ARTICLE

Factors associated with positive blood cultures in outpatients with suspected bacteremia

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Abstract Blood cultures are routinely taken in outpatients with fever and suspected bacterial infections. However, in the majority of cases, they are not informative and of limited value for clinical decision making. The aim of this study was therefore to investigate factors associated with positive blood cultures in outpatients presenting to an outpatient clinic and emergency room. This was a case–control study of all outpatients with positive blood cultures from January 1, 2006 to October 31, 2007 and matched control patients with negative blood cultures in the same time period. Microbiology results and medical charts were reviewed to determine factors associated with positive blood cultures. The presence of a systemic inflammation response syndrome (SIRS) (OR 2.7, 95% Cl 1.0–7.2) and increased C-reactive protein (CRP) (OR 1.1 per 10 mg/l, 95% Cl 1.0–1.2) were the most powerful predictive values for the development of positive blood cultures. In positive cases serum albumin was lower (35 mg/l versus 39 mg/l) than in controls. SIRS, increasing CRP and low albumin were associated with positive blood cultures in outpatients. With simple clinical assessment and few laboratory tests indicative of infection, it is possible to define a group at higher risk for bacteremia in outpatients.

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Introduction

Incidence of sepsis [1] in patients presenting to emergency departments (ED) remains high [2–5] with mortality rates up to 50% [6]. For this reason early detection and appropriate antibiotic therapy of suspected bacteremia is important.

Blood cultures are routinely taken during the diagnostic work-up of suspected sepsis despite low sensitivity. They are rarely positive in outpatients [7–14] and do not affect patient management when the infection can be established clinically or by microbiological sampling from other body sites [15, 16].

Several studies were conducted on inpatients with suspected sepsis to define factors associated with positive blood cultures and to develop guidelines for their rational use [6, 17–26]. Data that may guide management of outpatients with fever or suspected sepsis syndrome is lacking. The aim of this case–control study was to identify predictive factors for positive blood cultures in outpatients based on findings from clinical examination and routine laboratory testing.

Methods

Setting

The University Hospital of Basel is a 680-bed facility with 27,000 inpatients and 167,000 outpatients per year. It provides primary and tertiary care services.

Cases and controls

We evaluated all blood cultures entered into the electronic database of the microbiology laboratory of the University Hospital from January 1, 2006 to October 31, 2007 from patients aged 16 years or older who received ambulatory care or were admitted for less than 48 hours.

The number of blood cultures, the kind of pathogen detected and it's resistance testing, as well as all microbiology culture results from other body samples were extracted from the electronic database in patients with positive blood cultures (cases). White blood cell count, albumin and C-reactive protein (CRP) were collected by chart review, as well as the clinical parameters such as body temperature, heart rate, respiration rate, $PaCO_2$, and comorbidities with a higher risk for bacterial infections including immunosuppression, obstructive lung disease, insulin dependent diabetes, active malignant tumor and liver cirrhosis. Furthermore, data on antibiotic therapy were obtained. We randomly selected patients with negative blood cultures from the same study period as controls and collected the same data. Controls were matched to cases in a 3 to 1 ratio. Two infectious disease specialists independently revaluated all positive blood cultures. Cultures were classified as contaminated if typical skin flora was detected in the minority of blood cultures and another focus of infection could be identified. Discrepant judgement was resolved by consensus. In both groups we evaluated if there was a change in patient management due to the result obtained by blood cultures. Missing information was collected from the referring physician or family practitioner with a standardized letter.

Statistical analysis

We used the number of blood cultures as the selection criterion for suitable controls for each case. The frequency matching generated equal distributions for the number of blood cultures in cases and controls. To avoid bias of the estimated odds ratios, we included the matching factor as a covariate in the (unconditional) logistic regression model for positive blood cultures. In addition, further covariates were included (age, albumin, CRP, SIRS, presence of co-morbidities) in order to adjust for their possible confounding effect. Patients with missing data of vital signs were considered as not having SIRS. Analysis was made with Intercooled Stata Version 9.2 for Macintosh.

Results

During the 22-month observation period, 1,432 outpatients and inpatients with less than 48 hours stay had blood cultures taken. Ninety-one patients had positive blood cultures. Of these, 16 were interpreted as contamination, 23 had to be excluded because they were admitted from or went to another institution, and six had died within 48 hours, while data was missing in eight. This resulted in 38 cases with true positive blood cultures, a hospitalisation length ≤48 hours and a well-documented medical history. These cases were matched to 114 blood culture negative controls. In 66% of all patients (cases and controls), two sets of blood cultures were taken.

Parameters of interest differed between cases and controls (Table 1). Compared to controls, cases were older (58 vs. 42 years), were more likely to have SIRS (74% vs. 55%), had more underlying diseases and had a lower body temperature (38.5°C vs. 39.1°C). CRP was higher in cases compared to controls (70 mg/l, vs. 25 mg/l), mean albumin was lower (35 mg/l vs. 39 mg/l) and white cell count was higher (11.2/μl vs. 9.2/μl).

In positive cases, commonly found pathogens were *E. coli* (17/38, 45%) and *Staphylococcus aureus* (5/38, 13%). Polybacterial growth was detected in 7/38 (18.5%) cases. The detected pathogens were *Pseudomonas spp* and *Clostridium spp.* in a patient with diverticulitis, and *Enterococcus faecium* and *Proteus mirabilis* in a case of pyelonephritis; also found was bacteremia with *E. coli* and *Streptococcus pneumoniae*, urosepsis with detection of *Acinetobacter spp.* and *Peptostreptococcus asacharolyticus*, an intraabdominal abscess with *Klebsiella pneumoniae* and *E.coli*, bacteremia with *S. aureus* and viridans *Streptococci*, as well as bacteremia with detection of *Fusobacterium necrophorum* and *Bacteroides ureolyticus*. Frequent infections were urinary tract infection (39.9%), fever without focus (21%), pneumonia (7.9%), sepsis (5.3%), endocarditis (5.3%), unspecified infection (5.3%), and diverticulitis (2.2%). The most frequent infections in controls were fever without focus (30%), pneumonia (25%), viral infection (23%), soft tissue infection (5.3%), urinary tract infection (7.8%), and otolaryngological infections (3.5%). A total of 23 cases (61%) received initial antibiotic treatment, mostly with quinolones (12/38) or an aminopenicillin (6/38) and 45 control patients (40%) received antibiotic therapy with amoxicillin/clavulanate. In 21 cases (55%) cultures from other body sites had been taken (mostly urine cultures) and in 16 patients (76%) bacteria were detected in these cultures. In 14 (88%), identical isolates were found in the blood cultures.

In uni- and multivariate logistic regression analysis factors associated with positive blood cultures were the presence of SIRS (OR 2.7; 95%CI 2.0–7.2), serum albumin (OR per 10 mg decrease 0.4; 95%CI 0.4–0.9) and CRP (per

Table 1 Patients characteristics

Characteristics	Controls (n=114)	Cases (n=38)	Total (n=152)	Missing parameters
Age	42 (16–92)	58 (18–96)	43 (16–96)	–
Number of blood cultures				
1x2	18	6	24 (16%)	
2x2	75	25	100 (66%)	
3x2	18	6	24 (16%)	
4x2	3	1	4 (3%)	
Pulse (per minute)	93 (56–147)	104 (56–140)	94 (56–147)	13
Temperature (°C)	39.1 (37.1-42.3)	38.5 (36.1-40.5)	38.5 (36.1-42.3)	12
Respiration frequency (per minute)	16 (12–36)	16 (12–32)	16 (12–36)	105
aBGA: Alkalosis, n (%)	2 (2%)	1 (3%)	3 (2%)	140
White cell count (μL)	9.2 (0.8-27)	11.2 (2.5-26)	9.3 (0.8-27)	1
Premature neutrophils	14 (12%)	3 (8%)	17 (11%)	129
SIRS absent	23 (20%)	7 (18%)	30 (20%)	
SIRS present, n (%)	63 (55%)	28 (74%)	91 (60%)	
SIRS not defined, n (%)	28 (25%)	3 (8%)	31 (20%)	
CRP (mg/l)	25 (1–239)	70 (3–255)	35 (1–255)	1
Albumin (mg/l)	39 (22–50)	35 (16–47)	37 (16–50)	3
Comorbidities				
Immunodepression, n (%)	22 (19%)	11 (29%)	33 (22%)	
COPD, n (%)	14 (12%)	5 (13%)	19 (13%)	
Insulin dependent diabetes, n (%)	2 (2%)	4 (11%)	6 (4%)	
Active malignoma, n (%)	14 (12%)	6 (16%)	20 (13%)	
Liver cirrhosis, n (%)	–	1 (3%)	1 (1%)	
Number of comorbidities, n (%)				
0	82 (72%)	19 (50%)	101 (66%)	
1	15 (13%)	11 (29%)	26 (17%)	
2	14 (12%)	8 (21%)	22 (14%)	
3	3 (3%)	–	3 (2%)	

Noted as median and range, and percentage from the total

10 mg increase OR 1.1; 95%CI 1.0–1.2). Increased age and comorbidities were associated with higher odds for positive bloods cultures in uni- but not in multivariate analysis (Table 2).

Data on follow-up in cases was available in 38 patients. In controls, follow-up data was available in 95 of 114 patients. Thirteen cases (34%) were re-evaluated following positive results of their blood cultures—six were hospitalised, of

Table 2 Univariate and multivariable logistic regression analysis

Covariates	Unadjusted analysis		Adjusted analysis[a]	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age per 10 years	1.3 (1.0; 1.5)	0.02	1.2 (0.9; 1.5)	0.1
Albumin per 10 mg/l amount	0.2 (0.1; 0.5)	<0.001	0.4 (0.2; 0.8)	0.02
CRP per 10 mg/l amount	1.1 (1.0; 1.2)	<0.001	1.1 (1.0; 1.2)	0.01
SIRS: criteria fulfilled vs. not fulfilled or no definition	2.4 (1.0; 5.5)	0.04	2.7 (1.0; 7.2)	0.04
Comorbidities: yes vs. none	2.5 (1.2; 5.5)	0.02	1.5 (0.6; 3.7)	0.4

The number of patients was reduced to 149 because of missing data for albumin and CRP in three patients

[a] Adjustment for the number of blood cultures and all other co-variates

which four received additional antibiotics and two had a change in antibiotic therapy. Of seven cases with ambulatory management, two patients were newly started on antibiotic therapy and five had their antibiotic therapy changed. In seven patients with change of initial therapy, two had pathogens resistant to the previous antibiotic. In the control group we found no change in patient management stopping or shortening of the antibiotic therapy due to negative results of blood cultures.

Discussion

In this case control study of outpatients with suspected bacterial infection from a single academic centre in Switzerland, presence of SIRS, increases in CRP and decreases in albumin were factors most likely to be associated with positive blood cultures. However, results of positive blood cultures only affected patient management in one third of cases and in none of the controls, and the overwhelming majority o blood cultures remained negative. Our data further indicates that blood cultures add little information if a culture can be directly taken from the infected site. Findings on the number of positive blood cultures and outpatients undergoing therapeutic consequences from blood culture results are comparable to findings by others [27, 28]. However, our study included a control group and only looked at outpatients, which in comparison to previous studies on this topic, is a strength. We found lower rates of contaminated blood cultures than previous studies [16, 17, 22, 29–31].

Jaimes et al. [25] identified heart beat ≥90/min, temperature ≥37.8°C and white cell count >12/μl as predictors for bacteremia in inpatients. These factors are constituent of the SIRS definition and confirm our findings of increased odds for positive blood cultures in outpatients admitted with SIRS.

Hypoalbuminaemia is known to occur in severe infections [32]; however, to our knowledge no study so far has found an association for hypoalbuminemia and positive blood cultures.

Several studies have found an association between CRP and bacteremia [33–38] in intensive care patients and identified CRP as a marker for confirmed bacteremia [39], or a marker of sepsis in ICU patients with SIRS [40]. The kinetics and the low specificity of CRP are well known and therefore interpretation of CRP in patients with suspected bacterial infection should always be done in context with SIRS symptoms and clinical presentation.

Our study has some limitations. Confidence intervals for the associations found are wide, indicating the relative lack of power and need for careful interpretation. The retrospective design of our study precluded us from collecting additional data for the clinical indication to take blood cultures. Many patients had only one set of blood cultures taken. One blood culture set detects only 90–91.5% of bacteremia [41–43]. Thus, we may have included patients with false negative results in the control group. Finally, this data is from a single academic centre and needs confirmation in other settings.

In conclusion, this study indicates that the presence of SIRS, elevated levels of CRP and low albumin are associated with positive blood cultures in outpatients presenting with suspected infection to an ED. The identified factors need confirmation in prospective studies but may indicate a promising approach to reduce the number of blood cultures that will not affect patient management but add additional costs.

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