

Rising bacterial resistance to common antibiotics in Al Ain, United Arab Emirates

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ازدياد مقاومة الجراثيم للمضادات الحيوية الشائعة في إمارة العين في دولة الإمارات العربية المتحدة

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الخلاصة: تُنَدَّرُ المعلومات المحليّة في إمارة العين في دولة الإمارات العربية المتحدة حول أنماط المقاومة للمضادات الحيوية. وفي هذه الدراسة الاستيعادية أجرى الباحثون في أحد مستشفيات إحالة الثالثة تحليلاً لنتائج حساسية المضادات الحيوية للأدوية على مدى خمس سنوات من عام 2004 حتى 2008، وقورنت مع دراسة سابقة أجريت في نفس المستشفى من عام 1999 حتى 2002. وتبين أن العقودية الذهبية قد أظهرت انخفاضاً يُعتدّ به إحصائياً في حساسيتها للأوكساسيلين من 95.0% في الفترة 1999–2002 إلى 84.4% في عام 2008. وانخفضت حساسية الراكدة *Acinetobacter* للإيميبينيم من 99.0% في عام 2004 إلى 32.5% فقط في عام 2008. وظهرت في نفس الفترة مقاومة للسيفوكسيتين في حوالي نصف مُستفردات الإشريكية القولونية. كما اكتُشِفَ انخفاض يُعتدّ به إحصائياً في حساسية الزائفة الزنجارية بين عامي 1999 و2008 لجميع المضادات الحيوية التي جرى اختبارها تقريباً. ولم تُظهر الكلبسيلا أي تغير يُعتدّ به إحصائياً في المقاومة لأيّ من المضادات الحيوية التي جرى اختبارها. ويتبيّن من الدراسة أن الحاجة ماسّة إلى بذل جهود حثيثة حتى يمكن تقليص اختطار انتشار ذراري الجراثيم المقاومة للمضادات الحيوية.

ABSTRACT There is a dearth of local information in Al Ain, United Arab Emirates about antibiotic resistance patterns. In this retrospective study in a tertiary referral hospital, antibiotic susceptibility results were analysed over the 5-year period 2004–08 and compared with a previous study in the same hospital during 1999–2002. *Staphylococcus aureus* showed a significant decrease in sensitivity to oxacillin from 95.0% in the period 1999–2002 to 84.4% in 2008. Sensitivity of *Acinetobacter* spp. to imipenem dropped from 99.0% in 2004 to only 32.5% in 2008. During the same period, almost half of *Escherichia coli* isolates developed resistance to cefotaxime. Significant reductions in sensitivity to *Pseudomonas aeruginosa* between 1999 and 2008 were found for almost all the antibiotics tested. *Klebsiella* spp. did not show any significant change in resistance to any of the tested antibiotics. Serious efforts are needed to reduce the risk of the spread of resistant strains of bacteria.

Augmentation de la résistance bactérienne aux antibiotiques courants à Al Ain, (Émirats arabes unis)

RÉSUMÉ Il existe une pénurie d'informations locales à Al Ain (Émirats arabes unis) concernant les schémas de résistance aux antibiotiques. Dans la présente étude rétrospective conduite dans un hôpital de soins tertiaires, les résultats de sensibilité aux antibiotiques ont été analysés sur une période de 5 ans allant de 2004 à 2008 puis comparés aux résultats de l'étude précédente de 1999 à 2002 dans le même hôpital. La sensibilité de *Staphylococcus aureus* à l'oxacilline a diminué significativement, passant de 95,0 % entre 1999 et 2002 à 84,4 % en 2008. La sensibilité d'*Acinetobacter* spp. à l'imipénem a chuté, passant de 99,0 % en 2004 à seulement 32,5 % en 2008. Au cours de la même période, on a constaté un développement d'une résistance à la céfotaxime dans près de la moitié des isolats d'*Escherichia coli*. Des réductions importantes de la sensibilité de *Pseudomonas aeruginosa* entre 1999 et 2008 ont été observées pour presque tous les antibiotiques testés. La résistance de *Klebsiella* spp. aux antibiotiques testés est restée plutôt stable. Des efforts importants sont requis pour réduire le risque de propagation de souches bactériennes résistantes.

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Introduction

There is global concern about the growing problem of antimicrobial resistance, especially the appearance and rapid spread of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals and the community [1]. The phenomenon is complex, involving specific microbial characteristics, selective pressures of antimicrobial use and demographic and technological changes that enhance the transmission of drug-resistant organisms. Such infections are becoming virtually untreatable and are leading to rising morbidity, mortality and health care costs [2].

In the United Arab Emirates (UAE), as in other countries, there is a growing concern about the indiscriminate prescription of antibiotics and even self-medication for minor ailments for which they many not be required. This can lead to the development of antibiotic-resistant strains of bacteria, thus reducing the effectiveness of certain antibiotics when they are required for a specific infection [3]. There has been growing concern in Saudi Arabia too as hospital strains of resistant bacteria are finding their way into the community: steps have been taken to modify local guidelines about the optimum use of antibiotics [4]. As there are variations in the resistance pattern in different countries, a thorough understanding of the changing local trends provides valuable information to hospitals to help them evaluate and plan for the proper management of clinical cases and to guide antibiotic stewardship programmes.

The present study at a tertiary referral hospital in Al Ain Emirate aimed to determine the susceptibility of certain bacterial isolates over the 5-year period 2004–08 and compare the results with a previous study in the same hospital carried out during the period 1999–2002. There is a dearth of local information in Al Ain and it was hoped that this study would provide valuable information about current patterns of resistance.

Methods

This retrospective study was carried out in Tawam hospital, Al Ain, over the period 2004–08. The susceptibility results of the following bacterial isolates were analysed: *Staph. aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* spp., *Acinetobacter* spp. and *Stenotrophomonas maltophilia*. The results were compared with a previous study carried out during the period 1999–2002 [5]. The previous study was performed in the same hospital, under similar conditions, but by different workers. In some cases, comparable data were not available for the same antibiotics/strains and the trends in susceptibility were traced during the present study only.

The bacteria were identified by conventional microbiology methods. Initially, between January 2004 and June 2006, the Vitek 1 microbiological culture analyser (BioMérieux) and the Analytic Profile Index strips (BioMérieux) were used for identifying bacteria. Subsequently, the Vitek 2 analyser replaced the Vitek 1. Antibiotic susceptibility was tested by the disk diffusion method during the period January 2004–June 2006, and then the Vitek 2 was used to perform antibiotic susceptibility testing for most isolates, while the disk diffusion method was retained for testing in case the Vitek 2 failed to produce satisfactory results or if retesting of susceptibility for a particular organism was considered necessary. The Vitek 2 provided minimum inhibitory concentration values for the tested isolates. The Clinical and Laboratory Standards Institute's guidelines were used to interpret the antibiotic disk diffusion data [6].

Different antibiotic panels (as deemed appropriate, with the consensus of a microbiologist and the treating physicians) were applied for different organisms. The data were saved in a laboratory information system (*Epicenter*, version 4.0) which has the facility to eliminate patient duplicate specimens (i.e. repeat isolates from the same body

site and hospital service) from analysis. The algorithm used for handling repeat isolates was patient-based and only the first isolate per patient was included in the analysis. The calculation of percentage susceptible did not include isolates with intermediate susceptibility. Cumulative antibiogram reports of the different isolates and antimicrobials for the period of 2004–08 were compared with the study in 1999–2002.

Logistic regression analysis was done using SPSS, version 17.0 to assess the association between year of sampling and the antimicrobial resistance of the tested pathogens to determine whether there were significant changes in the percentage resistance over time.

Results

Staph. aureus strains showed a steady decrease in sensitivity to oxacillin from 94.0% in 2002 to 84.4% in 2008. Comparing the average rate of sensitivity over the period 1999–2002 in the previous study (96.0%) with the rate in 2008 showed that the decrease was significant ($P < 0.05$) (Table 1).

P. aeruginosa showed significant decreases in sensitivity ($P < 0.05$) between the average rate for 1999–2002 and the rate in 2008 to amikacin, cefepime, ciprofloxacin (88.9% to 81.6%), gentamicin, imipenem and piperacillin/tazobactam (Table 1). Sensitivity to azetreonam decreased significantly between 2004 and 2008 and to ceftazidime between 1999–2002 and 2007.

Acinetobacter spp. showed a significant decrease in sensitivity between 2004 and 2008 ($P < 0.05$) to all the tested antibiotics, imipenem, ceftazidime, ciprofloxacin, gentamicin and piperacillin/tazobactam (Table 1).

E. coli showed a significant decrease in sensitivity between the average for 1999–2002 study and 2008 ($P < 0.05$) to amikacin, ceftazidime, ciprofloxacin, gentamicin (Table 1). Data were not available for 1999–2002

Table 1 Antibigram for isolates from a tertiary referral hospital in Al Ain by year

Antibiotic	Previous study [5]		Current study									
	1999–2002		2004		2005		2006		2007		2008	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<i>Staphylococcus aureus</i>												
Oxacillin	100	96.0	607	94.0	679	94.0	620	92.7	642	91.1	787	84.4 ^a
<i>Pseudomonas aeruginosa</i>												
Amikacin	292	95.5	336	97.3	353	93.8	449	95.3	697	93.7	784	87.9 ^a
Azetreonam	–	–	308	94.8	373	93.3	449	77.7	700	65.7	793	61.1
Cefepime	55	96.4	172	96.1	266	95.1	341	92.4	663	77.9	783	79.6 ^a
Ceftazidime	270	90.0	430	94.8	422	95.2	480	91.0	710	79.6	–	–
Ciprofloxacin	397	88.9	399	92.9	424	92.2	478	90.2	710	81.9	788	81.6 ^a
Gentamicin	387	91.2	452	88.9	457	89.5	482	88.8	710	86.3	789	82.4 ^a
Imipenem	388	93.8	427	93.9	443	93.9	478	89.9	710	86.0	788	80.4 ^a
Piperacillin	170	82.9	198	93.9	343	94.4	416	84.6	710	73.5	788	80.1
Piperacillin/ tazobactam	385	95.3	430	95.5	364	95.9	470	87.2	710	76.2	790	86.3 ^a
<i>Acinetobacter spp.</i>												
Amikacin	–	–	80	85.0	78	70.5	64	90.6	120	84.2	126	61.2
Amoxicillin/ clavulanate	–	–	103	43.7	104	35.6	71	28.1	123	12.4	–	–
Cefotaxime	–	–	102	31.3	112	29.4	72	31.3	123	9.5	120	8.6
Ceftazidime	–	–	101	66.3	101	52.4	72	65.3	123	42.3	125	31.6 ^b
Ciprofloxacin	–	–	96	65.6	102	72.5	72	84.5	123	52.9	125	30.1 ^b
Gentamicin	–	–	110	77.2	105	69.5	72	88.9	123	67.5	129	42.4 ^b
Imipenem	–	–	101	99.0	106	94.3	72	91.7	123	61.5	127	32.5 ^b
Piperacillin	–	–	46	52.1	85	52.9	55	67.3	123	44.7	127	25.0
Piperacillin/ tazobactam	–	–	101	69.3	85	60.0	72	75.0	123	48.8	127	29.6 ^b
Trimethoprim/ sulfamethoxazole	–	–	57	59.6	93	53.7	72	73.6	123	70.3	127	28.9
<i>Escherichia coli</i>												
Amikacin	438	99.8	557	95.8	416	93.5	765	82.5	1333	65.9	1424	76.5 ^a
Amoxicillin/ clavulanate	–	–	934	70.3	921	73.2	1002	76.3	1310	66.8	1420	58.3 ^b
Ampicillin	1041	31.3	770	36.6	706	35.8	1004	35.9	1360	31.6	1435	27.8
Cefotaxime	–	–	948	90.9	858	89.3	926	86.5	1360	81.6	1425	76.3
Ceftazidime	1004	91.0	931	92.0	816	91.2	990	86.8	1360	82.7	1420	77.3 ^a
Cefuroxime	–	–	724	84.1	775	88.3	752	83.8	1088	75.4	1354	69.7 ^b
Cephalothin	–	–	731	53.7	788	56.5	828	51.8	1087	44.8	1354	38.3
Ciprofloxacin	1021	80.1	874	77.5	833	78.9	1004	78.1	1360	72.1	1431	65.2 ^a
Gentamicin	1023	88.9	973	86.2	924	90.0	1002	87.2	1360	81.8	1433	82.3 ^a
Imipenem	1012	100.0	928	99.9	892	99.6	994	100.0	1360	100.0	1434	99.9
Nitrofurantoin	–	–	735	93.6	786	93.0	803	93.0	1085	92.5	1347	92.6
Piperacillin	599	36.7	396	51.5	725	52.4	827	43.9	1360	33.5	1433	38.1
Piperacillin/ tazobactam	724	97.9	928	91.9	723	91.9	998	94.2	1360	95.6	1433	95.1
Trimethoprim/ sulfamethoxazole	1011	48.9	564	56.3	782	55.9	1001	60.0	1360	53.3	–	–

Table 1 Antibigram for isolates from a tertiary referral hospital in Al Ain by year (concluded)

Antibiotic	Previous study [5]		Current study									
	1999–2002		2004		2005		2006		2007		2008	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<i>Klebsiella</i> spp.												
Amikacin	–	–	213	93.4	190	94.2	282	95.4	371	94.1	397	93.9
Amoxicillin/ clavulanate	–	–	323	82.3	330	85.7	335	89.2	378	89.1	393	81.3
Cefoxitin	–	–	324	89.1	313	89.4	328	91.8	378	89.7	395	83.9
Ceftazidime	–	–	324	90.4	294	90.1	331	91.8	378	90.9	394	84.3
Cefuroxime	–	–	166	82.7	177	89.6	147	93.2	172	90.1	324	80.0
Cephalothin	–	–	157	80.2	180	81.6	167	89.2	166	85.5	324	78.4
Ciprofloxacin	–	–	306	90.5	300	91.3	336	93.7	378	92.9	395	91.0
Gentamicin	–	–	336	92.5	330	91.8	336	93.1	378	90.5	398	88.7
Imipenem	–	–	321	100.0	321	99.3	335	100.0	378	100.0	385	99.7
Nitrofurantoin	–	–	159	40.8	179	40.7	165	30.9	167	21.6	323	19.7
Piperacillin	–	–	129	63.5	272	66.5	285	20.0	378	3.4	397	39.0
Piperacillin/ tazobactam	–	–	323	86.6	253	88.5	335	92.8	378	95.8	397	90.2
Trimethoprim/ sulfamethoxazole	–	–	184	80.4	272	82.3	335	88.6	378	86.4	397	83.9
<i>Stenotrophomonas maltophilia</i>												
Trimethoprim/ sulfamethoxazole	–	–	26	100.0	42	95.2	38	97.4	63	95.2	63	88.7

^a*P* < 0.05 versus average data for years 1999–2002.^b*P* < 0.05 versus year 2004.*n* = number of isolates tested; – = not tested.

for other antibiotics; their sensitivities were shown to decrease significantly between 2004 and 2008: amoxicillin/clavulanate, cefuroxime and cefotaxime (90.9% to 75.9%). *E. coli* did not show any significant change in resistance to nitrofurantoin, piperacillin/tazobactam, imipenem and trimethoprim/sulfamethoxazole over the period 2004–08.

Klebsiella spp. did not show any significant change in resistance to any of the tested antibiotics between 2004 and 2008 (Table 1).

There was a drop in sensitivity of *Sten. maltophilia* to sulfamethoxazole between 2004 and 08 but this was not significant (Table 1).

The number of extended spectrum of beta-lactamase (ESBL)-producing isolates found increased significantly over the period 2004–08 (*P* < 0.05) (Figure 1). The increase was evident

for both isolates of *E. coli* (from 7.0% to 22.3%) and *Klebsiella* spp. (9.3% to 16.4%) (Figure 2).

Discussion

Bacterial resistance to β -lactam antibiotics first appeared in the 1960s, as methicillin began to be used in clinical practice and was identified in 1% of isolates [7]. By 1993, serious concern was being expressed about the emerging problem that Japanese hospitals were experiencing due to MRSA. Nowadays, MRSA, with its serious implications, has appeared all over the world [8]. According to an estimate, the rate of MRSA strains have almost doubled in the United States of America (USA), during the same period, from 127 000 in 1999 to 278 000 in 2005. The number of people dying due to MRSA infections reached

17 000 in 2005, an increase from 11 000 in 1999 [9]. A similar trend had also been observed in the United Kingdom, where MRSA was reported to be a cause of death in 1652 cases in 2006, a rise from 51 MRSA-related deaths in 1993, albeit with a subsequent gradual decline in mortality [10]. The data for oxacillin in the present study showed that the rate of MRSA increased from 5.0% in the period 1999–2002 [5] to 15.6% in 2008 in the present study.

Acinetobacter spp. are also notorious for their ability to develop resistance to all classes of antimicrobials. *A. baumannii* is a hospital-acquired organism and is therefore exposed to a broad range of antibiotics. Most probably these genetic determinants have been acquired from other nonfermenter organisms in the environment, as well as common members of the Enterobacteriaceae. β -lactamases and efflux pumps have

been implicated in the resistance mechanisms of *Acinetobacter* strains [11]. Over the years of our study, the sensitivity rates of *Acinetobacter* spp. to various antibiotics have than more halved and we have been left no good choice of antibiotics. Until recently, carbapenams would have been the choice against *Acinetobacter* spp. as our study showed that 99.0% of these organisms were sensitive to imipenem in 2004. By 2008, however, sensitivity had dropped to only 32.5%. *Acinetobacter* spp. commonly colonize patients in intensive care units, especially those who are intubated or have multiple intravenous lines or monitoring devices, postsurgical drains or urinary catheters. These organisms are found almost exclusively in patients admitted to hospitals. Irrespective of the fact that their role in disease causation is marginal and the cause of mortality and morbidity is due the underlying disease, their rising resistance against antimicrobial drugs is alarming [12].

E. coli is a ubiquitous organism, which may spread to human beings from animals, mainly poultry. It is becoming resistant to multiple drugs and the findings from poultry isolates are also reflected in the human isolates of this organism, mainly due to the extensive use of antibiotics in farming [12]. A study in the USA revealed that almost 331 of the 931 *E. coli* isolates from humans and poultry were resistant to 1 or more commonly used antibiotics [14]. During the same period, almost a quarter of *E. coli* isolates have developed resistance to cefotaxime. Moreover the organisms showing drug resistance have been shown to express high levels of virulence factors [15].

The problem of drug resistance in *P. aeruginosa* are multifold. The organism may accumulate intrinsic drug resistance mechanisms such as overproduction of cephalosporinase AmpC, increased drug efflux, fluoroquinolone target mutations and

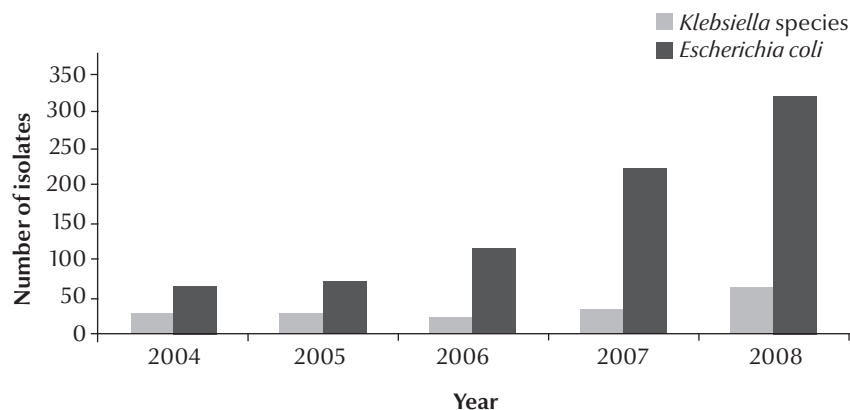


Figure 1 Total number of extended spectrum of beta-lactamase (ESBL)-producing isolates of *Escherichia coli* and *Klebsiella* spp. out of total ESBL isolates from a tertiary referral hospital in Al Ain for 2004–08

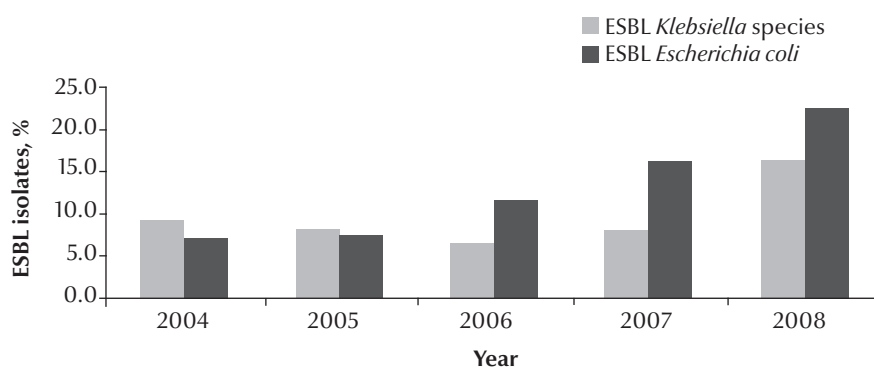


Figure 2 Percentage of extended spectrum of beta-lactamase (ESBL)-producing isolates of *Escherichia coli* and *Klebsiella* spp. from total ESBL isolates from a tertiary referral hospital in Al Ain for 2004–08

deficient production of porin OprD. Moreover, there are exogenous mechanisms such as production of secondary β -lactamases and aminoglycoside-modifying enzymes. These retain the ability to generate severe bloodstream infections. Therefore, multidrug-resistant *P. aeruginosa* may remain fully pathogenic [16]. We found significant reductions in sensitivity to *P. aeruginosa* between 1999 and 2008 for almost all the antibiotics tested.

Taking into consideration the local antibiogram data, guidelines have been issued for rational use of antibiotics in the UAE. The overuse of antibiotics is avoided and as far as possible the

most appropriate antibiotic is used for an adequate period and not beyond. The overuse of antibiotic for surgical prophylaxis is also discouraged. Antibiotics are reserved for those patients who can benefit from them, i.e. those are the shown to be infected with the relevant bacterial pathogen. As far as possible, a narrow spectrum drug is used to cover a particular organism identified. Serious efforts are needed to reduce the risk of development of resistant strains of bacteria in the environment and in hospitals. Surveillance of resistance should be a key factor to generate data to inform improvements in clinical practice.

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Excerpt from a podcast broadcast on the occasion of World Health Day 2011

Dr Mario Raviglione: Drug resistance or antimicrobial drug resistance is a real global threat.

- First, it kills. We don't have a precise number but it kills hundreds of thousands of people every year.
- Second, it challenges greatly - care and control of infectious diseases that in the past were curable - for some of them we are now in the pre-antibiotic era, we are back to the 1930s or 40s.
- Third, it has not yet been fully realized that drug resistance threatens the achievements of the Millennium Development Goals because it kills children, it kills mothers, it kills HIV, TB and malaria patients.
- Finally, it compromises health security, and may damage economies.

The full podcast can be heard via the link on this page:

http://www.who.int/mediacentre/multimedia/podcasts/2011/whd_20110408/en/index.html