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Can bacteremia be predicted in surgical intensive care unit patients?

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Abstract. *Objectives:* To determine which clinical features are associated with bacteremia in a SICU. To determine if infections are identified prior to bacteremia via culturing of other body fluids. To determine if antibiotic regimens are changed after the results of the blood culture were obtained.
Design: A retrospective, unit-based, case control study.
Setting: A 10 bed SICU in a 552-bed, tertiary care and Level I Trauma center.
Patients: All SICU patients with one or more positive blood cultures over a 2 year period ($n = 24$) were matched by diagnosis, procedure, and age to SICU patients with negative blood cultures ($n = 48$).
Measurements and results: Bacteremic and control patients had similar APACHE II scores though death was more likely in bacteremic patients ($p < 0.05$) and they had higher hospital charges ($p < 0.02$). There was no difference in any of the clinical variables studied (minimum and maximum temperature, maximum white blood cell count, minimum mean arterial blood pressure) between the bacteremic and control groups on the days leading up to and the day of the positive blood culture. Coincident infections of lung, bladder, wound, and central venous catheters were identified in 42% of bacteremic patients. The identification of organisms found in the blood had a direct impact on the antibiotic regimen of 54% of the bacteremic patients.
Conclusions: A better screen for obtaining blood cultures in this SICU was not identified. If antibiotics are begun empirically before the results of blood cultures are known, the results of other body fluid cultures can be used to guide therapy initially. However, the data obtained from positive blood cultures was often helpful in changing empirical therapy. Therefore, blood cultures remain important diagnostic tools.

Key words: Infection – Bacteremia – Fever – Surgical intensive care unit – Post-operative complications – Patient outcome assessment

Bacteremia is a sign of poor prognosis in critically ill patients and carries with it a high mortality, up to 60% in some series [1–3]. The gold standard for diagnosing bacteremia is a positive blood culture. A positive blood culture confirms the clinical suspicion of an infectious process, defines causative organisms, and guides antibiotic therapy.

Though the indications for culturing blood and other body fluids vary widely, the presence of fever and/or leukocytosis, and the pattern in which these change [4], are traditional screens for infection and lead to a diagnostic work-up in search of the infectious source. Hypothermia, hypotension, and/or subjective changes in mental status can herald severe infection, specifically septicemia, and warrant an infectious work-up. Such a diagnostic work-up involves the culturing of all body fluids, including blood, and indwelling central venous catheters (CVCs). Additionally, in surgical patients the work-up must include radiographic, ultrasound, or operative investigation if there is a high index of suspicion for deep wound or intraabdominal infections.

It would be useful to have information regarding the likelihood that a surgical intensive care unit (SICU) patient has bacteremia at the time it is first suspected in order to initiate further diagnostic and therapeutic maneuvers. Prior to this study we identified a high incidence of negative blood cultures from our SICU using traditional guidelines for infectious work-ups, specifically temperature of 38.5 °C or greater.

The lack of correlation between degree of fever and leukocytosis and bacteremia has been reported in other patient populations. Galacier reported that only one half of all postoperative infections in general surgical patients were associated with fever [5] and leukocytosis failed to differentiate noninfectious from infectious postoperative

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fever in another general surgical patient population [6]. A lack of correlation between fever and leukocytosis with bacteremia was also seen in patients following cardiac valve surgery [7]. Others have attempted to develop a clinical model to predict bacteremia in febrile medical patients, though fever, leukocytosis, and other traditional signs of infection were found not to be predictive [8]. On the other hand, the pattern of temperature increases may be predictive of serious infections [9, 10].

An objective of this study is to determine which clinical features, known at the time of an infection work-up, are significantly and independently associated with bacteremia in the hope of developing better clinical screening for obtaining blood cultures in a SICU.

Additionally, we suspected that serious infections in our SICU patients were being indentified prior to bacteremia via culturing of body fluids other than blood (sputum, urine, wound) and CVCs. We hypothesized that the high incidence of negative blood cultures from our SICU was being caused by the appropriate use of antibiotics whose regimen was guided by culture results other than blood. Furthermore, we suspected that even when bacteremia was detected, antibiotic regimens were rarely changed after the results of the blood culture were obtained because of the wide use of broad spectrum antibiotics.

Materials and methods

Following human investigation review board approval a retrospective, unitbased, case control study was carried out in the 10-bed SICU at the University of Virginia Health Services Center, a 552-bed, tertiary care and Level I Trauma center. A computer-generated-list of all SICU patients with one or more positive blood cultures over a 2 year period (1989–1990) was obtained from the microbiology department. Clinical culture methods consisted of blood (10 ml) obtained aseptically and inoculated into a two-bottle set. Two sets of blood cultures from two different sites were routinely obtained. Aspiration of blood through CVCs was not routinely done. Organisms were identified by conventional methods and in vitro sensitivities to a range of antibiotics were determined by the Kirby-Bauer disc method. Medical records of the bacteremic patients were reviewed to determine if the positive blood culture was a true positive or a probable contaminant. Coagulase negative *Staphylococcus* was considered a pathogen only when isolated from more than one set of blood cultures, when isolated also from a CVC, or when isolated from a clinically septic patient who had a CVC in place. Otherwise, if only one set of blood cultures was positive for a common skin organism it was classified as contaminated.

Individual decisions to culture the patient's blood were at the judgment of the attending or resident physician. In general, it was routine practice to initiate an infectious work-up of SICU patients when their rectal temperature was 38.5 °C or greater, or if sepsis was suspected (hypotension, leukocytosis, hypothermia, change in mental status). An infectious work-up included Gram stain and culture of sputum, urine, and wound drainage, the changing of CVCs in place longer than 72 h, and the drawing of venous blood for culture. Sinusitis as a source of infection was investigated with radiographs in patients with nasal catheters or tubes in place. Cerebrospinal fluid was only cultured when clinically indicated.

The medical records of the patients with true positive blood cultures were reviewed for age, gender, race, length of hospital admission, length of SICU stay, Apache II score on the day of SICU admission [11], and survival to discharge. Common Procedural Terminology (CPT) coded primary diagnosis, primary procedure, secondary diagnosis, and secondary procedures were obtained from the medical record. Hospital charges for the entire admission were obtained from the billing office.

The day on which the positive blood culture was obtained from the patients was designated as day 0. The time period for five days prior to and five days following this date was chosen as the period of observation for this study. For those patients with multiple positive blood cultures, the first date on which there was a positive result was considered as day 0. From the critical care flow sheets the following clinical variables were recorded for each day of the observational period: minimum and maximum temperature (T_{min}, T_{max}), maximum white blood cell count (WBC), minimum mean arterial blood pressure (MAP), minimum and maximum blood glucose, minimum pH, minimum and maximum PCO_2, and minimum PO_2. To find data for days not spent in the SICU, information was obtained from general purpose flow sheets, graphic records, laboratory records, or progress notes. Mean arterial pressure, if not indicated, was estimated:

$$MAP = [(\text{systolic} - \text{diastolic}) \div 3] + \text{diastolic}.$$

The cumulative clinical laboratory report was reviewed to determine which other body fluids were cultured during the observation period. For each type of body fluid the date, results, the organism found, and the antibiotics to which the organism was susceptible and resistant were noted. Additional information required to make the diagnosis of pneumonia, urinary tract infection (UTI), deep wound infection, or CVC-related infection was obtained from the medical record. Whenever possible, the likely source of bacteremia was established by simultaneous culture of the same organism in the blood and from another site.

The diagnosis of pneumonia required the report of a new infiltrate on chest radiograph and purulent sputum with 2+ or 3+ growth of an organism, based on a three quadrant streak technique. Common oropharyngeal organisms were considered contaminants and sensitivities were not obtained. The diagnosis of UTI required significant bacteriuria (growth of 10^5 or greater colony-forming units of an organism) with or without symptomatology. The diagnosis of a deep surgical wound infection required drainage of gross pus from drains placed beneath the fascial layer, wound dehiscence, or abscess formation. The etiological organism was determined by culture of fluid obtained from drainage, abscess aspiration, or surgical exploration. The diagnosis of a CVC-related infection required growth of 15 or more colony-forming units of an organism on semiquantitative culture of the catheter tip according to the method described by Maki et al. [12].

Antimicrobial therapy during the observation period was obtained from a standing medication record (for medical records prior to May 1989) or a computerized drug summary.

Matched controls

Control patients were selected by reviewing all patients with a negative blood culture admitted to the SICU over the same 2 year period. Control patients were matched to study patients by CPT coded primary diagnosis, primary procedure, secondary diagnoses and procedures, and age. Whenever possible, bacteremic patients were matched with more than one control. The day on which the negative blood culture was obtained was designated as day 0. For those patients with multiple negative cultures, the first date on which there was a negative result was considered as day 0. The time period for five days prior to and five days following day 0 was chosen as the period of observation. Patients were excluded if a positive blood culture was obtained prior to the SICU admission. Clinical and microbiological data identical to the bacteremic patients was obtained by review of the medical record.

Statistical analysis

Data is reported as mean ± standard deviation. Comparison of the demographic data of the bacteremic group and the nonbacteremic control group is made with unpaired Student's t test and Chi square test. To determine which clinical variables are significantly and independently associated with bacteremia we used unpaired Student's *t* test.

Table 1. Demographic data of bacteremic patients and their matched controls

	Bacteremic patients $n = 24$	Controls $n = 48$	p Value
Age (years)	52.7 ± 16.6 (19–86)	54.2 ± 15.7 (19–81)	NS
% Female	26.1	30.6	NS
Apache II	18.06 ± 5.85 (6–26)	17.53 ± 7.12 (2–30)	NS
% Intraabd Dis	39 ($n = 9$)	35 ($n = 17$)	NS
% Multi-trauma	35 ($n = 8$)	45 ($n = 22$)	NS
% OLT	17 ($n = 4$)	10 ($n = 5$	NS
% Neurosurg	9 ($n = 2$)	6 ($n = 3$)	NS
% Vascular	0	4 ($n = 2$)	NS
LOA (days)	56.6 ± 46.4 (7–224)	40.3 ± 35.7 (2–184)	$p = 0.10$
LOSICU (days)	24.3 ± 25.8 (2–114)	15.5 ± 24 (1–160)	$p = 0.16$
Hospital Charges	$ 119605 ± 91172	$ 76738 ± 49610	$p < 0.02$
% Mortality	34.8 ($n = 8$)	12.2 ($n = 6$)	$p < 0.05$

LOA, Length of hospital admission; LOSICU, length of SICU stay; Intraab dis, intraabdominal disease; OLT, orthotopic liver transplantation; Neurosurg, neurosurgical pathology; NS, not significant

Results

Study population

Over a 2 year period (1989–1990) the microbiology department received 1411 blood cultures from the SICU and reported 122 positive results; a raw positive rate of 8.6%. Blood cultures were considered to be contaminated in 51 cases, resulting in a true positive rate of 5%. The 71 truly positive blood cultures were obtained from 32 different patients. Complete medical records were available for retrospective review for 24 of these, representing the bacteremia patient group for this study.

The 24 bacteremic patients were matched to 48 control patients who had a negative blood culture. Bacteremic and control patients had a similar severity of illness at admission using Apache II scores. Death was nearly three times more likely in bacteremic patients than their matched controls ($p = 0.037$). Bacteremic patients accrued higher hospital charges ($p < 0.02$) and tended to have longer SICU admissions ($p = 0.16$) and hospital stays ($p = 0.10$) than controls (Table 1).

Univariate analysis

There was no statistical difference in any of the clinical variables studied between the bacteremic and control groups on the day that the blood culture was obtained (day 0). Additionally, no statistical relationship was found in the degree of fever, leukocytosis, and hypotension on the days leading up to day 0. However, the bacteremic patients had a lower minimum temperature than their matched controls two days prior to ($p = 0.033$), one day prior to ($p = 0.008$), and on day 0 ($p = 0.085$) (Table 2).

Afebrile bacteremia (Tmax 36.7 to 38.4 °C) was identified in 7 of the 24 bacteremic patients, though 6 of these 7 did have leukocytosis. The patients with afebrile bacteremia had a mortality rate of 57%, whereas the other bacteremic patients had a mortality rate of 24% ($p = 0.11$).

Table 2. Univariate analysis of clinical variables

	Bacteremic patients	Nonbacteremic controls	p Value
WBC day^{-1}	13.6 ± 5.9	14.4 ± 7.6	0.66
WBC day 0	15.0 ± 5.4	14.3 ± 6.9	0.67
T_{max} day^{-1}	38.0 ± 0.9	38.3 ± 0.6	0.11
T_{max} day 0	38.7 ± 1.0	38.8 ± 0.6	0.56
T_{min} day^{-1}	36.8 ± 1.1	37.4 ± 0.5	0.008
T_{min} day 0	36.9 ± 1.1	37.3 ± 0.7	0.085
MAP day 0	75.5 ± 17.5	79.5 ± 13.1	0.273

There was no statistical difference in any of the clinical variables studied between the bacteremic and control groups other than T_{min}
WBC, Maximum daily white blood cell count; T_{max}, maximum daily temperature; T_{min}, minimum daily temperature; MAP, lowest daily mean arterial pressure

Microbiology analysis

One blood organism was identified in 22 patients and two organisms were identified in 2 patients for a total of 26 separate blood isolates (Table 3).

The source(s) of bacteremia was identified in 14 of the 24 bacteremic patients by isolation of the same pathogen in the blood and another body fluid and/or a CVC, though the pathogen was identified prior to or on day 0 in only 10 bacteremic patients (42%). Of the remaining 14 patients, the positive blood culture revealed a new organism not yet found in other body fluids or on a CVC. Ultimately, the source of bacteremia was never identified in 42% of patients.

Amongst the 48 control patients with negative blood cultures, no infection was identified in 26. Infectious sources were identified in the other 22 control patients. Pneumonia and UTI were the most common infections. Systemic candidiasis was identified in 3 control patients. All three had yeast colonizing multiple sites and were started on systemic antifungals (Table 4). The infected controls had a statistically higher Tmax on day 0 than the noninfected controls, 38.9 ± 0.5 and 38.6 ± 0.6 respectively ($p = 0.036$), though there was no statistical difference in the degree of leukocytosis between the infected and noninfected controls, 15.5 ± 6.6 and 12.9 ± 5.6 respectively ($p = 0.143$).

Table 3. Organisms cultured from blood. One blood organism was identified in 22 bacteremic patients and two organisms were identified in 2 patients (patients a and b) for a total of 26 separate isolates. The source of bacteremia was identified in 14 of the 24 bacteremic patients by isolation of the same organism in the blood and another body fluid of CVC, though the organism was identified prior to or on day 0 in only 10 bacteremic patients

Organisms isolated from blood	Source of bacteremia Identified on or prior to day 0	Source of bacteremia Identified identified ater day 0	Primary bacteremia
Gram negative organisms (n = 12)			
3 *Citrobacter freundii*	1 wound 1 bilary tract[a]		1
3 *Pseudomonas aeruginosa*	1 [lung, wound and CVC]		2
2 *Acetinobacter calcoaceticus*	1 CVC	1 lung	
1 *Enterobacter* sp.		1 wound[a]	
1 *Pseudomonas maltophilia*			1[b]
1 *Serratia marcescens*			1
1 *Klebsiella pneumoniae*			1
Gram positive organisms (n = 11)			
6 *Staphylococcus aureus*	1 lung 1 [wound and CVC]	1 lung 1 [lung, wound, and other fluid][b]	2
3 *Staphylococcus epidermidis*	2 CVC 1 [wound and CVC]		
2 *Enterococcus*			2
Candida albicans (n = 3)	1 CVC		2

CVC, central venous catheter

Table 4. Coincident infections in control patients. There were 23 infectious sites identified in 22 control patients, as patient c had the same organism identified in the sputum and urine. Patients d, e, f, g and h each had two separate isolates cultured from a single infectious site. This resulted in a total of 28 separate isolates

	Pneumonia	UTI	Wound	Candidiasis
Gram negative organisms (n = 17)				
6 *Enterobacter* spp.	3[a]	3[a,e]	–	–
2 *Pseudomonas aeruginosa*	2	–	–	–
2 *E. coli*	–	2[e]	–	–
2 *Haemophilus influenzae*	2[b]	–	–	–
1 *Klebsiella pneumoniae*	1[b]	–	–	–
1 *Acetinobacter calcoaceticus*	1	–	–	–
1 *Serratia marcescens*	–	1[f]	–	–
1 *Legionella* spp.	1	–	–	–
1 *Hafnia alvei*	–	–	1[d]	–
Gram positive organisms (n = 6)				
3 *Enterococcus*	–	2[f]	1[c]	–
1 *Staphylococcus aureus*	–	–	1	–
1 *Streptococcus* spp.	–	–	1[d]	–
1 *Corynebacterium* spp.	–	–	1[c]	–
Candida albicans (n = 5)	–	2	–	3
Total isolates	10	10	5	3

UTI, urinary tract infection

Impact of blood culture results on antibiotic use

The identification and determination of sensitivities of organisms found in the blood had a direct impact on the antibiotic regimen in 13 of the 24 bacteremic patients (54%). Appropriate antibiotics were started after the positive blood culture was reported in 4 patients not previously on antibiotics. The antibiotic regimen was adjusted based on the identification and determination of sensitivities in an additional three patients begun on antibiotics prior to day 0 and 6 patients begun on antibiotics empirically on day 0. The results of the blood culture did not influence that antibiotic regimen of the remaining 11 bacteremic patients.

The impact of the negative blood culture on the antibiotic regimen of the control patients is blunted by the use of antibiotics for other reasons. Other body fluid infections were being treated prior to day 0 in 17 of the 48 non-bacteremic patients (35%). The remaining 31 control

patients were not receiving antibiotics on day 0 and 19 of these were never begun on antibiotics. The other 12 were begun on antibiotics empirically or to treat other body fluid infections.

Discussion

Prior to this study we identified a high incidence of negative blood cultures from our SICU. This triggered a Continuous Quality Improvement (CQI) investigation. In an attempt to identify which clinical features are predictive of bacteremia, we carried out a unit-based, case control study over a two year period of all bacteremic SICU patients. With the overutilization of expensive tests and antibiotics, it was hoped, both from a therapeutic and cost perspective, to develop an easy, inexpensive screen, such as Tmax, WBC, or a combination of clinical variables to predict bacteremia.

Unfortunately, our study failed to demonstrate this correlation in our SICU population. Using univariate analysis no variable on the day a blood culture was drawn independently and significantly associated with bacteremia. In addition, the pattern of change of the clinical variables we studied could not guide when to draw blood cultures nor predict whether the blood culture would in fact be positive. The only significant independent variable that predicted bacteremia was the minimum temperature one day and two days prior to day 0. Though statistically valid, minimum temperature is not clinically useful for screening because we could not identify a cut off minimum temperature that would have appropriate sensitivity due to the wide range of temperatures. Regression analysis of the different variables also failed to identify a model that would predict bacteremia in our SICU population.

It is recognized that afebrile bacteremia occurs in a variety of clinical settings. Advanced age, immunosuppression, malignancy, corticosteroid therapy, and hypothyroidism are all common entities in an ICU population and all may be risk factors for afebrile bacteremia [9, 13]. Non-specific abnormalities such as an alteration in mental status and general malaise may be the only heralds of severe infection in such patients.

Even in the presence of fever, post-operative surgical patients in our SICU present an additional problem due to the cryptic nature of postoperative febrile episodes. Though many postoperative febrile episodes resolve spontaneously without evidence of infection, up to 58% of postoperative febrile episodes are associated with infections [5, 6, 14]. Though speculation regarding the etiology of noninfectious postoperative febrile episodes continues (pulmonary atelectasis, hypersensitivity reactions to anesthetics and perioperative antibiotics, hematoma formation, phlebitis [15–19]), these studies support an aggressive approach to postoperative febrile episodes, recognizing that antibiotics need not be started if no source of infection is identified.

We suspected that serious infections in our SICU patients could be identified via culturing of body fluids other than blood (sputum, urine, wound) and CVCs. Additionally, we suspected that infections of these organs (lung, bladder, wound, and CVCs) could be identified prior to bacteremia. Our prior assumption that the treatment of coincident infections with appropriate antibiotic regimens reduced the incidence of bacteremia was incorrect. Blood culture results identified a new pathogen not suspected by culture results from other body fluids in 54% of our bacteremic patients. We determined that the blood culture result had a direct impact on the antibiotic regimen for only 13 patients over the 2 year study period. Total hospital charges for blood culturing and determination of sensitivities in the SICU for this two year period was $ 60084, resulting in a cost of $ 4622 per patient in whom the positive blood culture had a clinical impact. Our study confirms previous findings associating bacteremia with increased mortality in ICU populations [1, 3], though we did not investigate whether or not these antibiotic changes resulted in any improvements in outcome.

One problem with this case-control study is the bias that can ocur with the way in which cases and controls are selected. In order to minimize bias in our study, we established precisely, and in advance, the method by which cases and controls were to be identified and selected. We meticulous matched patients using primary and secondary CPT codes and there was no significant difference in other controlling parameters. This method of selection has resulted in two groups of patients with similar severity of illness as measured by APACHE II scores. However, bias may still have occurred by our failure to control all variables which may have influenced the incidence of bacteremia. For instance, the presence of a CVC may predispose a SICU patient to bacteremia. In fact, all CVC infections in our study were associated with bacteremia, and were identified as the source in 30% of bacteremias, yet we did not control for the presence of a CVC.

Another concern with this study is in the way in which we diagnosed pneumonia in our intubated patients. Numerous strategies have been outlined to help the clinician differentiate between colonization and infection. The trachea of intubated patients will become colonized with oropharyngeal organisms within a few days [20]. When organisms other than normal oropharyngeal flora appear in the sputum, one must decide if this represents colonization or an infectious process. We used clinical criteria based on physical, radiographic and laboratory findings along with analysis of tracheal aspirates using Gram stain and culture to aid our diagnosis of pneumonia. Some studies report that microscopic analysis and culture of sputum using this method is inaccurate and can lead to the selection of inappropriate antibiotic therapy. Alternative techniques for diagnosing pneumonia in intubated patients, such as protected specimen brush and bronchial alveolar lavage, are considered to be superior in diagnosing pneumonia in intubated patients. Though numerous reports indicate that these invasive methods are more accurate [21], their reliability has been questioned by others [22]. We have not routinely used these alternative techniques in our patient population.

In conclusion, we failed to identify better clinical predictors to guide when to obtain blood cultures and

predict bacteremia in our SICU population. In addition, we found that coincident infections of lung, bladder, wound, and CVCs often can be identified prior to bacteremia. Therefore, if antibiotics are begun empirically before the results of blood cultures are known, the results of other body fluid cultures can be used to guide therapy initially. However, we found that the data obtained from positive blood cultures is often quite important in changing empiric therapy and that blood cultures remain important diagnostic tools. Finally, the information from this study is obtained form a recent SICU population. Few studies address the concerns physicians have when caring for this population, and the data can be used for future evaluations.

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