Antibiogram of multidrug resistant *Acinetobacter baumannii* isolated from clinical specimens at King Hussein Medical Centre, Jordan: a retrospective analysis

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مخطط لتأثير المضادات الحيوية على الراكدة البومانية المقاومة لأدوية متعددة، والمعزولة من عينات سريرية مختلفة في مركز الملك حسين الطبي بالأردن: تحليل استعادي

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الخلاصة: لقد أجريت هذه الدراسة لتحديد الانتشار والمخطط المحلي لتأثير المضادات الحيوية على جرثومة الراكدة البومانية المقاومة لأدوية متعددة وتأثير المضادات الحيوية على هذه الجرثومة المعزولة في مستشفى الحسين بمدينة الحسين الطبية في عمان بالأردن. ففي دراسة استعادية من يناير/ كانون الثاني إلى ديسمبر/ كانون الأول من عام 2013 تم الاطلاع على بيانات لـ 116 عينة سريرية إيجابية غير مكررة من السجلات المختبرية للمرضى. فكانت معدلات مقاومة معزولات الراكدة البومانية عالية بالنسبة للسيفترياكسون والسيفوتاكسيم والتيكارسيلين (100٪)، والسيفنازيديم والسيفيبيم والبيبيراسيلين (98.3٪)، والإيميبينيم (97.4٪)، والبيبيراسيلين/ تازوباكتام (96.6٪)، والكينولونات (94.8٪)، والأمبيسلين/ سُلبكتام (89.7٪)، والجنتاميسين (87.9٪)، والتوبراميسين والتراسيكلين (76.7٪) والميثوبريم/ سلفاميثوكسازول (75.9٪)، لكنها كانت أقل بالنسبة للمينوسيكلين (26.7٪) والكوليستين (1.7٪). لقد كانت الراكدة البومانية – في مستشفانا – شديدة المقاومة لكل المضادات الحيوية – بما في ذلك التيجيسيكلين – باستثناء المينوسكلين والكوليستين اللذين اعتبرا الملاذ الأخير لمعالجة الراكدة البومانية.

ABSTRACT This study was conducted to determine the prevalence and the local antibiogram of multidrug-resistant *Acinetobacter baumannii* isolates in Al-Hussein Hospital at King Hussein Medical Centre in Amman, Jordan. In a retrospective study from January to December 2013, data on 116 non-repetitive positive clinical samples were retrieved from patients' laboratory records. The resistance rates of *A. baumannii* isolates were high for ceftriaxone, cefotaxime and ticarcillin (100%), ceftazidime, cefepime and piperacillin (98.3%), imipenem (97.4%), piperacillin/tazobactam (96.6%), quinolones (94.8%), ampicillin/sulbactam (89.7%), gentamicin, (87.9%), tobramycin and tetracycline (76.7%) and trimethoprim/sulfamethoxazole (75.9%), but lower for minocycline (26.7%) and colistin (1.7%). *A. baumannii* in our hospital were highly resistant to all antibiotics, including tigecycline, except for minocycline and colistin which are considered the last resort treatment for multidrug-resistant *A. baumannii*.

Antibiogramme d'isolats d'*Acinetobacter baumannii* multirésistants à partir de différents échantillons cliniques au Centre médical Roi Hussein en Jordanie : une analyse rétrospective

RÉSUMÉ La présente étude a été menée pour déterminer la prévalence et l'antibiogramme local des isolats d'*Acinetobacter baumannii* multirésistants à l'hôpital Al-Hussein du Centre médical Roi Hussein à Amman (Jordanie). Dans une étude rétrospective menée de janvier à décembre 2013, les données de 116 échantillons cliniques positifs uniques ont été recueillies à partir des dossiers de laboratoire des patients. Les taux de résistance des isolats d'*A. baumannii* étaient élevés pour la céftriaxone, la céfotaxime et la ticarcilline (100 %), la ceftazidime, la céfépime et la pipéracilline (98,3 %), l'imipénème (97,4 %), la pipéracilline/le tazobactam (96,6 %), les quinolones (94,8 %), l'ampicilline/le sulbactam (89,7 %), la gentamicine (87,9 %), le tobramycine et la tétracycline (76,7 %) et le triméthoprime/le sulfaméthoxazole (75,9 %), mais étaient moins élevés pour la minocycline (26,7 %) et la colistine (1,7 %). Dans notre hôpital, *A. baumannii* était très résistant à tous les antibiotiques, notamment à la tigécycline, sauf à la minocycline et à la colistine, qui étaient considérées comme le traitement de dernier recours contre les souches d'*A. baumannii* multirésistantes.

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Introduction

Acinetobacter baumannii resistant to multiple antimicrobial agents has been increasing worldwide over recent decades. This resistance pattern usually varies with time, and from one region to another or even within the same region (*1*). Furthermore, *A. baumannii* has become one of the most problematic multidrug resistant (MDR) pathogens in the health care environment and is responsible for many nosocomial infection outbreaks, especially in critical care areas. These include bloodstream, soft tissue, urinary tract, central nervous system and surgical site infections and ventilator-associated pneumonia (*1–3*), all of which have been associated with high mortality rates and treatment costs (*4*).

There is limited information in Jordan regarding the epidemiology, prevalence and resistance rates of *A. baumannii* isolates from different sites of infection (5–7). This study was therefore conducted to determine the current prevalence and the local antibiogram of MDR-AB isolates from different sites of infection in a tertiary teaching hospital at King Hussein Medical Centre, Amman.

Methods

This was a retrospective study conducted in the department of microbiology, Princess Iman Centre for Research and Laboratory Sciences, King Hussein Medical Centre, Amman, over a period of 12 months from January to December 2013. The study protocol was approved by the ethics committee of the Royal Medical Services.

Sampling

From a total of 374 positive cultures of *A. baumannii* 116 non-repetitive positive clinical samples for *A. baumannii* from various sources, including blood (n = 24), sputum (n = 28), urine (n = 7) and pus swabs (n = 57 from wounds, tips of catheters and body parts) were retrieved from patients' laboratory records at Al-Hussein Hospital, King Hussein Medical Centre.

Data collection

Clinical and Laboratory Standards Institute (CLSI) recommendations for 2012 were adopted for culture, isolation and identification of all *A. baumannii* isolates and for antibiotic susceptibility testing using the VITEK 2 Compact automated microbiology system (bioMérieux), with 2 complementary sets of antibiotic susceptibility testing (AST) cards (AST-N233 and AST-XN05) (*8*). Samples that were tested manually or against only one of the AST-cards or to different AST-cards were excluded, i.e. only samples that were tested against both AST cards were included in the study. The minimal inhibitory concentration (MIC) interpretive standards for *A. baumannii* were adopted from the CLSI guideline 2012 (*8*) for the following groups of antibiotics:

- group I: penicillins (ticarcillin and piperacillin), beta-lactames/beta-lactamase-inhibitor combinations (ampicillin/sulbactam and piperacillin/tazobactam), 3rd and 4th generation cephalosporins (ceftazidime, cefotaxime ceftriaxone, and cefepime);
- group II: carbapenems (imipenem);
- group III: fluoroquinolones (ciprofloxacin and levofloxacin);
- group IV: aminoglycosides (tobramycin and gentamicin);
- group V: tetracyclines (minocycline and tetracycline);
- group VI: folate pathway inhibitors (sulfamethoxazole/trimethoprim);
- group VII: lipopeptides (colistin), and potential antimicrobial agents; and
- tigecycline.

Definitions

Since there is no agreed single definition for MDR and pan-drug resistance (PDR) for *A. baumannii* in the literature (*9,10*) the following definitions were adopted in this study. MDR was defined as resistance to imipenem plus 3 or more different antibiotic classes, including: at least 2 beta-lactames (penicillin, beta-lactames/beta-lactamase-inhibitor combinations, 3rd- and 4th-generation cephalosporins); tobramycin or gentamicin; ciprofloxacin or levofloxacin; tetracyclines; or sulfamethoxazole/trimethoprim. PDR was defined as resistance to all tested antibiotics or only susceptible to colistin. Tigecycline was not included in this definition since no agreed breakpoints for tigecycline have been approved by the CLSI 2012 guideline (*8*).

Results

Over a period of 12 months, a total of 116 *A. baumannii* isolates were found. The distribution according to their site of infection is shown in Table 1. Isolates were obtained from swabs (49.1%), blood (24.2%), sputum (20.7%) and urine (6.0%). More of the isolates were from male (73, 62.9%) than female patients.

A. baumannii resistance to various antibiotics groups is summarized in Table 2. The percentage of resistant *A. baumannii* from various sources was highest for ceftriaxone, cefotaxime, and ticarcillin (100%), followed by ceftazidime, cefepime, and piperacillin (98.3%), while resistance to other tested antibiotics were: imipenem (97.4%), piperacillin/tazobactam (96.6%), ciprofloxacin and levofloxacin (94.8%), ampicillin/sulbactam (89.7%), gentamicin (87.9%), tobramycin and tetracycline (76.7%), sulfamethoxazole/trimethoprim (75.9%). On the other hand, the rate of resistance of *A. baumannii* isolates was remarkably low for colistin (1.7%) and minocycline (26.7%).

The resistance pattern differed significantly across samples of different origins ($P \leq 0.05$) for quinolones,

Table 1 Distribution of *Acinetobacter baumannii* isolates from different specimens, by patient's sex

Specimen	Males		Females		Total	
	No.	%	No.	%	No.	%
Blood	17	14.7	7	6.0	24	20.7
Sputum	16	13.8	12	10.3	28	24.2
Swab	33	28.4	24	20.7	57	49.1
Urine	7	6.0	0	0.0	7	6.0
Total	73	62.9	43	37.1	116	100.0

tetracyclines, gentamicin and sulfamethoxazole/trimethoprim. In addition, antibiotic resistance was lowest with urine samples for sulfamethoxazole/trimethoprim (42.9%) and with sputum samples for ampicillin/sulbactam (78.6%), followed by blood samples, especially with ciprofloxacin and levofloxacin (75.0%), gentamicin (70.8%), tobramycin (66.7%), tetracycline (58.3%) and minocycline (12.5%). Since there are no agreed breakpoints for tigecycline against *A. baumannii* in the CLSI guidelines or in the literature (*8,11*), we used the AST-XN05 card MIC breakpoints of susceptibility (susceptible ≤ 0.5 mg/L, resistant ≥ 8 mg/L). On this basis, 20 (17.2%) isolates were reported to be susceptible to tigecycline (Table 3).

According to our definitions, 90 *A. baumannii* isolates were multidrug resistant (77.6%), while 10 isolates were pan-drug resistant (8.6%) (Table 4).

Discussion

In the last decades, *A. baumannii* has been considered as one of the most resistant bacteria within the hospital environment, especially in critical care areas, which are responsible for the most severe nosocomial infections. These infections often start locally, then progress to bacteraemia and even septicaemia (*1,2,12,13*) due to several contributing factors, for example, inappropriate initial antimicrobial therapy, early interruption of treatment, sub-therapeutic doses, minimal tissue penetration and MDR, and also as a result of the overuse of 3rd-generation cephalosporin (*13*), quinolones or broad-spectrum antibiotics (*14*), and to a lack of proper instrument decontamination and personal hygiene (*2,13*). For these reasons, the *A. baumannii* resistance patterns differ internationally, regionally and locally in developing and developed countries (*1*).

More of the *A. baumannii* isolates identified in our study were from male (62.9%) than female patients, in agreement with observations in previous studies (*11–12*). The most common source of *A. baumannii* isolates was swabs (49.1%), followed by blood (24.2%), sputum (20.7%) and urine (6.0%). The *A. baumannii* resistance pattern across various sample origins was significantly different for quinolones, tetracyclines, gentamicin and sulfamethoxazole/trimethoprim. The different resistance pattern for *A. baumannii* from different sample sources is in agreement with previous findings from King Hussein Medical Centre in a 2001 study, and further investigations are needed to elucidate the cause of these differences (*6*).

In the present study, isolates of *A. baumannii* showed a high resistance rate (94–100%) to all generations of cephalosporins, penicillins, imipenem and quinolones, findings which are in general similar to the results of studies in Jordan, Islamic Republic of Iran, India and Italy, and a little higher than those from studies in Malaysia, Turkey and the United States of America (USA) (50–78%) (*7,15,16*).

The high resistance rates of isolates to penicillins and beta-lactamase inhibitors in the present study (89–96%) were consistent with the results from other studies obtained from Jordan, Islamic Republic of Iran, India, Turkey and Italy for piperacillin/tazobactam (*5,15–19*), but were higher than the results from south India (39%) and Malaysia (72%) (*20,21*). At the same time, lower resistance rates for ampicillin/sulbactam were found in studies in Italy and Malaysia (47.5% and 68.5% respectively) (*18,19*).

Historically, carbapenems have been considered the best therapeutic option for infections caused by MDR *A. baumannii*. Recently, carbapenem-resistant *A. baumannii* have been increasing worldwide, reaching an alarmingly high level in some countries, such as Turkey (78%), Islamic Republic of Iran (86%) and India (89.6%). At the same time, *A. baumannii* in Jordan demonstrated high resistance rates to meropenem (73.4–100%), while imipenem showed lower resistance rates (63–73.2%) in general, but this resistance usually varies over time, even at King Hussein Medical Centre, where it was only 6.7% in 2001 (*5–7,15,16,18*). Nevertheless, carbapenems are still considered one of the treatment options for MDR *A. baumannii*, which retains sensitivity to carbapenems. However, *A. baumannii* resistance to imipenem is still low in some studies, even from the same countries that were associated with high resistance rates: Islamic Republic of Iran (26.5%) and India (4.5%) (*20,22*). For carbapenem-resistant *A. baumannii*,

Table 2 Resistance pattern of *Acinetobacter baumannii* isolates from different clinical specimens

Antibiotic	Swab (*n* = 57)		Blood (*n* = 24)		Sputum (*n* = 28)		Urine (*n* = 7)		Total (*n* = 116)		*P*-value
	No.	%	No.	%	No.	%	No.	%	No.	%	
Ceftazidime	56	98.2	23	95.8	28	100.0	7	100.0	114	98.3	0.692
Ciprofloxacin	57	100.0	18	75.0	28	100.0	7	100.0	110	94.8	0.000
Ceftriaxone	57	100.0	24	100.0	28	100.0	7	100.0	116	100.0	–
Colistin	1	1.8	1	4.2	0	0.0	0	0.0	2	1.7	0.692
Cefotaxime	57	100.0	24	100.0	28	100.0	7	100.0	116	100.0	–
Cefepime	56	98.2	23	95.8	28	100.0	7	100.0	114	98.3	0.692
Gentamicin	53	93.0	17	70.8	26	92.9	6	85.7	102	87.9	0.034
Imipenem	56	98.2	22	91.7	28	100.0	7	100.0	113	97.4	0.237
Levofloxacin	57	100.0	18	75.0	28	100.0	7	100.0	110	94.8	0.000
Minocycline	12	21.1	3	12.5	12	42.9	4	57.2	31	26.7	0.015
Piperacillin	56	98.2	23	95.8	28	100.0	7	100.0	114	98.3	0.692
Ampicillin/sulbactam	51	89.5	24	100.0	22	78.6	7	100.0	104	89.7	0.063
Trimethoprim/sulfamethoxazole	47	82.5	20	83.3	18	64.3	3	42.9	88	75.9	0.040
Tetracycline	42	73.7	14	58.3	26	92.9	7	100.0	89	76.7	0.011
Ticarcillin	57	100.0	24	100.0	28	100.0	7	100.0	116	100.0	–
Tobramycin	42	73.7	16	66.7	25	89.3	6	85.7	89	76.7	0.217
Piperacillin/tazobactam	55	96.5	22	91.7	28	100.0	7	100.0	112	96.6	0.396

tigecycline and colistin are 2 of the most frequently used alternative agents according to the literature (*23*).

A. baumannii isolates in our hospital showed high resistance rates to aminoglycosides (87.9% and 76.7% for gentamicin and tobramycin respectively). The gentamicin resistance rate was also in line with the results from Islamic Republic of Iran and India (*15,17,18*). At the same time, the resistance rate was found to be lower (around 60%) in other countries such as south India, Malaysia and Italy. On the other hand, resistance rate of 37.9% and 70.8% for tobramycin and gentamicin respectively were recorded at King Hussein Medical Centre in 2001 (*6,7,19–21*). However, tobramycin resistance from Italy (44.3%) was much lower than in this study and in studies from Malaysia (64.8%) and India (80%) (*18,19,21*).

A. baumannii isolates have been found to have a variable degree of resistance to the sulfamethoxazole/trimethoprim combination, ranging from 59.8% in south India, 80% in Italy and up to 100% in Islamic Republic of Iran (*15,19,20*). In comparison with these previous reports, 75.9% of the *A. baumannii* isolates from the present study were found to be resistant to sulfamethoxazole/trimethoprim, while only 65.6% of the isolates were resistant at our Centre in 2001 (*6*).

The tetracycline resistance rate in this study was 76.7%, which is lower than rates from Malaysia (87%), Italy (93.8%) and Islamic Republic of Iran (100%) (*15,19,21*). On the other hand, the minocycline resistance rate was low in the present study (26.7%), which is similar to what was reported from Italy (21.3%), indicating that minocycline is one of the best antibiotics that can be used in combination with the other anti-*Acinetobacter* antibiotics (*19*).

Tigecycline is a parenteral broad-spectrum bacteriostatic minocycline derivative. It has been used alone or in combination with other

Table 3 Minimal inhibitory concentration (MIC) values for tigecycline in the tested *Acinetobacter baumannii* isolates (*n* = 116)

Tigecycline MIC (mg/L)	No. of isolates	%
≤ 0.5	20	17.2
1.0	27	23.3
2.0	49	42.2
4.0	15	12.9
≥ 8.0	5	4.3

anti-*Acinetobacter* drugs for MDR *A. baumannii*, but with varying degrees of success (*15,18,19,23,24*). According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the United States Food and Drug Administration (FDA) and the CLSI, there are no specific breakpoints for tigecycline as an anti-*Acinetobacter* agent (*21,24,25*). On the other hand, the British Society for Antimicrobial Chemotherapy (BSAC) has previously recommended the ≤ 1 mg/L breakpoint of susceptibility, but recently applied the EUCAST recommendations of "non-species-specific MIC breakpoint of susceptibility = 0.25 mg/L and *R* = > 0.5 mg/L to interpret susceptibility, while other studies recommended ≤ 2 mg/L breakpoints" (*25–27*). However, we considered the AST-XN05 card MIC of ≤ 0.5 mg/L to be the MIC breakpoint of susceptibility, as shown in Table 3. A study from Jordan showed no resistance to tigecycline (0%), even at MIC 1.5–2.0 mg/L (*7*). At the same time, tigecycline resistance in the present study was 17.3%, 59.5% and 82.8% according to the MIC breakpoints of ≤ 2.0 mg/L, ≤ 1.0 mg/L and ≤ 0.5mg/L respectively. Due to the wide range of resistance to tigecycline, there is a growing need for agreed breakpoints of susceptibility to be declared and accepted by CLSI, EUCAST, BSAC, FDA and other institutions. Tigecycline resistance rates were low in studies from Jordan (0%) and Italy (27.5%), moderately high in India (74.8%) and high in this study (82.8%) and one from Islamic Republic of Iran (98%) (*7,5,18,19*).

Colistin is still considered to be the most effective single antibiotic against MDR *A. baumannii*, and is always kept as a last resort (*23*) due to the growing rates of resistance to carbapenems in recent decades (*15,16,19*). At the same time, resistance and treatment failure rates have been increasing with colistin in some countries lately, and therefore different combinations of colistin with other anti-*A. baumannii* antibiotics have been tried, with varying success rates (*23,24*). In the present study the resistance rate of isolates to colistin was very low (1.7%), which is consistent with data reported from Jordan (0%), India (1.2%), Italy (1.2%) and Islamic Republic of Iran (7%) (*7,15,18,19*). However, resistance rates to colistin were as high as 25.9%, 30.6% and 40.7% in Malaysia, Spain and Korea respectively, presumably due to the intensive use of colistin recently (*7,15,21,23,28,29*).

Table 4 Antimicrobial susceptibility of multidrug resistant *Acinetobacter baumannii* isolates (*n* = 116) to various antibiotics tested

Variable	No. of isolates	Susceptibility (%)[c]
Multidrug resistant[a]	90	77.6
Colistin + minocycline	37	31.9
Colistin + tobramycin	1	0.9
Colistin + sulfamethoxazole/trimethoprim	12	10.3
Colistin + ampicillin/sulbactam	6	5.2
Colistin + ampicillin/sulbactam + sulfamethoxazole/trimethoprim	2	1.7
Colistin + sulfamethoxazole/trimethoprim + tobramycin	1	0.9
Colistin + minocycline + ampicillin/sulbactam	1	0.9
Colistin + minocycline + sulfamethoxazole/trimethoprim	9	7.8
Colistin + minocycline + tetracycline	10	8.6
Colistin + minocycline + tobramycin	2	1.7
Colistin + minocycline + tetracycline + tobramycin + sulfamethoxazole/trimethoprim	9	7.8
Pandrug resistant[b]	10	8.6
Not susceptible to any of the tested antibiotics	2	1.7
Susceptible only to colistin	8	6.9

[a]Resistant to imipenem plus 3 or more different antibiotic classes.; [b]Resistant to all tested antibiotics or only susceptible to colistin; [c]Percentage of total number of isolates tested (n = 116) susceptible to colistin only.

The extensive use of such broad-spectrum antibiotics as 3rd-generation cephalosporins, quinolones and carbapenems has been associated with emergence of MDR *A. baumannii* (*13–15,18*). Moreover, PDR to all available antibiotics has been reported worldwide, even against colistin, minocycline, tigecycline and sulbactam, which dictates the use of combinations of antibiotics, albeit with variable success rates (*30,31*). The current study reported high MDR resistance rates of *A. baumannii* against most antibiotics tested (77.6%). The highest rates have been reported from Israel (88%), while lower resistance rates (around 72%) were found in Malaysia, USA and south India (*20,21,32*). Finally, the most effective antibiotics against *A. baumannii* according to the current study were colistin (98.3%) and minocycline (73.3%), followed by sulfamethoxazole/trimethoprim (24.1%), then tetracycline and tobramycin (23.3%). Interestingly, tigecycline showed a high resistance rate (82.8%) when we considered the VITEK 2 system AST-XN05 card breakpoints (≤ 0.5 mg/L). However, only 8.6% of our *A. baumannii* isolates were reported to be PDR, which is lower than the south India results (17.2%) (*20*). In addition, the colistin and minocycline combination seems to be the most effective combination theoretically (31.9%), with a good bactericidal activity, as shown in Table 4. The prescription of colistin and minocycline should therefore be guided by the antibiotic protocols and only be ordered by infectious disease specialists in order to minimize the risk of side-effects and rising resistance rates and treatment failure rates (*33*).

The present study had some limitations due to the retrospective study design. Patients' data were missing or incomplete in many cases for data such as age, comorbidity and patient's location. Future studies with larger sample sizes are necessary to take into account other contributing factors such as irrational use of antibiotics, lack of strict application of infection control instructions, isolation measures, patient and staff hygiene and environmental decontamination. Studies are also needed into the prevalence of MDR and PDR in acute care settings, how to distinguish between colonization (which does not require antibiotic treatment) and infections (which might require antibiotics), and to assess the associated costs of treatment and the associated mortality rates.

Conclusions

A. baumannii isolates in Al-Hussein Hospital of Hussein Medical Centre in Amman were found to be highly resistant to almost all tested antibiotics, up to an alarming level, except mainly for colistin and minocycline, which showed relatively low resistance rates. However, the effectiveness and safety of colistin and minocycline need to be thoroughly investigated in the future. Therefore, it is important to create a new well-designed protocols or guidelines for both antibiotic use and isolation measures to help minimize the development and the spread of these MDR and PDR *A. baumannii* isolates in different hospital wards, cross-infection between patients, morbidity and mortality rates and, finally, the cost of treatment. Moreover, protocol-specified reviews of antibiotic susceptibility of all *A. baumannii* isolates is mandatory for escalation or de-escalation of antibiotic use.

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