Does This Adult Patient With Suspected Bacteremia Require Blood Cultures?

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CLINICAL SCENARIOS

Case 1
A 62-year-old woman presents to the emergency department with worsening cough, shortness of breath, and fever. Her temperature on presentation is 38.4°C (101.1°F). She is alert, oriented, and in no acute distress. Her blood pressure is 120/72 mm Hg; heart rate, 86/min; respiratory rate, 16/min; and oxygen saturation, 94% on room air. A complete blood count demonstrates mild normocytic anemia but neither leukocytosis nor leukopenia. She has a left-sided infiltrate on chest radiograph. Does she need blood cultures?

Case 2
A 47-year-old man with a history of hypertension feels unwell the first day after his elective knee meniscectomy, appears flushed, and is unwilling to move because of joint pain. His heart rate is 118/min; blood pressure, 108/56 mm Hg; and temperature, 37.4°C (99.3°F). He has a diffusely tender and effused knee but has no other abnormal physical examination findings, and the clinical suspicion is septic arthritis. The initial blood work demonstrates leukocytosis (white blood cell [WBC] count, 19 000/µL) and an elevated creatinine level (2.1 mg/dL [186 µmol/L]). Does he need blood cultures?

Context Clinicians order blood cultures liberally among patients in whom bacteremia is suspected, though a small proportion of blood cultures yield true-positive results. Ordering blood cultures inappropriately may be both wasteful and harmful.

Objective To review the accuracy of easily obtained clinical and laboratory findings to inform the decision to obtain blood cultures in suspected bacteremia.

Data Sources and Study Selection A MEDLINE and EMBASE search (inception to April 2012) yielded 35 studies that met inclusion criteria for evaluating the accuracy of clinical variables for bacteremia in adult immunocompetent patients, representing 4566 bacteremia and 25 946 negative blood culture episodes.

Data Extraction Data were extracted to determine the prevalence and likelihood ratios (LRs) of findings for bacteremia.

Data Synthesis The pretest probability of bacteremia varies depending on the clinical context, from low (eg, cellulitis: 2%) to high (eg, septic shock: 69%). Elevated temperatures alone do not accurately predict bacteremia (for ≥38°C [≥100.3°F], LR, 1.9 [95% CI, 1.4-2.4]; for ≥38.5°C [≥101.5°F], LR, 1.4 [95% CI, 1.1-2.0]), nor does isolated leukocytosis (LR, <1.7). The severity of chills graded on an ordinal scale (shaking chills, LR, 4.7; 95% CI, 3.0-7.2) may be more useful. Both the systemic inflammatory response syndrome (SIRS) and a multivariable decision rule with major and minor criteria are sensitive (but not specific) predictors of bacteremia (SIRS, negative LR, 0.09 [95% CI, 0.03-0.26]; decision rule, negative LR, 0.08 [95% CI, 0.04-0.17]).

Conclusions Blood cultures should not be ordered for adult patients with isolated fever or leukocytosis without considering the pretest probability. SIRS and the decision rule may be helpful in identifying patients who do not need blood cultures. These conclusions do not apply to immunocompromised patients or when endocarditis is suspected.

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CLINICIAN’S CORNER

WHY IS THIS QUESTION IMPORTANT?

Approximately 200 000 episodes of bacteremia occur in the United States each year, with an incidence of about 10 per 1000 hospital admissions. Bacterial bloodstream infections (BSIs) are associated with mortality of 14% to 37%. Mortality is especially high in critically ill patients admitted to intensive care units, where excess mortality of 35% is attributable to BSI. Bloodstream infections include infective endocarditis, central venous catheter–associated BSI, primary bacteremia, and those secondary to focal infections such as pneumonia, abscesses, osteomyelitis, or urinary tract infections. Infectious diseases include infective endocarditis, central venous catheter–associated BSI, primary bacteremia, and those secondary to focal infections such as pneumonia, abscesses, osteomyelitis, or urinary tract infections. Infectious diseases include infective endocarditis, central venous catheter–associated BSI, primary bacteremia, and those secondary to focal infections such as pneumonia, abscesses, osteomyelitis, or urinary tract infections.
productive endocarditis accounts for 3% to 8% of cases.1-3

Published guidelines do not clearly state when blood cultures should be drawn. Blood cultures are commonly obtained when patients have fever, chills, leukocytosis, focal infections, indications of sepsis, or suspected endocarditis or prior to starting parenteral antibiotics in emergency or medical patients. Because of the high mortality associated with bacteremia, the dangers of undertreating some infections, or concern about using inappropriate antibiotics, physicians tend to order blood cultures liberally. As a result, only 4% to 7% of blood cultures drawn are positive.9,10 The sensitivities of blood cultures drawn in tandem or triplet for bacteremia are 90% and 98%, respectively.11 However, obtaining cultures after antibiotic administration diminishes their sensitivity and clinical utility.11

The term bacteremia refers to any true-positive blood culture result, which reflects bacterial presence in the bloodstream. As many as half of the cultures that are positive represent contaminants—organisms inoculated from the skin into culture bottles at the time of sample collection. Such results are false-positive blood cultures that can lead to unnecessary investigations and treatments. In one analysis, false-positive blood cultures resulted in a 50% increase in total charges and a 64% increase in median length of stay compared with negative blood cultures.12 Molecular detection techniques such as polymerase chain reaction for bacterial and fungal DNA are being developed and validated to lower the number of false-negative and false-positive blood cultures but are not in widespread clinical use.13

Herein we seek to answer the following questions from the perspective of an emergency department or hospital-based physician evaluating an immunocompetent patient for possible infection: (1) Are fever or leukocytosis alone indicators of bacteremia? (2) Are there historical, physical examination, and laboratory findings available at the time blood cultures are drawn that allow clinicians to distinguish patients who have bacteremia from those who do not? (3) Do these clinical findings help inform the decision to obtain blood cultures?

**Pathophysiology**
The invasion of the blood by pathogens most often occurs as the result of seeding of the blood from a focal source of infection but also occurs without a clearly identifiable cause.3 Focal infections that commonly result in bacteremia include respiratory, urinary tract, abdominal, and central venous catheter–associated infections. Bacteremia can induce an inflammatory response that produces the symptoms of bloodstream infection. Mortality associated with bacteremia increases with the severity of sepsis, although it also varies with underlying illness and the source of initial infection.3,14 Early appropriate antibiotic administration is associated with decreased sepsis-associated mortality, suggesting that microbial growth and activity are linked to disease progression.15

**Examination for Signs of Bloodstream Infection**

**Patient History.** A number of historical clues commonly prompt the suspicion of bacteremia, including fever, chills, and a documented or suspected infection. History taking should include an assessment of symptoms to suggest a specific focus of infection including gastrointestinal, respiratory, abdominal, genitourinary, skin, and soft tissue symptoms. The presence of significant preexisting comorbidity, immunosuppression (eg, malignancy, steroid use, neutropenia), or recent invasive instrumentation, indwelling catheters, vascular devices, or intravenous line use should be elicited.

**Physical Examination.** Physical examination should begin with an assessment of vital signs. Temperature, heart rate, and respiratory rate should be measured and the presence of rigor should be noted. Cardiovascular, pulmonary, abdominal, skin, and mental status examinations are always indicated. All catheters, intravenous devices, or drain-

**METHODS**

**Literature Search and Selection**
To find studies of the accuracy of clinical findings for predicting bacteremia in emergency department or hospitalized adult patients, we searched EMBASE and MEDLINE (inception to April 2012) to identify relevant literature using the search string “(bacteremia OR ‘bloodstream infection’ OR infective OR endocarditis) AND (predict OR prediction).” The references of relevant publications were reviewed for additional studies. English-language primary articles, book chapters, abstracts, and reviews were included. Published studies in which epidemiologic data were presented but not stratified by group (positive or negative blood cultures) were excluded from analysis. One article contained data that allowed calculation of sensitivity but not specificity and was not included in the formal analysis (data reported herein).19 Studies in which raw data were not reported or could not be constructed from reported data were ex-
cluded. One retrospective cohort study restricted to patients with febrile neutropenia was excluded.20

To establish estimates for the pretest probability of bacteremia in specific clinical settings, we searched EMBASE and MEDLINE (from inception to January 2012) using “bacteremia OR bloodstream infection” and terms referring to the relevant clinical condition (eg, cellulitis or pyelonephritis). We also reviewed the reference sections of relevant publications (including narrative reviews, systematic reviews, and society guidelines). Bacteremia rates were included if they were based on consecutive adult patients with the defined clinical syndrome and more than 60% of patients in the study underwent blood cultures. The intent was to provide examples of pretest probabilities rather than a meta-analytic summary measure for all possible conditions that might be associated with bacteremia.

**Data Analysis and Statistical Methods**

Published raw data were used to calculate likelihood ratios (LRs) for the specific clinical variables.21 If 3 studies examined the same clinical variable, we calculated summary LRs and 95% confidence intervals (CIs) using the DerSimonian and Laird random-effects approach.22 Estimated variances of LRs were computed using the usual methods for ratios of proportions, with their reciprocals used as study weights. In studies with a zero cell count, the value 0.5 was added to each cell count to permit use of this variance estimator. The $I^2$ heterogeneity statistic was calculated for findings reported in multiple studies and a test of heterogeneity was based on the Cochran Q statistic.23 All univariate analyses were performed using R, version 2.13.0 (R-Project).

Study quality was assessed using a previously developed scoring system24 as follows:
- Level 1: a prospective study of at least 100 consecutive, unselected patients
- Level 2: a study of fewer than 100 patients meeting the same criteria as level 1
- Level 3: a retrospective study
- Level 4: any study of patients selected for the presence of bacteremia

**RESULTS**

**Search Results for Studies of Accuracy**

We retained 35 studies assessing clinical variables to predict bacteremia (eFigure; available at http://www.jama.com).9,15-38 that included a total of 4566 bacteremia and 25 946 control episodes in adult patients. All included studies (TABLE 1) used criteria to designate cultured organisms as a contaminant. Generally, this was defined as an organism commonly considered a contaminant, grown only in 1 culture and in the absence of other evidence of infection with that organism. No studies counted contaminants as positive culture results.

One study of burn patients34 reported data suitable for analysis for a single variable only (temperature $\geq 40.0^\circ C$ [ $\geq 103.9^\circ F$]). One study was in patients with nosocomial bacteremia admitted to a hematology/oncology service for a known malignancy or hematologic disorder.34 This study contributed 2 clinical variables (presence of a central venous catheter and prior antibiotic use) to the assessment. One retrospective study of patients with febrile neutropenia was excluded.20

In the remaining studies, only a small minority of cases had immunomodulating conditions or immunocompromised patients were excluded completely. There were no other studies limited to patients with human immunodeficiency virus (HIV), malignancy, or neutropenia or those taking immunosuppressive medications. Very few patients in the included studies had infective endocarditis.

Studies used to estimate the LRs for clinical variables were of 3 primary types: studies that predicted bacteremia in patients with fever (group 1)28,33-40,55; studies of bacteremia in patients with other specified indications for blood culture, such as focal infection, sepsis, specific infections, and burns (group 2)27,30-32,34,41-49,54; and studies of any patient in whom blood cultures were drawn, leaving the decision to draw cultures to the discretion of the ordering physician (group 3).9,25,26,29,33,50-53,57,58

**Pretest Probability of Bacteremia**

In 2 studies of consecutive blood cultures, the probabilities of true-positive blood cultures were 4.1% of 51 264 cultures (2.5% contamination rate; true-positive:contamination ratio, 1.6:1)10 and 7% of 1516 cultures (8% contamination rate; true-positive: contamination ratio, 0.88:1).9

The probability of bacteremia in patients with specific clinical conditions for which physicians often obtain blood cultures fell into 3 ranges (TABLE 2). Patients in whom the probability was low (<14%) included ambulatory outpatients, patients with cellulitis, and patients admitted to the hospital with community-acquired pneumonia or community-acquired fever.36,44,59,60 The probability of bacteremia was intermediate (19%-25%) in those with pyelonephritis.49,61 A high pretest probability of bacteremia (38%-69%) was reported in patients with severe sepsis, septic shock, or acute bacterial meningitis.14,32,62

A prospective study of hospitalized patients who had blood cultures for fever had a bacteremia probability of 12%;60 however, patients were identified and enrolled only after blood cultures had been drawn (ie, they were not consecutive inpatients with fever); thus, we believe the results overestimate the true probability of bacteremia in hospitalized febrile patients.

**Accuracy of Fever and Chills for Diagnosing Bacteremia**

As a symptom, patient report of subjective fever was an inaccurate predictor of bacteremia, with the range of the positive and negative LRs approaching 1.0 in 4 studies (TABLE 3).27,43,49,53 As a sign, varying temperature cutoffs were evaluated in 6231 patients with 1107 epi-
sodes of bacteremia,9,25-27,29,31,34,44,45,47,49,58
Patients with measured temperatures exceeding the commonly used threshold of 38°C or higher (≥100.3°F) had an increased likelihood of bacteremia (LR, 1.9; 95% CI, 1.4-2.4), while those with temperature lower than 38°C decreased the likelihood (LR, 0.54; 95% CI, 0.38-0.78).47 Only thresholds of

**Table 1. Study Characteristics**

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Quality Level</th>
<th>Study Population</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: studies of febrile patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mellors et al,19 1987</td>
<td>1 Yes</td>
<td>Patients with unexplained fever ≥37.9°C were excluded.</td>
<td></td>
</tr>
<tr>
<td>Leibovici et al,20 1991</td>
<td>1 Yes</td>
<td>Consecutively admitted febrile patients (≥38°C oral/≥38.2°C rectal)</td>
<td>Limited to patients with fever. Score performed poorly in subsequent trials.</td>
</tr>
<tr>
<td>Van Dessel et al,20 1998</td>
<td>1 Yes</td>
<td>Consecutively ED patients with fever (fever not defined in report)</td>
<td>ED patients only</td>
</tr>
<tr>
<td>Groeneveld et al,22 2001</td>
<td>1 Yes</td>
<td>Patients admitted to hospital with fever (≥38°C axillary/≥38.3°C rectal)</td>
<td>Febrile patients only; high proportion of patients had SIRS.</td>
</tr>
<tr>
<td>Chirouze et al,23 2002</td>
<td>1 Yes</td>
<td>Consecutively admitted patients with fever ≥38°C</td>
<td>Study of uncommon blood tests; minimal reported data included</td>
</tr>
<tr>
<td>Tokuda et al,24 2005</td>
<td>1 Yes</td>
<td>Consecutively admitted patients with fever ≥38°C</td>
<td></td>
</tr>
<tr>
<td>Yoshida et al,25 2005</td>
<td>3 No</td>
<td>Retrospectively identified inpatients with fever (≥38.5°C) in whom blood cultures were drawn</td>
<td>Retrospective study; raw data were reported for a single variable only.</td>
</tr>
<tr>
<td>Stryjewski et al,26 2009</td>
<td>1 Yes</td>
<td>Patients with health care-associated fever (≥38°C) in whom blood cultures were drawn</td>
<td>Limited to patients with health care-associated fever, enrolled after blood cultures ordered.</td>
</tr>
<tr>
<td>Group 2: studies of patients with specific indications for blood culture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fontanarosa et al,27 1992</td>
<td>3 No</td>
<td>Infection (not otherwise specified)</td>
<td>Limited to patients older than 65 y; types of infection not specified</td>
</tr>
<tr>
<td>Jones and Lowes,28 1996</td>
<td>4 Yes</td>
<td>Infection (not otherwise specified) in general medical ward inpatients</td>
<td>Febrile neutropenia patients excluded; indication for blood culture not further delineated</td>
</tr>
<tr>
<td>Yehezkelli et al,29 1996</td>
<td>1 Yes</td>
<td>General medicine inpatients with clinical evidence of infection</td>
<td>Validation of scoring systems of Bates et al9 and Leibovici et al,20 with significant deterioration of findings of earlier studies</td>
</tr>
<tr>
<td>Bates et al,29 1997</td>
<td>1 Yes</td>
<td>Emergency, ward, and ICU patients with sepsis</td>
<td>Limited to patients with sepsis defined by authors, which differs from generally used definition</td>
</tr>
<tr>
<td>Smith et al,30 1997</td>
<td>3 No</td>
<td>Women aged 16–44 y with pyelonephritis</td>
<td>Small sample of patients with pyelonephritis</td>
</tr>
<tr>
<td>Perl et al,31 1999</td>
<td>3 No</td>
<td>Adult patients with cellulitis</td>
<td>Small sample of patients with cellulitis</td>
</tr>
<tr>
<td>Crabtree et al,32 2001</td>
<td>1 Yes</td>
<td>Surgical patients with infection (lung, peritoneum, bloodstream, line, urinary tract, and wound infections)</td>
<td>Surgical patients only</td>
</tr>
<tr>
<td>Laupland et al,33 2004</td>
<td>1 Yes</td>
<td>ICU patients with SIRS</td>
<td>Prospective database review</td>
</tr>
<tr>
<td>Peralta et al,34 2006</td>
<td>3 No</td>
<td>Adult patients with cellulitis</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Chen et al,35 2006</td>
<td>4 No</td>
<td>Complicated pyelonephritis</td>
<td>Retrospective study of patients with pyelonephritis and functional or structural urinary tract abnormalities</td>
</tr>
<tr>
<td>Murray et al,36 2007</td>
<td>3 No</td>
<td>Burn patients</td>
<td>Retrospective chart review of patients admitted to a burn unit</td>
</tr>
<tr>
<td>Bahagon et al,37 2007</td>
<td>3 No</td>
<td>Admitted patients with urinary tract infection</td>
<td>Retrospective study; decision to order blood cultures was left to discretion of ordering physician.</td>
</tr>
<tr>
<td>Cham et al,38 2009</td>
<td>1 Yes</td>
<td>Consecutive ED patients with community-acquired pneumonia</td>
<td>Patients with community-acquired pneumonia only; data for limited variables reported</td>
</tr>
<tr>
<td>Falgueira et al,39 2009</td>
<td>3 No</td>
<td>All patients with community-acquired pneumonia admitted over a 10-y period</td>
<td>Admitted patients with community-acquired pneumonia only; retrospective database review</td>
</tr>
<tr>
<td>Apostolopoulou et al,40 2010</td>
<td>3 No</td>
<td>Patients with nosocomial bloodstream infection admitted to hematology/oncology unit for &gt;48 h prior to onset of bacteremia</td>
<td>Nosocomial bacteremia only; limited to patients with malignancy/hematologic disease; limited data reported were suitable for this analysis. Case definition included the presence of fever, chills or hypotension.</td>
</tr>
<tr>
<td>Kim et al,41 2011</td>
<td>3 No</td>
<td>Women with pyelonephritis defined as (1) fever (&gt;38.0°C), (2) pyuria, and (3) flank tenderness</td>
<td>Inclusion criteria included fever; limited to patients with pyelonephritis.</td>
</tr>
</tbody>
</table>

(continued)
| Table 2. Probabilities of Bacteremia in Specific Clinical Conditions From Published Reports |
|-----------------------------------|------------------|-----------------|-----------------|
| Patient Population               | Source           | No. of Patients | Pretest Probability |
| Low risk Cellulitis              | Perl et al.41 1999 | 553             | 0.02             |
| Ambulatory outpatients           | Laupland et al.39 2005 | 3102    | 0.02             |
| Community-acquired pneumonia     | Metersky et al.36 2004 | 13,043 | 0.07             |
| Community-onset fever requiring hospitalization | Chirouze et al.39 2002 | 165 | 0.13             |
| Intermediate risk Pyelonephritis | Kim et al.40 2011 | 735             | 0.19             |
|                                 | Velasco et al.39 2003 | 583            | 0.25             |
| High risk Severe sepsis          | Bates et al.38 1997 | 1342            | 0.38             |
| Acute bacterial meningitis       | Proulx et al.39 2005 | 118             | 0.53             |
| Septic shock                     | Rangel-Frausto et al.40 1995 | 194              | 0.69             |
were assessed in more than 1 study (summary LR, 1.4; 95% CI, 1.1-2.0) or 38.5°C or higher (summary LR, 1.2; 95% CI, 1.0-1.4).

Despite heterogeneity, chills in febrile patients (Table 3) appears more useful for identifying bacteremia (summary positive LR, 2.2 [95% CI, 1.4-3.3]; summary negative LR, 0.56 [95% CI, 0.41-0.76]) compared with the accuracy of chills evaluated independent of the presence of fever. In 1 study, characterizing the intensity of chills on an ordinal scale improves the diagnostic accuracy. Shaking chills, defined as “feeling extremely cold with rigor and generalized bodily shaking even under a thick blanket” has an LR of 4.7 (95% CI, 3.0-7.2), while the complete absence of chills has an LR of 0.24 (95% CI, 0.11-0.55).30

Accuracy of Patient History, Physical Examination, and Laboratory Evaluation for Diagnosing Bacteremia (Single Variables)

Patient History. Very few historical features have been evaluated in more than 1 study (eTable 3). Prior antibiotic use has an LR of 0.63 (95% CI, 0.41-0.98) though the studies do not allow an assessment of whether these data represent false-negative blood culture results.

Physical Examination. The presence of tachycardia alone (heart rate >100/min but defined as >90/min, >110/min, or >120/min in some studies) was not helpful (summary positive LR, 1.4 [95% CI, 1.2-1.8]; summary negative LR, 0.67 [95% CI, 0.59-0.77]) (eTable 4). The presence of hypotension or shock (systolic blood pressure <90-100 mm Hg or the need for pressors to maintain blood pressure) approximately doubled the likelihood of bacteremia (eTable 4).

Laboratory Evaluation. Of common laboratory tests associated with infection, WBC counts and the cellular differential are the most broadly used (eTable 5). At the cutoffs studied, WBC thresholds of 10 000/µL to 15 000/µL, no result produced an LR higher than 1.7, while the absence of an elevated

Table 3. Fever and Chills as Indicators of Bacteremiaa

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>Likelihood Ratio (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills (febrile patients only)</td>
<td>2.2 (1.4-3.3) 0.56 (0.41-0.76)</td>
</tr>
<tr>
<td>P value</td>
<td>.001</td>
</tr>
<tr>
<td>Subjective fever</td>
<td>1.0 (0.96-1.1) 0.95 (0.88-1.0)</td>
</tr>
<tr>
<td>P value</td>
<td>.48 .76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity of chills</th>
<th>Likelihood Ratio (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaking</td>
<td>4.7 (3.0-7.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.7 (1.0-2.8)</td>
</tr>
<tr>
<td>Mild</td>
<td>0.61 (0.26-1.4)</td>
</tr>
<tr>
<td>None</td>
<td>0.24 (0.11-0.55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Likelihood Ratio (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥39°C</td>
<td>1.1 (0.79-1.6) 0.95 (0.83-1.1)</td>
</tr>
<tr>
<td>≥38.5°C</td>
<td>1.4 (1.1-2.0) 0.50 (0.30-0.82)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001 .01</td>
</tr>
<tr>
<td>≥38.3°C</td>
<td>1.2 (1.0-1.4) 0.80 (0.61-1.0)</td>
</tr>
<tr>
<td>P value</td>
<td>.04 .003</td>
</tr>
<tr>
<td>≥38.0°C</td>
<td>1.9 (1.4-2.4) 0.54 (0.38-0.78)</td>
</tr>
<tr>
<td>≥37.8°C</td>
<td>1.5 (1.2-1.9) 0.65 (0.50-0.86)</td>
</tr>
</tbody>
</table>

a See eTable 1 and eTable 2 for results of individual studies.

b Likelihood ratios from single studies represent point estimates and 95% CI; results from 3 or more studies are random-effects summary measures.

c Chills were ordinalized based on patient descriptions and are thus categorized as a symptom. Values represent the serial likelihood ratio for a result at each level. Categories were defined as mild chills (feeling cold with equivalent of the need for an outer jacket); moderate chills (feeling very cold with equivalent of the need for a thick blanket); and shaking chills (feeling extremely cold with rigor and generalized bodily shaking even under a thick blanket).

Table 4. Multivariable Scores and Their Performance in Predicting or Excluding Bacteremia

<table>
<thead>
<tr>
<th>Index and Source</th>
<th>Performance (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Presence of SIRS</td>
<td></td>
</tr>
<tr>
<td>Jones and Lowes,30 1996</td>
<td>0.96 (0.74-1.00)</td>
</tr>
<tr>
<td>Wild et al,35 2011*</td>
<td>0.80 (0.64-0.90)</td>
</tr>
<tr>
<td>Clinical prediction rule (Shapiro et al, 2006)*</td>
<td>Summary statistic</td>
</tr>
<tr>
<td>Derivation set</td>
<td>0.98 (0.96-0.99)</td>
</tr>
<tr>
<td>Validation set</td>
<td>0.97 (0.94-1.00)</td>
</tr>
</tbody>
</table>

Abbreviations: LR, likelihood ratio; SIRS, systemic inflammatory response syndrome.

*The study quality is limited because SIRS criteria were not clearly defined and data were missing.
BLOOD CULTURES FOR BACTEREMIA

Box. Clinical Prediction Rules for Bloodstream Infection

Jones and Lowes\(^\text{30}\) Systemic inflammatory response syndrome (SIRS) present with at least 2 of the following:
- Temperature <36°C or >38°C
- Heart rate >90/min
- Respiratory rate >22/min OR pCO\(_2\) <32 mm Hg on arterial blood gas
- White blood cell count <4000/µL or >12,000/µL OR >10% immature neutrophils (band forms)

Shapiro et al\(^\text{33}\)
Blood culture indicated if 1 major OR 2 minor of the following:
- Major Suspicion of endocarditis
- Temperature >39.4°C
- Indwelling catheter
- Minor
- Temperature 38.3°C-39.3°C
- Age >65 years
- Chills
- Vomiting
- Systolic blood pressure <90 mm Hg
- White blood cell count >18,000/µL
- Creatinine >2 mg/dL (>177 µmol/L)

WBC count at the varying thresholds did not have an LR lower than 0.60.\(^\text{25-27,45,50}\) The presence of increased immature (band) forms of neutrophils conveyed similar information as total WBC counts.\(^\text{9,27,32,36-38}\) Three studies reported results for thrombocytopenia: platelet counts fewer than 150,000/µL increased the likelihood of bacteremia (positive LR, 2.0-2.1) but the negative LR was 0.68 to 0.91.\(^\text{49,58}\); platelet counts fewer than 25,000/µL had an LR of 1.6 (95% CI, 0.9-2.7), while platelet counts of 25,000/µL or more had an LR of 0.96 (95% CI, 0.90-1.0).\(^\text{25}\)

Three studies reported that lymphopenia (lymphocyte count <500/µL or <1000/µL)\(^\text{50,51,58}\) and a neutrophil-lymphocyte ratio greater than 10 were correlated with bacteremia.\(^\text{50,51}\) The presence of lymphopenia or a neutrophil-lymphocyte ratio greater than 10 increased the likelihood of bacteremia (positive LRs, 1.6-2.3 for lymphocytes <1000/µL or ratio >10 and 3.7 for lymphocytes <500/µL [95% CI, 2.6-5.1]). The absence of these factors decreased the likelihood of bacteremia (negative LRs, 0.45-0.51 for lymphocytes <1000/µL and 0.36-0.76 for ratio >10) (eTable 5).\(^\text{50,51}\)

Accuracy of Clinical Impression for Diagnosing Bacteremia

Pfitzenmeyer et al\(^\text{29}\) assessed the accuracy of the clinician’s impression of the likelihood of bacteremia in a study population with positive blood cultures in 8.2% (46/558) of cases. The clinicians categorized the probability of bacteremia as high (≥50%), intermediate (10%-49%), or low (<10%). The overall clinical impression of high probability increased the likelihood of bacteremia, with an LR of 2.3 (95% CI, 1.4-3.6); intermediate probability had an LR of 0.49 (95% CI, 0.27-0.89); and low probability impression decreased the likelihood, with an LR of 0.48 (95% CI, 0.24-0.97).

Value of Multivariable Scores for Prediction of Bloodstream Infections

Because individual symptoms and signs do not substantially alter the likelihood of bacteremia, we looked for data on explicit combinations of findings (TABLE 4). The systemic inflammatory response syndrome (SIRS), which was initially developed to categorize patients with sepsis-like signs and symptoms, and a clinical decision rule developed by Shapiro et al\(^\text{33}\) were both studied to help distinguish patients with bacteremia from those without (Box).

Jones and Lowes\(^\text{32}\) tested SIRS as a predictor of bacteremia. Among 270 consecutive blood culture episodes from general medical ward patients and 64 sequential cases of bacteremia, the presence of SIRS increased the likelihood of bacteremia (positive LR, 1.8; 95% CI, 1.6-2.0), while its absence (<2 criteria present) appreciably lowered the likelihood of bacteremia, with a negative LR of 0.09 (95% CI, 0.03-0.26). Two other studies reported data suitable for calculation of the sensitivity of SIRS criteria for bacteremia. In a prospective study of patients admitted to intensive care units, 108 patients had BSIs, of which 100 fulfilled at least 2 SIRS criteria (sensitivity, 0.93; 95% CI, 0.86-0.96 derived from reported data).\(^\text{46}\)

In a study of patients admitted to the hospital for febrile illness, SIRS (fever plus 1 additional SIRS criterion) was present in 51 of 53 cases of bacteremia (sensitivity, 0.96; 95% CI, 0.87-0.99).\(^\text{19}\)

One additional study assessed SIRS in patients who were discharged from the emergency department or had admissions of less than 48 hours’ duration,\(^\text{27}\) providing estimates of a positive LR of 1.1 (95% CI, 0.89-1.4) and a negative LR of 0.75 (95% CI, 0.35-1.6). This study had significant limitations. The SIRS criteria were not explicitly defined in the study and were not measured in 20% of the patient population. Forty-nine percent of patients with eligible positive cultures were excluded for lack of data, because they were transferred from or to another hospital, or because they died within 48 hours of admission. Shapiro et al\(^\text{33}\) developed and validated a clinical decision rule in 3901 patients who had blood cultures drawn in an emergency department or within 3 hours of admission to the hospital. The decision rule was highly sensitive (sensitivity, 0.97 [95% CI, 0.94-1.0]; negative LR, 0.08 [95% CI, 0.04-0.17]), implying that when no major and fewer than 2 minor criteria are present, the risk of bacteremia is very low (0.9% in the validation cohort). Similar to SIRS, this decision rule was not very specific (specificity, 0.29 [95% CI, 0.26-0.31]; positive LR, 1.4 [95% CI 1.3-1.4]).

Of the remaining studies in which prediction rules were developed,\(^\text{25,29,32,36,38}\)
none provided a score with superior sensitivity to SIRS or the rule developed by Shapiro et al\textsuperscript{33} (eTable 6). All of the remaining scoring systems have significant practical limitations, such as restriction to a specific patient population such as elderly patients or those with urinary tract infections,\textsuperscript{29,40} the need for complex calculations or use of rare or difficult-to-obtain variables,\textsuperscript{25,58} or poor performance when reevaluated in external studies.\textsuperscript{32} The details of these systems are reported in eTable 6.

**LIMITATIONS**

There are significant limitations to the data included in our analysis. The probabilities of bacteremia in the studies used to estimate the predictive accuracy of clinical variables was generally higher (6%-37%) than the true-positive probability for series of consecutive blood cultures (4.1%-7.3%),\textsuperscript{9,10} likely because patients were selected on the basis of signs or symptoms that suggested bacteremia. This selection process possibly resulted in biased estimates of the LRs for the clinical variable studied. The indications for blood cultures were heterogeneous and not reported in all studies. Infective endocarditis cases represented a small proportion of the total, and many manifestations of infective endocarditis were not assessed (eg, the presence of a new regurgitant murmur or persistent fever in a patient with a prosthetic heart valve). We therefore believe that these data do not apply to patients with suspected infective endocarditis.

Notably, there were no studies of large numbers of patients with common immunocompromising conditions such as HIV/AIDS, malignancy, or immunosuppressive drug use. Therefore, we believe that the data reported herein regarding the accuracy of clinical variables for predicting bacteremia apply only to immunocompetent patients. Immunocompromised patients are at increased risk of bactereic infection and are less likely to manifest signs, symptoms, and laboratory abnormalities associated with the inflammatory response to infection.

Some experts might advocate a more global and less quantitative approach that starts with the presence or absence of fever, then factors in a large amount of clinical information such as the natural history of fever patterns associated with specific infections, whether the patient is taking antibiotics, and the presence of some of the risk factors evaluated in this review (eg, central lines, underlying disease states). A quantitative evaluation of this approach would require large patient samples for each of these specific clinical scenarios to produce valid results. As well, this approach would lack generalizability beyond the narrow constraints of the specific patient populations. Experienced infectious diseases physicians also form clinical impressions using this approach, especially in patients referred after initial evaluation. However, a large number of physicians who are faced with the decision to order blood cultures are less experienced and do so earlier in the course of the illness.

For some findings, there was statistically significant heterogeneity between LRs. The LR summary estimates and confidence intervals that we derived are from random-effects models that incorporate between-study heterogeneity. The interpretation of the results is not likely affected by the heterogeneity because the majority of individual LRs fell in the range of limited clinical usefulness.

SIRS and the Shapiro criteria are both sensitive indicators, identifying patients unlikely to have bacteremia.\textsuperscript{30,33} Published estimates suggest that both are better negative predictors of bacteremia than the overall clinical impression (negative LR, 0.48; 95% CI, 0.24-0.97).\textsuperscript{29,30} However, the sample sizes in the studies of the SIRS criteria were small, and further empirical study is needed to corroborate this finding. The Shapiro decision rule has been studied in only 1 setting and therefore also requires prospective validation. Finally, as noted above, the accuracy of clinical impression almost certainly varies with experience and expertise.

**SCENARIO RESOLUTION**

**Case 1**

The patient in scenario 1, an emergency department patient with pneumonia, fulfills only 1 SIRS criterion—fever, in the context of a focal infection with low probability of bacteremia (community-acquired pneumonia, prior probability of bacteremia approximately 7%).\textsuperscript{60} The absence of SIRS and Shapiro criteria decreases the likelihood of bacteremia substantially (negative LRs, 0.09 and 0.08, respectively). Her estimated probability of bacteremia is low (0.67%) and likely much lower than the probability of a false-positive result; therefore, blood cultures should not be ordered for this patient.

**Case 2**

In case 2, the presence of tachycardia, knee effusion and pain, and elevated creatinine level in an otherwise healthy person warrants further investigation, especially for infectious postoperative complications. Although he is not febrile, this patient fulfills 2 SIRS criteria (tachycardia and leukocytosis) and has a suspected infection and evidence of organ dysfunction (criteria for severe sepsis). In addition, he fulfills 2 minor Shapiro criteria (leukocytosis and elevated creatinine level). His pretest probability of bacteremia is approximately 38% (for severe sepsis)\textsuperscript{32} and the presence of SIRS and Shapiro criteria increases the probability of bacteremia. Despite the absence of fever, blood cultures should be included in his diagnostic evaluation.

**CLINICAL BOTTOM LINE**

Although the probability of bacteremia is considerable in many specific clinical settings, the overall low probability of true-positive blood cultures in series of consecutive patients (4.1%-7.3%) suggests that many blood cultures for adult patients are ordered when the risk of bacteremia is low. This exposes patients to the potential harms of a false-positive result (ie, growing a contaminant that does not reflect true bacteremia), which include more tests.
(additional blood cultures, echocardiograms, etc), unnecessary antibiotic administration with possible adverse reactions, missed alternative (infectious or noninfectious) diagnoses, and increased length of stay in the hospital.

We believe the current literature supports the following conclusions for adults:

1. The pretest probability of bacteremia varies considerably and is determined largely by the clinical context (including the presence or absence of an identifiable focus of infection).
2. Blood cultures should not be ordered simply because isolated fever or leukocytosis is present in patients for whom the pretest probability of bacteremia is low.
3. The SIRS criteria and Shapiro decision rule show promise in further defining low-risk patients but require prospective validation.
4. The existing data do not allow generalization of these conclusions to immunocompromised patients or those under consideration for endocarditis.

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Study concept and design: Coburn, Detsky.

Acquisition of data: Coburn, Morris, Tomlinson, Detsky.

Drafting of the manuscript: Coburn.

Critical revision of the manuscript for important intellectual content: Coburn, Morris, Tomlinson, Detsky.

Statistical analysis: Tomlinson.

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