

## Original Article

# Drug resistance patterns of bacteria isolated from patients with nosocomial pneumonia at Tehran hospitals during 2009-2011

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### Abstract

**Introduction:** Nosocomial pneumonia remains an important cause of mortality and morbidity worldwide. Surveillance programs play an important role in the identification of common etiologic agents and local patterns of antimicrobial resistance.

**Methodology:** In this study we determined the frequency and antimicrobial susceptibility of pathogens isolated from patients with nosocomial pneumonia during 2009 to 2011.

**Results:** A total of 642 bacteria were isolated from 516 suspected samples. *Acinetobacter baumannii* (21.1%, n = 136), was the commonest isolated pathogen followed by *Pseudomonas aeruginosa* (17.4%, n = 112), *Staphylococcus aureus* (15.8%, n = 102) and enterococci (8.4% n = 54). The most effective therapeutic agents against *A. baumannii* were polymyxin B (95.5% susceptible), ceftriaxone/tazobactam (72% susceptible) and levofloxacin (52.9% susceptible). Polymyxin B (89.2% susceptible), ceftriaxone/tazobactam (89.2% susceptible) and piperacillin-tazobactam (80.3% susceptible) were found to be the most active agents against *P. aeruginosa*. Extended-spectrum beta-lactamases were detected among isolates of *K. pneumoniae* (45.4%) and *E. coli* (20.3%). Overall, the prevalence of methicillin-resistant *S. aureus* and vancomycin resistant enterococci were 80.4% and 40.7% respectively. Linezolid was found to be the most active antibiotic against these pathogens. The etiology of 50% of the nosocomial infection cases was polymicrobial.

**Conclusions:** The combination of ceftriaxone/tazobactam seems to be beneficial agent against multidrug-resistant Gram-negative bacilli isolated from respiratory tract infections. The results of our study can be used for guiding appropriate empiric therapy in this geographic region.

**Key words:** nosocomial pneumonia; drug resistance; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*; Tehran hospitals

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### Introduction

Nosocomial pneumonia (NP) is the second most common nosocomial infection and the leading cause of death attributed to hospital-acquired infections [1]. It accounts for 15% of all nosocomial infections. Because of its association with increased mortality rates, prolonged hospital stays and high costs of hospital care, NP is a major infection control problem [2]. It has been estimated that between one third to one half of all NP deaths stem from infection [1]. Approximately two thirds of these infections are caused by Gram-negative bacilli and in particular by *Pseudomonas aeruginosa* and *Acinetobacter* species, which cause higher mortality rates related to NP [1]. Importantly, Gram-positive cocci infections are on the rise and *Staphylococcus aureus* is most frequently associated with NP [3]. NP should be considered a microbiological emergency and delaying prompt treatment gives rise to adverse outcomes. It is therefore vital to initiate appropriate empiric therapy

until a microbiological diagnosis is established. Awareness of local prevalence of causative microorganisms and drug susceptibility patterns is critical for the proper formulation of initial empiric therapy prescription of antibiotics [2]. Limited data concerning the etiological agents of NP and their resistance to antibiotics was available in Iran. Therefore, the objective of the present study was to investigate the prevalence and antimicrobial resistance patterns of bacterial pathogens isolated from patients with NP over a period of three years (2009 to 2011) in Tehran hospitals.

### Methodology

This study was conducted in the Microbiology Department of Tehran University of Medical Sciences during 2009 to 2011. A total of 516 clinically suspected specimens including bronchoalveolar lavage (BAL) (n = 121), mini BAL (n = 232), tracheal aspirates (n = 99), and sputum (n = 64) were collected

from patients with NP from three main teaching hospitals in Tehran. NP was defined based on the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS)/guidelines [4].

The cut-off value for different types of laboratory specimens considered clinically significant in quantitative cultures was  $10^4$  cfu/ml for BAL,  $10^3$ – $10^4$  cfu/ml for mini BAL,  $10^5$  cfu/ml for undiluted tracheal secretions, and  $10^5$  cfu/ml for sputum [5].

All specimens were cultured directly on blood agar, chocolate agar, and eosin methylene blue agar or MacConkey agar and incubated overnight at 37°C aerobically. Also, 0.5 to 1 mL of the specimen was inoculated into a tube of enriched thioglycolate broth. Identification of bacterial isolates was based on Gram staining, colonial morphology, and biochemical properties [6].

Antimicrobial susceptibility tests were performed on Mueller-Hinton agar using the standard disk diffusion method according to the guidelines recommended by Clinical and Laboratory Standards Institute (CLSI) [7]. Antibiotics tested were amoxicillin/clavulanic acid, polymixin B, amikacin, gentamicin, tobramycin, imipenem, levofloxacin, cefepime, ceftriaxone, ceftriaxone/tazobactam, ceftazidime, ciprofloxacin, azithromycin, oxacillin, linezolid, vancomycin and piperacillin/tazobactam (Hi-Media, Mumbai, India). *Acinetobacter baumannii* (NCTC 19606), *Pseudomonas aeruginosa* (ATCC 27853), *Stenotrophomonas maltophilia* (NCTC 10257), *Klebsiella pneumoniae* (NCTC 5056), *Escherichia coli* (ATCC 25922), *Staphylococcus*

*aureus* (ATCC 29213), *Streptococcus pneumoniae* (NCTC 11910), *Enterococcus faecalis* (ATCC 29212) and *Enterococcus faecium* (D 366) were used as control strains. Detection of methicillin-resistant *S. aureus* (MRSA) was performed on Mueller-Hinton agar containing NaCl (4%w/v). According to CLSI criteria, isolates of *E. coli* and *K. pneumoniae* which showed an enhanced zone of inhibition toward ceftazidime ( $30 \mu\text{g} \leq 22 \text{ mm}$ ) and/or ceftriaxone ( $30 \mu\text{g} \leq 25 \text{ mm}$ ) were considered as extended-spectrum beta-lactamases (ESBL) producing organisms and were subjected for phenotypic confirmatory tests using the combined disk method. The zone of inhibition of discs containing cephalosporin with clavulanic acid ( $10 \mu\text{g}$ ) was compared to the zone around a disc containing cephalosporin alone. A  $\geq 5$ -mm increase in a zone diameter was used to indicate ESBL production. Statistical analyses were performed using the chi-square test and values of  $p < 0.05$  were considered statistically significant.

## Results

Of 516 clinical respiratory specimens, 81.3% ( $n = 420$ ) were positive for at least one bacterial pathogen. A total of 642 microorganisms were isolated and polymicrobial growth was observed in 50% of the cases. The frequency of the 10 most common pathogens isolated from patients with pneumonia hospitalized in the three teaching hospitals during the period of 2009, 2010, and 2011 are listed in Table 1. *A. baumannii* was the dominant organism isolated from patients (21.1%). It was followed by *P.*

**Table 1.** Frequency of isolated pathogens from patients with nosocomial pneumonia during three years

Rank	Isolated bacteria	Year of isolation (total number of pathogens)			
		2009 (274) n (%)	2010 (202) n (%)	2011 (166) n (%)	Total (642) n (%)
1	<i>A. baumannii</i>	36 (13.1)	58 (28.7)	42 (25.3)	136 (21.1)
2	<i>P. aeruginosa</i>	60 (21.8)	32 (15.8)	20 (12)	112 (17.4)
3	<i>S. aureus</i>	42 (15.3)	3 <sup>3</sup> 6 (17.8)	24 (14.4)	102 (15.8)
4	<i>Enterococcus spp</i> <sup>a</sup>	32 (11.6)	16 (7.9)	6 (3.6)	54 (8.4)
5	<i>E. coli</i>	22 (8)	10 (4.9)	16 (9.6)	48 (7.4)
6	<i>K. pneumoniae</i>	10 (3.6)	22 (10.8)	12 (7.2)	44 (6.8)
7	<i>S. maltophilia</i>	18 (6.5)	8 (3.9)	12 (7.2)	38 (5.9)
8	<i>Enterobacter spp</i> <sup>b</sup>	18 (6.5)	4 (1.9)	10 (6)	32 (4.9)
9	<i>S. epidermidis</i>	12 (4.3)	0 (0)	4 (2.4)	16 (2.4)
10	<i>S. pneumoniae</i>	4 (1.4)	2 (0.9)	8 (4.8)	14 (2.1)
11	Other 7 species <sup>c</sup>	20 (7.2)	14 (6.9)	12 (7.2)	46 (7.1)

Enterococci: *E. faecalis* (48), *E. faecium* (6)

<sup>b</sup> *Enterobacter spp.*, *E. cloacae* (18), *E. aerogenes* (14)

<sup>c</sup> includes *Proteus spp.* (6 isolates), *Morganella morganii* (2 isolates), *Serratia marcescens* (4 isolates), *Alcaligenes spp.* (6 isolates), other *Streptococci (viridians)*: 4 isolates, non enterococcal Group D (8 isolates), *Candida albicans* (12 isolates), *Aspergillus niger* (4 isolates)

*aeruginosa* (17.4%), *S. aureus* (15.8%), Enterococci (8.4%), and *E. coli* (7.4%). Overall, Gram-negative genera constituted 426 (66.3%) of all positive cultures, while Gram-positive bacteria account for 198 (30.8%) of the recovered pathogens.

#### Drug susceptibility of Gram-negative bacteria

The results of susceptibility testing for the five Gram-negative bacilli that most frequently cause pneumonia are summarized in Table 2. According to the antimicrobial susceptibility results of, polymyxin B (95.5% susceptible) ceftriaxone/tazobactam (72% susceptible), and levofloxacin (52.9% susceptible) would be the best therapeutic agents against *A. baumannii*.

Polymyxin B (89.2% susceptible), ceftriaxone/tazobactam (89.2% susceptible) and piperacillin-tazobactam (80.3% susceptible) were found to be the most effective drugs against *P. aeruginosa*. While no significant variation in proportion of imipenem-resistant *P. aeruginosa* was observed during 2009 (20%, n = 12 out of 60) and 2010 (18.75 %, n = 6/32), the resistance rate in 2011 (60%, n = 12/20) increased significantly (p < 0.01). Furthermore, 70% of imipenem-resistant isolates of *P. aeruginosa* were also resistant to one or two fluoroquinolones. Production of ESBLs was detected among isolates of *K. pneumoniae* (n = 20, 45.4%) and *E. coli* (n = 10, 20.8%). Most of other the common Gram-negative bacilli demonstrated high susceptibility toward ceftriaxone/tazobactam and piperacillin-tazobactam.

#### Drug susceptibility of Gram-positive bacteria

The results of the antimicrobial agents that were tested against *S. aureus* and enterococci are shown in Table 2. The frequency of MRSA was 80.4%. Linezolid and vancomycin (100% susceptible) were the most effective agents against *S. aureus* in this study. All enterococci were fully susceptible to linezolid, but 40.7% of them showed resistance to vancomycin.

### Discussion

In the current study the most common pathogens isolated from patients with nosocomial pneumonia were *A. baumannii* followed by *P. aeruginosa* and *S. aureus*. In another study conducted in southern Iran, *A. baumannii* was also ranked as the first agent. However, *S. aureus* was found to be the second most common agent of ventilator-associated pneumonia [8]. *A. baumannii* showed high resistance to most of the

assessed antimicrobials. In our study, 75% of the *A. baumannii* isolates were resistant to imipenem. High rates of resistance to imipenem (52.5%) have previously been described in literature from Iran [10]. In a global study performed in 2010, out of 515 isolates 471 (91.4%) exhibited resistance to imipenem [11]. The most effective compound tested against this pathogen was polymyxin B which could inhibit 100% of the isolates. Moreover, ceftriaxone/tazobactam showed good inhibitory effect against *A. baumannii*, suggesting this compound as a therapeutic agent against this pathogen.

*P. aeruginosa* was the second most common pathogen causing pneumonia in our study. Resistance of this organism to imipenem increased from 20% to 60% during the study period. Prior fluoroquinolone use has been identified as a risk factor for the emergence of imipenem-resistant *P. aeruginosa* (IRPA) [12,13]. A decrease in the permeability of the cellular wall in fluoroquinolone-resistant isolates of *P. aeruginosa* induces cross-resistance to carbapenems [12]. Out of 30 IRPA, 21 (70%) showed resistance to ciprofloxacin or levofloxacin, suggesting that cross-resistance developed for imipenem due to prior use of fluoroquinolones (p < 0.05). Prior use of imipenem has been identified as another risk factor giving rise to infection with IRPA [13].

Production of ESBLs was more frequently observed among *K. pneumoniae* isolates. In other studies reported from Iran, incidence of ESBL phenotypes varied from 45.2% to 67.2% for *E. coli* and 44.4% to 52% for *K. pneumoniae* [14]. Ceftriaxone/tazobactam and piperacillin/tazobactam were effective agents against both ESBL-producing *K. pneumoniae* and *E. coli*. Moreover, amikacin was also effective against ESBL-producing *E. coli*.

In our study ceftriaxone/tazobactam was found to be a potent antimicrobial agent against non-fermenting and other prevalent Gram-negative bacilli. A combination of tazobactam with other penicillin derivatives is widely used in clinical practices. The efficacy of the ceftriaxone/tazobactam combination has been assessed in animal models and certain bacterial species [15,16,17,18]; however, no data is available on the effect of this combination against non-fermenters. In this study we observed good inhibitory effects of ceftriaxone/tazobactam combination against non-fermenters.

In contrast to other investigations, enterococci were placed among the top four pathogens causing nosocomial pneumonia in our study. Pneumonia caused by enterococci has not been previously

**Table 2.** Drug susceptibility patterns of the most prevalent Gram-negative and Gram-positive pathogens causing pneumonia

Antibiotic	Disk content (µg)	Susceptibility of Gram-negative bacteria % S:I:R					
		<i>A. baumannii</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>S. maltophilia</i>	
Imipenem	10	4.4: 20.5: 75	50: 23.2:26.7	50:29.1:20.8	43.1:36.3:20.4	26.3:47.3:26.3	
Gentamicin	10	5.9: 4.4: 88.2	21.4:5.3:73.2	50:50:0	16:34:50	0:10.5:89.4	
Ciprofloxacin	5	23.5: 8.8: 67.6	67.8:7.1: 25	70.8:0:29.1	34:6.8:59	0:0:100	
Levofloxacin	5	52.9: 26.4:20.5	46.4: 17.8: 35.7	70.8:16.6:12.5	84:0:16	63.1: 13.1:23.6	
Amikacin	30	14.7: 36.7:48.5	67.8: 16:16	75:16.6:8.3	34:15.9:50	21:34.2:44.7	
Tobramycin	10	36.7:27.9:35.2	48.2:16:35.7	50:0:50	40.9:18.1:40.9	13.1: 23.6: 63.1	
Cefepime	30	2.9: 0:97	14.2:8.9:76.7	45.8:20.8:33.3	0:18.1:81.8	0:0:100	
Ceftriaxone	30	5.8: 17.6: 76.4	17.8: 8.9 : 73.2	25:16.6:58.3	0:4.5:95.4	0:0:100	
Ceftriaxone/ tazobactam *	80/10	72:-:-	89.2: -:-	79.1:-:-	81.8:-:-	84.2:-:-	
Ceftazidime	30	10: 4.4: 85.2	26.7: 3.5:69.7	0:25:75	2.2:2.2:95.4	0:0:100	
Piperacillin- tazobactam	100/10	47:17.6: 35.2	80.3: 16: 3.5	75:8.3:16.6	72.7:27.2:0	78.9:0:21	
Amoxicillin/ clavulanic acid	20/10	0:0:100	0:3.5:96.4	0:12.5:87.5	0:0:100	0:0:100	
Azithromycin	15	35.2: 14.7: 50	66:14.2: 19.6	50:50:0	59:41:0	50:26.3:23.6	
Polymyxin B	300 units	95.5:4.4:0	89.2:10.7:0	0:0:0	0:0:0	0:0:0	
		Susceptibility of Gram-positive bacteria					
		<i>S. aureus</i>			Enterococci		
		S	I	R	S	I	R
Clindamycin	2	19.6	9.8	70.6	11.1	0	88.88
Linezolid	30	100	0	0	100	0	0
Ciprofloxacin	5	15.6	9.8	74.5	22.2	37	40.7
Levofloxacin	5	66.6	9.8	23.5	59.2	25.9	14.8
Vancomycin	30	100	0	0	48.1	11.1	40.7
Amoxicillin/ clavulanic acid	20/10	13.7	17.6	68.6	55.5	11.1	33.3
Chloramphenicol	30	66.6	9.8	23.5	51.8	29.6	18.5
Oxacillin	1	13.7	5.9	80.4	0	0	0

\* Isolates showing inhibitory zone > 32 mm were considered as susceptible.

reported from Iran. Respiratory tract infections caused by enterococci are exceedingly rare [19]. The oropharynx has been identified as a colonization route of enterococci in the respiratory tract [19,20]. Gastric colonization of enterococci has been also suggested as a reservoir of enterococci involved in nosocomial infections [20]. Selective decontamination of the digestive tract and oropharynx is widely used to prevent nosocomial pneumonia in mechanically ventilated patients. Administration of antimicrobial prophylaxis causes modification of the bacterial flora of such patients, giving rise to increased colonization with species which are intrinsically resistant to the antibiotics used [21], which can lead to pneumonia caused by microorganisms which are rarely involved in respiratory tract infections [21].

## Conclusion

In summary, we observed a high prevalence of multidrug-resistant non-fermentative Gram-negative bacilli, MRSA, vancomycin-resistant enterococci (VRE), and ESBL-producing isolates. Co-ordinated multidisciplinary approaches are required to prevent and control infections caused by these antibiotic-resistant bacteria. These measures could be achieved by routine culturing and susceptibility testing to detect MRSA, VRE and other multidrug-resistant organisms. Misuse or overuse of antimicrobials and long-term prophylaxis should be avoided and antibiotics should be prescribed for diagnosed infections and not for colonization or contamination. The results of this study may be helpful for administration of effective empiric treatment regimens and reduction of drug resistance in this region.

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**Errata Corrige:**

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Haemophilus influenzae serotype e meningitis in an adult.

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**Erratum in:**

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The incidence of Haemophilus influenzae type b (Hib) invasive disease has declined significantly in countries with routine infant Hib immunization. Accordingly, infections caused by other H. influenzae serotypes or by encapsulated H. influenzae strains are of growing interest. H. influenzae serotype e (Hie) is a rare cause of infection. Invasive Hie infections reported in adults are generally in individuals who had previous underlying conditions, in contrast to infections in childhood. We present the first report of Hie meningitis in Turkey. It is of interest that meningitis due to this organism occurred as a complication of transsphenoidal hypophysectomy, which to our knowledge has never been documented. Further identification of H. influenzae strains isolated from patients with invasive disease, especially those with predisposing factors and/or who have been vaccinated, is essential.

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