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Current strategies for infectious diseases management

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Models for bacteraemia risk prediction. Clinical implications

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ABSTRACT

Bacteraemia has important consequences for the patient, as it is associated with worse clinical outcomes. On the other hand, unnecessarily obtaining samples for blood cultures increases costs and the workload in the microbiology laboratory. Its diagnosis implies a time delay, but decisions about start antibiotic treatment, discharge, or admits the patient must be taken during the first attention and, therefore, before known the blood cultures results. This manuscript reviews the different strategies based on clinical scores and biomarkers that are useful for predicting bacteraemia and improving initial decision-making.

Keywords: bacteraemia, model, risk, prediction, biomarkers

INTRODUCTION

Bacteraemia has an increasing incidence of up to 1-2 cases/1,000 treatments in hospital emergency departments (ED) and around 6-10 episodes/1,000 hospital admissions [1-3]. When an infectious disease is suspected, blood cultures (BC) are taken in 15% of all microbiological samples obtained [4]. It should be noted that the diagnostic profitability of BC obtained in ED is very variable, between 2-20% [5], of which 3-5% of the positive BC corresponding to "hidden bacteraemia" (BC with significant isolation in patients who have been discharged) and 3% correspond to "contaminated BC" [1,6].

CLINICAL IMPLICATIONS

The main importance of the diagnosis of bacteraemia lies in the fact that it reaches a 30-day-mortality between 10-25% [1], in direct relation to the severity, the site of infection and the characteristics of the patients (age, comorbidity) [7-9]. The highest number of true bacteraemia (TB) are obtained from patients with urinary tract infection and pneumonia, with the most frequent causative agents being *Escherichia coli*, with 35%, and *Streptococcus pneumoniae*, with 75%, for each of them, among the positive BC obtained in the ED. Ten percentage of bacteraemia correspond to an unknown source of infection [10-14].

The key problem is that the certainty diagnosis of bacteraemia will not be obtained until the isolation of the microorganism in the culture, which can lead to a delay of time during which it is necessary to make the first clinical decisions. Being able to predict TB during the initial assessment of patients with suspected infection is very important. The diagnosis, prognosis and initial decisions such as discharge, hospital admission or the early and appropriate administration of an antimicrobial depend on this. Knowing this information can be useful to avoid unfair discharges or unnecessary admissions. Properly establishing diagnostic suspicion and risk stratification during the first evaluation of a patient with an acute event is key to obtaining the best clinical outcome [15-19]. For this reason, these aspects are the focus of numerous research works in emergency medicine [20,21].

Microbiological isolates in patients discharged from the ED can lead to a delay in the start of treatment, as well as an increase in morbidity and mortality. That is why the goal of many authors [22-24] has focused on finding predictive models combining different epidemiological, clinical and analytical variables. These include inflammatory response and infection biomarkers (BM) that increase the predictive power of clinical models [25-28]. Between all BM, procalcitonin (PCT) has been found to be the most sensitive and specific to predict bacteraemia risk [22,3-6], with a high negative predictive value (NPV) that would rule out a TB [29].

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PREDICTIVE MODELS OF BACTERAEMIA

Shapiro model. Shapiro et al. [30] developed, in an already classic study, a prediction model of TB risk. For this purpose, they conducted a prospective observational study on a cohort of adult patients in whom BC were obtained. To develop the model, they divided the sample into a derivation and a validation cohort. They included 3,730 patients with 305 (8.2%) episodes of TB. The model described major criteria (temperature > 39.5°C, presence of permanent vascular catheter or clinical suspicion of endocarditis) and minor criteria (temperature 38.3 to 39.4°C, age > 65 years, presence of chills or vomiting, systolic blood pressure < 90 mm Hg, neutrophil percentage > 80%, white blood cell count > 18,000/mm^3, bands > 5%, platelets < 150,000/mm^3 and creatinine > 2.0 mg/dl). Based on the results obtained, BC were recommended if the patient had at least one major criterion or two minor criteria. Otherwise, patients were classified as "low risk" and it was recommended not to obtain them, since only 4 (0.6%) low-risk patients in the derivation cohort and 3 (0.9%) low-risk patients in the validation cohort had positive BC. The sensitivity of this approach was 98% (95% confidence interval [CI]: 96-100%) in the derivation cohort and 97% (95% CI: 94-100%) in the validation cohort.

Model 5MPB-Toledo. Agustín-Julián et al [31] developed a new predictive model through an observational retrospective cohort study that included all the BC obtained during their attention in a Spanish ED in adult patients (≥ 18 years) with suspected infection. They analysed 38 independent variables (demographic, comorbidity, functional status, clinical and analytical) that could predict the existence of bacteraemia.

They included 2,181 episodes of BC. Between these, 262 (12%) were considered TB. A predictive model of bacteraemia risk was defined with 5 variables (5MPB-Toledo): temperature > 38.3°C (1 point), a Charlson index ≥ 3 (1 point), respiratory rate ≥ 22 breaths per minute (1 point), leukocytes > 12,000/mm^3 (1 point) and PCT ≥ 0.51 ng/ml (4 points). Patients were categorized as low (0-2 points), moderate (3-5 points) and high (6-8 points) risk, with a probability of bacteraemia of 1.1%, 10.5% and 77%, respectively. The area under the operating receiver curve (ABC-COR) of the model after internal validation was 0.946 (95% CI: 0.922-0.969).

Later this model was externally validated through in other research of the infectious diseases group of the Spanish Emergency Medicine Society (INFURG-SEMES) [32]. Seventy-four Spanish hospitals participated in this observational prospective cohort study that was performed to analyse the accuracy of the 5MPB-Toledo model**.**

This study included 3,843 episodes of BC obtained in the ED of the participating hospitals, been TB 839 (21.83%). Patients were categorized as low (0-2 points), moderate (3-5 points) and high (6-8 points) risk, with a probability of bacteraemia of 1.5%, 16.8%, and 81.6%, respectively. The ABC-COR of the model was 0.930 (95% CI: 0.916-0.948). The diagnostic performance for the 5-point cut-off achieved a sensitivity of 94.76% (95% CI: 92.97-96.12), a specificity of 81.56% (95% CI: 80.11-82.92) and a NPV of 98.24% (95% CI: 97.62-98.70). Therefore, the 5MPB-Toledo model could be useful to predict TB in patients with infection in the ED.

Table 1 Bacteraemia Prediction Risk Model of the INFURG-SEMES group (MPB-INFURG-SEMES)

Variable	Score
Procalcitonin ≥ 0,51 ng/ml	4
Respiratory rate 22 rpm	1
Temperature > 38,3ºC	1
Charlson Index ≥ 3	1
Leukocytosis > 12,000/ mm^3	1
Chills-shivering	1
Thrombopenia < 150,000 /mm^3	1

Bacteraemia Risk Prediction Model of the INFURG-SEMES group (MPB-INFURG-SEMES). Subsequently, the INFURG-SEMES group designed its own TB risk prediction model by conducting a prospective and multicenter cohort study [33]. The study involved 71 Spanish ED and included a total of 4,439 adult patients in whom a BC had been requested during their evaluation in the emergency room. Of these, 899 (20.25%) were considered as TB. A predictive model of bacteremia risk with seven variables was defined (Table 1). The model reached an ABC-COR of 0.924 (95% CI: 0.914-0.934) in the derivation cohort and 0.926 (95% CI: 0.910-0.942) in the validation cohort. Based on these results, patients were divided into 10 risk categories based on the probability of having a TB: 0.2% (0 points), 0.4% (1 point), 0.9% (2 points), 1.8% (3 points), 4.7% (4 points), 19.1% (5 points), 39.1% (6 points), 56.8% (7 points), 71.1% (8 points), 82.7% (9 points) and 90.1% (10 points). The findings were similar in the validation cohort. The 5-point cut-off provided the best diagnostic accuracy with a sensitivity of 95.94%, a specificity of 76.28%, a positive predictive value (PPV) of 53.63% and a NPV of 98.50%. Recommendations for making-decisions based on the risk score are expressed in Table 2.

In conclusion, the MPB-INFURG-SEMES model may be useful for the risk stratification of TB in adult patients with infection evaluated in ED. The risk calculation can be done online through the following link: https://mpbscore.urgenciasclinico.com

Usefulness of biomarkers for the prediction of true bacteraemia risk. Several studies have investigated the power of different BM to identify the patient with TB [3-6]. Among them, the literature clearly shows that PCT is the BM that presents a greater diagnostic accuracy. In fact, as we have seen previously, has the greater weight among the variables necessary for the calculation of the risk of TB in the 5MPB-Toledo and MPB-INFURG-SEMES models.

Table 2 Recommendations for making-decision based on the score of the Bacteraemia Risk Prediction Model of the INFURG-SEMES group (MPB-INFURG-SEMES)

Score	Risk classification	Probability of TB (%)	Recommending
0-2	Very low	0.2-0.9	Do not extract blood cultures
3	Low	1.8	Do not extract blood cultures
4	Low-moderate	4.7	The decision to obtain blood cultures and the patient's admission should be made according to the characteristics of the patient
5	Moderate-high	19.1	Blood cultures should be obtained and the patient be admitted
6-7	High	39.1-56.8	Blood cultures should be obtained and the patient be admitted
8-10	Very high	71.1-90.1	Blood cultures should be obtained and the patient be admitted

TB: true bacteraemia

A recently published study [34] analyses and compares the ability of PCT, C-reactive protein (CRP) and leukocytes to differentiate TB from contaminated BC in patients attended in a ED for suspected infectious disease. A retrospective cohort study selected a population with positive BC requested during patient´s evaluation in the ED. A total of 266 BC with any isolation were included in the study. Of these, 154 (57.9%) were considered TB and 112 (42.1%) were considered contaminated BC. The AUC-ROC of the PCT to predict a TB was 0.983 (95% CI: 0.972-0.994) and, considering a cut-off value of 0.43 ng/ml, the PCT achieved a sensitivity of 94%, a specificity of 91%, a PPV of 94% and a NPV of 92%. Moreover, the AUC-ROC obtained for PCR was 0.639 (95% CI 0.572-0.707) and for leukocytes 0.693 (95% CI 0.630-0.756). It is also noteworthy in this study that the mean values of PCT were 3.44 (SD 6.30) ng/ml in TB vs 0.16 (SD 0.18) ng/ml in contaminated BC (P <0.001).

In conclusion, the PCT achieves the best diagnostic performance for TB identification between different BM. Therefore, high PCT values can guide for request or not BC, and in addition to starting antibiotic therapy, especially when its value is above 0.5 ng/ml.

CONCLUSION

The prediction of TB is very important for making-decisions during the initial evaluation of the patients with suspected infection for several reasons. First, to avoid the requested of unnecessary BC, which lead to work overload in the Microbiology laboratory and to increased costs. Second, to avoid unnecessary admission in low-risk patients. Third, to avoid inappropriate discharge of the patient, since TB increases the risk of poor outcomes. Therefore, the suspicion and detection of TB has an important diagnostic and prognostic significance, and forces to change some of the most important decisions that must be taken during the initial assessment of patients. The 5MPB-Toledo and MPB-INFURG-SEMES models are useful tools for predicting TB in patients attended for infection in the ED. Finally, we should note that PCT is a key variable when assessing BC extraction, and the best BM to predict this situation. However, we must remember that both, clinical models and PCT, must be accompanied by the clinical judgment of the attending physician, as well as other variables depending on the process and the patient, for the better making-decision.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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