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Repeating Blood Cultures in Neutropenic Children with Persistent Fevers When the Initial Blood Culture is Negative

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Abstract

Background—Febrile neutropenia is a common reason for the hospitalization of pediatric oncology patients. The initiation of antibiotics and the overall decline in rates of bacteremia, would predict a low yield of detection of bacteremia in repeated blood cultures. Despite little evidence supporting the utility of serial cultures, repeat culturing with fever persists.

Procedure—To determine the rate of follow-up blood culture growth when the initial blood culture showed no bacterial growth and patient risk factors for this occurrence, we reviewed the records of oncology patients admitted to the Children's Hospital at Montefiore Pediatric Hematology/Oncology service for febrile neutropenia from 2004-2009.

Results—We identified 457 febrile neutropenia episodes in 137 patients. The initial blood culture was positive in 84 episodes (18.4%). In 220 episodes comprising 105 patients, the initial blood culture was negative and a subsequent culture was obtained. In 24 episodes (10.9%), bacterial growth was detected in the repeat culture. Risk factors included a previous history of bacteremia and hospitalization for more than 48 hours prior to onset of fever.

Conclusions—In patients with febrile neutropenia, bacteremia is detected nearly twice as frequently in initial blood cultures than in repeat blood cultures obtained when the initial blood culture is negative. Despite an initial negative blood culture, bacteremia can be detected in more than 10% of episodes when a repeat blood culture is obtained. The risk more than doubles for patients with a previous history of bacteremia or hospitalized for more than 48 hours prior to the onset of fever.

Keywords

Febrile neutropenia; bacteremia; blood culture

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Conflict of Interest: Nothing to declare.

Introduction

The aggressive management of febrile neutropenia in children has decreased the mortality rate from more than 20% to 0.7-3%.[1-3] In recent adult and pediatric studies, 10 to 24% of patients have been found to be bacteremic, and the importance of empiric broad spectrum antibiotics for febrile neutropenia is well established.[4-6] However, there are little data to guide the continued monitoring of these patients for infection. The most recent Infectious Disease Society of America (IDSA) febrile neutropenia guidelines recommend that blood cultures be obtained twice daily for three days and then only for clinical changes in the persistently febrile patient.[7] In adults, studies looking at repetitive blood culturing of febrile bone marrow transplant patients and febrile patients in a surgical ICU showed no benefit to repeating blood cultures in the face of negative cultures.[8, 9] The validity of this recommendation in the pediatric population has not been assessed.

We examined the rate of detection of bacteremia in subsequent blood cultures when the initial blood culture was negative in pediatric febrile neutropenic patients.

Methods

Episode Identification

The patient database for the Children's Hospital at Montefiore from January 2004-December 2009 was reviewed for oncology patients discharged by the Pediatric Hematology/Oncology service with diagnoses related to febrile neutropenia. All patients being treated for a pediatric malignancy, regardless of age, were considered eligible for this study. Stem cell transplant patients were not included in this analysis. All records were manually reviewed to confirm the oncologic diagnosis and that an episode of febrile neutropenia had occurred during that admission. An episode of febrile neutropenia was defined as a febrile episode (temperature of $>38.3^{\circ}\text{C}$ once or $>38^{\circ}\text{C}$ twice within a 24 hour period, either by parental report or documented in the medical record) while a patient was neutropenic (absolute neutrophil count (ANC) <500 or $<1,000$ and decreasing) when the patient had been afebrile for the preceding 96 hours during which a blood culture was obtained. For purposes of analysis, each episode of febrile neutropenia concluded when either (1) a positive blood culture was obtained, (2) the ANC rose above 500 on its way to over 1,000 and the patient was afebrile or (3) the patient defervesced for 96 hours.

Patient data collected included age, gender, diagnosis, history of bacteremia, and type of vascular access. Episode data included the total number of blood cultures obtained during the episode, whether the patient had been in the hospital for greater than 48 hours prior to the onset of fever (as a marker for nosocomial infection), the duration of neutropenia (whether the patient was on antibiotics or antifungals at the start of the febrile episode) and the organism identified following the National Health Safety Network definition for skin contaminants in the setting of central line associated bloodstream infections.

This study was initially conceived as a quality improvement project and received approval from the Montefiore Medical Center Quality Assurance committee. Following completion of

the QI project, the Montefiore Medical Center Institutional Review Board determined that specific IRB approval was not necessary.

Patient Management

Upon presentation for an episode of febrile neutropenia, ambulatory patients were admitted to the hospital and had one blood culture drawn from every lumen of indwelling catheters using sterile technique as per guidelines from the Oncology Nursing Society;^[10] peripheral blood cultures were not routinely obtained. Patients received cefepime initially, plus therapy targeted toward a particular symptom or focus of infection (e.g., vancomycin for suspected skin infection). Patients with fevers persisting for 48 hours and no identifiable source of infection had their therapy broadened with vancomycin. Patients persistently febrile for five days received parenteral antifungal therapy with either an amphotericin formulation or micafungin. As per manufacturer guidelines, patients had 0.5-5 ml drawn for blood cultures drawn from every catheter lumen on every day of fever or based on determination of the treating clinician. Blood was cultured in BACTEC PEDS PLUS/F (Becton Dickinson, Franklin Lakes, NJ) blood culture bottles and incubated in a continuously monitored incubator (BACTEC 9240 Blood Culture System, Becton Dickinson, Franklin Lakes, NJ) for at least five days (longer if endocarditis or fungal infection was suspected). Patients who were already hospitalized when they developed an episode of febrile neutropenia had the same evaluation and management.

Statistical Analysis

For febrile neutropenic subjects with an initial negative blood culture, we determined the proportion of episodes where a subsequent positive blood culture during the febrile episode was obtained and estimated the 95% confidence intervals. Frequency tables were used to explore the association of a positive blood culture with patient characteristics and clinical variables. To identify the risk factors of a positive blood culture following an initial negative blood culture and take into account the correlation in data from the same patient, generalized estimating equations (GEE) analysis was conducted with SAS procedure PROC GENMOD using an independent working correlation matrix. All factors that demonstrated a p-value less than 0.2 in initial bivariate GEE analyses with positive blood culture as the outcome were considered as potential predictor variables in the multivariable GEE model. The final multivariable GEE model included only those variables that remained significant at the $p < 0.05$ level.

Results

Episodes of Febrile Neutropenia

During the study period, 137 patients had 457 episodes of febrile neutropenia during the study period. In 84 episodes (18.4% of all episodes, 95% confidence interval=(15%, 22.3%)), bacteria were isolated from the initial blood culture. Of these, 14 became positive after more than 24 hours. Although some of these patients had a repeat blood culture obtained prior to the initial blood culture returning as positive, these 14 episodes were not included in subsequent analyses. There were 220 episodes of febrile neutropenia involving 105 patients where the initial blood culture was negative and had additional blood cultures

obtained. The patient characteristics of these 105 patients are given in Table I. As all patients receiving therapy for a pediatric malignancy were included, 16 episodes occurred in patients over 21. In none of these cases was a positive blood culture on repeat culture when the initial blood culture was negative.

In 24 of the 220 episodes where the initial blood culture was negative (10.9%, 95% confidence interval=(7.3%, 16%)), bacterial growth was detected in a follow-up blood culture. Bacterial growth was detected in the second through ninth blood cultures obtained between days two and nine (Figure 1). Combining episodes where the initial blood culture was positive with episodes where the initial blood culture was negative and a positive blood culture was obtained subsequently, positive blood cultures were obtained in 108 of the total 457 episodes (23.6%).

Risk Factors for Bacterial Growth in Follow Up Blood Cultures

We reviewed patient charts to evaluate for risk factors for a patient having an episode of febrile neutropenia where bacteremia was not detected on the initial blood culture but was detected on a follow up blood culture. In bivariate analysis, several risk factors were identified. Patients with longer durations of neutropenia, having an episode of febrile neutropenia start after being hospitalized for more than 48 hours, being on an antifungal medication at the start of fever, or having a prior episode of bacteremia (a prior history of a positive blood culture before the present episode of febrile neutropenia) were more likely to have a positive blood culture following an initial negative culture (Table II). In multivariable analysis, a history of a prior episode of bacteremia (OR=2.77, 95% confidence interval = (1.04, 7.37)) and being hospitalized for more than 48 hours at the outset of the episode of febrile neutropenia (OR=3.38, 95% confidence interval=(1.45, 7.87)) remained significant risk factors.

Patients with a prior history of bacteremia were further evaluated. Since most bacterial infections can be cleared from a central venous catheter,[11] 10 of 12 patients with negative initial but positive subsequent blood cultures and history of prior bacteremia retained their catheter. Of these 10 patients who retained a catheter after a previous infection, 8 grew coagulase negative staphylococcus. Based on antibiotic resistance patterns, in 3 of these cases the same organism that previously had infected the catheter was detected at a subsequent febrile episode. In each of these 3 cases, the patients previously received appropriate antibiotics, which had been completed prior to the subsequently detected bacteremia. Although many patients retained the same catheter that had previously been infected, the continued presence of the catheter was not associated with an increased risk of having bacteremia detected on a follow up blood culture when the initial blood culture was negative (Table II).

The initial, empiric management of febrile neutropenia with an antipseudomonal beta lactam likely changed the rate of detection of bacteremia and the types of organisms detected in follow up blood cultures (Table III). While many Gram negative bacteria were detected on day one of febrile neutropenia, in only a single follow up episode was a Gram negative bacteria detected. Gram positive organisms detected on follow up blood culture tended to be

less pathogenic than those Gram positive organisms detected on day one of febrile neutropenia.

Discussion

Given the limited evidence in the pediatric population to support the IDSA febrile neutropenia guidelines, we evaluated the utility of serial blood cultures in pediatric cancer patients with febrile neutropenia.

The overall rate of bacteremia of 23.6% at our institution is within the range reported in the literature. Our review of 220 episodes of febrile neutropenia with negative initial blood culture found that in 24 episodes bacteremia was detected by follow up blood cultures. As would be expected with aggressive management of febrile neutropenia, many more bacterial infections were detected on the initial blood culture than in follow up blood cultures. The initiation of antibiotics would predict a low yield of detection of bacteremia in follow up cultures. However, the 10.9% rate (24/220 cases) of bacterial detection on subsequent cultures is clinically significant.

It is unclear what ideal number of blood cultures should be sampled in an effort to avoid missing a true bacteremia. In adult non-oncology patients 2 to 4 blood cultures obtained within a 24 hour period were necessary to detect 99% of bacteremias.[12-14] The optimal number of blood cultures necessary to detect 99% of bacteremic episodes in children with febrile neutropenia is unknown. As some institutions only perform a single set of blood cultures daily in the pediatric population (counter to the IDSA recommendations), it is likely that not all episodes of bacteremia are detected within the first day of fever. In the current study, bacterial growth was detected on blood cultures obtained between days two and nine despite an initial negative blood culture.

The continuing risk of infection during a period of neutropenia is known. Pizzo et al. showed that the occurrence of multiple episodes of fever separated by several days is a risk during long periods of neutropenia and that these patients retain risk of infection.[15] In our study population, patients who had an episode of febrile neutropenia remained hospitalized until neutropenia resolved, even if they had been afebrile for several days. This policy may have masked the independent effect of duration of neutropenia itself.

Most studies of children with febrile neutropenia focus on patient characteristics during the episode being studied. [4, 5, 16-19] A prior history of bacteremia has been found to be a risk factor for further episodes of bacteremia, but no distinction was made whether the subsequent episodes of bacteremia were detected on initial blood culture or after an initial blood culture was negative.[20] We found that a prior history of bacteremia was a risk factor for having a positive serial blood culture when the initial blood culture was negative. This effect was independent of retention of the previously infected catheter.

This study has several limitations. First, this is a retrospective, single institution study and the overall bacteremia rate identified in this population is toward the upper limit of published reports. Importantly, we cannot distinguish between episodes where the initial negative blood culture was a false negative, ie., the patient did indeed have a bacterial

infection that was not detected by this blood culture, and where the bacterial infection occurred subsequent to the blood culture obtained at the start of the episode of febrile neutropenia. With the increased duration of blood culturing, some infections not present on admission likely were detected in our patient population. Additionally, as the repetition of blood cultures was dependent on the clinical judgment of the treating physician, selection of only those patients who had a higher likelihood of having bacteremia may have occurred. Prospective research is necessary to determine the optimal number of blood cultures necessary.

Furthermore, the ability to detect bacterial growth is partially dependent on the volume of the inoculum and on the volume of blood submitted for culture. As Gaur *et al* showed, varying the volume of blood obtained for blood culture by patient weight improves the ability to detect bacteremia.[21] In our institution, all patients had the same range of blood volumes inoculated into a blood culture bottle and this may have contributed to the failure to detect bacterial infection at the onset of bacterial infection. However, manufacturer guidelines were followed for the specific culture system used.

Prior studies provide limited information regarding frequency of blood culture sampling. Modern blood culturing systems are able to detect bacterial growth more rapidly and with greater sensitivity, even in patients who are receiving antibiotics.[22] However, it is important to note that even in the setting of multiple negative blood cultures, bacterial infections may still be detected with further sampling. Over the past decades, many groups have attempted to identify candidates for less aggressive management of febrile neutropenia, including discharging patients prior to the resolution of neutropenia[11] or fever.[23] Others have proposed the use of oral antibiotics.[3, 24]

In conclusion, a prior history of bacteremia and hospitalization for more than 48 hours prior to the onset of fever were associated with an increased risk of subsequent blood culture positivity even when the initial blood culture was negative. The identification of positive blood cultures after several days of broad spectrum antibiotics in this patient cohort should lead to further research regarding the timing and appropriateness of any de-escalation in monitoring or therapy. Repeating blood cultures, even when several blood cultures have been negative, may identify patients with serious bacterial infections and allow for earlier targeted therapy of these infections.

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Table I
Patient Demographics for Patients with Negative Initial Blood Cultures who had Repeat Blood Cultures (n=105)

Age (years)	
Median	9
Range	0.5-27
Gender (n, %)	
Male	54 (51.4%)
Female	51 (48.6%)
Duration of Neutropenia ^a (days)	
Median	6
Range	2-89
Number of Blood Cultures	
Median	4
Range	2-27
Diagnosis (n, %)	
Leukemia/Lymphoma	54 (51.4%)
ALL	37
AML	11
Lymphoma	6
Solid tumor	51 (48.6%)
Osteosarcoma	15
Neuroblastoma	6
Rhabdomyosarcoma	8
Ewing sarcoma/PNET	4
Medulloblastoma	4
Brain tumor ^b	3
Other solid tumor ^c	11

^a Neutropenia defined as ANC <500 or less than 1,000 on its way to falling to <500;

^b Glioblastoma multiforme (1), atypical teratoid/rhabdoid tumor (1), low grade glioma (1)

^c Chondrosarcoma (2), hepatoblastoma (1), embryonal sarcoma of liver (1), epithelioid sarcoma (1), infantile fibrosarcoma (1), malignant fibrous histiocytoma (2), undifferentiated sarcoma (1), synovial sarcoma (1), desmoplastic small round cell tumor (1)

Table II
Bivariate Analysis of Risk Factors for Detection of Bacterial Growth When the Initial Blood Culture is Negative (n=220)

	Follow up Blood Culture Result		p-value
	Negative (n=196)	Positive (n=24)	
Age (years)	9.97±6.82	12.04±5.60	0.1736
Diagnosis			0.7022
Leukemia/Lymphoma	89 (88.1%)	12 (11.9%)	
Solid	107 (90%)	12 (10%)	
Duration of neutropenia (days)	9.12±9.25	16.54±20.65	0.0051
Gender			0.1710
Male	100 (86.2%)	16 (13.8%)	
Female	96 (92.3%)	8 (7.7%)	
Catheter Type			N/A
Peripheral IV	11 (100%)	0 (0%)	
External (tunneled and nontunneled)	110 (89.4%)	13 (10.6%)	
Internal (Port-A-Cath)	75 (87.2%)	11 (12.8%)	
History of Positive Blood Culture			0.0299
No	147 (92.5%)	12 (7.5%)	
Yes	49 (80.3%)	12 (19.7%)	
Current catheter ever bacteremic			0.0677
No	154 (91.7%)	14 (8.3%)	
Yes	41 (80.4%)	10 (19.6%)	
Nosocomial			0.0018
No	159 (92.4%)	13 (7.6%)	
Yes	37 (77.1%)	11 (22.9%)	
Already on antibiotics at onset of episode of febrile neutropenia			0.1398
No	174 (90.2%)	19 (9.8%)	
Yes	22 (81.5%)	5 (18.5%)	
Cefepime			0.1937
No	178 (89.9%)	20 (10.1%)	
Yes	18 (81.8%)	4 (18.1%)	
Vancomycin			0.5071
No	186 (89.4%)	22 (10.6%)	
Yes	10 (83.3%)	2 (16.7%)	
Aminoglycoside			0.2283
No	193 (89.4%)	23 (10.6%)	
Yes	3 (75%)	1 (25%)	
Other			0.4198
No	192 (89.3%)	23 (10.7%)	

	Follow up Blood Culture Result		p-value
	Negative (n=196)	Positive (n=24)	
Yes	4 (80%)	1 (20%)	
Already on antifungals at onset of episode of febrile neutropenia			0.0326
No	181 (91%)	18 (9%)	
Yes	15 (28.6%)	6 (71.4%)	
Amphotericin			N/A
No	196 (89.5%)	23 (10.5%)	
Yes	0 (0%)	1 (100%)	
Micafungin			N/A
No	196 (89.9%)	22 (10.1%)	
Yes	0 (0%)	2 (100%)	
Fluconazole			N/A
No	190 (88.8%)	24 (11.2%)	
Yes	6 (100%)	0 (0%)	
Voriconazole			N/A
No	187 (89.9%)	21 (10.1%)	
Yes	9 (75%)	3 (25%)	

Table III
Isolated Pathogens on Initial and Repeat Blood Culture

	Initial Blood Culture n=84 ^a	Repeat Blood Culture n=24	p-value
Gram positive	57 (73.1%)	21 (26.9%)	0.08
<i>Bacillus</i> species	4	3	
Coagulase negative <i>staphylococcus</i>	32	15	
<i>Enterococcus</i> species	1	2	
<i>Micrococcus</i> species	2	1	
<i>Streptococcus</i> species	10	0	
<i>Staphylococcus aureus</i>	6	0	
<i>Gemella</i> species	2	0	
Gram negative	32 (97%)	1 (3%)	0.005
<i>Acinetobacter baumannii</i>	1	0	
<i>Escherichia coli</i>	16	0	
<i>Enterobacter cloacae</i>	3	0	
<i>Klebsiella pneumoniae</i>	6	0	
<i>Moraxella catarrhalis</i>	1	0	
<i>Pseudomonas aeruginosa</i>	5	0	
<i>Stenotrophomonas maltophilia</i>	0	1	
Fungal	1 (33.3%)	2 (66.6%)	0.11
<i>Candida</i> species	1	2	
Polymicrobial	6 (100%)	0 (0%)	N/A

^aThe number of bacterial isolates exceeds the number of positive blood cultures because multiple organisms were detected in some blood cultures