

## Five-year evaluation of the antimicrobial susceptibility patterns of bacteria causing bloodstream infections in Iran

Babak Pourakbari<sup>1</sup>, Alireza Sadr<sup>2</sup>, Mohammad Taghi Haghi Ashtiani<sup>3</sup>, Setareh Mamishi<sup>1,4</sup>, Mahdi Dehghani<sup>2</sup>, Shima Mahmoudi<sup>1</sup>, Ali Salavati<sup>5</sup> and Farhad Asgari<sup>6</sup>

<sup>1</sup>*Pediatrics Infectious Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran*

<sup>2</sup>*School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

<sup>3</sup>*Department of Pathology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

<sup>4</sup>*Department of Infectious Disease, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

<sup>5</sup>*Students' Scientific Research Center (SSRC), Vice Chancellor for Research Tehran University of Medical Sciences, Tehran, Iran*

<sup>6</sup>*Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran*

### Abstract

**Introduction:** Bloodstream infections (BSI) are a serious cause of morbidity and mortality worldwide. Emerging antimicrobial drug resistance among bacterial pathogens causing BSI can limit therapeutic options and complicate patient management.

**Methodology:** To encourage the prudent use of appropriate antibiotics in our pediatric population at Children's Medical Center Hospital, Tehran, Iran, we studied the frequency and antibiogram patterns of blood culture isolates from January 2001 to December 2005.

**Results:** Of 25,223 blood cultures examined, 2,581 (10.23 %) were positive for bacterial growth. The frequency of Gram-positive bacteria isolated was 47.6% (1228 of 2581) and that for Gram-negatives was 52.4% (1353 of 2581). The rates of methicillin (oxacillin) resistance in *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) were 79% and 89%, respectively. About 45% of *Streptococcus pneumoniae* were resistant to trimethoprim-sulfamethoxazole and approximately 66% to penicillin. Among the Gram-negative isolates, *Pseudomonas aeruginosa* was most frequently isolated, representing 943 (36.7%) over five years. This possibly represents an unrecognized hospital outbreak or contamination of blood culture bottles or other products such as skin disinfectants. Additionally, this pathogen showed extremely high rates of antimicrobial resistance. There were notable differences in frequency of the five most common microorganisms isolated from blood cultures, which can help set priorities for focused infection control efforts.

**Conclusions:** Our findings underscore the need to monitor blood culture isolates and their antimicrobial resistance patterns to observe resistance trends that would influence appropriate empiric treatment and infection control strategies for bacteremic children.

**Key words:** bloodstream infections; antimicrobial susceptibility; Iran

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### Introduction

Clinically significant bacteremia is a serious consequence of a wide variety of initially localized infections, including those of the urinary tract, respiratory tract, surgical sites, and indwelling devices such as central lines [1]. Bloodstream infections (BSI) are an important cause of morbidity and mortality worldwide, affecting over 200,000 individuals annually with a mortality rate of 32% in the United States alone [2-5]. National vital statistics report an increase in age-adjusted death rates due to septicemia from 4.2 per 100,000 in 1980 to 13.2 per 100,000 in 1992, and a number of deaths due to septicemia from 31,224 in 2000 to 33,464 in 2006 in

the United States [6]. In several European studies, mortality attributed to bacteremias varied from 10% to 50% [7-9].

The epidemiology of invasive bloodstream pathogens has changed dramatically over the years [10-12]. The changes in the incidence and epidemiology of infecting organisms have also brought about an increase in resistance to many antibiotic compounds [10], resulting in a reduction in therapeutic options [11].

Appropriate surveillance by monitoring antimicrobial drug susceptibility trends is a prerequisite to implementing rational measures to tackle the resistance problem [13]. In Iran and many

other countries, bacterial antimicrobial resistance is a common cause of treatment failure of BSIs. In this report, we describe the frequency, distribution and antimicrobial resistance patterns of blood culture isolates recovered from pediatric patients in Children's Medical Center (CMC) Hospital in Tehran, Iran, from 2001 through 2005.

## Methodology

### *Study design*

This investigation was the second phase of a ten-year comprehensive retrospective study conducted in two five-year phases. The first phase utilized the microbiology laboratory records of 24,600 blood cultures collected from CMC Hospital during 1996-2000 [14]. This study represents the second phase of the study and utilized the microbiology laboratory records of 25,223 blood cultures during 2001-2005. In addition to being a referral tertiary care centre, CMC Hospital is one of the educational hospitals of Tehran University of Medical Sciences. This hospital admits patients from all regions of Iran, representing a wide spectrum of socioeconomic levels.

### *Microbiology data*

Microbiology records were reviewed retrospectively. The identification and antimicrobial susceptibility profiles of bacteria isolated from one conventional aerobic blood culture bottle per patient were collected and recorded. The blood culture bottles consisted of trypticase soy or brain-heart infusion broth and were prepared in-house. The bottles were incubated at 35°C for seven days and subcultured to chocolate agar plates within 12 to 24 hours after collection [15,16]. Due to annual changes in the hospital formulary, antimicrobial agents utilized and tested varied from year to year. Data regarding the clinical significance of each isolate and whether the BSI was community or hospital-acquired were not available. The antimicrobial agents selected for analysis were those commonly used in the treatment of BSI or septic patients in Iran. Antimicrobial susceptibility results of the isolates were presented as whole numbers that were rounded down at < 0.5 and rounded up at  $\geq 0.5$ .

### *Organism identification and antimicrobial susceptibility testing*

All bacterial isolates were identified in the microbiology laboratory of CMC using standard biochemical identification methods. The biochemical

tests included catalase, oxidase, sugar fermentation, bile solubility, coagulase test, motility test, and others routinely used for identification to the genus or species level [15,16]. Antimicrobial susceptibility testing was performed by the Kirby-Bauer disk diffusion method, which is the predominant assay utilized in Iran. The guidelines current at the time of the study for interpretation of disk zone diameters as susceptible or resistant followed the National Committee for Clinical Laboratory Standards (NCCLS), which is currently known as the Clinical and Laboratory Standards Institute (CLSI). Due to the high risk of morbidity and mortality among BSI patients, bacteria with intermediate susceptibility results were categorized as resistant to that antimicrobial agent. Quality control bacterial isolates were utilized routinely in the CMC microbiology laboratory to ensure accurate performance of the susceptibility tests [17].

## Results

### *Frequency of occurrence of bloodstream isolates*

A total of 25,223 blood culture results from the CMC Hospital in Tehran were analyzed, of which 2,581 (10.23 %) were positive and bacteria were isolated. BSI isolates are displayed in Table 1 by grouping the nine most common bacterial species or groups by frequency of occurrence and year. Gram-negative bacilli were recovered in slightly greater numbers (52.4%; 1,353 of 2,581) than Gram-positive bacteria (47.6%; 1,228 of 2,581). This finding was largely due to a substantial increase in isolates of *Pseudomonas aeruginosa* during February and March of 2004, resulting in a frequency of 57.9% as opposed to other years which ranged from 13.9 to 34.5% (Table 1). Therefore, the total prevalence of *P. aeruginosa* was 36.7% of total cases, even surpassing that of coagulase-negative staphylococci (CoNS). This unusual finding may misrepresent the true distribution of pathogen frequency.

The five most frequently isolated sepsis-causing bacteria were as follows: *P. aeruginosa*, 36.7%; *Staphylococcus aureus*, 8.4%; *Escherichia coli*, 5.4% *Klebsiella* spp. 3.5%; and *Enterobacter* spp. 2.6%, collectively accounting for almost 56.6% of the total number of blood culture isolates. The frequency of CoNS and alpha-hemolytic streptococci (except *S. pneumoniae*) was 31.2% and 3.1%, respectively. These two groups of bacteria probably represent skin

**Table 1.** Frequency of occurrence of bacteria isolated from blood cultures of hospitalized patients 2001-2005

Rank	Bacteria	Year										Total	
		2001		2002		2003		2004		2005		No.	%
		No.	%	No.	%	No.	%	No.	%	No.	%		
1	<i>Pseudomonas</i> spp.	49	13.9	57	18.0	190	34.5	517	57.9	130	28.4	943	36.7
2	<i>S. aureus</i>	39	11.0	29	9.1	39	7.1	73	8.2	37	8.1	217	8.4
3	<i>E. coli</i>	27	7.6	21	6.6	15	2.7	36	4.0	40	8.8	139	5.4
4	<i>Klebsiella</i> spp.	13	3.7	14	4.4	20	3.6	28	3.1	15	3.3	90	3.5
5	<i>Enterobacter</i> spp.	23	6.5	8	2.5	17	3.1	17	1.9	2	0.4	67	2.6
6	<i>S. pneumoniae</i>	7	2.0	12	3.8	17	3.1	6	0.7	4	0.9	46	1.8
7	<i>Salmonella</i> spp.	12	3.4	4	1.3	1	0.2	20	2.2	5	1.1	42	1.6
8	<i>Acinetobacter</i> spp.	4	1.1	1	0.3	12	2.2	4	0.4	4	0.9	25	1.0
9	<i>Haemophilus</i> spp.	5	1.4	1	0.3	4	0.7	3	0.3	5	1.1	18	0.7

contaminants. The frequency of *Enterobacter* spp. decreased from 6.5% in 2001 to 0.4% in 2005. The frequency of all other pathogens remained essentially stable during the study period (Table 1).

#### Antimicrobial susceptibility of the most common Gram-positive bacteria

The *in vitro* susceptibility profiles of the most prevalent Gram-positive bacteria to 10 antimicrobial agents are summarized in Table 2. The rate of methicillin (oxacillin) resistance in CoNS (89%) was higher than that of *S. aureus* isolates. Only 79% (37 of 178) *S. aureus* was susceptible to methicillin (oxacillin). Methicillin-resistant *S. aureus* (MRSA) showed a relatively high rate of resistance to trimethoprim-sulfamethoxazole and gentamicin ( $\geq 50\%$ ) compared to MSSA (Table 2). Only 34% of our *S. pneumoniae* isolates was susceptible to penicillin. The susceptibility of *S. pneumoniae* to erythromycin and gentamicin was only 31% and 22%, respectively, whereas susceptibility to clindamycin exceeded 91% (Table 2). Lastly, chloramphenicol showed high activity against the Gram-positive isolates in our study, including staphylococci and *S. pneumoniae*, with susceptibility rates ranging from 75% to 89% (Table 2).

#### Antimicrobial susceptibility of Gram-negative bacteria

The antimicrobial susceptibility profiles of the most prevalent Gram-negative bacteria are shown in Table 3. Chloramphenicol was the most active antibiotic against *E. coli*, *K. pneumoniae*, and *Enterobacter* spp., with susceptibility ranging from 53% to 77%. The isolates of *P. aeruginosa* were

extremely resistant to the majority of the antimicrobial agents tested, including ceftazidime (92%). The most active compound against this pathogen was carbenicillin (38% susceptibility). For *E. coli*, more than 76% of isolates were susceptible to the aminoglycosides (amikacin, gentamicin, tobramycin), cefotaxime, ceftriaxone, and chloramphenicol; however, susceptibility to ampicillin, cephalothin and kanamycin was only 14%, 37% and 45%, respectively. Among the *E. coli*, ceftazidime resistance, a commonly used phenotypic marker for estimating extended-spectrum beta-lactamase (ESBL), was 37% (Table 3).

*Klebsiella* spp. was the third most prevalent Gram-negative isolate. The ESBL rate can be estimated from the low susceptibility to cefotaxime (26%) and ceftazidime (9%). Among the aminoglycosides tested, *Klebsiella* spp. was most susceptible to amikacin (53%). Chloramphenicol and carbenicillin were the most effective antimicrobial agents against *Enterobacter* spp., with a susceptibility rate of 57% and 56% respectively, and ampicillin had the lowest susceptibility (9%).

Lastly, more than 80% of *Salmonella* spp. was susceptible to amikacin, gentamicin and tobramycin, and only 24% were susceptible to ceftriaxone. *Haemophilus* isolates were most susceptible to chloramphenicol (92%), gentamicin (82%), cefotaxime (81%) and ceftriaxone (80%). They were least susceptible to ampicillin (35%) and trimethoprim-sulfamethoxazole (28%) (Table 3).

#### Discussion

In our study, the prevalence of *P. aeruginosa* was exceptionally high in 2004 when compared to other years studied and possibly represents an

**Table 2.** *In vitro* antimicrobial susceptibility of Gram-positive blood culture isolates

Antimicrobial Agents	**CoNS		***MSSA		****MRSA		<i>S. pneumoniae</i>	
	No.	(%) S*	No.	(%) S	No.	(%) S	No.	(%) S
Ampicillin	692	28	36	19	-	-	43	56
Amikacin	-	-	33	87	139	61	-	-
Cefazolin	418	56	26	89	-	-	-	-
Chloramphenicol	548	81	37	100	116	79	33	76
Clindamycin	599	67	33	97	132	81	33	91
Erythromycin	649	39	33	82	139	50	42	31
Gentamicin	690	60	36	86	143	55	46	22
Oxacillin	541	11	37	100	141	0	-	-
Penicillin	643	9	34	3	-	-	41	34
Trimethoprim-sulfamethoxazole	694	31	34	84	144	50	46	18

\*S = susceptible    \*\*CoNS: Coagulase-negative staphylococci    \*\*\*MSSA: Methicillin susceptible *Staphylococcus aureus*  
 \*\*\*\*MRSA: Methicillin-resistant *Staphylococcus aureus*    - Not measured or not reported

**Table 3.** *In vitro* antimicrobial susceptibility of Gram-negative blood culture isolates

Antimicrobial Agents	<i>P. aeruginosa</i>		<i>E. coli</i>		<i>Klebsiella</i> spp.		<i>Enterobacter</i> spp.		<i>Salmonella</i> spp.		<i>Acinetobacter</i> spp.		<i>Haemophilus</i> spp.	
	No.	(%)S	No.	(%)S	No.	(%)S	No.	(%)S	No.	(%)S	No.	(%)S	No.	(%)S
Amikacin	903	20	131	76	89	53	65	42	42	83	24	71	14	57
Ampicillin	930	3	139	14	89	1	67	9	42	45	24	17	17	35
Carbencillin	773	38	-	-	-	-	25	56	-	-	-	-	-	-
Cefotaxime	888	4	132	77	85	26	36	42	-	-	23	26	16	81
Ceftazidime	858	8	95	63	68	9	31	26	28	65	20	15	-	-
Ceftriaxone	891	6	131	76	83	24	40	43	38	24	21	29	15	80
Cephalothin	-	-	139	37	87	16	-	-	39	51	-	-	-	-
Chloramphenicol	804	12	123	77	78	54	58	57	39	74	17	47	13	92
Gentamicin	922	21	134	77	88	31	65	46	42	86	25	76	17	82
Kanamycin	-	-	128	45	-	-	-	-	32	60	-	-	15	53
Tobramycin	888	21	131	76	83	31	43	49	39	85	24	83	14	71
Trimethoprim-sulfamethoxazole	931	22	139	59	87	33	66	50	41	78	24	29	18	28

- Not measured or not reported

unrecognized hospital outbreak or contamination of blood culture bottles or other products such as skin disinfectants. *Enterococcus* spp., with 0.4% frequency, was the 17<sup>th</sup> most common BSI pathogen in the current study, in marked contrast to many reports which show enterococci among the top four most frequent BSI pathogens [7,18,19].

Among Gram-positive bacteria recovered from blood cultures, 79% were MRSA, as opposed to much lower rates reported from the USA and Canada [20]. In this study, 89% of CoNS were methicillin (oxacillin)-resistant compared to 32% to 37% reported in the SENTRY study, and 68% in Europe [20,21].

However, rates of methicillin-resistant CoNS is similar to those of other reported studies in the United Kingdom (76%) [1], SENTRY 2004 (85%) [22] and the USA (77%) [22,23,24]. In contrast to the current data, results from the first five-year phase of the study showed 60% methicillin resistance in *S. aureus* isolates and 61% among the CoNS isolates [14]. Both MRSA and methicillin resistance CoNS isolates were highly susceptible to chloramphenicol, but this antimicrobial is used only rarely in children due to the adverse reaction of aplastic anemia. We suggest that risk-to-benefit studies be undertaken to reconsider the use of chloramphenicol in managing methicillin-resistant staphylococcal pathogens [25].

In the current survey, only 14 (34%) of the *S. pneumoniae* isolates were susceptible to penicillin. In some reports from North America, Latin America, Europe and Egypt, the susceptibility rate to penicillin for *S. pneumoniae* was 60% to 70% [22,26,27,28] while in the United Kingdom the rate of susceptibility was 100% [1]. In a previous report from this center, 44% of *S. pneumoniae* isolates were susceptible to penicillin. In comparison with our last report and other reports from Iran, we have lower rates of penicillin susceptibility among *S. pneumoniae* isolates, warranting a possible modification of treatment guidelines for this pathogen in our medical center [14,29].

In the present report, none of the antimicrobial agents tested were sufficiently effective against *P. aeruginosa* isolates *in vitro*. Therefore, physicians and hospital formulary groups need to search for other effective antimicrobial agents to treat *P. aeruginosa* infections [24,30].

*E. coli* susceptibility against aminoglycosides (77% for gentamicin) is less than the rates cited in many reports from Latin America, the USA, and Canada [23,31,32]. The third-generation cephalosporins (ceftazidime and ceftriaxone) showed lower activity than that observed in our previous report [14]. Only 9% of *Klebsiella* spp. and 63% of *E. coli* isolates were susceptible to ceftazidime which suggests a high prevalence of ESBL-producing strains. This high rate of resistance is rare in other reports (1% in Canada and 2% in the USA) [32]. Our isolates were not tested further to confirm ESBL production.

Despite the higher frequency of antimicrobial resistance in *Enterobacteriaceae*, there are some obvious similarities in patterns: aminoglycosides (amikacin in particular) has the best activity and there are no preferences for third-generation cephalosporins, such as ceftriaxone and ceftazidime. Trimethoprim-sulfamethoxazole, with a 78% susceptibility rate, may be an appropriate treatment for *Salmonella* infections rather than ceftriaxone, which has a 24% susceptibility rate. In our study, most Gram-negative bloodstream isolates were highly susceptible to chloramphenicol, most probably due to the long time this agent has not been in use.

Our data underscore the need for annual antimicrobial resistance surveillance reports, which can provide valuable insight into resistance trends at a particular medical facility to assist in guidance in the appropriate choice of empiric therapy.

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### Corresponding author

Dr. Setareh Mamishi  
 Department of Pediatric Infectious Disease  
 Children Medical Center Hospital  
 School of Medicine  
 Tehran University of Medical Sciences  
 100 Gharib St, Keshavarz Blvd  
 Tehran, Iran

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