforts, it was not possible to completely confirm through microbiological data that all cases were true bacterial infections. Some patients may in fact have been suffering from viral pathogens. However, recovery from eosinopenia likely does not apply to viral infections. Indeed, the spontaneous evolution of such infections suggests that the changes in eosinophil count over time may act differently. Moreover, the different microorganisms involved were not detailed precisely, considering the fact that they were mostly urinary tract infections due to *Enterobacteriaceae*, and also because most cases of pneumonia are not routinely investigated through invasive procedures.

Although this cohort included some cases of bacteremia, which are specific of bacterial infection, it was not possible to establish whether eosinopenia was a marker of bacteremia as previously described in adults (Wibrow et al., 2011; Setterberg et al., 2004). Indeed, despite the prospective nature of this study, the sample size and lack of a control arm (with an eosinophil count $>100/\text{mm}^3$) did not allow such an evaluation.

Another limitation of the eosinophil count is that the eosinopenic response occurs in the acute phase of infection and may not be relevant for chronic infections such as osteomyelitis (Bass et al., 1980). Besides, eosinopenia is a non-specific marker of infection. In the case of drug allergy, especially when dealing with antibiotics, the physician can be misled. However, only immediate hypersensitivity typically occurs in the next 24 h and therefore can be considered to potentially interfere with the interpretation of the eosinophil count. Yet, in such a condition the patient presents other symptoms simultaneously such as Quincke's oedema or a cutaneous rash attesting to anaphylaxis. Likewise, a delayed-type hypersensitivity reaction usually occurs after 6 days (Trubiano et al., 2016) of drug challenge; this would not have interfered with the present results which were obtained in the first 5 days.

Also, it can be argued that the antimicrobial therapies differed a little between the two groups. Indeed, fluoroquinolones were more often employed in group 1 and TMP-SMX in group 2, and there was no prescription of piperacillin-tazobactam in group 1. However, all patients had a favourable outcome regardless of the assigned group. Thus this cannot exclusively explain the various increases observed in eosinophil count over time.

Finally, the results of this study are discussed in a context in which historical data were supported by a previous definition of sepsis (American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, 1992; Levy et al., 2003); the definition was completely reworded at the most recent sepsis conference (SEPSIS-3) (Singer et al., 2016), with the inclusion of organ dysfunction or failure. It was not, however, within the task force brief to examine definitions of infection. Therefore, it is difficult to compare some previous statements regarding eosinopenia and sepsis with the present findings based on the definition of infection which remains unchanged.

The eosinophil count appears to normalize faster than CRP and the PMN count in eosinopenic patients on appropriate antimicrobial therapy and thus is predictive of a favourable outcome. More data and a randomized controlled trial are required, but these preliminary results are promising and highlight an easily available tool with no additional cost.

Funding

This study was supported by internal funding.

Ethical approval

Not required. All procedures in this study were performed as part as routine care, in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

BD and JS designed the study. SM supervised data collection and data management. BD, SM, and AD analyzed the data. SM, BD, and MM prepared the first draft of the manuscript. All authors participated in manuscript preparation and approved the final manuscript for publication.

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