Predicting Bacteremia in Patients with Sepsis Syndrome

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The goal of this study was to develop and validate clinical prediction rules for bacteremia and subtypes of bacteremia in patients with sepsis syndrome. Thus, a prospective cohort study, including a stratified random sample of 1342 episodes of sepsis syndrome, was done in eight academic tertiary care hospitals. The derivation set included 881 episodes, and the validation set included 461. Main outcome measures were bacteremia caused by any organism, gram-negative rods, gram-positive cocci, and fungal bloodstream infection. The spread in probability between low- and high-risk groups in the derivation sets was from 14.5% to 60.6% for bacteremia of any type, from 9.8% to 32.8% for gram-positive bacteremia, from 5.3% to 41.9% for gram-negative bacteremia, and from 0.6% to 26.1% for fungemia. Because the model for gram-positive bacteremia performed poorly, a model predicting *Staphylococcus aureus* bacteremia was developed; it performed better, with a low- to high-risk spread of from 2.6% to 21.0%. The prediction models allow stratification of patients according to risk of bloodstream infections; their clinical utility remains to be demonstrated.

Sepsis is a serious condition, with a reported mortality of 35%–60% [1–3], and estimates suggest that there are ~500,000 cases/year in the United States, making it the 13th leading cause of death [4]. Despite the use of increasingly advanced therapeutic technology for its treatment, there has been little change in mortality over time. Because of this, substantial effort has been directed toward developing novel agents directed at different levels in the sepsis cascade; such therapies hold substantial potential for reducing mortality in this frequently fatal condition [5]. However, these agents require large investments by pharmaceutical and biotechnology companies and, thus, will be expensive [6]. For example, one such drug that was released in Europe, the monoclonal antibody HA-1A, was priced at $3000–4000 per dose [6]. To date, no novel therapy has been shown to be clearly efficacious [5, 7]. How-

ever, it seems likely that at least one of the novel therapies currently being developed will prove effective.

For these agents to be maximally effective, basic science research suggests that they should be given as soon as possible after the onset of sepsis [7]. An important problem has been that most patients with sepsis syndrome do not have bacteremia, and some do not even have a serious bacterial infection. Thus, there is substantial interest in identifying groups of patients who are particularly likely to benefit from novel therapies, some of which would only be expected to be effective against specific types of organisms.

This goal might be accomplished by using a combination of clinical data to develop models for identifying patients likely to benefit from a novel therapy effective against a particular group of organisms, such as gram-negative bacteria. These models could also be supplemented by a rapid diagnostic test or tests, such as measurement of endotoxin or cytokine levels [8, 9]. Such models, if sufficiently discriminatory and validated, could facilitate rigorous assessment of new therapeutic interventions as they become available, and they could be used to guide the use of any approved interventions.

To determine which factors might be candidates for inclusion in models to identify these groups, we searched the literature for previous reports of associations between variables and each type of bacteremia, and we canvassed experts to identify addi-

tional variables. We then undertook a prospective multicenter cohort study [10], collecting data on these and many other variables. The goals of this part of the study were to develop and validate prediction rules for documented infections to which novel therapy might be directed, including bloodstream infection of any cause (including fungal), gram-negative rod bacteremia; gram-positive coccal bacteremia, and fungal bloodstream infection.

Methods

Patient population.   All participating centers were members of the Academic Medical Center Consortium. All 8 centers were large tertiary care centers, with ~18,800–43,700 admissions annually [10]. Patient enrollment occurred between January 1993 and April 1994.

Patients surveyed represented a stratified random sample of patients in or not in intensive care units (ICUs) and with either a positive or negative blood culture, as previously described [10]. In addition, data were obtained for all patients who died in an emergency department or an ICU and for all patients who received a novel therapy for sepsis syndrome.

A randomly selected subset of sepsis episodes, the derivation set, was used to derive clinical prediction rules. These rules were then validated (tested for accuracy) in the remaining episodes, the validation set. The split between derivation and validation sets was two-thirds to one-third [11]; the same sets were used for all four rules developed.

Definitions.   Patients were enrolled if they met the prospectively derived definitions. Sepsis syndrome was defined as previously described [10], using a modification of the criteria developed by Bone [12]. Bloodstream infection was defined as any event meeting the Centers for Disease Control and Prevention's definition of bloodstream infection occurring within 24 h before or 48 h after the onset of sepsis syndrome [13]. For all bloodstream infections, the culture results were reviewed by a study investigator. Prior to development of the predictive models, each episode was classified according to whether any or only a gram-negative organism, any or only a gram-positive organism, or any or only a fungal bloodstream infection was present. Herein, we often use the term ''bacteremia'' to refer to bloodstream infection involving either bacteria or fungi, as there is no convenient term encompassing both. The initial rule developed to predict gram-positive bacteremia performed poorly. We hypothesized that this might have been due to the heterogeneity of infections produced by these organisms, and because *Staphylococcus aureus* was responsible for ~40% of the episodes of gram-positive bacteremia, we developed a separate rule predicting the presence of *S. aureus* bacteremia.

Among candidate predictors of bacteremia, documented focal infection was considered present if a culture from a usually sterile site was already positive at the time of onset of sepsis syndrome. Suspected focal infection was considered present if there was a note in the patient's chart indicating a strong suspicion of focal infection (e.g., cellulitis or perforated viscus) and antibiotics had already been or were being started. Suspected gram-negative infection was considered present if the site was the urinary tract, bowel, biliary, or another intra-abdominal source. Suspected gram-positive infection was considered present if the site was the respiratory tract, the skin, or a wound, if the infection was device-related, if suspected bacteremia from an unknown site was present, or if the patient had endocarditis. Suspected *S. aureus* infection was considered present if the patient had gram-positive infection at any site except the respiratory tract. Suspected bacteremia from an unknown site was considered present if the physicians caring for the patient indicated a strong suspicion of bacteremia on the basis of the clinical picture (e.g., presence of fever, chills, and hypotension without another obvious etiology) but no focal site could be identified. Focal fungal infection at onset was considered present only if a culture or Gram's stain revealed fungi. Acute abdomen was defined as presence of rebound tenderness or guarding of at least a moderate degree.

Data collection.   Surveyors recorded the presence of all screening criteria every day that a patient was a valid member of the surveillance group [10]. If screening criteria were met, the patient was enrolled as a case, and detailed information, including all the potential predictors of bacteremia and subtypes, were prospectively abstracted from the medical record. Additional data, including information about whether bacteremia or infection was indeed present in the initial episode and information about the outcome and treatment of the episode, were gathered 28 days after entry.

Factors evaluated as potential predictors included variables identified as correlates of bacteremia in previous analyses [14–17] and variables suggested by members of the study group. The following five types of variables were assessed for association with bacteremia of any type as assessed at sepsis onset: (1) historic factors, including the presence of shaking chills, liver disease (cirrhosis, chronic hepatitis, or hepatic failure), diabetes, or bowel perforation (during current admission), intravenous drug abuse, or history of bacteremia or organ transplantation (bone marrow, liver, heart, kidney, lung, or small bowel); (2) physical examination findings, including elevated temperature, presence of hypotension, maximum pulse rate, acute abdomen, presence of confusion or delirium, low urine output (<30 mL/h for 2 h); (3) laboratory findings, including the presence of pyuria (mean leukocyte count ≥4/high-power field in urine), elevated leukocyte count, presence of neutropenia, percent bands >12, decreased platelet count, presence of renal failure (creatinine ≥3 mg/dL, on dialysis, or acute renal failure noted in chart by a physician within 24 h of onset), presence of hyperglycemia (glucose ≥250 mg/dL), low systemic vascular resistance (≤900 dyne-s-cm^{-5}); (4) treatment factors, including immunosuppressive drug therapy, location at onset (ICU, emergency department, or general care unit), absence of antibiotic therapy, antibiotic therapy for >4 days before onset, number of antibiotics received prior to onset during hospitalization, whether using vasopressors, presence of a Hickman catheter, presence of a Foley catheter for a prolonged period, and whether receiving mechanical ventilation; and (5) severity of underlying disease and comorbidity.

Severity was assessed by use of the APACHE II and III scores [18–20], the SAPS (simplified acute physiology) II score [21], the MPM (mortality probability models) II score [22], and a modification of McCabe and Jackson's scale in which patients were stratified into 3 groups, the rapidly fatal group (>50% predicted chance of fatality within 1 month, secondary to any underlying disease), the eventually fatal group (>50% predicted chance of fatality within 5 years from underlying disease), and nonfatal (no

underlying disease likely to be fatal within 5 years) [16]. In the analyses, data are presented only using the sepsis-specific APACHE III, the SAPS II, and the modification of McCabe and Jackson's scale; the first two scores best predict mortality in this data set (Hibberd P, unpublished data), and the latter was inexpensive to assess in comparison. Comorbidity was assessed by use of the Charlson comorbidity score [23].

Variables evaluated for association with subtypes of bacteremia included all of the above. In addition, variables for gram-negative bacteremia included documented or presumed focal gram-negative infection, presence of a biliary stent, and history of gram-negative bacteremia. Variables for gram-positive bacteremia included documented or presumed focal gram-positive infection and history of gram-positive bacteremia. Variables for *S. aureus* bacteremia included documented or presumed *S. aureus* infection, and variables for fungal bloodstream infection included isolation of fungus from another site and history of fungal bloodstream infection.

Analysis. The primary issue of interest in this analysis was to optimize clinical decision-making at the time when novel therapy might be considered; therefore, the unit of analysis chosen was the episode of sepsis syndrome. Similarly, only information available at the time of onset of sepsis was eligible for entry into the predictive models, although data that became available within the following 6 h were collected and used in the mortality analyses (Hibberd P, unpublished data).

Because of the sampling plan (for details see Sands et al. [10]), individual episodes carried different weights, and all data presented are weighted, including the multivariate analyses. In particular, only 10% of non-ICU patients with negative blood cultures were sampled, so cases in this group, compared with ICU patients, received a weight of 3.8.

Relationships between variables collected at the time of onset of sepsis and the outcome of interest in the derivation set were first evaluated using univariate analysis, using the weighted χ^2 statistic for categorical variables, weighted t tests for normally distributed continuous variables, and weighted Wilcoxon rank sum tests for nonparametric comparisons. Univariate correlates of bacteremia ($P < .10$) were then entered into stepwise logistic regression analyses. Factors with $P < .05$ were retained, except for fungemia, in which the threshold was .10, because of the small number of outcomes and because with a threshold of .05, only one factor would have entered the model. For all models, the unit of analysis was the episode of sepsis syndrome, and altogether there were 1342 episodes among 1166 patients with 1190 hospital admissions. Because of correlation among episodes within the same patient, all the models were reestimated using a generalized estimating approach [24] that allows objective evaluation of the extent to which this is an issue. None of the P values in these models changed significantly (or crossed a level of .05); these results are not presented.

The results of the multivariate analyses were next used to develop clinical prediction models. The relative values of β coefficients for significant predictor variables were adjusted for ease of use by clinicians. This meant that the lowest β coefficient value, after rounding, was assigned a score of 1, and other values were rounded to integer multiples of that score. For example, in a model with three variables, with coefficients of 0.5, 0.7, and 1.2, the first two variables would be assigned a score of 1, and the third variable would be assigned a score of 2. The risk score for an individual

patient can thus be determined by adding the points for each of the significant predictor variables.

The performance of models was tested in the validation sets. Discriminatory performance of the model in the derivation set and the validation set were compared using receiver-operating characteristic (ROC) curve analysis [25, 26], and calibration performance was assessed by plotting observed and predicted event frequencies by risk group as derived from logistic regression analysis [27]. The ROC curve plots sensitivity against 1 minus specificity, using a range of ''cut-off'' values for a positive prediction. The ROC curves in this case thus describe the relationship between the true-positive and false-positive predictions of bacteremia. The area under the curve is a measure of the accuracy of discrimination of the rules' predictions; it would be 0.5 by chance alone, and increases toward 1 as the accuracy of the rule improves. To make the models easier to interpret, likelihood ratios were derived for each clinically relevant stratum; the likelihood ratio for a test result is the ratio of its probability of occurrence if the disease is present (true-positive rate) to its probability of occurrence if the disease is absent (false-positive rate) [28].

Results

The dataset included 1342 episodes of sepsis syndrome, which were divided randomly into 881 episodes in the derivation set and 461 episodes in the validation set (table 1). Just over half the patients were male, ~60% were on medical ser-

Table 1. Patient characteristics in the derivation and validation sets for patients with sepsis syndrome.

Characteristic	Derivation set ($n = 881$)	Validation set ($n = 461$)
Age, years, mean ($\pm$SD)	58.6 (17.2)	59.2 (17.1)
Male, no. (weighted %)	494 (56.4)	267 (59.2)
Hospital service, no. (weighted %)		
Medical	518 (60.9)	268 (60.7)
Surgical	355 (37.6)	190 (38.8)
Obstetrics-gynecology	8 (1.5)	3 (0.5)
Nonwhite race, no. (weighted %)	228 (26.5)	103 (20.8)
SAPS II score prior to onset of sepsis, mean ($\pm$SD)	25.7 (14.4)	26.4 (13.9)
APACHE III chance of 28-day survival, mean ($\pm$SD)	0.68 (0.24)	0.66 (0.24)
Charlson score prior to onset of sepsis, mean ($\pm$SD)	2.8 (2.4)	2.6 (2.4)
Length of stay, days, median (25th, 75th percentiles)	21 (11, 28)	22 (10, 28)
Level of care at onset, no. (weighted %)		
General care unit	219 (35.2)	103 (29.3)
Intensive care unit	564 (52.5)	312 (60.4)
Emergency department	96 (12.3)	46 (10.4)

NOTE. SAPS II is simplified acute physiology score II. APACHE III refers to sepsis-specific model. %s are weighted by sampling fraction. No characteristics differed between sets except that weighted % of patients in intensive care unit at onset of sepsis was lower in derivation set than in validation set ($P < .02$).

vices, and almost all of the rest were on surgical services. About one-fourth of the patients were nonwhite. At the onset of sepsis syndrome, about one-third of the patients were on general care units, half were in ICUs, and the remainder were in the emergency room. All these characteristics were similar between the 2 groups, except that the weighted percent of patients in ICUs at the onset of sepsis was lower in the derivation set than in the validation set (52.5% vs. 60.4%; $P = .02$).

In the derivation set, 283 (26.6%) of the episodes were associated with bacteremia (table 2). Episodes of bacteremia that included gram-positive cocci were the most frequent (13.6% of all sepsis episodes), followed by gram-negative rods (10.1%); fungi were found in 2.3% of episodes in the derivation set. These percentages were similar between the derivation and validation sets. Results are presented both for episodes that included any of a specific organism type and for those that included only that type. In general, the differences were small, and the analyses reported here use the ''any'' endpoint as the primary outcome. Infection was eventually found to be present in 94.4% of episodes in the derivation set; in most cases this was documented by a positive culture from a normally sterile site (54.7% of episodes), compared with only 39.7% in which it was presumed but not documented (e.g., cellulitis).

Each episode was also categorized according to the specific type of organism present (table 3). Gram-positive cocci accounted for 42.2% of the episodes, with the two leading types being *S. aureus* (17.1%) and coagulase-negative staphylococci (11.1%). Gram-negative rods accounted for 33.2% of all bacteremic episodes; pseudomonal bacteremia accounted for about one-fifth of these. Most of the episodes of fungal bloodstream infection were caused by *Candida species*. Polymicrobial infections accounted for 10.5% of the episodes.

Univariate correlates of bloodstream infection. In univariate analyses, 14 variables were correlated with the presence of

Table 3. Organism identification and frequencies in the derivation set for patients with sepsis syndrome.

Results, no. (weighted %)	True positive ($n = 283$)
Gram-positive cocci and no other organisms	112 (41.9)
Staphylococcus aureus	45 (16.8)
Staphylococcus epidermis	26 (11.1)
Enterococcus species	21 (6.2)
Streptococcus pneumoniae	13 (5.5)
Streptococcus pyogenes (group A)	2 (0.7)
Other *Streptococcus* species	5 (1.6)
Gram-negative rods and no other organisms	99 (33.2)
Enterobacteriaceae	80 (26.8)
Pseudomonas species	19 (6.4)
Fungi and no other organisms	20 (7.0)
Candida species	17 (5.9)
Other fungus	3 (1.1)
Polymicrobial	31 (10.5)
Other	21 (7.4)
Clostridium species	5 (1.8)
Neisseria gonorrhoeae	2 (0.7)
Miscellaneous	14 (4.9)

any bacteremia at the $P < .10$ level (table 4), with the strongest clinical correlates being presence of a suspected or documented infection at onset of sepsis ($P < .001$) and several antibiotic factors, including absence of current antibiotic therapy ($P < .001$). Patients in ICUs at onset were less likely to be bacteremic ($P < .001$), while those in the emergency department had a higher risk of bacteremia ($P < .004$). Among severity and comorbidity measures, neither the APACHE III nor the SAPS II score nor the Charlson comorbidity index was correlated with the presence of bacteremia.

There were 6 significant correlates of gram-positive bacteremia. The strongest clinical correlate was suspected or documented focal infection with gram-positive cocci at onset ($P < .001$). Location in an ICU ($P < .005$) and higher SAPS II score were both negatively correlated with likelihood of gram-positive bacteremia ($P < .019$). For *S. aureus* bacteremia, there were eight univariate correlates, and suspected or documented focal infection with *S. aureus* ($P < .001$) and intravenous drug abuse ($P < .018$) were the strongest.

The strongest correlates of gram-negative bacteremia were presence of chills ($P < .001$), focal abdominal signs ($P < .002$), and not receiving antibiotics at the onset of the episode ($P < .001$). Among the 17 correlates of fungal bloodstream infection, the strongest included documented fungal infection at the beginning of the episode ($P < .001$) and any liver disease ($P < .004$).

Multivariate analyses. Independent predictors of bacteremia of any type were suspected or documented focal infection at onset, absence of antibiotic therapy at onset, presence of liver disease, presence of a Hickman catheter, altered mental status within 24 h of sepsis onset, and focal abdominal signs within 24 h of onset (table 5). The two strongest of these

Table 2. Blood culture and infection results in the derivation and validation sets for patients with sepsis syndrome.

Results, no. (weighted %)	Derivation set ($n = 881$)	Validation set ($n = 461$)
Any bacteremia	283 (26.6)	153 (31.0)
Any gram-positive cocci	139 (13.6)	70 (13.6)
Only gram-positive cocci	113 (11.2)	51 (10.0)
Any gram-negative rods	114 (10.1)	63 (13.5)
Only gram-negative rods	99 (8.8)	52 (11.5)
Any fungi	25 (2.3)	19 (3.4)
Only fungi	20 (1.9)	14 (2.5)
Others*	22 (2.1)	15 (3.0)
Any infection	828 (94.4)	436 (95.1)
Documented[†]	512 (54.7)	302 (62.1)
Presumed[†]	316 (39.7)	134 (33.0)

* Includes *Clostridium, Corynebacterium, Neisseria, and Mycobacterium* species.

[†] See Methods for definitions.

Table 4. Univariate correlates of true-positive blood cultures in the derivation set for patients with sepsis syndrome.

Variable, no. (weighted %)	True-positive	All other results	P
Outcome: any bacteremia	(n = 283)	(n = 598)	
History or physical			
Suspected or documented focal infection at onset*	167 (58.5)	231 (39.7)	.001
Altered mental status within 24 h of onset	81 (27.2)	118 (18.1)	.004
Focal abdominal signs within 24 h of onset	43 (15.8)	60 (9.4)	.008
Chills[†]	69 (27.0)	76 (19.0)	.011
Any liver disease[‡]	38 (13.6)	45 (8.8)	.039
Laboratory			
Neutrophil band count >12% within 24 h of onset	61 (20.7)	77 (14.4)	.025
Severity or comorbidity, mean (±SD)			
Charlson comorbidity index	3.0 (2.6)	2.7 (2.4)	.152
SAPS II score	24.9 (14.3)	26.0 (14.5)	.253
APACHE III chance of 28-day survival	0.68 (0.25)	0.68 (0.23)	.942
Treatment			
No antibiotics prior to onset	477 (78.0)	173 (62.8)	.001
In ICU at onset	118 (38.7)	446 (57.3)	.001
In emergency ward at onset	51 (17.7)	45 (10.4)	.004
Antibiotic use for >4 days prior to onset	93 (32.7)	252 (41.9)	.015
Pressor use within 24 h	47 (14.7)	164 (21.4)	.028
Use of >5 antibiotics before onset	36 (13.1)	109 (19.2)	.037
Hickman catheter present	45 (16.6)	56 (11.7)	.056
Ventilator use prior to sepsis onset	76 (26.7)	148 (20.8)	.063
Outcome: any gram-positive cocci	(n = 139)	(n = 742)	
History or physical			
Suspected or documented focal infection with any gram-positive cocci at onset	72 (49.2)	242 (30.2)	.001
Intravenous drug use	10 (7.0)	10 (2.3)	.006
Renal failure[§]	27 (22.0)	116 (14.7)	.042
Severity or comorbidity			
SAPS II score	23.1 (13.7)	26.1 (14.5)	.019
Charlson comorbidity index	2.6 (2.4)	2.8 (2.5)	.200
APACHE III chance of 28-day survival, mean (±SD)	0.69 (0.22)	0.67 (0.25)	.332
Treatment			
In ICU at onset	63 (40.4)	501 (52.2)	.005
Pressor use within 24 h	20 (11.9)	191 (20.8)	.024
Outcome: any *Staphylococcus aureus*	(n = 55)	(n = 826)	
History or physical			
Suspected or documented focal infection with *S. aureus* at onset	24 (40.7)	99 (10.4)	.001
Intravenous drug abuse	5 (8.9)	15 (2.6)	.018
Any liver disease[‡]	7 (17.5)	76 (9.7)	.087
Severity or comorbidity			
SAPS II score	21.4 (14.1)	25.9 (14.4)	.023
Charlson comorbidity index	2.6 (2.4)	2.8 (2.5)	.597
APACHE III chance of 28-day survival, mean (±SD)	0.72 (0.20)	0.67 (0.24)	.089
Treatment			
Hemodialysis prior to onset	4 (11.0)	34 (4.0)	.028
Ventilator use prior to onset	18 (34.9)	206 (21.6)	.036
Outcome: any gram-negative rods	(n = 114)	(n = 767)	
History or physical			
Chills	39 (35.7)	106 (19.5)	.001
Focal abdominal signs within 24 h of onset	23 (21.1)	80 (10.0)	.002
History of gram-negative bacteremia	10 (8.9)	24 (3.3)	.014
High temperature (≥39°C) within 24 h of onset	9 (7.9)	21 (3.5)	.050
Suspected or documented focal infection with gram-negative rods at onset*	26 (23.4)	105 (16.1)	.084
Laboratory			
Neutrophil band count >12% within 24 h of onset	29 (24.4)	109 (15.2)	.025
Low SVR (≤900 dyne-s-cm^5)	6 (5.1)	114 (12.6)	.044

Table 4. (*Continued*)

Variable, no. (weighted %)	True-positive	All other results	P
Severity or comorbidity			
Charlson comorbidity index	3.0 (2.8)	2.8 (2.4)	.315
SAPS II score	25.1 (13.9)	25.7 (14.5)	.650
APACHE III chance of 28-day survival, mean (±SD)	0.67 (0.24)	0.68 (0.24)	.827
Treatment			
No antibiotics prior to onset	591 (76.6)	59 (50.4)	.001
In ICU at onset	40 (33.1)	524 (54.5)	.001
In emergency ward at onset	24 (22.1)	72 (11.2)	.004
Hickman catheter present	22 (20.2)	79 (12.2)	.036
Use of >5 antibiotics prior to onset	12 (10.2)	133 (18.4)	.057
Total parenteral nutrition prior to onset	5 (4.1)	11 (1.3)	.060
On antibiotics for >4 days prior to onset	34 (30.9)	311 (40.4)	.085
Outcome: any fungus	(n = 25)	(n = 856)	
History or physical			
Fungal infection at any site prior to onset of sepsis	11 (42.6)	41 (4.5)	.001
Any liver disease[‡]	8 (30.3)	75 (9.6)	.004
Status after liver transplant	4 (13.9)	16 (2.5)	.007
Status after organ transplant[∥]	6 (22.1)	55 (6.8)	.013
History of any fungemia	2 (8.2)	9 (1.4)	.029
Bowel perforation in current admission	3 (12.3)	32 (3.3)	.041
Immunocompromised	13 (50.8)	242 (30.3)	.053
Altered mental status within 24 h of onset	9 (36.9)	190 (20.1)	.070
Laboratory			
Hyperglycemia (>250 mg/dL)	7 (28.7)	122 (12.1)	.032
Pyuria (mean leukocytes in urine ≥4)	7 (28.7)	122 (14.4)	.078
Severity or comorbidity			
Charlson comorbidity index	3.6 (2.2)	2.8 (2.5)	.064
APACHE III chance of 28-day survival, mean (±SD)	0.59 (0.27)	0.68 (0.24)	.114
SAPS II score	27.0 (15.6)	25.6 (14.4)	.658
Treatment			
Antibiotic use for >4 days prior to onset	17 (67.2)	328 (38.8)	.013
In hospital >10 days prior to onset	15 (59.0)	278 (32.5)	.016
Steroid use within 1 week of onset	12 (46.7)	192 (23.8)	.022
Hickman catheter present	8 (30.3)	93 (12.6)	.025
Pressor use within 24 h of onset	10 (38.5)	201 (19.2)	.036
On ventilator prior to onset	10 (41.0)	214 (21.9)	.046

NOTE.　All %s weighted by sampling fraction. ICU, intensive care unit; SVR, systemic vascular resistance; TPN, total parenteral nutrition; SAPS, simplified acute physiology score.

* Sites for suspected gram-negative rods at time of onset: urinary tract, bowel, biliary, other intraabdominal sites. Sites for suspected gram-positive cocci at time of onset: respiratory tract, skin, wound, device-related, endocarditis, infection site unknown.

[†] Shaking chills or rigor on physical examination.

[‡] Defined as cirrhosis with or without portal hypertension, chronic hepatitis within last 6 months, hepatic failure with coma or encephalopathy within last 6 months.

[§] Urine output ≤30 mL/h for 2 h.

[∥] Bone marrow, liver, heart, renal, lung, or small bowel transplant.

were absence of antibiotic therapy at onset and suspected or documented infection at onset. Had we excluded absence of antibiotic therapy at onset, the model would have included presence of chills and elevated band count, while presence of focal abdominal signs would have dropped out.

Predictors of bacteremia caused by gram-positive cocci were intravenous drug abuse and suspected or documented focal infection with gram-positive cocci at onset (table 5). Because it was not possible to develop a model that adequately stratified the patients, a model using *S. aureus* bacteremia as the outcome was developed. Independent predictors were suspected or documented focal infection with *S. aureus* at onset, hemodialysis, and mechanical ventilation at sepsis onset.

The independent predictors of gram-negative bacteremia were different; they included use of total parenteral nutrition before onset, absence of antibiotic therapy before onset, history of gram-negative bacteremia, presence of a Hickman catheter, focal abdominal signs, and presence of chills (table 5).

Table 5. Independent predictors of bacteremia identified by logistic regression analysis in patients with sepsis syndrome.

Variable	β	Odds ratio	Lower CI	Upper CI	Points*
Any bacteremia					
Intercept	−2.03				
Suspected or documented focal infection					
at onset	0.86	2.4	1.7	3.3	3
No antibiotics before onset	0.84	2.4	1.6	3.3	3
Any liver disease[†]	0.59	1.8	1.1	3.0	2
Hickman catheter present	0.57	1.8	1.1	2.8	2
Altered mental status within 24 h	0.61	1.8	1.3	2.6	2
Focal abdominal signs within 24 h	0.49	1.6	1.0	2.6	2
Any *Staphylococcus aureus*					
Intercept	−3.62				
Suspected or documented focal infection					
with *S. aureus* at onset	1.89	6.6	3.4	12.7	2
Hemodialysis before onset	1.09	3.0	1.1	8.4	1
Ventilator use before onset	0.79	2.2	1.1	4.3	1
Any gram-negative rods					
Intercept	−3.1				
Total parenteral nutrition before onset	1.57	4.8	1.3	17.2	3
No antibiotics before onset	1.30	3.7	2.2	6.0	2
History of gram-negative bacteremia	1.15	3.2	1.3	8.0	2
Hickman catheter present	0.72	2.1	1.1	3.8	1
Focal abdominal signs within 24 h	0.63	1.9	1.0	3.5	1
Chills	0.51	1.7	1.0	2.8	1
Any fungemia					
Intercept	−5.27				
Fungal infection at any site	2.32	10.1	3.6	28.6	5
Bowel perforation	1.58	4.9	1.0	25.0	3
Pyuria	1.27	3.6	1.2	10.8	2
Any liver disease[†]	1.16	3.2	1.0	10.2	2
Hickman catheter present	1.10	3.0	0.9	10.0	2
Altered mental status within 24 h	0.99	2.7	1.0	7.6	2

NOTE. CI, confidence interval; TPN, total parenteral nutrition.

* Points for each organism category were assigned by dividing β coefficients by appropriate denominator to yield integer scores.

[†] Defined as cirrhosis with or without portal hypertension, chronic hepatitis within last 6 months, hepatic failure with coma or encephalopathy within last 6 months.

The factors predicting fungal bloodstream infection were presence of a documented (as determined by positive culture or microscopy) non-bloodstream fungal infection, pyuria, any liver disease, or a Hickman catheter; bowel perforation; or altered mental status within 24 h (table 5). Because of the small number of outcomes, $P < .10$ was used as the threshold for entering the model; a threshold of $P < .05$ only permitted entry of patients with documented fungal infection.

Clinical prediction rules. As shown in table 6, the prediction rule for presence of any bacteremia stratified episodes into risks ranging from 14.5% to 60.6% in the derivation set; 20% of the bacteremia episodes were in the 2 lowest-risk groups. The rule performed comparably well in the validation set (ROC area, 0.69 ± 0.02 in derivation set vs. 0.67 ± 0.03 in validation set; figure 1). The distribution of episodes and cases across the risk groups is shown in figure 2. A problem with this rule,

however, is that 30% of episodes fall into group 3, which has a probability of bacteremia after the test that is similar to the pretest probability (likelihood ratio, 0.9). The remaining 70% of the cases could, however, be placed into groups with higher and lower risks. Calibration performance of the model was good (figure 3).

The rule for gram-positive bacteremia was the least discriminatory of the four rules, with a spread in probability of from 9.8% to 32.8% in the derivation set. The ROC areas were 0.62 ± 0.03 in the validation set and 0.60 ± 0.04 in the derivation set (data not shown); there was no significant difference in ROC areas between the sets. A rule using *S. aureus* bacteremia as the outcome had an ROC area of 0.70 ± 0.04 in the derivation set and 0.74 ± 0.05 in the validation set (figure 1). Most of the cases were placed in the 2 groups at highest risk (figure 2).

**Table 6.** Performance of the prediction rules for bacteremia and subtypes of bacteremia.

	Bacteremia present	Risk score				
		0	1–2	3–4	5–6	≥7
Any bacteremia						
Derivation set	Yes	32 (14.5)	25 (18.5)	74 (20.5)	90 (38.0)	62 (60.6)
	No	162 (85.5)	101 (81.5)	195 (79.5)	112 (62.0)	28 (39.4)
Validation set	Yes	19 (15.0)	11 (18.6)	52 (32.0)	45 (39.6)	26 (64.4)
	No	84 (85.0)	46 (81.4)	106 (68.0)	58 (60.4)	14 (35.6)
	LR	0.4 (0.3, 0.6)	0.5 (0.4, 0.7)	0.9 (0.7, 1.0)	1.7 (1.4, 2.0)	4.4 (3.1, 6.2)

		Risk score				
		0	1	2	≥3	
Any *Staphylococcus aureus*						
Derivation set	Yes	18 (2.6)	11 (4.8)	20 (18.9)	6 (21.0)	
	No	522 (97.4)	194 (95.2)	86 (81.1)	24 (79.0)	
Validation set	Yes	9 (2.7)	4 (4.6)	11 (19.0)	5 (33.3)	
	No	295 (97.3)	85 (95.4)	42 (81.0)	10 (66.7)	
	LR	0.5 (0.4, 0.7)	0.8 (0.5, 1.3)	3.6 (2.6, 4.9)	4.9 (2.5, 9.0)	

		Risk score				
		0	1	2	3	≥4
Any gram-negative rods						
Derivation set	Yes	27 (5.3)	16 (6.2)	31 (12.8)	18 (20.3)	22 (41.9)
	No	385 (94.7)	151 (93.8)	165 (87.2)	49 (79.7)	17 (58.1)
Validation set	Yes	16 (5.7)	13 (20.0)	17 (17.7)	12 (32.5)	5 (24.8)
	No	224 (94.3)	59 (80.0)	71 (82.3)	31 (67.5)	13 (75.2)
	LR	0.5 (0.4, 0.6)	0.9 (0.6, 1.3)	1.3 (1.0, 1.7)	2.5 (1.7, 3.6)	5.9 (3.6, 9.6)

		Risk score			
		0	1–3	4–6	≥7
Any fungus					
Derivation set	Yes	3 (0.6)	5 (1.3)	6 (5.1)	11 (26.1)
	No	418 (99.4)	317 (98.7)	98 (94.9)	23 (73.9)
Validation set	Yes	5 (1.9)	1 (0.6)	5 (5.9)	8 (35.9)
	No	213 (98.1)	160 (99.4)	58 (94.1)	11 (64.1)
	LR	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	2.1 (1.2, 3.4)	16.5 (10.1, 25.9)

NOTE. Data are no. (weighted %), except for LRs (likelihood ratios), which were calculated from combined derivation and validation sets.

The gram-negative bacteremia rule achieved a spread of from 5.3% to 41.9% in the derivation set. In the validation set, the ROC area was 0.70 ± 0.03, versus 0.67 ± 0.04 in the derivation set (figure 1). However, in the validation set, two anomalies occurred. First, the risk in the group with a risk score of 1 (group 2) had a higher probability of bacteremia (20.3%) than the group with a risk score of 2 (group 3; 17.7%), and group 4 also had a higher probability of bacteremia (32.5%) than did group 5 (24.8%). Nonetheless, this rule may be quite useful because 52% of the validation set fell into the lowest-risk group, which had only a 5.7% probability of gram-negative bacteremia. In addition, the rule identified small high-risk groups; the 2 highest-risk groups had likelihood ratios of 2.5 (group 4) and 5.9 (group 5). For the highest-risk groups, the calibration curves show that the observed probabilities are somewhat higher than predicted (figure 3).

The rule for predicting fungemia performed well in both the derivation and validation sets. In the derivation set, it achieved a spread in risk from 0.6% to 26.1% between the lowest- and highest-risk groups. Correspondingly, this rule had the highest ROC areas: 0.82 ± 0.05 in the derivation set and 0.75 ± 0.08 in the validation set (figure 1). Moreover, when the 2 highest-risk groups were combined in the validation set, the rule identified a small population (only 18% of the validation set), which included 13 of the 19 cases; the risk of fungemia was very low in the remaining 82% of episodes. This reflects in large part the strength of the associ-
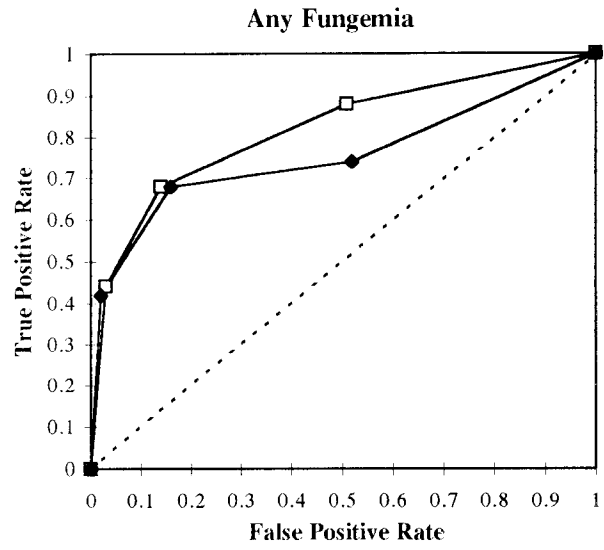
Any Bacteremia
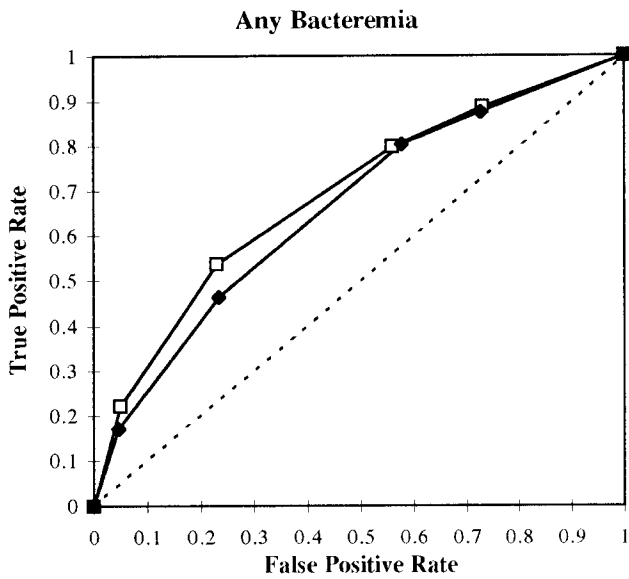
Derivation set area (+/-SD) = 0.69 (0.02)
Validation set area (+/-SD) = 0.67 (0.03)
P value = 0.291

Any Staphylococcus Aureus
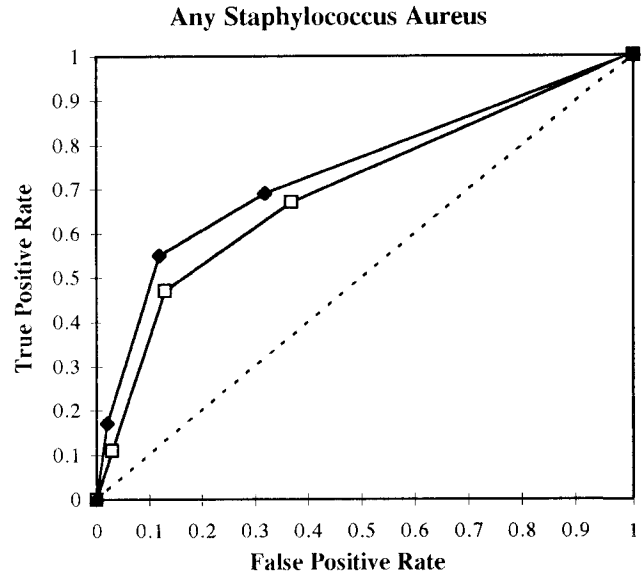
Derivation set area (+/-SD) = 0.70 (0.04)
Validation set area (+/-SD) = 0.74 (0.06)
P value = 0.274

Any Gram-Negative Rods
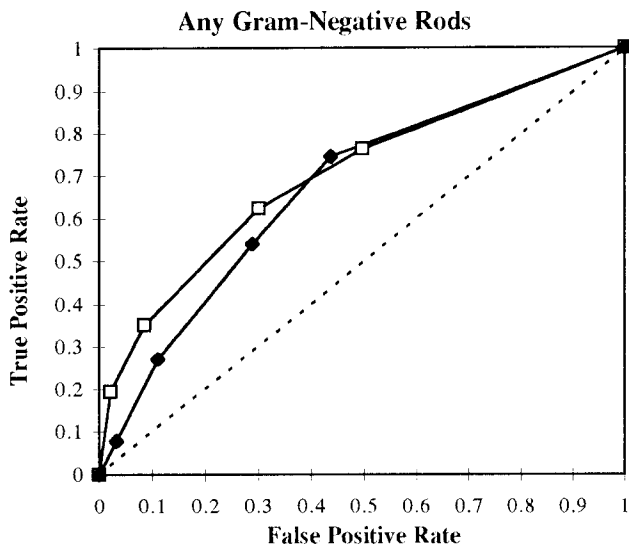
Derivation set area (+/-SD) = 0.70 (0.03)
Validation set area (+/-SD) = 0.67 (0.04)
P value = 0.262

Any Fungemia

Derivation set area (+/-SD) = 0.82 (0.05)
Validation set area (+/-SD) = 0.75 (0.08)
P value = 0.238

Figure 1. Receiver-operating characteristic curves for derivation set (□) and validation set (■) in study to determine prediction rules for bacteremia in sepsis. Dashed line represents test of no discriminative ability. *P* is probability that area of derivation curve is not greater than area of validation curve.

Any Bacteremia

Any Staphylococcus Aureus

Any Gram-Negative Rods

Any Fungemia
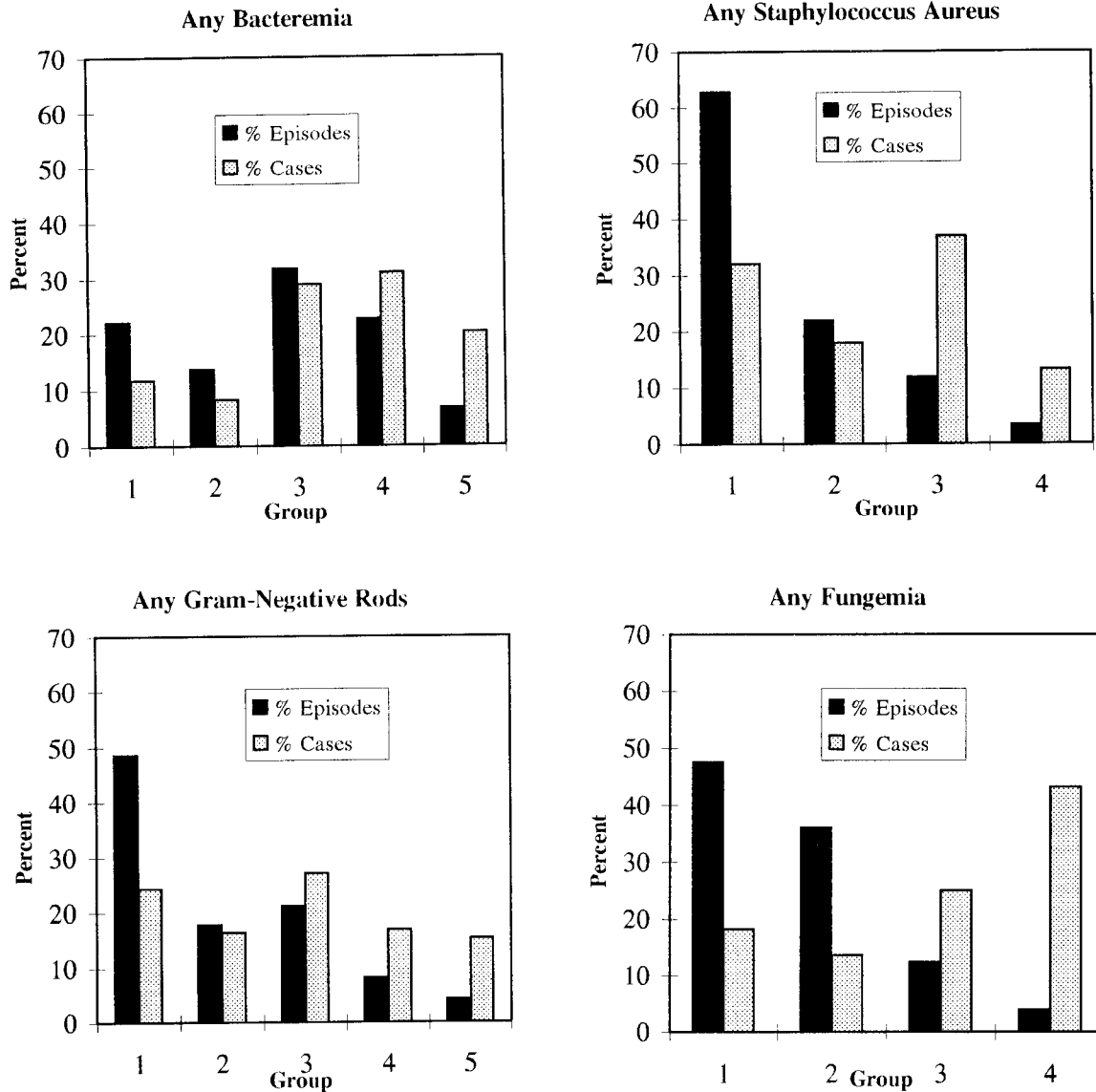
Figure 2. Distribution of episodes across risk groups in each of 4 prediction models in study to determine prediction rules for bacteremia in sepsis. Black columns, % of total episodes of sepsis syndrome in group; stippled columns, % of total bacteremia cases in group. Derivation and validation sets are combined.

ation between positive fungal cultures (other than blood-stream) at sepsis onset and fungemia.

Discussion

In this study, we determined the frequency of bacteremia in patients with sepsis syndrome and the frequency of the main subtypes that may be targeted by novel therapies. We also derived and validated clinical prediction rules for bloodstream infections for these outcomes. The rule for bacteremia of any type performed well in that it achieved a 4-fold difference in percent risk between the highest- and lowest-risk groups, although 26% of bloodstream infections fell into the 2 lowest-

risk groups. The rules for gram-negative bacteremia and fungemia may be most useful clinically. For gram-negative bacteremia, the rule identified a group comprising 52% of the patients in the validation set with only a 6% probability of gram-negative bacteremia and a much smaller group with a >20% probability of gram-negative bacteremia. For fungemia, a subgroup including only 18% of those with sepsis syndrome was identified, which included 68% of the episodes of fungemia in the validation set; in the remainder of the episodes, the probability of fungemia was only ~2%. The rule for gram-positive bacteremia performed poorly; however, the rule predicting *S. aureus* bacteremia performed better. The 2 lowest-risk groups included 85% of the validation set and had a proba-
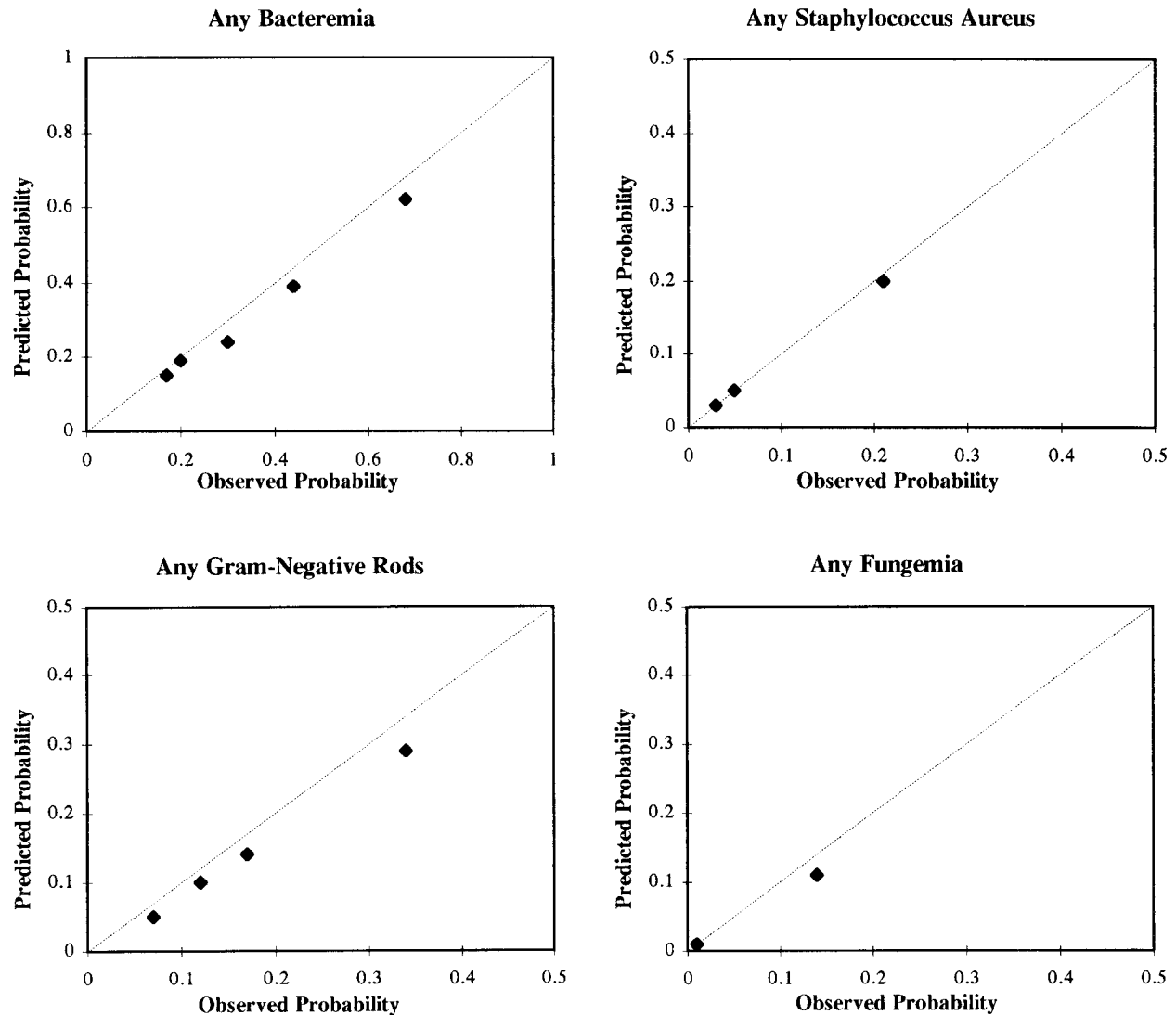
Figure 3. Observed vs. predicted probability of positive result for 4 prediction models in study to determine prediction rules for bacteremia in sepsis. Each ■ represents mean probability for subgroup of study patients, as defined using Hosmer and Lemeshow goodness-of-fit test. Dashed line corresponds to perfect agreement between observed and predicted values.

bility of *S. aureus* bacteremia of only 3%, while the higher-risk groups had probabilities of 19% and 33%.

Important proportions of cases for all the rules fall into the group at low risk of bacteremia. This suggests that other information, specifically new rapid diagnostic tests, which either suggest the presence of a specific infection or identify an episode as particularly likely to result in an adverse outcome, may be useful. This information can be used in conjunction with these or similar rules that use readily available clinical information to stratify patients according to likelihood of subtypes of bacteremia.

The clinical utility of these rules remains to be determined. Clinical prediction rules in general have not received as much use as might be expected [29], although the increasing use of computers in medicine offers a promising way of helping

physicians remember these rules and of making them available when needed [30]. Fundamental to the clinical utility of the rules is whether the degree of stratification that has been achieved crosses a threshold that affects clinical decision-making. Clinical decision thresholds are a function of the clinical benefits and risks and of the financial costs of treatment strategies and the probability of their occurrence. Patient preferences also affect these decisions. Such issues are complex, and the answers are often not evident a priori; they can best be resolved by use of modeling or formal decision analysis [31]. When Schulman et al. [32] performed a simulated analysis of the cost-effectiveness of a monoclonal anti-endotoxin antibody, they used a base case probability of 36% for gram-negative bacteremia, which was present only in the highest-risk group in this study. With that probability, the novel therapy appeared

cost-effective. However, as the probability of gram-negative bacteremia fell, cost-effectiveness worsened asymptotically, suggesting that use of this agent under their other assumptions would not have been cost-effective.

Another key issue is whether the presence of documented bacteremia is the outcome that should be predicted [9]. There are some patients, for example with intraabdominal sepsis, who never have positive blood cultures, yet who have adverse outcomes that are clearly related to sepsis. In addition, the prior use of antibiotic therapy affected the likelihood of obtaining a positive blood culture in this study, although it has not always in other studies [16]; the extent to which this is a problem cannot be determined because false-negative blood cultures cannot currently be identified. Advantages of using bacteremia as an outcome are that it is relatively reliable compared with clinical judgments and it allows grouping of patients by the type of organism present. Other approaches include developing rules to predict infection-related outcomes, such as specific types of organisms (independent of bacteremia), or other outcomes, such as organ failure [9], short- or long-term mortality, and quality of life.

A number of previous studies have attempted to develop indices to predict bacteremia of all causes in hospitalized patients with sepsis [14] and in other hospitalized patients who have blood cultures performed [16, 17, 33]. Most studies have included data from only a single institution, a fact that raises questions about whether the results can be generalized. In addition, many randomized trials have reported the frequency of bacteremia of different types, although the patients in these studies were highly selected and may not be representative of all hospitalized patients with sepsis [34]. In a population of patients at VA Medical Centers, Peduzzi et al. [14] found that elevated temperature, low systolic blood pressure, and low platelet count were independently predictive of bacteremia, although these factors did not predict bacteremia with sufficient accuracy to be clinically helpful.

We previously [16] found in a cohort of hospitalized patients who had blood cultures performed that elevated temperature, rapidly or ultimately fatal disease, shaking chills, intravenous drug abuse, acute abdomen on examination, and major comorbidity were independent predictors of bacteremia. These factors were used to develop a prospectively validated clinical prediction rule that stratified patients into groups with a probability of bacteremia ranging from 2% to 14% in the validation set. However, when Imperiale et al. [35] attempted to validate this rule in another institution, there was significant degradation in performance, particularly in the low-risk group, with a probability of bacteremia ranging from 6% to 15%. They also developed and validated another rule, using hypotension, pulse ≥120, band count >20%, significant bacteriuria, and not receiving antibiotics as risk factors [17].

In an analysis from Israel, Mozes et al. [33] found independent predictors of bacteremia to be temperature of ≥39°C, elevated serum alkaline phosphatase, current immunosuppres-

sive therapy, and hospitalization in an ICU. Some factors important in the United States were not found in Israel (e.g., Israeli surgeons did not perform blood cultures in patients with an acute abdomen and there was little intravenous drug abuse). In this analysis, we included only patients with sepsis syndrome, so factors such as tachycardia were present to some degree in all patients. Independent predictors of any bacteremia were presence of a suspected or documented infection at sepsis onset, absence of antibiotic therapy at onset, liver disease, presence of a Hickman catheter, altered mental status, and focal abdominal signs. This rule performed well in both the derivation and validation sets, with one limitation being that the middle group, which comprised about one-third of each set, had a probability of bacteremia similar to that of the entire cohort.

Although there are thousands of publications regarding infections caused by gram-positive organisms, we could not identify another study in which a clinical prediction rule targeting gram-positive bacteremia as a group was developed. One reason, for example, may be that within the gram-positive bacteria, there is more heterogeneity between the infections caused by the main pathogens—*Staphylococcus epidermidis, S. aureus, Streptococcus pneumoniae,* and enterococci—than between gram-negative organisms. However, it is possible that novel therapies will be developed that are effective against these organisms as a group. Neither of the variables with an independent predictor—intravenous drug abuse or suspected or documented focal infection with gram-positive organisms at onset—was surprising. Although this rule identified a small group at high risk of gram-positive bacteremia, most of the episodes of bacteremia fell into the remaining groups.

Because this rule performed poorly, we developed and validated a rule predicting *S. aureus* bacteremia. Intravenous drug abuse did not enter the model because it was closely related to suspected staphylococcal infection. This rule performed much better, although still only 47% of the cases in the derivation set fell within the 2 highest-risk groups. Taken together, the above data suggest that rapid diagnostic laboratory tests may be particularly useful for patients with suspected gram-positive bacteremia.

Gram-negative bacteremia has received a great deal of attention recently because of its high morbidity and mortality and because many of the novel therapies—notably anti-endotoxin antibodies—would be expected to be effective against this group of organisms [36–38]. The trials have reported a prevalence of gram-negative bacteremia of about 40% [37–38]. The highest-risk groups we could identify in the derivation set had bacteremia rates of 20% and 42%, and in the validation set, these figures were 33% and 25%; combined, these groups made up 12% of the episodes. These data suggest that the patients enrolled in the trials to date have been very highly selected and that they represent, at most, 12% of patients with sepsis syndrome. In fact, 52% of the validation set patients with sepsis syndrome fell into a group with only a 6% risk of gram-negative

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bacteremia. The factors we identified as predictive of gram-negative bacteremia included use of total parenteral nutrition, absence of antibiotic therapy at onset, history of gram-negative bacteremia, presence of a Hickman catheter, focal abdominal signs, and chills. This rule may be useful in future trials.

Although there have been many case series of patients with fungemia [39–41], we identified only three previous studies that included controls and evaluated predictors of fungemia [15, 42, 43]. In a case control study, Wey et al. [15] studied 28 potential risk factors in 88 pairs of patients with candidemia. Independent risk factors included number of antibiotics prior to infection, isolation of candida species from sites other than blood, prior hemodialysis, and prior use of a Hickman catheter. Schwartz et al. [42] found that prolonged chemotherapy and fungal colonization were risk factors in cancer patients, while Karabinis et al. [43] identified colonization by *Candida* species, central catheterization, and neutropenia. The factors we identified as important were isolation of fungi from sites other than blood, bowel perforation, presence of pyuria, liver disease, presence of a Hickman catheter, and altered mental status within 24 h. These factors allowed stratification of the cohort into groups with increasing risks of fungemia, with the most important factor by far (odds ratio, 10.1) being isolation of fungi (virtually all *Candida* species) from sites other than blood. The overall picture is consistent with clinical experience; most patients who develop fungemia are immunocompromised (Hickman catheters are strongly associated with immunocompromise; $P < .001$) and many patients have received long courses of antibiotic therapy for problems such as bowel perforation. In patients like these, cultures positive for fungi from non-bloodstream sites represent an ominous prognostic sign.

This study has several limitations. Among the general care unit patients, only patients who had blood cultures performed were sampled, since it seems likely that few patients with sepsis syndrome do not have blood cultures performed. There may have been other factors that were not included, and some clinical findings that correlate strongly with bacteremia may occur too rarely to exhibit significance in this dataset. Using antibiotic therapy at onset as a predictor may be problematic because it could result in ascertainment bias; it was included because it is readily available and because delay in beginning antibiotic therapy is thought to be associated with worse clinical outcomes. A different threshold ($P < .10$) was used in the model for predicting fungemia, because there were relatively few outcomes. However, these factors had good clinical face validity, and the rule was prospectively validated. Another issue is that all data were collected in academic medical centers, so it is not clear how well the results generalize to other settings, such as community hospitals.

We conclude that this information should help providers stratify patients according to the likelihood of bacteremia and its subtypes, although the prognostic ability of the rules is modest for many patients, and the clinical utility of the rules is thus uncertain. The rules should also help designers of novel therapy trials choose variables that can best identify patients

at high risk of infection by specific types of organisms. When novel therapies become available, as seems likely, these models may also help providers stratify patients according to their risk of infection by specific organism type. Such models will probably eventually be most useful when used in conjunction with rapid diagnostic tests, either for mediators of sepsis or for the organisms themselves.

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