

Procalcitonin as a Predictive Marker for Bacteremia in Children With a Central Line and Fever

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OBJECTIVES: Unnecessary use of antibiotics is an increasing problem. In this study, we sought to determine the diagnostic accuracy of procalcitonin in predicting bacteremia in children with a central line and fever, and we sought to determine optimal cutoff values to maximize sensitivity and specificity. This is the largest study to date in which procalcitonin is examined as a predictive marker of bacteremia in pediatric patients with a central line and fever.

METHODS: We conducted a retrospective cohort study of children aged 0 to 23 years with a central line and fever of 38°C who had procalcitonin and blood cultures drawn before initiation of antibiotics and had no other identified bacterial infection. Patients were also prospectively monitored via a custom-built electronic medical record dashboard for eligibility.

RESULTS: There were 523 patients and >2500 procalcitonin values reviewed for eligibility. Of these, 169 (47%) patients and 335 blood cultures with procalcitonin were included. There were 94 (28%) positive bacterial blood cultures and 241 (72%) negative bacterial blood cultures. In bacteremic cultures, the mean procalcitonin level was 9.96 ± 15.96 ng/mL, and the median procalcitonin level was 4.85 ng/mL (interquartile range 1.8-5). In nonbacteremic cultures, the mean procalcitonin level was 1.23 ± 10.37 ng/mL, and the median procalcitonin level was 0.3 ng/mL (interquartile range 0-0.7). A receiver operating characteristic analysis indicated a procalcitonin level of ≥ 0.6 ng/mL as the best cutoff point that produced a sensitivity of 85.6% and a specificity of 65.7% (area under the curve 0.85).

CONCLUSIONS: Procalcitonin is a sensitive biomarker in predicting bacteremia in children with a central line and fever.

ABSTRACT

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Unnecessary use of broad-spectrum antibiotics in children with suspected central line–associated bloodstream infections (CLABSIs) is an increasing problem, especially because children with chronic illnesses who require central-line access are living longer. In children with a central venous catheter (CVC) and fever, the current standard of care often involves inpatient treatment with broad-spectrum antibiotics, even if clinical suspicion of CLABSI is low. Like healthy children, pediatric patients with a CVC are subject to fevers because of viral illnesses that do not require antibiotics. This is supported by previous studies that have revealed that the majority of children hospitalized for suspected CLABSI had negative blood cultures.¹ Traditional serological markers of inflammation, such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), have been shown to lack sensitivity and specificity for predicting bacteremia.² An early biomarker for predicting bacteremia in children with a CVC and fever could lead to a significant decrease in unnecessary antibiotic use, thus decreasing multidrug resistant organisms, hospital admissions, and acute care costs.

Procalcitonin is a 116-amino-acid precursor peptide from the hormone calcitonin, and elevated levels are strongly correlated with systemic bacterial infection.³ Previous studies have revealed that procalcitonin levels are elevated in Gram-positive and, to a greater extent, Gram-negative bacterial sepsis but not in viral infections.^{4–6} Procalcitonin is fast and quantitative, and levels are elevated quickly after bacterial infection.^{2,7–10} Procalcitonin has been shown to increase within 4 hours of bacterial infection and has been shown to correlate with disease severity.¹¹ Gomez et al¹² examined febrile children <3 months of age, procalcitonin was the only independent predictor of serious bacterial infection. Procalcitonin has been used to aid in the diagnosis of serious bacterial infection in febrile infants as well as pediatric patients with congenital heart defects, urinary tract infections, neutropenia, and sickle cell disease^{12,13}; however, there has only been 1 study to date involving patients with a CVC

and fever.¹ This previous study indicated promising results but was limited to a small sample size of 62 patients.

Our objective for this study was to determine the diagnostic accuracy of procalcitonin in predicting bacteremia in children with a CVC and fever and to determine optimal cutoff values to maximize sensitivity and specificity.

METHODS

Study Design

After obtaining institutional review board approval, a retrospective chart review was performed by using the Stanford Translational Research Integrated Database Environment (STRIDE). STRIDE contains information on >1.6 million pediatric and adult patients cared for at a major university medical center attached to a pediatric hospital. By using STRIDE, a custom data query was built that captured all pediatric patients admitted with a CVC who also had procalcitonin drawn either in the emergency department or during hospital admission. This query captured patient encounters since the initiation of our electronic medical record (EMR) system between May 2014 and June 2017. All patients from our pediatric gastroenterology intestinal rehabilitation center were also reviewed for eligibility.

This study also had a prospective monitoring component. After obtaining separate institutional review board approval, we created an EMR dashboard that was custom built to automatically track all patients admitted to our pediatric hospital who had a CVC in place. The dashboard also tracked maximum temperature over the previous 48 hours, enabling easy recognition of all patients admitted with a CVC who developed fever. For those who met inclusion criteria, if procalcitonin was not already drawn as part of a sepsis evaluation, the primary teams were contacted to determine if procalcitonin could be ordered as an add-on laboratory test before initiation of antibiotics. For these patients, procalcitonin must have been drawn within the previous 48 hours.

Patient Population

All pediatric patients aged 0 to 23 years with an indwelling CVC (including tunneled, arterial, femoral, or jugular catheters and implanted ports) or a peripherally inserted central catheter who had a fever $\geq 38^{\circ}\text{C}$ and had procalcitonin and blood cultures drawn before initiation of antibiotics were included in this study. Patients were excluded if they received antibiotics within 24 hours before procalcitonin or blood cultures were drawn and if they had other documented source of bacterial infection. Cultures that grew yeast ($n = 9$) were considered negative for bacteria (Fig 1).

Data Collection

The principal investigator reviewed all patients from the prospective data monitoring, from the retrospective chart review cohort, and from the intestinal rehabilitation center patient list. There was a total of 523 patients from the above-mentioned groups who had a central line in place and procalcitonin drawn since the initiation of the institution's EMR system. Medical records of each of the 523 patients were meticulously reviewed for eligibility. To begin, all procalcitonin laboratory values were documented for each patient. Those values were then compared with blood cultures obtained on the patient. If a blood culture and procalcitonin were drawn simultaneously, then charts were reviewed further to determine if patients met inclusion and exclusion criteria. To review for eligibility, vital signs, medication administration records, and daily progress notes were reviewed to confirm the presence of fever at time of laboratory draws and to ensure that patients had not received antibiotics during the previous 24 hours. Other documented sources of bacterial infections were identified via an extensive chart review of laboratory results (urine, skin, sputum culture, etc) or radiographs (documenting pneumonia, abscess, etc) as well as progress notes, consultation notes, and discharge summaries. If a patient was found to have another bacterial infection within several days before or after their procalcitonin laboratory test, they were excluded. For the 169 patients who qualified for the study, the

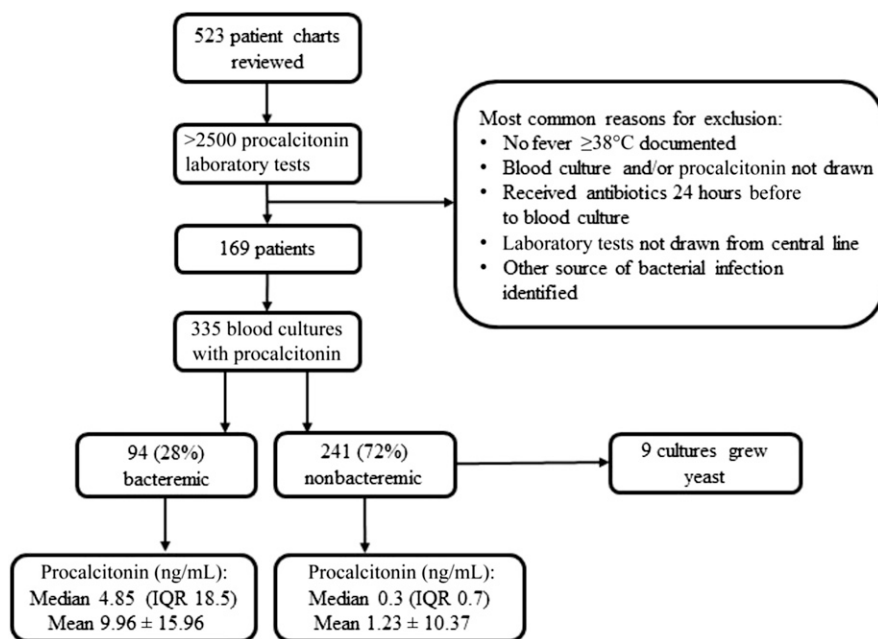


FIGURE 1 Patient selection and results flow sheet.

dialysis, respiratory failure, and neurologic, rheumatologic, or metabolic disorders. Of the patients who had bacteremic cultures, 68 (72%) had intestinal failure, 14 (15%) had heart disease, 5 (5%) had cancer, and 4 (4%) had liver transplant. Of the nonbacteremic cultures, 107 (44%) had heart disease, 64 (27%) had intestinal failure, 18 (7%) had cancer, and 12 (5%) had liver transplant. In the bacteremic group, the mean procalcitonin level was 9.96 ± 15.96 ng/mL, and the median procalcitonin level was 4.85 ng/mL (interquartile range [IQR] 18.5). In the nonbacteremic group, the mean procalcitonin level was 1.23 ± 10.37 ng/mL, and the median procalcitonin level was 0.3 ng/mL (IQR 0.7; Fig 1). A ROC curve analysis revealed a procalcitonin level of ≥ 0.6 ng/mL as the best cutoff point that produced a sensitivity of 85.6% and a specificity of 65.7% (AUC 0.85; Fig 2). Of the 243 nonbacteremic blood cultures, 84 (35%) had an elevated procalcitonin level (false-positive) by using a cutoff of ≥ 0.6 ng/mL (Table 2). Of these, 47 (56%) had heart disease, 13 (15%) had intestinal failure, 7 (8%) had cancer, and 7 (8%) had liver transplant. Of the 94 bacteremic blood cultures, 17 (18%) had a low procalcitonin level (false-negative) by using a cutoff of < 0.6 ng/mL. Of these, 16 (94%) had intestinal failure, and 1 (6%) had heart disease. An analysis of various other procalcitonin cutoff points that maximize either sensitivity or specificity revealed that a procalcitonin level of ≥ 0.3 ng/mL produced a sensitivity of 93.3% and a specificity of 42%, and a procalcitonin level of ≥ 1.1 ng/mL produced a sensitivity of 74.4% and a specificity of 78.4% (Supplemental Table 4). Given the high number of false-positives in the gastrointestinal (GI) patients with a central line and intestinal failure, a subanalysis of this group was performed. This revealed a total of 132 cultures, 68 (52%) of which were bacteremic. In the bacteremic group, the mean procalcitonin level was 11.29 ng/mL, and the median procalcitonin level was 4.95 ng/mL. In the nonbacteremic group, the mean procalcitonin level was 0.5 ng/mL, and the median procalcitonin level was 0.22 ng/mL (Table 3).

following data were recorded: patient date of birth, type of CVC, date of blood culture and/or procalcitonin laboratory test, procalcitonin value, result of blood culture, blood culture organisms, maximum temperature, admitting service, admitting diagnosis, discharge diagnosis, and any other pertinent diagnoses. A blood culture was considered positive if any bacterial organism grew that was not considered a contaminant by the infectious disease specialist. If the infectious disease team was consulted and determined that a positive blood culture was a contaminant, and antibiotics were discontinued because of high enough suspicion of a contaminant, that culture was considered negative. If a blood culture was a "possible contaminant," but antibiotics were continued because of uncertainty, that culture was considered positive.

Data Analysis

Data were analyzed by using nonparametric receiver operating characteristic (ROC) curves that were plotted by connecting cut points generated from the corresponding specificity and sensitivity. The area under the curve (AUC) was computed by the trapezoidal rule. From this analysis, we were able to determine sensitivities and

specificities at different procalcitonin cutoff points. Comparability of demographics and results between bacteremic and nonbacteremic groups was assessed by using χ^2 tests for categorical variables and independent sample *t* tests for continuous variables. Statistical significance was assessed at the level of $\alpha = .05$.

RESULTS

A total of 523 patients and > 2500 procalcitonin values were reviewed for eligibility. Of these, 169 (47%) patients and 335 blood cultures with procalcitonin were included in the study (Table 1). Of the 335 included blood cultures, 188 (56%) were from male patients with a mean age of 5 years (14 days–23 years), and there were 94 (28%) positive bacterial blood cultures. Of the bacteremic cultures, 50 (53%) were from male patients with a mean age of 5.8 years (14 days–23 years). Of the nonbacteremic cultures, 138 (57%) were from male patients with a mean age of 4.7 years (15 days–23 years). In reviewing the primary diagnoses of all patient cultures, 132 (39%) had intestinal failure, 121 (36%) had heart disease, 23 (7%) had cancer, 16 (5%) had liver transplant, and 43 (13%) had other diagnoses, including renal failure on

TABLE 1 Patient Demographics and Results

	Total	Bacteremic	Nonbacteremic	<i>P</i>
Patients	169	—	—	—
Cultures	335	94 (28%)	241 (72%)	<.001
Patient age, mean	5 y (range 14 d–23 y)	5.8 y (SD 5.7)	4.7 y (SD 5.3)	.447
Sex, <i>n</i> (%)				.502
Female	147 (44)	44 (47)	103 (43)	
Male	188 (56)	50 (53)	138 (57)	
Primary service for cultures, <i>n</i> (%)				<.001
GI	156 (47)	69 (73)	87 (36)	
Cardiology	122 (36)	16 (17)	106 (44)	
PICU	32 (10)	3 (3)	29 (12)	
Oncology	16 (5)	5 (5)	11 (5)	
Other	9 (3)	1 (2)	8 (3)	
Primary diagnosis for cultures, <i>n</i> (%)				<.001
Intestinal failure	132 (39)	68 (72)	64 (27)	
Heart disease	121 (36)	14 (15)	107 (44)	
Cancer	23 (7)	5 (5)	18 (7)	
Liver transplant	16 (5)	4 (4)	12 (5)	
Other	43 (13)	3 (4)	40 (17)	
Procalcitonin, ng/mL	—	0.1–161	0.1–23.1	<.001
Mean	—	9.96 ± 15.96	1.23 ± 10.37	
Median (IQR)	—	4.85 (IQR 18.5)	0.3 (IQR 0.7)	

In bacteremic cultures, the median procalcitonin level was 4.85 ng/mL (IQR 18.5). In nonbacteremic cultures, the median procalcitonin level was 0.3 ng/mL (IQR 0.7). —, not applicable.

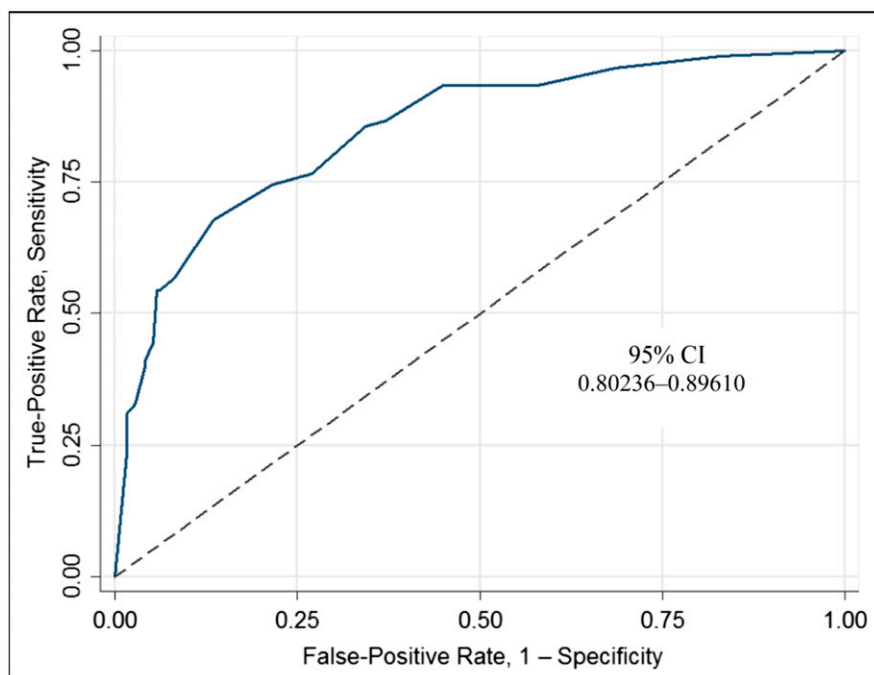


FIGURE 2 ROC analysis revealed a procalcitonin level of ≥ 0.6 ng/mL as the best cutoff point that produced a sensitivity of 85.6% and a specificity of 65.7% (AUC 0.85).

DISCUSSION

Judicious use of antibiotics is a top public health priority (especially for children with a CVC) for which the current standard care for any fever is often 48-hour inpatient treatment with broad-spectrum antibiotics, even if suspicion of CLABSI is low. There is an urgent need to discover a new biomarker to accurately detect CLABSI in this patient population. Previous studies have revealed that procalcitonin levels are elevated in bacterial sepsis but not in viral infections.^{4–6} There have been many studies in which procalcitonin and its role in bacterial infections have been evaluated, but this study is the largest longitudinal cohort study on procalcitonin in children with a CVC with retrospective and prospectively monitored samples. Data from this study reveal that procalcitonin has a high sensitivity in detecting bacteremia in children with a CVC and fever and therefore has the potential to be a useful prognostic test to inform clinical decision-making. When used as part of a clinical decision-making algorithm, procalcitonin has the potential to prevent or reduce unnecessary use of antibiotics, unnecessary lengths of hospital stay, and unnecessary costs of care in this vulnerable pediatric population.

Although this study indicates that procalcitonin is a sensitive marker for bacteremia, given the severity of untreated bacteremia, a false-negative result of procalcitonin could have serious consequences. Therefore, procalcitonin should always be used in conjunction with other clinical variables, such as vital signs, infectious risk factors, and physical examination. In high-risk patient populations, particularly children with a central line, sensitivity should be maximized because of the consequences of not treating patients with bacteremia who may have a false-negative procalcitonin result. This is especially important given that some patients in this study had a low procalcitonin level (by using a cutoff of <0.6 ng/mL) yet were found to be bacteremic (false-negative procalcitonin result; Table 2). In this study, 72% of all bacteremic cultures were from patients with intestinal failure; however, these

TABLE 2 Patients With False-positive and False-negative Procalcitonin Values by Using 0.6 ng/mL as the Cutoff

	False-positive Procalcitonin (Procalcitonin Level of ≥ 0.6 ng/mL With Negative Blood Culture)	False-negative Procalcitonin (Procalcitonin Level of < 0.6 ng/mL With Positive Blood Culture)
Cultures	85 of 243 negative cultures	17 of 94 positive cultures
Patient age, range (mean)	20 d–23 y (4.3 y)	4 mo–23 y (4 y)
Sex, <i>n</i> (%)		
Female	38 (45)	5 (30)
Male	47 (55)	12 (70)
Primary diagnosis (cultures), <i>n</i> (%)		
Heart disease	47 (56)	1 (6)
Intestinal failure	13 (15)	16 (94)
Cancer	7 (8)	—
Liver transplant	7 (8)	—
Other	11 (13)	—

—, not applicable.

patients made up 94% of the false-negative procalcitonin values. Although the reason for this cannot be determined by this study, 1 potential explanation could be that patients from this institution's intestinal rehabilitation center are repeatedly counseled to go to the emergency department the moment any fever is suspected or measured, so there may not have been adequate time for procalcitonin levels to rise despite the presence of bacteremia. Again, further studies are needed to evaluate the time-to-rise of procalcitonin. Conversely, many patients in this study had an elevated procalcitonin level (by using a cutoff of ≥ 0.6 ng/mL) but a negative blood culture (false-positive procalcitonin result). Of all the nonbacteremic cultures, 44% were from

patients with heart disease. However, patients with heart failure made up 56% of the false-positive procalcitonin results. The reason for this cannot be determined by this study, but this does raise the question of whether higher levels of procalcitonin are found in certain patient populations, such as those with heart failure, without bacteremia. Whether providers maximize sensitivity or specificity would vary depending on multiple factors, and we have included a table of additional cutoffs that maximize both sensitivity and specificity (Supplemental Table 4).

Although procalcitonin should not be used alone to predict bacteremia, it may be a useful tool as part of a larger clinical decision algorithm. When used along with other markers of inflammation, such as CRP,

ESR, and white blood cell count, procalcitonin may be able to help determine the likelihood of a central-line infection and aid in the decision to empirically treat with antibiotics versus observation alone or even to decrease antibiotic duration. Despite its limitations, procalcitonin has the potential to play an important role in reducing empirical antibiotic treatment and length of hospital stay in otherwise well-appearing patients who are admitted with a “rule-out” central-line infection.

This study has several limitations. Cases were reviewed retrospectively, so data rely on the accuracy of clinical documentation by care teams. A large percentage of patients included in this study were also hospitalized, so many patients had blood cultures and procalcitonin drawn quickly after fever developed. This may have led to normal procalcitonin values in patients with bacteremia because of inadequate time for procalcitonin levels to become elevated despite the presence of a bacterial infection. This patient population in this study was also heterogenous, including patients who were immunosuppressed; however, studies have revealed that procalcitonin is still an accurate marker even in the setting of neutropenia. In a study by Koivula et al,⁶ the authors evaluated procalcitonin in patients with febrile neutropenia and found that the kinetics of procalcitonin and CRP were similar, concluding that an elevated procalcitonin level within 24 hours after the onset of neutropenic fever predicts bacteremia in hematologic patients. In a study in which the authors evaluated procalcitonin as a marker of bacteremia in children with a CVC and fever, Kasem et al¹ also included patients with neutropenia. In this study, 27 patients (44%) had neutropenia, and blood cultures were positive in 4 of these patients. The mean procalcitonin value in these patients with neutropenia and bacteremia was 19.16 ng/mL, compared with 0.65 ng/mL in those with negative cultures. There was no significant difference when compared with the entire group, which revealed a mean procalcitonin level of 18.47 ng/mL in patients with bacteremia, compared with 0.65 ng/mL in patients without bacteremia.

TABLE 3 Subanalysis of GI Patients With a Central Line and Intestinal Failure

	Total	Bacteremic	Nonbacteremic	<i>P</i>
Cultures, <i>n</i> (%)	132	68 (52)	64 (48)	$< .001$
Patient age, y, mean (SD)	5.44 (4.79)	5.8 (5.44)	5.0 (4.0)	.299
Sex, <i>n</i> (%)				.448
Female	56 (42)	31 (46)	25 (39)	
Male	76 (58)	37 (54)	39 (61)	
Procalcitonin, ng/mL	—	0.1–161	0.1–8.1	$< .001$
Mean	—	11.29 \pm 21.2	0.50 \pm 1.1	
Median (IQR)	—	4.95 (0.6–19.5)	0.22 (IQR 0.1–0.5)	

In bacteremic cultures, the median procalcitonin level was 11.29 ng/mL (IQR 0.6–19.5). In nonbacteremic cultures, the median procalcitonin level was 0.5 ng/mL (IQR 0.1–0.5).

Another potential limitation of this study is that many patients were complex hospitalized patients with multiple comorbidities. Although charts were thoroughly reviewed to exclude possible confounding variables, it is impossible to account for all potential factors that may affect procalcitonin levels in these complex patients. A prospective study would be extremely valuable to help account for some of these variables, including, for example, precise timing of laboratory test draws compared to onset of fever. Another limitation of this study is the lack of comparison with other commonly used biomarkers, such as CRP, ESR, and white blood cell count. It would be useful to include comparison groups with these other commonly used biomarkers in future studies. Another limitation to this study is the use of procalcitonin as an add-on laboratory test. In this study, although there were few patients who had procalcitonin as an add-on laboratory test, it is unclear if there could have been protein degradation of procalcitonin that could have altered the result. It is important to note that our aim for this study was to evaluate the diagnostic accuracy of procalcitonin in predicting bacteremia, not fungal infections. Our study had 9 blood cultures that grew yeast, and these were considered negative for bacteria. In this small number of cases, we found that procalcitonin levels were not significantly elevated in patients whose blood cultures only grew yeast.

Although this study has limitations, it is the largest study to date in which procalcitonin was examined as a predictive marker of bacteremia in pediatric patients with a CVC and fever. This study also includes children from multiple subspecialties in both outpatient and inpatient settings. Despite heterogeneity in the patient population, this study has good homogeneity in laboratory results because the vast majority of blood cultures and procalcitonin values were run

in the same hospital laboratory, decreasing potential errors due to differences in laboratory assays.

CONCLUSIONS

Procalcitonin is a sensitive biomarker in predicting bacteremia in children with a central line and fever. Obtaining a screening of procalcitonin levels at the time of suspected central-line infection appears to have clinical utility and has potential to be useful as part of a clinical decision tree in children with a central line and fever. This could lead to decreased use of empirical antibiotics and shorter length of hospital stay.

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