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ORIGINAL ARTICLE

Bacteriological profile and antimicrobial resistance of blood culture isolates

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ABSTRACT

Background: Bloodstream infection (BSI) is an important cause of mortality and morbidity and among the most common health-care associated infections. In this study we described the frequency of occurrence and antimicrobial susceptibility patterns of nosocomial and community-acquired BSI isolates from a teaching hospital in Tehran, Iran.

Patients and methods: This cross-sectional study was conducted in 850-bed Rasul Akram university hospital from April 2006 to April 2007. All patients with a positive blood culture were enrolled. Antimicrobial susceptibility testing was performed with disk diffusion and E-test MIC.

Results: During the study period, 456 isolates were obtained from blood cultures, from a total of 8818 collected sets, among which 291were felt to represent true bacteremia and 98 were nosocomial. Acinetobacter spp. were the most frequently isolated agents in the hospital and community acquired BSIs (32%), followed by Escherichia coli (13.7%) and Klebsiella spp. (12%). The most effective antibiotics for gram-negative and gram-positive bacteria were ciprofloxacin (13% resistance rate) and vancomycin and oxacillin (with 13% resistance rate), respectively. Analysis of antibiotic resistance pattern showed that 20.43% of Acinetobacter spp. and 15.4% of Pseudomonas aeruginosa were multi drug resistant (MDR), while 48.7% of Klebsiella spp were ESBL-producing isolates and 15% of Staphylococcus aureus were oxacillin-resistant.

Conclusion: We did not observe any vancomycin-resistant strains among isolates of S. aureus. Rifampin and ciprofloxacin showed good activity against most of gram-positive and gram-negative organisms, respectively. Carbapenems (imipenem and meropenem) were highly active against strains of Enterobacteriaceae (E. coli, Klebsiella) that showed resistance to third generation of cephalosporines.

Keywords: *Bloodstream infection, Nosocomial infection, Antimicrobial susceptibility pattern.*.
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INTRODUCTION

Bloodstream infection (BSI) is an important cause of mortality and morbidity and among the most common health-care associated infections (1). Wide spectrums of organisms have been described and this spectrum is subject to geographical alteration.

In a prospective multicenter study of BSI, Weinstein et al. noted substantial changes in the microbiology, epidemiology and clinical and prognostic significance of positive blood cultures over a 20-year period. They found that

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Staphylococcus aureus and Escherichia coli continued to be the most common etiologic agents of BSI and noted important increases in BSI due to coagulase-negative staphylococcus, fungi, and Pseudomonas aeruginosa (community acquired) (2).

One of the more alarming recent trends in infectious diseases is the increasing frequency of antimicrobial resistance among microbial pathogens causing nosocomial and community-acquired infections. Numerous classes of antimicrobial agents have become less effective as a result of the emergence of antimicrobial resistance, often as result of selective pressure of antimicrobial usage (3).

These resistance trends and the clinical significance and changing spectrum of microbial pathogens argue strongly for antimicrobial resistance surveillance. Such a program will play a critical role in guiding physicians toward appropriate agents for use in the treatment of both community- and hospital-acquired BSI, as well as identifying changing patterns of etiologic agents and drug susceptibility. Most previous studies of BSI have been performed in temperate developed countries (1-9). These studies have mainly focused on nosocomial infections (10-12), especially those acquired in an intensive care unit (13,14).

In the present study we described the frequency of occurrence and antimicrobial susceptibility patterns of nosocomial and community-acquired BSI isolates from a teaching hospital in Tehran.

PATIENTS and METHODS

This cross sectional study was conducted in 850-bed Rasul Akram university hospital from April 2006 to April 2007. All patients with a positive blood culture were enrolled.

All clinical and laboratory data were prospectively collected. The initial data including age, sex, underlying disease, source of infection, nosocomial and previous antibiotic use were gathered by a prepared questionnaire. Laboratory data including culture and sensitivity results from blood were also recorded. Antimicrobial susceptibility testing was achieved with disk diffusion and E-test MIC. The antimicrobial agents tested were as follows: amikacin; ampicillin; cephalothin, ceftriaxone, ciprofloxacin, ceftazidime, trimethoprim-sulfamethoxazole, gentamicin, imipenem, and cefixime. Blood cultures were taken on a routine basis when sepsis was suspected on clinical ground such as fever, tachycardia, tachypnea, or leukocytosis/leucopenia (15).

All blood samples were processed in microbiology laboratory according to the standard procedures (16). Indeed, 5 ml of blood was obtained from each adult patient and inoculated immediately into 50 ml of 'Brain Heart Infusion (BHI)' broth. The broths were subcultured on 5% sheep blood agar and MacConkey agar after overnight incubation. Subcultures were performed on days 1, 2, 3, 5, 7 and 10. Positive growth was identified by gram staining, colony characteristics, and standard biochemical tests.

Disk diffusion testing was performed by standard NCCLS methodology (17), using Muller-Hinton plates supplemented with 5% added sheep blood inoculated with a 0.5 Mcfarland suspension. After overnight incubation in both air and 5% CO2 at 35˚C, zone diameters were measured with calipers.

Standard methodology was used to determine E-test MICs (18). Muller-Hinton plates supplemented with added 5% sheep blood were inoculated with a 0.5 Mcfarland suspension scraped from plates, and E-test strips (AB Biodisk, Solna, Sweden) were placed on each plate. After overnight incubation at 35˚C, the MIC was read as the intersect where the ellipse of growth inhibition intersects the strip. E-test MICs were determined both in air and in CO2. The breakpoints used to define susceptible, resistant and intermediate

categories for each antimicrobial agent were those recommended by the National Committee for Clinical Laboratory Standards (NCCLS). E.coli ATCC 25922, S.aureus ATCC 29213, E. faecalis ATCC 29212, and P. aeruginosa ATCC 27853 were used as control.

A blood culture was considered to be contaminated if one or more of the following organisms were identified in only one of a series of blood culture specimens: coagulase-negative Staphylococcus species, Propionibacterium acnes, Micrococcus species, viridians-group streptococci, Corynebacterium species, or Bacillus species (19). Previous antibiotic use was defined as any antibiotic treatment during 4 weeks preceding hospital admission. Long-term oral corticosteroid use was defined as administration of corticosteroids (≥ 20 mg/day) for ≥1 month during the previous 3 months. Considered comorbidities included the presence of diabetes mellitus, malignant neoplasm, renal failure and IV abusing. The bacterial isolates were considered nosocomial isolates if they were cultured more than 48 hours after admission or within 30 days of hospital discharge. Otherwise, the isolates were considered community-acquired. The sources of infections were classified as one of the following: respiratory tract, genitourinary tract, intra-abdominal, unknown (when no obvious source of bacteremia was identified), or others. Klebsiella spp. isolates with increased MIC results (≥2 µg/ml) for ceftazidime and/or ceftriaxone were considered as potential ESBL (extended-spectrum β-lactamas)-producing isolates (9,18). MDR-P. aeruginosa and -Acinetobacter were defined as resistant to three or all four following antibiotics: ceftazidime, ciprofloxacin, gentamicin, and imipenem (17,20). The study protocol was approved by the Medical Ethics Committee of Iran University of Medical Sciences.

Results are presented as frequency (%) for qualitative or mean ± standard deviation (SD) for quantitative variables. The association between variables was assessed using the McNemar test.

RESULTS

During the study period, there were 456 (5.17%) episodes in which an isolate was obtained from blood cultures, from a total of 8818 collected sets. Of these, 291(3.3%) were felt to represent true bacteremia, and 98(33.7%) of these were nosocomial and 166 patients (57%) had no underlying disease. Characteristic of 291 patients with true bactremia are presented in table 1.

Table 1. Characteristics of 291 patients with true bacteremia admitted in Rasul Akram hospital

	Number (%)
Sex	
Male	157(54.0)
Female	134(46.0)
Age (years)	
0-18	72(24.0)
19-39	51(17.0)
40-59	42(14.4)
60-79	90(30.9)
≥ 80	36(12.4)
With comorbidity	
Diabetes mellitus	45(15.5)
Corticosteroid use	45(15.5)
Malignant neoplasm	25(8.6)
IV addiction	20(6.9)
Renal failure	19(6.5)
Source of infection	
Unknown	111(38.3)
Respiratory tract	55(18.9)
Genitourinary tract	39(10.7)
Intra-abdominal	24(8.2)
Others	70(24.0)
Ward	
Internal	116(39.9)
ICU	75(25.8)
Emergency	45(15.5)
Pediatric	30(10.3)
Surgery	25(8.6)
Nosocomial infections	98(33.7)
Previous antibiotic use	103(35.4)
Nursing home	8(2.7)

The study population included 157 males and 134 females with the mean age (±SD) of 46.0±29.6 years (a range, 1-98 years). Sources of bacteremia included respiratory tract (18.9%), genitourinary tract (10.7%), and intra-abdominal (8.2%) (table 1).

Four bacterial genera were identified in nearly 70% of episodes of bacteremia. These were Acinetobacter spp. (32%; 21 A. baumanii and 72 A. lowfii), E.coli (13.7%), Klebsiella (12%; 13 K. pneumoneae and 22 others), Pseudomonas aeruginosa (12%), Alkalginosa (7.2%), Enterobacter (6.9%), Staphylococcus aureus (6.9%), Moraxella (5.5%), Serratia (2.7%), Enterococcus (1.7%), Proteus (0.7%), group-D Streptococcus (0.7%), Viridanse Streptococcus (0.3%), Strptococcus pneumoneae (0.3%), and Hafnia (0.3%).

Overall resistances are shown in tables 2 and 3. Among gram-negative isolates, 13% were resistant to ciprofloxacin, nevertheless, ciprofloxacin was superior to all antimicrobial agents ($p< 0.001$). Similarly, among gram-positive isolates, 13.8% were resistant to oxacillin and 13.4% to vancomycin, even though, oxacillin and vancomycin were superior to penicillin G, ceftriaxone, and cefixime ($p<0.001$, 0.03, and 0.001, respectively), with a trend towards imipenem, gentamicin, and erythromycin superiority that was not statistically significant ($p<1.00$, 0.50, and 0.25, respectively). All S. aureus isolates were sensitive to vancomycin. Rifampin and oxacillin were superior to penicillin G, cefixime, and ceftriaxone ($p<0.001$, 0.001 and 0.03, respectively), with a trend towards ciprofloxacin, erythromycin, and meropenem that was not statistically significant ($p<0.12$, 0.25 and 1.00, respectively) for S. aureus isolates.

Analysis of antibiotic resistance pattern showed that 20.4% of Acinetobacter spp. and 15.4% of P. aeruginosa were MDR, while 48.7% of Klebsiella spp were ESBL-producing isolates. The rate of ESBL-producing Klebsiella spp. was higher among young patients (≤18y) at rate of 80%. Moreover, patients aged 60-79 years were more likely to be infected with an oxacillin-resistant strain of S. aureus (50%) than patients in the other age groups (0-33.3%) (table 4).

Table 3. Resistance among gram-positive isolates by E.test

Antimicrobial agent	S.aureus		Enterococcus		Total[#]
	MIC_{50}/MIC_{90}[†]	%R[‡]	MIC_{50}/MIC_{90}	%R	%R
B-lactams					
Penicillin G	8/256	95.0	8/256	100	89.7
Oxacillin	0.5/64	15.0	NT	NT	13.8
Cephalothin	3/256	25.0	256/256	100	20.7
Cefixime	12/256	88.9	NT	NT	55.2
Ceftriaxone	8/256	68.8	NT	NT	44.8
Imipenem	0.064/32	21.1	1.5/32	75.0	31.0
Meropenem	0.19/32	33.3	8/32	75.0	24.1
Aminoglycosides					
Gentamicin	0.19/192	31.3	256/256	75.0	31
Others					
Clindamycin	0.094/256	26.3	NT	NT	24.1
Erythromycin	0.125/256	33.6	NT	NT	31.0
Rifampin	0.016/0.38	6.7	4/16	75.0	20.7
Vancomycin	1/1.5	0	2/2	50.0	13.8
Ciprofloxacin	0.19/32	36.8	32/32	75.0	34.5

[†] MIC_{50} and MIC_{90}, MICs at which 50% and 90% of the isolates, respectively, were inhibited. The units for all MICs are micrograms per milliliter; [‡] %R: percent of isolates resistance per NCCLS criteria (17); [#] Total resistances in all 5 gram-positive isolates. NT: not tested.

Patients in ICUs were at a higher risk for acquiring a BSI caused by MDR-P.aeuginosa (31.8%), ESBL-producing Klebsiella spp. (77.8%), and oxacillin-resistant S.aureus (60%) compared to patients hospitalized in a non-ICU setting, where these pathogens were isolated at rates of 26.8%, 50%, and 0% , respectively (table 4).

Patients who derived their infection from the hospital environment were at a higher risk for sepsis by a pathogen with a resistant phenotype compared to patients with community-acquired infections. MDR-acinetobacter, MDR-P.aeuginosa, ESBL-producing Klebsiella spp., and oxacillin-resistant S.aureus were more common among nosocomial isolates (22.2%, 34.5%, 62.5%, and 37.5%, respectively) compared to strains acquired from community infections (11.8%, 14.1%, 52.9%, and 0%, respectively) (table 4). Similar scenario was found for a history of antibiotic and corticosteroid use (table 4).

Oxacillin-resistant S. aureus was more common among patients with diabetes mellitus (66.7%) compare to non-diabetics (6.3%) (table 4).

Table 2. Resistance among gram-negative isolates by E. test.

Antimicrobial agent	Acinetobacter		E.coli		Klebsiella		Pseudomonas		Total[#]
	MIC_{50}/MIC_{90}[†]	%R[‡]	MIC_{50}/MIC_{90}	%R	MIC_{50}/MIC_{90}	%R	MIC_{50}/MIC_{90}	%R	%R
β- lactams									
Ampicillin	256/256	81.7	256/256	87.5	256/256	94.3	256/256	76.2	77.9
Cephalothin	256/256	92.5	256/256	60.0	256/256	68.8	256/256	76.9	79.8
Ceftazidime	6/256	30.1	6/256	20.0	0.5/256	37.1	4/256	26.9	28.6
Cefixime	256/256	92.5	8/256	53.8	1/256	54.3	256/256	69.2	72.1
Ceftriaxone	256/256	91.4	96/256	50.0	4/256	51.4	256/256	65.4	69.5
Imipenem	32/32	73.1	0.19/0.75	2.5	0.25/0.75	5.7	4/32	42.3	35.5
Meropenem	32/32	62.4	0.047/0.25	5.0	0.047/0.125	5.7	1.5/32	30.8	29.8
Aminoglycosides									
Amikacin	64/256	50.5	2/16	2.5	4/48	14.3	33/256	46.2	29.8
Gentamicin	32/256	67.7	64/256	70.0	64/256	57.1	24/256	57.7	61.1
Others									
Trimethoprim-sulfamethoxazole	0.5/32	18.3	32/32	67.5	2/32	42.9	1.5/32	34.6	34.4
Ciprofloxacin	2/32	8.6	0.38/32	47.5	0.094/16	17.1	0.25/2	11.5	13.7

[†] MIC_{50} and MIC_{90}, MICs at which 50% and 90% of the isolates, respectively, were inhibited. The units for all MICs are micrograms per milliliter; [‡] %R: percent of isolates resistance per NCCLS criteria (17); [#] Total resistances in all 10 gram-negative isolates.

Table 4. Patient risk factor assessment for resistant phenotypes among bloodstream infection pathogens

Organism	Risk factors (% resistant)[†]														
	Age (years)					Intensive care		Source of infection		DM		Prior AB use		Cortico-steroid use	
	1-18	19-39	40-59	60-79	>80	Yes	No	NI	Community-acquired	Yes	No	Yes	No	Yes	No
MDR-P. aeruginosa[‡]	15.4	0	0	25.0	0	11.1	17.6	22.2	11.8	0	16.0	28.6	10.5	50.0	9.1
MDR-Acinetobacter spp[‡]	16.7	14.3	23.5	20.0	28.6	31.8	26.8	34.5	14.1	22.2	20.0	30.8	13.0	38.5	17.5
ESBL-phenotype Klebsiella spp[#]	80.0	66.7	40.0	25.0	100	77.8	50.0	62.5	52.9	26.0	64.3	64.3	52.5	85.7	50.0
Oxacillin-resistant S. aureus	0	0	33.3	50.0	0	60.0	0	37.5	0	66.7	6.3	50.0	6.7	66.7	6.3

[†] Resistant criteria according to NCCLS criteria (17).
[‡] Strains were resistant to three or all four following antibiotics: ceftazidime, ciprofloxacin, gentamicin, and imipenem.
[#] Rates were based upon an MIC value of ≥ 2μg/ml for ceftazidime or ceftriaxone.
MDR: Multi drug resistant, **ESBL**: Extended-spectrum β-lactamas**, DM**: Diabetes mellitus, **AB**: Antibiotic, **NI**: Nosocomial infection.

DISCUSSION

In this study, 63% of positive blood cultures were felt to represent true bacteremia, which is near to Douglas et al. (52%) (21) but more than Uslan et al. (38%) (6) and Sucu et al. (46%) (22).

The most commonly isolated group in most of the prior studies was gram-positive organisms (1,6,8), although the range of organisms causing bacteremia differ widely. S. aureus was the most common in some (1,3,4,5,7,9,21) and E.coli in others (6,8). In our setting, Acinetobacter spp. was more frequently isolated. Reports of Acinetobacter spp. bacteremia are increasing (8,23) especially from Asian countries, and neighborhood countries of Iran such as Iraq, Kuwait, Turkey and Afghanistan (24-27). Although the trend of these infections has been focused on hospitalized patients, there is another patient population that may be affected by this important pathogen; namely, patients in community setting that have some form of morbidity, especially in the tropical and sub-tropical climates (24,28).

Similarly to others, the most common source of BSI was respiratory tract (18.9%), followed by genitourinary tract (10.7%). Moreover, DM was the most frequently reported underlying disease (8,21).

The percentage of carbapenem-resistant Acinetobacter spp. isolates (approximately 70%) was substantially more than other reports, in which this figure ranged 3-30% (7,20,30-33), however, in Ranjbar study it all isolates were resistant to carbapenems (29). Carbapenem resistance among acinetobacter isolates appears to be increased, partly because of wide-spread unnecessary use of carbapenem in Iran.

In our study, the resistance rate of acinetobacter and P. aeruginosa (non-fermenting bacteria) to ciprofloxacin was relatively low (8.6% and 11%, respectively). This in agreement with studies performed in Far East and United Kingdom (32,34, 35). Nevertheless, a much higher rate of ciprofloxacin resistance was reported from North America and north European countries where resistance ranged from 33 to 92% (7,20,30,31,36) for acinetobacter, Furthermore, in America (3,7,20) and India (23) P. aeruginosa resistance to ciprofloxacin ranged from 20 to 50%. Resistance of non-fermenting bacteria to fluoroquinolones is a major problem in many parts of the worlds. It appeared that the selection pressure caused by the indiscriminate use of flouroquinolones was responsible for the persistence and spread of resistant acinetobacter (33). This selection pressure is much stronger when the antimicrobial agents are given intravenously than when they are given orally (37). Although oral forms of flouroquinolones are used frequently in Iran, its only available intravenous agent (ciprofloxacin) is rarely used. Trimethoprim-sulfamethoxazole has the same story in Iran.

Not surprisingly, amikacin was more active than gentamicin in non-fermenting bacteria. Accordingly, in a study from USA, amikacin resistance rate (11.3-15.7%) was significantly lower than gentamicin (44.4-51.9%) (20). Moniri et al reported similar findings, in which P. aeruginosa resistance to amikacin (17%) was lower than gentamicin (31%) (38). Superiority of amikacin was also reported by others (3,7,39).

The rate of MDR-acinetobacter is increasing in many parts of the world and poses a serious therapeutic dilemma. In some institutes, the treatment of MDR-acinetobacter is being limited to polymixin B (24,30). In this study, the rate of MDR-acinetobacter isolates was low (20.43%) compared to other study from Iran (100%) (29), but the same as Halstead et al. study (29.3%) (40). MDR-P.aeruginosa were slightly isolated (15.4%) compared to other study from Iran (73.9%) (41). This discrepancy could be in part explained by different definitions for MDR.

There were no significant differences in resistance pattern of E.coli and Klebsiella spp. Carbapenems and amikacin were the most active

agents against these organisms, a finding that was demonstrated by prior investigators (3,7,41).

In this study, the resistance rate of E.coli to ciprofloxacin (47.5%) was similar to another study in Iran (40.2%)(42), however, the resistance rate of E.coli and Klebsiella to ampicillin, cefixime, and trimethoprim-sulfamethoxazole were high. This is in agreement with other studies (3,7,23). These drugs have been commonly overused in outpatients for many years, hence, high resistance rate is expected.

Prior investigators have proposed high resistance of S.aureus to penicillin (7,23), for example, in USA, the incidence of resistance of S.aureus from blood cultures to penicillin was 90% (3). Our results revealed more or less the same resistance rate (95%).

Antimicrobial resistance to erythromycin, gentamicin, ciprofloxacin, meropenem were above 30%, but none of the strains showed resistance to vancomycin, therefore, vancomycin could be safely used in multidrug resistant strains. Similar results have been reported by other researchers (7,23,43).

Although high rates of antimicrobial resistance were observed in this study, there were several encouraging observations regarding specific antimicrobial agents. Firstly, we did not observe any vancomycin-resistant or –intermediate strains among isolates of S. aureus. Secondly, rifampin had a good activity against most of gram-positive organisms so could help us in the treatment of severe and life threatening gram-positive infections. Thirdly, ciprofloxacin had a good activity against most of gram-negative organisms, and finally, carbapenems (imipenem and meropenem) were strongly active against strains of Enterobacteriaceae (E. coli, Klebsiella) that were resistant to third generation of cephalosporines.

In conclusion, our data demonstrate an unusual range of organisms causing bloodstream infections, which differs significantly from previously published data. Of particular interest is the high rate of Acinetobacter spp. These results highlight the important role of local microbiology laboratories to address appropriate empiric antibiotic therapy. Prompt, effective therapy requires up to date knowledge of locally prevalent organisms, and ongoing surveillance for emerging antibiotic resistance. The rise in antibiotic resistance in blood isolates emphasis the importance of hospital infection control, rational prescribing policies, and need for new antimicrobial drugs and vaccines. Our results seem helpful in providing useful guidelines for choosing an effective antibiotic in cases of septicemia and salvage therapy against hospital resistant strains. Lastly, we emphasize that empiric therapy should be guided by local susceptibility data when available, however, in the absence of such information, surveillance data can help with therapeutic choices.

Our results should be interpreted cautiously since this study included a single referral hospital with few numbers of bacteremia, as well as a short study period.

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