

Resistance patterns of bacterial isolates to antimicrobials from 3 hospitals in the United Arab Emirates

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ABSTRACT

الأهداف: مراجعة الأنواع الشائعة من البكتيريا المرضية، ومقارنة أنماط مقاومتها للعلاجات الشائعة الاستخدام.

الطريقة: تم جمع المعلومات والاحصائيات عن استجابة الميكروبات للمضادات الحيوية خلال الفترة ما بين 1994م وحتى 2005م، من مختبرات علم الأحياء في ثلاثة مستشفيات بالامارات العربية المتحدة. قمنا بتقييم أنماط مقاومة أربعة كائنات دقيقة *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella spp*, *Pseudomonas aeruginosa* لعدة علاجات من الخط الأول. تم استخدام جهاز (Vitek 2) الألكتروني لمعرفة وتحديد أقل نسبة تزامن في تثبيط التركيز.

النتائج: لاحظنا زيادة مقاومة *Staphylococcus aureus* للاريثرومايسين (2005 - 315 = n) (حوالي 6 أضعاف - مستشفى العين فقط)، الكلوكساسيلين (مستشفى العين)، والجنيتاميسين (أكثر من 3-10 أضعاف - جميع المستشفيات). لم نلاحظ أي تزايد في المقاومة للينيسيلين. أما بالنسبة للكائنات سلبية الغرام الشائعة وجدنا أن مقاومتها للامبيسيلين، الجنيتاميسين، السيفترياكسون، السيبروفلوكساسين والامبيبينيم والتي إزدادت بنسبة (4.2- 200%، 2005، 305 = n) لميكروب ال *Escherichia coli*. كانت مقاومة الامبيبينيم ضعيفة جدا (0.4%) في مستشفى توام. كما وجدنا أن أنماط مقاومة ميكروبات ال *Pseudomonas aeruginosa*، *Klebsiella spp*، مقابل الامينوجلايكوسايدات، السيفالوسبورينات، والسيبروفلوكساسين والنورفلوكساسين كانت متغيرة.

خاتمة: كان هناك زيادة ملحوظة في مستويات المقاومة للبكتيريا المرضية لعدد من العلاجات من 1-120 ضعف خلال مدة 11 عام.

Objectives: To compare the resistance pattern of common bacterial pathogens to commonly used drugs.

Methods: Information and statistics of antimicrobial resistance for 1994 and 2005 were collected from the 3 hospital microbiology laboratories in the United Arab Emirates. The resistance patterns of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella spp*, and *Pseudomonas*

aeruginosa to several front-line drugs were estimated. All laboratories used automatic machines (Vitek 2), which identifies and determines minimum inhibitory concentrations simultaneously.

Results: Increased resistance was observed for *Staphylococcus aureus*, (n=315, 2005) to erythromycin (approximately 6 fold, Al-Ain Hospital only), cloxacillin (Al-Ain Hospital), and gentamicin (more than 3-10 folds in all hospitals). Increased penicillin resistance was not observed. For the common Gram-negative organisms, there was a high resistance to ampicillin, gentamicin, ceftriaxone, ciprofloxacin, and imipenem, which seemed to increase for *Escherichia coli*, (by 4.2-200%, n=305, 2005); however, there was very little resistance to imipenem (0.4%) in Tawam Hospital. Variable resistance patterns were obtained for *Pseudomonas aeruginosa* (n=316, 2005) and *Klebsiella spp*, (n=316, 2005) against aminoglycosides, cephalosporins, ciprofloxacin, and norfloxacin.

Conclusion: Overall, there was an obvious increase in resistance of bacteria and the prevalence rate to a number of drugs from 1-120 folds during the 11-year period.

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The discovery of penicillin and its indiscriminate usage has resulted in the development of resistant microorganisms, and this is a matter of great concern in patient care, both in hospitals and the community.^{1,2} Now virtually all strains of *Staphylococcus aureus* (*S. auerus*) are resistant to penicillin and many other

antibiotics. The organism was also sensitive to methicillin, but the emergence of methicillin resistance among clinical isolates has aggravated the problem even further. Methicillin-resistant *S. aureus* (MRSA) is a major cause of nosocomial, and lately also, community acquired infections. Unfortunately, most MRSA are now resistant to aminoglycosides and rifampicin in many countries.^{3,4} Resistance to fluoroquinolones is rapidly emerging in clinical isolates of *S. aureus*⁵ and *Pseudomonas aeruginosa* (*P. aeruginosa*)^{6,7} but various Enterobacteriaceae, especially *Klebsiella pneumoniae* (*K. pneumoniae*) has also been observed to be resistant. The introduction of newer cephalosporins such as, cefotaxime and ceftazidime has improved our ability to treat serious infections caused by Gram-negative pathogens. However, increased use of these agents has been followed by the emergence of resistance. *Klebsiella spp.* (*K. spp.*) have generally been susceptible to the third-generation cephalosporins but since 1983 strains of *K. pneumoniae*, *Escherichia coli* (*E. coli*), and other Gram-negative bacteria that make extended-spectrum or inducible β -lactamase have been described from many parts of the world.⁸⁻¹⁰

Surveillance of antimicrobial resistance has been reported in many countries, including developed¹¹⁻¹³ and developing countries.¹⁴⁻¹⁷ Antimicrobial resistance, in the 80's had been shown to be higher in the developing world than the developed world.¹⁸ Trimethoprim resistance among pathogenic Gram-negative bacteria was 64% in South India,¹⁹ 63.3% in Nigeria²⁰ and 49.1% in South Africa,²¹ while the level of resistance was only 14-19% in Finland²² and 23% in Scotland.²³ The resistance trend for trimethoprim has continued to increase in India, at least being 70-80% for *E. coli* for the year 1997-1999²⁴ when compared to the early 80's.¹⁹ A similar increase in resistance was reported in South Africa, but to a lesser extent; it increased to 52% of the isolates.²⁵ Similarly, there was an increase in resistance patterns in Scotland, being 26-50% of the isolates.^{23,26} In Finland, the resistance of *E. coli* to trimethoprim has increased to 40% from 14-19% in the early 1980's or late 1970's.^{22,27}

Very few studies have been carried out in the United Arab Emirates (UAE): One was in a referral hospital,²⁸ while the other was in the same 3 hospitals.²⁹ Therefore, the aim of the present study was to determine the changes in the patterns of resistance to antimicrobials of the 4 common pathogens, namely: *S. aureus*, *K. spp.*, *E. coli*, and *P. aeruginosa* in 3 different hospitals in the UAE for the years 1994 and 2005.

Methods. Three different hospitals in the UAE were chosen for this study. The Dubai Hospital (DH) is found in Dubai city, whose population is approximately

1,100,000 people, while the other 2, Al-Ain and Tawam Hospitals are found in Al-Ain, a city of approximately 400,000 people, and situated approximately 150 km from Dubai. The DH and Al-Ain Hospital are large with a capacity of 293 and 461 beds, while the Tawam Hospital has 415 beds. The DH and Al-Ain Hospitals cater for both nationals and expatriate staff in the UAE with a predominance of expatriates, while the Tawam Hospital caters mostly for nationals of the UAE.

The *S. aureus*, *E. coli*, *K. spp.*, and *P. aeruginosa* were selected for retrospective studies involving antimicrobial resistance analysis. For each organism, all the clinical isolates tested in the diagnostic laboratory during the years of study, 1994 and 2005 were included. The number of organisms tested varied greatly but were not less than 265 for each antibiotic (Tables 1-4). The laboratory data available on the organisms and drugs tested were copied on specially prepared sheets for ease of analysis. All laboratories used automatic machines (Vitek 2, bioMérieux, France), which identifies and determines minimum inhibitory concentrations (MIC) simultaneously. Previously, Al-Ain and Tawam Hospitals have used standard disc diffusion techniques for antimicrobial susceptibility testing according to the National committee for Clinical Laboratory Standards (NCCLS, 1995).³⁰ For each organism, only clinically useful drugs were analyzed. A count of resistant isolates were made and expressed as a percentage of the number tested and reported as the "resistance rate".

This study was approved by the Ethical Committee of the United Arab Emirates University.

Results. The resistance rates of *S. aureus* to 6 commonly used antimicrobials are shown in Table 1. Increased resistance was observed for *S. aureus* (Table 1) to erythromycin (approximately 6 fold, Al-Ain Hospital only), but declined in Tawam and DH. Similarly, increased resistance was observed for cloxacillin (Al-Ain Hospital), but no change was observed for Tawam and DH. Increase in resistance was observed for gentamicin (more than 3-10 folds in all hospitals), but hardly any change in resistance to penicillin in Al-Ain and Tawam Hospitals. Penicillin was not used against *S. aureus* in DH since it is no longer used against this organism. The resistance to fusidic acid increased from 0.7-30.1% in Al-Ain and 11-21.5% in Tawam Hospitals while it was not tested in 2005 in DH.

The *E. coli* resistance rates are shown in Table 2. The organism was highly resistant to ampicillin in 1994 with the rates varying between 58-89%, but the resistance increased for the 2 hospitals (Al-Ain and Tawam) in 2005, but declined in DH in 2005. The organism was however, more sensitive to augmentin (amoxicillin + clavulanic acid) in 1994 in Al-Ain Hospital, the resistance

Table 1 - Antibiotic resistance rates for *Staphylococcus aureus* isolates.

Antibiotics	Al-Ain Hospital		Tawam Hospital		Dubai Hospital	
	1994	2005	1994	2005	1994	2005
	(442)	(316)	(450)	(483)	(382)	(318)
Penicillin	99.5	98.4	94	95.7	77	---
Erythromycin	6.2	35.7	13	8.3	4	2
Cephalothin	4	---	1	---	0	---
Gentamicin	6.2	61.4	7	6.4	0	3
Cloxacillin	3.3	43.6	0	---	0	0
Fusidic Acid	0.7	30.1	11	21.5	6	---

--- Not tested, () average no. tested

Table 3 - Antibiotic resistance rates for *Klebsiella spp.* isolates.

Antibiotics	Al-Ain Hospital		Tawam Hospital		Dubai Hospital	
	1994	2005	1994	2005	1994	2005
	(348)	(316)	(390)	(265)	(444)	(605)
Ampicillin	88.5	98.9	100	100	92.1	---
Augmentin	8.1	50.5	18	14.3	19	---
Cotrimoxazole	---	45.7	12	---	23	30
Norfloxacin	0	77.5	4	---	3	---
Ciprofloxacin	4.8	29.4	3	8.7	0	---
Amikacin		56.7	2	5.8	0	2
Gentamicin	3	28.7	8	8.2	3	18
Ceftriaxone	0	49.1	---	9.3	2	20
Imipenem	0	29.8	0	0.7	---	---

--- Not tested, () average no. tested

rate in Tawam Hospital in 2005 was 26.8% while it was not tested in DH. There was very little resistance to imipenem in Tawam Hospital in 2005, but increased in 2005 in Al-Ain Hospital. Similar resistance pattern was observed for norfloxacin, gentamycin, ceftriaxone, cotrimoxazole, and ciprofloxacin (Al-Ain Hospital).

The rates and patterns of resistance of *K. spp.* are shown in Table 3. This organism showed a higher rate of resistance to all the 9 antimicrobials tested. However, in all 3 hospitals, the levels of resistance to ampicillin were higher and not much different from 1994. Similarly to Al-Ain Hospital, the pattern of resistance in Tawam Hospital was similar except for imipenem, for which the organism was highly susceptible. The resistance pattern for DH varied ranging from 23-30% for cotrimoxazole, 3-18% for gentamicin, and 2-20% for ceftriaxone. The organism remained susceptible to amikacin in Tawam and DH, but resistance increased in Al-Ain Hospital. Table 4 shows the resistance pattern of *P. aeruginosa* to 10 antimicrobials. While this organism was sensitive to

Table 2 - Antibiotic resistance rates for *Escherichia coli* isolates.

Antibiotics	Al-Ain Hospital		Tawam Hospital		Dubai Hospital	
	1994	2005	1994	2005	1994	2005
	(342)	(305)	(382)	(732)	(566)	(318)
Ampicillin	69	83.6	58	64.2	89	65
Augmentin	10	61.6	---	26.8	---	---
Cotrimoxazole	50	66.2	42	---	26	45
Norfloxacin	0.9	79.4	4	---	---	---
Ciprofloxacin	2.7	41.3	---	21.1	---	---
Gentamicin	3	27.9	6	10	0	10
Ceftriaxone	0	62	---	15.8	0	18
Imipenem	0	35.7	---	0.4	---	---

--- Not tested, () average no. tested

Table 4 - Antibiotic resistance rates for *Pseudomonas aeruginosa* isolates.

Antibiotics	Al-Ain Hospital		Tawam Hospital		Dubai Hospital	
	1994	2005	1994	2005	1994	2005
	(442)	(316)	(450)	(408)	(382)	(328)
Amikacin	4.7	21.4	4	15.2	2	3
Gentamicin	13.9	47.6	11	27.5	10	3
Netilmicin	4.9	87.5	---	---	10	3
Ceftriaxone	34.8	97.4	---	---	16	---
Norfloxacin	25	97.7	14	---	---	---
Ciprofloxacin	0.8	97.4	8	37.9	---	---
Piperacillin	---	35.4	7	23.1	10.9	5
Aztreonam	---	31.9	10	32.4	13	10
Ceftazidime	0.7	19.4	10	16.3	0	5
Imipenem	1.4	23	8	15.8	---	---

--- Not tested, () average no. tested

ciprofloxacin in 1994, in 2005 this organism had nearly become completely resistant to the drug in Al-Ain Hospital while the resistance increased from 8-37.9% in Tawam Hospital. As the resistance to piperacillin and aztreonam increased in Tawam Hospital, it decreased in DH. This organism showed resistance to all the drugs tested namely; amikacin (except in DH where it was still sensitive), gentamicin (except in DH where it declined), Netilmicin (except in DH where it became more sensitive), norfloxacin, ceftazidime, and imipenem. In addition, in Al-Ain Hospital, ceftriaxone resistance increased from 34.8% in 1994 to 97.4% in 2005, a worrying trend.

Discussion. In this study we selected *S. aureus*, *E. coli*, *K. spp.*, and *P. aeruginosa*, as 4 pathogens that

commonly cause disease in hospitals to represent the bacterial resistance rates and changes during an 11-year period. These hospitals are located in 2 different cities, and the results would indicate whether the changing pattern of resistance was either localized (Tawam or Al-Ain) or wide spread. As can be seen from the presented data, the resistance patterns of the 4 organisms to antimicrobials differ. This difference is due to many different reasons, including the methods of antimicrobial susceptibility testing and interpretation of the results. This is also influenced by the proportion of outpatient to inpatient strains in the different hospitals and by differences due to faster development of resistance in one area than in another. The *S. aureus* showed maximum resistance to penicillin, a very well established fact today that nearly all hospital-associated *S. aureus* strains are resistant to penicillin. However, the resistance was lower in DH. The reason for this unusual low resistance rate was approximately 70% as 260/372 in 1991 and 271/382 in 1994 of the isolates were from outpatients residing in rural areas, which were more sensitive to penicillin. Resistance to erythromycin and gentamicin was generally low, but an increase was apparent in Al-Ain Hospital for the years 1994 and 2005. However, there was no increased resistance to first generation cephalosporins or cloxacillin except in Al-Ain Hospital, which showed a 13-times increase. The reason for the discrepancies between Al-Ain Hospital, and Tawam and Dubai Hospitals were the number of expatriates, which was much higher in Al-Ain Hospital than in Tawam and DH, which could explain partly the sensitivity of different antimicrobials. Another reason could be that these antibiotics were used more often in Al-Ain Hospital compared to DH and Tawam Hospitals. The Tawam and DH have only locals as patients. Occasional sporadic cases of MRSA strains were seen in these hospitals. The increasing antimicrobial resistance of *S. aureus*, and particularly the emergence of MRSA is a major therapeutic problem.^{31,32} In Kuwait, fusidic acid resistance showed a much greater increasing trend than in the UAE, with the proportions of resistance isolates increasing from 22% in 1994 to 92% in 2004.^{33,34} This is a worrying trend and a cause for concern to the microbiologist and health professionals.

Although, *E. coli* was resistant to ampicillin in Al-Ain and Tawam Hospital, the rate dropped in DH during the 11 years. This may be due to the decrease in its empirical use by practitioners in DH. The resistance trend to augmentin in Al-Ain is similar for *E. coli* and *Klebsiella*, but the lower resistance rate for *Klebsiella* in Tawam only, may be due to a more strict sensitivity interpretation for this antibiotic in relationship to other drugs tested. This criterion may not be strictly followed by the other 2 laboratories. This indicates

that both organisms have developed their resistance to ampicillin predominantly through beta-lactamase production.³⁵ Cotrimoxazole resistance was higher for *E. coli* than *Klebsiella* in all hospitals, and there was a very large increase in resistance over the study period, possibly reflecting higher antibiotic usage and misuse. The low initial resistance rate of the 2 quinolones tested, namely, norfloxacin and ciprofloxacin, which were a recent introduction in 1994, indicated that they were not extensively used, but the increased resistance shown by both *E. coli* and *K. spp.* to the quinolones in Al-Ain Hospital showed that these drugs were used more often in this hospital than in Tawam and DH.

Klebsiella showed nearly 100% resistant rates to ampicillin, as demonstrated by 1994 and 2005 strains. Susceptibility of *K. spp.* to ceftriaxone, amikacin, imipenem, and gentamicin have reduced, which is a bad indicator of their continued usefulness in this country. Imipenem was the most effective drug with hardly any resistant strains in Tawam and DH while the organism showed increased resistance in Al-Ain Hospital.

Pseudomonas aeruginosa is a clinically significant pathogen and is responsible for the higher mortality rate in various nosocomial infections such as, urinary tract infections, pneumonias, septicemias, and surgical wound infections.³⁶ This organism is characterized by intrinsic resistance to several antimicrobial agents, but the development of resistance to agents generally exhibiting potent antibacterial activity against this organism, such as carbapenems and fluoroquinolones, is being encountered with increasing frequency.^{37,38} In this study, clinically isolates of *P. aeruginosa* showed resistance to most of the indicated antimicrobial agents, though resistance rates declined in DH. Among the aminoglycosides, resistance rates to amikacin increased in both Al-Ain and Tawam Hospitals, which is worrying that resistance has more than trebled and quadrupled over such a short period, while for gentamicin, resistance rate of the organism decreased in DH, which is heartening in a sea of despair. The greatest increase noted in resistance by the organism was to ceftriaxone, ciprofloxacin, and norfloxacin. However, these are not the drugs of choice in *Pseudomonas* infections. Since its innate resistance to many antimicrobials due to low outer-membrane permeability combined with inactivation by an inducible chromosomally encoded β -lactamase,^{39,40} the range of β -lactam antibiotics available for therapeutic use is limited to carboxypenicillins, ureidopenicillins, a few third-generation cephalosporins, monobactams, and carbapenems. In the 3 hospitals tested in UAE, the most effective drugs for empirical therapy would be amikacin, piperacillin, ceftazidime, and imipenem.

In conclusion, the increase in the patterns of resistance seen in this study is a common occurrence

and is a universal phenomenon. There was general agreement between the 3 hospitals as to the level of resistance and trends of this change, though a more favorable trend was seen in DH. Overall, there was an obvious increase in resistance of bacteria and the prevalence rate to a number of drugs from 1-120 folds during the 11-year period. This difference over a period of time is due to many different reasons, including the methods of antimicrobial susceptibility testing and interpretation of the results. This is also influenced by the proportion of outpatient to inpatient strains in the different hospitals and by differences due to faster development of resistance in one area than in another. The study has some limitations in that Tawam and Al-Ain Hospitals have their own guidelines regarding the use of antimicrobials, which are different to DH guidelines and thus, there may be differences in the MIC breakdown interpretation of the results even though the Ministry of Health had introduced the UAE Antibiotic Policy and Guidelines to their use in 1995. Strict following of the antibiotic policy and guidelines should go a long way to slow down the increase seen in resistant microorganisms to the commonly used antimicrobials.

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