MAJOR ARTICLE

Predicting Bacteremia at the Bedside

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Our aim was to develop a clinical prediction rule for detection of bacteremia in a cohort of patients observed prospectively at a reference center in Medellín, Colombia. The significant predictors of bacteremia were an age of ⩾30 years (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.19–3.60), a heart rate of ⩾90 beats/min (OR, 1.90; 95% CI, 1.13–3.17), a temperature of ⩾37.8°C (OR, 2.42; 95% CI, 1.41–4.14), a leukocyte count of ⩾12,000 cells/μL (OR, 2.40; 95% CI, 1.41–4.10), use of a central venous catheter (OR, 1.89; 95% CI, 1.02–3.50), and a length of hospitalization of ⩾10 days (OR, 2.02; 95% CI, 1.25–3.24). The Hosmer-Lemeshow test revealed a goodness-of-fit of 2.99 ($P = .981$), and the area under the receiver operating characteristics curve was 0.7186. Simple variables obtained from the clinical history of patients are associated with bloodstream infection in a reproducible fashion and should be instrumental for prioritizing the requests for blood cultures by clinicians.

Sepsis and bacteremia are critical issues in hospitalized patients. Early detection of pathogens in the blood is of indisputable clinical importance, because this is an indicator of disseminated infection, which is associated with a worse prognosis than that for patients with local infection. In addition, early detection allows initiation of appropriate and opportune therapy that hinders onset of the complex phenomenon of sepsis, which continues to be associated with a high mortality rate, despite the availability of new and complementary therapies [1].

The microbiology laboratory is of limited usefulness for bloodstream infection detection, because ⩽5%–10% of blood cultures have positive results, and the final results take at least 24 h to be known [2]. On the other hand, requests for blood cultures are guided by clinical judgment, according to different health care settings and patient characteristics [3]. Thus, it is very important to identify clinical predictors that are involved in requests for testing and associated with bacteremia in patients at risk for bloodstream infection. There are few studies of this issue anywhere in the world [3–7], and, in Colombia, only our research group has begun to study this important problem [8–10].

Our aim was to develop a prediction model for bacteremia, using data from a cohort of patients hospitalized at the San Vicente de Paul University Hospital (HUSVP; Medellín, Colombia) from September 2001 through February 2002. Our hypothesis was that knowledge of certain simple variables from results of physical examination and basic laboratory tests will strongly support the request for and analysis of blood cultures. Furthermore, a comprehensive analysis of clinical findings is a worthwhile step in the correct diagnosis and treatment of life-threatening infection.

PATIENTS AND METHODS

Patients. During a 6-month period, complete clinical and laboratory data were collected prospectively for 500 patients hospitalized in different services of HUSVP from whom at least 2 blood samples for culture had been requested. HUSVP is a 550-bed university hospital in Medellín and is a referral center for ~3,000,000 in-

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dividuals. The investigation was approved by the institutional review boards of the University of Antioquia (Medellín) and HUSVP, and informed consent was obtained from all participants.

Patients were included in the study if they had been hospitalized in adult services for at least 48 h, they were >14 years of age, and there was a complete report of results of at least 2 blood cultures during their stay. If several sets of cultures were requested at different times for the same patient, only the information corresponding to culture of the first sample was considered in the analysis. Patients were excluded on the basis of pregnancy, receipt of a transplant during the year before study entry, incomplete or unavailable clinical records, and death or discharge ≤24 h after the initial blood culture was requested.

Predictor and outcome variables. The following were considered to be predictor variables: age; comorbidity, defined as presence of HIV infection, chronic renal failure, diabetes mellitus, use of immunosuppressant chemotherapy during the previous 3 months, use of systemic corticosteroids for at least 1 month, or cancer diagnosis in the previous year; the presence of chills ≤24 h before the blood culture was requested; heart rate; systolic blood pressure; temperature; Glasgow Coma Scale score; leukocyte count; neutrophil count; band (i.e., immature WBC) count; platelet count; trauma or surgery associated with the current hospitalization; use of a central venous catheter or mechanical ventilation concomitant with or ≤72 h before obtainment of blood samples for culture; duration of hospitalization; and use of antibiotics for at least 24 h during the previous week.

The outcome variable was a positive blood culture result, defined as growth of bacteria with recognized pathogenic capacity in ≥1 blood culture or as growth of common skin pathogens (i.e., coagulase-negative *Staphylococcus* species, diphtheroids, *Bacillus* species, *Propionibacterium* species, or micrococci) in ≥2 blood cultures, in the presence of systemic inflammatory response syndrome (defined as the presence of ≥2 of the following symptoms: a heart rate of >90 beats/min, a respiratory rate of >20 breaths/min, a temperature of >38°C or <36°C, and a leukocyte level of >12,000 or <4000 cells/μL) and/or clinical evidence or microbiological findings suggesting a primary focus of infection. Two investigators determined the outcome definition independently in each case, and the differences were resolved by consensus.

Statistical analysis. Univariate analysis was performed using Student's *t* test for continuous variables and χ^2 analysis for binary variables. Factors with a *P* value of <.15 were eligible for inclusion in the model. Locally weighted regression analysis between significant continuous variables and the log odds of the outcome was performed to explore which cut points were the best predictors of true-positive blood culture results [11]. Univariate logistic regression analysis was performed using linear and spline terms and/or dummy variables for continuous predictors. Evaluation of colinearity was done using variance inflation factors, in which colinearity was considered in the presence of a mean variance inflation factor of >1 [12]. Interaction terms were evaluated with a likelihood ratio test. Evaluation of fit was performed using a multivariate logistic regression model with a forward stepwise procedure and a *P* value of <.05. Calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test. Evaluation of discrimination was performed using a receiving operating characteristics (ROC) curve. Internal validation was done with 2000 bootstrap replications of the model. The final results are presented as ORs with 95% CIs. All data processing and analysis was performed with Stata software, version 8.0 (Stata).

RESULTS

During the study period, 517 patients were considered eligible. A total of 17 patients were excluded because of unavailable or incomplete information (10 patients), death or discharge ≤24 h after the initial blood culture was requested (4 patients), receipt of a transplant (2 patients), or pregnancy (1 patient). Results of blood cultures for these patients were negative. Of the 500 remaining patients, 293 (58.6%) were male. The mean age (±SD) was 45 ± 20 years, and the median length of hospitalization at the time that the blood sample was obtained for culture was 6 days (interquartile range, 3–15 days).

In 311 patients (62.2%), there were not any important antecedent conditions associated with their present illness. In the remainder, the most important antecedent conditions, some of them in the same patient, were trauma or surgery (114 patients [22.8%]), use of a central venous catheter (61 [12.2%]), chronic renal failure, (59 [11.8%]), diabetes mellitus (49 [9.8%]), use of mechanical ventilation (36 [7.6%]), receipt of corticosteroid therapy (34 [6.8%]), HIV infection (33 [6.6%]), receipt of immunosuppressant chemotherapy (29 [5.8%]), hematological cancer (27 [5.4%]), and other cancers (23 [4.6%]). The main condition that was diagnosed at hospitalization involved the respiratory system in 96 patients (19.2%), the neurological system in 76 (15.2%), the gastrointestinal system in 73 (14.6%), the cardiovascular system in 72 (14.4%), the hematological system in 54 (10.8%), bone and articulation in 41 (8.2%), the immune system in 34 (6.8%), and other systems (not classified) in 54 (10.8%). At the time that blood cultures were performed, the majority of requests involved the presumption of sepsis and/or bacteremia (318 [63.6%] of 500 patients) or pneumonia (156 [31.2%] of 500); there were different presumed diagnoses for 26 patients (5.2%). Of the 500 patients, 255 (51%) were receiving antibiotics at hospitalization of during the previous

week. The 28-day mortality rate for the total cohort was 22.6% (113 patients).

Cultures of biological specimens obtained from 147 patients (29.4%) yielded microorganisms. Of these, 102 patients (20.4%) had at least 1 blood sample that yielded some pathogen on culture, and blood culture results for 89 patients (17.8%) were considered to be true positives. The main pathogens recovered from true-positive blood cultures for these patients were *Staphylococcus aureus* (18 patients [20.2%]), *Escherichia coli* (14 [15.7%]), coagulase-negative *Staphylococcus* species (13 [14.6%]), *Acinetobacter calcoaceticus/baumannii* (8 [8.9%]), *Pseudomonas* species (7 [7.9%]), *Candida* species (5 [5.6%]), *Klebsiella pneumoniae* (3 [3.4%]), *Enterobacter cloacae* (3 [3.4%]), *Stenotrophomonas maltophilia* (3 [3.4%]), *Proteus vulgaris* (2 [2.2%]), *Cryptococcus neoformans* (2 [2.2%]), *Streptococcus pyogenes* (2 [2.2%]), *Streptococcus pneumoniae* (2 [2.2%]), *Streptococcus intermedius* (2 [2.2%]), and *Klebsiella oxytoca, Enterococcus faecalis, Enterococcus faecium, Salmonella* species, and *Morganella morganii* (1 [1.1%] each). The primary source of infection in these 89 patients was skin and soft tissue in 19 (21.3%), central venous catheter in 17 (19.1%), urogenital system in 15 (16.9%), abdominal cavity in 14 (15.7%), unknown or not determined for 14 (15.7%), and respiratory system in 10 (11.2%). The most frequent complications in this group were adult respiratory distress syndrome in 25 patients (28.1%) and shock in 22 (24.7%), and mortality (32 patients [36%]) was almost twice as frequent as that observed in the total cohort.

In the univariate analysis, the following variables were not considered to be statistically significant: comorbidities, use of antibiotics, chills, systolic blood pressure, neutrophil count, and platelet count (table 1). Bands were found in just 9 patients, and only 1 patient—who had a band proportion of 5% of WBCs—had true bacteremia. The strongest potential univariate predictors of bacteremia and their optimal cut points were age of ⩾30 years, heart rate of >90 beats/min, temperature of >37.8°C, Glasgow coma scale score of <10, leukocyte count of >12,000 cells/μL, use of central venous catheter, use of mechanical ventilation, and duration of hospitalization of >10 days (table 2). There was no evidence of colinearity, and the following interaction terms were ruled out: duration of hospitalization and use of mechanical ventilation, duration of hospitalization and use of a central venous catheter, age and trauma and/or surgery, age and comorbidity, and heart rate and temperature.

In the final stepwise logistic regression (table 3), the significant predictors of bacteremia were age of ⩾30 years (OR, 2.07; 95% CI, 1.19–3.60), heart rate of ⩾90 beats/min (OR, 1.90; 95% CI, 1.13–3.17), temperature of ⩾37.8°C (OR, 2.42; 95% CI, 1.41–4.14), leukocyte count of ⩾12,000 cells/μL (OR, 2.40; 95% CI, 1.41–4.10), use of a central venous catheter (OR, 1.89; 95% CI, 1.02–3.50), and length of hospitalization of ⩾10 days (OR, 2.02; 95% CI, 1.25–3.24). The Hosmer-Lemeshow test revealed a goodness-of-fit of 2.99 ($P = .9817$), which suggested excellent calibration, whereas the value of the area under the ROC curve was 0.7186 (95% CI, 0.6763–0.7571) for an acceptable discrimination. The bootstrapped coefficients for 2000 replications exhibited SEs of <10% of those observed in the model, and the values for the Hosmer-Lemeshow goodness-of-fit test and the area under the ROC curve in this set were 3.96 ($P = .942$) and 0.6819 (95% CI, 0.6392–0.7328), respectively. Given the potential selection bias in defining positive blood cultures as those from which coagulase-negative *Staphylococcus* species were recovered, the model was rerun using only positive blood cultures without growth of this microor-

Table 1. Univariate analysis for variables that were not associated with positive blood culture results.

Variable	Blood culture result[a] Negative ($n = 411$)	Positive ($n = 89$)	P[b]
Presence of comorbidity[c]	159 (38.7)	32 (36)	.630
Presence of chills[d]	43 (10.4)	9 (10)	.769
Antibiotic use[e]	210 (51.1)	45 (50.6)	.785
Systolic blood pressure, mean mm Hg ± SD	121.6 ± 25	121 ± 25.7	.828
Neutrophil count, mean cells/μL ± SD	9242 ± 9250	10,310 ± 7214	.232
Platelet count, mean cells/μL ± SD	269,827 ± 145,937	294,107 ± 184,198	.218

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] For definitions, see Patients and Methods.

[b] By χ^2 analysis or Student's t test.

[c] HIV infection, chronic renal failure, diabetes mellitus, recent receipt of immunosuppressant chemotherapy, use of systemic corticosteroid therapy, and/or cancer diagnosis.

[d] During the 24-h period before blood was obtained for culture.

[e] For at least 24 h during the week before study entry or at the time that the blood sample was obtained for culture.

Table 2. Univariate analysis and selected cut points for variables potentially associated with positive blood culture results.

Variables	Blood culture result[a]		
	Negative (n = 411)	Positive (n = 89)	OR (95% CI)
Age, years			
Mean ± SD	44.2 ± 20.1	49 ± 20.1	…
⩾30	280 (68)	71 (80)	1.85 (1.06–3.22)
Heart rate, beats/min			
Mean ± SD	94.7 ± 17.9	98.5 ± 17.6	…
⩾90	240 (58)	65 (73)	1.93 (1.16–3.20)
Temperature, °C			
Mean ± SD	37.5 ± 1.1	37.9 ± 0.9	…
⩾37.8	164 (40)	54 (61)	2.32 (1.45–3.71)
Glasgow coma score			
Median (IQR)	15 (15–15)	14 (15–15)	…
⩽10	19 (4.6)	9 (10)	2.32 (1.01–5.32)
Leukocyte count, cells/μL			
Mean ± SD	12,380 ± 10,927	13,841 ± 6848	…
⩾12,000	156 (38)	56 (63)	2.77 (1.73–4.46)
Trauma	87 (21.2)	26 (29.2)	1.54 (0.92–2.57)
Use of central venous catheter	40 (9.7)	21 (23.6)	2.86 (1.59–5.16)
Use of mechanical ventilation	24 (5.8)	12 (13.5)	2.51 (1.20–5.24)
Length of hospitalization, days			
Mean ± SD	8.8 ± 13.8	14.7 ± 18.2	…
⩾10	115 (28)	42 (47)	2.30 (1.44–3.67)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Analysis was performed using univariate logistic regression. Cut points were determined by locally weighted regression [11]. IQR, interquartile range.

[a] For definitions, see Patients and Methods.

ganism as the outcome, and the results were not statistically significantly different (data not shown).

DISCUSSION

Sepsis and its complications are important causes of morbidity and mortality throughout the world. In the United States, there are at least 500,000 new cases each year, with a mortality rate ranging between 20% and 50% during the first month after diagnosis [13]. Although aggregate data do not exist for Colombia, our estimates suggest that the situation is proportionally similar, with 50,000 cases yearly and a mortality rate ranging between 20% and 40% [8, 9].

Despite developments of new antibiotics and advances in critical care in recent decades, the mortality rate associated with sepsis has remained almost the same [14]. Possible causes for this phenomenon have pointed to an incomplete understanding of the pathogenic process and the lack of a consensus definition of the illness. Different attempts to address the latter problem have been made [1, 15], but it seems clear that there is a continuum between bacteremia and several expressions of a systemic response to the infection. The clinical manifestations may precede bacteremia, but they also may be too subtle to be detected, or the microorganisms may be considered too occult for detection by the microbiology laboratory. However, it is also clear that, in a defined group of patients, the presence of bacteremia is a strong marker of mortality and complications [2, 5, 10, 13]. In this context, the early and correct identification of this set of patients among those considered septic could be extremely useful in medical decision making and clinical research [16].

The most comprehensive evaluation of prediction models for bacteremia has come from successive studies by Bates and colleagues [3–5, 17]. They have systematically proposed and tested the following variables as predictors for true-positive blood culture results: temperature, acute abdomen on examination, suspicion of endocarditis, comorbidity, indwelling vascular catheter, age, WBC count, platelet count, creatinine level, chills, hypotension, vomiting, and others. Nevertheless, at the time of writing, a single and useful clinical prediction rule has not been derived from these studies. Other investigators, using routine clinical findings [6, 18] and a variety of circulating

Table 3. Independent multivariate predictors of positive blood culture results.

Variable	OR (95% CI)	P^a
Age of ⩾30 years	2.07 (1.19–3.60)	.010
Heart rate of ⩾90 beats/min	1.90 (1.13–3.17)	.015
Temperature of ⩾37.8°C	2.42 (1.41–4.14)	.001
Leukocyte count of ⩾12,000 cells/μL	2.40 (1.41–4.10)	.001
Use of central venous catheter	1.89 (1.02–3.50)	.043
Length of hospitalization of ⩾10 days	2.02 (1.25–3.24)	.004

NOTE. Analysis was performed using a multivariate logistic regression model with a forward stepwise procedure.

[a] Likelihood ratio statistic.

inflammatory mediators [7], have faced the same problems in reproducing and validating their data. This highlights the inherent heterogeneity of sepsis and offers a solid justification for the necessity to develop new prediction models that address specific environments and conditions to complement to the existing knowledge, rather than exclusively to validate the current models.

There are several aspects to our study that merit attention. This is a young and relatively healthy population, with 62.2% of the patients lacking a major significant comorbidity. The association of trauma or surgery with hospitalization as the main potential risk factor for infection (22.8%) is a reflection of the general environment of Colombia, where >50% of the deaths among those aged 15–64 years are associated with violence [19]. However, a wide range of diseases could be included in a classification of medical diagnoses according systems, and the 28-day mortality rate of 22.6% is within the reported range for sepsis. The types of microorganisms that were recovered are not in accordance with the trend over the past decade, during which >50% of bloodstream infections were caused by gram-positive bacteria [13, 14, 20]. Our study showed that 56% of the cases of bacteremia in the study population were caused by gram-negative bacteria or fungi. This pattern has been found in our previous studies [8, 9], in contrast with the remarkable predominance of gram-positive bacteria in cases of community-acquired bloodstream infection [10]. Similarly, the percentage of positive blood culture results in our study, which was almost 20%, was notably higher than the percentage reported in most of studies throughout the world [5, 17, 21]. We do not have a clear explanation for these facts, but it is possible that, in addition to the patient characteristics and microorganisms specific to our study, we also have some differences in health care services and methods of patient care in Colombia.

We could not find a statistically significant relationship between bacteremia and many commonly associated factors, such as chills, low systolic blood pressure, neutrophil count, band count, and platelet count [3, 6, 17, 22]. Instead, we were able to identify 6 independent predictors of bloodstream infection in our population, all of which were commonly described in the literature. Length of hospitalization and use of a central venous catheter are logical determinants of bacteremia; the former is directly associated with all the complications in an inpatient setting, and the latter is a recognized source of local and systemic infection. The other 4 clinical variables—age of ⩾30 years, heart rate of ⩾90 beats/min, temperature of ⩾37.8°C, and leukocyte count of ⩾12,000 cells/μL—also have been consistently reported to be associated with bacteremia or sepsis [3, 6, 17, 22, 23], but our results showed substantially lower values as critical cut points for the outcome. These differences could be results of the following 2 closely related situations: (1) the particular characteristics of our population with respect to their patterns of response against the infection, or (2) a quicker-than-usual spread of the microorganisms (i.e., before the host is able to assemble an adequate clinical response). Special attention should be given to the absolute lack of an association of bacteremia with previous use of antibiotic therapy. This is a surprising finding, because it is expected that the presence of antibiotics in organic fluids should prevent the growth of microorganisms in culture media. Noticeably, our group has found the same apparently null effect of previous antibiotic use on the ability to recover microorganisms from patients admitted to emergency departments with clinical evidence of overwhelming infection [24].

Our study has some potential limitations. First, although bootstrapping methods are accepted procedures for internal validation of predictive models [25], the clinical application of a prediction rule implies that independent and external validation methods should be used for each new sample of patients. The relative importance of each factor also should be weighted and averaged to completely distinguish between different probabilities associated with achievement of a positive blood culture result. These facts underline the necessity to continue this research with much larger sample sizes and different clinical settings in our country. Second, our sample population comprised patients located in different inpatient settings throughout the hospital and for whom blood cultures were requested. Thus, it was impossible to precisely characterize the entire cohort of patients who were at risk for sepsis and bacteremia before the samples were requested. In addition to the previously mentioned limitations involving the stated characteristics of the sampling design, the lack of a universally accepted definition of the illness also hindered our ability to accurately characterize at-risk patients [15]. Finally, in the face of the wide spectrum of comorbidities that present in an inpatient setting, we cannot discard the possible effects of confounding—which are potential limitations that are associated with any observational design. For instance, (1) some diseases that seem to be commonly associated with bacteremia, such as pancreatitis or liver failure,

were underrepresented in our investigation; (2) transitory procedures (e.g., endoscopy) were not considered; and (3) the failure to detect an association between bacteremia and use of mechanical ventilation or altered mental status could be a consequence of an insufficient sample size with respect to these covariates.

The study provides valuable insights into an extremely complex and poorly understood problem. In developing countries, in which the access to health care is limited and scarce resources are available to the health care system, any attempt to characterize potential predictors of morbidity, mortality, or disease-related complications is a helpful tool for clinical decision making. In summary, our research showed that simple and reproducible variables that are easily obtained from clinical examination or basic diagnostic tests are clearly associated with bloodstream infections. These factors, in the appropriate context, should be instrumental for prioritizing clinicians' requests for blood cultures.

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