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Original Article

Using procalcitonin levels to predict infection and reduce unnecessary antibiotic usage in febrile children aged 3-36 months

Piyanuch Thongsamer[1], Kamolwish Laoprasopwattana[1]

[1] Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

Abstract

Introduction: High risk features including body temperature (BT) ≥ 39 °C, inactive appearance, white blood cells (WBC) ≥ 15,000 cells/mm^3, or absolute band count (ABC) ≥ 1,500 cells/mm^3 have low sensitivity and negative predictive value (NPV) to discriminate between bacterial and viral infections, leading to overuse of antibiotics. We aimed to determine whether procalcitonin (PCT) level ≥ 0.5 ng/mL can differentiate bacterial from viral infections.

Methodology: The medical data of children aged 3 to 36 months who presented with fever without localizing signs or having initially undetermined cause of respiratory tract infection and/or non-mucus bloody diarrhea for 1 to 7 days and were hospitalized between January 2017 and December 2018 with one of the high-risk features were recorded. Children with an immunocompromised condition, who had previously received antibiotics, and/or had clinical sepsis were excluded.

Results: Non-serious bacterial infection (SBI) and SBI (occult bacteremia) were found in 17.2% and 4.5%, respectively. The proportions of children with high-risk features were not significantly different between children with and without bacterial infection, except for absolute band count which was significantly higher in the bacterial infection group (419 cells/mm^3, IQR [0, 1429]) than the non-bacterial group (76 cells/mm^3, IQR [0,455]). A PCT level ≥ 0.5 ng/mL had the highest sensitivity and NPV (100%, 100%, respectively) to predict bacterial infection when compared with the other high-risk features.

Conclusions: Antibiotics can be safely withheld while waiting for hemoculture in acute febrile children with one of the high-risk features of bacterial infection with PCT level < 0.5 ng/mL.

Key words: fever; procalcitonin; infant; antibiotic.

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Introduction

In recent years, multidrug-resistant microorganisms have become prevalent worldwide [1]. Restricted use of antibiotics, especially in high-risk patients is necessary to decrease further antibiotic resistance. Infants aged less than 3 months are at high risk of serious bacterial infection (SBI) resulting in widespread prescription of empirical antibiotics for infants who have acute fever without source in order to reduce mortality and morbidity. Children aged 3-36 months have a relatively lower risk of getting a serious bacterial infection (SBI) than the younger age group. The American Academy of Pediatrics (AAP) recommends that empirical antibiotics should be used only in acute fever without localizing signs in children with high-risk features of bacterial infection such as body temperature (BT) ≥ 39 °C, drowsiness, white blood cell count greater than 15,000 cells/mm^3, and/or absolute band count greater than 1,500 cells/mm^3 [2]. However, these high-risk criteria have low sensitivity and specificity to differentiate viral from bacterial infections, leading to overuse of empirical antibiotics [3]. Overuse of empirical antibiotics is common in children not only with acute fever without localizing signs but also with respiratory tract and gastrointestinal tract infections.

Procalcitonin (PCT), a precursor of calcitonin, can be elevated in cases with bacterial infection. Among the acute phase proteins such as PCT, C-reactive protein, serum amyloid A, and interleukin-6 (IL-6), PCT was reported to be the best indicator of bacterial infection [4,5]. A systematic review found that a PCT level ≥ 0.5 ng/mL could distinguish SBI from other causes of acute fever with a sensitivity of 78% and specificity of 72% [4].

To date, there have been few studies examining whether PCT levels reliably guide antibiotic management in febrile children aged 3-36 months without localizing signs or with an initially undetermined cause.

Methodology

The medical data of children aged 3-36 months who presented between January 2017 and December 2018 at our institute, Songklanagarind Hospital, a medical teaching hospital and the major tertiary care facility in southern Thailand were included in the study. Inclusion criteria were: fever for less than 7 days with one of the high-risk features, no localizing infection or undetermined-cause respiratory tract infection and/or non-mucus bloody diarrhea at initial manifestation of their fever. High-risk features were defined as one or more of the following: 1) high fever (defined as an axillary temperature ≥ 39 °C), 2) drowsiness, 3) white blood cells (WBC) ≥ 15,000 cells/mm^3, 4) absolute neutrophil count (ANC) ≥ 10,000 cells/mm^3, 5) absolute band count (ABC) ≥ 1,500 cells/mm^3.

The patients were excluded if they had an immunocompromised condition, had previously received antibiotics, had clinical sepsis, had a clinically documented bacterial infection such as urinary tract infection or skin and soft tissue infection, and/or did not have blood culture results. Febrile patients were classified by PCT levels into 3 groups: 1) no-PCT, 2) PCT level < 0.5 ng/mL (low PCT group), and PCT level ≥ 0.05 ng/mL (high PCT group).

Statistical analysis

Categorical variables were analyzed using Pearson Chi square test and Fisher's exact test and presented as percentages. Non-parametric continuous data were analyzed using Mann-Whitney U test and presented as medians and interquartile ranges. All *p* values were two-tailed and *p* values less than 0.05 were deemed to indicate statistical significance.

Ethical approval

This study was approved by the Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University (REC.63-034-1-4).

Results

Baseline characteristics, CBCs, and PCT levels of febrile children aged 3-36 months with and without bacterial infection

Out of total 883 patients assessed for eligibility, 134 patients met the inclusion criteria in which their initial diagnosis was inconclusive concerning whether they had a bacterial or viral infection. In the summary discharge records, bacterial and non-bacterial infections were diagnosed in 29 and 105 patients, respectively.

The baseline characteristics including gender, age, previous pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* type b (Hib) vaccine, and Rota vaccine immunizations, localizing symptoms including upper respiratory tract infection, dyspnea, and vomiting, and body temperature were not significantly different between the two groups. However, non-mucus bloody diarrhea was significantly higher in the bacterial infection group than in the non-bacterial infection group (62.1% vs 31.4%, $p < 0.01$) (Table 1).

The mean WBCs, ANC, hemoglobin levels, and platelet count were not significantly different between the two groups. The median ABC and PCT levels were significantly higher in the bacterial infection group than in the non-bacterial infection group (Table 1).

Table 1. Comparison of characteristics, CBCs, and PCT levels of patients with or without bacterial infection.

Variable	Bacterial infection (N = 29)	Non-bacterial infection (N = 105)	*p* value
Male, n (%)	18 (62.1)	55 (52.4)	0.35
Age, months, median (IQR)	15 (9.5, 24.5)	17 (9.5, 27.0)	0.55
PCV, n (%)	1 (3.4)	14 (13.3)	0.19
Hib vaccination, n (%)	11 (37.9)	33 (31.4)	0.51
Rota vaccination, n (%)	10 (34.5)	28 (26.7)	0.41
URI, n (%)	15 (51.7)	64 (61.0)	0.37
Dyspnea, n (%)	6 (20.7)	17 (16.2)	0.57
Non-mucous bloody diarrhea, n (%)	18 (62.1)	33 (31.4)	< 0.01
Vomiting, n (%)	5 (17.2)	22 (21.0)	0.66
Body temperature, (°C), mean (SD)	39.5 (2.2)	39.1 (2.1)	0.86
WBCs x10^3 cells/mm^3, mean (SD)	18.1 (10.6)	16.7 (7.2)	0.89
ANC x10^3 cells/mm^3, mean (SD)	10.5 (5.1)	10.4 (5.8)	0.35
ABC, cells/mm^3, median (IQR)	419 (0, 1429)	76 (0, 455)	0.04
Hemoglobin, g/dL, mean (SD)	11.4 (1.3)	11.5 (1.0)	0.50
Plt x10^3 cells/mm^3, mean (SD)	362.1 (116.5)	358.4 (120.1)	0.68
PCT level, median (IQR)	4.7 (1.3, 13.0), n = 10	0.4 (0.2, 2.0), n = 39	< 0.01

PCV: pneumococcal conjugate vaccine; Hib: *Haemophilus influenzae* type b vaccine; URI: upper respiratory tract infection; WBCs: white blood cells; ANC: absolute neutrophil count; ABC: absolute band count; IQR: interquartile range.

High-risk features, management, and outcomes between children with bacterial and non-bacterial infection

The proportions of patients with high-risk features including toxic appearance, high body temperature (BT ≥ 39 °C), high WBCs (≥ 15,000 cells/mm^3) and ANCs (≥ 10,000 cells/mm^3) between the bacterial and non-bacterial infection groups were not significantly different. The proportions of children with high ABC (≥ 1,500 cells/mm^3) and high PCT levels (PCT ≥ 0.5 ng/mL) were significantly higher in the bacterial infection group than the non-bacterial infection group (Table 2).

The empirical antibiotic prescription rate on the first day of hospitalization was not significantly different between the bacterial infection group (18/29 patients, 62.1%) and the non-bacterial infection group (50/105 patients, 47.6%), p = 0.17. The median durations of intravenous antibiotics, admission, or fever were not significantly different between the two groups (Table 2). None of the patients in either group developed sepsis, septic shock, or had a fatal outcome.

Using a procalcitonin level ≥ 0.5 mg/mL to differentiate bacterial infection from non-bacterial infection

None of the 21 patients with low PCT levels had a bacterial infection. Empirical antibiotic prescription was significantly higher in the high PCT group (96.4%) than in the no-PCT (71.8%) and low PCT groups (52.4%) (Table 3).

Of the 28 patients with high PCT levels, 18 patients (64.3%) had a viral infection and all except one patient with viral exanthem received antibiotics. The final diagnoses were viral pneumonia in 4 cases, Kawasaki in 3 cases, viral exanthem in 4 cases, viral upper respiratory tract infection (URI) in 4 cases, and one each of chikungunya, viral acute gastroenteritis (AGE), and acute febrile illness (AFI). The median PCT levels and durations of fever, empirical intravenous antibiotics, and hospitalization in the high PCT group were not different between patients who had and did not have bacterial infection. The median duration of receiving an antibiotic was longer in patients with bacterial than non-bacterial infection, 7.5 (5.7, 10) days vs 3.0 (1.5, 7.0) days, respectively (p = 0.03).

Of the 21 patients with low PCT levels, comparing between the 11 patients who were empirically treated with ceftriaxone and the 10 patients without antibiotics, all high-risk features were not significantly different. Of the 11 patients who were empirically treated with ceftriaxone, the final diagnoses were viral pneumonia in 6 cases, URI in 2 cases, and one each of viral exanthem, AFI, and AGE.

In this study, a high PCT level (≥ 0.5 mg/mL) could differentiate bacterial infections from non-bacterial infections with high sensitivity and negative predictive value (NPV) of 100% each, but with low specificity of 53.8% and positive predictive value (PPV) of 35.7%.

Of the 85 patients who had not been PCT tested, bacterial infection was found in 19 patients (22.4%). The proportions of patients who received empirical antibiotics on the same day of hospitalization were not significantly different between the bacterial infection group (13/19 patients, 68.4%) and the non-bacterial infection group (37/66 patients, 56.1%).

Causes of bacterial and non-bacterial infections

Of the 29 patients with bacterial infections, all except a 5-month-old boy with *Salmonella* AGE with low fever (BT 38.0 °C) were treated with antibiotics. Occult bacteremia, bacterial acute gastroenteritis (AGE), pneumonia, and other bacterial infection were diagnosed in 6, 14, 5, and 4 cases, respectively.

Of the 6 cases with occult bacteremia, hemocultures found *S. pneumoniae*, *H. influenza*, and *K. pneumoniae* with *E. coli* bacteremia in 3 cases, 2 cases, and 1 case,

Table 2. Comparison of high-risk features, management, and outcomes between children with bacterial and non-bacterial infections.

Variable, n (%)	Bacterial infection (n = 29)	Non-bacterial infection (n = 105)	p value
Drowsiness/irritable, n (%)	3 (10.3)	6 (5.7)	0.38
BT ≥ 39°C, n (%)	22 (75.9)	67 (63.8)	0.22
WBCs ≥ 15,000 cells/mm^3, n (%)	18 (62.1)	58 (55.2)	0.51
ANC ≥ 10,000 cells/mm^3, n (%)	12 (41.4)	51 (48.6)	0.49
ABC ≥ 1,500 cells/mm^3, n (%)	7 (24.1)	9 (8.6)	0.02
PCT ≥ 0.5 ng/mL, n (%)	10 (100), n = 10	18 (42.6), n = 39	< 0.01
Antibiotic prescription, n (%)	28 (96.6)	71 (67.6)	< 0.01
Duration of intravenous antibiotic, days, median (IQR)	2.5 (1.3, 5.5), n = 28	2.0 (1.0, 4.0), n = 71	0.33
Total duration of all forms of antibiotics, days, median (IQR)	6.5 (5, 9), n = 28	4.0 (2.0, 7.3), n = 71	0.01
Duration of fever, days, median (IQR)	3.0 (2.0, 5.0)	4.0 (3.0, 6.0)	0.15
Duration of admission, days, median (IQR)	4.0 (3.0, 6.0)	3.0 (2.0, 5.0)	0.08

WBCs: white blood cells; ANC: absolute neutrophil count; ABC: absolute band count; IQR: interquartile range.

respectively. None of the *S. pneumoniae* patients were vaccinated with PCV, and none of the *H. influenza* patients were vaccinated with Hib vaccine. The PCT levels in 1 patient each with *S. pneumoniae* and *K. pneumoniae* with *E. coli* bacteremia were 14.3 and 9.1 ng/mL, respectively. Four patients had received an empirical antibiotic on the same day of hospitalization, two of them were initially diagnosed as URI from RSV and subsequently developed bacteremia and began antibiotics on day 4 and day 2 after hospitalization.

Of the 14 cases with bacterial AGE, all stool cultures identified *Salmonella* spp.; 13 cases had WBCs and 1 case had RBCs.

Bacterial pneumonia was diagnosed from an abnormal chest x-ray in 5 cases (patchy infiltration in 4 cases and round pneumonia in 1 case). Sinusitis and acute otitis media were found in 3 cases and 1 case, respectively.

Of the 105 cases with non-bacterial infection, 70 cases (66.7%) were empirically treated with an antibiotic due to initial diagnoses of occult bacteremia (44 cases), bacterial pneumonia (9 cases), tonsillitis (9 cases), and AGE (8 cases).

Discussion

Children aged 3-36 months who had acute fever with unknown cause of infection with ≥ 1 high-risk features had non-SBI in 17.2% and SBI (occult bacteremia) in 4.5% of the cases. A PCT level ≥ 0.5 ng/mL had high sensitivity and NPV but low specificity and PPV to predict bacterial infection.

We found that PCT ≥ 0.5 ng/mL together with an absolute band count of ≥ 1,500 cells/mm^3 were associated with a higher risk of bacterial infection, while none of the other high-risk criteria could help differentiate between the two types of infection. These results were also reported in a previous systematic review using multivariable logistic regression analysis which found that the absolute band count and PCT level were the only two screening tests independently associated with SBI, with PCT showing the largest area under the receiver operating characteristic (ROC) curve (0.80, 95% CI = 0.71-0.89) [6].

We found that PCT ≥ 0.5 ng/mL was associated with bacterial infection with sensitivity and NPV of both of 100%. The higher sensitivity and NPV in our study than in previous studies (sensitivities of 50-90% and NPVs of 86-96%) [4,6,7] could be explained by different cut-off levels for PCT ranging from 0.59 to 2 in the previous studies [6,7].

PCT-guided antibiotic management seems to be useful in helping the physicians reduce antibiotic exposure in children, according to a systematic review from China, in which PCT-guided antibiotic management was associated with significantly reduced general antibiotic prescription rate (54.64% versus 83.91%, 95% CI: –38.31 to –20.22) and antibiotic exposure in children with lower respiratory tract infection (a 2.7-day reduction; 95% CI: –3.21 to –2.16) [8]. Another systematic review found that PCT-guided antibiotic management was associated with a 2.4-day reduction in antibiotic exposure (5.7 versus 8.1 days, 95% CI -2.71 to -2.15, $p < 0.001$) [9].

Our study found that the duration of intravenous antibiotic, duration of fever, and duration of admission were not significantly different in children with or without bacterial infection. These findings could be explained by the inclusion criteria that enrolled only children whose hemodynamic status was stable, thus antibiotic extension and hospital stay were less likely to have been required for the patients in this study.

In our study, although a PCT level < 0.5 ng/mL could help to exclude cases of bacterial infection leading to lower antibiotic prescription, the low specificity of the PCT level ≥ 0.5 ng/mL in diagnosing bacterial infection led to similar overall antibiotic prescription rates in both PCT-guided (38/49, 77.5%) and not PCT-guided (61/85, 71.8%) febrile children.

As the cost of this test is quite high, it is recommended that Thailand or other low-income settings, consider this test only in select cases. In settings where PCT is not yet available, we suggest that

Table 3. Proportions of bacterial infection, empirical antibiotics, and high-risk features among no-, high- and low- PCT groups.

Variable	No-PCT (N = 85)	High-PCT (N = 28)	Low-PCT (N = 21)	*p* value
Bacterial infection, n (%)	19 (22.4)[a]	10 (35.7)[a]	0 (0)[b]	0.01
Empirical antibiotic, n (%)	61 (71.8)[a]	27 (96.4)[b]	11 (52.4)[a]	< 0.01
Drowsiness/irritable, n (%)	5 (5.9)	4 (14.3)	0 (0)	0.13
Body temperature ≥ 39 °C, n (%)	59 (69.4)[a]	24 (85.7)[a]	6 (28.6)[b]	< 0.01
WBCs ≥ 15,000 cells/mm^3, n (%)	54 (63.5)[a]	15 (53.6)[a]	7 (33.3)[b]	0.04
ANC ≥ 10,000 cells/mm^3, n (%)	43 (50.6)	13 (46.4)	7 (33.3)[b]	0.37
ABC ≥ 1,500 cells/mm^3, n (%)	11 (12.9)	4 (14.3)	1 (4.8)	0.53

[a,b,c]values within a row that do not have a common superscript differ significantly ($p < 0.05$). WBCs: white blood cells; ANC: absolute neutrophil count; ABC: absolute band count; IQR: interquartile range.

the children who appear healthy with complete Hib and PCV immunizations and who have acute fever with unknown cause and one or more high-risk features, except for bandemia, can be safely followed-up daily without an empirical antibiotic while waiting for a hemoculture [3].

The notable limitation of this study was possible selection bias, in that some of the patients had not had hemoculture studies, thus some patients with clinical symptoms that are usually suspicious of a viral infection may not have been included in the study. The other limitation was the retrospective nature of the study, thus decisions concerning patient management and antibiotic prescription depended on the individual doctor's experience and clinical judgment. However, this retrospective design did not influence the results of bacterial infection.

In summary, the incidence of bacterial infection in febrile children aged 3-36 months without localizing signs or with an initially undetermined cause was 21.6%. In these cases, a PCT ≥ 0.5 ng/mL was associated with bacterial infection with sensitivity and NPV of 100% each. Bacterial infection was not found in any patients with a PCT < 0.5 ng/mL, thus we believe it is safe to withhold antibiotics while waiting for hemoculture in acute febrile children with one of the high-risk features of bacterial infection but with a PCT level < 0.5 ng/mL.

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Authors' Contributions

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Corresponding author

Kamolwish Laoprasopwattana, MD
Head of the Infectious Diseases Unit, Department of Pediatrics,
Faculty of Medicine, Prince of Songkla University,
Hat Yai 90110, Thailand.
Tel: (66)74451250
Fax: (66)74429618
E-mail: kamolwish@gmail.com; lkamolwi@medicine.psu.ac.th

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