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Diagnostic and Prognostic Value of Procalcitonin and C-Reactive Protein in Malnourished Children

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KEY WORDS

malnutrition, infectious diseases, C-reactive protein, procalcitonin, developing countries, Sahel, sensitivity, specificity

ABBREVIATIONS

AUC—area under the curve

CI—confidence interval

CRP—C-reactive protein

IBI—invasive bacterial infection

IQR—interquartile range

NBI—no proven bacterial infection

PCT—procalcitonin

poc—point-of-care

ROC—receiver operating characteristic

SAM—severe acute malnutrition

UTI—urinary tract infection

Dr Page participated in the study design, carried out the analyses, and drafted the initial manuscript; Dr de Rekeneire participated in the study design and in the elaboration of the plan of analysis, coordinated data collection in the field, and reviewed and revised the manuscript; Dr Sayadi supervised clinical data collection in the field, participated in the data interpretation, and reviewed and revised the manuscript; Dr Aberrane participated in the study design, gave expert opinion on all microbiology results, and reviewed and revised the manuscript; Ms Janssens coordinated the laboratory activities in the field, supervised laboratory data collection, and revised the manuscript; Dr Dehoux coordinated data collection at Hôpital Bichat and participated in writing the initial manuscript; Dr Baron participated in the study conceptualization and the data analysis, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Biomarkers such as C-reactive protein (CRP) and procalcitonin are elevated in children with severe bacterial infections. Children with severe malnutrition are at increased risk of bacterial infections and early markers for the diagnosis of infection in these children are needed.



WHAT THIS STUDY ADDS: Despite elevated values in severely malnourished children with invasive bacterial infection or infectious diarrhea, CRP and procalcitonin have limited diagnostic value. CRP could predict death in these children with a good negative predictive value.

abstract



BACKGROUND: Early recognition of bacterial infections is crucial for their proper management, but is particularly difficult in children with severe acute malnutrition (SAM). The objectives of this study were to evaluate the accuracy of C-reactive protein (CRP) and procalcitonin (PCT) for diagnosing bacterial infections and assessing the prognosis of hospitalized children with SAM, and to determine the reliability of CRP and PCT rapid tests suitable for remote settings.

METHODS: From November 2007 to July 2008, we prospectively recruited 311 children aged 6 to 59 months hospitalized with SAM plus a medical complication in Maradi, Niger. Blood, urine, and stool cultures and chest radiography were performed systematically on admission. CRP and PCT were measured by rapid tests and by reference quantitative methods using frozen serum sent to a reference laboratory.

RESULTS: Median CRP and PCT levels were higher in children with bacteremia or pneumonia than in those with no proven bacterial infection ($P < .002$). However, both markers performed poorly in identifying invasive bacterial infection, with areas under the curve of 0.64 and 0.67 before and after excluding children with malaria, respectively. At a threshold of 40 mg/L, CRP was the best predictor of death (81% sensitivity, 58% specificity). Rapid test results were consistent with those from reference methods.

CONCLUSIONS: CRP and PCT are not sufficiently accurate for diagnosing invasive bacterial infections in this population of hospitalized children with complicated SAM. However, a rapid CRP test could be useful in these settings to identify children most at risk for dying. *Pediatrics* 2014;133:e363–e370

Children with severe acute malnutrition (SAM) are at increased risk of infections and malnutrition is estimated to be the underlying cause of up to 10% of the global disease burden in children <5 years of age.^{1,2} In children hospitalized with SAM plus a medical complication, clinical diagnosis of infection is complicated by the paucity of clinical signs; classic symptoms of infection (eg, fever in response to bacteremia, or respiratory symptoms in children with pneumonia) are not always present in children with SAM, who instead often present with unspecific apathy.^{3,4} Furthermore, laboratory diagnostic capacity is often limited in regions with the highest burdens of malnutrition. Consequently, treatment is empirical, and broad-spectrum antibiotics are recommended for all hospitalized children with complicated SAM.⁵ In this context, biological markers would be valuable clinical tools for identifying children with bacterial infections, especially invasive bacterial infections (IBIs), and children most at risk for dying. To be useful in settings with little or no laboratory infrastructure, these tools must be available as point-of-care (poc) tests.

During the acute phase response, levels of many proteins in the blood increase in response to inflammation, including C-reactive protein (CRP) and procalcitonin (PCT). CRP and PCT have been shown to perform better than other traditionally used markers, such as leukocyte counts, to differentiate between serious bacterial infections and nonserious or viral infections, but their diagnostic accuracy remains controversial.^{6–10} Nevertheless, they are used routinely in some emergency departments and critical care settings in industrialized countries to identify patients at high risk for serious bacterial infections, due to the advantage of being fast and reducing the long wait for bacteriology results, as well as

their ability to rule out serious bacterial infection, particularly for PCT.^{11,12} Although CRP and PCT have been investigated extensively for different types of infection in industrialized countries, few studies have evaluated their diagnostic and prognostic value in African settings, where infection profiles are different.^{13–16} Malaria also leads to increased levels of these markers,^{17,18} which compromises their usefulness for identifying bacterial infections in malaria-endemic countries.¹⁴ In addition, SAM, particularly edematous malnutrition, could be associated with reduced levels of acute-phase proteins.¹⁹ However, to our knowledge, the accuracy of CRP and PCT as markers of infection had not yet been studied in a population of children with SAM in Africa.

The aims of this study were to evaluate (1) the diagnostic and prognostic value of CRP and PCT in identifying children with bacterial infection and those most at risk for dying, in a population of children with complicated SAM hospitalized in intensive care; and (2) the reliability of CRP and PCT rapid tests that could potentially be used in developing countries with limited laboratory capacity.

METHODS

Study Population

This work was a substudy of a larger, previously published study on the prevalence of infections in children with SAM, conducted in an inpatient therapeutic feeding center in Maradi, Niger.⁴ The study population consisted of all consecutive children aged 6 to 59 months with complicated SAM admitted to the ICU or transition phase of the inpatient therapeutic feeding center. Children who received antibiotics within 7 days before admission were excluded. SAM was defined as weight-for-height <3 z-score below the median, by using the World Health

Organization Child Growth Standards and/or mid-upper arm circumference <110 mm and/or bilateral edema.^{20,21} Complicated SAM was defined as SAM accompanied by anorexia and/or kwashiorkor with major edema and/or another severe medical condition. All patients included in the study had a clinical examination on admission. Blood was systematically collected on the day of admission (or next day in 4 exceptions), urine and stool samples were systematically collected within 48 hours of admission (72 hours in 3 exceptions), and a chest radiograph was performed within 72 hours of admission. Two blood samples for culture were collected within 20 to 30 minutes of each other and 1 mL of each was inoculated in blood culture bottles.⁴ Urine was collected using a Foley catheter. Lumbar puncture was performed when at least 1 clinical sign of involvement of the central nervous system was present.

Study Groups

Patients were categorized into 5 infection groups based on culture and radiograph results. In case of coinfections, children were included in the group corresponding to the infection most likely to trigger the highest inflammatory response. The bacteremia group was composed of children with growth of an unambiguous pathogen (*Salmonella* spp, *Escherichia coli*, *Klebsiella* spp, *Citrobacter freundii*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*) in blood culture. The 1 child with bacteriology-proven bacterial meningitis (*H influenzae*) also was included in this group. The pneumonia group included children with an alveolar consolidation on chest radiography and no bacteremia, regardless of clinical signs, as these are less reliable in children with SAM.³ Bacteremia and pneumonia were also

grouped together as IBIs. The urinary tract infection (UTI) group included children with a cytology- and culture-proven UTI and no bacteremia or pneumonia. The bacterial diarrhea group was composed of children with diarrhea and a bacterial agent identified in stool, and no bacteremia, pneumonia, or UTI. Finally, children with none of the above-mentioned laboratory-confirmed infections were included in the group with no proven bacterial infection (NBI) if all other analyses (ie, blood, urine, stool culture, and chest radiography) were negative. Children with inconclusive blood culture results (ie, positive blood culture with bacteria that could be either a pathogen or a contaminant) and those for whom some laboratory and/or radiography tests were not performed but all available results were negative, were excluded from these categories.

Laboratory Methods

Blood, urine, and stool cultures were performed and interpreted by using standard microbiological methods as described elsewhere.⁴ For the diagnosis of malaria, thick and thin smears were stained with Giemsa 10% for 20 minutes and read by trained technicians. Normal range values were obtained from the *Nelson Textbook of Pediatrics*.²²

CRP was measured on site using a rapid immunometric method (Nycocard CRP Single Test; Axis-Shield, Dundee, Scotland) on whole venous blood. This rapid test uses 5 μ L of whole blood, serum, or plasma and provides quantitative results within a linear range between 5 and 120 mg/L, and qualitative results outside this range. PCT was measured on site using a rapid immunochromatographic test (Brahms PCT-Q; Brahms Diagnostica, Hennigsdorf, Germany) on 200 μ L of plasma, giving semi-quantitative results (<0.5, 0.5–2, 2–10, >10 ng/mL). These rapid tests were performed and read by trained laboratory

technicians, following the manufacturer's recommendations.

Sera were stored at -80°C and sent to the central laboratory of Bichat-Claude Bernard Hospital where measurements were performed by using reference quantitative methods: time-resolved amplified cryptate emission technology (Kryptor procalcitonin; Brahms Diagnostica, Hennigsdorf, Germany) for PCT and an immunoturbidimetric assay (Modular P; Roche Diagnostics, Mannheim, Germany) for CRP. Rapid and reference tests were performed independently, with technicians blinded to the results of these and all other findings.

Statistical Analysis

Double entry was done by using the EpiData 3.0 software (The EpiData Association, Odense, Denmark) and analyzed using Stata 11.0 (Stata Corporation, College Station, TX).

Children's characteristics and the values of CRP and PCT level were compared across infection groups by using χ^2 , Fisher exact, and Kruskal-Wallis tests.

Receiver operating characteristic (ROC) curves were plotted and areas under the curve (AUC) estimated with 95% confidence intervals (95% CI) by using the CRP and PCT values measured with reference quantitative methods. Different cutoffs were determined to tentatively privilege either sensitivity (>80%; ruling out a condition) or specificity (>80%; ruling in a condition), or to maximize the Youden index (sensitivity + specificity – 1). These cutoffs, or their closest practical values (ie, values measured by the CRP or PCT rapid tests), were then used to estimate the diagnostic accuracy (sensitivity, specificity, predictive values, and likelihood ratios) of rapid tests to diagnose IBI, any bacterial infection, or to predict death.

The values within the CRP rapid test linear range were compared with the reference values by using the concordance correlation coefficient. In addition, to include all available values in the comparison, the values were categorized (<5, 5–20, 20–40, 40–80, 80–120, and >120 mg/L) and compared by using the unweighted and linearly weighted κ coefficients.

The PCT rapid test results were compared with the values of the categorized reference test by using the unweighted and linearly weighted κ coefficients.

Ethical Considerations

Ethical approval was obtained from the National Ethics Committee of Niger and the "Comité de Protection des Personnes," Ile de France XI, France. The study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all study participants' parents or legal guardian.

RESULTS

Characteristics of the Study Population

Between November 2007 and July 2008, 311 children were included in the general study, with a median age of 13 months (interquartile range [IQR] 10 to 24). There were no subject dropouts during the study. Of these, 31 children did not have enough serum to perform the pocCRP and pocPCT assays, 3 had pocPCT but not pocCRP performed on site, 27 had pocCRP but not pocPCT. A total of 261 sera were sent to Bichat-Claude Bernard Hospital for reference testing, 5 of which were insufficient for performing any assay and 2 were sufficient for PCT but not CRP. Finally, the study population for the main analysis by using reference results consisted of 256 children with a median age of 14 months (IQR 10 to 24). Forty-two (16.4%) children had bilateral edema and,

among the 214 children with marasmus, the median weight for height z-score was -3.8 (IQR -4.5 to -3.3), similar to the overall study population described elsewhere.⁴ Of these 256 children, 21 (8.2%) died, similar to the proportion in the overall cohort. None of the 3 HIV-infected children of the overall cohort were included in our study population.

A total of 51 children could not be classified in the infection groups; 19 were excluded because of inconclusive blood culture results (9 *Leuconostoc* spp, 2 *Enterococcus faecalis*, 2 *Enterococcus faecium*, 1 *Streptococcus equinus*, 1 *Gemella morbillorum*, 3 positive by Gram stain but no subculture), and another 32 children had negative but incomplete analyses (Supplemental Table 6).

The characteristics of the remaining 205 children and infection groups are shown in Table 1. Overall, 68.8% (141/205) of the children presented with a bacterial infection. There were significant differences in the presence of fever, acute diarrhea, and severe dehydration among the groups. There

was no significant difference in the proportions of children with hyperleukocytosis.

Levels of CRP and PCT in Each Group

Compared with the NBI group, CRP and PCT levels were significantly higher in the bacteremia and the pneumonia, but not the UTI group (Table 2). Levels of CRP, but not PCT, were significantly higher in the bacterial diarrhea group than in the NBI group. Thirteen of the 20 children in this group had *Shigella* spp isolated from their stools; these children had high CRP values, with a median of 108 mg/L (IQR 35 to 172), compared with a median of 25.9 mg/L (IQR 1 to 111) in the remaining 7 children with *Salmonella* spp infection.

Diagnostic Value of CRP and PCT to Identify Bacterial Infections

The ROC analysis to assess the accuracy of CRP and PCT for diagnosing bacteremia, IBI, or any bacterial infection showed low to moderate AUCs, even after excluding children with malaria (Table 3 and Fig 1). Accordingly, the

optimal cutoffs maximizing the Youden index for the tests showed moderate theoretical sensitivities and specificities (Table 4).

Agreement Between On-Site Rapid Tests and Reference Method

Within the linear range of the pocCRP rapid test ($n = 151$), the concordance coefficient between the pocCRP values compared with the reference values indicated strong agreement ($\rho = 0.91$, 95% CI 0.88–0.94). When categorized ($n = 244$), pocCRP and reference values showed moderate agreement when using the unweighted κ coefficient (69.7%) but good agreement when using the linear weighted κ coefficient (92.3%). The pocPCT values compared with the reference PCT values showed moderate agreement when estimated by using the unweighted κ coefficient (69.8%) and good agreement when using the linear weighted κ coefficient (90.8%) ($n = 232$).

Performance of poc Tests for Identifying IBIs

Table 5 summarizes the diagnostic performances of pocCRP and pocPCT to

TABLE 1 Sociodemographic and Clinical Characteristics of Patients by Infection Group

	Bacteremia ($n = 44$)		Radiograph-Proven Pneumonia, $n = 56$		UTI, $n = 22$		Infectious diarrhea, $n = 19$		NBI, $n = 64$		P Value ^a
Gender: male, n (%)	22	(50.0)	27	(48.2)	14	(63.6)	11	(57.9)	41	(64.1)	.38
Age, mo, median [IQR]	15.5	[10 to 24]	16.5	[10 to 24]	11	[10 to 24]	20	[11 to 24]	15.5	[9 to 24]	.54
Malnutrition											
Edema, n (%)	10	(22.7)	6	(10.7)	3	(13.6)	1	(5.3)	15	(23.4)	.18
z-score, median [IQR]	-3.6	$[-4.3$ to $-3.3]$	-3.7	$[-4.5$ to $-3.2]$	-4.2	$[-5.0$ to $-3.5]$	-4.3	$[-5.1$ to $-3.9]$	-3.7	$[-4.6$ to $-3.2]$.15
Albumin, median [IQR]	31	[21 to 36]	31	[25 to 38]	37	[25 to 42]	37	[25 to 40]	34	[25 to 41]	.43
Fever, n (%)	12	(27.3)	17	(30.4)	3	(13.6)	4	(21.10)	14	(21.9)	.58
Acute diarrhea, n (%)	26	(59.1)	24	(42.9)	17	(77.3)	19	(100.0)	34	(53.1)	<.001
Severe dehydration, n (%)	1	(2.3)	2	(3.6)	2	(9.1)	2	(10.5)	0	(0.0)	.041
Fast breathing, n (%)	20	(45.5)	30	(53.6)	6	(27.3)	5	926.3)	22	34.4	.08
SIRS, n (%)	23	(52.3)	30	(53.6)	9	(40.9)	7	(36.8)	29	(45.3)	.64
Lethargy, n (%)	19	(43.2)	17	(30.4)	10	(45.5)	11	(57.9)	17	(26.6)	.06
Hyperleukocytosis, n (%)	5	(12.5)	12	(24.0)	5	(22.7)	4	(21.0)	13	(21.3)	.72
Deaths, n (%)	7	(15.9)	2	(3.6)	3	(13.6)	1	(5.3)	3	(4.7)	.11
Coinfections, n (%)											
Pneumonia	12	(27.3)									
UTI	11	(25.0)	4	(7.1)							
Infectious diarrhea	7	(15.9)	2	(3.6)	2	(9.1)					
Malaria	3	(6.8)	7	(12.5)	2	(9.1)	0	(0.0)	18	(28.6)	

SIRS, systemic inflammatory response syndrome.

^a P value from comparison across infection groups.

TABLE 2 Median CRP and PCT Reference Values by Infection Group or in Children Who Survived or Died

	CRP, mg/L			PCT, ng/mL		
	Median	IQR	<i>P</i> Value ^a	Median	IQR	<i>P</i> Value ^a
Infection groups						
Bacteremia, <i>n</i> = 44	62.6	15.3 to 147.3	.0002	1.3	0.4 to 5.3	.0008
Pneumonia, <i>n</i> = 56	40.8	16.1 to 126	.0014	0.7	0.3 to 5.2	.012
UTI, <i>n</i> = 22	16.1	7.4 to 52.6	.74	0.5	0.2 to 4.5	.14
Infectious diarrhea, <i>n</i> = 19	73.1	14.2 to 164.4	.0087	0.5	0.3 to 3.6	.1
NBI, <i>n</i> = 64	12	4.5 to 46.6	ref	0.3	0.1 to 1.8	ref
Death						
Survived, <i>n</i> = 234	26.1	8 to 93.9	ref	0.5	0.2 to 2.8	ref
Died, <i>n</i> = 20	80.9	42.5 to 186.5	.004	2.2	0.7 to 13.4	.001

^a *P* value for comparison with the group with NBI (Infection groups) or group that survived (Death).

TABLE 3 ROC Analyses Using CRP and PCT Values Measured With Reference Methods

	CRP		PCT	
	AUC	95% CI	AUC	95% CI
All				
Bacteremia versus no bacteremia	0.63	(0.53–0.72)	0.62	(0.53–0.71)
Invasive versus localized or no bacterial infection	0.64	(0.56–0.72)	0.64	(0.55–0.72)
Bacterial versus no bacterial infection	0.66	(0.59–0.74)	0.65	(0.56–0.73)
No malaria				
Bacteremia versus no bacteremia	0.64	(0.55–0.74)	0.63	(0.54–0.73)
Invasive versus localized or no bacterial infection	0.67	(0.58–0.76)	0.67	(0.58–0.75)
Bacterial versus no bacterial infection	0.72	(0.63–0.80)	0.68	(0.59–0.77)

identify IBI or any bacterial infection after excluding children with malaria, using the cutoffs determined previously (or the closest practical value). Both positive and negative predictive values remained low, regardless of the threshold used.

Prognostic Value of CRP and PCT

Among the 256 children for whom CRP and PCT were measured, both markers on admission were significantly higher

in children who died than in those who survived (Table 2).

Both CRP and PCT (measured with the reference methods) had moderate performances for the identification of children at risk for dying, with AUC of 0.69 (95% CI 0.59–0.80) and 0.73 (95% CI 0.63–0.83), respectively. The optimal cutoff maximizing the Youden index in the ROC curve was 41.5 mg/L for CRP and 0.59 ng/mL for PCT (Table 4). Using cutoffs of 40 mg/L for CRP and 0.5 ng/

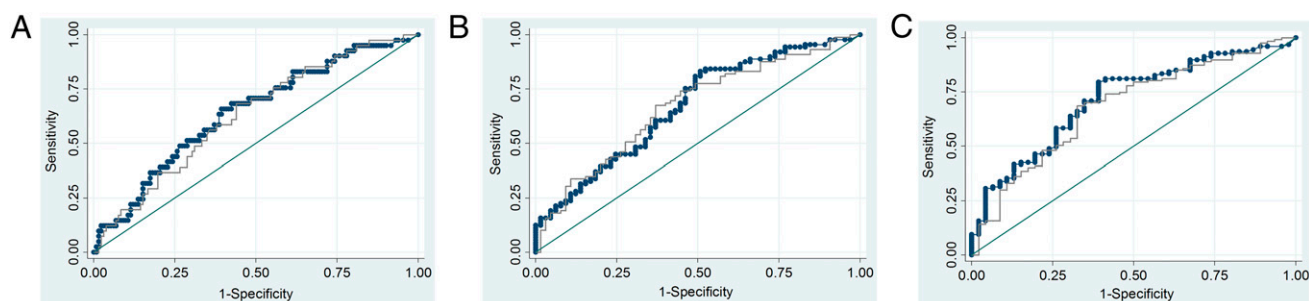
mL for PCT, each marker remained significantly associated with death after adjusting for age, gender, and albumin levels with odds ratios of 6.6 (95% CI 1.4–31.2, *P* = .017) and 6.4 (94% CI 1.3–30.9, *P* = .020), respectively.

By using the pocCRP test on site, a cutoff of 40 mg/L showed the best performance for predicting death overall and particularly for ruling out fatal outcome with a good negative predictive value of 97.4% (Table 5).

DISCUSSION

This study is, to the best of our knowledge, the first to address the diagnostic and prognostic performances of the inflammatory markers CRP and PCT in a population of children hospitalized with complicated SAM in an ICU in Africa.

As shown in other contexts for well-nourished children,^{23–25} or even some populations with immune deficiencies such as neutropenia,²⁶ PCT and CRP levels were elevated in our population of children with SAM and IBIs (bacteremia and pneumonia), although the median values found here were lower than generally reported in well-nourished children. Acute pyelonephritis also has been associated with increased CRP and PCT levels in children.^{27,28} Here, the UTIs could not be classified as upper or lower infections, as renal ultrasound was unavailable on site. Whether the low CRP and PCT values in the UTI group

**FIGURE 1**

ROC curve of the performances of CRP (black dots) and PCT (gray line) to detect bacteremia (A), IBIs (B), or any bacterial infection (C) after exclusion of malaria.

TABLE 4 Cutoffs and Corresponding Theoretical Sensitivity and Specificity Determined Using the ROC Curves for Identifying Bacterial Infection or Predicting Death

	CRP			PCT		
	Cutoff, mg/L	Se, %	Sp, %	Cutoff, ng/mL	Se, %	Sp, %
IBIs^a						
Rule-in, specificity >80%	85.0	37.3	80.0	2.2	40.0	80.0
Rule-out, sensitivity >80%	13.7	83.2	49.2	0.3	81.1	43.1
Youden index	13.7	83.2	49.2	0.4	71.1	56.9
Bacterial infections^a						
Rule-in, specificity >80%	47.5	46.5	80.4	1.7	40.3	80.4
Rule-out, sensitivity >80%	13.0	81.1	58.7	0.2	80.6	45.7
Youden index	13.2	79.5	60.9	0.4	67.4	67.4
Death^b						
Rule-in, specificity >80%	150.5	35.0	84.2	5.2	38.1	82.6
Rule-out, sensitivity >80%	41.5	80.0	59.4	0.6	81.0	54.9
Youden index	41.5	80.0	59.4	0.6	81.0	54.9

Se, sensitivity; sp, specificity.

^a Children with malaria excluded, *n* = 173 for CRP, *n* = 175 for PCT.

^b Children with malaria included, *n* = 254 for CRP, *n* = 256 for PCT.

reflect limited response or a low prevalence of acute pyelonephritis remains unclear. Finally, infectious diarrhea was associated with elevated levels of CRP, but not PCT. Our data are consistent with findings that gastrointestinal *Shigella* infection, and the resulting inflammation,²⁹ can lead to increased CRP levels, as described in adults.^{30,31} Because diarrhea due to *Shigella* spp requires antibiotic treatment, in contrast to most other diarrhea etiologies, this suggests an interesting possible use of CRP, which should be investigated further.

Despite these increased levels, the value of CRP and PCT for identifying

bacterial infections, or specifically invasive infections, is lower in our study population than in other studies from pediatric emergency departments or ICUs,³² or from another study in African children (where the AUCs in the ROC analysis were 0.81 and 0.86 for CRP and PCT, respectively).¹⁶ This finding was confirmed within our study by the low diagnostic performances of the rapid tests, even after excluding malaria, which can be done in the field using malaria rapid diagnostic tests. We could not identify a threshold with sufficient positive predictive value to rule-in an IBI or with sufficient negative predictive value to rule it out and

thereby avoid the use of unnecessary antibiotics, or even to use as a screening tool for children needing blood culture, as proposed elsewhere.¹⁵ Combining both rapid tests also failed to improve classification (data not shown).

The relationship between malnutrition and the acute phase inflammatory response remains unclear. Several authors have suggested that malnutrition does not affect CRP production in response to infections.^{33,34} In a study in Malawi, although children with kwashiorkor had reduced rates of protein breakdown and synthesis, their CRP levels were similar to those without kwashiorkor.³⁵ To our knowledge, only 1 study found that CRP levels in response to infection are lower in malnourished than in well-nourished children.³⁶ In our study, all children were malnourished, and we could not detect an association between the level (z-score) or type (marasmus versus kwashiorkor) of malnutrition and CRP or PCT levels in the group with IBIs (data not shown). However, the fact that the median levels of CRP and PCT in the children with IBIs found here were lower than generally reported elsewhere in non-malnourished children, suggests reduced responses to infection.

TABLE 5 Performance of On-site pocCRP and pocPCT Tests to Identify Invasive or Any Bacterial Infection or Predict Death Using Different Cut-offs

	Sensitivity		Specificity		PPV		NPV		LR+		LR-	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
IBIs^a												
pocCRP ≥10 mg/L	84.5	75.8–91.1	27.8	17.9–39.6	61.2	52.4–69.5	57.1	39.4–73.7	1.17	0.99–1.38	0.56	0.31–1.01
pocCRP ≥90 mg/L	39.2	29.4–49.6	86.1	75.9–93.1	79.2	65.0–89.5	51.2	42.0–60.4	2.82	1.51–5.28	0.71	0.59–0.85
pocPCT ≥0.5 ng/mL	51.8	40.7–62.7	63.5	50.4–75.3	65.7	53.1–76.8	49.4	38.1–60.7	1.42	0.96–2.08	0.76	0.57–1.01
pocPCT ≥2 ng/mL	34.1	24.2–45.2	77.8	65.5–87.3	67.4	51.5–80.9	46.7	36.9–56.7	1.54	0.89–2.66	0.85	0.69–1.04
Bacterial infections^a												
pocCRP ≥10 mg/L	82.5	75.1–88.4	32.1	19.9–46.3	75.8	68.2–82.5	41.5	26.3–57.9	1.21	0.99–1.48	0.55	0.32–0.93
pocCRP ≥50 mg/L	46.7	38.1–55.4	81.1	68.0–90.6	86.5	76.5–93.3	37.1	28.3–46.5	2.48	1.38–4.45	0.66	0.54–0.81
pocPCT ≥0.5 ng/mL	48.8	39.8–57.9	65.9	50.1–79.5	80.3	69.5–88.5	31.2	22.0–41.6	1.43	0.91–2.24	0.78	0.59–1.02
pocPCT ≥2 ng/mL	34.4	26.1–43.4	84.1	69.9–93.4	86	73.3–94.2	31.1	22.9–40.2	2.16	1.05–4.45	0.78	0.65–0.93
Death^b												
pocCRP ≥40 mg/L	81.0	58.1–94.6	58.6	52.3–64.7	13.8	8.3–21.2	97.4	93.5–99.3	1.96	1.52–2.52	0.33	0.13–0.79
pocPCT ≥0.5 ng/mL	64.7	38.3–85.8	57.2	50.6–63.6	9.8	5.0–16.9	95.7	91.0–98.4	1.51	1.03–2.21	0.62	0.32–1.19

LR, likelihood ratio; NPV, negative predictive value; PPV, predictive positive value.

^a Children with malaria excluded, *n* = 190 for pocCRP and *n* = 169 for pocPCT.

^b Children with malaria included, *n* = 277 for pocCRP and *n* = 253 for pocPCT.

Increased CRP and PCT levels remained fair indicators of condition severity, as suggested by their association with fatal outcome. This contrasts with data from a study on malnourished children in Bangladesh, which found that CRP was not a predictor of death, but the number of children in this study was small and the cutoff level (10 mg/L) was not very discriminatory.³⁷ Here, the best predictor of death was CRP with a threshold of 40 mg/L, and the pocCRP test showed good performance for ruling out the risk of fatal outcome in the field. Although this test requires some equipment and manipulation, it can be set up in a simple laboratory and provide results rapidly.

Our study presented several limitations. One major challenge in evaluating bacterial infection markers is in constituting appropriate categories, and the variety of reference standards used in different studies probably partly explains the variable results.³² Despite our efforts to establish an appropriate diagnostic laboratory, the available tests and examinations were limited, and many children had no laboratory-confirmed

diagnosis. In addition, multiple infections were frequent in our study population.⁴ Finally, the less-than-optimal sensitivity of blood cultures, and the high prevalence of bacterial infections in this population, might have caused some serious infections to be misclassified, possibly leading to underestimation of the markers' performance. It also should be noted that our study included all children regardless of fever, whereas most other studies focus only on febrile children. Our rationale was that children with SAM show indeterminate clinical signs, as illustrated by the fact that fewer than a quarter of those with bloodstream infection had fever.⁴ However, repeating the analysis on the subset of febrile children did not change our results significantly (data not shown).

CONCLUSIONS

The inflammatory proteins CRP and PCT do not appear to be adequate markers of IBIs in a sub-Saharan African population of hospitalized children with SAM plus medical complications, and therefore cannot help reduce an-

tibiotic use. Whether the markers' low performances in this context are due to malnutrition, high prevalence of infections, and/or other factors specific to this population, remains unclear. However, these markers could be helpful in identifying children most at risk for dying, which could potentially be useful for triage purposes. The availability of a simple, reliable test for measuring CRP makes it a good candidate for such a use in settings with access to some laboratory capacity.

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Diagnostic and Prognostic Value of Procalcitonin and C-Reactive Protein in Malnourished Children

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