REVIEW

Predicting bacteraemia in validated models—a systematic review

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Abstract

Bacteraemia is associated with high mortality. Although many models for predicting bacteraemia have been developed, not all have been validated, and even when they were, the validation processes varied. We identified validated models that have been developed; asked whether they were successful in defining groups with a very low or high prevalence of bacteraemia; and whether they were used in clinical practice. Electronic databases were searched to identify studies that underwent validation on prediction of bacteraemia in adults. We included only studies that were able to define groups with low or high probabilities for bacteraemia (arbitrarily defined as below 3% or above 30%). Fifteen publications fulfilled inclusion criteria, including 59 276 patients. Eleven were prospective and four retrospective. Study populations and the parameters included in the different models were heterogeneous. Ten studies underwent internal validation; the model performed well in all of them. Twelve performed external validation. Of the latter, seven models were validated in a different hospital, using a new independent database. In five of these, the model performed well. After contacting authors, we found that none of the models was implemented in clinical practice. We conclude that heterogeneous studies have been conducted in different defined groups of patients with limited external validation. Significant savings to the system and the individual patient can be gained by refraining from performing blood cultures in groups of patients in which the probability of true bacteraemia is very low, while the probability of contamination is constant. Clinical trials of existing or new models should be done to examine whether models are helpful and safe in clinical use, preferably multicentre in order to secure utility and safety in diverse clinical settings.

Keywords: Bacterial bloodstream infections, blood cultures, prediction models, sepsis, validation

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Introduction

Among patients with infection, bacteraemia portends a poor prognosis, and clinicians' ability to predict it is low [1,2]. Bacterial bloodstream infections are associated with mortality of 14% to 37% [3–6]. Knowledge (or high suspicion) that a patient has a bloodstream infection can guide treatment—aggressively (or not) treating the patient, transferring the patient to an intensive care unit, empirically initiating appropriate antibiotic treatment and thinking of differential diagnosis.

Poses and Anthony [7], in a prospective cohort study, assessed inappropriate physicians' judgements of the probability of bacteraemia. They found that physicians significantly overestimated the likelihood of bacteraemia for most of their patients. Their receiver operating characteristic (ROC) curve for this diagnosis showed only moderate discriminating ability (area = 0.687, SE = 0.073). Generally only about 5% to 10% of blood cultures are positive, and of those that are positive, 30% to 50% represent contaminants—organisms inoculated from the skin into culture bottles at the time of sample collection [8–11]. The costs of performing and handling negative and false-positive blood culture results are significant. False-positive

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results lead to unnecessary investigations and treatment with unneeded antibiotic therapy. In one analysis, patients with falsely positive blood cultures were compared with those with truly negative blood cultures, and false-positive findings were associated with a 50% increase in total charges and a 64% increase in median length of hospitalization stay, along with higher pharmacy charges and laboratory charges [12]. Defining of a group of patients with a very low probability of bacteraemia, in which blood cultures are not necessary or not cost-effective, has the potential to reduce costs and prevent unnecessary antibiotic treatment. In addition, selection of a group with a high likelihood for bacteraemia caused by specific pathogens could assist physicians in choosing treatment or determining whether to perform new, costly tests such as PCR testing for bacterial and fungal DNA [13].

This is the logic for developing tools that can predict bacteraemia accurately in patients suspected of harbouring a moderate to severe bacterial infection. To be useful, such a tool should fulfil a few conditions. It should be able to define a group with a very low prevalence of bacteraemia, and this group should be of a useful size. We can be further reassured if the few truly positive blood cultures included in this group were expected and would have been covered by empirical antibiotic treatment so that the results of the positive blood culture would not have changed management. Definition of a group with a high prevalence of bacteraemia might also be useful for triaging patients for culture-free, expensive techniques of looking for bacteria or their products in the blood. The tool should use data that are readily available at the time of decision making, within the time frame of the decision whether or not to obtain blood samples for culture. It should be validated externally to assure its users that it performs well in multiple settings.

Many models for predicting bacteraemia have been developed. Some have been developed in specific populations of adult patients (e.g. elderly, hematology–oncology populations, neutropenic patients) or for specific settings (emergency room (ED), community or hospitalized patients). Models have also been developed for specific sources of infection (e.g. urinary tract, pneumonia, skin, soft tissue). However, not all models were validated, and even when the models were validated, the validation processes varied.

We reviewed the literature and asked which models for predicting bacteraemia have been developed; whether the models were successful in defining a group with a very low prevalence of bacteraemia and a group with a high prevalence; and whether they have been validated to such a degree that their use in clinical practice can be recommended. We also examined the components of the different models. Finally, we examined whether the models are being used in routine clinical practice.

Methods

We conducted a comprehensive search in an attempt to identify studies offering a model to predict bacteraemia. We searched the PubMed database (inception to September 2014), combining the terms (predict OR predicting OR prediction) AND (bacteraemia OR blood stream infection). The bibliographies of all included studies and pertinent reviews were scanned for additional references.

We included studies of adult populations where the model underwent internal or external validation. We extracted data on baseline study characteristics, whether the original study was prospective or retrospective, baseline study's population characteristics, which parameters were included in the model, whether the model underwent validation, and if so, which kind, and the probability of bacteraemia in the high- and low-risk group. We examined the cutoffs used in the studies against an arbitrarily chosen definition of high- or low-risk groups for bacteraemia: we defined high risk as >30% and low risk as <3%. We chose a low-risk cutoff that would be lower than the rates of contamination of blood cultures (which is approximately 3% to 5%) and a high-risk cutoff based on previous studies [14].

We addressed three types of validation: validation that is done in a single data set, with techniques such as jackknifing or bootstrapping, validation done in a second group of patients different from the original cohort but at the same centre and validation at a different centre. We defined internal validation as testing of the model on a group of patients, different than the derivation group, either from the same cohort or from a different cohort at the same centre. External validation was defined as testing of the model in a different group than the derivation group, in a different centre and at a different time. We searched for interventional studies that used the models to change the practice of obtaining blood cultures. We also wrote to the authors of validated models and asked whether, to their knowledge, their models are being used in routine clinical practice.

Results

Search results

We identified 710 records on electronic database searches and retrieved 36 publications for full-text inspection, of which 21 were excluded because they did not have any form of validation.

Description of included studies

Fifteen publications [2,8,14–26], conducted from 1990 through 2014 and including 59 276 patients, were included in the review (Table 1). All were published in journals; two were in Spanish

TABLE 1. Model characteristics

Study ID	Study population	Prospective study	Parameters included in model: Sepsis signs and symptoms	Parameters included in model: Source	Parameters included in model: Background	Parameters included in model: Inflammation markers or laboratory values
Bates 1990 [8]	Hospitalized patients in whom blood cultures were drawn	Yes	Temp ≥38.3°C, chills	Acute abdomen at examination	Major comorbidities, iv drug abuse, fatal disease	—
Leibovici 1991 [2]	Admitted febrile patients	Yes	Chills	Suspected urinary infection	Low premorbid performance status	Renal failure, low albumin
Mozes 1993 [16]	Hospitalized patients in whom blood cultures were drawn	Yes	Temp ≥39°C		Current immunosuppressive therapy, hospitalization in ICU	Serum alkaline phosphatase >100 IU
Bates 1997 [15]	Emergency, ward, and ICU patients with sepsis (defined by authors)	Yes	Altered mental status, focal abdominal signs within 24 hours of sepsis onset	Suspected or documented focal infection at onset	Hickman catheter, absence of antibiotics at onset, liver disease	—
Metersky 2004 [17]	CAP admitted	No	SBP <90 mm Hg, temp <35°C or ≥40°C, pulse ≥125 bpm	—	Liver disease, prior antibiotic therapy	BUN ≥30 mg/dL, Na ≤130 mmol/L, WBC <5000/mm^3 or >20 000/mm^3
Lizarralde 2004 [18]	Hospitalized patients in whom blood cultures were drawn within 48 hours	Yes	Temp >38.3°C	Urinary focus	—	Band forms, ESR ≥70 mm, Plt <200,000 /μL, Glu ≥140 mg/dL, urea ≥50 mg/dL, CRP ≥12 mg/dL, albumin <3 g/dL
Paul 2006 [14]	Hospitalized patients in whom blood cultures were drawn	Yes	Bayesian prediction model (causal probabilistic network) using the site of infection, sepsis signs and symptoms and inflammation markers	—	—	—
Shapiro 2008 [19]	ED or 3 hours from admission in whom blood cultures were drawn	Yes	Temp >39.5°C, temp 38.3–39.4°C, chills, vomiting, SBP <90 mm Hg	Indwelling vascular catheter, clinical suspicion of endocarditis	Age >65 years	Neutrophils >80%, WBC >18 000/mm^3, bands >5%, Plt <150 000/μL, creatinine >2mg/dl
Falguera 2009 [20]	CAP admitted	No	Tachycardia tachypnea, systolic hypotension	Pleuritic pain	Liver disease, absence of prior antibiotic treatment	—
Lipsky 2010 [21]	Hospitalized patients with SSSI, with blood culture obtained within 48 hours of hospitalization	No	RR <10 or >29 bpm, pulse <49 or >125 bpm, temp <35.6 or ≥38°C	Device or prosthesis infection	Healthcare-associated infection, male sex, coronary artery disease, age	WBC ≥11 × 10^9 cells/L, white blood cell band ≥7%, albumin ≤3 g/dL
Müller 2010 [22]	CAP admitted	Yes	—	—	—	PCT
Tudela 2010 [23]	Patients in ED whom blood cultures were drawn	Yes	—	—	Charlson index ≥2	PCT >0.4 ng/mL
Kim 2011 [24]	Women with pyelonephritis at ED (fever, pyuria, flank tenderness)	No	Vomiting, pulse >110 bpm	—	Age ≥65 years	Segmented neutrophils >90%, urine WBCs ≥50/HPF
Jin 2013 [25]	Hospitalized patients in whom blood cultures were drawn	Yes	Hyperthermia, hypothermia, tachycardia, tachypnea, low SBP	Central venous catheter	Sex, age, steroid therapy, antibiotic therapy	Leukocytosis, leukopenia, elevated CRP, low Plt, elevated PT, elevated creatinine, low albumin, elevated alkaline phosphatase
Lee 2014 [26]	CAP admitted	Yes	SBP <90 mm Hg, HR >125 bpm, Temp <35°C or >40°C	—	—	WBC <4000 or >12 000 cpm, Plt <130 000 cpm, albumin <3.3 g/dL, CRP >17 mg/dL

bpm, beats per minute; BUN, blood urea nitrogen; CAP, community-acquired pneumonia; cpm, cells per microliter; CRP, C-reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate; Glu, glucose; HPF, high-power field; ICU, intensive care unit; iv, intravenous; Na, natrium; PCT, pro calcitonin; Plt, platelets; PT, prothrombin time; RR, respiratory rate; SBP, systolic blood pressure; SSSI, skin and soft tissue infection; Temp, temperature; WBC, white blood cells.

[18,23] and the rest were in English. Study populations were heterogeneous, mainly hospitalized patients in which blood cultures were drawn for any reason (five studies), hospitalized with community-acquired pneumonia (four studies) and patients in the ED for whom blood cultures were drawn (two studies). Eleven studies were prospective and four retrospective. All included studies used criteria to define cultured organisms as contaminants. Generally, this was defined as an organism commonly considered a contaminant, grown only in one culture bottle and in the absence of other evidence of infection. Contaminants were counted as negative culture results in all studies. The parameters included in the different models were signs and symptoms of sepsis, source of sepsis, background and medical history and biomarkers of inflammation. There were no studies that included the same parameters, and parameters were greatly different among studies.

Two studies used a Bayesian prediction model (causal probabilistic network). The rest used a logistic model derived by multivariable analysis. Ten studies underwent internal validation where the validation group was from the same site as the derivation group. The model performed well in all of them. Five studies performed validation in different populations at a single site. Seven models were validated externally in a different hospital, using a new independent database. In two of these, the model performed poorly.

Validation properties and performance of models in included studies

To define risk groups of bacteraemia, patients were classified into three to six risk groups in different studies, with variable definitions. This resulted many times in a small number of patients in the groups of interest: the low- and high-risk groups for bacteraemia. Thus, sometimes the probability for true bacteraemia seemed impressive (very low in the low-risk group or very high in the high-risk group) but in actuality was less so because the denominator was very small (including only a few patients), and thus of dubious significance for clinical practice (Table 2).

Only three studies met our predefined cutoff criteria for both high and low risk of bacteraemia, and they found a high-risk group for bacteraemia of >30% and a low-risk group of <3% [2,14,26]. One of these performed poorly on external validation [2], but the two other performed well. Seven other studies defined a low-risk group of patients with <3% of bacteraemia but a high-risk group with a lower percentage than defined, and five showed only a high-risk group of >30% but were not successful in defining a low-risk group. Ten models published an area under the ROC curve value for the model. Values were heterogeneous between models, between 0.6 and 0.83, but were not different in derivation versus validation groups in each study (Table 2).

Use of models in clinical practice

Seven of 15 authors replied our query of whether their models are being used in routine clinical practice, all of them declaring that the model was not implemented. We found one study that measured the impact of using the model in practice and compared the accuracy of the attending physician in diagnosing bacteraemia (2). This study concluded that use of the model could have improved the diagnosis accuracy in 5% of the patients in the low-risk group and 18% in the high-risk group.

Discussion

We found only 15 studies offering a model for prediction of bacteraemia that underwent validation, evenly divided between internal and external validation. The models used differing clinical and laboratory predictors. At least part of the reason for this is that the models studied different patient populations, thus resulting in different prediction models, but there are also variations in practice among settings that could have had an impact. Ten studies showed a percentage of bacteraemia lower than 3% in the low-risk group, but in some of these studies, the model stratified patients into more than three groups (up to six), resulting in a small percentage of patients in the low-risk group.

None of the validated models was used in routine clinical practice after validation, although they may have been helpful to clinicians in considering whether or not to perform cultures. Reasons for this might be that the models were too diagnosis specific or cumbersome, or they may have relied on a series of variables that were not available early enough.

Coburn *et al.* [27] performed a systematic review in order to define clinical and laboratory findings informative for the decision to obtain blood cultures in suspected bacteraemia. Running a search strategy very similar to ours, they found that systemic inflammatory response syndrome and a multivariable decision rule with major criteria (suspicion of endocarditis, temperature >39.4°C, indwelling catheter) and minor criteria (temperature 38.3°C to 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), were sensitive but not specific predictors of bacteraemia (negative likelihood ratio 0.09, 95% confidence interval 0.03–0.26; and negative likelihood ratio 0.08, 95% confidence interval 0.04–0.17, respectively). They concluded that systemic inflammatory response syndrome and this decision rule may be helpful in identifying immunocompetent patients who do not need blood cultures. However, their review took into account all models, regardless of whether or not they were validated, and they did not include models from the year 2012 and later.

TABLE 2. Validation properties and probabilities of bacteraemia

Study	Internal validation		External validation	Area under the ROC curve for mode		Probability of true bacteraemia low-risk group		Probability of true bacteraemia high-risk group	
	One database	Two different databases		Deviation	Validation	Deviation	Validation	Derivation	Validation
Bates 1990 [8] (d = 1007, v = 509)	Yes		Performed poorly			4/303 (1%)	3/155 (2%)	41/264 (16%)	
Leibovici 1991 [2] (d = 244, v = 257)		Yes	Performed poorly			7/146 (5%)	1/131 (1%)	5/6 (83%)	11/7 (65%)
Mozes 1993 [16] (d = 474, v = 438)	Yes		Not done			12/240 (5.1%)	9/194 (4.6%)	23/62 (38%)	8/65 (12.1%) (p < 0.01)
Bates 1997 [15] (d = 881, v = 461)		Yes	Not done	0.60 ± 0.04	0.62 ± 0.03	32/220 (14.5%)	19/126 (15%)	62/102 (60.6%)	26/40 (64.4%)
Metersky 2004 [17] (d = 13 043, v = 12 771)	Yes		Not done	0.68 (95% CI 0.66–0.70)	0.68 (95% CI 0.66–0.70)	53/2243 (2%)	61/2245 (3%)	322/2297 (14%)	376/2417 (16%)
Lizarralde 2004 [18] (d = 298, v = 150)	Yes		Not done	0.81 (95% CI 0.76–0.86)	0.77 (95% CI 0.69–0.85)	2/84 (2.4%)	2/49 (4.1%)	26/40 (65%)	12/15 (80%)
Paul 2006 [14] (d = 790, v = 1724)		Yes	Performed well—3 sites	0.68 95% CI 0.63–0.73; p < 0.001)	0.70 (95% CI 0.67–0.73; p < 0.001)	3/123 (2.4%)	4/300 (1.3%)	55/184 (29.9%)	80/184 (28.1%)
Shapiro 2008 [19] (d = 2466, internal v = 1264, external v = 1526)	Yes		Performed well—independent hospital emergency department	0.8	I = 0.75, E = 0.83	4/659 (0.6%)	I = 3/338 (0.9%)	106/414 (26%)	I = 33/214 (15%)
Falguera 2009 [20] (d = 1386, internal v = 900, external v = 1127)	Yes		Performed well—independent multicentre cohort			4/133 (3%)	I = 2/66 (3%), E = 4/133 (3%)	16/42 (38%)	I = 20/31 (63%), E = 10/34 (29%)
Lipsky 2010 [21] (d = 755, v = 266)	Yes		Not done			3%	4%	46%	44%
Müller 2010 [22] (d = 463, v = 462)	Yes		Not done	0.83 (95% CI 0.78–0.89)	0.79 (95% CI 0.72–0.88)	1/117 (0.9%)	0%	61/364 (16.8%)	11%
Tudela 2010 [23] (d = 206, v = 206)		Yes	Not done	0.8	0.74	0%	2.9%	35%	27.2%
Kim 2011 [24] (d = 494, internal v = 241, external v = 169)	Yes		Performed well—independent academic hospital emergency department	0.792	I = 0.707, E = 0.792	9/208 (4.3%)	I = 9/106 (8.5%), E = 3/53 (5.7%)	60/118 (50.9%)	I = 21/50 (42%), E = 31/55 (56.4%)
Jin 2013 [25] (d = 11 061, v = 2341)		Yes	Not done	0.70 ± 0.007	0.70 ± 0.018	68/3594 (1.9%)	1/260 (0.4%)	97/486 (20%)	25/136 (18.4%)
Lee 2014 [26] (d = 1475, v = 947)	Yes		Performed well—cohort from an independent hospital		0.75	31/1144 (2.7%)	I = 20/746 (2.6%), E = 25/1070 (2.3%)	11/37 (29.7%)	I = 5/16 (31.2%), E = 10/44 (22.7%)

d, deviation cohort number; CI, confidence interval; E, external; I, internal; ROC, receiver operating characteristic; v, validation cohort number.

Two of the predictive models we identified performed poorly in external validations [2,8]. Mylotte *et al.* [28] tested the model of Bates *et al.* [8] and found an ROC area of only 0.64, compared with 0.72 in the original model. Yehezkelli *et al.* [29] tested the 2 models developed by Bates [8] and Leibovici [2] and also found significant deterioration in performance. Mozes *et al.* [16] suggested several factors contributing to these limitations of previous models: varying inclusion criteria, differences in definitions of predictors, overrepresentation of groups, varying practice styles and variation in measurement and interpretation of data. An example of differences between sites is that intravenous drug abuse was a strong predictor of bacteraemia in the Bates model, but there were few intravenous drug abusers where it was validated.

We found two attempts to predict bacteraemia using a computerized decision-support system. Paul *et al.* [14] constructed a system based on a causal probabilistic network (TREAT). The area under the ROC curve for prediction of bacteraemia was 0.68 in the derivation cohort and 0.70 in the validation cohort. The prevalence of bacteraemia was 2.4% in the low-risk group and 29.9% in the high-risk group. The TREAT system performance was validated in different settings (internal and external validation). Jin *et al.* [25] constructed a Bayesian prediction model. The model underwent only internal validation and performed well; the area under the ROC curve for prediction of bacteraemia was 0.7 in the derivation and validation cohort. The prevalence of bacteraemia was 0.4% in the low-risk group and 20% in the high-risk group.

Schurink *et al.* [30] discussed the historical developments, possibilities and limitations of various computer-based decision-support models for infectious diseases. They stated that because clinical experience is limited and clinicians are generally reluctant to use computerized guidelines if they require additional data entry, time and effort, prospective evaluation is needed to provide evidence on which implementation and wide-scale use of decision-support systems can be based. However, things are changing as electronic health records are becoming the norm, and it may be possible to use clinical data to predict who is infected and at risk of sepsis or bacteraemia [31]. In one recent study, Schmidt *et al.* [32] evaluated the impact of evaluating changes in vital sign parameters in hospitalized patients, and when a deterioration was found suggesting decompensation, this was communicated to providers. This resulted in a mortality reduction in two geographically separated hospitals. A host of sensors are becoming available, and when linked to communication tools and used with analytics, these approaches have substantial potential for improving outcomes, including in patients with suspected infection [33]. An important general frontier in informatics, as the use of electronic health records rises, is how to get clinicians to use prediction rules like these, and how to manage issues such as missing data in the rules in real time.

Conclusions

Although many models for predicting bacteraemia in adults have been developed, very few have been prospectively validated and performed well. Moreover, even these are not yet used in clinical practice. Reluctance to use these models is probably rooted in the additional work required to enter data and use the models; in the availability of the models' components in real time for septic patients; and in the additional information that might be gained from blood cultures even in patients with an *a priori* low probability of bacteraemia.

Future research

In an ideal world, the way to move forward would be to use the existing, recent, prospective databases in order to reach an acceptable model (or adopt from present ones). A threshold for the low-risk group (defined by us arbitrarily as <3%) should be defined in a formal cost-effectiveness analysis. The model should be tested in a clinical trial to examine whether it is helpful and safe in clinical use. Clinical trials preferably should be multicentred in order to secure utility and safety in diverse clinical settings. It may be possible to develop such models soon and implement them in routine care, given the advent of electronic health records and the growing availability of electronic clinical data, especially vital signs and laboratory parameters.

Transparency declaration

This review was conducted as part of our routine work. LL is on the scientific board of TREAT Systems. DWB serves as a consultant to and has received research support from EarlySense. The other authors report no conflicts of interest relevant to this article.

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