Evaluation of *in vitro* activity of ceftazidime/avibactam and ceftolozane/tazobactam against ESBL-producing Enterobacterales isolated from Intensive Care Units from Qatar

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Abstract

Objectives: Extended-spectrum β-lactamases (ESBLs) mechanism of resistance in Enterobacterales leads to poor clinical outcomes. Ceftazidime/avibactam and ceftolozane/tazobactam are broad-spectrum antimicrobials that are effective against multidrug-resistant organisms with regional variations. This study aims to evaluate the antimicrobial susceptibility test (AST) for both combinations against ESBL-producing Enterobacterales isolated from intensive care units (ICUs) in tertiary hospitals from Qatar.

Methods: A total of 629 Enterobacterales isolates from ICUs were screened for ESBL production using BD-Phoenix™ confirmed by double-disk potentiation, while ESBL-genes were detected by PCR. The ASTs for ceftazidime/avibactam and ceftolozane/tazobactam were assessed by MIC test strips. A single isolate that was resistant to both combinations underwent whole-genome sequence.

Results: The prevalence of ESBL-producing Enterobacterales isolated from ICUs is 17.3% (109/629) with predominance of *Klebsiella pneumoniae* (51.4%) and *Escherichia coli* (34.9%). The susceptibility of ceftazidime/avibactam and ceftolozane/tazobactam against ESBL-producers was 99.1% (108/109), the majority of which (74.3%) had MICs <0.5 for both combinations. The predominant ESBL-gene was $bla_{\text{CTX-M}}$ (66.1%) while a single isolate that was resistant to both combinations harbored multiple ESBL resistant-genes including $bla_{\text{VEB-5}}$ and $bla_{\text{VIM-2}}$.

Conclusions: ESBL producing Enterobacterales isolated from ICUs were predominant by *K. pneumoniae* and *E. coli*, mainly harbouring $bla_{\text{CTX-M}}$. Isolates were highly susceptible to ceftazidime/avibactam and ceftolozane/tazobactam suggesting potential alternatives to current available therapeutic options.

Keywords: Enterobacterales, ESBL, Antimicrobial Resistance, ceftazidime/avibactam, ceftolozane/tazobactam.

Introduction

In healthcare, the management of infections secondary to multidrug-resistant organisms (MDROs) that encompasses Gram-negative bacteria (GNB) is a global challenge not only because of limited available treatment

options but also for their associated significant morbidity and mortality as well as the substantial cost of management [1, 2].

In secondary and tertiary hospitals, the ultimate antimicrobial resistance (AMR) is encountered at intensive care units (ICUs) where the critical nature of patients' cohort, concurrent comorbidities, invasive procedures, prior colonization as well as environmental exposure to MDROs that is accelerated by high antibiotics consumption are inevitable acquisition hazards [3, 4]. Over the past decade, internal microbiological surveillance and monitoring of GNB particularly Enterobacterales from Qatar established alarmingly rising trends of AMR particularly for extended-spectrum β-lactamases (ESBLs) in line with shifting regional epidemiology [5, 6]. In critical care settings, typical recommended approach for the management of ESBL-producing Enterobacterales is the treatment with carbapenems particularly if there is an associated serious invasive or high inoculum disease [7]. The concern of diminishing limited treatment options and the development of accumulated resistance led infection specialists to seek alternatives carbapenem sparing antimicrobial therapy. Ceftazidime/avibactam and ceftolozane/tazobactam, are β-lactam/β-lactamase inhibitors (BLBLIs) combinations that are approved by both the United States Food and Drug Administration (US-FDA) and the European Medicines Agency (EMA) demonstrating comparable or superior activity against MDROs particularly in GNB for the treatment of complicated urinary tract and intra-abdominal infections as well as infections secondary to hospital or ventilation associated pneumonia [8]. Avibactam is a non-BLBLI that potently inhibits most but not all class A ESBLs, class C (including AmpC enzymes), and some of class D β-lactamases [9]. Furthermore, due to its different mode of action, it has been considered as one of the most effective BLBLIs displaying a broader inhibitory range and spectrum [10]. On the other hand, ceftolozane is a novel cephalosporin that is not affected by OprD loss which is a weak substrate for drug efflux pump mechanism rendering the drug exhibiting less affinity for hydrolysis by AmpC and hence better efficacy [11]. To expand its efficacy, the addition of the classical β-lactamase inhibitor, tazobactam broadened its activity to include most ESBL-producing GNB [12].

The presented study aims mainly to evaluate the antimicrobial activity of ceftazidime/avibactam and ceftolozane/tazobactam against109 ESBL-producing Enterobacterales isolates from ICUs in Qatar [13], describe its microbiological characteristics as well as underlying genomic resistance profiles.

Methods

The research project was approved by the Institutional Review Board at Hamad Medical Corporation (HMC), which complies with international ethical standards and regulations (Protocol no. RC/75813/2013). The study was conducted on routine specimens processed by the Microbiology Division, Department of Laboratory Medicine and Pathology, HMC, Qatar. All ESBL positive samples were collected prospectively over one year period from patients admitted to all ICUs (medical 29%, surgical 29%, trauma 16%, pediatric 16%, and neonatal 10%) at HMC. Out of 629 Enterobacterales tested isolates, the overall prevalence of ESBL-producers was 17.3% (109/629) which was collected from 87 different patients between 1st of November 2012 to 31st October 2013. Isolated pathogens were collected from a variety of clinical samples that comprise respiratory 35.8% (n = 39), blood 27.5% (n = 30), urine 24.8% (n = 27), fluids 6.4% (n = 7), and others 5.5% (n = 6).

The study definitions recognized duplicates of the same species of bacteria as isolates from the same patient displaying identical antimicrobial susceptibility patterns when isolated within 30 days regardless of sample sites which were considered repetitive and excluded. Isolates with major differences in antimicrobial susceptibilities were counted as new even within the defined 30 days' time frame. The single isolate that was resistant to ceftazidime/avibactam and ceftolozane/tazobactam underwent standard diagnostic work-up then stored at – 80 °C pending further genomic analysis.

Microbiological identification and antimicrobial susceptibility tests (AST) were performed using BD Phoenix™ automated system according to manufacturer recommendations. Samples tested positive for ESBL by Phoenix or showed a MIC of >8 μg/mL for 3rd generation cephalosporins or aztreonam were consequently confirmed by a double-disk potentiation test with ceftazidime, amoxicillin/clavulanic acid, ceftriaxone, and cefoxitin antibiotics interpreted as described [14]. AST and minimum inhibitory concentration (MIC) for ceftazidime/avibactam and ceftolozane/tazobactam were performed using MIC Test Strips (Liofilchem®, Diagnostics, Italy), *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, and *Pseudomonas aeruginosa* ATCC 27853 were used as controls. Susceptibility reporting was based on the CLSI recommendations [14]. Since there were no recommended intermediate susceptibility categories available for ceftazidime/avibactam against Enterobacterales, isolates were therefore described as susceptible if the MIC was ≤ 8 mg/L and non-susceptible if

the MIC was >8 mg/L as outlined in supplementary S1.[14] To achieve consistency, intermediate and resistant categories were grouped as non-susceptible for all reported antimicrobial agents.

Bacterial DNA extraction and detection of ESBL resistance genes were performed through an in-house PCR techniques, using the boiling lysis methods [15]. Performed PCR reactions for the ESBL genes were (TEM, SHV and CTX-M-1) using protocols that were previously described [16].

Whole-genome sequencing (WGS) was performed to study isolates genomic relationship for annotate antibiotic resistance genes (ARGs). Extracted DNA was sent to GATC Service (Eurofins Genomics, Germany) for sequencing using Illumina HiSeq 2000 system (Illumina, San Diego, California). Genes were assembled using SPAdes, Version 3.13.0 (https://cab.spbu.ru/software/spades/) while Multi-locus sequence typing (MLST) of the described resistant isolate of *E. coli* was performed on MLST server 1.8 provided (https://cge.cbs.dtu.dk/services/MLST/). ARGs were annotated using Comprehensive Antibiotic Resistance Database (CARD), Version 1.2.0 (https://card.mcmaster.ca/).

Patients and isolates demographics as well as antimicrobial susceptibility patterns of ESBL-producing Enterobacterales including resistant genes were presented as numbers and percentages (%) using Stata statistical software (Stata Corp LLC, College Station, Texas version 16.1).

Results

Out of 629 Enterobacterales tested isolates, 17.3% (109/629) were ESBL positive, collected from 87 different patients predominantly identified as *Klebsiella pneumoniae* (51.4%) and *E. coli* (34.9%) while others were only 13.7%. The majority of isolates were from males 65 (59.6%), ranging between one month - 86 years of age. According to age groups, the majority were adults 57 (52.3%) between 14–65 years, followed by pediatric < 14 years as well as geriatric 26 (23.9%) > 65 year of age.

The predominant identified ESBL-producing genes were $bla_{\text{CTX-M-1}}$ (66.1%) followed by bla_{SHV} (53.2%) and bla_{TEM} (40.4%). All three β-lactamase genes (TEM, SHV, and CTX-M-1) were detected in 46.4% of *K. pneumoniae* isolates, while two genes (SHV/CTX-M-1) were present in 17.8% of *K. pneumoniae* and 2.6% of *E. coli* isolates, with TEM/CTX-M-1 being present in 18.4% of *E. coli* and 7.1% of *K. pneumoniae* and TEM/SHV being detected in only 5.3% of *E. coli* isolates.

The activity of ceftazidime/avibactam and ceftolozane/tazobactam against 109 ESBL-producing Enterobacterales isolates demonstrated 99.1% (108/109) susceptibility for both combinations. Only meropenem showed higher susceptibility at 100% followed by imipenem at 99.1% while ertapenem and amikacin susceptibility was 97.2%. Other antimicrobial demonstrated moderate to low susceptibility rates with 78% for piperacillin/tazobactam, 64% for tigecycline, 60% for ciprofloxacin, and 38.5% for co-trimoxazole while as predicted cephalosporin had high-level resistance (99.1% for ceftriaxone and 93.6% for cefepime) (Figure 1). Furthermore, most of the ESBL-producing Enterobacterales were highly susceptibility to ceftazidime/avibactam at low MICs ($MIC_{50/90}$ 0.19/0.38 µg/ml) and ceftolozane/tazobactam ($MIC_{50/90}$ 0.38/1 µg/ml) (Table 1), with the majority of isolates demonstrating MICs < 0.5 (81, 74.3%) (Table 2). The additional microbiological and molecular characterization including susceptibility testing results are shown in supplementary S1.

Figure 1: Antimicrobial susceptibility results for ceftazidime/avibactam, ceftolozane/tazobactam, and comparator agents against clinical ESBL-producing Enterobacterales isolates from Qatar. AMC, amoxicillin/clavulanic acid; AMK, amikacin; CIP, ciprofloxacin; CRO, ceftriaxone; C/T, ceftolozane/tazobactam; CZA, ceftazidime/avibactam; ERT, ertapenem; FEP, cefepime; FOX, cefoxitin; IMP, imipenem; GEN, gentamicin; MEM, meropenem; TGC, tigecycline; TZP, piperacillin/tazobactam; TOB, tobramycin

Table 1: Minimum inhibitory concentration for ceftazidime/avibactam and ceftolozane/tazobactam against 109 clinical ESBL producing- Enterobacterales isolates collected from intensive care units, Hamad Medical Corporation, Qatar

Organism	Number of isolates	Antibiotic	Range	Number of Susceptible isolates (%)	MIC50	MIC90
	55	CZA	0.094-0.75	55 (100)	0.25	0.38

Klebsiella pneumoniae ssp pneumoniae		C/T	0.25-1.5	55 (100)	0.38	1
Escherichia coli	38	CZA	0.064-256	37 (97.4)	0.125	0.38
		C/T	0.19-256	36 (94.7)	0.38	0.75
Enterobacter aerogenes	4	CZA	0.094-0.25	4 (100)	0.19	0.25
		C/T	0.38-0.5	4 (100)	0.38	0.5
Enterobacter cloacae	4	CZA	0.094-0.19	4 (100)	0.094	0.19
		C/T	0.19-0.25	4 (100)	0.25	0.25
Serratia marcescens	2	CZA	0.02-0.125	2 (100)	0.02	0.125
		C/T	0.19	2 (100)	0.19	0.19
Citrobacter braakii	1	CZA	0.25	1 (100)	0.25	0.25
		C/T	0.75	1 (100)	0.75	0.75
Citrobacter freundii	1	CZA	0.064	1 (100)	0.064	0.064
		C/T	0.38	1 (100)	0.38	0.38
Citrobacter amalonaticus	1	CZA	0.125	1 (100)	0.125	0.125
		C/T	0.19	1 (100)	0.19	0.19
Klebsiella oxytoca	1	CZA	0.125	1 (100)	0.125	0.125
		C/T	0.38	1 (100)	0.38	0.38
Klebsiella pneumoniae ssp ozaenae	1	CZA	0.094	1 (100)	0.094	0.094
		C/T	0.25	1 (100)	0.25	0.25
Proteus penneri	1	CZA	0.047	1 (100)	0.047	0.047
		C/T	1	1 (100)	1	1
Total	109	CZA	0.02-256	108 (99.1%)	0.19	0.38
		C/T	0.19-256	108 (99.1%)	0.38	1

MIC; minimum inhibitory concentration.

Amongst the 109 identified ESBL-producing Enterobacterales only one *E. coli* isolate (0.9%) was completely resistant to both ceftolozane/tazobactam and ceftolozane/tazobactam, with MIC > 256 (Table 1). The resistant isolate was collected from peritoneal fluid of a fatal case of complicated intra-abdominal infection, which was subsequently identified as sequence type ST38. Genomic data analysis revealed that the resistant isolate possessed different ARGs including 11 different β-lactamase genes from all classes; Class A ESBL (CTX-M-1 and VEB-5), Class B metallo-β-lactamase (MBL) including *bla*$_{\text{VIM-2}}$, class C β-lactamase including *bla*$_{\text{PDC-3}}$. Class D β-lactamase such as *bla*$_{\text{OXA-4}}$, *bla*$_{\text{OXA-10,}}$ and *bla*$_{\text{OXA-486}}$ (Table 3).

Discussion

Antimicrobial Resistance (AMR) is a global healthcare challenge with ominous outcomes. Its ultimate challenge is witnessed at critical care units where the majority of the risk factors culminate such as a hazardous environment, vulnerable host, and highly resistant pathogens [17]. In critical care settings, such as at ICUs, one of the foremost challenges of MDROs is infections secondary to GNB particularly ESBL-producing Enterobacterales being resistant to most antimicrobials' classes including most β-lactam penicillins, BLBLIs as well as cephalosporins [17, 18]. To overcome such hurdles, last decades witnessed an exponential reliance on carbapenems to combat the growing problem of ESBL-producing Enterobacterales to the point of being the *sine qua non* for its management [17]. At critical care settings, infections secondary to ESBLs are classically managed with carbapenems especially when encountered in the context of invasive or high burden disease [17, 19]. In complicated ESBL infections, randomized control trials demonstrated superiority of carbapenems over comparators including BLBIs [19]. To overcome the growing problem, new antibiotics regimens such as ceftazidime/avibactam and ceftolozane/tazobactam have been sought to circumvent classical resistance mechanisms [8]. Following observing the promising results of ceftazidime/avibactam and ceftolozane/tazobactam against GNB, there have been several global studies to evaluate its spectrum for both *in-vitro* and *in-vivo* efficacy particularly amongst highly resistant strains including ESBL producers with regional variations [20-25].

Over the last two decades, there has been a significant upwards trend in the epidemiology of infections secondary to ESBL-producing Enterobacterales. A study conducted in 2010 from the same institution of 450 episodes of invasive bacteremia, demonstrated 61% prevalence of GNB, the majority of which were *E. coli and K. pneumoniae* being ESBL producers in 27.8% and 17.9% respectively [26]. To comprehend the scale of the problem at the same institution, results of culture-positive complicated urinary tract infections collected from adult patients admitted to surgical ICUs over 10 years period demonstrated 36% of isolated pathogens were ESBLs [27]. Because of the escalating trend and paucity of options to treat MDROs, healthcare leaders in the Gulf Cooperation Council (GCC) countries recognized the problem as a priority which necessitated interregional collaboration to combat growing challenges [28].

Of note, in our study, 99.1% of ESBL isolates were highly susceptible and most of isolates (74.3%) exhibited MIC < 0.5 for both ceftazidime/avibactam and ceftolozane/tazobactam (Table 2). Notably, the observed high-level susceptibility for ceftazidime/avibactam and ceftolozane/tazobactam against ESBL-producing Enterobacterales isolates collected from prospective critical care clinical cases, pre-dates the introduction of these agents into clinical practice in Qatar. This microbiological evaluation suggests these novel agents might be rational empirical treatment options sparing carbapenems.

Table 2: Comparison of minimum inhibitory concentration for ceftazidime/avibactam vs ceftolozane/tazobactam against 109 clinical ESBL-producing Enterobacterales isolates from Qatar.

Antibiotic		**Ceftolozane/tazobactam**					
	MIC	**<0.25**	**<0.5**	**<0.75**	**<4**	**>256**	**Total**
Ceftazidime/avibactam	**<0.1**	13 (11.92%)	6 (5.50%)	1 (0.92%)	1 (0.92%)	0	21 (19.27%)
	<0.25	7 (6.42%)	13 (11.92%)	0	0	0	20 (18.34%)
	<0.5	5 (4.59%)	37 (33.94%)	14 (12.84%)	7 (6.42%)	0	63 (57.80%)
	<0.75	0	0	0	3 (2.75%)	0	3 (2.75%)
	<1	0	1 (0.92%)	0	0	0	1 (0.92%)
	>256	0	0	0	0	1 (0.92%)	1 (0.92%)
	Total	25 (22.94%)	57 (52.29%)	15 (13.76%)	11 (10.09%)	1 (0.92%)	109 (100%)

Distinctively, our findings are different from other regional studies where ceftazidime/avibactam demonstrated superior activity when compared to ceftolozane/tazobactam against ESBL-producer (Table 4), which suggests a potential correlation of embedded ESBL resistance genes not demonstrated in our study because of paucity of resistant isolates (Table 3) [29].

Table 3: Genotypic profiles of different β-lactamase enzymes detected among ESBL-producing *E. coli* isolated from Hamad Medical Corporation, Qatar.

Resistance gene	**Gene family**	**% of gene identity**
CTX-M-15	Class A β-lactamase	100

VEB-5	Class A β-lactamase	100
VIM-2	Class B β-lactamase	100
E. coli ampC	Class C β-lactamase	97.88
E. coli ampC1	Class C β-lactamase	99.31
E. coli ampH	Class C β-lactamase	99.22
CMY-42	Class C β-lactamase	100
PDC-3	Class C β-lactamase	100
OXA-10	Class D β-lactamase	100
OXA-4	Class D β-lactamase	100
OXA-486	Class D β-lactamase	100

Table 4: Summary of studies comparing *in-vitro* activity of ceftazidime/avibactam and ceftolozane/tazobactam against ESBL-producing Enterobacterales form different geographical regions worldwide.

Study	Geographic location	Susceptibility testing method	Inclusion Criteria	Collection years	Number included	Number (%) Susceptible to MEM
Alatoom *et al*, 2017	Abu Dhabi, United Arab Emirates	Etest	Resistant to ≥1 agent from ≥3 antimicrobial classes	2015-2016	31	15 (48.4%)
Sader et al., 2020	70 medical centers, USA	Broth microdilution	ESBL producing Enterobacterales from patients hospitalized with pneumonia	2017–2018	285	283 (99.3%)
Viala et al., 2019	Montpellier, France	Etest	3rd G cephalosporin resistant Enterobacteriaceae	2017	62	NA
Araj et al., 2020	Beirut, Lebanon	MIC gradient Strip Test	MDR and ESBLs *E. coli and K. pneumonia*e	2017-2018	199	NA
Hirsch et al., 2020	Boston, MA; and, Philadelphia, PA	Broth microdilution	carbapenem-susceptible (meropenem MIC ≤ 1 mg/L),	2013-2016	119	119 (100%)

CZA, ceftazidime/avibactam; C/T, ceftolozane/tazobactam; MDR, multi-drug resistant; MEM, meropenem; NS, non-susceptible
**All studies reported the isolates as susceptible if the MIC was ≤ 8 mg/L for ceftazidime/avibactam and ≤4 mg/L for ceftolozane/tazobactam*

Regionally, the high volume of travel coupled with population diversity and high antibiotic consumption are contributing factors towards the rising trends of ESBLs in GNB to the point of being a major healthcare challenge. The escalating problem started initially as an epidemic then reached an endemic state which necessitates exploring other alternative management options [6, 30].

While examining molecular and genomic results, the observation that $bla_{\text{CTX-M}}$ in conjunction with bla_{SHV} and bla_{TEM} are the main ARGs for ESBL-producing Enterobacterales are in line with regional and global molecular data as well as emphasizes the role of cephalosporins as the main driving resistance precipitant [5, 25, 31]. In Qatar, the molecular epidemiology of Enterobacterales from the pediatric population follows the same trends in the region when a large study of 327 sequenced ESBL producers from clinical samples at the largest children

hospital in the region demonstrated dominance of *E. coli and K. pneumoniae* as main pathogens with predominance of $bal_{CTX\text{-}M\text{-}1}$ and coproduction of $bla_{OXA\text{-}1}$ and $bla_{TEM\text{-}1B}$ as ARGs [32]. In contrast, in the adults' population, there are no detailed recent studies to evaluate the wider molecular epidemiology of ESBL in the country but the study of 149 non-repetitive carbapenem-resistant Enterobacterales confirmed regional preponderance of bla_{NDM} and bla_{OXA48} [33].

Not surprisingly, following undergoing WGS, the only concomitant isolate resistant to both ceftazidime/avibactam and ceftolozane/tazobactam harboured multitude of different ARGs.

The ESBL-producing *E. coli* which belonged to ST38 possessed β-lactamase genes from all classes as shown in Table 3. Intriguingly, the detailed study demonstrated the presence of $bla_{VIM\text{-}2}$ MBL which is known to play a fundamental role in ceftazidime/avibactam and ceftolozane/tazobactam resistance [34]. In addition to the endemic class A $bla_{CTX\text{-}M}$ the resistant isolate also harboured $bla_{VEB\text{-}5}$, which was initially detected in *E. coli* in the USA (GenBank accession number EF420108). The ARG, bla_{VEB} confers high-level resistance to cephalosporins as well as monobactams and has been shown to inactivate ceftolozane/tazobactam [35]. However, $bla_{VEB\text{-}5}$ is known to be inhibited by avibactam which restored the MIC of ceftazidime from 256 µg/ml to 2 µg/ml for ceftazidime/avibactam combination [36]. In addition to that, the resistant isolate has multiple underlying ARGs including $bla_{PDC\text{-}3}$ (AmpC), which drives ceftolozane/tazobactam resistance [37] as well as class D β-lactamases $bla_{OXA\text{-}10}$, which has recently reported to enhance ceftolozane/tazobactam and ceftazidime/avibactam resistance [38].

Despite its wide mechanism of action against MDROs including class A, C, and D β-lactamases, both ceftazidime/avibactam and ceftolozane/tazobactam remain vulnerable when encountering embedded class B β-lactamases such as the potent carbapenemase $bla_{VIM\text{-}2}$ MBL as in our case [25, 39]. Although there have been some developed molecular tests to screen for ceftazidime/avibactam and ceftolozane/tazobactam resistance, the current recommendations remain to interpret activity through the golden routes of ASTs [40].

As a consequence, from our study, the prime recommendation is the urgent need for clinical evaluation of the novel antibiotics as alternative therapeutic option for MDROs including ESBLs particularly in critical care settings. This can be certainly strengthened by surveillance and monitoring mechanisms to evaluate the prevalence of AMR in the region.

Conclusion:

ESBL-producing Enterobacterales represent a significant threat to healthcare, particularly in critical care settings. MDROs such as *K. pneumoniae* and *E. coli* harbouring multiple ARGs continue to predominate. Promising high *in-vitro* antimicrobial susceptibility to ceftazidime/avibactam and ceftolozane/tazobactam against ESBLs producing Enterobacterales suggest plausible alternatives management options to overcome the growing resistance problem.

Abbreviation

ARGs: Antibiotic resistance genes; AMR: Antimicrobial resistance; BLBLIs: β-lactam/β-lactamase inhibitors; CLSI: Clinical Laboratory Standards Institute; ESBL: Extended-spectrum β-lactamase; GNB: Gram-negative bacteria; HMC: Hamad Medical Corporation; ICUs: Intensive care units; MBL: Metallo-β-lactamase; MIC: Minimum inhibitory concentration; MDROs: Multidrug resistant organisms; ST: Sequence type; WGS: Whole-genome sequencing

Authors' contributions

MAS, EBI, MAA, AA, and HAH conceived and designed the study and drafted the manuscript. MAS, JMH, AHA, and MAA performed the experimental work. MAS, JD, and HAH analyzed the data. All authors read and approved the final manuscript.

Declarations

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Ethics approval and consent to participate

This study was approved by the Research Ethics Committee (Protocol number. RC/75813/2013) at Hamad Medical Corporation, Doha, Qatar.

Consent for publication

The findings achieved herein are solely the responsibility of the author[s]. The funders were not involved in the conduct of the study, the preparation of the manuscript or the decision to submit the manuscript for publication.

Availability of data and material

We are disclosing that strictest confidence was maintained for data collection as well as access and application in the study. Data were never shared at any level with any individuals not authorized to access research material. Data were only available upon request by the authors following permission from the Medical Research Center at HMC. We fully understand that the use of confidential data for personal purposes is prohibited.

Competing interests

The authors declare that they have no competing interests

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Table S1. Microbiological characteristics, molecular characterization, and susceptibility testing results for 109 ESBL-producing Enterobacteriaceae isolates.

Isolate number	Collection m-y	Organism	Location	Specimen Type	Disk confirmation test	Molecular Results			Antimicrobial susceptibility test (MIC)	
						SHV	TEM	CTX M1	CZA	C/T
1	Nov-12	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Sputum	Positive	Negative	Negative	Positive	0.25	0.75
2	Nov-12	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Urine	Positive	Positive	Positive	Positive	0.25	0.5
3	Nov-12	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Sputum	Positive	Positive	Positive	Positive	0.75	1
4	Nov-12	*Escherichia coli*	SICU	Wound Swab	Positive	Negative	Negative	Positive	0.125	0.38
5	Nov-12	*Serratia marcescens*	MICU	Blood	Positive	Negative	Negative	Negative	0.125	0.19
6	Nov-12	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Endotracheal Tube Secretion	Positive	Positive	Negative	Negative	0.19	0.38
7	Nov-12	*Klebsiella pneumoniae ssp pneumoniae*	NICU	Peritoneal fluid	Negative +AmpC	Negative	Positive	Positive	0.19	0.25
8	Nov-12	*Escherichia coli*	MICU	Urine	Negative +AmpC	Negative	Positive	Negative	0.5	2
9	Nov-12	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Negative	Negative	0.75	1.5
10	Nov-12	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Endotracheal Tube Secretion	Positive	Positive	Positive	Positive	0.19	0.38
11	Dec-12	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Endotracheal Tube Secretion	Positive	Positive	Positive	Positive	0.19	0.38
12	Dec-12	*Klebsiella oxytoca*	NICU	Tracheostomy Site Swab	Positive	Negative	Negative	Negative	0.125	0.38
13	Dec-12	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Urine	Positive	Positive	Positive	Positive	0.25	0.5
14	Dec-12	*Escherichia coli*	NICU	Conjunctival Swab	Positive	Negative	Negative	Positive	0.094	0.38

15	Dec-12	*Enterobacter aerogenes*	MICU	Blood	Positive	Positive	Negative	Negative	0.19	0.5
16	Dec-12	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Endotracheal Tube Secretion	Positive	Positive	Positive	Positive	0.19	0.38
17	Jan-13	*Escherichia coli*	MICU	Urine	Negative	Negative	Negative	Negative	0.38	0.5
18	Jan-13	*Escherichia coli*	SICU	Blood	Positive	Negative	Positive	Negative	0.25	0.38
19	Jan-13	*Escherichia coli*	TICU	Blood	Positive	Negative	Positive	Positive	0.125	0.25
20	Jan-13	*Enterobacter cloacae*	TICU	Blood	Negative	Negative	Negative	Negative	0.125	0.25
21	Jan-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Sputum	Positive	Positive	Positive	Positive	0.25	0.38
22	Jan-13	*Escherichia coli*	MICU	Blood	Negative +AmpC	Negative	Positive	Negative	0.38	1.5
23	Jan-13	*Proteus penneri*	MICU	Blood	Positive	Negative	Negative	Negative	0.047	1
24	Jan-13	*Escherichia coli*	PICU	Urine	Positive	Negative	Negative	Positive	0.125	0.38
25	Jan-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Endotracheal Tube Secretion	Positive	Positive	Negative	Negative	0.25	0.38
26	Jan-13	*Klebsiella pneumoniae ssp pneumoniae*	TICU	Urine	Positive	Positive	Positive	Positive	0.25	0.75
27	Jan-13	*Citrobacter braakii*	TICU	Blood	Negative	Negative	Negative	Negative	0.25	0.75
28	Jan-13	*Escherichia coli*	TICU	Sputum	Positive	Negative	Negative	Positive	0.94	0.38
29	Jan-13	*Escherichia coli*	PICU	Urine	Positive	Negative	Positive	Positive	0.125	0.38
30	Feb-13	*Serratia marcescens*	MICU	Sputum	Negative	Negative	Negative	Negative	0.02	0.19
31	Feb-13	*Escherichia coli*	MICU	Urine	Positive	Negative	Positive	Positive	0.064	0.25
32	Feb-13	*Escherichia coli*	MICU	Blood	Positive	Negative	Negative	Positive	0.125	0.5
33	Feb-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Tracheal Aspirate	Positive	Positive	Positive	Positive	0.19	0.38
34	Feb-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Urine	Positive	Positive	Negative	Positive	0.094	0.38
35	Feb-13	*Escherichia coli*	MICU	Blood	Positive	Negative	Negative	Positive	0.19	0.38
36	Mar-13	*Escherichia coli*	TICU	Ascitic Fluid	Positive	Negative	Negative	Positive	0.125	0.38
37	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	TICU	Sputum	Positive	Positive	Negative	Negative	0.25	0.38
38	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Urine	Positive	Negative	Negative	Positive	0.38	0.38
39	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	NICU	Blood	Positive	Positive	Negative	Positive	0.25	0.38
40	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Negative	Positive	0.25	0.38
41	Mar-13	*Escherichia coli*	SICU	Peritoneal fluid	Positive + AmpC	Negative	Negative	Positive	256	256
42	Mar-13	*Escherichia coli*	SICU	Peritoneal fluid	Negative + AmpC	Negative	Negative	Positive	0.19	0.75
43	Mar-13	*Escherichia coli*	SICU	Urine	Positive	Positive	Negative	Positive	0.125	0.38
44	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Urine	Positive	Positive	Positive	Positive	0.19	0.5
45	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Sputum	Positive	Positive	Positive	Positive	0.38	1
46	Mar-13	*Klebsiella pneumoniae ssp ozaenae*	MICU	Sputum	Positive	Negative	Negative	Negative	0.094	0.25
47	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Tracheal Aspirate	Positive	Negative	Positive	Positive	0.125	0.25
48	Mar-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Urine	Positive	Positive	Positive	Positive	0.38	1.5
49	Mar-13	*Escherichia coli*	TICU	Urine	Positive	Negative	Positive	Positive	0.094	0.38
50	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	TICU	J VAC Fluid	Positive	Negative	Positive	Positive	0.19	0.5
51	Apr-13	*Escherichia coli*	TICU	J VAC Fluid	Positive	Negative	Negative	Positive	0.094	0.75
52	Apr-13	*Escherichia coli*	PICU	Urine	Positive	Negative	Negative	Positive	0.125	0.38
53	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Endotracheal Tube Secretion	Positive	Positive	Positive	Positive	0.19	0.75
54	Apr-13	*Enterobacter aerogenes*	MICU	Tracheal Aspirate	Positive	Positive	Positive	Positive	0.25	0.38
55	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Negative	Negative	0.75	1
56	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Endotracheal Tube Secretion	Positive	Positive	Negative	Negative	0.25	0.38
57	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Negative	Positive	0.19	0.38
58	Apr-13	*Escherichia coli*	SICU	Wound Swab	Positive	Negative	Negative	Positive	0.125	0.5
59	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Sputum	Positive	Positive	Negative	Negative	0.25	0.38
60	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Negative	Negative	0.19	0.25
61	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	NICU	Blood	Positive	Positive	Positive	Positive	0.19	0.38
62	Apr-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Endotracheal Tube Secretion	Positive	Positive	Negative	Negative	0.25	0.25

63	May-13	*Citrobacter freundii*	TICU	Blood	Negative	Negative	Negative	Negative	0.064	0.38
64	May-13	*Escherichia coli*	MICU	Urine	Positive	Negative	Negative	Positive	0.064	0.25
65	May-13	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Tracheostomy Site Swab	Positive	Positive	Positive	Positive	0.25	0.75
66	May-13	*Klebsiella pneumoniae ssp pneumoniae*	NICU	Endotracheal Tube Secretion	Positive	Positive	Positive	Positive	0.25	0.38
67	May-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Sputum	Positive	Positive	Negative	Negative	0.19	0.38
68	May-13	*Klebsiella pneumoniae ssp pneumoniae*	TICU	Blood	Positive	Positive	Negative	Positive	0.19	0.75
69	May-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Sputum	Positive	Positive	Negative	Negative	0.38	0.38
70	May-13	*Enterobacter cloacae*	SICU	Sputum	Positive	Positive	Negative	Negative	0.19	0.19
71	Jun-13	*Klebsiella pneumoniae ssp pneumoniae*	TICU	Wound Swab	Positive	Positive	Negative	Positive	0.38	0.38
72	Jun-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Negative	Negative	0.19	0.38
73	Jun-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Positive	Positive	0.19	1
74	Jun-13	*Escherichia coli*	PICU	Endotracheal Tube Secretion	Positive	Negative	Negative	Positive	0.125	0.38
75	Jun-13	*Escherichia coli*	PICU	Urine	Positive	Negative	Negative	Positive	0.125	0.38
76	Jun-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Positive	Positive	0.38	1.5
77	Jul-13	*Klebsiella pneumoniae ssp pneumoniae*	NICU	Blood	Positive	Positive	Negative	Negative	0.38	0.38
78	Jul-13	*Escherichia coli*	NICU	Blood	Positive	Negative	Negative	Negative	0.125	0.38
79	Jul-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Sputum	Positive	Positive	Negative	Positive	0.25	0.75
80	Jul-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Endotracheal Tube Secretion	Positive	Positive	Positive	Positive	0.19	0.38
81	Jul-13	*Escherichia coli*	PICU	Urine	Positive	Negative	Negative	Positive	0.125	0.38
82	Jul-13	*Escherichia coli*	SICU	Urine	Positive	Negative	Positive	Negative	0.25	0.5
83	Jul-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	BAL	Positive	Positive	Negative	Positive	0.25	0.75
84	Jul-13	*Escherichia coli*	MICU	Urine	Positive	Negative	Negative	Negative	0.094	0.25
85	Jul-13	*Citrobacter amalonaticus*	PICU	Urine	Positive	Positive	Negative	Negative	0.125	0.19
86	Jul-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Sputum	Positive	Positive	Positive	Positive	0.25	0.5
87	Jul-13	*Enterobacter cloacae*	NICU	Eye Swab	Negative + AmpC	Negative	Negative	Negative	0.094	0.25
88	Jul-13	*Enterobacter cloacae*	TICU	Blood	Negative + AmpC	Negative	Negative	Negative	0.094	0.25
89	Jul-13	*Enterobacter aerogenes*	TICU	Blood	Positive	Positive	Negative	Negative	0.094	0.38
90	Aug-13	*Escherichia coli*	MICU	Ascitic fluid	Positive	Negative	Positive	Positive	0.125	0.25
91	Aug-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Urine	Positive	Positive	Negative	Positive	0.38	0.75
92	Aug-13	*Enterobacter aerogenes*	TICU	Sputum	Positive	Positive	Negative	Negative	0.25	0.38
93	Aug-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Sputum	Positive	Positive	Positive	Positive	0.19	0.75
94	Sep-13	*Escherichia coli*	NICU	Blood	Positive	Negative	Negative	Positive	0.19	0.75
95	Sep-13	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Urine	Positive	Positive	Positive	Positive	0.25	0.5
96	Sep-13	*Escherichia coli*	MICU	Urine	Positive	Negative	Positive	Positive	0.094	0.38
97	Sep-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Urine	Positive	Positive	Positive	Positive	0.25	0.75
98	Sep-13	*Escherichia coli*	SICU	Sputum	Positive	Negative	Negative	Positive	0.125	0.5
99	Sep-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Sputum	Positive	Positive	Positive	Positive	0.25	0.75
100	Sep-13	*Klebsiella pneumoniae ssp pneumoniae*	PICU	Blood	Positive	Negative	Positive	Positive	0.125	0.25
101	Sep-13	*Escherichia coli*	PICU	Urine	Positive	Negative	Negative	Positive	0.064	0.25
102	Sep-13	*Klebsiella pneumoniae ssp pneumoniae*	MICU	Sputum	Positive	Positive	Positive	Positive	0.19	0.38
103	Sep-13	*Klebsiella pneumoniae ssp pneumoniae*	NICU	Central line Tip	Positive	Positive	Negative	Positive	0.25	0.5
104	Sep-13	*Escherichia coli*	TICU	Sputum	Positive	Negative	Positive	Positive	0.19	0.25
105	Oct-13	*Escherichia coli*	SICU	Blood	Positive	Negative	Negative	Positive	0.064	0.19
106	Oct-13	*Escherichia coli*	SICU	Sputum	Positive	Positive	Positive	Negative	0.064	0.19
107	Oct-13	*Escherichia coli*	SICU	Urine	Positive	Negative	Negative	Positive	0.094	0.25
108	Oct-13	*Klebsiella pneumoniae ssp pneumoniae*	SICU	Blood	Positive	Positive	Positive	Positive	0.38	1
109	Oct-13	*Escherichia coli*	TICU	Sputum	Positive	Positive	Positive	Negative	0.064	0.25

White, susceptible; grey, non-susceptible, susceptibility was reported according to Clinical Laboratory Standards Institute (CLSI) breakpoints (Clinical Laboratory Standards Institute, 2020). m, month; y, year; MICU, intensive care unit; NICU, intensive care unit; PICU, intensive care unit; SICU, intensive care unit; TICU intensive care unit; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam.

Reference

Clinical Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 30th Edition ed. Wayne, PA, USA2020 January 21, 2020.