

# Antimicrobial resistance patterns of *Pseudomonas aeruginosa* in tertiary care hospitals of Makkah and Jeddah

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Ann Saudi Med 2016; 36(1): 23-28

DOI: 10.5144/0256-4947.2016.23

**BACKGROUND:** The clinical significance of *Pseudomonas aeruginosa* has greatly increased due to its ability to rapidly develop resistance to major groups of antibiotics.

**OBJECTIVES:** Our objective was to determine the pattern of antimicrobial resistance of *P aeruginosa*.

**DESIGN:** Prospective, descriptive study.

**SETTING:** Four tertiary care hospitals in Makkah and Jeddah.

**METHODS:** Clinical isolates of *P aeruginosa* were processed following standard microbiological procedures. A Microscan Walk Away system was used for the identification and antibiotic susceptibility of *P aeruginosa* isolates.

**MAIN OUTCOME MEASURES:** Percentage of resistance of *P aeruginosa* to antibiotics.

**RESULTS:** The overall drug resistance among 121 strains of *P aeruginosa* was low to moderate to commonly used anti-pseudomonal drugs (4.9% to 30.6%). Significantly less resistance was exhibited by piperacillin-tazobactam (4.9%;  $P < .05$ ) and meropenem showed significantly high resistance (30.6%;  $P < .05$ ) as compared to other antibiotics, followed by ticarcillin (22.3%) and imipenem (19%), irrespective of the site of infection. The antibiotics with  $< 10\%$  resistance were cefepime (8.3%), amikacin (7.4%) and piperacillin-tazobactam, which showed lowest resistance (4.9%). Although, data varied between hospitals, meropenem and ticarcillin had the highest drug resistance in all hospitals. Multidrug resistance was 10.7%.

**CONCLUSION:** Low-to-moderate rates of drug resistance among *P aeruginosa* isolates were observed. Meropenem resistance was high irrespective of the site of infection. This pattern of resistance indicates probable overuse of broad-spectrum antibiotics like carbapenems. Overuse needs to be addressed by each institution, and consideration given to regulating use of broad-spectrum antibiotics.

**LIMITATIONS:** Results cannot be generalized as the study did not include all tertiary hospitals in these cities.

**P***seudomonas aeruginosa* is one of the most challenging organisms involved in a variety of infections. It is a leading cause of nosocomial infections and is associated with a high mortality rate. The reason for this high mortality is the rapidly emerging resistance to many currently available antibiotics.<sup>1</sup>

Over the years, increases in the rate of antibiotic resistance to *P aeruginosa*, in particular to  $\beta$ -lactams, aminoglycosides, and fluoroquinolones, has been reported from many parts of the world.<sup>2</sup> Regional variations in antibiotic resistance patterns for different organisms including *P aeruginosa* also occur, which could be due to differences in antibiotic prescribing

practices.<sup>3</sup> In Saudi Arabia *P aeruginosa* has appeared as the most commonly isolated organisms in hospitals, causing 11% of all nosocomial infections up to 31% of which are due to gram-negative organisms.<sup>4</sup>

Better understanding of global trends in antibiotic resistance for the organism is obtained through local and regional surveillance studies. Periodic testing and evaluation of antibiotic resistance of bacterial agents would enable physicians to detect trends in the resistance pattern to commonly prescribed antibiotics in a given organism and may also assist in the selection of an appropriate antibiotic for empiric treatment in a particular setting.<sup>5,6</sup> Therefore, this study aimed to de-

termine the status of antimicrobial resistance to anti-pseudomonal agents and the magnitude of the multi-drug resistance to *P aeruginosa*.

## METHODS

This prospective descriptive study was carried out from August 2013 to January 2014 at the Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Umm Al Qura University, Makkah, Saudi Arabia, after getting approval from the institutional bioethical committee. Clinical and demographic data on the patients was collected using a predesigned questionnaire. The identification of *P aeruginosa* and the sensitivity pattern for each isolate was performed using a Microscan Walk Away system (40SI, Siemens). The Microscan microtiter plate for gram-negative identification and susceptibility panel (NCB 42) contained wells for biochemical agents for identification and separate wells in the same plate for antimicrobial agents with different concentrations in double dilutions for sensitivity testing. The test was performed by touching five freshly grown colonies of the test organism using specific prompts for the purpose. These colonies were suspended in 25 mL of pluronic fluid (suspension fluid). The inoculated fluid was dispensed in special trays and transferred to dehydrated substrates in the microtiter plate using a RENOK system. The inoculated plates were then placed in the Microscan Walk Away system for identification and antibiotic sensitivity testing. The results were read automatically between 16-24 hours.

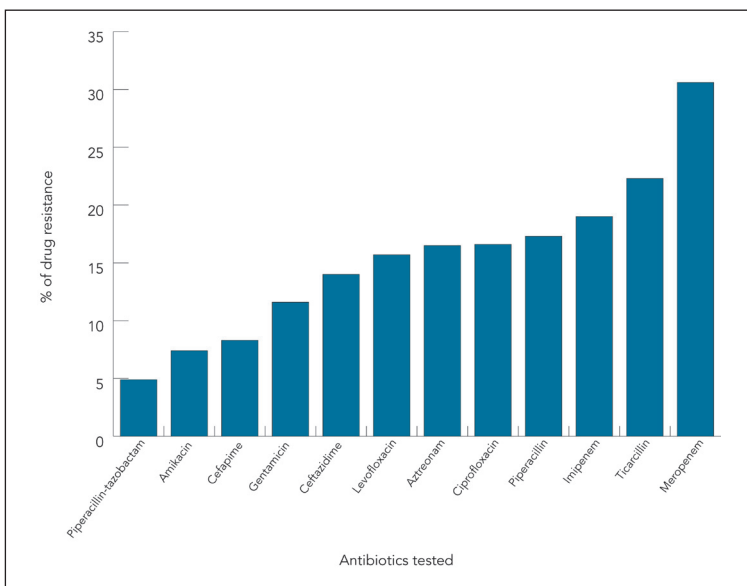
The data on isolates was analyzed using Microsoft Excel 2007. The drug resistance pattern of *P aeruginosa* with site of infection, and a comparison between different hospitals was summarized in terms of frequencies and percentages. Statistical comparison was performed using chi-square and the Fisher exact test for comparison of resistant patterns of different antibiotics, using the computer program "Open Epi Version 2" (Ref: <http://www.openepi.com/SampleSize/SSPropor.htm>). In all statistical analyses a *P* value <.05 was considered significant.

## RESULTS

In the 121 clinical isolates of *P aeruginosa* from the four hospitals, the overall drug resistance was low to moderate (4.9% - 30.6%) to all anti-pseudomonal drugs tested. Resistance with piperacillin-tazobactam to *P aeruginosa* strains was significantly less (4.9%; *P*<.05) as compared to eight antibiotics (ceftazidime, levofloxacin, aztreonam, ciprofloxacin, piperacillin, imipenem, ticarcillin and meropenem). However, isolates showed significantly high resistance (30.6%; *P*<.05) to meropenem as compared to the other 10 antibiotics (**Figure 1**). Next in order of resistance were ticarcillin (22.3%), imipenem (19%), piperacillin (17.3%), and the others. Isolates showed significantly high resistance (22.3%) to ticarcillin as compared to the other four antibiotics (piperacillin-tazobactam, amikacin, cefepime and gentamicin (*P*<.05).

Of 121 strains of *P aeruginosa* isolated from various sources, the majority 53 (43.8%) were isolated from the respiratory tract. In the respiratory tract, 46 (86.8%) were from the lower respiratory tract and 7 (13.2%) from the upper respiratory tract. Significantly high resistance to meropenem was shown by respiratory isolates (41.5%; *P*<.05) and no significant difference was observed in other infections (*P*<.05) (**Table 1**).

The susceptibility pattern of *P aeruginosa* isolated from the lower respiratory tract indicates that aminoglycosides appear to be the most potent antibiotic (data not shown). The isolates showed significantly less resistance to gentamicin (19.6%) and amikacin (21.7%) (*P*<.05). There was resistance in 21.7% of strains to cefepime (a fourth generation cephalosporin anti-pseudomonal antibiotic). Next in order of resistance were the fluoroquinolones, such as ciprofloxacin and levofloxacin (21.7%, each). The same resistance was also exhibited by tazobactam (21.7%). Aztreonam was 32.6% resistant. Significantly high resistance was shown by isolates to ticarcillin (55%) and meropenem (52.1%)(*P*<.05) by pseudomonas isolated from the lower respiratory tract. Isolates were less resistant to imi-



**Figure 1.** Overall drug resistance pattern of *Pseudomonas aeruginosa*.

**Table 1.** Resistance pattern of *P aeruginosa* isolates by site of infection.

Antibiotics	Resistance pattern of isolates by site of infection No (%) (n=121)							
	Respiratory (n=53)	Surgical (n=26)	Genital (n=17)	Urinary (n=13)	Blood (n=4)	Ear (n=3)	Eye (n=3)	Burn (n=2)
Amikacin	6 (11.3)	1 (3.8)	0	1 (7.6)	0	0	1 (33.3)	0
Aztreonam	14 (26.4)	2 (7.7)	0	3 (17.6)	0	0	1 (33.3)	0
Cefepime	8 (15.0)	2 (7.7)	0	1 (7.6)	0	0	1 (33.3)	0
Ceftazidime	13 (24.5)	1 (3.8)	0	2 (15.3)	1 (25)	0	1 (33.3)	0
Ciprofloxacin	14 (26.4)	2 (7.7)	1 (5.8)	2 (15.3)	1(25)	0	1 (33.3)	0
Gentamicin	10 (19.0)	1 (3.8)	0	2 (15.3)	0	0	1 (33.3)	0
Imipenem	15 (28.3)	3 (11.5)	1 (5.8)	1 (7.6)	1 (25)	1 (33.3)	1 (33.3)	0
Levofloxacin	13 (24.5)	2 (7.7)	0	2 (15.3)	1 (25)	0	0	0
Meropenem	22 (41.5)	5 (19.2)	3 (17.6)	4 (30.7)	1 (25)	0	1 (33.3)	1 (50)
Piperacillin	8 (15.0)	2 (7.7)	1 (5.8)	2 (15.3)	0	0	1 (33.3)	0
Piperacillin-tazobactam	4 (7.5)	0 (0.0)	0	0	0	0	1 (33.3)	0
Ticarcillin	19 (36.0)	4 (15.3)	0	3 (17.6)	1 (25)	0	0	0

**Table 2.** Antibiotic resistance pattern of *P aeruginosa* in participating hospitals.

Antibiotics	Antibiotic resistance pattern (n=121) n (%)			
	Saudi National Guard Hospital Jeddah (n=35)	Al-Noor Specialist Hospital Makkah (n=32)	Maternity and Children Hospital Jeddah (n=22)	Maternity and Children Hospital Makkah (n=32)
Amikacin	3 (8.6)	10 (31.2)	0	3 (9.4)
Aztreonam	4 (11.4)	12 (37.5)	1 (4.5)	3 (9.4)
Cefepime	4 (11.4)	5 (15.6)	0	2 (6.2)
Ceftazidime	6 (17.1)	10 (31.2)	0	3 (9.4)
Ciprofloxacin	6 (17.1)	12 (37.5)	1 (4.5)	2 (6.2)
Gentamicin	4 (11.4)	15 (46.8)	1 (4.5)	2 (6.2)
Imipenem	8 (22.8)	12 (37.5)	4 (18.1)	2 (6.2)
Levofloxacin	6 (17.1)	15 (46.8)	0	2 (6.2)
Meropenem	9 (25.7)	20 (62.5)	5 (22.7)	7 (21.9)
Piperacillin	3 (8.6)	12 (37.5)	2 (9.1)	6 (18.8)
Piperacillin-tazobactam	2 (5.7)	5 (15.6)	0	0
Ticarcillin	8 (22.8)	15 (46.8)	1 (4.5)	4 (12.5)

penem (from the same group of carbapenems) (30.5%) compared to meropenem (52.1%).

Antibiotic sensitivity results from upper respiratory infections showed that all respiratory isolates were uniformly sensitive (100%) to tazobactam followed by

ceftazidime, which is the mainstay anti-pseudomonal antibiotic (85% sensitive). Isolates were uniformly sensitive (71.4%) to other antibiotics such as piperacillin, cefepime, aztreonam, imipenem, gentamicin, amikacin, levofloxacin and ciprofloxacin. Pseudomonal

isolates showed high resistance to ticarcillin (57%) and meropenem (28%).

The drug resistance pattern of *P aeruginosa* clinical isolates from the four participating hospitals was variable (**Table 2**). The isolates from Al-Noor Specialist Hospital, Makkah showed moderate-to-high drug resistance (15.6–62.5%) whereas drug resistance at other hospitals was low to moderate: Saudi National Guard Hospital (SNGH), Jeddah (5.7–25.7%); Maternity and Children Hospital (MCH), Jeddah (4.5–22.7%) and Makkah (6.2–21.9%), respectively. Significantly high drug resistance (62.5%;  $P < .05$ ) was found at Al-Noor Specialist Hospital, Makkah as compared to all other hospitals. The lowest rate of resistance was exhibited to piperacillin-tazobactam among all the drugs tested at Al-Noor Specialist Hospital, Makkah (15.6%), and SNGH, Jeddah (5.7%), while no resistance was found to this drug at Maternity and Children Hospitals both at Makkah and Jeddah (**Table 2**).

Overall, multidrug resistance (MDR) was 10.7% (13/121) in *P aeruginosa* isolates. The hospitals at Makkah showed MDR in 8/64 strains (12.5%) and Jeddah in 5/57 strains (8.7%). The maximum MDR rate was seen at Al-Noor Specialist hospital, Makkah 7/32 strains (21.8%) followed by SNGH, Jeddah 5/35 strains (14.3%). The lowest MDR rate, 1/32 strains (3.1%) was seen at MCH, Makkah. No MDR strain was found at MCH, Jeddah.

## DISCUSSION

The drug-resistance pattern of *P aeruginosa* isolates obtained in this study indicates that the antibiotics that are the first line of therapy according to CLSI 2015 are still sensitive, showing low resistance to these drugs, i.e., piperacillin-tazobactam (4.9%), aminoglycosides such as amikacin (7.4%), gentamicin (11.6%) and ceftazidime (14%) and cefepime (8.3%). Determining antibiotic resistance pattern of antibacterial agents may assist in appropriate drug selection. Consistent with other studies,<sup>7-11</sup> the current study showed low-to-moderate antibiotic resistance (4.9% - 30.6%) in *P aeruginosa* isolates, whereas *P aeruginosa* showed high drug resistance (>50% - 98%) in studies from Turkey, Bangladesh, Iran and Saudi Arabia.<sup>12-15</sup>

The highest rate of drug resistance of *P aeruginosa* was to meropenem (30.6%) in the current study, which is comparable with recently reported studies from Saudi Arabia: (38.3%<sup>16</sup> and 36.4%;<sup>17</sup> however, some studies reported a low rate of resistance to meropenem: (5% and 18%)<sup>8,18</sup> The reason for the high resistance to meropenem in our study is that the drug is commonly used in the settings we studied. This warrants a need to de-escalate therapy based on cultures, as it is not just *Pseudomonas*

that will be resistant, but many other members of Enterobacteriaceae would be resistant, including emergence of carbapenem-resistant Enterobacteriaceae. In our study, resistance to ticarcillin was 22.3%, which is less as compared to an earlier study from Makkah (56.3%).<sup>17</sup> However, a very high rate of resistance to ticarcillin (93%) was reported from Turkey.<sup>19</sup> This variation in drug resistance rate may be correlated with the inappropriate use of relevant antibiotics.

The resistance to imipenem in this study was 19%. Comparable rates were found in some studies from Saudi Arabia; (20%<sup>18</sup> and 25.3%<sup>15</sup>), while other studies reported variable rates of resistance to imipenem; low rates (5.8%<sup>7</sup> and 9%<sup>8</sup>) and high rates (38.6%<sup>16</sup>). Similar rates of imipenem resistance were also reported from Croatia (10.2%-31.6%).<sup>20</sup> In a study from Malaysia,<sup>9</sup> resistance rate to meropenem was 23% and imipenem (20%). Geographical variation in the resistance rates of *P aeruginosa* may be related to antibiotic prescribing practices in different parts of the world.

In this study, the resistance rate of *P aeruginosa* to piperacillin was moderate (17.3%), which is comparable to piperacillin resistance (25%) reported from Jamaica.<sup>21</sup> However, studies from Saudi Arabia reported a high rate of resistance to piperacillin; (47%),<sup>17</sup> (49.4%),<sup>15</sup> and (54%)<sup>16</sup> while a study from Dhahran showed low resistance to piperacillin (4-11%).<sup>7</sup> These differences in the resistance rates are probably related to differences in antibiotic use in different settings and selective pressure.

Resistance of *P aeruginosa* to ciprofloxacin is a rising problem in many parts of the world. In our study, the resistance rate to ciprofloxacin was 16.5%. A much higher rate was reported in earlier studies from Saudi Arabia and other parts of the world. In Saudi Arabia, resistance to ciprofloxacin was 50.9%,<sup>15</sup> 42.8%<sup>17</sup> and 35%.<sup>18</sup> Comparable rates were also reported from Iran (58%),<sup>22</sup> India (49%)<sup>23</sup> and Turkey (48.9%).<sup>12</sup> A quite high rate of resistance to ciprofloxacin (75.5%) was reported from Bangladesh.<sup>13</sup> However, a lower rate (2.6%) of ciprofloxacin resistance was reported from Trinidad.<sup>11</sup> The difference in the rate of ciprofloxacin resistance is usually related to the frequency of use of fluoroquinolones and availability of oral doses.

Resistance to ceftazidime in this study was 14%, which is identical (i.e., 14%) to the data reported in a study from Riyadh.<sup>8</sup> However, a much higher rate of resistance for ceftazidime was reported in earlier studies from Makkah (52.7%<sup>15</sup> and 51.3%<sup>17</sup>) and other parts of Saudi Arabia: (45.1%<sup>16</sup> and 53%<sup>18</sup>). Variable rates of ceftazidime resistance were reported from different parts of the world: Singapore (23.4%),<sup>10</sup> India (40%)<sup>24</sup> and Iran (68%).<sup>22</sup> Thus, the differences in the resistance rates usually correlate

with the prescribing practices of each hospital and the selective pressure of certain antibiotics. To avoid emergence of resistance, ceftazidime either alone or in combination with aminoglycosides according to severity of the infection should be considered as a primary therapeutic agent for the treatment of serious pseudomonal infections or should be rotated with cefepime.

The encouraging finding of our study is that lowest rate of resistance was shown to piperacillin-tazobactam (4.9%), which is one of the mainstays for the treatment of pseudomonal infections. Similar results were shown for piperacillin-tazobactam resistance from Malaysia (12%)<sup>9</sup> and Singapore (11.7%).<sup>10</sup> However, other studies from Saudi Arabia showed a much higher rate of resistance to this antibiotic combination: (33.5%),<sup>15</sup> (50.3%)<sup>16</sup> and (41.2%).<sup>17</sup>

In current study, individual hospital data showed variable rates of drug resistance for each hospital; however, isolates showed high resistance to meropenem and ticarcillin in all hospitals. This pattern of resistance indicates probable overuse of broad-spectrum antibiotics like carbapenems, an issue that needs to be addressed by each institution with regard to regulations on use of broad-spectrum antibiotics. However, low rates (<10%) of resistance to amikacin, cefepime and piperacillin-tazobactam in our study are encouraging as these can be used appropriately in these hospitals because these agents are commonly used as anti-pseudomonal antibiotics and should necessarily be prescribed after proper identification and antibiotic sensitivity has been obtained. The advantage of this will be that these antibiotics will remain available for a long time for the treatment of potentially serious infections caused by *Pseudomonas*, which has the capability to become quickly resistant to antibiotic therapy, at times during therapy.

The resistance rate of *P aeruginosa* to different antimicrobials isolated from different sites in other countries has varied greatly. In a study from Bangladesh, organisms isolated from surgical wound infections were more resistant to azithromycin (100%), ceftazidime (86.8%), and ciprofloxacin (75.5%). However, isolates from respiratory infections were 100% resistant to ciprofloxacin, ceftazidime, and amikacin.<sup>13</sup> In contrast, in a study from Saudi Arabia, piperacillin showed high resistance among isolates from respiratory, urinary and wound infections.<sup>7</sup> A similar pattern was seen in our study among *P aeruginosa* strains isolated from respiratory, surgical, and urinary tract infections, which had high resistance to meropenem. In our study most of the respiratory isolates

were from the lower respiratory tract because it is precisely the site of the majority of nosocomial infections in a hospital setting as patients may be dependent on assisted respiration and therefore show high resistance to meropenem and ticarcillin. This could be attributed to random and uncalled for use of meropenem in the hospital setting, which could be the reason for abnormal resistance exhibited by the organism.

The rate of MDR *P aeruginosa* is increasing in many parts of the world and poses a serious therapeutic problem. In some healthcare settings, the treatment of MDR *P aeruginosa* is being limited to polymyxin B.<sup>25</sup> In our study, the rate of MDR *P aeruginosa* was 10.7%, which is high considering the definition used to declare MDR (resistance to three or more classes of antibiotics). A study from Malaysia<sup>9</sup> (using the same definition for MDR as ours) reported a high rate of MDR *P aeruginosa* (19.6%). In contrast, studies from Saudi Arabia, using the same definition, reported 1-2% MDR from Dhahran<sup>7</sup> and 3% MDR *P aeruginosa* in 2004 and 2% in 2005 from Riyadh.<sup>8</sup> Continuous monitoring of drug resistance patterns at healthcare facilities will be helpful in evaluating the trend of MDR among *P aeruginosa* in Saudi Arabia.

On the basis of this type of resistance shown by different antibiotics, guidelines should be made and the antibiotic policy moderated in hospitals, which may include rotational policies and stop policies to make the antibiotics available for a longer period for the therapy of organisms that tend to attain resistance *de novo* and during the course of therapy.

A limitation of this study is that not all tertiary care hospitals from Makkah and Jeddah have been included in the study; therefore the results cannot be generalized for all the hospitals in these cities.

The current study reported low-to-moderate rates of resistance in *P aeruginosa* isolates in four hospitals in Makkah and Jeddah. The highest rate of drug resistance was to meropenem, which was found in all the hospitals, irrespective of site of infection. This pattern of resistance indicates probable overuse of broad-spectrum antibiotics like carbapenems, an issue that needs to be addressed by each institution with regard to regulations on use of broad-spectrum antibiotics. Low resistance rates (<10%) to some antibiotics, such as amikacin, cefepime and piperacillin-tazobactam, is encouraging as these antibiotics will remain available for a long time for the treatment of potentially serious infections caused by *Pseudomonas*, if rationally used according to antibiotic policies specific to the health care setting.

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