J Microbiol Immunol Infect.
2007;40:438-444

Original Article

Clinical significance of potential contaminants in blood cultures among patients in a medical center

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Received: May 16, 2006 Revised: July 28, 2006 Accepted: August 10, 2006

Background and Purpose: Blood culture is important for the diagnosis of sepsis, but it is sometimes difficult to differentiate true bacteremia from pseudobacteremia. This study proposed clinical criteria and evaluated the role of repeat blood cultures in assessing the clinical significance of potential contaminants in blood cultures (PCBCs).

Methods: From February to May in 2004 (prospective study) and 2003 (retrospective study), adult patients with growth of coagulase-negative staphylococci, *Bacillus* spp., *Micrococcus* spp., *Propionibacterium* spp., Gram-positive bacilli, or *Clostridium perfringens*, collectively referred to as "PCBCs", in at least 1 set of blood cultures in a medical center were included. The demographic and clinical data of patients with PCBCs were collected, and proposed clinical criteria for true bloodstream infections were used to evaluate their clinical outcome. Also, the potential role of repeating blood cultures to differentiate true bacteremia from pseudobacteremia was evaluated.

Results: There were 212 cases with 214 PCBCs, of which coagulase-negative staphylococci predominated (182 isolates, 85.0%). The overall contamination rate was 83.9% (178/212). Repeating 2 sets of blood cultures might be useful in the clinical differentiation of true bacteremia and pseudobacteremia, since the contamination rate of patients with potential contaminants in 1 set of blood cultures declined from 95% to 87% (p=0.04) with such a strategy. Those with true bloodstream infections had a significantly higher all-cause mortality rate at 14 days than those with pseudobacteremia (23.8% vs 7.3%, p=0.028), suggesting the validity of the clinical criteria. Of the 178 cases with pseudobacteremia, 73 (41.0%) were unnecessarily treated by systemic antibiotics, of which glycopeptides accounted for 20.0%. For these cases, antimicrobial therapy offered no survival benefit.

Conclusions: In an era of increasing glycopeptide resistance among Gram-positive cocci, clinical strategies for the early diagnosis of pseudobacteremia in cases with PCBCs are urgently required, in order to avoid the unnecessary use of glycopeptides. The proposed criteria and repeat blood culturing seem to be useful in the assessment of the clinical significance of PCBCs, and for reduction of the inappropriate use of glycopeptides.

Key words: Bacteriological techniques; Cross infection; Staphylococcal infections; *Staphylococcus aureus*

Introduction

The culturing of blood for pathogens is a simple procedure, and provides information essential for the evaluation of a variety of infectious diseases, including endocarditis, pneumonia, pyelonephritis, and fevers of unknown origin [1,2]. Unfortunately, contamination is not uncommon during the manipulation process, and creates serious problems for interventions, rendering much effort and expense superfluous for both laboratory and ward personnel [1]. Most contaminants are probably introduced from the patient's skin during blood culture collection [3]. According to data from the National Nosocomial Infections Surveillance System [4] and

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the surveillance data of pathogens of nosocomial bloodstream infections in our hospital [5], coagulase-negative staphylococci (CoNS) are the leading cause of bloodstream infections, but CoNS are also frequent contaminants of blood cultures in hospitals. In addition to CoNS, the potential contaminants in the literature are *Bacillus* spp., *Corynebacterium* spp., *Micrococcus* spp., *Propionibacterium* spp., Gram-positive bacilli, and *Clostridium perfringens* [6,7]. Therefore, judging the clinical significance of those potential contaminants is essential, and can have a profound impact on the bloodstream infection rates in an institution.

As the diagnosis of true bloodstream infections in patients with potential contaminants found in blood cultures (PCBCs) remains a difficult clinical challenge, numerous clinical and laboratory criteria have been described as predictors of true bloodstream infections in the literature [8-11]. The role of repetitive blood cultures in predicting clinical significance in patients with PCBCs is not well defined. Therefore, the aims of the present study were to assess the contamination rates of PCBCs, as retrospectively interpreted by the proposed clinical criteria, to reveal the clinical benefit of repeating blood cultures in patients with PCBCs, and to analyse the clinical outcome of patients with pseudobacteremia or true bacteremia caused by PCBCs.

Methods

Clinical setting

This study was conducted in an approximately 1000-bed teaching hospital with nearly 100 beds in the intensive care units, in southern Taiwan. Adults (at least 18 years of age) with growth of CoNS, *Bacillus* spp., *Micrococcus* spp., *Propionibacterium* spp., Gram-positive bacilli, or *C. perfringens*, referred to as "PCBCs" in this study, in at least 1 set of blood cultures were included. Exclusion criteria included death or discharge before the results of blood cultures were available, growth of microorganisms other than PCBCs in blood cultures, and the usage of glycopeptide before or on the day of positive blood cultures.

Study population

Two patient groups, a retrospective group and a prospective group, that were enrolled for a pharmacist intervention program aimed at reducing glycopeptide usage in patients with pseudobacteremia, were included in the present analysis. During the prospective study period, from February to May 2004, records of blood cultures at the clinical microbiology laboratory were reviewed daily. Attending physicians were informed if potential contaminants were isolated from at least 1 bottle of the initial 2 sets of blood cultures. A pharmacist actively advised attending physicians to repeat 2 sets of blood cultures cautiously performed with all appropriate antiseptic procedures before initializing antimicrobial therapy for presumed true bacteremia caused by PCBCs. The medical records of patients with PCBCs from February to May 2003 were retrospectively reviewed with the same inclusion and exclusion criteria. Patient number was the same as in the prospective group; however, there was no pharmacological intervention in this period.

The demographic and clinical data of patients were collected, including underlying diseases, hospital location, relevant symptoms and signs related to sepsis, vital signs, invasive procedures, repeated blood cultures, antimicrobial therapy, and clinical outcome. Clinical outcome was evaluated at 7 and 14 days after the initial sampling of blood cultures, and all-cause mortality was considered. In the present study, attending physicians independently made decisions as to the administration of antimicrobial agents and not the investigators. Nosocomial infection was defined as an infection that occurred more than 48 h following admission, an infection that occurred less than 48 h following admission to the hospital in those who had been hospitalized within 2 weeks prior to this admission, or an infection that occurred more than 48 h following admission in those who had been transferred from another hospital or nursing home.

On the basis of previous studies on CoNS bacteremia [10,12,13], clinical criteria for true bloodstream infections were developed for this study (Table 1). The episodes that did not meet the above definition were considered as pseudobacteremia. Briefly, patients with the same species isolated from at least 2 sets of blood cultures, or patients with the same species isolated in 1 set of the initial blood cultures and additional blood cultures in the presence of systemic inflammation reaction syndromes, were considered to have true bloodstream infections. Moreover, those with at least a potential concomitant in 1 set of blood cultures and systemic inflammation reaction syndromes, but with no obvious infectious focus, with an indwelling intravascular device, regular hemodialysis or peritoneal dialysis, or presenting with multiorgan dysfunction, were regarded as having true bloodstream infections.

Table 1. Clinical criteria for true bloodstream infections

One of the following clinical settings:

I. Patients with the same species isolated from 2 or more sets of blood cultures

II. Patients with the same species isolated in 1 of initial 2 sets of blood cultures and additional blood cultures, have systemic inflammation reaction syndrome

III. Patients with a species growing in 1 set of blood cultures, and without an obvious evidence of an infectious source, in the presence of systemic inflammation reaction syndromes, had at least one of the following:
   1. Shock, metabolic acidosis, or disseminated intravascular coagulation
   2. Indwelling intravascular devices[a] for more than 48 h
   3. Receipt of hemodialysis or peritoneal dialysis

[a]Including central venous catheters, temporary or permanent pacemakers, or arterial catheters.

Sampling and processing of blood cultures

Blood sampling was performed by nurses or residents, and 2 sets of blood cultures were done from different peripheral veins or arteries with at least 30 min between the 2 samplings routinely. A set of blood cultures is routinely composed of 1 bottle of aerobic culture and another of anaerobic culture. Approximately 5-8 mL of blood per bottle (10-16 mL in total/culture) was collected from each adult. Blood culture bottles were transported immediately to the hospital laboratory, where they were loaded into the BACTEC 9240 automated blood culture system (Becton Dickinson and Company, Franklin Lakes, NJ, USA) and incubated for a total of 5 days or until the instrument indicated the culture was positive. Aerobic and anaerobic BACTEC blood culture bottles that became positive underwent Gram staining, and the contents of bottles were plated onto biplate agar with blood (Trypticase™ soy agar II 5% sheep blood; Becton Dickinson and Company) and Levine EMB agar (Becton Dickinson and Company), chocolate, and CDC anaerobic blood agars (Becton, Dickinson and Company). The biplate and chocolate agars were incubated in carbon dioxide overnight at 35°C for aerobes, and the CDC anaerobic blood agars were cultured anaerobically at 35°C for at least 48 h.

Statistical analysis

The results were analyzed using the Statistical Package for the Social Sciences for Windows (Version 11.0; SPSS, Chicago, IL, USA). For categorical data, proportions were compared using the chi-squared test. The mean and medians of continuous variables were compared by the Mann-Whitney *U* test. All tests of significance were 2-tailed. A p value ≤ 0.05 was considered statistically significant.

Results

Between the months of February and May in 2003 and 2004, 106 patients were included each of in the retrospective and prospective groups and a total of 214 potential contaminants were found in blood cultures. Of potential contaminants, CoNS predominated (182 isolates, 85.0%), followed by unidentified Gram-positive bacilli (15 isolates, 7.0%) [Table 2]. Of the 182 CoNS isolates, 159 (87.4%) were resistant to oxacillin, highlighting the potential overuse of glycopeptides for patients with pseudobacteremia. The demographics, underlying illnesses, infectious signs at the time of blood sampling, and numbers of invasive procedures and repeat blood cultures are shown in Table 3.

Table 2. Contamination rates in blood cultures with potential contaminants

Bacterial species	No. of contaminated cases/no. of total cases (%)		
	Prospective period	Retrospective period	Overall
Coagulase-negative staphylococci[a]	72/86 (83.7)	78/96 (81.3)	150/182 (82.4)
Gram-positive bacilli	13/14 (92.9)	1/1 (100)	14/15 (93.3)
Micrococcus spp.	4/4 (100)	4/4 (100)	8/8 (100)
Bacillus spp.	4/4 (100)	1/2 (50)	5/6 (83.3)
Clostridium perfringens	0	2/2 (100)	2/2 (100)
Propionibacterium spp.	0	1/1 (100)	1/1 (100)
Total number of strains	91/108 (84.2)	87/106 (82.1)	178/214 (83.1)

[a]In addition to coagulase-negative staphylococci, Gram-positive bacilli and *Micrococcus* spp. were found concurrently in the same blood culture in each patient.

Table 3. Demographic and clinical characteristics of 178 cases with pseudobacteremia[a]

Variable	No. of cases/no. of total cases (%)			*p*
	Prospective group (n = 91)	Retrospective group (n = 87)	Overall (n = 178)	
Age (years; mean ± SD)	66.2 ± 12.0	65.3 ± 16.5	65.7 ± 14.1	0.215
Male gender	56 (61.5)	48 (55.2)	104 (58.4)	0.389
Intensive care unit[b]	21 (23.1)	32 (36.8)	53 (29.7)	0.046
General ward				
Internal medicine ward	62 (68.1)	56 (64.4)	118 (66.2)	0.595
Surgery ward	28 (30.8)	30 (34.5)	58 (32.5)	0.597
Malignancy	30 (33.0)	31 (35.6)	61 (34.2)	0.708
Nosocomial infections	38 (41.8)	43 (49.4)	81 (45.5)	0.305
Infectious signs				
Body temperature ≥38°C or <36°C	62 (54.9)	65 (60.9)	127 (71.3)	0.332
Respiratory rate >24 times/min	27 (29.7)	31 (35.6)	58 (32.5)	0.396
Heart rate >90/min	73 (80.2)	67 (77.0)	140 (78.6)	0.602
White blood cells >12,000/mm^3	37 (40.7)	28 (32.2)	65 (36.5)	0.240
Septic shock	2 (2.2)	1 (1.1)	3 (1.6)	1.000
Invasive procedures[c]	38 (41.8)	38 (43.7)	76 (42.6)	0.796
Repeat blood cultures	31 (34.1)	18 (20.7)	49 (27.5)	0.046

Abbreviation: SD = standard deviation

[a]Those with growth of unspecified Gram-positive bacilli, coagulase-negative staphylococci, *Bacillus* spp., *Micrococcus* spp., *Propionibacterium* spp., or *Clostridium perfringens* in at least 1 set of blood cultures.

[b]The unit where initial blood cultures were obtained.

[c]Including central venous catheters, port-A catheter, temporary or permanent pacemakers, peritoneal dialysis or hemodialysis, or arterial catheters.

The overall contamination rate of the PCBCs, as judged by the clinical criteria, was 83.9% (178/212), and there was no significant difference in the contamination rates of the retrospective and prospective groups (84.2% and 82.1%, respectively; p=0.45). The contamination rates of individual species ranged from 82.4% to 100% (Table 2).

The growth of potential contaminants was found in only 1 set of blood cultures in 184 (86.8%) of the 212 patients. The yield of repeat (at least 2 sets) blood cultures before the initiation of antimicrobial therapy is shown in Table 4. Repeat blood cultures were performed in 54 (29.3%) of the 184 patients with PCBCs in initial blood sampling. According to the clinical criteria alone, there was a contamination rate of 95% in 130 patients, with potential contaminants found in 1 set of blood culture. In contrast, of the 54 patients with repeated blood sampling, there were 7 patients with a potential contaminant with the same antibiogram found in the additional blood cultures. Thus, after repeating of 2 sets of blood cultures, the culture contamination rate of patients with PCBCs declined to

Table 4. Blood culture results and clinical significance as determined retrospectively by clinical criteria in patients with potential contaminants found in blood cultures[a]

Initial blood cultures	Follow-up blood cultures	No. of total cases	No. of contaminated cases	Contamination rate (%)
Growth in 1 set of blood cultures (n = 184)	Not done	130	124	95
	No growth	48	47	98
	Growth in 1 set	6	0	0
	Growth in 2 sets	0	0	0
Growth in 2 sets of blood cultures (n = 28)	Not done	19	5	26
	No growth	1	0	0
	Growth in 1 set	1	0	0
	Growth in 2 sets	1	0	0

[a]Those with growth of unspecified Gram-positive bacilli, coagulase-negative staphylococci, *Bacillus* spp., *Micrococcus* spp., *Propionibacterium* spp., or *Clostridium perfringens* in at least 1 set of blood cultures.

87% (47/54, p=0.04). Among patients with potential contaminants found in both sets of blood cultures, contamination rates were similar in those without and with repeat blood cultures (5/19, 26.3% vs 2/9, 22.2%; p=0.60).

Thirteen patients were transferred to other hospitals or discharged within a week of hospitalization, and therefore were excluded from the outcome analysis. A higher all-cause mortality rate was found in patients with true bloodstream infections at 2 weeks after the initial blood culture than in patients with pseudobacteremia (23.8%, 5/21 vs 7.3%, 13/178; p=0.03). Of the 178 patients with pseudobacteremia, 73 patients (41%) were treated with parenteral antibiotics and 20% of these were glycopeptides. In patients with pseudobacteremia, there was no difference in the age, receipt of intensive care, hospitalization for at least 72 h, hospital stay before initial blood sampling, or presence of systemic inflammatory response syndromes or septic shock among patients with or without antimicrobial therapy (Table 5). Male gender (69.8% vs 50.4%, p=0.01) and underlying malignancy (49.3% vs 23.8%, p<0.001) were more common in patients with pseudobacteremia and concurrent antimicrobial therapy, and the receipt of invasive procedures before the initial blood sampling was more common in patients with pseudobacteremia without concurrent antimicrobial therapy (49.5% vs 32.9%, p=0.03). However, the 1-week and 2-week all-cause mortality rates of patients with pseudobacteremia and concurrent antimicrobial therapy were significantly higher than those of patients with pseudobacteremia but no antimicrobial therapy (1-week: 9.6% vs 1.9%, p=0.033; 2-week: 13.7% vs 2.9%, p=0.006). The causes of death of the 9 patients with pseudobacteremia dying within 7 days included pneumonia, respiratory failure, and documented septic shock or multiple organ failure caused by Gram-negative bacilli or *Candida*. The deaths were not clinically related to the bloodstream infections caused by potential contaminants.

Discussion

Several clinical studies of bloodstream infections have provided guidelines for differentiating true pathogens from contaminants [1,6], and various definitions and algorithms have been discussed [10,12,14]. Of these, the definition of primary bloodstream infections by the Centers for Disease Control and Prevention is perhaps the most commonly used [15]. However, a gold standard for differentiating pathogens from contaminants does

Table 5. Clinical characteristics of 178 cases with pseudobacteremia[a] according to whether or not antibiotic therapy was received

Variable	No. of cases/total cases (%)		*p*
	Antibiotics (n = 73)	No antibiotics (n = 105)	
Age (years; mean ± SD)	65.8 ± 15.1	65.7 ± 16.2	0.992
Male gender	51 (69.8)	53 (50.4)	0.010
Intensive care unit[b]	18 (24.7)	35 (33.3)	0.213
Underlying malignancy	36 (49.3)	25 (23.8)	<0.001
Hospitalization for at least 72 h	33 (45.2)	48 (45.7)	0.947
Indwelling intravascular devices[c]	24 (32.9)	52 (49.5)	0.027
Hospital stay before blood culture sampling (days; mean)	16.0	19.5	0.071
Infectious signs			
Body temperature ≥38°C or <36°C	50 (68.5)	77 (73.3)	0.482
Respiratory rate >24 times/min	20 (27.4)	38 (36.2)	0.218
Heart rate >90/min	60 (82.2)	80 (76.2)	0.337
White blood cells >12,000/mm^3	24 (32.9)	41 (39.0)	0.400
White blood cells <4000/mm^3	9 (12.3)	13 (12.4)	0.992
Septic shock	1 (1.4)	2 (1.9)	1.000
All-cause mortality			
7-day	7 (9.6)	2 (1.9)	0.033
14-day	10 (13.7)	3 (2.9)	0.006

Abbreviation: SD = standard deviation

[a]Those with growth of unspecified Gram-positive bacilli, coagulase-negative staphylococci, *Bacillus* spp., *Micrococcus* spp., *Propionibacterium* spp., or *Clostridium perfringens* in at least 1 set of blood cultures.

[b]The unit where initial blood cultures were obtained.

[c]Including central venous catheters, port-A catheter, temporary or permanent pacemakers, peritoneal dialysis or hemodialysis, or arterial catheters.

not exist [7,8,16]. In previous literature, clinical evidence of infection and 2 or more positive blood cultures were important in determining the clinical significance of CoNS bacteremia [14,17,18]. In addition, several studies have proposed the importance of the presence of central catheters, peritoneal catheters for peritoneal dialysis, or vascular catheters for hemodialysis [12,13,19]. In the present study, clinical criteria for diagnosing true bacteremia were proposed, involving the number of positive blood cultures, and the presence of systemic inflammatory signs and indwelling intravascular devices.

As in previous reports [6,19], CoNS were the leading cause of bloodstream contaminants in the present study. Our criteria found that 17.6% of CoNS isolates were true pathogens, with the range reported in the literature being 10% to 30% [6,10-14,20]. Based on the surveillance data and previous reports [13,14], methicillin resistance was common in these CoNS isolates, irrespective of the isolates being true pathogens or contaminants. In order to reduce the unnecessary consumption of glycopeptides and delay the emergence of glycopeptide resistance among Gram-positive cocci, it is important for clinicians to differentiate true pathogens from contaminants.

In order to evaluate the validity of the clinical criteria, the clinical outcome of patients regarded as having pseudobacteremia and those with true bacteremia were compared. A higher mortality rate was found among the latter patients. Although some deaths did occur in patients with pseudobacteremia, none of these deaths were directly attributable to the contaminants in blood cultures. Thus, the criteria appeared to be useful in clinical differentiation of the pathogenic significance of potential contaminants discovered in blood cultures.

Among patients with pseudobacteremia, a higher mortality rate was noted in patients receiving antibiotic therapy than in those without antibiotic treatment, indicating that antimicrobial therapy offered no clinical benefit for these patients. Although the clinical characteristics of patients receiving or not receiving antimicrobial therapy were different in certain aspects, the presence of systemic inflammatory response syndromes or septic shock in patients with pseudobacteremia was similar in both groups. Moreover, admission to intensive care was no more common in the former (23.1%) than in the latter (36.8%). However, it remained likely that the former were more critically ill, and clinicians were more likely to give antimicrobial therapy for an episode of suspected pseudobacteremia.

To our knowledge, a potential contaminant in only 1 set of initial blood cultures is often regarded to be of no clinical significance [2,7,14]. Sequential blood cultures can determine the clinical importance of the common contaminants, such as CoNS [21]. Our study also demonstrated that repeating blood cultures could decrease the rate of contamination in patients with a potential contaminant in 1 set of initial blood cultures. On the other hand, repeating blood cultures did not decrease contaminant rates when bacterial growth was noted in both sets of initial blood cultures, probably because of the higher probability of being true pathogens in such clinical settings. Unless the genetic relatedness is shown by molecular genotyping, the discovery of the same bacterial species with the same antibiogram does not exclude the limited possibility of being a contaminant in blood cultures for either isolate, which is a limitation of the present work.

In conclusion, the clinical characteristics and outcome of patients with PCBCs were analyzed, and clinical criteria were proposed and applied to retrospectively differentiate true bacteremia from pseudobacteremia. About 40% of patients with pseudobacteremia were unnecessarily treated with systemic antibiotics, which of course offered no therapeutic benefits. Thus, it is essential to develop plausible measures for early diagnosis of pseudobacteremia, in order to minimize the unprofitable use of antimicrobial agents.

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