European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:1523–1532
https://doi.org/10.1007/s10096-019-03583-2

ORIGINAL ARTICLE

White blood cell count and eosinopenia as valuable tools for the diagnosis of bacterial infections in the ED

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Received: 19 February 2019 / Accepted: 6 May 2019 / Published online: 22 May 2019

Abstract

Identifying an infection may be difficult in the ED. Neutrophilic leukocytosis is often used in the diagnosis of infection despite its lack of specificity in situations of stress. Our objective was to study the value of each parameter of the WBC count, in particular eosinopenia, to diagnose bacterial infections in the ED. We conducted a retrospective and observational study over a period of 6 months. All patients with one of the following diagnoses were eligible: pneumonia (9.9%), pyelonephritis (26.2%), prostatitis (8.4%), appendicitis (26.2%), cholecystitis (8.4%), and diverticular sigmoiditis (5%). A total of 466 infected patients were included for statistical analysis, and a control group of 466 uninfected patients was randomly selected in the same period of time. All leukocyte count parameters were significantly modified ($p < 0.001$) in the infected group compared with the control group. Neutrophils and total leukocytes remain the two most suitable parameters for the diagnosis of infections in the ED. Eosinopenia represented the most efficient parameter of the WBC count for the diagnosis of urinary and biliary tract infections. Deep eosinopenia presented a specificity of 94% for the diagnosis of infection. Any modification of the WBC count associated with an elevation of CRP (> 40 mg/L) or fever (> 38.5 °C) showed a high specificity for the diagnosis of infection. A careful analysis of the WBC count remains a valuable tool for the diagnosis of infection in the ED.

Keywords Sepsis · Eosinopenia · White blood cells · Infection

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Abbreviations

ICU	Intensive care unit
ED	Emergency department
OR	Odds ratio
WBC	White blood cell
CRP	C-reactive protein
D3	Third day
D7	Seventh day
ROC	Receiver operating characteristic
AUC	Area under curve

Introduction

Sepsis accounts for nearly 2% of hospitalizations in developed countries [1]. In the emergency department (ED), clinical situations often remain unclear and identifying an infection may sometimes be difficult [2]. An early treatment of infections in the ED has led to improved outcomes [3]. Neutrophilic leukocytosis is often used in the diagnosis of infectious diseases. However, this biological marker lacks specificity in emergency situations due to the impact of stress on white blood cell (WBC) count, such as in trauma patients for example [3–6]. Other modifications of WBC count may also be associated with bacterial infections but are less often taken into account. Some studies showed a correlation between eosinopenia, lymphopenia, or monocytosis with bacterial infections [7, 8]. Conversely, basopenia is rarely described and appears to be less effective [8]. Several studies carried out in internal medicine or in the ICU focused on the value of eosinopenia to diagnose infections, compared with other pathologies causing inflammatory syndrome [7–11]. Thus, deep eosinopenia (less than 40/mm^3) appears to be a prognostic marker in infected patients admitted to the ICU and a predictor of early readmission [11, 12]. Eosinopenia has also been described as a factor increasing the length of hospitalization, the mortality, and the mechanical ventilation rate in chronic obstructive pulmonary disease's infectious decompensation [13]. Deep eosinopenia seems also to have a good specificity for the early diagnosis of bacterial infections in the ED [14].

Our main objective was to study the value of each parameter of the WBC count, in particular eosinopenia, to diagnose infectious diseases frequently encountered in the ED. Thereby, we studied the contribution of each parameter of the WBC count first for all the infected patients and then each parameter in reference to the site of infection. We also studied the impact of clinical severity on the modification of the WBC count. Moreover, we sought to identify a relationship between the depth of eosinopenia with the length of hospitalization or mortality.

Methods

This retrospective and observational study was carried out in the ED over a 6-month period from 1 September 2015 to 29 February 2016. It was held in the adult emergency department of the Strasbourg University Hospital that accounts for nearly 70,000 ED visits each year.

During the study period, all patients with one of the following diagnosis were eligible: pneumonia, pyelonephritis, prostatitis, appendicitis, cholecystitis, and diverticular sigmoiditis. The positive diagnosis of bacterial infection was verified by two experienced emergency physicians by analyzing the hospitalization files, bacteriological findings, and imaging. The diagnosis of pneumonia was made by computed tomography or based on hospital report. Urinary tract infection was confirmed by positive urinary culture with relevant clinic and/or imaging. Patients with asymptomatic bacteriuria were excluded. The diagnosis of digestive infections was based on imaging or on report of pathology on the surgical specimen. Patients were excluded from the study if the diagnosis of bacterial infection was uncertain. If a doubt remained, a third senior investigator decided. The exclusion criteria resumed other causes of leukocyte count modifications: corticosteroid therapy, immunosuppressive treatment, antitumoral chemotherapy, malignant hemopathy, and progressive cancer. Demographics, comorbidities, clinical, biological data, and data about in-hospital procedures were also collected.

The study group, with one of the bacterial infections (pyelonephritis, prostatitis, pneumonitis, appendicitis, cholecystitis, and sigmoiditis), was compared with an uninfected control group randomly selected among other patients visiting the ED during the same period. All leukocyte subtypes were compared with C-reactive protein (CRP), as a reference marker that showed high sensitivity and specificity in bacterial infections' diagnosis [15, 16]. Procalcitonin was not measured because of its marginal use in our center.

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Three clinical severity stages were established according to the new international definition of sepsis: infection without severity criteria, sepsis, and septic shock [17, 18]. The relationship between circulating eosinophil levels and the three stages of clinical severity was assessed. Eosinophil counts at the third day (D3) and the seventh day (D7) were measured when available, to study the impact of eosinopenia on the length of hospital stay and mortality.

Ethics

This study was approved by our institution's (Strasbourg University Hospital, France) ethics review board (reference: FC/2018/2018-10). Patients' consent was not necessary

according to local requirements in this observational and retrospective study.

Statistical analysis

The comparison between the infected and uninfected groups was performed by Student's *t* test, and a Mann-Whitney *U* test was used when appropriate. The characteristics of the laboratory diagnostic tests were estimated (sensitivity, specificity, positive predictive value, and negative predictive value) with a 95% confidence interval by the binomial method. Receiver operating characteristic (ROC) curves were used to evaluate the best cut-off value for each variable. The overall diagnostic accuracy for each biological marker, or combination of markers, was evaluated by areas under the ROC curves. The relationship between circulating eosinophil levels and the three stages of clinical severity was assessed by the Kruskal-Wallis method. The impact of eosinophils on D3 and D7 on hospital stay was assessed by the Pearson correlation test, with a 95% confidence interval. A two-tailed p value < 0.05 was considered significant. Statistical analyses were carried out using software R in version 3.1.0.

Data availability All data analyzed as part of the study are included.

Results

During the study period, 876 patients were enrolled. A total of 466 infected patients were included for statistical analysis and 410 patients had exclusion criteria. A control group of 466 uninfected patients was randomly selected in the general population who visited the ED during the same period of time (Fig. 1). In the infected group, the mean age was 57.9 ± 24.7 years and the sex ratio was 0.94. One hundred and sixty patients (34.3%) had acute pyelonephritis, 122 (26.2%) appendicitis, 72 (15.5%) pneumonia, 46 (9.9%) cholecystitis, 39 (8.4%) prostatitis, and 24 (5%) diverticular sigmoiditis. In the study group, an infection without sepsis was found in 318 patients (68.2%), 135 (29.0%) patients presented with sepsis while only 13 (2.8%) patients were in septic shock.

Parameters of the WBC count

All leukocyte count parameters were significantly modified ($p < 0.001$) in the infected group compared with the control group, with an increase in total leukocytes (13,502/mm^3 versus 9247/mm^3), neutrophilia (11,094/mm^3 versus 6566 /mm^3), and monocytosis (980/mm^3 versus 674/mm^3). The baseline characteristics of the two groups are reported in Table 1. The infected group also had a decrease in the mean level of eosinophils (59/mm^3 versus 129/mm^3), basophils (34/mm^3 versus 44/mm^3), and lymphocytes (1295/mm^3 versus 1870/ mm^3).

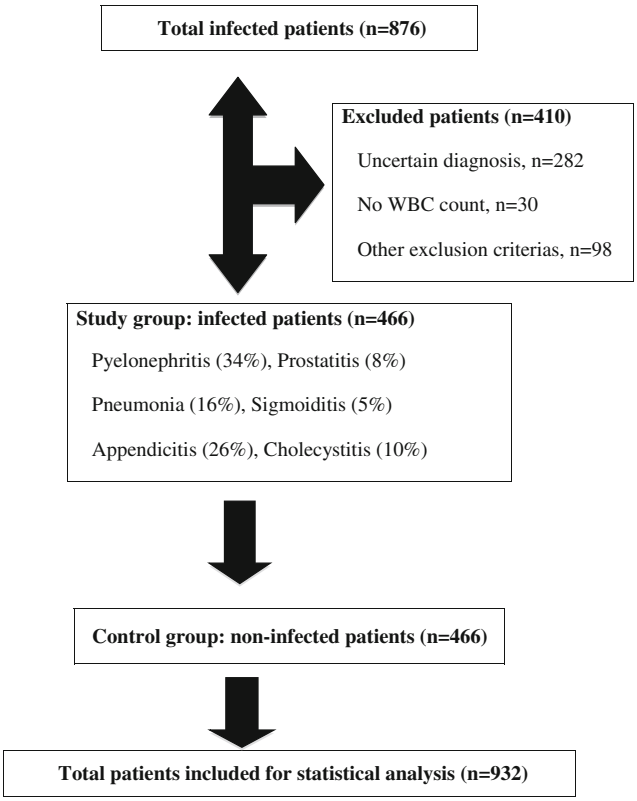

Fig. 1 Flow chart of the study. WBC, white blood cells

Total leukocytes

The use of a ROC curve enables us to determine a cut-off at 10,380 leucocytes per mm^3 for the diagnosis of bacterial infection, for all types of infections combined. The sensitivity and specificity of leukocytosis at this cut-off were 74.2 and 70.4%, respectively (Table 2). Hyperleukocytosis of more than 12,000/mm^3 had a sensitivity of 59.4% and a specificity of 82.2% with positive and negative likelihood ratios of 3.3 and 0.5, respectively. The area under the curve (AUC) was 77.5% (Fig. 2). Regarding the CRP, the AUC for all type of infections combined was 89.4%. Diagnostic accuracy of leukocytosis for each infection is reported in Table 3. An increased performance of leukocytosis in prostatitis (AUC 82.5%), appendicitis (AUC 81.7%), and diverticular sigmoiditis (AUC 80.4%) was noted. The AUC was 77.9% for pneumonia, 73.8% for acute pyelonephritis, and 72.4% for acute cholecystitis.

Neutrophilia greater than 8000/mm^3 had a sensitivity of 73.6%, a specificity of 74.2%, and positive and negative likelihood ratios of 2.9 and 0.4, respectively, for all infections combined. The area under the neutrophil curve was 79.6% (Fig. 2). The diagnostic performance of neutrophils was increased in prostatitis (AUC 84.8%), sigmoiditis (AUC

Table 1 Mean values of the different leukocyte parameters for each pathology

	Leukocytes (/mm^3)	Neutrophils (/mm^3)	Eosinophils (/mm^3)	Basophils (/mm^3)	Lymphocytes (/mm^3)	Monocytes (/mm^3)	CRP (mg/L)	*p* value
Pyelonephritis	12,765 ± 766	10,679 ± 229	43 ± 14	32 ± 5	1084 ± 102	988 ± 80	137 ± 17	< 0.001
Prostatitis	15,008 ± 1882	12,677 ± 3537	52 ± 56	31 ± 9	1046 ± 217	1088 ± 164	103 ± 24	< 0.05
Appendicitis	14,035 ± 393	11,143 ± 765	82 ± 24	38 ± 5	1641 ± 141	987 ± 76	58 ± 13	< 0.001
Cholecystitis	12,874 ± 1558	10,692 ± 2954	39 ± 19	27 ± 6	1214 ± 208	890 ± 160	100 ± 32	< 0.05
Sigmoiditis	12,914 ± 1502	10,663 ± 1438	55 ± 23	31 ± 10	1344 ± 275	817 ± 138	139 ± 40	< 0.05
Pneumonia	13,850 ± 1358	11,143 ± 765	75 ± 37	40 ± 9	1355 ± 278	976 ± 102	120 ± 50	< 0.05
All infected	13,502 ± 449	11,094 ± 419	59 ± 11	34 ± 3	1295 ± 74	980 ± 43	108 ± 9	< 0.001
Controls	9247 ± 331	6566 ± 320	129 ± 12	44 ± 2	1870 ± 99	674 ± 25	11 ± 2	< 0.001

All results expressed as mean ± standard deviation

83.9%), and pneumonia (AUC 80.1%). The AUC of neutrophils was 78.8% in pyelonephritis, 79.1% in appendicitis, and 75.4% in acute cholecystitis (Table 3).

Eosinopenia, with a cut-off at 50/mm^3, showed in our study a sensitivity of 67.2% and a specificity of 75.8% for all sites of infection combined (Table 2). Deep eosinopenia (< 10/mm^3) showed a sensitivity of 35.4%, a specificity of 94.4%, and positive and negative likelihood ratios of 6.3 and 0.7, respectively (Table 2). The AUC of eosinophils was 75.9%, for all infections combined. Eosinopenia's diagnostic accuracy was increased in prostatitis (AUC 83.5%), pyelonephritis (AUC 80.7%), and acute cholecystitis (AUC 79.7%). The AUC was estimated at 74.9% in pneumonia, 68.6% in sigmoiditis, and 67.3% in appendicitis (Table 3).

The cut-off for infections was 30 basophils per mm^3. At this rate, basopenia had a sensitivity of 40.3%, a specificity of 79.8%, and positive and negative likelihood ratios of 2% and 0.7%, respectively (Table 2). The area under the basophilic polynuclear curve for all infections combined was 63.1%.

With a cut-off at 1320/mm^3 for the diagnostic of infection, lymphopenia had a sensitivity of 60.5% and a specificity of 74.7%. Below 700/mm^3, lymphopenia showed a sensitivity of 22.3%, a specificity of 94.2%, and positive and negative likelihood ratios of 3.9 and 0.8, respectively (Table 2). The AUC in all infections combined was 77.3%. The AUC of lymphocytes was 78.3% for pyelonephritis, 77.9% for prostatitis, 73.6% for cholecystitis, 70.5% for pneumonia, 65.8% for sigmoiditis, and 56.7% for appendicitis (Table 3).

With a cut-off at 1000/mm^3, monocytosis presented a sensitivity of 45.7% and a specificity of 88.4%, for all infection sites combined (Table 2). Positive and negative likelihood ratios were 3.9 and 0.6, respectively. The AUC was 72%. For the diagnosis of male urinary tract infection, the AUC of monocytes was 75.2%, 72.7% in pneumonia, 72.5% in

Table 2 Diagnostic performance of various leukocyte parameters (all infections combined)

Parameters	Value	Sensitivity (%)	Specificity (%)	LR+	LR−	AUC (%)
Leukocytes	> 10,380/ mm^3	74.2	70.4	2.5	0.4	77.5
	> 12,000/mm^3	59.4	82.2	3.3	0.5	
Neutrophils	> 7140/mm^3	81.3	68	2.5	0.3	79.6
	> 8000/mm^3	73.6	74.2	2.9	0.4	
Eosinophils	< 100/mm^3	82	48.9	1,6	0.4	
	< 50/mm^3	67.2	75.8	2.8	0.4	75.9
	< 10/mm^3	35.4	94.4	6.3	0.7	
Basophils	< 30 /mm^3	40.3	79.8	2	0.7	63.1
Lymphocytes	< 1320/mm^3	60.5	74.7	2.4	0.5	70.3
	< 700/mm^3	22.3	94.2	3.9	0.8	
Monocytes	> 790/mm^3	62.9	75.8	2.6	0.5	72
	> 850/mm^3	57.9	80.7	3	0.5	
CRP	> 16 mg/L	80.2	86.1	5.8	0.2	89.4
	> 40 mg/L	64.2	94.8	12.3	0.4	
	> 100 mg/L	44.8	99	42.8	0.6	

All results are expressed in mean ± standard deviation

CRP C-reactive protein

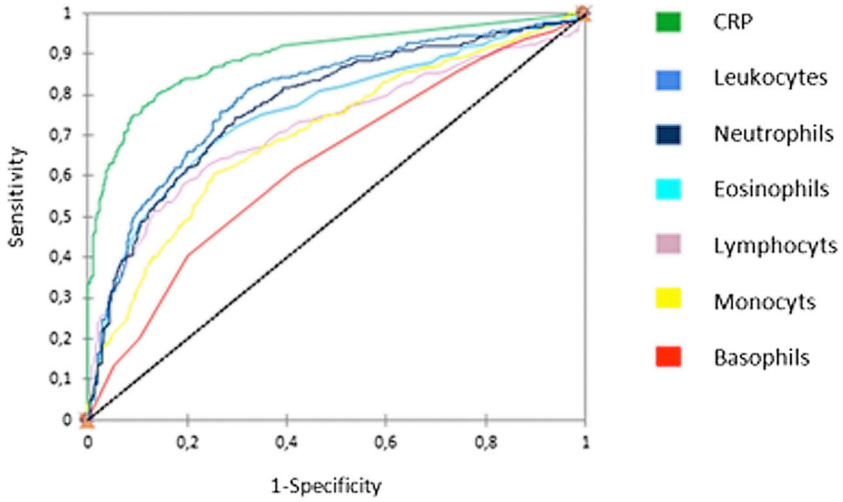

Fig. 2 ROC curves of each biological variable for the diagnosis of infection (all combined). CRP, C-reactive protein

pyelonephritis, 75.1% in appendicitis, 61.2% in cholecystitis, and 67.0% in sigmoiditis (Table 3).

Modification of WBC count according to infection severity

In the present study, hyperleukocytosis showed a tendency for increase along with clinical severity. The mean leukocyte count in patients without sepsis was 13,295/mm^3 versus 13,838/mm^3 for patients with sepsis and 15,063/mm^3 for patients with septic shock ($p = 0.5$), (Table 1). We also observed an increase of leukocytes according to the stage of clinical severity with an average rate of 10,746/mm^3 for infected patients without sepsis, 11,711/mm^3 in the sepsis group, and 13,209/mm^3 in the septic shock group ($p = 0.09$) (Table 4). Eosinopenia observed in infected patients appeared to increase between infected patients and patients in the sepsis group, with mean eosinophil counts of 65/mm^3 and 44/mm^3, respectively ($p < 0.0001$). We also observed a significant decrease of basophils according to clinical severity with an average rate of 36/mm^3, 30/mm^3, and 27/mm^3, respectively, in the infected, sepsis, and septic shock groups ($p < 0.001$). Lastly, we observed the same trend for lymphocytes with average rates of 1427/mm^3, 1023/mm^3, and 876/mm^3 in the three different groups ($p < 0.0001$). In contrast, mean monocyte levels did not differ significantly according to severity ($p = 0.5$).

Association of clinical or biological parameters

Modification of each leucocyte subtypes, associated with the presence of fever (temperature > 38.5 °C), showed specificity close to 100% for the diagnosis of sepsis, with high positive likelihood ratios (Table 5). The combination of deep eosinopenia (< 10/mm^3) or deep lymphopenia (< 700/mm^3) with CRP > 40 mg/L showed a specificity of 100% for the diagnosis of bacterial infection (Table 6).

Eosinopenia and length of hospital stay

We observed a small tendency for a rise in hospital length of stay with increasing eosinopenia with a Pearson correlation coefficient of − 0.062 (95% CI, − [0.191–0.068]) for D3 and − 0.076 (95% CI − [0.278–0.133]) for D7.

Mortality

The in-hospital mortality rate secondary to septic shock in the infected patients group was 1.9%. The comparison of the eosinophil level at day 1 between non-survivors and the surviving patients did not show any significant difference, with a mean rate of 58/mm^3 in the surviving patients versus 78/mm^3 ($p = 0.54$). The same comparison at D3 found a mean eosinophil rate at 16/mm^3 in non-survivors versus 70/mm^3 in the surviving patients. The difference was not statistically significant ($p = 0.06$).

Discussion

WBC count contribution for the diagnosis of infection

The present study focused on the value of each WBC count parameter for the diagnosis of common infections encountered in the ED. In accordance with the literature, infections were associated with significant changes in the WBC count compared with the control group [3, 7–9]. In the infected patients, a significant rise in total leukocytes, polynuclear cells, and monocytes was observed, whereas eosinophils, lymphocytes, and basophils were decreased. All infections combined, neutrophils were the most relevant parameter for the

Table 3 Diagnostic performance of each leukocyte subtype for each pathology

	Parameters	Cut-off	Sensitivity (%)	Specificity (%)	LR+	LR−	AUC (%)
Pyelonephritis $n = 160$	Leukocytes	> 12,000/mm^3	57.5	82.2	3.2	0.5	73.8
	Neutrophils	> 8000/mm^3	77.5	68.9	2.5	0.3	78.8
	Eosinophils	< 40/mm^3	73.1	80.3	3.7	0.3	80.7
	Basophils	< 30/mm^3	45	79.8	2.2	0.7	65.3
	Lymphocytes	< 700/mm^3	31.3	94.2	5.4	0.7	78.3
	Monocytes	> 900/mm^3	55.6	84.3	3.6	0.5	72.5
	CRP	> 40 mg/L	76.3	94.8	14.6	0.3	93.8
Prostatitis $n = 39$	Leukocytes	> 12,000/mm^3	69.2	84.3	4.4	0.4	82.5
	Neutrophils	> 8000/mm^3	84.6	74.2	3.3	0.2	84.8
	Eosinophils	< 40/mm^3	82.1	80.3	4.2	0.2	83.5
	Basophils	< 30/mm^3	46.2	79.8	2.3	0.7	64.4
	Lymphocytes	< 700/mm^3	41	94.2	7.1	0.6	77.9
	Monocytes	> 1000/mm^3	61.5	87.8	5	0.4	75.2
	CRP	> 40 mg/L	71.1	94.8	13.6	0.3	94
Appendicitis $n = 122$	Leukocytes	> 12,000/mm^3	60.7	82.2	3.4	0.5	81.7
	Neutrophils	> 8000/mm^3	73.8	74.5	2.9	0.4	79.1
	Eosinophils	< 40/mm^3	54.1	75.8	2.2	0.6	67.3
	Basophils	< 30/mm^3	59	58.4	1.4	0.7	59.1
	Lymphocytes	< 700/mm^3	39.3	94.2	1.3	1.0	56.7
	Monocytes	> 1000/mm^3	66.4	77.3	2.9	0.4	75.1
	CRP	> 40 mg/L	38.0	94.8	7.3	0.7	79.7
Cholecystitis $n = 46$	Leukocytes	> 12,000/mm^3	58.7	82.2	3.3	0.5	72.4
	Neutrophils	> 8000/mm^3	71.7	74.2	2.8	0.4	75.4
	Eosinophils	< 40/mm^3	76.1	70	2.5	0.3	79.7
	Basophils	< 30/mm^3	76.1	58.4	1.8	0.4	70.5
	Lymphocytes	< 700/mm^3	23.9	94.2	4.1	0.8	73.6
	Monocytes	> 1000/mm^3	52.2	77.3	2.3	0.6	61.2
	CRP	> 40 mg/L	52.2	94.8	10.0	0.5	83.8
Sigmoiditis $n = 24$	Leukocytes	> 12,000/ mm^3	54.2	82.2	3.0	0.6	80.4
	Neutrophils	> 8000/mm^3	79.2	74.2	3.1	0.3	83.9
	Eosinophils	< 40/mm^3	50.0	75.8	2.1	0.7	68.7
	Basophils	< 30 /mm^3	75	58.4	1.8	0.4	66.2
	Lymphocytes	< 700/mm^3	12.5	94.2	2.2	0.9	65.8
	Monocytes	> 1000/mm^3	50	77.3	2.2	0.7	67
	CRP	> 40 mg/L	83.3	94.8	15.9	0.2	96.3
Pneumonia $n = 74$	Leukocytes	> 12,000/mm^3	58.3	82.2	3.9	0.5	77.9
	Neutrophils	> 8000/mm^3	77.8	74.2	3	0.3	80.1
	Eosinophils	< 40/mm^3	65.3	75.8	2.7	0.5	74.9
	Basophils	< 30/mm^3	38.9	79.8	1.9	0.8	59.1
	Lymphocytes	< 1000/mm^3	65.3	75.8	2.7	0.5	70.5
	Monocytes	> 980/mm^3	52.8	88.2	4.5	0.5	72.7
	CRP	> 40 mg/L	77.8	94.8	14.9	0.2	94.2

AUC area under curve, *CRP* C-reactive protein, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio

diagnosis of infection with the highest AUC, followed by total leukocytes and eosinophils. Basophils, lymphocytes, and monocytes were the least useful parameters. However, all WBC count parameters remained less efficient than CRP. Total leukocytes and neutrophils were the most effective parameters in the diagnosis of sigmoiditis or appendicitis.

Table 4 Mean rate of different WBC count parameters and clinical severity

Parameters	All infections ($n = 466$)	Infections without sepsis ($n = 318$)	Sepsis ($n = 135$)	Septic shock (n = 13)	p value
Leukocytes (/mm^3)	13,501 ± 450	13,295 ± 516	13,838 ± 911	15,063 ± 405	0.5
Neutrophils (/mm^3)	11,094 ± 419	10,746 ± 475	11,711 ± 848	13,209 ± 3899	0.09
Eosinophils (/mm^3)	58.6 ± 6	65.2 ± 14	44 ± 15	49.2 ± 32	< 0.0001
Basophils (/mm^3)	34 ± 2	36 ± 3	29.9 ± 3	26.9 ± 11	< 0.01
Lymphocytes (/mm^3)	1295 ± 72	1427 ± 83	1023 ± 151	876 ± 269	< 0.0001
Monocytes (/mm^3)	980 ± 43	982 ± 50	991 ± 86	814 ± 121	0.5
CRP (mg/L)	108 ± 9	97 ± 11	124 ± 17	205 ± 52	< 0.0001

All results are expressed in mean ± standard deviation

Moreover, we found that total leukocytes had a better diagnostic accuracy than CRP for appendicitis; these results were similar to those published by Shellekens et al. [19].

Furthermore, deep eosinopenia (less than 10/mm^3) had a good specificity for bacterial infections (94%) and showed an interesting positive likelihood ratio in all types of infections. This outcome seems to confirm the findings of our previous study of 125 infected patients in the ED, where deep eosinopenia had a specificity of 91% for the diagnosis of infection [14]. In these infected patients, eosinopenia showed a particular value for the diagnosis of urinary tract and biliary tract infections. Indeed, our results confirmed that eosinophils had a higher AUC than total leukocytes or neutrophils for pyelonephritis and cholecystitis and, thus, had a better diagnostic performance. In prostatitis, AUC for eosinophils was higher than AUC for total leukocytes. Kaminsky et al. [8] obtained similar results in a study with 187 patients about urinary and biliary tract infections. They described a good positive predictive value of the association between eosinopenia (< 50/mm^3), lymphopenia (< 700/mm^3), and neutrophilia (> 8000/mm^3). In contrast, we found that eosinopenia had a weak diagnostic performance for pneumonia, appendicitis, and diverticular sigmoiditis. Davido et al. [20] recently described eosinophils in monitoring the efficacy of antibiotic therapy and concluded that eosinophils normalized faster than other biomarkers or fever when antibiotic therapy was appropriate. Our methodology did not allow us to study precisely the kinetics of eosinophils, but an increase in the length of hospitalization with eosinopenia was observed. Besides, the non-survivors had a persistent deep eosinopenia on D3 compared with survivors. The pathophysiology of eosinopenia in bacterial infections is not yet fully understood. Eosinophilic polynuclear cells have multiple functions including an immunomodulatory role with initiation and propagation of the immune response as well as a direct bactericidal role [21–23]. It seems, however, that the margination of eosinophils under stress is the result of both the secretion of endogenous glucocorticoids and the production of chemotactic factors within the infected site [24]. Complement proteins also seem to have a role to play [25]. Finally, the degranulation of basophils and monocytes could participate in the sequestration of eosinophils within the infectious site [26].

In the present study, lymphocytes and monocytes showed a lower diagnostic performance than total leukocytes, neutrophils, or eosinophils, based on their respective AUC. The lymphopenia that accompanies bacterial infections results both from a response to the endogenous secretion of cortisol and the activation of their diapedesis [27], though previous studies have shown that serious infections can also be associated with a deeper immune dysfunction leading to apoptosis of a part of the lymphocyte population [28, 29]. Although the diagnostic value of lymphopenia was described in association with other elements of the WBC count, lymphopenia is mainly cited as a prognostic marker, whether alone for lymphopenia less than 700/mm^3 or in combination with neutrophils as reported by Riché et al. and De Jager et al. [30–33]. In our study, lymphopenia significantly increased with the clinical severity.

Table 5 Diagnostic performance of the association between fever and WBC count modification

Associated parameters with fever (> 38.5 °C)		Sensitivity (%)	Specificity (%)	LR+	LR−
Leukocytes	> 10,380/mm^3	35.9	99.8	170.7	0.6
Monocytes	> 850/mm^3	28.1	99.6	65.4	0.7
Eosinophils	< 50/mm^3	39.1	99.4	61	0.6
Basophils	< 30/mm^3	22.8	99.4	35.5	0.8
Neutrophils	> 7140/mm^3	41.9	99.1	48.6	0.6
Lymphocytes	< 1320/mm^3	35	99.1	40.7	0.7

LR+ positive likelihood ratio, *LR−* negative likelihood ratio

Table 6 Diagnostic performance of the association between fever and CRP

CRP > 40 mg/L associated with	Sensitivity (%)	Specificity (%)	LR+	LR −
Eosinophils < 10/mm^3	22.6	100	–	0.8
Lymphocytes < 700/mm^3	16.4	100	–	0.8
Eosinophils < 50/mm^3	47.2	98.9	45	0.5
Basophils < 30/mm^3	29.5	98.7	22.5	0.7
Neutrophils > 7140/mm^3	54.1	98.2	29.6	0.5
Leukocytes > 10,380/mm^3	47.8	98.2	26.1	0.5
Lymphocytes < 1320/mm^3	41.1	97.6	17.4	0.6
Monocytes > 850/mm^3	40.3	97.6	17.1	0.6

LR+ positive likelihood ratio, *LR−* negative likelihood ratio

Only few studies described, to our knowledge, the diagnostic performance of monocytosis for bacterial infections. Lymphocytes and monocytes showed weak correlation with infection, in contrast with our findings where the infected patients had a significant increase in monocyte levels compared with the uninfected ones. A retrospective study by López et al. [34] about 244 ICU patients found that eosinopenia and monocytosis combined together have a negative predictive value greater than 95%, thus describing a possible tool to rule out bacterial infections.

Finally, basophilic polynuclear cells were the least relevant parameter to make the diagnosis of bacterial infection in the ED. Deibener-Kaminsky et al. [4] found basophils at significantly lower rates in patients with adverse outcomes, suggesting a prognostic value of basophils in infected patients. Nevertheless, in our study, basopenia increased significantly with the clinical stage of severity.

Combination of biological and clinical parameters

The modification of each parameter of the WBC count (leukocytosis, neutrophilia, eosinopenia, basopenia, lymphopenia, or monocytosis) with a concomitant elevation of CRP (> 40 mg/L), or with the presence of fever (> 38.5 °C), had a good specificity for bacterial infection. In particular, we found that fever with eosinopenia (< 10/mm^3) or lymphopenia (< 700/mm^3) was associated with bacterial infection in 100% of cases. Few authors have studied, to our knowledge, the association of the objective clinical parameter of infection, such as fever, with a modification of the WBC count. Bouldoires et al. [35] recently described the value of a combination of laboratory findings and clinical parameters to diagnose infections. They proposed the CIBLE score (CRP bacterial infection leukocytes eosinophils) including eosinopenia, CRP, and fever over 38.3 °C. This score obtained an AUC greater than any parameter taken alone [35, 36]. Our study also seems to confirm the interest of coupling the analysis of several biological markers with clinical parameters like fever to diagnose bacterial infections.

Limitations

Our results should be interpreted with caution on account of several limitations. First of all, the difficulty in obtaining complete information retrospectively limited us in the collection of data. In addition, we sought to obtain a high degree of certainty regarding our primary endpoint, but this forced us to exclude a large number of patients, especially respiratory infections (mostly due to the lack of certainty for microbiological diagnosis), explaining the difference with recent epidemiological data [37]. On the other hand, our study has several strengths. The study sample was large and involved both groups of infected and non-infected patients, but it did not represent the real prevalence of each pathology encountered in the ED population. The exclusion of viral infections and the inflammatory syndrome-mediated diseases may explain the remarkable diagnostic performance of the association between leukocyte subtypes and fever, or the value of CRP, compared with previous studies [15, 16]. Fever is indeed a clinical parameter that lacks specificity and sensitivity [4]. Further work comparing bacterial infections with viral infections in particular would be useful to refine our results. It should also be noted that our study was monocentric. A prospective and multi-center study is now ongoing to confirm those results.

Conclusion

Neutrophils and total leukocytes remain the two most useful leukocyte parameters for the diagnosis of infections in the ED (all infections combined). Eosinopenia represented the most efficient parameter of the WBC count for the diagnosis of urinary and biliary tract infections. Deep eosinopenia presented a specificity of 94% for the diagnosis of infection regardless of the type of infection. Any modification of the WBC

count associated with an elevation of CRP (> 40 mg/L) or fever (> 38.5 °C) showed a high specificity for the diagnosis of infection. In the ED, a prompt diagnosis of sepsis remains a key issue. A careful analysis of the WBC count in the ED, which is easily accessible, fast, and affordable, represents a valuable tool to highlight an infection and thus to quickly start appropriate therapy.

Acknowledgments We thank Dr. C. Brunhuber for her English proofreading of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics This study was approved by our institution's (Strasbourg University Hospital, France) ethics review board (reference: FC/2018/2018-10).

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