Investigation of the antibiotic susceptibility patterns of pathogens causing nosocomial infections

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ABSTRACT

Objective: The aim of this study is to determine the resistance patterns of bacteria causing nosocomial infections. The outcome of this resistance was followed for 3 years.

Methods: This study was carried out during 2000 to 2002 at a university hospital in Turkey. The resistance patterns of 570 bacteria (390 Gram-negative, 180 Gram-positive) against meropenem, imipenem, ceftazidime, cefotaxime, cefepime, piperacillin/tazobactam, ciprofloxacin and tobramycin were investigated using the E-test. Extended-spectrum beta-lactamase (ESBL) production was determined using ceftazidime and ceftazidime/clavulanic acid E-test strips.

Results: Meropenem was the most effective antibiotic against Gram-negative organisms (89.0%); this was followed by imipenem (87.2%) and piperacillin/tazobactam (66.4%). The most active antibiotic against Gram-positive bacteria was imipenem (87.2%) and this was followed by piperacillin/tazobactam (81.7%) and meropenem (77.8%). The rates of production of ESBL by *Escherichia coli* were 20.9%, *Klebsiella pneumoniae* 50% and *Serratia marcescens* were 46.7%. Extended-spectrum beta-lactamase production increased each year (21.7%, 22.1% and 45.5%). All of the ESBL producing isolates were sensitive to meropenem and 98.5% sensitive to imipenem. AmpC beta-lactamase was produced by 20.9% of the *Enterobacter species spp*, *Citrobacter spp*. and *Serratia marcescens.* All of these were sensitive to meropenem and 77.8% to imipenem and ciprofloxacin. Multi-drug resistance rates in *Acinetobacter spp* were 45.4% and 37.7% in *Pseudomonas aeruginosa* isolates.

Conclusion: As in the entire world, resistance to antibiotics is a serious problem in our country. Solving of this problem depends primarily on prevention of the development of resistance.

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Almost all bacteria have developed some type of resistance against antibiotics.[1] The importance of antimicrobial resistance among nosocomial and community-acquired pathogens is now appreciated worldwide.[2] Clinical microbiology has focused on the problem of antimicrobial resistance for the last decade.[3] Antimicrobial surveillance have provided important information on changes in the spectrum of microbial pathogens and trends in antimicrobial resistance patterns in nosocomial and community-acquired infections.[2]

Methods. Aerobic bacteria causing nosocomial infections were included in this study according to the criteria of the Centers for Disease Control and

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Prevention.[4,5] For this purpose, during a period of 3-years, each year approximately 200 bacteria were collected (180 Gram-positives and 390 Gram-negatives making a total of 570 isolates). Their antibiotic sensitivity patterns were evaluated using the E-test (AB-BIODISK, Solna, Sweden). Conforming to National Committee for Clinical Laboratory Standards (NCCLS)[6] proposals the E-test was performed on Mueller Hinton agar and the results were evaluated according to the NCCLS criteria. The percentage of the resistant bacteria was expressed as the sum of the percentages of resistant and moderately resistant isolates.

In the establishment of ESBL production by *Klebsiella pneumoniae (K. pneumoniae*), *Klebsiella oxytoca* (*K. oxytoca*) and *Escherichia coli (E. coli*) strains, since the minimum inhibitory concentration (MIC) of ceftazidime is ≥ 2 mg/L, the criteria was an 8-fold decrease in the MIC of ceftazidime with an additional of 4 mg/L clavulanic acid.[6,7] *Enterobacter spp, Citrobacter spp* and *Serratia marcescens* (*S. marcescens)* have been reported to be potential AmpC producers. Also, *Morganella morganii* and *Providencia spp* are included in the AmpC producers. High levels of resistance against ceftazidime, cefotaxime and piperacillin/tazobactam were interpreted as evidence of AmpC production.[7]

Multi-drug resistance (MDR) isolates, particularly *Acinetobacter spp* and *Pseudomonas aeruginosa (P. aeruginosa)*, were organisms resistant to 3 or more antibiotic groups. In this case, the MIC values taken as criteria for carbapenems (meropenem or imipenem, or both) was ≥16 mg/L, ceftazidime ≥32 mg/L, piperacillin/tazobactam ≥128/4 mg/L, ciprofloxacin ≥4 mg/L and tobramycin ≥16 mg/L. Methicillin-resistant *Staphylococci, Enterococcus faecium* and *Stenotrophomonas maltophilia* known to be resistant to carbapenems were not included in the study. Control strains included *Staphylococcus aureus* ATCC 29213, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and 3 *K. pneumoniae spp* (1951-high level ESBL producers, 1204-moderate level ESBL producers and 911-non-ESBL producers).

Results. In this study, the most Gram-negative organisms were *E. coli* (22%), *Klebsiella spp* (22%), *Acinetobacter spp* (19.7%) and *P.aeruginosa* (17.7%) and Gram-positives were Staphylococci (41.7%), *Enterococci* (37.8%) and *Streptococci* (20.5%) (**Table 1**). The most effective antibiotic against Gram-negative bacteria was meropenem (89.0%), followed by imipenem (87.2%) and piperacillin/tazobactam (66.4%) (**Table 2**). All *Klebsiella spp.* were sensitive to carbapenems. As for *E. coli*, all were sensitive to imipenem and an average of 98.8% to meropenem (100% in 2000 and 2002; and 96.5% in 2001). Resistant bacteria such as *Acinetobacter spp*. and *Pseudomonas spp*. were most sensitive to meropenem (79.2%) and to piperacillin/tazobactam (84.1%) (**Table 3 and *Appendix 1**). The antibiotic sensitivities of the isolates tested (cumulative percentage inhibition at MIC) are shown in ***Appendix 1**. The MIC_{50} and MIC_{90} values of Gram-negative bacteria are shown

Table 1 - Species and number of Gram-positive and Gram-negative bacteria according to the year.

Micro-organisms	2000 n	(%)	2001 n	(%)	2002 n	(%)	Total n	(%)
Gram-negative bacteria								
Escherichia coli	25	(18.9)	29	(23)	32	(24.2)	**86**	**(22)**
Klebsiella spp	27	(20.4)	29	(23)	30	(22.7)	**86**	**(22)**
Acinetobacter spp	25	(18.9)	30	(23.8)	22	(16.7)	**77**	**(19.7)**
Pseudomonas aeruginosa	27	(20.4)	14	(11.1)	28	(21.2)	**69**	**(17.7)**
Others*	28	(21.2)	24	(19)	20	(15.2)	**72**	**(18.5)**
Total	**132**	**(100)**	**126**	**(100)**	**132**	**(100)**	**390**	**(100)**
Gram-positive bacteria								
Staphylococci	25	(52.1)	33	(50.8)	17	(25.4)	**75**	**(41.7)**
Enterococci	14	(29.2)	25	(38.5)	29	(43.3)	**68**	**(37.8)**
Streptococci	9	(18.7)	7	(10.8)	21	(31.3)	**37**	**(20.5)**
Total	**48**	**(100)**	**65**	**(100)**	**67**	**(100)**	**180**	**(100)**

**Enterobacter spp.* (21), *Serratia spp.* (15), *Proteus spp.* (14), *Citrobacter spp.* (7), *Pseudomonas vesicularis* (5), *Morganella morganii* (3), *Salmonella spp.* (2), *Aeromonas veronii* (2), *Providencia rettgeri* (2), *Hafnia alvei* (1).

*The full text including Appendix 1 is available in PDF format on Saudi Medical Journal website (www.smj.org.sa)

Table 2 - Antibiotic susceptibility of Gram-negative bacteria according to the year.

Antibiotics	2000 N=132 %	2001 N=126 %	2002 N=132 %	Total N=390 %	Total N=390 MIC_{50}	Total N=390 MIC_{90}
Meropenem	91.7	86.5	88.6	**89.0**	**0.064**	**6**
Imipenem	88.6	87.3	85.6	**87.2**	**0.38**	**32**
Ceftazidime	66.7	55.6	50.8	**57.7**	**4**	**256**
Cefotaxime	58.3	54.0	35.6	**49.2**	**12**	**256**
Cefepime	72.0	63.5	51.5	**62.3**	**2**	**256**
Piperacillin/Tazobactam	77.3	69.0	53.0	**66.4**	**4**	**256**
Ciprofloxacin	66.7	67.5	59.8	**64.6**	**0.125**	**32**
Tobramycin	65.2	63.5	56.1	**61.0**	**1.5**	**256**

MIC - minimum inhibitory concentration

Table 3 - Species, antibiotic susceptibility (S) and MIC_{50}, MIC_{90} values of Gram-negative bacteria according to the year.

Species and antibiotics susceptibility	2000 n	2000 MIC_{50}	2000 MIC_{90}	2000 S (%)	2001 n	2001 MIC_{50}	2001 MIC_{90}	2001 S (%)	2002 n	2002 MIC_{50}	2002 MIC_{90}	2002 S (%)	Total n	Total MIC_{50}	Total MIC_{90}	Total S (%)
Escherichia coli	25				29				32				**86**			
Meropenem		0.12	0.047	100		0.023	0.064	96.5		0.023	0.19	100		**0.016**	**0.094**	**98.8**
Imipenem		0.19	0.38	100		0.19	0.75	100		0.25	0.38	100		**0.19**	**0.38**	**100**
Ceftazidime		0.064	4	92		0.125	64	82.7		1	256	71.9		**0.25**	**64**	**81.4**
Cefotaxime		0.19	256	85		0.064	256	82.7		1	256	50		**0.125**	**256**	**70.9**
Cefepime		1.5	24	85		0.047	32	89.6		2	256	53.1		**0.125**	**256**	**74.4**
Piperacillin/ Tazobactam		0.064	32	85		2	256	89.6		32	256	43.7		**2**	**256**	**70.9**
Ciprofloxacin		0.19	32	52		0.094	32	69.0		4	32	46.9		**0.125**	**32**	**55.8**
Tobramycin		2	16	85		1	32	75.9		1.5	64	62.5		**1.5**	**32**	**73.3**
Klebsiella spp	27				29				30				**86**			
Meropenem		0.016	0.064	100		0.064	0.125	100		0.032	0.125	100		**0.032**	**0.125**	**100**
Imipenem		0.19	0.25	100		0.25	0.75	100		0.25	0.38	100		**0.25**	**0.38**	**100**
Ceftazidime		0.5	256	74.1		24	256	27.6		64	256	43.3		**12**	**256**	**47.7**
Cefotaxime		0.032	256	66.7		24	256	48.3		96	256	46.7		**6**	**256**	**53.5**
Cefepime		1.5	48	81.5		4	256	55.2		2	256	53.3		**1.5**	**256**	**62.8**
Piperacillin/ Tazobactam		0.38	256	75		16	256	55.2		32	256	46.7		**8**	**256**	**59.3**
Ciprofloxacin		0.38	32	85.2		0.125	32	72.4		0.047	20	66.7		**0.047**	**32**	**74.4**
Tobramycin		3	128	55.5		24	256	44.8		16	256	46.7		**8**	**256**	**48.8**
Acinetobacter spp	25				30				22				**77**			
Meropenem		0.5	16	80.0		1	32	73.3		0.5	6	86.4		**0.75**	**32**	**79.2**
Imipenem		0.75	32	72.0		0.75	32	73.3		0.5	6	86.4		**0.75**	**32**	**77.9**
Ceftazidime		256	256	16.0		32	256	33.3		64	256	18.2		**48**	**256**	**24.7**
Cefotaxime		32	256	20.0		256	256	23.3		256	256	22.7		**256**	**256**	**22.0**
Cefepime		3	256	36.0		48	256	30		32	256	16.7		**48**	**256**	**31.2**
Piperacillin/ Tazobactam		48	256	36.0		16	256	50		256	256	27.3		**256**	**256**	**39.0**
Ciprofloxacin		32	32	28.0		1	32	60		32	32	45.4		**8**	**32**	**45.5**
Tobramycin		256	256	52.0		1.5	256	66.7		0.75	32	86.4		**1.5**	**256**	**67.5**
Pseudomonas aeruginosa	27				14				28				**69**			
Meropenem		0.019	32	77.8		6	32	42.8		2	32	64.3		**0.75**	**32**	**65.2**
Imipenem		1	32	74.1		4	32	50		3	32	57.1		**2**	**32**	**62.3**
Ceftazidime		1	256	70.4		6	256	57.1		3	256	60.7		**4**	**256**	**63.8**
Cefotaxime		12	256	37.0		256	256	7.1		256	256	10.7		**64**	**256**	**20.3**
Cefepime		1.5	256	70.4		12	256	35.7		8	256	50		**6**	**256**	**55.1**
Piperacillin/ Tazobactam		3	32	96.3		16	256	64.3		16	256	82.1		**12**	**256**	**84.1**
Ciprofloxacin		0.125	32	70.4		32	32	21.4		0.25	32	57.1		**0.25**	**32**	**55.0**
Tobramycin		1	256	59.2		256	256	28.6		16	256	46.4		**16**	**256**	**46.4**

in **Table 3**. The antibiotic with lowest MIC_{90} for *E. coli* (0.094) and *Klebsiella spp* (0.125) was meropenem; this was followed by imipenem (0.38 for both). When we compared the MIC_{50} values of Gram-negative bacteria, the antibiotics with lowest MIC_{50} were meropenem against *E. coli* and *Klebsiella spp.* (0.016 and 0.032), meropenem=imipenem against *Acinetobacter spp.* (0.75) and ciprofloxacin against *P. aeruginosa* (0.25). The lowest MIC_{50} values were for meropenem (0.064), ciprofloxacin (0.125) and imipenem (0.38) to all Gram-negative organisms (**Table 2**).

The most effective antibiotic against Gram-positive bacteria was imipenem (87.2%) followed by piperacillin/tazobactam (81.7%) and meropenem (77.8%). The antibiotic with lowest MIC_{50} for Gram-positive bacteria was imipenem (0.25), followed by meropenem (0.5) and ciprofloxacin (0.75) (**Table 4)**. Species, antibiotic susceptibility and MIC_{50}, MIC_{90} values of Gram-positive bacteria are shown in **Table 5**.

Discussion. Carbapenems are the most effective antibiotics with the lowest MICs against both Gram-negative and Gram-positive organisms.[2,8,9] In our study, meropenem was the most effective antibiotic Gram-negative organism (89%), this was followed by imipenem (87.2%), piperacillin-tazobactam (66.4%), ciprofloxacin (64.6%), cefepime (62.3%), tobramycin (61%), ceftazidime (57.7%) and cefotaxime (49.2%) (**Table 2**). The most active antibiotic against Gram-positive bacteria was imipenem (87.2%), and this was followed by piperacillin/tazobactam (81.7%), meropenem (77.8%), ciprofloxacin (61.7%), cefepime (54.4%), cefotaxime (53.9%), tobramycin (49.4%) and ceftazidime (31.1%) (**Table 4**). These percentages are in accordance with those reported in the literature but are somewhat lower. Cefotaxime (49.2%) showed <50% activity against Gram-negatives and tobramycin (49.4%) and ceftazidime (31.1%) against Gram-positives. This shows us that we are confronted with a serious resistance problem.

In a similar study including 10 European countries, the most effective antibiotics against *K. pneumoniae* was found to be the carbapenems (98-100%).[10] In another study which included 25 European countries, *E. coli* isolates were found to be 100% sensitive to carbapenems.[11] The results of these studies were comparable to our studies in that all of the *Klebsiella spp*. were sensitive to meropenem and imipenem. Of the *E. coli* isolates, 100% were sensitive to imipenem and 98.8% were sensitive to meropenem (only one isolate in 2001 was resistant). Meropenem had a lower MIC_{90} value than imipenem (**Table 3**). The MIC_{90} of meropenem for *E. coli* was 0.094 and *Klebsiella spp* was 0.125 and this was followed by imipenem with a MIC_{90} of 0.38 for both organisms. The highest levels of resistance were seen in *E.coli spp.* (44.2%) against ciprofloxacin and in *Klebsiella spp*. (52.3%) against ceftazidime. Fontana et al[12] reported that in their study, meropenem was 8-fold more active against *Enterobacteriaceae* as compared to imipenem and 4 to 8-fold more active compared to ceftazidime.

In other similar studies, carbapenems were found to be the most effective antibiotics against *Acinetobacter* isolates that are known to be more resistant than *Enterobacteriaceae*. In these studies, the sensitivity rates of *Acinetobacter spp.* were 78-81%, 79.6-82.2%, 88.1-89.3% and 84-86%.[13-16] In previous studies in our country, the carbapenems were found to be the most effective antibiotics.[17,18] Our *Acinetobacter* isolates had a higher pattern of resistance. While the most effective antibiotics were meropenem (79.2%) and imipenem (77.9%); and cefotaxime (78%) was the antibiotic with the highest level of resistance (**Table 3**). In 4 different studies involving several European countries, the most effective antibiotics against *P.aeruginosa* in one of the studies were meropenem and piperacillin/tazobactam. In another studies, carbapenems (65-82%) were more effective. In the third study, meropenem (76.1%) and imipenem (68.2%) were the most effective and in the fourth study, piperacillin/tazobactam (85%) and meropenem (84%).[10,11,14,19] In a study in the United States of America (USA), the most effective antibiotics against *P. aeruginosa* were meropenem, tobramycin and piperacillin/tazobactam; in a Brazilian study carbapenems, cefepime and piperacillin/tazobactam; and in the Philippines, piperacillin/tazobactam.[8,13,20] The most effective antibiotics against *P. aeruginosa* isolated in Mexico, Brazil and USA were piperacillin/tazobactam (81%), ceftazidime (79%) and meropenem (77%). The most resistant *P. aeruginosa* in these 3 countries were isolated in Brazil. In Brazil, the most effective antibiotics were piperacillin/tazobactam (71%) and meropenem (70%).[2] In our study, the most effective antibiotic was piperacillin/tazobactam (84.1%) followed by meropenem (65.2%) and ceftazidime (63.8%). Cefotaxime was the least effective antibiotic (20.3%) (**Table 3**). When the yearly resistance patterns of Gram-negatives were taken into account, development of the highest level of resistance was found in the cephalosporins (ceftazidime, cefotaxime and cefepime) and piperacillin/tazobactam (**Table 2**).

Various studies reported that the most effective antibiotics were carbapenems against Gram-positive organisms such as Gram-negatives.[8,9,19,21] The effectiveness of carbapenems on

Table 4 - Antibiotic susceptibility and MIC_{50}, MIC_{90} values of Gram-positive according to the year.

Antibiotics	2000 N=48 %	2001 N=65 %	2002 N=67 %	Total N=180 %	Total N=180 MIC_{50}	MIC_{90}
Meropenem	83.3	75.4	76.1	**77.8**	**0.5**	32
Imipenem	91.7	89.2	82.1	**87.2**	**0.25**	32
Ceftazidime	43.8	23.1	29.9	**31.1**	**48**	256
Cefotaxime	62.5	55.4	46.3	**53.9**	**6**	256
Cefepime	60.4	52.3	52.2	**54.4**	**4**	256
Piperacillin/Tazobactam	85.4	81.5	79.1	**81.7**	**1.5**	256
Ciprofloxacin	68.8	67.7	50.7	**61.7**	**0.75**	32
Tobramycin	54.2	63.1	32.8	**49.4**	**6**	256

MIC - minimum inhibitory concentration

Table 5 - Species, antibiotic susceptibility and MIC_{50}, MIC_{90} values of Gram-positive bacteria.

Species and antibiotics susceptibility	MIC_{50}	MIC_{90}	Susceptibility n	(%)
Staphylococcus aureus (44)				
Meropenem	0.064	1	41	(93.2)
Imipenem	0.032	0.125	42	(95.5)
Ceftazidime	8	256	26	(59.1)
Cefotaxime	1.5	12	39	(88.6)
Cefepime	1.5	4	40	(90.9)
Piperacillin/Tazobactam	1	48	39	(88.6)
Ciprofloxacin	0.19	16	37	(84.1)
Tobramycin	0.38	16	37	(84.1)
***Coagulase-negative Staphylococci* (N=31)**				
Meropenem	0.125	1	28	(90.3)
Imipenem	0.047	0.25	29	(93.5)
Ceftazidime	12	64	13	(41.9)
Cefotaxime	1.5	6	28	(90.3)
Cefepime	1.5	8	28	(90.3)
Piperacillin/Tazobactam	0.75	3	29	(93.5)
Ciprofloxacin	0.125	4	23	(74.2)
Tobramycin	0.19	8	26	(83.9)
Enterococci (N=68)				
Meropenem	2	32	50	(73.5)
Imipenem	0.75	2	63	(92.6)
Ceftazidime	256	256	2	(2.9)
Cefotaxime	256	256	12	(17.6)
Cefepime	256	256	12	(17.6)
Piperacillin/Tazobactam	3	256	58	(85.3)
Ciprofloxacin	1.5	32	30	(44.1)
Tobramycin	24	256	17	(25.0)
Streptococci (N=37)				
Meropenem	0.5	32	22	(59.5)
Imipenem	0.5	32	23	(62.2)
Ceftazidime	128	256	15	(40.5)
Cefotaxime	12	256	18	(48.6)
Cefepime	12	256	18	(48.6)
Piperacillin/Tazobactam	3	256	21	(56.8)
Ciprofloxacin	1	32	21	(56.8)
Tobramycin	48	256	9	(24.3)

methicillin-sensitive *Staphylococcus* isolates was found to be 97-99%, 98-100% and 100%.[10,1319] In our study, the most effective antibiotic against Gram-positive bacteria was imipenem (87.2%) followed by piperacillin/tazobactam (81.7%) and meropenem (77.8%). Between 2001 and 2002, yearly increase in resistance against ciprofloxacin and, in particular, against tobramycin was noticeable (**Table 4**). Imipenem (94.7%) and meropenem (92.0%) were most active antibiotics against methicilline-sensitivite *Staphylococci* (*S. aureus* and coagulase-negative *Staphylococci*) and the least effective antibiotic against them was ceftazidime (52%). When we considered the sensitivities of *Streptococci* and *Enterococci* (*E. faecalis*) isolates, it is very clear that we face a serious problem of resistance. The most effective antibiotics against *Streptococci* were imipenem (62.2%) and meropenem (59.5%); and with the least effective antibiotic being tobramycin (24.3%). The most effective antibiotics against *Enterococci* isolates were imipenem (92.6%), piperacillin/tazobactam (85.3%) and meropenem (73.5%). Ceftazidime was the least effective antibiotic (2.9%) (**Table 5**). In previous studies in Turkey, the percentages of ESBL producers were 19.5% and 50% and in Russia was 28%.[10,22,23] In an extensive study that also included these 2 countries, the percentages of ESBL producing organisms were found to be 27.9-39.6% in Turkey, Russia and Italy but were much lower in other European countries (2.5-10.8%).[14] The percentage of ESBL producers was found to be 58.9% in 10 centers in India and 1.8-10.7 in Canada and USA.[24,25] In various studies, the percentages of *E. coli* isolates producing ESBL were 6.7%, 10.1%, 14.6%, 16.7%, 23.3% and 27.8-33.9%.[8,26-30] In *Klebsiella* isolates, these percentages were 21.7%, 25.7%, 30%, 33.3%, 47.3%, 41.7-46.7% and 59.2% in other countries and 50% and 60% in Turkey.[8,23,26-32] In our study, the average percentage of ESBL producing isolates was 36.4% for *E. coli, Klebsiella spp*. and *S. marcescens* combined; but 20.9% for *E.coli* and 50% for *K. Pneumoniae* and 46.7% for *S.marcescens*. Carbapenems have been reported to be the most effective antibiotics against ESBL producers.[20,27,32,33] In our study, meropenem was 100% effective against these isolates and imipenem was 98.5%. The percentages of pathogens producing AmpC were reported to be 47% in Russia and 16.8-55.4% in a study including 29 European countries.[10,14] In the Philippines, *Citrobacter spp*. (29.2%) and *Enterobacter spp* (45.8%) produce AmpC; this percentage was 10.5-31.4% in *Enterobacter spp*., *Serratia spp.* and *Citrobacter spp.* in Colombia and 10-37% in Venezuela.[25,27,28] It has been reported that the most effective antibiotics against AmpC producers were carbapenems (95.7-100%) and cefepime (89-98.9%).[20,29,34] In our study, the percentage of potential AmpC producers (*Serratia spp., Enterobacter spp.* and *Citrobacter spp.*) was 20.9%. The efficacy of meropenem against these AmpC producing isolates was 100%; that of ciprofloxacin and imipenem 77.8%; and that of cefepime 66.7%. The studies in 1998 to 1999 was shown that the MDR isolates of *P. aeruginosa* are a serious problem in Turkey.[10] In our study that was carried out between 2000 and 2002, the percentage found to be 37.7% in *P. aeruginosa* and 45.5% in *Acinetobacter* isolates. These high percentages suggest that the MDR isolates are still a problem in our country.

Antibiotic resistance is alarmingly high in some countries but much lower in others. However, this continues to be a global problem. The incorrect and indiscriminate use of antibiotics will increase this problem. Surveillance studies in each country and even in each hospital will show how to carry out empiric treatment and will help to control and prevent infections caused by resistant organisms.

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Appendix 1 - Antimicrobial activity of antibiotics tested against Gram-negative and Gram- positive isolates.

Organism (number of tested)/antimicrobial	Cumulative percentage inhibition at minimum inhibitory concentration (MIC) (mg/L)														
Staphylococcus aureus (N=44)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	0	0	5	18	52	77	84	84	91	91	93	95	95	100
Ciprofloxacin	0	0	0	0	2	9	20	66	80	84	89	89	89	91	100
Imipenem	0	2	7	36	68	84	91	91	91	93	93	95	100	100	100
MIC	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	0	0	0	0	0	0	2	14	59	86	89	89	89	100
Cefotaxime	0	0	0	2	2	7	32	68	86	89	91	91	91	91	100
Cefepime	0	0	0	2	5	9	27	82	91	91	91	91	91	91	100
Piperacillin/Tazobactam	0	2	2	5	9	36	68	77	89	89	89	89	91	91	100
Tobramycin	2	9	9	23	48	66	80	82	84	86	91	98	98	98	100
Coagulase Negative Staphylococci (31)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	0	0	0	16	26	61	68	84	90	90	90	90	90	100
Ciprofloxacin	0	0	0	0	3	23	52	68	68	74	81	90	90	90	100
Imipenem	0	0	3	16	48	77	77	90	94	94	94	94	94	94	100
MIC	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	0	0	0	0	0	0	0	29	42	77	84	90	90	100
Cefotaxime	0	0	0	0	0	16	42	65	84	90	90	90	90	90	100
Cefepime	0	0	0	0	3	13	39	74	84	90	90	90	94	94	100
Piperacillin/Tazobactam	0	0	0	6	16	42	74	87	94	94	94	94	94	94	100
Tobramycin	3	16	32	48	52	55	61	71	84	90	94	94	94	94	100
Streptococci (37)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	0	14	16	19	27	40	49	51	54	59	59	59	59	100
Ciprofloxacin	0	0	0	3	3	3	5	11	22	57	76	81	81	81	100
Imipenem	0	0	0	11	14	27	43	49	54	54	59	62	62	62	100
MIC	**0.0016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	0	0	3	5	11	19	30	38	40	40	40	46	51	100
Piperacillin/Tazobactam	3	5	11	22	24	30	41	49	57	57	59	62	62	62	100
Tobramycin	0	0	0	0	0	5	8	8	24	41	46	49	57	57	100
Cefotaxime	0	11	16	24	27	43	43	43	46	49	51	54	57	57	100
Cefepime	3	14	17	30	32	35	41	43	49	49	51	51	54	54	100
Enterococci (68)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	0	0	0	0	0	1	4	10	24	60	74	87	90	100
Ciprofloxacin	0	0	0	0	0	0	0	3	19	44	65	66	66	66	100
Imipenem	0	0	0	0	0	0	1	7	41	81	91	93	93	94	100
MIC	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	0	0	0	0	0	0	0	1	3	10	13	21	21	100
Piperacillin/Tazobactam	0	0	0	0	0	0	13	47	81	85	87	89	89	89	100
Tobramycin	0	0	0	0	0	0	1	4	25	32	41	57	59	59	100
Cefotaxime	0	0	0	0	0	0	3	6	12	18	24	28	29	31	100
Cefepime	0	0	0	0	1	4	7	12	15	18	22	32	46	49	100
Escherichia coli (86)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	0	7	52	72	85	95	98	98	99	99	99	100	100	100
Ciprofloxacin	0	3	22	37	40	44	53	56	56	56	56	57	57	57	100
Imipenem	0	0	0	1	1	3	27	77	95	98	100	100	100	100	100
MIC	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	0	9	35	52	65	69	71	76	81	86	88	91	93	100
Piperacillin/Tazobactam	0	0	0	0	1	12	28	56	66	71	71	79	80	81	100
Tobramycin	1	1	1	2	6	15	42	60	73	76	84	92	94	95	100
Cefotaxime	1	22	43	52	56	63	66	71	71	71	71	72	72	74	100
Cefepime	6	27	43	52	58	63	69	72	73	74	74	78	79	80	100
Klebsiella spp (86)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	0	1	27	63	83	98	98	99	99	100	100	100	100	100
Ciprofloxacin	1	1	1	13	45	58	66	71	72	74	76	77	77	78	100
Imipenem	0	0	0	0	0	8	19	79	93	98	100	100	100	100	100
MIC	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	1	2	11	29	31	40	42	45	48	56	60	64	69	100
Piperacillin/Tazobactam	0	0	0	0	0	1	7	33	48	53	59	67	70	72	100
Tobramycin	3	6	6	6	6	12	30	48	49	50	53	59	70	79	100
Cefotaxime	5	15	33	33	35	40	44	48	49	53	55	56	58	59	100
Cefepime	1	19	28	33	34	38	47	56	60	63	67	70	73	73	100
Acinetobacter spp (77)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	1	1	1	4	9	13	22	45	66	75	79	83	84	100
Ciprofloxacin	0	0	0	0	3	9	19	27	36	45	49	49	52	56	100
Imipenem	0	0	0	0	0	8	16	22	47	71	75	78	82	83	100
MIC	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	0	0	0	1	1	4	9	17	24	32	48	57	58	100
Piperacillin/Tazobactam	14	16	16	16	16	21	25	27	34	35	39	42	43	44	100
Tobramycin	1	1	1	2	7	18	41	61	67	72	80	82	86	88	100
Cefotaxime	0	0	1	1	1	1	4	13	19	22	27	30	31	31	100
Cefepime	0	1	1	1	4	7	14	22	26	31	36	49	54	58	100
Pseudomonasaeruginosa (69)															
MIC	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**
Meropenem	0	0	1	1	1	7	22	33	46	54	59	65	72	72	100
Ciprofloxacin	0	0	0	1	3	13	36	51	54	55	58	62	67	68	100
Imipenem	0	0	0	0	0	0	0	1	4	26	51	62	67	68	100
MIC	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**
Ceftazidime	0	0	0	0	0	7	25	41	57	64	71	72	75	75	100
Piperacillin/Tazobactam	0	0	0	0	0	0	1	20	36	48	65	77	84	86	100
Tobramycin	0	0	0	1	3	9	35	46	46	46	54	54	58	62	100
Cefotaxime	0	0	0	0	0	1	1	1	6	20	38	46	54	54	100
Cefepime	0	0	0	0	0	0	16	36	46	55	70	77	80	81	100