

### Prospective evaluation of blood cultures in a Turkish university hospital: epidemiology, microbiology and patient outcome

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The aims of this prospective study were to: (1) determine the rate of blood culture contamination; (2) describe and compare the epidemiologic, clinical and microbiological characteristics of hospital- and community-acquired bloodstream infections; and (3) determine the mortality resulting from bloodstream infections. The rate of true bacteremia was 12.1%, and 10.7% of cultures were contaminated. Of the 567 episodes of bloodstream infection, 73.4% were hospital-acquired, and 26.6% were community-acquired. The most commonly isolated microorganisms were staphylococci (44%, methicillin resistant 69.4%), enterococci (15%) and *Escherichia coli* (12.5%) in hospital-acquired episodes, and *Brucella* spp. (21.9%), *E. coli* (19.2%) and *Staphylococcus aureus* (14.6%, methicillin resistant 9.1%) in community-acquired episodes. While the overall mortality rate was 25.4%, death attributable to bloodstream infections was 16.6% in hospital-acquired episodes and 13.9% in community-acquired episodes. The highest mortality occurred in patients with bacteremia due to *Pseudomonas aeruginosa* (37.5%) in hospital-acquired episodes, and in patients with bacteremia due to *Streptococcus pneumoniae* (50%) in community-acquired episodes. Underlying diseases, severity of illness, presence of bladder catheter, previous use of antibiotics, tracheal intubation and adequacy of treatment were found to be significantly associated with death.

**Keywords** Blood culture, bloodstream infection, antimicrobial resistance

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The detection of viable organisms in a patient's blood is of great diagnostic and prognostic importance, because invasion of the bloodstream, particularly with nosocomial microorganisms, leads to considerable morbidity and mortality [1–3]. However, there are some pitfalls in the interpretation and treatment of bloodstream infections: contamination by microbial flora of the skin represents up to 50% of all positive blood cultures [1,4], the spectrum of microorganisms causing bloodstream infections changes in parallel with the evolution of medical care [1,3,5], and increasing antimicrobial resistance causes difficulties in treatment, especially in the empirical treatment of bloodstream infections [6–8]. Every institution should conduct surveillance of contamination in blood cultures, and of the most important microorganisms causing bloodstream infections and their antibiotic

susceptibility, in order to evaluate the clinical significance of positive blood cultures.

The objectives of this prospective analysis of blood cultures in our hospital were to: (1) determine the contamination rate; (2) describe and compare the epidemiologic, clinical and microbiological characteristics of hospital- and community-acquired bloodstream infections; and (3) determine the mortality associated with bloodstream infections.

This prospective study was conducted from 15 March 2001 to 15 March 2002 at the Erciyes University Hospital, a tertiary-care hospital with 1300 beds, four intensive care units, a severe burns unit, and an active program of renal transplantation and bone marrow transplantation.

Blood was inoculated into BACTEC aerobic-plus F bottles, and the bottles were incubated in

BACTEC 9240 blood culture systems (Becton Dickinson, Sparks, MD, USA) until flagged as positive or for 5 days. If there was suspicion of brucellosis or fungemia, incubation was prolonged to 14 days. When blood cultures became positive, the broth was Gram-stained and subcultured onto sheep blood agar, eosin–methylene blue agar and chocolate agar plates. The organisms were identified using standard methods. Susceptibility testing was performed using the Kirby–Bauer disk diffusion test according to the NCCLS recommendations [9].

*Set:* A set is defined as all blood culture bottles filled with a single blood extraction.

*Contaminant microorganism:* Coagulase-negative staphylococci and other common skin flora were considered to be pathogens only if one of the following criteria was met: (1) the organism was recovered from two or more sets; (2) the significance was clinically obvious; and (3) the patient had an indwelling vascular catheter or prosthetic device. Otherwise, they were considered to be contaminants.

*False-positive blood culture:* When a blood culture bottle was flagged as positive but no microorganism was seen on Gram-stained smears and no growth was observed in the agar plates, it was defined as a false-positive blood culture.

*Polymicrobial bacteremia:* This was defined as the isolation of more than one microorganism during a single bacteremic episode.

*Bacteremic episode:* All microorganisms isolated from blood within 1 week were considered to constitute a single episode.

*Hospital- or community-acquired bloodstream infections:* If the positive blood cultures were drawn more than 72 h after the patient had been admitted to the hospital, or if the patient had been recently discharged from the hospital, the infection was classified as 'hospital-acquired'. If the cultures were drawn within the first 72 h after admission to the hospital, the infection was classified as 'community-acquired'.

Patients were assessed for a 12-month period and all blood cultures that had been taken from inpatients and outpatients >18 years of age were recorded on a standard sheet. At the end of the incubation period, all negative blood cultures were recorded as 'no growth'. All positive blood cultures were reported by microbiology laboratory staff to the infectious diseases consultation team at a daily conference. One of the physicians on the team then reviewed the patients' medical records

and all microbiological data within 24 h of the report of a positive blood culture result, and performed a physical examination. When the positive blood culture was classified as true bacteremia, not resulting from a contaminant, data collected from the medical records of the patient were recorded on another standard sheet, which included demographic information, predisposing conditions, severity of illness, severity of underlying diseases, and co-morbidity indexes. All patients with significant bloodstream infections were followed until their death or discharge.

*Severity of illness:* This was categorized as sepsis, severe sepsis, septic shock, or multi-organ failure [10].

*Predisposing factors:* These were: (1) bladder catheter, intravenous catheter, intubation, neutropenia or prosthetic materials, if they were present at the time of infection; (2) surgery, if this was performed during hospital stay; (3) antibiotics, if the patient received any oral or parenteral antibiotic in the 15 days prior to the episode; (4) corticosteroids at a dose of 20 mg of prednisone daily (or equivalent) for at least 2 weeks, or 30 mg of prednisone daily for at least 1 week, before the positive blood culture; (5) cytotoxic therapy within the 4 weeks prior to the episode; (6) endoscopy, urologic intervention and other invasive procedures if they were performed in the 72 h prior to the episode.

*Underlying diseases:* These were categorized as non-fatal, ultimately fatal, and rapidly fatal, according to the McCabe and Jackson groups [11].

*Co-morbidity index:* The Charlson weighted index was used as co-morbidity index [12].

*Inadequate treatment:* Treatment was considered inadequate if the patient did not receive appropriate antibiotic for at least 7 days.

*Death attributable to bloodstream infection:* Death was considered as attributable to bloodstream infection if it occurred during the phase of active infection or antibiotic treatment.

Continuous variables were expressed as the mean and standard deviation (SD) when normally distributed, or as percentages if the variables were discrete. Statistical significance was calculated with the chi-square or Fisher exact test.

During the study period, 7563 sets of blood cultures from 5042 patients were evaluated, and the rates of positive blood cultures associated with significant bacteremia and contamination were 12.1% and 10.7%, respectively (Table 1). During

**Table 1** Results of a one-year evaluation of blood cultures

	No. of patients (%)	No. of sets (%)
No growth	3704 (73.4)	5708 (75.5)
Positive blood cultures		
Significant bacteremia	545 (10.8)	918 (12.1)
Contamination	684 (13.6)	811 (10.7)
Undefined	90 (1.8)	107 (1.4)
False positive	19 (0.4)	19 (0.3)
Total	5042 (100)	7563 (100)

this period, 567 episodes of clinically significant bloodstream infection occurred in 545 patients. Of the episodes, 416 (394 patients) (73.4%) were hospital-acquired, and 151 (151 patients) (26.6%) were community-acquired.

A polymicrobial etiology was responsible for 56 (13.5%) of the hospital-acquired episodes. While the most commonly isolated microorganisms were staphylococci, enterococci, and *Escherichia coli*, respectively, in nosocomial bloodstream infections, it was found that *Brucella* spp., *E. coli*, *Staphylococcus aureus* and *Streptococcus pneumoniae* were responsible for the majority of community-acquired bloodstream infections.

Antimicrobial resistance among significant bacteria isolated from blood during the study period

is summarized in Table 2. Overall, 56% of *S. aureus* isolates were resistant to methicillin. Although the resistance rates among hospital-acquired microorganisms were higher than those among community-acquired microorganisms, there were no differences between the groups regarding *E. coli* ( $P > 0.05$ ).

When the predisposing factors for hospital-acquired bloodstream infections were evaluated, it was seen that an intravenous catheter (77%), a bladder catheter (55.6%), previous use of antibiotics (43%), previous surgery (31%) and intubation (19.5%) were the most common and important predisposing factors in hospital-acquired bloodstream infections ( $P < 0.05$ ).

The mean co-morbidity index was 2.19 (range 0–10) in hospital-acquired bloodstream infections, and 1.59 (range 0–8) in community-acquired bloodstream infections. The majority of the patients had underlying diseases considered as non-fatal. The number of patients who had ultimately fatal diseases was higher with hospital-acquired bloodstream infections than with community-acquired bloodstream infections. Regarding the severity score, the majority of the episodes were considered as sepsis (87.7%), but there were no differences between hospital- and community-acquired bloodstream infections ( $P > 0.05$ ).

**Table 2** Antimicrobial resistance among significant bacteria isolated from blood<sup>a</sup>

Microorganism	Antibiotic	Hospital-acquired		Community-acquired	
		Non-susceptible/ Total	% of resistance	Non-susceptible/ Total	% of resistance
<i>Staphylococcus aureus</i>	Methicillin	68/103	66	2/22	9.1
CNS	Methicillin	59/80	73.7	0/4	0
<i>E. coli</i>	AMC	16/52	30.8	5/29	17.2
<i>E. coli</i>	Ciprofloxacin	13/52	25	9/29	31
<i>E. coli</i>	Cefotaxime	4/52	7.7	2/29	6.9
<i>E. coli</i>	Netilmicin	3/52	5.8	1/29	3.4
<i>Klebsiella</i> spp.	AMC	15/34	44.1	3/8	37.5
<i>Klebsiella</i> spp.	Ciprofloxacin	12/34	35.3	1/8	12.5
<i>Klebsiella</i> spp.	Cefotaxime	15/34	44.1	1/8	12.5
<i>Klebsiella</i> spp.	Netilmicin	11/34	32.4	1/8	12.5
<i>P. aeruginosa</i>	PIP/TAZ	14/32	43.8	0/5	0
<i>P. aeruginosa</i>	Ceftazidime	6/32	18.8	0/5	0
<i>P. aeruginosa</i>	Ciprofloxacin	15/32	46.9	1/8	12.5
<i>P. aeruginosa</i>	Imipenem	12/32	37.5	0/5	0
<i>Acinetobacter</i> spp.	Cefotaxime	34/42	81	0/1	0
<i>Acinetobacter</i> spp.	Ciprofloxacin	20/42	47.6	0/1	0
<i>Acinetobacter</i> spp.	Imipenem	18/42	42.9	0/1	0

AMC, amoxicillin-clavulanate; PIP/TAZ, piperacillin-tazobactam; CNS, coagulase-negative staphylococci.

<sup>a</sup>Non-susceptible strains also include intermediate strains.

**Table 3** Comparison of the patients according to the outcome

	Hospital-acquired		Community-acquired	
	Patients who survived ( <i>n</i> = 325)	Patients who died ( <i>n</i> = 69)	Patients who survived ( <i>n</i> = 130)	Patients who died ( <i>n</i> = 21)
Charlson index (SD)	2.07 (1.63)	2.04 (1.38)	1.53 (1.68)	1.95 (1.80)
McCabe and Jackson				
Non-fatal <sup>a</sup>	199 (61.2%)	49 (71%)	104 (80%)	10 (47.6%)
Ultimately fatal <sup>b</sup>	108 (33.2%)	13 (18.8%)	24 (18.5%)	6 (28.6%)
Rapidly fatal <sup>a</sup>	18 (5.6%)	7 (10.1%)	2 (1.5%)	5 (23.8%)
Severity <sup>c</sup>				
Sepsis <sup>a,b</sup>	317 (91.4%)	43 (62.3%)	127 (97.6%)	10 (47.6%)
Severe sepsis <sup>a,b</sup>	19 (5.5%)	16 (23.2%)	1 (0.8%)	5 (23.8%)
Septic shock <sup>a,b</sup>	8 (2.3%)	8 (11.6%)	1 (0.8%)	5 (23.8%)
Multi-organ failure	3 (0.8%)	2 (2.9%)	1 (0.8%)	1 (4.7%)
Intravenous catheter	247 (76%)	57 (82.6%)	45 (34.6%)	7 (33.3%)
Bladder catheter <sup>b</sup>	164 (50.5%)	55 (79.7%)	25 (19.2%)	7 (33.3%)
Previous use of antibiotic <sup>b</sup>	130 (40%)	40 (58%)	12 (9.2%)	0 (0%)
Previous surgery	97 (29.8%)	25 (36.2%)	5 (3.8%)	1 (4.7%)
Intubation <sup>b</sup>	49 (15.1%)	28 (40.6%)	2 (1.5%)	1 (4.7%)
Neutropenia	11 (3.4%)	2 (2.9%)	2 (1.5%)	0 (0%)
Polymicrobial infection	45 (13.8%)	11 (15.9%)	0 (0%)	0 (0%)
Inadequate treatment <sup>a,b</sup>	35 (10.8%)	49 (71%)	9 (6.9%)	17 (81%)

<sup>a</sup>*P* < 0.05 for community-acquired episodes.

<sup>b</sup>*P* < 0.05 for hospital-acquired episodes.

<sup>c</sup>*n* = 567 (hospital-acquired episodes = 416, community-acquired episodes = 151).

Although the mortality rate was found to be higher in hospital-acquired bloodstream infections (28.1%) than in community-acquired ones (17.9%), the rate of mortality attributable to bloodstream infection was not statistically different (*P* > 0.05). This rate was 16.6% for hospital-acquired bloodstream infections, and 13.9% for community-acquired bloodstream infections.

In hospital-acquired episodes, mortality was associated with an ultimately fatal underlying disease, the presence of a bladder catheter, previous use of antibiotics, and tracheal intubation (*P* < 0.05). However, in community-acquired episodes, mortality was significantly higher in the patients with rapidly fatal underlying diseases (*P* < 0.05). Severity of illness and inadequate treatment were also important in both groups (*P* < 0.05) (Table 3). Twelve of 32 (37.5%) patients with *Pseudomonas aeruginosa* bacteremia died, and this microorganism was found to be significantly associated with death in hospital-acquired episodes (*P* < 0.05). Seven of 14 (50%) patients with *S. pneumoniae* bacteremia died, and this bacterium was found to be the most important microorganism causing death in cases of community-acquired bloodstream infections (*P* < 0.05).

The incidence of bloodstream infections has increased, new microbial pathogens have been described, and the spectrum of pathogens isolated from blood and their susceptibility to antibiotics have changed; thus bloodstream infection continues to be one of the most important medical problems and the subject of many studies [1–3,5–8,13]. Although the presence of viable microorganisms in blood is an indicator of disseminated infection and poor prognosis, a positive blood culture is not always clinically significant, due to transient bacteremia and pseudobacteremia. The contamination rate is calculated by dividing the number of contaminated cultures by the total number of cultures obtained, and ideally should not exceed 2–3% in a hospital. This rate is closely associated with the collection technique, collection site (catheter or venipuncture), and the staff collecting blood from patients [1,4]. Our contamination rate was 10.7%. We think that our high contamination rate is associated with the staff collecting blood. Since there is no trained phlebotomist in our hospital, residents and medical students obtain blood cultures. We are not sure whether the proper aseptic collection technique is being used.

It is known that, with adequate volumes of blood, two or three blood cultures are sufficient to detect nearly all episodes of bloodstream infection [4]. The average number of blood cultures drawn per patient was 1.5 during the study in our hospital. This frequency is lower than recommended.

The majority of the episodes (73.4%) were found to be acquired in hospital in the present study. Although Weinstein et al. [1] found that the proportions of episodes of community- and hospital-acquired bloodstream infections were nearly equal, the proportion of nosocomial bloodstream infections has been increasing worldwide in recent years [2,3,14]. The frequency of hospital-acquired bloodstream infections, their epidemiology and the invading microorganisms have changed in parallel with the evolution of medical care, particularly with the emergence of an increasingly ill and immunocompromised population of hospitalized patients who are often heavily dependent on medical support and indwelling devices [3,6,14,15]. Although approximately 75% of nosocomial infections were caused by Gram-negative bacilli in the 1970s, by the early 1980s Gram-positive cocci began to be predominant pathogens, due to indwelling catheters, intravenous administration of lipid emulsions, injecting drug use, the increase in virulence of Gram-positive cocci, and the use of third-generation cephalosporins [1,3,5,14,16]. In this study, it was observed that Gram-positive cocci were responsible for 60% of hospital-acquired bloodstream infections and the leading pathogens were staphylococci.

In community-acquired bloodstream infections, *Brucella* spp. were found to be the leading pathogens. Brucellosis is hyperendemic in this region. Whereas 36% of cases of bacteremia due to *E. coli* were community-acquired, nearly 74% of cases of pneumococcal bacteremia were community-acquired. *Candida* spp., staphylococci, enterococci and *Acinetobacter* spp. were disproportionately common in hospital-acquired bloodstream infections. These observations are consistent with previous reports [1,13,15,17].

The spectrum of microbial pathogens is changing in parallel with the change in their antimicrobial susceptibility patterns. It is of great importance to know the susceptibility profile of the whole range of likely pathogens in order to select appropriate empirical antibiotics [6–8,18,19]. In this study, the proportions of methicillin-

resistant *S. aureus* were 66% in hospital-acquired bloodstream infections and 9.1% in community-acquired bloodstream infections. It is known that methicillin resistance is a growing threat throughout the world [6,8,13,16,20]. Even in community-acquired infections, the prevalence of methicillin-resistant *S. aureus* is steadily increasing, especially in injection drug users. However, the origins of these community-acquired strains is a matter of debate [20].

It was surprising that, although the antimicrobial resistance rates were higher in hospital-acquired *Klebsiella* spp., *P. aeruginosa* and *Acinetobacter* spp. infections than in community-acquired ones, for *E. coli* the prevalence of resistance to all antibiotics was almost equal in both groups. The most striking finding from these data was the high quinolone resistance of *E. coli* strains in both groups. This may be explained by widespread quinolone usage in this region. Not surprisingly, imipenem resistance in *Pseudomonas* and *Acinetobacter* spp. was nearly 40%. The reason for this high resistance rate may be the use of carbapenems in empirical treatment and inadequate infection control practices in our hospital. Not only in Turkey [7], but also in other countries [2,18,19], Gram-negative bacteria highly resistant to broad-spectrum antibiotics constitute one of the most important problems in treatment.

The most frequently observed predisposing factors were intravenous catheter, bladder catheter and previous use of antibiotics in the patients with hospital-acquired bloodstream infection. The mean co-morbidity index of the patients who had nosocomial bloodstream infections was higher (2.19) than that of the patients who had community-acquired bloodstream infections (1.59). These findings are in accordance with those of previous reports [1,2,14].

The death rate attributable to bloodstream infection varies from 2.6% to 53%, depending on the place of acquisition and the microorganism isolated [2,15,21]. Lark et al. [22] have found that infections with *Candida* had the highest crude mortality rate (67%), followed by those with *E. coli*, *P. aeruginosa*, and coagulase-negative staphylococci. In general, mortality due to Gram-positive microorganisms is lower than that due to Gram-negative bacilli [1,15,21]. In our study, it was observed that *P. aeruginosa* caused the highest mortality rate in hospital-acquired bloodstream infections ( $P < 0.05$ ), and *S. pneumoniae* in

community-acquired bloodstream infections ( $P < 0.05$ ). Despite some studies reporting that polymicrobial etiology was associated with high mortality [1,15,22], the mortality rate was not statistically different between the patients with polymicrobial bloodstream infections and those with monomicrobial bloodstream infections in our study. As expected, the most important factors associated with death in both groups of bloodstream infections were severity of illness, underlying diseases and inadequate treatment.

In conclusion, this study shows that the contamination rate of blood cultures is too high in our hospital. Efforts should therefore be concentrated on the training of staff collecting blood from patients or using alternative antiseptics, such as commercially available kits that are superior to conventional swabs [23]. The epidemiology, microbiology, patient outcome and mortality are different for hospital- and community-acquired bloodstream infections. Nosocomial infections are more severe than the others. Antibiotic-resistant bacteria will continue to challenge all who care for patients with bloodstream infections. Therefore, it is important to take infection control measures to limit the spread of resistance in microorganisms, and to reduce the rates of infection with these organisms.

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