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Immature neutrophils in young febrile infants

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Abstract

Background—To describe the diagnostic value of the absolute band count (ABC) and ratio of immature to total neutrophils (I:T) for invasive bacterial infections (IBIs; bacterial meningitis and bacteraemia) among young febrile infants.

Methods—We performed a cross-sectional study in a paediatric emergency department of febrile infants 60 days over 12 years to evaluate the accuracy of the ABC and I:T for IBI.

Results—Of 2930 included patients, 75 (2.6%) had IBIs. The area under the curve (AUC; 95% CI) for ABC was 0.69 (0.62 to 0.76) with sensitivity 0.27 (0.17 to 0.38) and specificity 0.94 (0.93 to 0.95) at cutoff 1500 cells/ μ L. The AUC for I:T was 0.65 (0.59 to 0.72) with sensitivity 0.29 (0.19 to 0.41) and specificity 0.88 (0.87 to 0.89) at cutoff 0.2. Only the ABC in infants 29–60 days was minimally accurate.

Conclusion—The ABC and I:T were generally inaccurate for detecting IBI in febrile infants. Guidelines without these parameters may be better for risk assessment.

Introduction

The management of febrile infants is a persistent challenge in paediatric medicine. Common risk-stratification methods utilise the complete blood count with differential (CBC) to identify low-risk patients, though their value in the diagnosis of invasive bacterial infections (IBIs, bacteraemia and bacterial meningitis) remains controversial. A recent multicentre prospective study in 4313 infants 60 days demonstrated that the white blood cell count (WBC), absolute neutrophil count (ANC) and platelet count had poor diagnostic accuracy for IBI.¹

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Contributors SR designed the study, performed the analysis and drafted the manuscript. LWW designed the study, acquired the data, interpreted the data and revised the manuscript for important intellectual content. ATC, MAV and AJN designed the study and revised the manuscript for important intellectual content. All authors provide final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The role of immature neutrophil forms in the diagnosis of IBI remains underinvestigated. Despite this, the absolute band count (ABC) or the ratio of immature to total neutrophils (I:T) are used to identify high-risk infants in the Rochester² and Philadelphia³ criteria, respectively. In this study, we utilise a large retrospective cohort of infants < 60 days of age evaluated in the emergency department (ED) for fever in order to investigate the performance characteristics of the ABC and I:T in the diagnosis of IBI.

Methods

We performed a single centre cross-sectional study of consecutive infants < 60 days with fever who received testing for IBI between 1 January 2006 and 31 December 2017. In our institution, these infants undergo testing that includes urinalysis, urine culture, CBC and blood culture. Cerebrospinal fluid (CSF) cytology and CSF culture are performed for all patients with the exception of infants 29–60 days with bronchiolitis. We obtained institutional board review approval with a waiver of informed consent prior to data acquisition.

Patients were identified by performing a medical record search of infants < 60 days presenting to the ED who received any culture. Charts were reviewed to identify infants with fever ($\geq 38.0^{\circ}\text{C}$) by history or initial vital signs. Patients were excluded if they did not receive blood, urine and CSF cultures, they received antibiotics prior to culture, records were missing, local infection was reported, CBC was not performed or if they had UTI without IBI.

Our primary outcome was IBI, a priori defined as growth of a single organism from blood or CSF cultures, excluding known contaminants. In ambiguous cases, an infectious disease specialist (LWW and AJN) blinded to the clinical context reviewed results and made a determination on the basis of expert opinion and literature review. Primary predictors of interest were ABC and I:T. Secondary predictors were WBC and ANC. CBCs were performed through an automated process (Beckman Coulter LH 780, 500 and DXH 500, Beckman Coulter Diagnostics, Pasadena, California, USA). If an immature cell is detected, a manual or image differential is performed to obtain the ABC. For those patients for whom no immature cells are detected, a differential is not performed and the ABC was assigned a count of zero for this study. The I:T was calculated by dividing ABC by the sum of the ABC and ANC.

We used the Wilcoxon rank-sum test to compare parameters among infants with and without IBI. For predictors of interest, we reported test characteristics and determined an optimal cut-off value by identifying the point on the ROC curve closest to the point (0, 1), also known as the Euclidean method. We defined accuracy a priori as follows: area under the curve (AUC) < 0.7 as poor, 0.7–0.8 as minimal, 0.8–0.9 as good and > 0.9 as excellent.¹ For primary predictors, we repeated the analysis in subgroups by age (0–28 and 29–60 days). Analysis was performed using the cutpointR V.0.7.4, epi.R V.2.32 and pROC V.1.13.0 packages in R V.3.5.0.

Results

Of 5508 screened patients, 2930 were included (1652 (56.4%) males; 872 (29.8%) 0–28 days of age). Reasons for exclusion were absence of 1 culture (n=348), antibiotics received prior to culture collection (n=694), absence of fever (n=1233), diagnosis of UTI without IBI (n=224), missing records (n=28), absence of CBC (n=40) and local infection (n=11). 97.2% of infants were delivered at 36 weeks of gestational age.

Seventy-five patients (2.6%) had IBIs, including 65 (2.2%) with isolated bacteraemia, 5 (0.2%) with bacterial meningitis without bacteraemia and 5 (0.2%) with bacteraemia and meningitis. Twenty-nine of seventy-five IBIs were in infants 0–28 days (online supplementary table).

Infants with IBI had higher ABCs, I:T, ANCs and WBC compared with those without IBI ($p<0.05$). The AUC of the ABC in 29–60 day infants narrowly reached a classification of minimally accurate with an AUC 0.71 (95% CI 0.63 to 0.79). All other studies had poor accuracy with AUC <0.70 (figure 1). At optimal thresholds, an ABC of 370 cells/ μ L resulted in a sensitivity of 0.61 (95% CI 0.49 to 0.72) and specificity of 0.72 (0.70 to 0.73). An optimal I:T ratio of 0.06 resulted in a sensitivity of 0.65 (95% CI 0.53 to 0.76) and specificity of 0.60 (0.58 to 0.62; table 1).

Discussion

We found that the AUC for the ABC and I:T had only slightly better performance than those for WBC and ANC. These results suggest that parameters based on band cells have poor discriminatory ability to identify those infants at higher risk of IBI.

No investigation has evaluated the diagnostic value of the ABC and I:T for IBI on a large sample of infants. Outcomes combining IBI with UTI, such as one study reporting an AUC of 0.81 among 1009 febrile infants 60 days may have differed if only IBI were considered.⁴ Studies using outcomes of IBI have largely been limited by small size, such as that reported by Caspe *et al*, who reported a lack of association of the ABC with bacteraemia from 305 patients.⁵

Our evaluation of WBC is similar to that reported by Cruz *et al*, who found an AUC of 0.57 for WBC, though the AUC for ANC in that study was higher (0.70).¹ These findings help to confirm the generalisability of the results of our primary analysis. An important consideration, however, is that commonly used risk-stratification criteria have primarily optimised sensitivity, with the goal of capturing all patients with disease. Notably, at conventional cutoffs, the specificities of the ABC and I:T are high. This suggests that these tests, which demonstrate high proportions of true negatives among those free of disease, may be able to correctly identify those without IBI. Furthermore, the high positive likelihood ratio of the ABC suggests that a positive test increases the post-test probability of IBI.

The results of this study are subject to limitations. This was a single-centre retrospective study. This study was unable to account for febrile infants not screened for IBI and for whom inclusion may have been missed. Though we relied on expert advice to identify true

from false positive cultures, this methodology carries an inherent degree of ambiguity. Automated or manual differentials were only performed if an immature cell was detected. If a manual differential was reported for all infants with IBI, the sensitivity of the band count may have been higher. Despite these limitations, the results from this study provide data which may assist in the management of febrile well-appearing young infants who are being assessed for IBI in the hospital setting.

Conclusion

While ABCs and I:T are significantly higher in febrile infants 60 days of age with IBI as compared with those without, these parameters have poor discriminatory value at any cut-off. With the increasing availability of other biomarker tests, guidelines which do not utilise CBC parameters may be more ideal to assess IBI risk in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What is already known on this topic?

- The white blood cell count, absolute neutrophil count and platelet count are poor markers of invasive bacterial infection (IBI) in febrile infants.
- The absolute band count (ABC) and immature to total neutrophil ratio (I:T ratio) are commonly used to risk stratify febrile infants in many centres.
- Studies which have evaluated ABC and I:T ratios in infants have outcome measures which include urinary tract infection (UTI), an entity that is readily diagnosed by other means.

What this study adds?

- The ABCs and I:T ratios are significantly higher in febrile infants < 60 days of age with IBI as compared with those without.
- The diagnostic value of these tests is suboptimal in respect to their sensitivity and predictive value, both at commonly used and optimal cut-offs.
- Given the unreliability of these parameters in the diagnosis of IBI, better biomarkers are needed to assess risk for IBI in this population.

Figure 1.

Receiver operator curves for haematological parameters and IBI in febrile infants ≤ 60 days of age using (A) absolute band count (ABC), (B) immature to total neutrophil ratio (I:T) and (C) white blood cell count (WBC) and absolute neutrophil count (ANC). AUC, area under curve; IBI, invasive bacterial infection.

Table 1

Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratios of haematological parameters in febrile infants 60 days of age

Parameter	Sensitivity	Specificity	PPV	NPV	LR (+)	LR (-)
ABC (cells/ μ L)						
All ages						
1500	0.27 (0.17 to 0.38)	0.94 (0.93 to 0.95)	0.10 (0.06 to 0.15)	0.98 (0.97 to 0.98)	4.28 (2.86 to 6.39)	0.78 (0.68 to 0.90)
370 *	0.61 (0.49 to 0.72)	0.72 (0.70 to 0.73)	0.05 (0.04 to 0.07)	0.99 (0.98 to 0.99)	2.17 (1.79 to 2.62)	0.54 (0.41 to 0.72)
0–28 days						
1500	0.38 (0.21 to 0.58)	0.91 (0.89 to 0.93)	0.13 (0.07 to 0.22)	0.98 (0.96 to 0.99)	4.32 (2.58 to 7.22)	0.68 (0.51 to 0.91)
380 *	0.62 (0.42 to 0.79)	0.65 (0.62 to 0.68)	0.06 (0.03 to 0.09)	0.98 (0.97 to 0.99)	1.77 (1.32 to 2.39)	0.58 (0.37 to 0.93)
29–60 days						
1500	0.20 (0.09 to 0.34)	0.95 (0.94 to 0.96)	0.08 (0.04 to 0.15)	0.98 (0.97 to 0.99)	3.79 (2.05 to 7.00)	0.85 (0.74 to 0.98)
330 *	0.63 (0.48 to 0.77)	0.73 (0.71 to 0.75)	0.05 (0.03 to 0.07)	0.99 (0.98 to 0.99)	2.31 (1.83 to 2.91)	0.51 (0.35 to 0.74)
I:T ratio						
All ages						
0.20	0.29 (0.19 to 0.41)	0.88 (0.87 to 0.89)	0.06 (0.04 to 0.09)	0.98 (0.97 to 0.98)	2.46 (1.71 to 3.55)	0.80 (0.69 to 0.93)
0.06 *	0.65 (0.53 to 0.76)	0.60 (0.58 to 0.62)	0.04 (0.03 to 0.05)	0.99 (0.98 to 0.99)	1.64 (1.38 to 1.94)	0.58 (0.42 to 0.79)
0–28 days						
0.20	0.31 (0.15 to 0.51)	0.86 (0.84 to 0.89)	0.07 (0.03 to 0.13)	0.97 (0.96 to 0.98)	2.27 (1.29 to 4.02)	0.80 (0.62 to 1.02)
0.07 *	0.59 (0.39 to 0.76)	0.63 (0.60 to 0.66)	0.05 (0.03 to 0.08)	0.98 (0.96 to 0.99)	1.58 (1.15 to 2.18)	0.66 (0.42 to 1.02)
29–60 days						
0.20	0.28 (0.16 to 0.43)	0.89 (0.87 to 0.90)	0.05 (0.03 to 0.09)	0.98 (0.97 to 0.99)	2.53 (1.57 to 4.07)	0.81 (0.67 to 0.97)
0.06 *	0.67 (0.52 to 0.80)	0.61 (0.59 to 0.63)	0.04 (0.03 to 0.05)	0.99 (0.98 to 0.99)	1.74 (1.41 to 2.14)	0.53 (0.35 to 0.81)
WBC, all ages (cells/ μ L)						
15 000						
	0.29 (0.19 to 0.41)	0.87 (0.85 to 0.88)	0.05 (0.03 to 0.08)	0.98 (0.97 to 0.98)	2.18 (1.52 to 3.14)	0.82 (0.71 to 0.95)
5000 or 15 000						
	0.37 (0.26 to 0.49)	0.79 (0.78 to 0.81)	0.05 (0.03 to 0.07)	0.98 (0.97 to 0.99)	1.82 (1.34 to 2.46)	0.79 (0.66 to 0.94)
10 600 *						
	0.60 (0.48 to 0.71)	0.57 (0.55 to 0.59)	0.04 (0.03 to 0.05)	0.98 (0.97 to 0.99)	1.41 (1.16 to 1.70)	0.70 (0.53 to 0.92)
ANC, all ages (cells/ μ L)						

Parameter	Sensitivity	Specificity	PPV	NPV	LR (+)	LR (-)
10 000	0.17 (0.10 to 0.28)	0.96 (0.95 to 0.96)	0.09 (0.05 to 0.15)	0.98 (0.97 to 0.98)	3.90 (2.31 to 6.57)	0.87 (0.78 to 0.96)
4600 *	0.52 (0.40 to 0.64)	0.73 (0.71 to 0.74)	0.05 (0.03 to 0.06)	0.98 (0.98 to 0.99)	1.89 (1.51 to 2.37)	0.66 (0.52 to 0.84)

* Denotes optimal threshold. Number in parenthesis represents 95% CI.

I:T ratio, immature to total neutrophil ratio; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.