Epidemiology of Blood Culture Utilization in a Cohort of Critically Ill Children

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Abstract

Blood culture acquisition is integral in the assessment of patients with sepsis, though there exists a lack of clarity relating to clinical states that warrant acquisition. We investigated the clinical status of critically ill children in the timeframe proximate to acquisition of blood cultures. The associated rates of systemic inflammatory response syndrome (72%) and sepsis (57%) with blood culture acquisition were relatively low suggesting a potential overutilization of blood cultures. Efforts are needed to improve decision making at the time that acquisition of blood cultures is under consideration and promote percutaneous blood draws over indwelling lines.

Keywords
- sepsis
- blood culture
- pediatric intensive care units

Introduction

Sepsis remains a major cause of morbidity and mortality in children.[1–3] Blood culture acquisition is integral in the assessment of patients with sepsis as it may identify the cause and aid in the targeting of appropriate antimicrobial therapy. Among pediatric practitioners, however, there still exists a lack of clarity relating to clinical states that warrant acquisition of blood cultures as no standards or guidelines exist.[4]

The evaluation of sepsis in the pediatric intensive care unit (PICU) continues to be a difficult balancing act. Delay in the recognition and treatment of patients at risk of sepsis can be catastrophic. Critically ill children, while vulnerable to the development of sepsis, may also exhibit features of disordered physiology from noninfectious causes. Blood culture acquisition in patients at lower risk of sepsis may lead to over treatment with antibiotics, which is associated with adverse drug reactions, predisposition to secondary infections (e.g., *Clostridium difficile*), and emergence and selection of drug-resistant organisms.[5] We sought to investigate the clinical status of critically ill children in the timeframe proximate to acquisition of blood cultures.

Methods

The Institutional Review Board at the University of Virginia School of Medicine approved this study. We conducted a retrospective database review to identify all blood cultures obtained in patients admitted to the PICU, a 17-bed combined cardiac and medical/surgical unit, from November 2013 to May 2016 at the University of Virginia Children's Hospital, an academic, tertiary-care center. Cultures obtained from patients receiving extracorporeal life support were excluded.

Review of the electronic medical record was conducted to assess patient clinical status in the timeframe proximate to culturing. We employed the 2005 International Pediatric Sepsis Consensus Conference definitions to establish clinical conditions including systemic inflammatory response syndrome (SIRS), sepsis, and organ dysfunction.[6] The criteria for

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a diagnosis of sepsis include (1) presence of SIRS and (2) suspected or proven invasive infection, including administration of parenteral antibiotics and acquisition of blood cultures.[6] The presence of SIRS was established if the patient met criteria in the 12-hour time window prior to blood culture acquisition.[7] Suspected or proven invasive infection was established if the patient received parenteral antibiotics within 6 hours of blood culture acquisition. We performed a sensitivity analysis on the duration of time between blood culture acquisition and receipt of parenteral antibiotics to assess if increasing to a 12-hour time window impacted the rate of sepsis. It is the practice at our institution to initiate a combination of vancomycin and cefepime or piperacillin/tazobactam when sepsis is suspected in a PICU patient. Organ dysfunction was established if the patient met criteria in the 12-hour time window prior to blood culture acquisition or in the subsequent 12-hour time window.[8] Demographic and clinical data were abstracted from the electronic medical record. If obtained, serum lactate, C-reactive protein, and base deficit values were recorded for the 12-hour time window prior to blood culture or in the subsequent 24-hour time window, employing the value most proximate to blood culture acquisition if multiple samples were obtained.

Continuous variables were compared using Student's *t*-test or Wilcoxon rank sum test as appropriate. Normality of continuous variables was assessed using Shapiro–Wilk testing. Categorical variables were compared using chi-square or Fisher's Exact test as appropriate. The area under the receiver operating characteristic curve was assessed to evaluate the discriminatory abilities of variables for the outcome of culture positivity. Type-one error was set at 0.05. All calculations were performed using Stata/IC 12.1 (Stata Corporation, College Station, Texas, United States).

Results

There were 1,109 blood cultures obtained in 255 unique patients during the period of study representing 10.2 cultures per 100 patient days. Demographic and basic clinical characteristics of the patients are displayed in ►**Table 1**. The sites of blood culture acquisition included central venous lines (44% of cultures drawn), percutaneous draws (31%), arterial lines (17%), and peripherally inserted central catheters (8%). After accounting for simultaneous culturing from multiple sites at one point in time (e.g., simultaneous acquisition from central venous line and percutaneous draw), there were 931 total blood culture events. Of these events, 443 (48%) occurred within 7 days following a previous culture acquisition in a unique patient. Eighty-one percent of events were associated with receipt of parenteral antibiotics. Fifty-seven events (6%) occurred in patients < 29 days of age at time of blood culture acquisition.

There were 672 events (72%) and 532 events (57%) in patients that met SIRS and sepsis criteria, respectively. The most common SIRS criteria attained were temperature (core temperature of > 38.5°C or < 36°C) in 550 events (59%) and respiratory rate in 784 events (84%). An additional 63 cultures were obtained in patients with a core temperature between 38.0 and 38.5°C. Thus, 34% of blood culture events were associated with a "normal" core temperature of 36.0 to 37.9°C. Of the 140 events meeting SIRS criteria but not sepsis, extending the time window of receipt of parenteral antibiotics from 6 to 12 hours would have yielded only eight more (6%) sepsis events. We compared clinical characteristics of the events stratified by SIRS and sepsis (►**Table 2**).

Table 1 Patient demographic and clinical characteristics

Characteristic	Number (%) ($n = 255$)
Age on admission (months)	12 (IQR, 2–90)
Male sex	138 (54%)
Admission diagnosis	
Congenital heart disease	93 (36%)
Lower respiratory tract infection	28 (11%)
Neurological	21 (8%)
Trauma/poisoning	21 (8%)
Sepsis	18 (7%)
Acquired heart disease	17 (7%)
Oncological	13 (5%)
Aspiration	5 (1.5%)
Endocarditis	4 (1.5%)
Other	39 (15%)
Hospital LOS (days)	21 (IQR, 8–44)
Central venous catheter	137 (54%)
Case fatality	45 (18%)

Abbreviations: IQR, interquartile range; LOS, length of stay.

Table 2 Event characteristics stratified by clinical state

Characteristics	No SIRS ($n = 259$)	SIRS ($n = 672$)	Sepsis ($n = 532$)
Culture positive	16 (6%)	44 (7%)	35 (7%)
SIRS heart rate	73 (28%)	371 (55%)	302 (57%)
SIRS respiratory rate	160 (62%)	624 (93%)	496 (93%)
SIRS temperature	28 (11%)	522 (78%)	405 (76%)
SIRS WBC	29 (11%)	380 (57%)	322 (61%)
Vasoactive use	66 (25%)	148 (22%)	124 (23%)
Severe sepsis	0	185 (28%)	185 (35%)
CV dysfunction	70 (27%)	190 (28%)	165 (31%)
Respiratory dysfunction	214 (83%)	441 (66%)	346 (65%)
Hematologic dysfunction	26 (10%)	56 (8%)	52 (10%)
Renal dysfunction	14 (5%)	44 (7%)	37 (7%)
Hepatic dysfunction	2 (1%)	15 (2%)	12 (2%)

Abbreviations: CV, cardiovascular; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

There were 60 blood culture events (6%) that were positive for bacterial growth. There were no differences in culture positivity based on the presence or absence of SIRS or sepsis. The site of blood culture acquisition was not associated with culture positivity. Five-hundred-ninety patients (63%) received antibiotics prior to blood culture acquisition, though this was not associated with culture positivity or negativity. Antibiotics had been administered prior to 39 of the 60 positive blood culture events (65%). Upon review of the positive cultures, seven (12%) were considered contaminated. Leukocytosis or leukopenia by SIRS criteria was associated with culture positivity ($p = 0.03$), but was neither sensitive (69%) nor specific (47%) and had poor discrimination (area under the receiver operating characteristic curve = 0.6037). Serum lactate was obtained proximate to 561 events (60%), and an elevated level was associated with culture positivity ($p = 0.004$). Serum lactate values > 2.4 mmol/L provided a sensitivity of 64% and specificity of 61% for culture positivity yet, overall, had poor discrimination (area under the receiver operating characteristic curve = 0.6385). Of the 871 culture negative events, 36 (4%) were positive for infectious agents from other sources at the time of blood culture acquisition (urine [24], cerebrospinal fluid [1], respiratory virus [11]).

The incidence of respiratory dysfunction, irrespective of SIRS or sepsis diagnosis, was high (70%) proximate to the time of the blood culture event. There were no differences in serum lactate, C-reactive protein, or base deficit obtained proximate to blood culture events based on sepsis diagnosis.

Discussion

Analysis of our results suggests a potential overutilization of blood cultures as evidenced by a considerable number of events occurring in the absence of SIRS or sepsis. The acquisition of blood cultures in patients without SIRS or sepsis may have contributed to an overtreatment of low-risk patients with parenteral antibiotics.

Providers are faced with several difficult decisions on a daily basis in the care of critically ill children. On the one hand, failure to recognize the patient at risk of, or in the early stages of, sepsis could have devastating consequences.[9] On the other hand, the reflexive acquisition of blood cultures in patients with fever or other nonspecific signs of infection can lead to antibiotic overuse with potential negative consequences of drug-related adverse events and contribution to the emergence of drug resistant pathogens.[10]

The culture positivity rate in our study was 6%, which is in range with what has been reported in the adult literature.[11] Abnormal leukocyte count and an elevated lactate were the only markers that were associated with culture positivity. Interestingly, we did not find an association between the presence of SIRS or sepsis and culture positivity. We surmise that in some of our patients the presence of SIRS may reflect noninfectious pathological states seen commonly in critically ill patients such as opiate-benzodiazepine withdrawal or heart failure. Assessment of the individual patient with SIRS, which may include the evaluation of inflammatory markers (e.g., white blood cell count), may help distinguish the etiology of SIRS.

Woods-Hill et al recently demonstrated that the use of a clinical practice guideline in a tertiary-care PICU that employs a fever/sepsis-screening checklist and blood culture decision algorithm decreased blood culture utilization without negatively impacting morbidity and mortality outcomes.[12] Furthermore, use of the clinical practice guideline led to a decrease in the acquisition of blood cultures drawn from central venous catheters.[12] Inspired by, and in collaboration with, Woods-Hill et al, we developed our own unit-specific clinical practice guideline at the conclusion of the timeframe reported in this study. Our guideline requires the assessment of the patient for noninfectious causes of SIRS (e.g., opiate-benzodiazepine withdrawal) and discussion with the in-house attending physician prior to blood culture acquisition and antibiotic administration. Since the implementation of our guideline 2 years ago, our cultures obtained dropped by nearly 50% (10.2 to 5.3 cultures per 100 patient days). Our use of indwelling lines for blood culture acquisition decreased from 69 to 35% while that of percutaneous draws more than doubled from 31 to 65%.

Our study has several limitations, most notably the single center retrospective study design. Nearly half of our patient cohort was admitted with a diagnosis of acquired or congenital heart disease possibly affecting the generalizability of our results to a wider array of PICUs. We were not able to reliably capture adverse events associated with antibiotic use, which would be helpful in our understanding of the costs associated with potential antibiotic overuse. We were also unable to distinguish cultures that were drawn in clinically improving patients for the purpose of reassurance with safe discontinuation of antibiotics. With the recent adoption of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) for adult patients in 2016, it is expected that pediatric sepsis definitions will be reassessed in the near future.[13] When that point comes, it will be important to assess the impact of new definitions on the rates of blood culture acquisition.

Diligent bedside assessment of the critically ill patient combined with sound clinical decision-making is needed to balance the competing forces of sepsis recognition and reflexive blood culture acquisition with antibiotic overuse. The implementation of unit-specific clinical guidelines may serve to aid the clinician in their decision-making, improving patient outcomes.

Note

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Conflict of Interest

None declared.

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