Susceptibility of the multidrug-resistant nosocomial pathogens isolates in Jordan for the new antimicrobial agents

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Abstract

Background: To study resistance rates of the multidrug-resistant bacteria isolates for the new cephalosporines before their widespread use in Jordan.

Methods: During September 2019 - May 2020, MDR-bacteria isolates were prospectively collected from microbiology laboratories of three hospitals, to investigate their susceptibility to the extended-spectrum β -lactamases-producing *Enterobacteriaceae* (ESBL), *K. pneumoniae*-carbapenemases strains (KPC), carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *P. aeruginosa* (CRPa), carbapenem-resistant *A. baumannii* (CRAb), and Methicillin-resistant *Staphylococcus aureus* (MRSA) were tested. Demographic details for patients were recorded. Antimicrobials evaluated were ceftazidime-avibactam, ceftolozane-tazobactam, and ceftobiprole medocartil.

Results: Non-duplicate 263 MDR clinical isolates were collected from sterile sites; ESBL (128), *P. aeruginosa* (57), MRSA (37), KPC (22), *A. baumannii* (11), and CRE (n = 8). The age was dominated by the older age group (Age > 64, Pearson R = 0.985, $R^2 = 0.969$, P = 0.000). Males were 143 and females 107 (P < 0.000). There were (194) isolate from the wards and (55) were from the ICUs. Sources of isolates were urine (96), blood (36), soft tissues (49), abdomen (24), URT (14), and osteo-skeletal (12). Clinical diagnoses were recorded as follow: urinary tract infection (UTI, 90), Bacteremia (36), Skin and soft tissue infections (SSTI, 45), intraabdominal infection (IAI, 23), pneumonia (17), Uper res-

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piratory tract infection (URTI, 13), osteomyelitis (11), and diabetic foot (6). The susceptibility of the ESBL-producing bacteria was 100% for meropenem, 99% for ceftazidime-avibactam, and 90% for ceftolozane-tazobactam. *P. aeruginosa* was, 73% for ceftazidime-avibactam, 62% susceptible to ceftolozane-tazobactam, 62% for meropenem, and 45% to ceftobiprole. CRE was 38% susceptible to ceftazidime-avibactam and KPC 15%, while ceftolozane-tazobactam susceptibility was zero, and 14% for CRE, and 0% for Ceftobiprole. *A. baumannii* was 13% susceptible to ceftazidime-avibactam, meropenem 9%, and 2% for ceftolozane-tazobactam, respectively.

Conclusion: Ceftazidime-avibactam and ceftolozane-tazobactam may be useful alternatives for the treatment of ESBL-producers and *P. aeruginosa*, though the MDR-bacteria isolates demonstrated few percentage of resistance to the newly introduced agents before their wide spread use in the country.

Keywords

MDR-Bacteria, Ceftazidime-Avibactam, Ceftolozane-Tazobactam, Ceftobiprole Medocartil, Nosocomial Pathogens.

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Introduction

Our region is plagued with multidrug-resistant bacteria (MDR), especially those carrying the acronym "ESKAPE pathogens" including *Enterobacter spp.*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Enterococci spp.*, they comprise the largest burden of the hospital-related infections [1]. The treatment of the MDR bacteria entails the use of the advanced generations antimicrobials and complicated regimens, the need for new antimicrobials is advocated as the old ones are becoming ineffective with an unacceptable high rates of resistance [2-4]. In Jordan, few studies addressed the MDR bacteria, but mostly were for a single microorganism and their molecular patterns in the community individuals and Syrian refugees [5, 6]. However, other studies from the Jordan University Hospital addressed a

10-months incidence of the respiratory MDR *Acinetobacter baumannii* isolates in hospital; ized patients in ICUs and found that their colonization was rarely associated with blood sepsis and mortality. Another study demonstrated from the same hospital showed high occurrence of MDR *P. aeruginosa* isolates carrying blaCTX-M genes, but no specific associations were found between antibiotic resistance, virulence genes and genotypes among the isolates [7, 8]. Also, other Studies from Jordan evaluating the resistance pattern of the nosocomial *Acinetobacter baumannii* infections demonstrated high resistant rates (> 94%) for the third and fourth generations cephalosporines, piperacillin-tazobactam, carbapenems and quinolones, reliable antimicrobials pointed at minocycline and colistin. Additionally, high MRSA rates (31.6%) among *S. aureus* isolates were reported [9, 10].

Battling the resistance patterns of the MDR bacteria with the new antimicrobials, whether as a single molecules like ceftriaxone, ceftazidime, ceftolozane-tazobactam, ceftazidime-avibactam in combinations with β -lactamase inhibitor like ceftolozane-tazobactam and ceftazidime-avibactam were introduced in the North American market and Europe, with a hiatus close to a decade before their introduction into the region and Jordan.

We utilized this opportunity to examine the antimicrobial susceptibility rates of common clinical isolates for some of these agents as they are being sporadically utilized in the regions' hospitals in the recent few years.

Materials and Methods

Settings

This study was conducted in three private hospitals: Jordan Hospital, the Specialty Hospital, and Al Khalidi Hospital, they encompass around 710 beds with 65 ICU beds. The three hospitals are accredited by the international committee for hospital accreditation (JCI), and the local Health Care Accreditation Council (HCAC). The hospitals have a busy schedule with diverse types of services including open-heart surgery, renal transplant, also, Jordan hospital performs liver transplants, in addition to the general surgery, medical, pediatric, obstetrics/gynecology, and other specialty services.

Collection of data

The study has evaluated the susceptibility of the MDR bacteria isolates including the extended-spectrum β -lactamases producing *Enterobacteriaceae* (ESBL), *K. pneumoniae* carbapenemases (KPC), carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *P. aeruginosa* (CRPa), and carbapenem-resistant *A. baumannii* (CRAb) to the relatively new antimicrobials: ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam, and ceftobiprole in Jordan. Meropenem and vancomycin are agents

used in Jordan and the region for the treatment of the gram-negative bacteria and MRSA, respectively, meropenem susceptibility was used as a reference agent for ESBL-producers and *P. aeruginosa* in the evaluation against ceftazidime-avibactam and ceftolozane-tazobactam. Additionally, ceftobiprole medocarbil was compared to vancomycin for MRSA. Bacteria isolates and susceptibilities were identified by VITEK 2 (*BioMerieux* diagnostics system). Some bacterial susceptibilities were performed by E-test and later by Kirby-Bauer diffusion disc due to the limited E-test supplies, besides, the newer antimicrobials were not included in the Vitek 2 software, namely ceftazidime-avibactam, ceftolozane-tazobactam and cefepime. Starting in September 2019 until May 2020, 263 clinical isolates were collected from the microbiology laboratories of the three hospitals with a documented clinical diagnoses, with the characteristics and demographic features for patients. The cephalosporins were not included against VREs (being part of the ESKAPE) because of their lack of the in vivo activity.

Statistical analysis

Susceptibility rates were calculated, and charts were built for visual comparisons. The aim is to test the susceptibility rates and compare the ceftazidime-avibactam and ceftolozane-tazobactam with meropenem, and to compare the ceftobiprole for *P. aeruginosa* with meropenem, and with vancomycin for MRSA, and whether a difference could be made by their introduction considering their local high cost. Non-parametric Z-test was used to calculate the significance of the difference for the binomial variables. Trends were tested by regression analysis.

Results

Non-duplicate 263 MDR clinical isolate were prospectively collected between August 2019 –May 2020 from the microbiology laboratories of the participating hospitals; ESBL (n = 128), *P. aeruginosa* (n = 57),

Table 1. Demographic features and characteristics of patients who had MDR-bacterial infections.

Characteristics	N° of Patients
Age (Years)	
< 21	34
21 – 64	88
>64	125
NA	16
Gender	
Male	143
Female	107
NA	13
MDR and counts	
Extended-spectrum β -lactamase producers	128
K. pneumonia carbapenemases producers	22
Carbapenems-resistant <i>P. aeruginosa</i>	57
Carbapenems-resistant <i>A. baumannii</i>	11
Methicillin-Resistant <i>S. aureus</i>	37
Country of Origin	
Jordan	235
Others	12
NA	16
Hospital location	
Intensive Care Unit	55
Ward	194
NA	14
Specimen source	
Blood	36
Urine	96
Lungs	15
Upper respiratory	14
Skin and muscles	49
Abdomen	24
Osteo-skeletal*	12
Other sources**	3
NA	14

Characteristics	N° of Patients
Infectious diagnosis	
Bacteremia	36
Urinary Tract Infection	90
Pneumonia	17
Upper Respiratory Tract Infection	13
Skin and Soft Tissues Infections	45
Intra-Abdominal Infection	23
Osteomyelitis***	11
Diabetic foot	6
Others	23

MDR: Multi-Drug Resistant.
*: Osteo-skeletal: 11 bone, 1 synovial fluid.
**: Other sources: 1 pressure ulcer, 1 tip of a peripherally inserted central catheter (PICC) and one undefined catheter tip, and the rest were wounds.
***: One patient had MRSA osteomyelitis with bacteremia.

MRSA (n = 37), KPC (n = 22), *A. baumannii* (n = 11), and CRE (n = 8). The age of the patients ranged from 1 to 98 years, dominated by older agegroup (> 64) years (n = 125), followed by the age group 21-64 (n = 88), and 34 isolates were for patients less than 21 years old (PearsonR = 0.985, $R^2 = 0.969$, $P = 0.000$). Males were 143 versus 107 females ($P < 0.000$). Most isolates came for Jordanian (235) and 28 for patients from other countries. Clinical isolates from the wards were 194 and 55 were from the ICUs. Sources were from urine 96, blood 36, skin and muscle 49, abdomen 24, URT 14, and osteo-skeletal 12. The clinical diagnoses from whom the MDR isolates were collected: UTI 90, bacteremia 36, SSTI 45, IAI 23, pneumonia 17, URTI 13, osteomyelitis 11, and diabetic foot 6 (**Table 1**).

Bacteria isolated from the clinically diagnosed patients were as follows: ESBL-producers were frequently isolated from UTI (n = 69), bacteremia (n = 16), SSTI (n = 14) and IAI (n = 13). *P. aeruginosa* was mostly isolated from SSTI (n = 14), UTI (n = 12) and pneumonia (n = 8). KPC/CRE UTI (n = 8), SSTI (n = 5), pneumonia (n = 5), URTI (n = 3) and 2 isolates for other diagnoses. MRSA was isolated from SSTI (n

= 14) and bacteremia (n = 10), Osteomyelitis (n = 4), IAI (n = 4) and 2 isolates from the other diagnoses (Figure 1).

Figure 1: Absolute counts of the MDR-bacteria and the relative distribution according to the infectious diagnoses.

KPC/CRE (n = 26) 8 were CRE. ESBL (n = 90). MRSA (n = 36). P. aeruginosa (n = 53). KPC/CRE: K. pneumoniae-carbapenemases/ Carbapenem-resistant enterobacteriaceae. ESBL: Extended-spectrum β -lactamase producing enterobacteriaceae. MRSA: Methicillin-resistant S. aureus. IAI: Intraabdominal infections. SSTI: Skin and soft tissues infection. URTI: Upper respiratory tract. UTI: Urinary tract infection

The susceptibility of the ESBL-producing bacteria was 100% for meropenem, 99% for ceftazidime-avibactam, and 90% for ceftolozane-tazobactam. P. aeruginosa was 73% susceptible to ceftazidime-avibactam, 62% to ceftolozane-tazobactam, 62% for meropenem, and 45% to ceftobiprole. CRE were 38% (n = 8) susceptible to ceftazidime-avibactam and KPC 15% (n = 20), KPC (n = 22) were 0% susceptible for ceftolozane-tazobactam and 14% for CRE (n = 7) and 0% for Ceftobiprole Medocartil (n = 20). A. baumannii was 13% susceptible to ceftazidime-avibactam, meropenem 9%, and 2% for ceftolozane-tazobactam, respectively (Figure 2).

There were 62 MIC-tested isolates with ceftazidime-avibactam: ESBL-producing Enterobacteriaceae (n = 37), all isolates were susceptible and 89% were $\leq 0.5 \mu\text{g}/\text{ml}$. P. aeruginosa (n = 20): 80% were susceptible ($< 8 \mu\text{g}/\text{ml}$) and 20% were resistant with MIC $> 256 \mu\text{g}/\text{ml}$. Five KPC isolates were sensitive with MIC $\leq 2 \mu\text{g}/\text{ml}$. There were

Figure 2: Susceptibility of the MDR-bacteria to the evaluated antimicrobials in the study. Numbers on the Y-axis refer to the absolute number for each tested MDR-bacteria, note the different Y-scales.

CRE: carbapenem-resistant enterobacteriaceae. KPC: K. pneumoniae carbapenemases. ESBL: extended-spectrum β -lactamase producing enterobacteriaceae. R: resistant. S: susceptible.

Figure 3: The Minimum inhibition concentration (MIC) of some evaluated antimicrobials. Numbers on the Y-axis refer to the absolute number for the tested MDR bacteria, note the different scale for meropenem

CRE: carbapenem-resistant enterobacteriaceae. ESBL: extended-spectrum β -lactamase producing enterobacteriaceae.

74 MIC-tested isolates with ceftolozane-tazobactam: ESBL-producing Enterobacteriaceae (n = 40) showed MIC distribution < 1 µg/ml and one isolate was 16 µg/ml. *P. aeruginosa* (n = 30) isolates, 63% with MIC ranged 0.25 – 1.5 µg/ml, and resistance was 37% with MIC $\geq$ 4, and 23% of the isolates were > 256 µg/ml. There were 55 MIC-tested isolates against Ceftobiprole medocartil: MRSA (n = 33) MIC distribution was $\leq$ 2 µg/ml (EUCAST breakpoint) in 91% of the isolates [11]. *P. aeruginosa* isolates (n = 19), 95% were susceptible with MIC $\leq$ 1.5 µg/ml except one isolate, and three ESBL-producing Enterobacteriaceae with low MIC (< 0.1 µg/ml).

There were 111 isolates tested by meropenem: ESBL-producing Enterobacteriaceae (n = 77), all were susceptible with MIC $\leq$ 0.1 µg/ml. *P. aeruginosa* (n = 34) isolates with 50% of the isolates have MIC $\leq$ 4 µg/ml (Figure 3). The breakpoints for susceptibility was according to CLSI (clinical and laboratory standards-USA) except where indicated.

Discussion

In our study the MDR-bacteria were dominant in the older age group (P = 0.000), a well-observed phenomenon as the elderly patients suffer from more comorbidities, longer hospital stay, more interventions, and more antimicrobial agents exposure [12]. The current burden of the MDR bacteria in Jordan requires newer agents for the treatment of the seriously sick patients; empirically and appropriately, inexorably, the currently used broad-spectrum antimicrobials started to lose their hold, leading to failure to meet the appropriateness measure with the worst outcome [13].

The gram-negative activity of meropenem was compared with the newer agents, ESBL-producing Enterobacteriaceae were 100% susceptible with 100% MIC distribution < 1 µg/ml, meanwhile ceftazidime-avibactam was active against 99% of the isolates, and the MIC of 37/37 (100%) tested

isolate were $< 1.5 \mu\text{g}/\text{ml}$, ceftolozane-tazobactam 92% susceptible and 95% of the MIC were $< 2 \mu\text{g}/\text{ml}$, those findings are consistent with an earlier published report [14]. Parenthetically, one would use here an equally active and less costly agent on prescribing an antimicrobial with a proper dosing regimen: a cost-effective approach [15].

Pseudomonas aeruginosa was 46% susceptible to meropenem, with 44% of the MIC were $< 4 \mu\text{g}/\text{ml}$, 70% for ceftazidime-avibactam tested isolates were susceptible and 75% with MIC $< 4 \mu\text{g}/\text{ml}$, ceftolozane-tazobactam 62% susceptible and 63% with MIC $\leq 4 \mu\text{g}/\text{ml}$, and ceftobiprole medocartil 45% susceptible and 63% MIC $< 4 \mu\text{g}/\text{ml}$. Compared with the other two relatively new agents i.e. ceftazidime-avibactam and ceftolozane-tazobactam, ceftobiprole did not show a good activity against *P. aeruginosa* prior to their introduction to the local market [16].

Though the CRE numbers were very low to have a decent analysis they gave an idea on the three tested antimicrobial agents: KPC was 15% susceptibility to ceftazidime-avibactam and CRE 38%, ceftolozane-tazobactam was 0% for KPC and CRE 14%, and 0% for Ceftobiprole Medocartil, all agents are not trustable for the empiric or the definitive use in this regard. USA-based reports for septic patients caused by CRE or KPC and were treated with ceftazidime-avibactam monotherapy or in combination were viewed, they showed some promise [17, 18]. Hitherto, it was not validated by a prospective randomized trial.

Acinetobacter baumannii was 25% susceptible to ceftazidime-avibactam, 8% to ceftolozane-tazobactam, and meropenem 9%; discouraging their empiric use in units suffering from high *Acinetobacter* infection rates, this is consistent with Po-Ren Hsueh et al., when they demonstrated that the recent cephalosporins and the new associated molecules were not sufficient to be used for the treatment of CRAB except for the newer agent cefiderocol [19].

The newly introduced anti-MRSA cephalosporines in the country and the region showed some increased resistance in African countries. Our data demonstrated that ceftobiprole was 91% active against MRSA with 76% of strains in the MIC range $0.38 - 2 \mu\text{g}/\text{ml}$. Both agents are currently available in the country but ceftobiprole dominated the seen although both agents can be used interchangeably [20].

Conclusion

Our isolates were assessed at a time with a very low prescribing rates of the three newer cephalosporines, thus capturing the opportunity to evaluate the activity of those agents before their use becomes a common practice. Meropenem demonstrated a preserved anti-ESBL activity, making it difficult to recommend other agents especially with cost concerns, unless an urgent need is considered to utilize a carbapenem-sparing attitude. The new cephalosporines with β -lactamases inhibitor combinations did not meet the need for treating *A. baumannii*, though ceftazidime-avibactam followed by ceftolozane-tazobactam were reliable agents for the use against *Pseudomonas aeruginosa*. Another point of major interest is the ongoing imprudent antimicrobial use paved the way for the resistance to the newer agents denoting some cross-resistance with the previous third and fourth generations cephalosporines, this is occurring at a time before their use in the market.

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Disclosure

Jamal Wadi Al Ramahi receives honoraria for lectures, seminars, webinars, and advisory boards for Pfizer, Hikma, Dar Al Dawa, and MSD.

Conflict

All other authors do not have conflicts.

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