ORIGINAL ARTICLE

Predicting bacteraemia in the patients atended for infections in an emergency departments: the 5MPB-Toledo model

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Objectives. To develop a simple risk score to predict bacteremia in patients in our hospital emergency department for infection.

Methods. Retrospective observational cohort study of all blood cultures ordered in the emergency department for adults (aged 18 or older) from July 1, 2018, to March 31, 2019. We gathered data on 38 independent variables (demographic, comorbidity, functional status, and laboratory findings) that might predict bacteremia. Univariate and multiple logistic regression analyses were applied to the data and a risk scale was developed.

Results. A total of 2181 blood samples were cultured. True cases of bacteremia were confirmed in 262 (12%). The remaining 1919 cultures (88%) were negative. No growth was observed in 1755 (80.5%) of the negative cultures, and 164 (7.5%) were judged to be contaminated. The 5MPB-Toledo model identified 5 predictors of bacteremia: temperature higher than 38.3°C (1 point), a Charlson comorbidity index of 3 or more (1 point), respiratory frequency of at least 22 breaths/min (1 point), leukocyte count greater than 12 000/mm^3 (1 point), and procalcitonin concentration of 0.51 ng/mL or higher (4 points). Low risk for bacteremia was indicated by a score of 0 to 2 points, intermediate risk by 3 to 5 points, and high risk by 6 to 8 points. Bacteremia in these 3 risk groups was predicted for 1.1%, 10.5%, and 77%, respectively. The model's area under the receiver operating characteristic curve was 0.946 (95% CI, 0.922–0.969).

Conclusion. The 5MPB-Toledo score could be useful for predicting bacteremia in patients attended in hospital emergency departments for infection.

Keywords: Emergency health services. Bacteremia. Risk score. Blood cultures. Procalcitonin. Predictors.

Modelo 5MPB-Toledo para predecir bacteriemia en los pacientes atendidos por infección en el servicio de urgencia

Objetivo. Diseñar un modelo sencillo de riesgo para predecir bacteriemia en los pacientes atendidos por un episodio de infección en el servicio de urgencias hospitalario (SUH).

Métodos. Estudio observacional, de cohortes retrospectivo, de todos los hemocultivos (HC) extraídos en un SUH en los pacientes adultos (≥ 18 años) atendidos por infección desde el 1 de julio de 2018 hasta el 31 de marzo de 2019. Se analizaron 38 variables independientes (demográficas, comorbilidad, funcionales, clínicas y analíticas) que pudieran predecir la existencia de bacteriemia. Se realizó un estudio univariado y multivariable, mediante regresión logística, y después se construyó una escala de puntuación de riesgo.

Resultados. Se incluyeron 2.181 episodios de HC extraídos. De ellos se consideraron como bacteriemias verdaderas 262 (12%) y como HC negativos 1.919 (88%). Entre los negativos, 1.755 (80,5%) no tuvieron crecimiento y 164 (7,5%) se consideraron contaminados. Se definió un modelo predictivo de bacteriemia con 5 variables (5MPB-Toledo). El modelo incluyó la temperatura > 38,3°C (1 punto), un índice de Charlson ≥ 3 (1 punto), la frecuencia respiratoria ≥ 22 respiraciones por minuto (1 punto), leucocitos > 12.000/mm^3 (1 punto) y procalcitonina ≥ 0,51 ng/ml (4 puntos). Se categorizó a los pacientes en bajo (0-2 puntos), moderado (3-5 puntos) y alto (6-8 puntos) riesgo, con una probabilidad de bacteriemia de 1,1%, 10,5% y 77%, respectivamente. El ABC-COR del modelo tras remuestreo fue de 0,946 (IC 95%: 0,922-0,969)..

Conclusiones. El Modelo 5MPB-Toledo podría ser de utilidad para predecir bacteriemia en los pacientes atendidos por un episodio de infección en los SUH.

Palabras clave: Servicio de Urgencias. Bacteriemia. Escala pronóstica. Hemocultivos. Procalcitonina. Factores predictores.

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Introduction

Currently, about 15% of patients seen in hospital emergency departments (ED) are diagnosed with an infectious disease. In their first consultation, samples are taken for microbiological studies in 43% of cases, where blood culture (BC) extraction predominates, which is carried out in 15% of patients with ED infection[1,2].

Bacteremia is defined as the presence of bacteria in the blood, as evidenced by the isolation of these bacteria in BCs3. Despite new techniques for rapid detection (pathogen DNA or mass spectrometry)[3], BC allow the etiological diagnosis of the infection, providing information on the sensitivity of the isolated microorganism as well as optimizing antimicrobial treatment[3-6].

The incidence of community bacteremia has increased to 2/1,000 ED admissions and to 10 episodes/1,000 hospital admissions from these units[4,7]. In relation to the focus or origin of true bacteremias (TB) or significant bacteremias, urinary tract infection (UTI) with 45-55% and respiratory focus (10-25%) are the most frequent, while bacteremia of unknown focus stands at about 10% in EDs[4,7,8]. The etiology is due to Gram-negative bacteria in 60-70% (most frequent Escherichia coli), Gram-positive bacteria in 30-40% (mainly Staphylococcus aureus and Streptococcus pneumoniae) and anaerobic bacteria around 1%[4,7,8].

The 30-day mortality of patients with TB from the ED has been between 10-25%[4]. This is related to the severity of the clinical situation (existence of sepsis-shock), the type of primary focus (urinary, respiratory, abdominal, nervous system, unknown) and the characteristics of the patients (age, comorbidity, particular situations)[7-11].

One of the controversies that arises when indicating BC extraction in EDs refers to its diagnostic cost-effectiveness. The cost-effectiveness of BC extracted in the EDs is highly variable (2-20%)[4]. On the other hand, when the rate of "contaminated BC" is less than 3%, it is considered optimal[3,4]. However, in reality they can reach much higher rates[8,12]. In addition, BC with significant isolation in patients discharged from the ED (BPAE)[13] may represent 3-5% of those extracted in the ED[4,13]. These facts represent real problems, as they lead to an increase in diagnostic tests performed, hospital stay, costs and the administration of unnecessary antibiotic treatments or, as the case may be, inappropriate discharges in cases of BPAE[3,4,11,14].

Therefore, the suspicion and confirmation of TB has a relevant diagnostic significance, prognosis and requires changing some of the most important decisions to be taken in the ED. Among others: indicate discharge or admission, extract BC, administer the adequate and early antimicrobial[2,14].

Taking into account the above, it explains why knowing the predictive factors of identifiable TB in EDs has become the objective of many authors, who include in their studies different clinical, epidemiological and analytical variables[15-23]. Among the latter, the biomarkers of inflammatory response and infection (BMIRI) have been shown to significantly increase the diagnostic performance of the predictive models initially proposed[24-27]. The objective of this study was to design a simple risk model to predict bacteremia in patients treated in the ED for an episode of infection.

Method

Observational, retrospective, descriptive and analytical study of all BCs extracted in an ED from adult patients (18 years old) treated by some infectious disease and who, after a follow-up of 30 days, continued to be diagnosed with infection. The study was carried out in a 786-bed third level University Hospital belonging to the Castilla La Mancha Health Service (SESCAM). From July 1, 2018 to March 31, 2019, all BC obtained from patients clinically diagnosed with an infectious process in the ED were included consecutively, proving that vital signs had also been recorded in the clinical history and analytical samples had been obtained to perform hemogram, basic biochemistry and BMIRI [in this case procalcitonin (PCT) and C reactive protein (CRP)]. Patients in pediatrics and obstetrics/gynecology were excluded. The indication of the BC application was carried out according to the criteria of the physician in charge.

The extraction of the BC was performed by the standard technique of percutaneous venepuncture. For each patient, two extractions (three if endocarditis was suspected) were performed 20 minutes apart and in different venepuncture areas. For each extraction (BC), two bottles (BD BACTECÆ) were inoculated: one to the aerobic environment and one to the anaerobic. The BC were manually transported to the microbiology unit for immediate processing with the Bactec/AlertÆ automatic reading system (BioMérieux,Durham,NC,USA). The incubation time of the BC was 5-7 days, except in cases of suspected endocarditis, brucellosis or at the request of the physician in charge where it lasted up to 30 days. True (or significant) bacteremia was defined as the isolation of habitually pathogenic bacteria in one or both BC with a compatible clinical picture. And as BC contaminated by the isolation in a single bottle of BC of *Staphylococcus coagulasa-negative, Bacillus spp, Streptococcus viridans, Micrococcus spp, Propionibacterium spp, Corynebacterium spp*, and other Gram-positive bacilli, when the absence of clinical significance in these cases was interpreted (confirmed by history or at the discretion of the physician in charge). In other cases, as there are 2 positive BC and a clinical significance attributed to them (especially in immunocompromised or in carriers of vascular catheters or after invasive tests), TB was considered and treated with antibiotics.

For the BMIRI the reference values of our laboratory were assumed. For the CRP of 0-8 mg/L, a quantitative enzymatic immunoassay method (Slides VITROS CRP®) with a sensitivity of 1 mg/L was used. For PCT, concen-

trations <0.5 ng/mL were used as normal reference values, with a quantitative ELECSYS electrochemiluminescence immunoassay method (BRAHMS PCT®), which gives a sensitivity of 0.02 ng/mL.

The result variable was the existence of true bacteremia. In relation to the independent variables collected, sociodemographic variables were recorded (age, sex, institutionalization), antibiotic intake in the previous 72 hours and/or the previous 3 months, admission in the previous 3 months and the existence of comorbidities (solid tumoral or oncohematological disease, hepatopathy, nephropathy, diabetes, chronic or cerebrovascular heart disease, chronic obstructive pulmonary disease, peripheral arterial or connective tissue disease and infection by the human immunodeficiency virus). The Charlson[28] index was calculated weighted by age (and dichotomized ≥ 3 points) and functional status (Barthel index[29] and dichotomized index 60). Clinical and severity data were also recorded: temperature (Tª) in degrees Celsius (°C), altered consciousness defined with < 15 points on the Glasgow Coma Scale (GCS), systolic blood pressure (SBP), sepsis criteria, severe sepsis or septic shock and the variables that define them according to the 2001 sepsis expert conference[30]. Prognostic patient selection criteria were also applied in the definitions of the quick Sepsis Related Organ Failure Assessment (qSOFA) ≥ 2 and the variables that constitute it according to the third sepsis consensus conference (SEPSIS-3)[31]. Evolution and destination variables were also included: previous clinical days, initial patient destination, days of hospital stay, reconsultation in the ED in the following 30 days and hospital mortality and at 30 days. Finally, leukocyte counts were recorded (as well as leukocytosis > 12,000/mm^3, leukopenia < 4).000/mm^3 or stems > 10%), CRP concentration in mg/L (and dichotomized for ≥ 9 mg/L and for ≥ 21 mg/L) and PCT concentration in ng/mL (and dichotomized for PCs chosen according to previous studies of ≥ 0.43 ng/mL, ≥ 0.51 ng/mL and ≥ 1 ng/mL)[25,27].

In order to ensure the achievement of a sufficient sample size, the frequency of extractions and the proportion of expected TB were taken into account according to previous studies of our centre and surroundings[4,7,8]. The development of predictive models establishes that it is necessary to have at least 10 events of the dependent variable (positive BC) for each independent variable finally included in the multivariate logistic regression model. Given that our intention was to include in the multivariate model a limited (to make it simple and practical) but exhaustive number of variables, it was estimated that it would be necessary to obtain at least 150 events from the dependent variable in the derivation sample to ensure that the regression model could converge adequately. Thus, it was established that at least 1,500 BC extractions would therefore be necessary to find and "secure" more than 100 events in the derivation sample.

The statistical analysis used means and their standard deviations (SD) for the quantitative and percentages for the qualitative. The chi square or exact tests of Fisher, Student t and Mann-Whitney U, as applicable, were used to investigate the relationship between the existence of TB versus negative BC (contaminated and non-isolated) and independent variables (and those that were dichotomized). A value of $p < 0.05$ was considered significant, the contrasts were bilateral. A descriptive analysis (absolute numbers and percentages) of both groups (TB versus BC negative) was performed in relation to the type of pathogen found globally and a differentiated analysis according to the isolation of Grampositive, Gramnegative or anaerobic bacteria. As well as depending on the focus or clinical diagnosis carried out in the ED. A strategy of construction of a logistic regression model was established to evaluate the probability of existence of TB in BC extracted from the ED. Variables with a value of $p < 0.05$ were introduced in the univariate analysis together with those interactions that, following the hierarchical principle, had clinical significance. The selection of the final set of variables for the score scale was performed using the backward-selection algorithm ($p < 0.05$ to remain in the model). The discrimination capability of the predictive model was analyzed by calculating the area under the curve (AUC) of the receptor operating characteristic (ROC) and its 95% confidence interval (95% CI). Calibration of the model was evaluated using the Hosmer-Lemeshow goodness-of-fit test. Subsequently, the result obtained was internally validated by bootstrapping analysis with 1000 resamples and the AUC-ROC was calculated with its 95% CI. For the design of the scoring scale a risk scoring system was constructed in which a score was assigned to each factor, dividing each coefficient β by the lowest coefficient obtained. The risk score of each patient was calculated by adding the points of each factor present. Finally, the subjects were divided into low, moderate and high risk groups, depending on the predicted probabilities of the model. In all the contrasts, the null hypothesis was rejected with an error of less than 0.5. The statistical analysis was performed with IBM-SPSS® Statistics 22 for Windows and STATA 12.0.

The study has followed all international and our centre's protocols and standards (Declaration of Helsinki) for the use of patient data that were coded to ensure patient confidentiality. Computerized and primary care medical records were reviewed when required. The study was evaluated and approved by the Clinical Research Ethics Committee of the University Hospital Complex of Toledo.

Results

During the study period, 85,178 patients were treated in the ED. A total of 2,979 BC extractions were performed, i.e. 34.97 BC per 1,000 patients attended in the ED. Out of these, only 2,181 (73.21%) cases that met the inclusion criteria mentioned above were finally included by opportunity in the study. The mean age of the patients in whom BC was obtained was 52.84 (SD

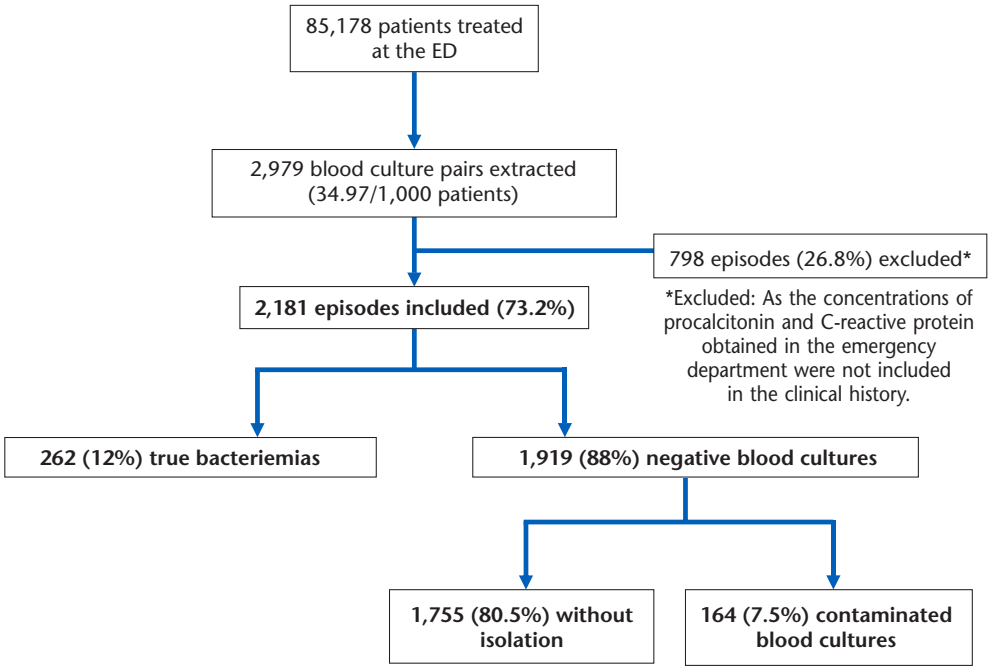

Figure 1. Case Inclusion Flowchart.

19.01) years with a range between 18 and 98 years. 30.6% (668) were over 65 years of age and 52.9% were women (1,153). Of the total number of episodes, 262 (12%) (7 of which were polymicrobial) were considered as true bacteremias and 1,919 (88%) as negative BC. Among those considered negative BC, 164 contaminated BC (7.5%) were confirmed. Finally, it should be noted that 2.67% (7 cases) of TB were classified as BPAE.

The aetiology grouped by microorganisms of the TB and of the contaminated BC is shown in Table 1. The most frequent isolations in TB were Escherichia coli with/without extended spectrum Betalactamases (ESBL) 81 times (19%) and *Streptococcus pneumoniae* 65 times (15.3%). *Escherichia coli* on 5 occasions (71.4%) was also the most frequent pathogen of the 7 BPAE. In relation to contaminated BC the most frequent were *Staphylococcus epidermidis* (54 episodes; 12.7%) and *Staphylococcus coagulasa-negative* (52 episodes; 12.2%).

The outbreak or clinical origin of presumption in the ED of true bacteremias and negative BC is shown in Table 2.

Table 3 shows the socio-demographic, epidemiological, comorbidity, functional, clinical, severity, evolution and destination of patients. When comparing TB and BC negative patients, only significant differences were found in age, the existence of solid neoplasia, chronic obstructive pulmonary disease, peripheral arterial disease and the weighted and dichotomized Charlson index (Charlson Index $\geq$ 3). Significant differences were also found in the proportion of patients who had taken antibiotics in the previous 72 hours, as well as in the history of admission in the previous 3 months, in both cases higher in episodes of TB ($p < 0.05$). In relation to clinical presentation data, both Tª in °C (and dichotomized > 38.3°C), heart rate (HR) (and > 90 beats per minute), respiratory rate (RR) (and $\geq$ 22 breaths per minute), SBP < 100 mmHg, an GCS < 15 points, together with the existence of the classical sepsis criteria (two or more criteria of systemic inflammatory response syndrome): SIRS $\geq$ 2), severe sepsis and septic shock, plus a qSOFA $\geq$ 2, were significantly superior in cases of TB.

With regard to the comparison of the analytical values (Table 4), significant differences were found in the absolute leukocyte count in the presence of leukocytosis > 12,000/mm^3, a proportion > 10% of stems and leukopenia < 4,000/mm^3. For CRP there were differences with higher mean concentrations in the TB and with the PC $\geq$ 9 mg/L and PC $\geq$ 21 mg/L. Finally, when comparing the values in the cases of TB with negative BC, for PCT the greatest differences were obtained between concentrations and also with both PC $\geq$ 0.43 ng/mL, PC $\geq$ 0.51 ng/mL and PCT $\geq$ 1 ng/mL.

The predictive bacteremia model (PBM) (Table 5) included the following variables in the first step: the existence of solid neoplasia, peripheral arterial disease, Charlson 3 index, antibiotic intake in the previous 72 hours, history of admission in the previous 3 months, Tª > 38.3°C, HR > 90 beats per minute, RR $\geq$ 22 breaths per minute, SBP < 100 mmHg, GCS < 15 points, SIRS $\geq$ 2, septic shock, qSOFA $\geq$ 2, leukocytosis > 12,000/mm^3, > 10% stems, CRP 21 mg/L and PCT 0.51 ng/mL. The 5 variables that were maintained in

Table 1. Microbiological characteristics of the global sample according to the type of isolation (true bacteremia versus contaminated blood cultures)

Type of microorganism	Total N = 426 n (%)	True bacteremia N = 262 n (%)	Negative blood cultures N = 64 n (%)
Gram negative bacteria[122(%)]			
Escherichia coli[a]	81(19.0)	81 (30.9)	0 (0.0)
Pseudomonas aeruginosa	8 (1.9)	8 (3.1)	0 (0.0)
Proteus spp	8 (1.9)	8 (3.1)	0 (0.0)
Klebsiella pneumonia[a]	5 (1.2)	5 (1.9)	0 (0.0)
Klebsiella spp	4 (0.9)	4 (1.6)	0 (0.0)
Salmonella spp	3 (0.7)	3 (1.1)	0 (0.0)
Serratia spp	3 (0.7)	3 (1.1)	0 (0.0)
Enterobacter spp	3 (0.7)	3 (1.1)	0 (0.0)
Other Gram negatives[n (%)][b]	4 (0.9)	4 (1.6)	0 (0.0)
Gram positive bacteria [288 (%)]			
Streptococcus pneumoniae	65 (15.3)	65 (24.8)	0 (0.0)
Sthapylococcus coagulasa-negativo (ECN)[c]	127 (29.8)	0 (0.0)	127 (77.4)
Enterococcus spp	19 (4.5)	19 (7.3)	0 (0.0)
Propionibacterium spp	15 (3.5)	0 (0.0)	15 (9.1)
Micrococcus spp	14 (3.3)	0 (0.0)	14 (8.6)
Staphylococcus aureus	14 (3.3)	14 (5.3)	0 (0.0)
SAMR[n (%)]	12 (2.8)	12 (4.6)	0 (0.0)
Other Gram positive [n (%)][d]	22 (5.2)	14 (5.3)	8 (4.9)
Anaerobic Bacteria [16 (%)]			
Bacterioides spp	8 (1.9)	8 (3.1)	0 (0.0)
Clostridium spp	4 (0.9)	4 (1.6)	0 (0.0)
Other anaerobic bacteria [n (%)][e]	4 (0.9)	4 (1.6)	0 (0.0)

[a]Includes pathogens that carry and do not carry ESBL (Extended Spectrum Betalactamases. [b]*Haemophilus influenzae* (2) and *Neisseria meningitidis* (2). [c]*Sthapylococcus* coagulasa-negative (NEC): the most frequent: *Staphylococcus epidermidis* (54) and *Staphylococcus hominis-hominis* (48). [d][14 true bacteremias: *Streptococcus spp* (13) and *Listeria monocytogenes* (1)] and [8 contaminants: *Streptococcus group viridans* and *Corynebacterium spp.*] [e]*Fusobacterium spp* (2), *Prevotella spp* and *Veillonella spp.*
SAMR: *Staphylococcus aureus* methicillin resistant.

the last step and that finally constitute the model are shown in Table 5 and Figure 2.

The AUC-ROC of the 5MPB-Toledo model was 0.946 (95% CI 0.933-0.960, p<0.001). The Hosmer-Lemeshow goodness-of-fit test showed a p value of 0.620. Internal validation by bootstrapping was 0.946 (95% CI 0.922-0.969; p<0.001).

Figure 2 shows the 5MPB-Toledo score scale (Tª > 38.3°C, Charlson index ≥ 3, RR ≥ 22, Leukocytosis > 12,000/mm^3 and PCT ≥ 0.51 ng/ml), the score for each of the model variables, and the predicted and observed probability based on the low (0-2 points), moderate (3-5 points) or high (6-8 points) risk of bacteremia (1.1%, 10.5% and 77%, respectively). The percentage of patients included in the low, moderate and high groups was 65.2%, 23.4% and 11.3%, respectively.

Discussion

The results of this study allow us to design a simple risk model to predict bacteremia in adult patients treated in the ED for an episode of infection. The 5MPB-Toledo score scale (Toledo 5-variable Predictive Bacteremia Model) includes variables, easily obtainable in the first moment of patients with suspected severe infection, exploratory (Tª and RR), comorbidity (Charlson index) and analytical (leukocyte count and serum PCT concentration). Therefore, it can represent a useful aid tool when predicting the existence of bacteremia, in order to optimize the indications for BC extraction, administer an adequate and early antimicrobial therapy and hospital admission, among the most important[2,14].

Table 2. Clinical focus/diagnosis of presumption in the emergency department of the global sample based on the existence or non-existence of isolates in blood cultures

Clinical focus/diagnosis	Total (N=2,181) n (%)	True bacteremia N = 262 n (%)	Negative blood cultures* N = 1,919 n (%)
Urinary tract infection	752 (34.5)	112 (42.7)	640 (33.4)
Respiratory infection]	643 (29.5)	73 (27.9)	570 (29.7)
Abdominal infection	244 (11.2)	23 (8.8)	221 (11.5)
Fever with no clear focus	225 (10.3)	23 (8.8)	202 (10.5)
Infection skin and soft tissue	207 (9.5)	19 (7.3)	188 (9.8)
Central nervous system infection	45 (2.1)	6 (2.3)	39 (2.0)
Other áreas	65 (3)	6 (2.3)	59 (3.1)

Other areas: Gynaecological, suspected endocarditis, by external devices.
*Negative hemocultures: includes the 1,755 without isolation and the 164 defined as contaminated.

Nowadays, although BC extraction techniques are well protocolised[3,4], there are still important controversies regarding the indications of when we should obtain them in the ED[3,10,14]. Despite this, obtaining BC is a growing practice in the initial valoration of patients with suspected infection in the ED[1,2,4]. The suspicion and confirmation of bacteremia has an important diagnostic, prognostic and therapeutic significance. However, BC are also obtained in the ED as a guarantee of continuity of care, since the management and subsequent evolution of the patient in his final destination will depend on knowledge of the results[2,14,25].

In this context, in recent years, the study of bacteremia predictors has been accentuated and different predictive models have been proposed for EDs of different complexity[15-26]. The role that BMIRI, and especially PCT[24-27], can play as independent predictors of bacteremia has acquired great relevance in these models. It has been demonstrated that their diagnostic capacity can equal, and even surpass, that of different models[24-27].

Shapiro et al[15]. published a proposed model that classifies the risk of bacteremia as low (< 1%), moderate (7-9%) and high (15-26%), depending on higher criteria (Tª > 39.4°C, presence of vascular catheter or suspected endocarditis) and lower criteria (Tª > 38.3°C, age > 65 years, chills, vomiting, SBP < 90 mmHg, leukocytosis > 18.000/mm^3, > 5% stems, thrombopenia < 150.000/mm^3 or creatinine > 2 mg/dl). This scale, for many years, and after being validated[16], became the

Table 3. Clinical-epidemiological characteristics, evolution and destination of the global sample and univariate study depending on the existence or not of isolates in blood cultures

	Total N = 2,181 n (%)	Lost values	True bacteremia N = 262 n (%)	Negative blood cultures* N = 1,919 n (%)	Value of p
Demographic-epidemiological data					
Age (years), mean (SD)	52.84 (19.01)	0 (0.0)	57.72 (16.12)	52.18 (19.26)	0.001
Age > 65 years [n (%)]	668 (30.6)	0 (0.0)	87 (33.2)	581 (30.3)	0.185
Female gender [n (%)]	1.153 (52.9)	0 (0.0)	126 (48.1)	1.027 (53.5)	0.057
Institutionalized [n (%)]	170 (7.8)	0 (0.0)	28 (10.7)	142 (7.4)	0.063
Intake of AB in the previous 3 months [n (%)]	633 (29.2)	0 (0.0)	89 (35.6)	544 (28.3)	0.224
Intake of AB in the previous 72 hours [n (%)]	450 (20.7)	0 (0.0)	76 (30.4)	374 (19.5)	0.001
Admission in the previous 3 months [n (%)]	361 (16.6)	0 (0.0)	64 (24.4)	297 (15.5)	0.001
Comorbidities					
Solid neoplasia [n (%)]	126 (5.8)	6 (0.3)	41 (15.6)	85 (4.4)	< 0.001
Leukaemia/Lymphoma [n (%)]	62 (2.8)	6 (0.3)	11 (4.2)	51 (2.7)	0.116
Liver disease n (%)]	59 (2.7)	6 (0.3)	6 (2.3)	53 (2.8)	0.424
Chronic heart disease [n (%)]	233 (10.7)	6 (0.3)	35 (13.4)	198 (10.3)	0.135
Chronic kidney disease [n (%)]	167 (7.7)	6 (0.3)	26 (9.9)	141 (7.3)	0.092
Cerebrovascular disease [n (%)]	63 (2.9)	6 (0.3)	5 (1.9)	58 (3.0)	0.213
COPD [n (%)]	235 (10.8)	10 (0.5)	28 (10.6)	207 (10.7)	0.329
Diabetes[n (%)]	338 (15.5)	6 (0.3)	50 (19.1)	288 (15.0)	0.055
Peripheral arterial disease [n (%)]	74 (3.4)	12 (0.6)	22 (8.4)	52 (2.7)	0.001
Connective tissue disease [n (%)]	27 (1.2)	12 (0.6)	4 (1.5)	23 (1.2)	0.414
HIV [n (%)]	36 (1.7)	6 (0.3)	5 (1.9)	31 (1.6)	0.428
Charlson indexa [mean (SD)]	2.13 (2.32)	10 (0.5)	2.76 (2.38)	2.04 (2.30)	0.001
Charlson index ≥ 3 [n (%)]	758 (34.9)	12 (0.6)	132 (51.0)	626 (32.8)	< 0.001
Barthel indexb [mean (SD)]	93.37 (15.62)	16 (0.7)	93.47 (14.53)	93.35 (15.76)	0.906
Barthel index ≤ 60 [n (%)]	123 (5.7)	16 (0.7)	8 (3.1)	115 (6.1)	0.047
Clinical and severity data					
Temperature in degrees C [mean (SD)]	38.10 (0.64)	0 (0.0)	38.36 (0.66)	38.06 (0.63)	< 0.001
Temperature > 38.3°C [n (%)]	604 (27.7)	0 (0.0)	140 (53.4)	464 (24.2)	< 0.001
HR in bpm [mean (SD)]	92.80 (12.12)	6 (0.3)	102.05 (18.22)	91.53 (10.40)	< 0.001
HR > 90 bpm [n (%)]	1092 (50.1)	6 (0.3)	197 (75.2)	895 (46.6)	< 0.001
RR in brpm [mean (SD)]	22.14 (4.99)	84 (3.9)	28.21 (6.16)	21.34 (4.21)	< 0.001
RR ≥ 22 brpm [n (%)]	977 (45.1)	84 (3.9)	209 (79.8)	768 (40.3)	< 0.001
Altered consciousness GCS < 15 [n(%)]	130 (6.1)	44 (2.02)	35 (13.5)	95 (5.0)	< 0.001
SBP in mmHg [mean (SD)]	123.1 (19.9)	0 (0.0)	117.57 (22.29)	123.79 (19.49)	0.001
SBP < 100 mmHg [n (%)]	142 (6.5)	0 (0.0)	35 (13.4)	107 (5.6)	< 0.001
Sepsis criteria (SIRS ≥2) [n (%)]	1,248 (57.2)	10 (0.5)	226 (86.3)	1.022 (53.3)	< 0.001
Criteria for severe sepsis [n (%)]	167 (7.7)	10 (0.5)	44 (16.8)	123 (6.4)	< 0.001
Criteria for septic shock [n (%)]	15 (0.7)	12 (0.6)	10 (3.8)	5 (0.3)	< 0.001
qSOFA ≥ 2 [n (%)]	180 (8.4)	92 (4.2)	56 (21.6)	124 (6.6)	< 0.001
Evolution and destination data					
Days since start of clinic [mean (SD)]	2.31 (1.28)	71 (3.2)	3.45 (1.50)	2.16 (1.18)	< 0.001
Initial destination of patients [n (%)]	2,181 (100.0)	0 (0.0)			< 0.001*
Discharge	878 (40.3)	0 (0.0)	10 (3.8)	868 (45.2)	
Observation	636 (29.2)	0 (0.0)	68 (26.0)	568 (29.6)	
Hospitalization Ward	607 (27.8)	0 (0.0)	155 (59.2)	452 (23.6)	
Operating room (urgent surgery)	35 (1.6)	0 (0.0)	19 (7.3)	16 (0.8)	
Intensive Care Unit	25 (1.1)	0 (0.0)	10 (3.8)	15 (0.8)	
Hospital stay in days [mean (SD)]	2.92 (5.09)	0 (0.0)	11.01 (5.09)	1.81 (3.96)	< 0.001
Reconsultation after discharge from ED [n (%)]	130 (6.0)	0 (0.0)	39 (14.9)	91 (4.7)	< 0.001
Intrahospital mortality [n (%)]	87 (4.0)	0 (0.0)	41 (15.6)	46 (2.4)	< 0.001
Mortality at 30 days [n (%)]	115 (5.3)	0 (0.0)	51 (19.5)	64 (3.3)	< 0.001

[a]Charlson index: age-weighted (one point is added to the Charlson index value for every decade after age 50) (reference 28). [b]Barthel index (reference 29). Sepsis criteria (SRIS 2) according to 2001 Consensus conference (reference 30)
Sepsis criteria (qSOFA 2) according to the third consensus conference (Sepsis-3) (reference 31)
*Negative hemocultures: includes the 1,755 without isolation and the 164 defined as contaminated.
SD: standard deviation; n: number; AB: antibiotics; h: hours; m: months; COPD: chronic obstructive pulmonary disease;
HIV: human immunodeficiency virus; C: centigrade; HR: heart rate; bpm: beats per minute; RR: respiratory rate; brpm: breaths per minute;

most important reference for EDs[25]. According to this decision model, BC extraction would be indicated when one major criterion or at least two minor criteria were met. Shapiro's model achieves an AUC-ROC of 0.83. Undoubtedly, this is a scale with a very relevant performance (although lower than that of the 5MPB-Toledo model which was 0.946), but it is too complex for EDs and does not take into account the unquestionable

Table 4. Analytical characteristics of the global sample and univariate study depending on the existence or non-existence of isolates in blood cultures

	Total N = 2.181 n (%)	Lost values	True bacteremia N = 262 n (%)	Negative blood cultures* N = 1,919 n (%)	Valor p
Leukocytes per mm³ [mean (SD)]	11.231 (6.684)	0 (0.0)	15.322 (16.426)	10.672 (3.387)	< 0.001
Leukocytes > 12,000/ mm³ [n (%)]	713 (32.7)	0 (0.0)	162 (61.8)	551 (28.7)	< 0.001
Leukocytes < 4,000/ mm³[n (%)]	98 (4.6)	0 (0.0)	4 (1.6)	96 (5.0)	0.002
Stems (bands) > 10% [n (%)]	446 (20.4)	0 (0.0)	102 (38.9)	344 (17.9)	< 0.001
Platelets per mm³ [mean (SD)]	206,079 (98.557)	0 (0.0)	218,422 (103.355)	204,394 (97,791)	0.039
Thrombopenia < 100,000/mm³ [n (%)]	164 (7.5)	0 (0.0)	15 (5.7)	149 (7.8)	0.146
Procalcitonin in ng/ml [mean (SD)]	0.73 (3.09)	0 (0.0)	3.07 (5.56)	0.41 (2.41)	< 0.001
Procalcitonin ≥ 0,43 ng/ml [n (%)]	508 (23.3)	0 (0.0)	235 (89.7)	273 (14.2)	< 0.001
Procalcitonin ≥ 0,51 ng/ml [n (%)]	422 (19.3)	0 (0.0)	227 (86.6)	195 (10.2)	< 0.001
Procalcitonin ≥ 1 ng/ml [n (%)]	233 (10.7)	0 (0.0)	179 (68.3)	54 (2.8)	< 0.001
C-reactive protein in mg/l [mean (SD)]	31.03 (29.43)	0 (0.0)	49.69 (42.89)	28.48 (26.08)	< 0.001
C-reactive protein ≥ 9 mg/l [n (%)]	1683 (77.2)	0 (0.0)	235 (89.7)	1448 (75.5)	< 0.001
C-reactive protein ≥ 21 mg/l [n (%)]	1043 (47.8)	0 (0.0)	184 (70.2)	859 (44.8)	< 0.001

*Negative hemocultures: includes the 1,755 without isolation and the 164 defined as contaminated.
SD: standard deviation; n: number.

contribution that the BMIRI could make[24-27]. Under these premises, another simpler proposal, by Tudela et al[17], which related clinical and analytical variables and the Charlson comorbidity index, after multivariate analysis defined two significant variables: the Charlson index ≥ 2 and a PCT > 0.4 ng/ml (1 and 2 points, respectively). With these 2 variables, 4 groups of increasing probability of bacteremia were established and obtained an AUC of 0.80 and a NPV of 95.3% to "rule out" the existence of bacteremia. When comparing the Tudela model with the 5MPB-Toledo scale, the latter includes (with other cut-off points) the two variables of the previous model plus the Tª, RR and leukocytes (which are present in the prognostic scales of severity and criteria defining sepsis: qSOFA and SIRS). Therefore, the 5MPB-Toledo, together with the assessment of SBP, HR and altered level of consciousness, could easily help to perform a comprehensive diagnostic assessment (of infection and bacteremia) and prognosis (severity and mortality) of patients with infection in the ED[2].

Recently, Contenti et al[32] obtained the same AUC-ROC from Shapiro's model (0.83), only with one of the variables defined in our study, the PCT, but raising the PC of this to concentrations greater than 2.25 ng/ml. Also in this line, Tudela et al26 with a PC > 1 ng/ml of PCT publish an AUC-ROC of 0.80. In other words, the inclusion of PCT in any model or as an individual factor today should be considered in EDs as suggested by different authors[11,24-27]. In our study, the PCT is the heaviest factor on the scale (4 points) with an OR of 59.95 (95% CI 38.89-92.42) with the PC chosen by other previous PCT studies ≥ 0.51 ng/ml[25].

Table 5. Independent Predictors of Bacteremia Identified in Multivariate Analysis

Variable	ß	*Odds Ratio*	95% CI	p
Temperature > 38.3°C	1.078	2.93	1.97-4.36	< 0.001
Charlson Index ≥ 3	1.368	3.92	2.61-5.90	< 0.001
Respiratory rate ≥ 22 brpm	1.116	3.20	2.11-4.86	< 0.001
Leukocytosis > 12,000/ mm³	1.190	3.28	2.21-4.87	< 0.001
Procalcitonin ≥ 0.51 ng/ml	4.094	59.95	38.89-92.42	< 0.001

95% CI: 95% confidence interval; C: centigrade; brpm: breaths per minute

Other models, which include some of the factors identified in our study, although useful, fail to achieve the performance of the Shapiro model[15]. But some of them are easier to evaluate and implement in the ED[18,22]. Such as Su et al[18], which includes as variables the Tª ≥ 38.3°C, tachycardia ≥ 120 brpm, lymphopenia < 500/mm³ and a PCT > 0.5 ng/ml with other analytical data. This Su et al. model[18] achieves an AUC-ROC of 0.85, somewhat lower than the performance of 5MPB-Toledo. And, precisely, the fact that the model is simple and quick to perform in the ED has been pointed out as a fundamental factor for success in recent meta-analyses and reviews[19,20]. Although, paradoxically, it has been proven that none of the 15 models of these reviews have been implemented in daily clinical practice by their respective authors[20].

However, contrary to what has been mentioned previously, another review article analyzing 35 studies[19] has not been able to identify the independent factors that predict bacteremia. For this reason, it does not recommend the systematic removal of BC only with the existence of fever and leukocytosis. What for the 5MPB scale would be 2 points (low risk of 1%). And it suggests that we should continue looking for an ideal model that incorporates other variables such as BMIRI and clinical assessment of patient severity (with vital signs: Tª, HR, RR, SBP and level of consciousness)[19,25].

Our study has different limitations that must be pointed out. In the first place, it is a unicentric and retrospective study, where the indication to obtain BC is made according to the decisions of the physician in charge. Therefore, together with this clinical variability, it should be remembered that 26.79% of BC were not recorded because they did not meet the inclusion criteria (as they did not have CRP and PCT data), all of which could lead to selection bias as not all the episodes were considered. In addition, the selection of clini-

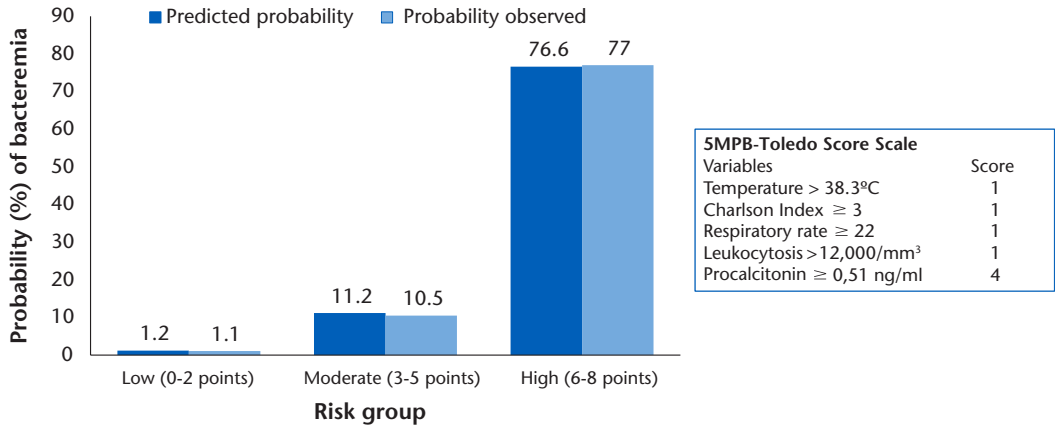

Figure 2. 5MPB-Toledo Model Scale Score.

cal variables could have been more complete (some variables such as chills, shivering or nausea-vomiting were not included, as there was a percentage of loss of these data greater than 50%)[21,23]. Although, on the other hand, in relation to the variables included and specifically those that make up qSOFA (alteration of consciousness, RR, SBP) or the Charlson and Barthel indices and the BMIRI, and as a positive fact, attention should be drawn to the low rate of loss of records. This could be so because prior to the start of the study, consensus had been reached in our ED (in order to reduce the variability of care and to be able to record all these data for various studies) that from triage and first care all these variables would be systematically recorded.

It is also important to point out the important rate of contaminated BC (7.5%), a fact that does not represent an obstacle to analysing the results, as has already been published by our group[8]. However, despite these limitations, we believe that the results represent a faithful reflection of the reality of an ED, but they cannot be extrapolated and lack external validity. Therefore, a multicenter and prospective study would be necessary to confirm these findings.

In conclusion, the 5MPB-Toledo model could be useful for stratification of bacteremia risk in adult patients with an infectious process in the ED, as it is capable of adequately predicting it with readily available variables.

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