

Full Length Research Paper

Prevalence of multi-drug resistance and pandrug resistance among multiple gram-negative species: experience in one teaching hospital, Tehran, Iran

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Resistance in specific gram-negative bacteria, including *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* is of great concern, for there are growing numbers of reports of how these microorganisms have become resistant to all available antibacterial agents used in therapy. A descriptive study was conducted in a teaching hospital in Tehran, Iran, in 2008. A Total of 295 clinical gram negative species were isolated at Microbiology Laboratory Hospital from patients' specimens. Anti-biograms were done on Mueller-Hinton agar plates with disk diffusion method according to Kirby-Bauer method. Among 295 isolated gram-negative, *Escherichia coli* was the most common organism then followed by *K. pneumoniae*, *Enterobacter*, *P. aeruginosa*, *Acinetobacter*, *Proteus* and *Citrobacter*. Multi-drug-resistant (MDR) gram negative strains were detected in 162(55%) of isolates. These included *E. coli* [67(41.35%)], *K. pneumoniae* [35(21.6%)], *P. aeruginosa* [27(16.7%)], *Enterobacter* [19(11.73%)], *Acinetobacter* [14(8.65%)]. Ten patients were identified to have infection due to pandrug-resistant (PDR) gram-negative bacteria including: *P. aeruginosa* [3 cases (30%)], *A. baumannii* [3 cases (30%)], *Enterobacter* [2 cases (20%)], *K. pneumoniae* [1 case (10%)], *E. coli* [1 case (10%)]. Presence of MDR and PDR resistance and reduced susceptibility to third generation cephalosporins, carbapenems and fluoroquinolones, aminoglycosides, and Trimethoprim-sulfamethoxazole is considered a serious clinical problem.

Key words: Multi-drug-resistant, pandrug-resistant, gram-negative bacteria, sensitivity

INTRODUCTION

Resistance of bacteria to antibiotics first occurred within a decade after the onset of the antibiotic era (4th Decennial International Conference on Nosocomial and Healthcare-Associated Infections, 2001). Among gram-negative bacteria, *Escherichia coli* is the most frequently isolated in hospitals and the most common cause of infections (Amazian et al., 2010). Extended Spectrum Beta Lactamase (ESBL) production in *E. coli* and *Klebsiella pneumoniae* bacteremia was more likely to lead to the choice of inappropriate empirical therapy, which, in turn, increased the risk of treatment failure or death (Du et al., 2002). Emergence of Extended Spectrum Beta

Lactamase-producing isolates has important clinical and therapeutic implications. Antibiotic selection for treatment of serious infections due to ESBL-producing *E. coli* and *K. Pneumonia* is a clinical challenge because of the complex nature of *in vitro* susceptibility testing and *in vivo* correlation (Paterson and Yu, 1994). In an effort to improve the management of infections caused by ESBL-producing strains, use of carbapenems and fluoroquinolones was recommended (Ramphal and Ambrose, 2006).

Because *Pseudomonas aeruginosa* has a predilection for moist environments, there is a potential for the organism to be problematic in the hospital environment. Aqueous solutions used in medical care (e.g., disinfectants, soaps, irrigation fluids, eye drops, and dialysis fluids) may all become contaminated with *P. aeruginosa* (Morrison and Wenzel, 1984). *P. aeruginosa*

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is also frequently found in the aerators and traps of sinks (Cross et al., 1966), in respiratory therapy equipment (Teres et al., 1973), and on showerheads (Kiska and Gilligan 2003). *P. aeruginosa* may contaminate bronchoscopes and lead to outbreaks of infection (Srinivasan et al., 2003). Long or artificial fingernails may also harbor *P. aeruginosa* and may be associated with outbreaks of *P. aeruginosa* infection (Moolenaar et al., 2000). Finally, *P. aeruginosa* may be found on the surface of many types of raw fruits and vegetables (Kiska and Gilligan, 2003). The incidence of imipenem-resistant *P. aeruginosa* (IRPA) is increasing (National Nosocomial Infection Surveillance System, 1999). Imipenem has been identified as a risk factor for imipenem-resistant *P. aeruginosa* (IRPA) in some studies (Troillet et al., 1997; Krcmery et al., 1996 ;Harris et al., 2002) determined other antibiotics as risk factors for IRPA, which suggests that limiting the use of imipenem alone may not be sufficient to contain the increasing incidence of IRPA.

Acinetobacter species can survive in both moist and dry environments. Villegas and Hartstein (Villegas and Hartstein, 2003) have published a comprehensive review of hospital outbreaks of infection with *Acinetobacter* species. Their review provides examples of locations in the hospital environment where *Acinetobacter* species have been found, including ventilator tubing, suction catheters, humidifiers, containers of distilled water, urine collection jugs, intravenous nutrition, multidose vials of medication, potable water, moist bedding articles, and inadequately sterilized reusable arterial pressure transducers (Villegas and Hartstein, 2003). A recent example of an outbreak of multi-drug-resistant *Acinetobacter* species infection associated with moist-site contamination is one that occurred during pulsatile lavage wound treatment, a high-pressure irrigation treatment used to debride wounds (Maragakis et al., 2004). Contamination of the hospital environment with *Acinetobacter* species apparently occurs quite frequently (Denton et al., 2004), and, because the organism can survive in dry conditions for a prolonged period (Jawad et al., 1998), it is not surprising that even dry parts of the hospital environment may be potential reservoirs of infection (Bureau-Chalot et al., 2004).

Multi-drug resistance in *P. aeruginosa* or *Acinetobacter* species has been variously defined as resistance to at least 2 (Ortega et al., 2004), 3 (Defez et al., 2004), 4 (Wisplinghoff et al., 2000), or 8 (Nouer et al., 2005) of the antibiotics typically used to treat infections with these organisms. Pan-drug resistance (PDR) in *P. aeruginosa* or *Acinetobacter* species has been defined resistant to all 7 anti-pseudomonal antimicrobial agents (Falagas et al., 2005). Antibiotic resistant mutants producing ESBL emerged among gram-negative bacteria, predominantly *E. coli* and *K. pneumonia* (Livermore, 1995).

Institutional anti-biograms or local patterns of susceptibility should be used to determine the choice of

drugs. There has been many problems with MDR gram-negative diseases so this research was conducted to determine prevalence of multi-drug resistance and Pan-drug resistance among multiple gram-negative species in the teaching hospital.

MATERIALS AND METHODS

A descriptive study was conducted in a teaching hospital in Tehran, Iran, in 2008. A Total of 295 clinical gram negative species were isolated at Microbiology Laboratory Hospital from patients' specimens. The majority of isolates [n=179 (61%)] were recovery from urine samples.

Antibiograms were done on Mueller-Hinton agar plates with disk diffusion method according to Kirby-Bauer method (Bauer et al., 1966). The following disks (Padtan Teb Company, Iran) were tested: ceftriaxone (30 µg/disk), ceftazidime (30 µg/disk), ceftizoxime (30 µg/disk) trimethoprim-sulfamethoxazole (25 µg/disk,) amikacin (30 µg/disk), gentamicin (10 µg/disk), ciprofloxacin (5 µg/disk), norfloxacin (10 µg/disk) and imipenem (10 µg/disk) (Becton, Dickinson and Company, USA). Multi-drug-resistant (MDR) gram negative strains were defined if resistance of the isolates was observed in at least 3 out of the 5 following classes of antimicrobial agents; third generation cephalosporins (antipseudomonal cephalosporins for *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*), imipenem, quinolones, aminoglycosides, and Trimethoprim-sulfamethoxazole. Pandrug resistance (PDR) in gram negative strains were defined if resistance of the isolates was observed in all the following classes of antimicrobial agents; third generation cephalosporins (antipseudomonal cephalosporins for *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*), imipenem, quinolones, aminoglycosides and trimethoprim-sulfamethoxazole. SPSS 11.5 software (descriptive analysis, Chi-square) was used for statistical analysis of this study. A P-value of <0.05 was considered to be statistically significant.

RESULTS

Among 295 isolated gram-negative, *E. coli* was the most common organism [130 (44%)], followed by *K. pneumoniae* [56 (19%)], *Enterobacter* [46 (15.5%)], *P. aeruginosa* [39(13.2%)], *Acinetobacter* [16 (5.5%)], *Proteus* [5 (2%)] and *Citrobacter* [3 (1%)]. The majority of isolates [179 (61%)] were recovery from urine samples. Distribution of the kind of patient's samples was shown in Table 1.

99% of isolated *E. coli* was sensitive to imipenem, as were 94% of all isolated gram-negative in this study.

The resistant pattern of isolated gram-negative has been shown in Table 2. There was a significant

Table 1. Distribution of the different kinds of patients' samples in one teaching hospital, South of Tehran, Iran in 2008.

Kind of sample	Number of sample(s)	Percent of total sample
Urine	179	61%
Blood	32	11%
Tissue	40	13.5%
Ear discharge	3	1%
Angiocatheter	4	1.5%
Fully urine catheter	3	1%
Ulcer	15	5%
Gall bladder fluid	1	0.3%
Cerebrospinal fluid	3	1%
Rectal soap	2	0.7%
Nasal Discharge	2	0.7%
Sputum	3	1%
Abscess	2	0.7%
Ascitis	1	0.3%
Liver cyst	1	0.3%
Joint fluid	2	0.7%
Pleural tube discharge	2	0.7%
Total	295	100%

Table 2. Resistant pattern of isolated gram-negative bacteria, in one teaching hospital, South of Tehran, Iran in 2008.

ORGANISM ANTIBIOTICS	CITROB ACTER		PROTE		ENTROBAC TER		ACINETOBA CTER		PSEUDOM ONA		KLEBSIEL A		ECOLI	
	R %	S %	R %	S %	R %	S %	R %	S %	R %	S %	R %	S %	R %	S %
IMIPENEM	0	100	0	100	6.5	93.5	56	44	10	90	2	98	1	99
CEFTRIAXON	0	100	0	100	51	49	87.5	12.5	79.5	20.5	62.5	37.5	54	46
CEFTIZOXIM	0	100	20	80	49	51	100	0	83.5	16.5	59	41	55	45
CEFTAZIDIM	67	33	0	100	68	32	86	14	87	13	87	13	58	42
CIPROFLOXACIN	33	67	20	80	33	64	75	25	49	51	42	58	46	54
Trimethoprim- sulfamethoxazole	0	100	0	100	45.5	54.5	90	10	87	13	64	36	58	42
GENTAMICIN	67	33	0	100	47	53	93	7	58	42	63.5	36.5	43	57
AMIKACIN	0	100	0	100	16	84	77	23	40	60	39	61	33	67
NORFLOXACIN	33	67	0	100	19.5	80.5	69	31	36	64	42	58	47	53

R=Resistance

S=Sensitive

correlation between the kind of organism with the kind of resistance pattern to antibiotics ($P < 0.0001$).

Multi-drug-resistant (MDR) gram negative strains were detected in 162(55%) of isolates. These included *E. coli* [67(41.35%)], *K. pneumoniae* [35(21.6%)], *P. aeruginosa* [27(16.7%)], *Enterobacter* [19(11.73%)], *Acinetobacter* [14(8.65%)]. MDR pattern was not detected among *Proteus* and *Citrobacter*. This kind of antimicrobial resistant pattern was shown in 96 isolates of urine, 23 isolates of tissue, 8 isolates of ulcer, 15 isolated of blood, 3 isolated from ear discharge, 4 isolated of angiocatheter, 3 isolated of fully catheter, 2 cases isolated from CSF, one case isolated from gall bladder sample, 1 case isolated from ascetic fluid, 1 case isolated from abscess, 2 isolated from sputum, 2 isolated from rectal discharge, 1 case isolated from pleural tube's discharge.

Ten patients were identified to have infection due to pandrug-resistant gram-negative bacteria including: *P. aeruginosa* [3 cases (30%)], *A. baumannii* [3 cases (30%)], *Enterobacter* [2 cases (20%)], *K. pneumoniae* [1 case (10%)], *E. coli* [1 case (10%)]. Pandrug-resistant pattern was not detected among *Proteus* and *Citrobacter*. This kind of antimicrobial resistance pattern was shown in 4 isolated from urine, 3 isolated from tissue, 2 isolated from ulcer, 1 case isolated from CSF sample.

DISCUSSION

In this research, multi-drug-resistant (MDR) gram negative strains were detected in 162(55%) of isolates that included *E. coli* as the most common, and also MDR

K. pneumoniae, *P. aeruginosa*, *Enterobacter*, *Acinetobacter*, respectively.

In this study, 14 out of 16 (85.5%) *Acinetobacter* was MDR and there was resistance to ceftazidime (86%), trimethoprim-sulfamethoxazole (90%), ciprofloxacin (75%), norfloxacin (69%), gentamicin (93%), amikacin (77%), imipenem (56%). *Acinetobacter* resistance to all major classes of antibiotics (except polymyxins) in *A. baumannii* has substantially increased worldwide in the past decade (Infectious Diseases Society of America, 2004; Talbot et al., 2006; Peleg et al., 2006). *A. baumannii* is now regarded as one of the most difficult nosocomially acquired pathogens to treat and control (Infectious Diseases Society of America, 2004; Talbot et al., 2006). No novel antibiotics against multi-drug-resistant *A. baumannii* will be commercially available within the next few years (Infectious Diseases Society of America, 2004; Talbot et al., 2006). Mezzatesta (2008) showed widespread *Acinetobacter* resistance to ceftazidime, ciprofloxacin and aztreonam in more than 90% of the strains; resistance to imipenem and meropenem was 50 and 59% respectively, 70% of the strains was resistance to amikacin and gentamicin (Mezzatesta et al., 2008). The outbreak of infection with ceftazidime- and imipenem-resistant *Acinetobacter* species occurred despite ongoing restriction of the use of imipenem (Go et al., 1994).

Our finding showed 27 out of 39 (69%) *Pseudomonas* isolates were MDR and there was resistance to ceftazidime (87%), trimethoprim-sulfamethoxazole (87%), ciprofloxacin (49%), norfloxacin (36%), gentamicin (58%), amikacin (40%), imipenem (10%). *P. aeruginosa* is a ubiquitous organism, an opportunistic pathogen, and human infections caused by *P. aeruginosa* can range from superficial skin infections to fulminant sepsis (Kiska, 1999). Antimicrobial resistance among clinical isolates of *P. aeruginosa* may complicate the treatment of infections and can adversely affect clinical outcomes and costs of treating patients (Carmeli et al., 1999; Harris et al., 1999). Previous studies reported that rates of multi-drug resistance (resistance to ≥ 3 antimicrobial agents) increased from 7.2% in 2001 to 9.9% in 2003 and were significantly higher for isolates from the East North Central and Mid-Atlantic regions of the United States, than for isolates from other regions. During 2001–2003, the *in vitro* susceptibilities of all agents tested against *P. aeruginosa* were $\leq 87\%$ (Karlowsky et al., 2005). Published reports from the National Nosocomial Infections Surveillance System presents data on the resistance of *P. aeruginosa* to imipenem, quinolones, ceftazidime, and piperacillin (National Nosocomial Infections Surveillance, 2004).

In this study, 67 out of 130 (51.5%) isolates of *E. coli* were MDR and there was resistance to 3rd generation of cephalosporins (54-58%), Trimethoprim-sulfamethoxazole (58%), ciprofloxacin (46%), norfloxacin (47%), gentamicin (43%), amikacin (33%), imipenem

(1%). Turner (2004) reported that 99.6% of all Enterobacteriaceae isolated between 1997 and 2003 from 130 centers in Europe, North America and Latin America remained susceptible to imipenem.

In this study, 32 out of 56 (57%) *K. pneumoniae* was MDR and there was resistance to ceftazidime (87%), trimethoprim-sulfamethoxazole (64%), ciprofloxacin (42%), norfloxacin (42%), gentamicin (63.5%), amikacin (39%), imipenem (2%). Bratu (2005) reported an outbreak of KPC class A carbapenemase-positive *Klebsiella* that all 94 isolates were carbapenem-resistant, and most were resistant to cephalosporins and fluoroquinolones.

In this research, pandrug-resistant gram-negative bacteria were isolated from ten clinical specimens (3.4%). Those bacteria were resistant to all the following classes of antimicrobial agents: third generation cephalosporins (antipseudomonal cephalosporins for *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*), imipenem, quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole. Colistin was used for about two decades after its discovery in 1950, but the reported nephrotoxicity and neurotoxicity led to gradual decrease of its use (Michalopoulos et al., 2005). The reuse of colistin is associated with a possible significant therapeutic problem, namely the advent of bacteria resistant to all classes of available antimicrobial agents, including the polymyxins. These bacteria are pandrug-resistant. It should be noted that the definition of pandrug-resistant gram-negative bacteria does not include always testing for colistin in many countries. Hsueh (2002) and Kuo (2003) both reported a high mortality rate (60%) due to *A. baumannii* infections from Taiwan; however, no colistin was used in the *in vitro* susceptibility testing and, most importantly, the drug was not given to patients. Falagas (2005) showed that the isolation of a pandrug-resistant gram-negative rod from clinical specimens does not necessarily mean a bad outcome. Epidemiological and surveillance studies have found that the carbapenems remain highly active against cephalosporin-resistant gram-negative bacteria (Goossens, 2001; Hoban et al., 2003).

CONCLUSION

Determination of resistance patterns can help us to choose the best antibiotic in our hospital. This study indicates that *E. coli* and *K. pneumoniae* are very sensitive to imipenem. However, many of the gram-negative bacteria isolated during this study show MDR to several other antibiotics. *A. baumannii* and *P. aeruginosa* isolates resistant to various classes of antibiotics are emerging worldwide, and the recent resistance or reduced susceptibility to carbapenems is considered a serious clinical problem due to the role of first choice therapy that these drugs have had until now.

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