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Original Research Article

The Role of Eosinopenia as a Marker of Bacterial Infection in Children Admitted with Acute Febrile Illness: A Prospective Observational Study from a Tertiary Care Centre in Southern India

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Abstract

Background: Discriminating bacterial from viral aetiology in febrile children remains a persistent clinical challenge. Eosinopenia is an inexpensive, universally available parameter derived from the complete blood count, but paediatric evidence is scarce.

Objectives: To evaluate eosinopenia as a marker of bacterial infection in children admitted with acute febrile illness and to compare its performance with leukocytosis, neutrophil predominance, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Methods: A prospective observational study was conducted over 18 months at a tertiary paediatric hospital in Mysuru, Karnataka. Ninety children aged 1 to 18 years admitted with acute febrile illness of under 14 days' duration were enrolled after excluding chronic illness, malignancy, immunodeficiency, malnutrition, central nervous system infection and recent steroid or antibiotic exposure. Blood was sampled before antibiotic initiation. Participants were classified as definitive bacterial infection (positive blood culture), suspected bacterial infection (3 of 5 predefined laboratory criteria), or non-bacterial infection. Eosinopenia was defined as eosinophils below 1% of total leukocytes.

Results: Eleven children (12.2%) had culture-confirmed bacteraemia, 50 (55.6%) had suspected bacterial infection and 29 (32.2%) had non-bacterial illness. Eosinopenia occurred in 90.9%, 80.0% and 10.3% of these groups respectively ($p<0.001$). For any bacterial infection, eosinopenia yielded a sensitivity of 82.0%, specificity of 89.7%, positive predictive value of 94.3% and negative predictive value of 70.3%. Eosinopenia was significantly associated with leukocytosis ($p=0.022$), neutrophil predominance ($p<0.001$), raised CRP ($p=0.004$), raised ESR ($p=0.001$) and toxic granulation ($p<0.001$).

Conclusion: Eosinopenia performed comparably to conventional acute-phase reactants and merits evaluation as a first-tier discriminator in resource-limited settings.

Keywords: Eosinopenia; Eosinophil count; Bacterial infection; Acute febrile illness; C-reactive protein; Child; Biomarkers.

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Introduction

Acute febrile illness is the single most frequent reason for paediatric hospital admission worldwide, and in low- and middle-income countries it accounts for a disproportionate share of both outpatient attendance and inpatient bed-days. The overwhelming majority of these episodes are self-limiting viral infections, yet a small but clinically critical minority represent serious bacterial infection with the potential for rapid deterioration, organ dysfunction and death. Reported prevalence of serious infection among febrile children presenting to emergency and paediatric assessment settings ranges widely, from approximately 4.5% to 29.3%, depending on case mix and referral filter [1]. The clinician at first contact must therefore make a probabilistic judgement with imperfect information, balancing the risk of missing invasive bacterial disease against the harms of reflexive empirical antibiotic prescription. Those harms are neither trivial nor hypothetical. Unnecessary antibiotic exposure drives the selection of resistant organisms, disrupts the developing paediatric microbiome, exposes children to adverse drug reactions and inflates the cost of care. In settings where antimicrobial resistance is already endemic and where diagnostic stewardship infrastructure is limited, the value of any inexpensive test that shifts probability meaningfully in either direction is

correspondingly amplified.The biomarkers in routine use for this purpose are the total leukocyte count, the absolute neutrophil count, the band count, the erythrocyte sedimentation rate, C-reactive protein and, increasingly, procalcitonin. Their individual and combined performance has been examined systematically. In a review of 14 diagnostic accuracy studies conducted in ambulatory and emergency settings, C-reactive protein and procalcitonin emerged as the most informative single tests, with C-reactive protein yielding a pooled positive likelihood ratio of 3.15 (95% CI 2.67 to 3.71) and a pooled negative likelihood ratio of 0.33 (95% CI 0.22 to 0.49) across five studies comprising 1379 children [1]. The white blood cell count, by contrast, was found to add little for ruling in serious infection and to be effectively useless for ruling it out [1]. The best-performing composite decision rule, combining C-reactive protein, procalcitonin and urinalysis, achieved a positive likelihood ratio of 4.92 (95% CI 3.26 to 7.43) and a negative likelihood ratio of 0.07 (95% CI 0.02 to 0.27) [1]. Even these figures fall short of a definitive rule-in or rule-out test, and the assays involved are not universally affordable. Considerable effort continues to be directed towards novel host-response markers, including interleukin-6, interleukin-10, soluble triggering receptor expressed on myeloid cells-1 and combinatorial signatures, but none has yet displaced the conventional panel in routine paediatric practice [2].

Blood culture remains the reference standard for bacteraemia. It is, however, a poor operational guide to immediate decision-making. Results take 24 to 72 hours, yield is heavily reduced by prior antibiotic exposure, and in paediatric practice the small volumes obtainable further depress sensitivity. A clinician needs a signal available within the first hour of contact. This is precisely the niche that a parameter derived from the complete blood count could occupy, provided it carries genuine discriminatory information.

Eosinophils constitute a small fraction of circulating leukocytes, typically 1% to 4% of the total in healthy children, with the great majority of the body’s eosinophil mass residing in tissues rather than in blood. Their production in the bone marrow is tightly regulated by interleukin-3, interleukin-5 and granulocyte-macrophage colony-stimulating factor, and in the absence of these three cytokines eosinophil survival in circulation falls to under 48 hours. Because the circulating pool is small, short-lived and cytokine-dependent, it is exquisitely sensitive to perturbation, which is the biological basis for its behaviour as an acute-phase parameter.That behaviour has been recognised for well over a century. The abrupt fall in circulating eosinophils during acute infection was described in the 1890s and was subsequently rediscovered and re-characterised at intervals throughout the twentieth century, earning it the description of an "old" marker in need of revisiting [5]. The mechanistic work of Bass and colleagues in the 1970s established that eosinopenia during acute inflammation is not simply a corticosteroid epiphenomenon. In a series of experiments demonstrating that the response did not depend on adrenal function [3], and subsequently that intravascular activation or injection of the chemotactic factors of acute inflammation, specifically C5a and N-formyl-methionyl-leucyl-phenylalanine, reproduced the eosinopenic response in both rabbits and humans [4], these investigators showed that complement-derived and bacterial-derived chemoattractants directly drive eosinophils out of the circulation.

The contemporary understanding integrates several mechanisms. Bacterial endotoxin and lipopolysaccharide activate macrophages, neutrophils and dendritic cells to release interleukin-1, interleukin-6 and tumour necrosis factor alpha. These cytokines activate the hypothalamic-pituitary-adrenal axis, increasing glucocorticoid release, which in turn suppresses interleukin-3, interleukin-5, granulocyte-macrophage colony-stimulating factor, chemokine expression and integrin-mediated adhesion, reducing eosinophil production and survival [4,5]. Concurrently, complement activation products and bacterial chemotactic peptides induce rapid margination and sequestration of eosinophils at the site of infection and within the reticuloendothelial system. The net effect is a fall in the circulating count that begins early, often within hours of the onset of systemic inflammation, and that reverses rapidly with clinical recovery. This early kinetics is a potential advantage over C-reactive protein, which characteristically begins to rise only around 12 hours after fever onset.

Adult critical care provided the modern re-entry point for this marker into clinical research. In a prospective study of 177 consecutive admissions to a medical intensive care unit, the eosinophil count discriminated infected from non-infected patients with an area under the receiver operating characteristic curve of 0.89 (95% CI 0.83 to 0.94), significantly outperforming C-reactive protein at 0.77 (95% CI 0.70 to 0.84, p=0.010) [6]. A threshold below 50 cells/mm3 produced a sensitivity of 80% and a specificity of 91%, with a positive likelihood ratio of 9.12; median eosinophil counts were 109/mm3 in non-infected and 13/mm3 in infected patients (p<0.001) [6]. The same group later reported that eosinopenia at admission carried prognostic weight, with median counts of 30 cells/mm3 in survivors versus 0 cells/mm3 in non-survivors (p=0.004) [7]. Eosinopenia and a

sustained neutrophil-lymphocyte count ratio above 7 were subsequently identified as independent markers of mortality in adults with bacteraemia [10].

These findings were not universally replicated. A retrospective analysis from Barcelona concluded that eosinopenia was not a reliable marker of infection in critically ill patients and that C-reactive protein retained superiority [8]. In a critical care cohort of 68 patients, an eosinophil count below 50 cells/mm3 achieved a sensitivity of 81% but a specificity of only 65%, compared with a sensitivity of 94% and specificity of 84% for C-reactive protein at 70 mg/L, and a sensitivity of 84% and specificity of 92% for procalcitonin at 1.5 microgram/L [9]. A systematic review and meta-analysis of seven studies encompassing 3842 subjects reported pooled sensitivity of 0.66 (95% CI 0.53 to 0.77) and pooled specificity of 0.68 (95% CI 0.56 to 0.79), with a summary area under the curve of 0.73 (95% CI 0.68 to 0.76), and concluded that eosinopenia is highly prevalent in sepsis but not superior to conventional biomarkers [15]. Reported incidence of eosinopenia across the included studies varied from 23.2% to 92.7%, a spread that largely reflects heterogeneous threshold definitions [15].

Paediatric data are sparser and more discordant still. A case-control study comparing 85 paediatric and 157 adult patients with bloodstream infection against culture-negative controls found eosinopenia in 46.5% of cases versus 21.5% of controls, yet in the paediatric subgroup the eosinophil count had almost no discriminatory ability, with an area under the curve of 0.448 (95% CI 0.363 to 0.533, p=0.237), a sensitivity of 54% and a specificity of 56%; only C-reactive protein and neutrophil count remained significant in multivariate analysis [11]. Conversely, a retrospective study of 878 ill-appearing febrile children found that an eosinophil count of 50/mm3 or below yielded a sensitivity of 61%, specificity of 67%, positive predictive value of 73.1% and negative predictive value of 54%, values statistically indistinguishable from those of neutrophil count and C-reactive protein, with respective areas under the curve of 0.671, 0.655 and 0.710 ($p>0.05$) [12]. In paediatric meningitis, an eosinophil count below 5/mm3 distinguished bacterial from aseptic meningitis with a sensitivity of 80% and specificity of 73% [13], and in early-onset neonatal sepsis eosinopenia below 140 cells/mm3 achieved a specificity of 90.0% and a positive predictive value of 94.7%, albeit with a modest sensitivity of 60.0% [14].The literature therefore leaves an unresolved question of direct clinical consequence: does eosinopenia carry usable discriminatory information in the general population of febrile children admitted to hospital, as distinct from selected neonatal, meningitic or bacteraemic subgroups? The question matters most in exactly those settings where procalcitonin is unavailable and where blood culture yield is low. The present study was undertaken to address this gap in an Indian tertiary care paediatric population.

Aims and Objectives

Aim: To determine the significance of eosinopenia as a marker of bacterial infection in children admitted with acute febrile illness.

Primary Objective: To compare the eosinophil count between children with bacterial infection and those with non-bacterial (viral) infection.

Secondary Objective: To compare the performance of eosinopenia against the conventional acute-phase reactants used in this setting, namely leukocytosis, neutrophil predominance, C-reactive protein, erythrocyte sedimentation rate and peripheral smear evidence of toxic granulation or band forms.

Materials and Methods

Study Design and Setting: This was a prospective observational study conducted in the Department of Paediatrics, Cheluvamba Hospital, Mysore Medical College and Research Institute, Mysuru, Karnataka, India, a tertiary care teaching hospital serving a predominantly urban and peri-urban catchment population. The study was carried out over a period of 18 months, with recruitment between June 2022 and 2023.

Study Population: The study population comprised all children admitted to the paediatric wards with acute febrile illness who fulfilled the eligibility criteria during the recruitment period.

Inclusion Criteria: Children aged 1 year to 18 years admitted with acute febrile illness of less than 14 days' duration were eligible for inclusion.

Exclusion Criteria: Children were excluded if they had any chronic disease, a diagnosed malignancy, a congenital or acquired immune disorder, malnutrition, proven or suspected acute central nervous system infection, or if they had received systemic corticosteroids or antibiotics within one week preceding admission.

These exclusions were applied to remove conditions independently associated with altered eosinophil kinetics and to avoid the confounding effect of prior antimicrobial exposure on blood culture yield.

Sample Size: The required sample size was calculated as 90 children using the formula $n = (Z\alpha + Z\beta)^2 \times \sigma^2 / d^2$, where the standard deviation of the eosinophil parameter in the reference population (σ) was taken as 34, the clinically worthwhile effect size to be detected (d) was 18, the type I error rate

(α) was 0.05 with a corresponding Zα of 1.96, and the power was set at 80% with a corresponding Zβ of 0.84.

Ethical Considerations: Institutional ethics committee approval was obtained prior to commencement. Written informed consent was obtained from the parent or legal guardian of every participant, and assent was obtained from older children where developmentally appropriate. No investigation was performed solely for the purposes of the study beyond those already indicated in the routine evaluation of a febrile admission.

Study Procedure and Laboratory Methods: Following enrolment, venous blood was collected at the time of admission and, critically, before the initiation of any antibiotic therapy. Samples were processed for complete blood count, erythrocyte sedimentation rate, peripheral smear examination, quantitative C-reactive protein and blood culture. The complete blood count including the five-part differential leukocyte count was performed on an automated haematology analyser. Erythrocyte sedimentation rate was measured by the Westergren method. Quantitative C-reactive protein was estimated by immunoturbidimetry. Peripheral smears were examined by trained laboratory personnel for toxic granulation and band forms. All children received treatment according to the standard institutional protocols, independent of the study parameters.

Operational Definitions: Eosinopenia was defined as an eosinophil count below 1% of the total leukocyte count, corresponding to a number fraction below 0.01. Leukocytosis was defined as a total leukocyte count above the age-specific reference range.

Neutrophil predominance was defined as neutrophils exceeding 70% on the differential count. A raised erythrocyte sedimentation rate was defined as greater than 10 mm in the first hour.

Peripheral smear evidence of bacterial infection was defined as the presence of toxic granules or greater than 5% band forms, indicating a left shift. C-reactive protein was interpreted as raised when above the laboratory reference range.

Classification of participants

Participants were assigned to one of three mutually exclusive groups.

Group A, Definitive Bacterial Infection: children with growth of a pathogenic organism on blood culture.

Group B, Suspected Bacterial Infection: children who satisfied at least three of the following five criteria, namely leukocytosis by age-specific reference values, neutrophil predominance on the differential count, quantitative C-reactive protein above the laboratory reference range, peripheral smear showing greater than 5% band forms or toxic granules, and erythrocyte sedimentation rate greater than 10 mm/hour.

Group C, Non-bacterial Infection: children who did not fulfil the above criteria and in whom there was no clinical, laboratory, serological or radiological evidence of bacterial infection.

Statistical Analysis: Data were entered into a spreadsheet and analysed using SPSS version 21.0. Continuous variables were summarised as mean and standard deviation with range. Categorical variables were expressed as frequencies and percentages. Associations between categorical variables were assessed using the Pearson chi-square test. Odds ratios with 95% confidence intervals were computed for two-by-two comparisons. Sensitivity, specificity, predictive values, likelihood ratios and diagnostic accuracy of eosinopenia were derived against the composite reference standard of bacterial infection, comprising Groups A and B combined, with Group C serving as the comparator. A two-tailed p-value below 0.05 was considered statistically significant.

Results

Baseline Characteristics: Ninety children fulfilling the eligibility criteria were enrolled. The mean age of the cohort was 5.2 years (standard deviation 3.3 years, range 1.0 to 15.0 years) and the mean duration of illness at presentation was 4.8 days (standard deviation 1.9 days, range 2.0 to 14.0 days). The cohort was weighted towards younger children, with 61 of 90 participants (67.7%) aged below 7 years. Females slightly outnumbered males. Baseline characteristics are presented in Table 1.

Table 1: Baseline demographic and clinical characteristics of the study population (n = 90)

Characteristic	Category	Frequency (n)	Percentage (%)
Age group	< 3 years	22	24.4
	3 to 6 years	39	43.3
	7 to 9 years	15	16.7
	≥ 10 years	14	15.6
Sex	Female	49	54.4
	Male	41	45.6
Age (years)	Mean ± SD	5.2 ± 3.3	Range 1.0 to 15.0
Duration of illness (days)	Mean ± SD	4.8 ± 1.9	Range 2.0 to 14.0

Blood culture	Positive	11	12.2
	Negative	79	87.8

Distribution of Clinical Diagnoses: Blood culture was positive in 11 children (12.2%), all of whom were classified as definitive bacterial infection. Fifty children (55.6%) met the criteria for suspected bacterial infection, and 29 children (32.2%) were classified as non-bacterial infection. The commonest single diagnosis in the cohort was dengue fever, accounting for 17 children (18.9%), followed by urinary tract infection in 15 (16.7%) and pneumonia in 14 (15.6%). Probable enteric fever and culture-proven sepsis each accounted for 11 children (12.2%).

Among the culture-positive isolates, methicillin-resistant *Staphylococcus aureus* was the organism reported most frequently. The full distribution of final diagnoses is shown in Table 2.

Table 2: Distribution of study subjects by final clinical diagnosis (n = 90)

Diagnostic category	Diagnosis	Frequency (n)	Percentage (%)
Definitive bacterial infection	Sepsis (culture positive)	11	12.2
Suspected bacterial infection	Urinary tract infection	15	16.7
	Pneumonia	14	15.6
	Probable enteric fever	11	12.2
	Acute tonsillitis	3	3.3
	Dysentery	2	2.2
	Parotid abscess	2	2.2
	Acute suppurative otitis media	2	2.2
	Pulmonary tuberculosis	1	1.1
Non-bacterial infection	Dengue fever	17	18.9
	Probable viral fever	9	10.0
	Acute viral hepatitis	3	3.3
Total		90	100.0

Frequency of Acute-Phase Reactant Abnormalities: Abnormalities of the conventional acute-phase reactants were common across the cohort. Raised C-reactive protein was the most frequent abnormality, present in 62 children (68.9%), followed by neutrophil predominance in 51 (56.7%) and raised erythrocyte sedimentation rate in 53 (58.9%).

Eosinopenia, defined by the percentage criterion, was present in 55 children (61.1%). A low absolute eosinophil count was less frequent, occurring in 28 children (31.1%), reflecting the fact that the percentage-based and absolute definitions do not identify identical populations in the presence of leukocytosis. These distributions are presented in Table 3.

Table 3: Frequency of laboratory abnormalities among study subjects (n = 90)

Parameter	Abnormal, n (%)	Normal, n (%)
Eosinopenia (< 1% of total leukocytes)	55 (61.1)	35 (38.9)
Low absolute eosinophil count	28 (31.1)	62 (68.9)
Leukocytosis	47 (52.2)	43 (47.8)
Neutrophil predominance (> 70%)	51 (56.7)	39 (43.3)
Raised C-reactive protein	62 (68.9)	28 (31.1)
Raised erythrocyte sedimentation rate (> 10 mm/h)	53 (58.9)	37 (41.1)
Toxic granules or band forms on smear	45 (50.0)	45 (50.0)

Eosinophil Count by Infection Category: The distribution of eosinophil counts differed markedly and significantly across the three infection categories. Eosinopenia was present in 10 of 11 children with culture-proven bacterial infection (90.9%), in 40 of 50 children with suspected bacterial infection (80.0%), and in only 3 of 29 children with non-bacterial infection (10.3%). The association was highly significant (chi-square = 42.09, degrees of freedom 2, $p < 0.001$). When the two bacterial groups were combined and compared against the non-bacterial group, eosinopenia was present in 50 of 61 children with bacterial infection (82.0%) versus 3 of 29 (10.3%), giving an odds ratio of 39.4 (95% CI 10.1 to 153.7, chi-square = 41.65, $p < 0.001$). These findings are presented in Table 4.

Table 4: Eosinophil count by infection category

Eosinophil count	Definitive bacterial (n = 11)	Suspected bacterial (n = 50)	Non-bacterial (n = 29)	p-value
Normal	1 (9.1%)	10 (20.0%)	26 (89.7%)	< 0.001
Eosinopenia	10 (90.9%)	40 (80.0%)	3 (10.3%)	
Total	11 (100.0%)	50 (100.0%)	29 (100.0%)	

Pearson chi-square test, chi-square = 42.09, df = 2.

Association of eosinopenia with other acute-phase reactants: Eosinopenia showed a statistically significant positive association with every other acute-phase reactant examined. Among the 55 children with eosinopenia, 34 (61.8%) had leukocytosis compared with 13 of 35 (37.1%) of those with a normal eosinophil count (odds ratio 2.74, 95% CI 1.14 to 6.57, p = 0.022). Neutrophil predominance was present in 40 of 55 eosinopenic children (72.7%) versus 11 of 35 (31.4%) non-eosinopenic children (odds ratio 5.82, 95% CI 2.30 to 14.72, p < 0.001). Raised C-reactive protein was present in 44 of 55 (80.0%) versus 18 of 35 (51.4%) respectively (odds ratio 3.78, 95% CI 1.48 to 9.63, p = 0.004). Raised erythrocyte sedimentation rate was present in 40 of 55 (72.7%) versus 13 of 35 (37.1%) (odds ratio 4.51, 95% CI 1.82 to 11.18, p = 0.001).

The strongest single association was with peripheral smear evidence of bacterial infection: toxic granules or band forms were present in 38 of 55 eosinopenic children (69.1%) compared with only 7 of 35 (20.0%) non-eosinopenic children (odds ratio 8.94, 95% CI 3.27 to 24.46, p < 0.001). A low absolute eosinophil count co-existed with percentage-defined eosinopenia in 26 of 55 children (47.3%) but in only 2 of 35 (5.7%) of those with a normal percentage count (odds ratio 14.79, 95% CI 3.23 to 67.79, p < 0.001). These associations are summarised in Table 5.

Table 5: Association of eosinopenia with other acute-phase reactants

Parameter	Eosinopenia present (n = 55)	Eosinophil count normal (n = 35)	Odds ratio (95% CI)	p-value
Leukocytosis	34 (61.8%)	13 (37.1%)	2.74 (1.14 to 6.57)	0.022
Neutrophil predominance > 70%	40 (72.7%)	11 (31.4%)	5.82 (2.30 to 14.72)	< 0.001
Raised C-reactive protein	44 (80.0%)	18 (51.4%)	3.78 (1.48 to 9.63)	0.004
Raised erythrocyte sedimentation rate	40 (72.7%)	13 (37.1%)	4.51 (1.82 to 11.18)	0.001
Toxic granules or band forms	38 (69.1%)	7 (20.0%)	8.94 (3.27 to 24.46)	< 0.001
Low absolute eosinophil count	26 (47.3%)	2 (5.7%)	14.79 (3.23 to 67.79)	< 0.001

Pearson chi-square test used throughout.

Diagnostic performance of eosinopenia: Against the composite reference standard of bacterial infection, eosinopenia demonstrated a sensitivity of 82.0%, a specificity of 89.7%, a positive predictive value of 94.3% and a negative predictive value of 70.3%, with an overall diagnostic accuracy of 84.4%. The positive likelihood ratio was 7.92 and the negative likelihood ratio was 0.20. When performance was assessed against culture-proven bacterial infection alone, with the non-bacterial group as comparator, sensitivity rose to 90.9% and the negative predictive value to 96.3%, at the cost of a fall in positive predictive value to 76.9%, reflecting the low prevalence of bacteraemia in the cohort. These metrics are presented in Table 6.

Table 6: Diagnostic performance of eosinopenia for bacterial infection

Metric	Any bacterial infection (n = 61) vs non-bacterial (n = 29)	Culture-proven bacterial infection (n = 11) vs non-bacterial (n = 29)
True positives	50	10
False positives	3	3
False negatives	11	1
True negatives	26	26
Sensitivity	82.0%	90.9%
Specificity	89.7%	89.7%
Positive predictive value	94.3%	76.9%
Negative predictive value	70.3%	96.3%
Diagnostic accuracy	84.4%	90.0%
Positive likelihood ratio	7.92	8.79
Negative likelihood ratio	0.20	0.10

Discussion

This prospective study of 90 children admitted with acute febrile illness found that eosinopenia was strongly and significantly associated with bacterial infection, occurring in 90.9% of culture-proven cases and 80.0% of clinically and biochemically defined suspected bacterial infections, but in only 10.3% of children with non-bacterial illness. The resulting diagnostic metrics, a sensitivity of 82.0% and specificity of 89.7% with a positive likelihood ratio of 7.92, place eosinopenia in the range of clinically useful discriminators in this population.

These figures sit towards the upper end of the published range. The closest methodological comparator is the retrospective study of 878 ill-appearing febrile children by Alkan Bal and colleagues, in which 521 had confirmed or presumed bacterial infection and 355 had confirmed or presumed viral infection [12]. In that cohort, an eosinophil count of 50/mm3 or below produced a sensitivity of 61%, specificity of 67%, positive predictive value of 73.1% and negative predictive value of 54%, with an area under the receiver operating characteristic curve of 0.671, statistically indistinguishable from neutrophil count at 0.655 and C-reactive protein at 0.710 [12]. The central conclusion of that study, that the discriminant power of the eosinophil count is comparable to that of neutrophil count and C-reactive protein and superior to the total leukocyte count, is directly concordant with our finding that eosinopenia performed at least as well as any conventional reactant in our cohort.

The higher point estimates in our series most plausibly reflect three differences: our use of a percentage-based rather than an absolute threshold, our exclusion of children with recent antibiotic or steroid exposure, and the fact that our comparator group was restricted to children with no clinical, serological or radiological evidence of bacterial infection rather than an all-comers viral group. It should be noted that the comparison against that study's culture positivity rate requires correction: it did not report a 69% blood culture positivity rate, but rather classified 59.3% of participants as having confirmed or presumed bacterial infection, a broader composite category.

Our findings contrast sharply with the case-control study of Wibrow and colleagues, which examined 85 paediatric and 157 adult patients with bloodstream infection against culture-negative controls [11]. Although eosinopenia was more frequent among cases than controls overall (46.5% versus 21.5%), the eosinophil count had essentially no discriminatory value in the paediatric subgroup, with an area under the curve of 0.448 (95% CI 0.363 to 0.533, p = 0.237), a sensitivity of 54% and a specificity of 56%; in multivariate analysis only C-reactive protein and neutrophil count remained independently associated with bloodstream infection [11]. Two design differences may account for this divergence. First, their control group consisted of children in whom bloodstream infection was clinically suspected and blood culture obtained, a group that will have been enriched for non-bacteraemic systemic inflammation, and any inflammatory stimulus regardless of aetiology will depress the eosinophil count. Our comparator group, by contrast, comprised children in whom bacterial infection had been actively excluded. Second, their case group was defined exclusively by bacteraemia, whereas the majority of serious bacterial infection in children is non-bacteraemic. The apparent conflict may therefore be less a contradiction than a demonstration that the discriminatory value of eosinopenia depends critically on what it is being asked to discriminate from.The adult critical care literature displays a similar polarity. Abidi and colleagues, in 177 consecutive medical intensive care admissions, found an area under the curve of 0.89 (95% CI 0.83 to 0.94) for eosinophils, significantly better than C-reactive protein at 0.77 ($p = 0.010$), with a sensitivity of 80% and specificity of 91% at a threshold of 50 cells/mm3, and median counts of 109/mm3 versus 13/mm3 in non-infected and infected patients respectively ($p < 0.001$) [6]. Smithson and colleagues reached the opposite conclusion in a retrospective series, arguing that eosinopenia was not reliable and that C-reactive protein retained superiority both diagnostically and as a severity marker [8]. Shaaban and colleagues, in 68 critical care patients, found eosinopenia below 50 cells/mm3 to have a sensitivity of 81% but a specificity of only 65%, inferior on both counts to C-reactive protein at 70 mg/L (94% and 84%) and to procalcitonin at 1.5 microgram/L (84% and 92%) [9]. The most rigorous synthesis available, a meta-analysis of seven studies and 3842 subjects, reported pooled sensitivity of 0.66 and specificity of 0.68 with a summary area under the curve of 0.73, and concluded that eosinopenia has a high incidence in sepsis but no superiority over conventional biomarkers [15]. Reported eosinopenia incidence across studies ranged from 23.2% to 92.7% [15], a spread that maps closely onto threshold heterogeneity and that our own contrast between the percentage definition (61.1% of the cohort) and the absolute eosinophil count definition (31.1%) directly illustrates. This is the single most important unresolved methodological issue in the field: two definitions applied to the same 90 children identified populations differing by a factor of nearly two.

Within paediatrics, the evidence is more favourable where the comparator condition is well defined. In bacterial versus aseptic meningitis, an eosinophil count below 5/mm3 achieved a sensitivity of 80%,

specificity of 73% and likelihood ratio of 2.9, and the authors emphasised that the absence of any incremental cost makes it particularly attractive where procalcitonin is unavailable [13]. In early-onset neonatal sepsis, eosinopenia below 140 cells/mm3 produced a specificity of 90.0% and positive predictive value of 94.7% with a sensitivity of 60.0% [14]. Work from Turkish paediatric populations has similarly concluded that the absolute eosinophil count and the absolute eosinophil count to white blood cell ratio are promising discriminators of bacterial infection in children, with the bacterial group showing the highest C-reactive protein and the lowest eosinophil parameters [18]. In the internal medicine setting, the eosinophil count has been shown to normalise faster than C-reactive protein and neutrophil count in eosinopenic patients receiving appropriate antimicrobial therapy [16], and serial eosinophil counts have been proposed as a means of assessing treatment response [19]. Earlier work had already flagged the eosinophil count as a predictor of bacteraemia [17], and the marker has more recently been repurposed in the context of viral disease, where eosinopenia below 100/microlitre was reported as a marker of active COVID-19 [20], a reminder that eosinopenia is a marker of systemic inflammation rather than of bacterial infection specifically.

Our observation that eosinopenia correlated significantly with leukocytosis ($p = 0.022$), neutrophil predominance ($p < 0.001$), raised C-reactive protein ($p = 0.004$), raised erythrocyte sedimentation rate ($p = 0.001$) and toxic granulation ($p < 0.001$) requires careful interpretation and is, in our view, the principal internal limitation of this study. Group B was defined by the presence of at least three of these same five parameters. Consequently, a substantial part of the observed association between eosinopenia and the individual reactants is a mathematical consequence of the classification rule rather than independent corroboration, a form of incorporation bias. The comparison of eosinopenia against Group A, which was defined solely by blood culture positivity and is therefore free of this circularity, is the more secure of our findings, and it is reassuring that it is also the stronger one, with eosinopenia present in 90.9% of culture-positive children.

Several further limitations warrant explicit statement. The blood culture positivity rate of 12.2% was low, which is characteristic of paediatric practice but which limits the precision of estimates against the culture-defined reference standard; the 95% confidence intervals around the sensitivity of 90.9% in a group of 11 children are necessarily wide. The sample size of 90 was adequate for the primary comparison of means for which it was calculated but is modest for the derivation of diagnostic accuracy metrics. Procalcitonin was not measured, precluding comparison against the biomarker with the strongest evidence base in this population [1]. Eosinophil counts were measured at a single time point at admission, so the kinetic behaviour of the marker, which several authors have identified as its most valuable property [16,19], could not be assessed. Finally, this was a single-centre study in an urban tertiary hospital, and the case mix, notably the high proportion of dengue fever, may not generalise to primary care or to other geographic settings. Notwithstanding these constraints, the practical implication is worth stating plainly. The eosinophil count is already generated by every automated differential count performed. It requires no additional sample, no additional reagent and no additional cost. Where our results are confirmed, incorporating eosinopenia into the initial assessment of the febrile child would represent a genuinely free addition to the diagnostic panel. This is precisely the argument advanced by investigators working in resource-constrained settings [13], and it is the reason the question remains worth pursuing despite an equivocal aggregate literature. Adequately powered prospective multicentre studies, using a standardised absolute threshold, incorporating procalcitonin as a comparator, and employing a reference standard independent of the acute-phase reactants under evaluation, are needed before the marker can be recommended for routine use.

Conclusion

In this prospective study of 90 children admitted with acute febrile illness of less than 14 days' duration, eosinopenia was significantly more frequent among children with bacterial infection than among those with non-bacterial illness, occurring in 90.9% of culture-proven bacterial infections, 80.0% of suspected bacterial infections and 10.3% of non-bacterial infections ($p < 0.001$).

Against a composite reference standard of bacterial infection, eosinopenia achieved a sensitivity of 82.0%, specificity of 89.7%, positive predictive value of 94.3% and overall diagnostic accuracy of 84.4%, with a positive likelihood ratio of 7.92. Eosinopenia demonstrated predictive value comparable to that of neutrophilic leukocytosis and raised C-reactive protein, and it correlated significantly with all conventional acute-phase reactants examined, although this latter finding is partly attributable to the incorporation of those reactants into the classification criteria. Blood culture remains the diagnostic gold standard, and methicillin-resistant *Staphylococcus aureus* was the organism most frequently isolated in this series.

The eosinophil count is obtained at no incremental cost from a test already performed universally in febrile children, and on the strength of these findings it merits formal evaluation as a first-tier adjunctive discriminator between bacterial and non-bacterial illness, particularly in resource-limited settings where procalcitonin is unavailable. Confirmation in adequately powered multicentre studies, using standardised absolute thresholds and a reference standard independent of the markers under test, is required before routine clinical adoption can be recommended.

References

1. Van den Bruel A, Thompson MJ, Haj-Hassan T, Stevens R, Moll H, Lakhanpaul M, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ. 2011; 342:d3082.
2. Bernardi L, Bossù G, Dal Canto G, Giannì G, Esposito S. Biomarkers for serious bacterial infections in febrile children. Biomolecules. 2024; 14(1):97.
3. Bass DA. Behavior of eosinophil leukocytes in acute inflammation. I. Lack of dependence on adrenal function. J Clin Invest. 1975; 55(6): 1229-36.
4. Bass DA, Gonwa TA, Szejda P, Cousart MS, DeChatelet LR, McCall CE. Eosinopenia of acute infection: production of eosinopenia by chemotactic factors of acute inflammation. J Clin Invest. 1980;65(6):1265-71.
5. Gil H, Magy N, Mauny F, Dupond JL. Value of eosinopenia in inflammatory disorders: an "old" marker revisited. Rev Med Interne. 2003; 24(7): 431-5.
6. Abidi K, Khoudri I, Belayachi J, Madani N, Zekraoui A, Zeggwagh AA, et al. Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units. Crit Care. 2008; 12(2):R59.
7. Abidi K, Khoudri I, Belayachi J, Derras Y, Khayari ME, Madani N, et al. Eosinopenia, an early marker of increased mortality in critically ill medical patients. Intensive Care Med. 2011; 37(7): 1136-42.
8. Smithson A, Perelló R, Nicolás JM. Is eosinopenia a reliable marker of sepsis? Crit Care. 2009;13(3):409.
9. Shaaban H, Daniel S, Sison R, Slim J, Perez G. Eosinopenia: is it a good marker of sepsis in comparison to procalcitonin and C-reactive protein levels for patients admitted to a critical care unit in an urban hospital? J Crit Care. 2010;25(4):570-5.
10. Terradas R, Grau S, Blanch J, Riu M, Saballs P, Castells X, et al. Eosinophil count and neutrophil-lymphocyte count ratio as prognostic markers in patients with bacteremia: a retrospective cohort study. PLoS One. 2012;7(8):e42860.
11. Wibrow BA, Ho KM, Flexman JP, Keil AD, Kohrs DL. Eosinopenia as a diagnostic marker of bloodstream infection in hospitalised paediatric and adult patients: a case-control study. Anaesth Intensive Care. 2011; 39(2): 224-30.
12. Alkan Bal U, Anil M, Gökalp G, Bicilioglu Y, Anil AB, Kamit F, et al. Comparison of the eosinophil count to C-reactive protein, leukocyte count, and neutrophil count for the detection of bacterial infection in ill-appearing children with fever admitted to the emergency department. Signa Vitae. 2015;10(2):163-76.
13. Debray A, Nathanson S, Moulin F, Salomon J, Davido B. Eosinopenia as a marker of diagnosis and prognostic to distinguish bacterial from aseptic meningitis in pediatrics. Eur J Clin Microbiol Infect Dis. 2019;3 8(10): 1821-7.
14. Wilar R. Diagnostic value of eosinopenia and neutrophil to lymphocyte ratio on early onset neonatal sepsis. Korean J Pediatr. 2019; 62(6): 217-23.
15. Lin Y, Rong J, Zhang Z. Silent existence of eosinopenia in sepsis: a systematic review and meta-analysis. BMC Infect Dis. 2021; 21(1): 471.
16. Karakonstantis S, Gryllou N, Papazoglou G, Lydakis C. Eosinophil count (EC) as a diagnostic and prognostic marker for infection in the internal medicine department setting. Rom J Intern Med. 2019;57(2):166-74.
17. Setterberg MJ, Newman W, Potti A, Smego RA Jr. Utility of eosinophil count as predictor of bacteremia. Clin Infect Dis. 2004;38(3):460-1.
18. Ata A, Anil M, Helvaci M. The role of eosinopenia in the diagnosis of bacterial infection in children. Pamukkale Med J. 2022;15(3):541-9.
19. Davido B, Makhloufi S, Matt M, Calin R, Senard O, Perronne C, et al. Changes in eosinophil count during bacterial infection: revisiting an old marker to assess the efficacy of antimicrobial therapy. Int J Infect Dis. 2017; 61:62-6.
20. Outh R, Boutin C, Gueudet P, Suzuki M, Saada M, Aumaître H. Eosinopenia <100/microlitre as a marker of active COVID-19: an observational prospective study. J Microbiol Immunol Infect. 2021;54(1):61-8.