European Journal of Clinical Microbiology & Infectious Diseases (2022) 41:841–847
https://doi.org/10.1007/s10096-022-04425-4

BRIEF REPORT

Characteristics and outcomes of carbapenemase harbouring carbapenem-resistant *Klebsiella* spp. bloodstream infections: a multicentre prospective cohort study in an OXA-48 endemic setting

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Received: 3 December 2021 / Accepted: 15 February 2022 / Published online: 17 March 2022

Abstract

A prospective, multicentre observational cohort study of carbapenem-resistant *Klebsiella* spp. (CRK) bloodstream infections was conducted in Turkey from June 2018 to June 2019. One hundred eighty-seven patients were recruited. Single OXA-48-like carbapenemases predominated (75%), followed by OXA-48-like/NDM coproducers (16%). OXA-232 constituted 31% of all OXA-48-like carbapenemases and was mainly carried on ST2096. Thirty-day mortality was 44% overall and 51% for ST2096. In the multivariate cox regression analysis, SOFA score and immunosuppression were significant predictors of 30-day mortality and ST2096 had a non-significant effect. All OXA-48-like producers remained susceptible to ceftazidime-avibactam.

Keywords OXA-48 · OXA-232 · ST2096 · *Klebsiella pneumoniae* · Ceftazidime-avibactam

Carbapenem-resistant *Klebsiella pneumoniae* is the fastest growing subset of antibiotic-resistant bacteria in Europe [1]. Carbapenem resistance is primarily mediated by three major carbapenemases (KPC, OXA-48 and NDM). OXA-48 was first isolated in Turkey and remains as the predominant carbapenemase type in Turkey and most of Europe [2]. Dissemination of OXA-48 occurs via a diverse array of clonal types [3]. OXA-232 is an OXA-48-like carbapenemase reported mainly from the Indian subcontinent, with sporadic occurrences around the world [4–7]. Knowledge on OXA-232 is limited to a few molecular studies [8] and the clinical characteristics of OXA-232 infections are yet to be described. We conducted this study in an OXA-48 endemic setting shortly before the introduction of ceftazidime-avibactam for clinical use. Our aims were to describe 1- the carbapenemases and clonal types of CRK, 2- the effect of treatment and clonal type on patient mortality, and 3- baseline ceftazidime-avibactam susceptibility profile to guide future clinical studies.

This was a prospective, observational, multicentre study of patients with CRK BSI from 13 tertiary care centres in Turkey (June 2018–June 2019). All consecutive adult patients (≥18 years old) with clinically significant CRK bacteremia were included. Those with polymicrobial BSI were excluded. The study was approved by the Koc University Institutional Review Board (approval number: 2018.151.IRB1.018) and was registered with ClinicalTrials.gov (identifier: NCT03597841) prior to commencement. CRK was defined as carbapenemase harbouring *Klebsiella* spp. that were non-susceptible to at least one carbapenem according to EUCAST 2018 breakpoints (i.e., MIC > 2 µg/mL for meropenem or imipenem and > 0.5 µg/mL for ertapenem). Antibiotics were classified as inactive if the isolate demonstrated in vitro resistance according to EUCAST 2018 criteria. Active treatment was defined as described previously [9].

Bacterial identification was performed with MALDI-TOF MS. Meropenem and colistin susceptibilities were determined using broth microdilution [10], ceftazidime-avibactam susceptibility was determined using Sensititre

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Gram Negative EURGNCOL Plate (Thermo Fisher), and ertapenem susceptibility was determined using Etest (bioMérieux). All other antibiotic susceptibilities were determined using automated systems. Carbapenemase genes were detected on whole bacterial genomes using Abricate v0.8.10 (https://github.com/tseemann/abricate) with the NCBI database [11]. Whole-genome sequencing was performed at the Australian Centre for Ecogenomics using the Illumina NextSeq500 instrument. Lineage STs were assigned using MLST (https://github.com/tseemann/mlst) with MLST profiles from pubMLST (https://pubmlst.org/). The clonal relationship of the isolates was evaluated by pulsed-field gel electrophoresis (PFGE) using the XbaI restriction endonuclease.

Continuous variables were compared using *t*-test or Mann–Whitney *U* test. Categorical variables were compared with the Pearson's χ^2 test, Fisher's exact test or the global test. Two-tailed tests were used to determine statistical significance and a *p* value of ≤ 0.05 was considered significant. Univariable Cox regression analyses were performed to evaluate the effect of predefined covariates on 30-day mortality. A multivariable Cox regression analysis was employed among those who survived the first 48 h to evaluate the effect on 30-day mortality of covariates with a *p* value of < 0.2 in the univariable analyses. All analyses were performed using Stata software version 16.0.

Of the 187 CRK isolates, 95% (178) were speciated as *K. pneumoniae* using MALDI-TOF MS at the reference laboratory. Seven were speciated as *K. variicola*, one *K. quasipneumoniae* and one *K. oxytoca*. All isolates were ertapenem non-susceptible and 96% (179/187) of the isolates were meropenem non-susceptible. OXA-48-like carbapenemases comprised the largest carbapenemase group (170/187, 91%). OXA-48 constituted half (97/170, 51%) of the OXA-48-like group, with the other half consisting of OXA-232, OXA-244 and OXA-181 (60/170, 31%; 18/170, 11% and 5/170, 3%; respectively). OXA-48-like carbapenemases were accompanied by a metallo-beta-lactamase (MBL) in 29 isolates. Eleven isolates harboured a single MBL and four harboured a single KPC (Table 1). All MBLs, except one NDM-5 and one VIM-1, were NDM-1. ST2096 (61/187, 33%), ST101 (37/187, 20%) and ST14 (28/187, 15%) were the three main clonal types. ST groups were spread across 13 different centres (Fig. 1) and PFGE demonstrated multiclonal spread. OXA-232 was mainly carried on ST2096 and OXA-244 on ST101 (59 of 60 and 15 of 18, respectively). The majority of OXA-48-like/MBL coproducers were carried on ST14 (20 of 29). Seventy-seven percent of the isolates (144 of 187) were resistant to colistin. The Mcr-1 gene was not detected in any of the isolates. ST2096 was the clonal type with the highest resistance to colistin, tigecycline, amikacin and trimethoprim-sulfamethoxazole (Table 2). All non-MBL producing isolates were susceptible to ceftazidime-avibactam.

Thirteen tertiary care centres from three metropolitan cities (i.e., Istanbul, Ankara, Bursa) were included (Fig. 1). The median age was 62 (IQR 50–76) and 55% were male (Table 3). One-quarter of the patients were immunosuppressed and two-thirds were in the ICU at presentation. CVC was the predominant source of infection. The greatest number of immunosuppressed patients were in the ST14 group, while the ST2096 group had the lowest number of immunosuppressed patients (39% vs 10%, respectively).

Table 1 MLST and carbapenemases of CRK isolates

	Total	OXA-48-like				OXA48-like[b]/MBL[c]	MBL[c]	KPC-2	KPC-2/MBL[c]
		OXA48	OXA232	OXA244	OXA181				
ST2096	61	2	56	…	…	3[d]	…	…	…
ST101	37	20	…	15	…	2[e]	…	…	…
ST14	28	6	…	1	…	20	1	…	…
ST16	14	8	1	…	3	1	1[g]	…	…
ST307	7	4	…	…	…	…	…	3	…
ST981[a]	6	6	…	…	…	…	…	…	…
ST11	5	3	…	…	…	…	2	…	…
ST15	5	1	…	…	…	1	1	…	2
ST395	5	1	…	…	…	…	4	…	…
Other	19	11	…	1	2	2[f]	2	1	…
Total	187	62	57	17	5	29	11	4	2

MBL, metallo-β-lactamase. [a]All isolates in this MLST are speciated as *Klebsiella variicola*, [b]OXA-48 unless specified otherwise, [c]NDM-1 unless specified otherwise, [d]OXA-48-like type is OXA-232 for all three isolates, [e]OXA-48-like type is OXA-244 for one of the two isolates, [f]NDM type is NDM-5 for one of the two isolates, [g]NDM type is NDM-5

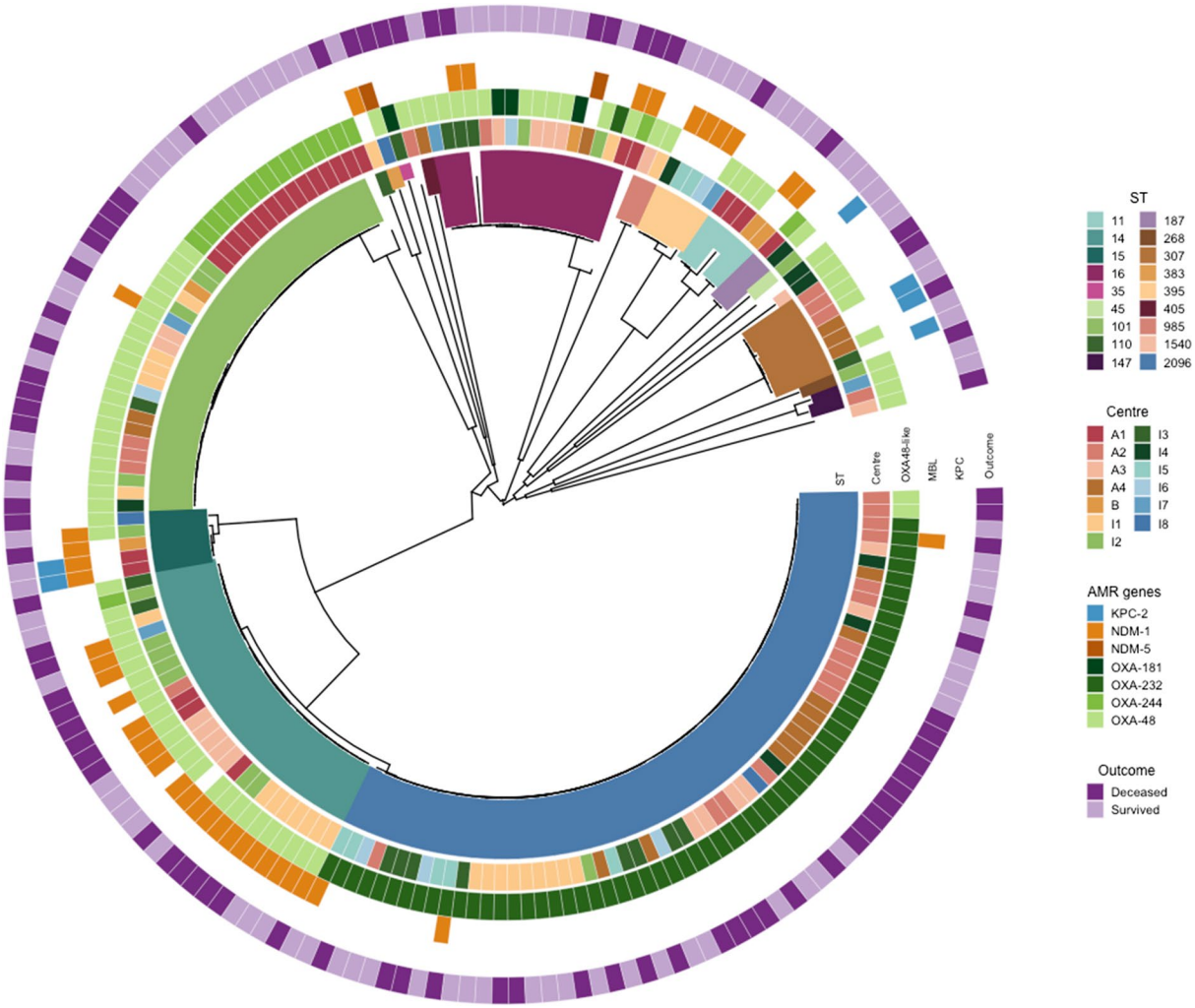

Fig. 1 Core genome mid-point rooted phylogeny of 178 *Klebsiella pneumoniae* isolates built using Parsnp v1.2 with default settings against the reference genome KP64 (GenBank accession: AP018750.1). Clinical metadata, ST and detected carbapenem resistance conferring genes shown

Eighty patients (43%) received active antibiotic treatment (Table 3). The ST14 group had the least number of patients with active treatment (29%). Tigecycline monotherapy constituted the majority of active treatment regimens (40%, 32/80), followed by colistin (21%, 17/80), aminoglycosides (14%, 11/80), dual active regimens (14%, 11/80) and others (11%, 9/80). Thirty-day mortality was 44% (82/187). Twenty-nine (36%) patients died in the active treatment group and 53 (50%) died in the inactive treatment group ($p=0.07$). Mortality rates were 57%, 51% and 43% for ST14, ST2096 and ST101 clonal types, respectively, and 31% for other clonal types ($p=0.065$). In the univariable Cox regression analyses, ICU admission at disease presentation, invasive mechanical ventilation, per unit increase in SOFA score and ST2096 and ST14 clonal types were found to be significantly associated with 30-day mortality, whereas active treatment did not have a significant effect (Table 4). In the multivariable Cox regression analysis, the SOFA score remained strongly associated with mortality

Table 2 Antibiotic susceptibilities of CRK isolates

Susceptibility (susceptible/total tested)	Total, *n* (%)	ST2096, *n* (%)	ST101, *n* (%)	ST14, *n* (%)
Colistin	43/187 (23)	11/61 (18)	5/37 (14)	10/28 (36)
Tigecycline	67/157 (43)	12/51 (24)	24/33 (73)	8/26 (31)
Amikacin	45/177 (25)	7/59 (12)	7/32 (22)	5/27 (19)
Gentamicin	42/164 (26)	7/59 (12)	11/26 (42)	3/26 (12)
Trimethoprim-sulfamethoxazole	20/165 (12)	1/60 (2)	6/26 (23)	1/25 (4)
Ceftazidime-avibactam	152/187 (81)	61/61 (100)	37/37 (100)	9/28 (32)

Table 3 Patient characteristics according to MLST

	Total ($n=187$)	ST2096 ($n=61$)	ST101 ($n=37$)	ST14 ($n=28$)	Other ($n=61$)	p-value
Age	62 (50–76)	67 (48–78)	65 (54–76)	61 (44–78)	58 (48–69)	0.37
Male	102 (55%)	32 (52%)	21 (57%)	15 (54%)	34 (56%)	0.97
Infection source						0.85
CVC	63 (34%)	23 (38%)	7 (19%)	12 (43%)	21 (34%)	
Respiratory	41 (22%)	15 (25%)	12 (32%)	4 (14%)	10 (16%)	
Urinary	24 (13%)	6 (10%)	5 (14%)	5 (18%)	8 (13%)	
Intraabdominal	22 (12%)	6 (10%)	6 (16%)	2 (7%)	8 (13%)	
Other	37 (19%)	11 (18%)	7 (19%)	5 (19%)	14 (24%)	
Source control	56 (30%)	18 (30%)	9 (24%)	8 (29%)	21 (34%)	0.32
Metastatic/hematologic malignancy	48 (26%)	12 (20%)	10 (27%)	8 (29%)	18 (30%)	0.62
Immunosuppression	46 (25%)	6 (10%)	9 (24%)	11 (39%)	20 (33%)	**0.006**
CCI	3 (2–5)	2 (1–4)	4 (2–6)	3 (2–5)	3 (2–4)	**0.018**
ICU at presentation	120 (64%)	45 (74%)	25 (68%)	18 (64%)	32 (52%)	0.099
Invasive mechanical ventilation	80 (43%)	31 (51%)	17 (46%)	12 (43%)	20 (33%)	0.24
SOFA score	5 (3–8)	7 (4–9)	5 (2–8)	6 (4–7.5)	4 (3–8)	0.17
OXA-48-like only	141 (75%)	58 (95%)	35 (95%)	7 (25%)	41 (67%)	**< 0.001**
Other carbapenemases	46 (25%)	3 (5%)	2 (5%)	21 (75%)	20 (33%)	
Active treatment	80 (43%)	24 (39%)	19 (51%)	8 (29%)	29 (48%)	0.23
30-day mortality	82 (44%)	31 (51%)	16 (43%)	16 (57%)	19 (31%)	0.065

Table 4 Univariable and multivariable analyses of variables associated with 30-day mortality

	Univariable analysis			Multivariable analysis[b]		
	HR	CI	p	HR	CI	p
Demographics						
Age	0.98	0.86–1.13	0.82	…	…	…
Male sex	1.34	0.82–2.20	0.24	…	…	…
Source						
Non-UT source	2.25	0.90–5.60	**0.08**	1.34	0.52–3.46	0.54
Source control	0.60	0.34–1.04	**0.07**	0.69	0.39–1.23	0.21
Comorbidities						
Metastatic/hematologic malignancy	1.27	0.73–2.20	0.40	…	…	…
Immunosuppression	1.43	0.83–2.46	**0.20**	2.14	1.15–4.00	**0.02**
CCI score	0.97	0.88–1.07	0.56	…	…	…
Disease severity						
ICU at presentation	1.82	1.05–3.16	**0.03**	0.88	0.41–1.93	0.76
Invasive mechanical ventilation	1.99	1.22–3.25	**0.01**	1.18	0.58–2.40	0.65
SOFA score (per unit)	1.25	1.17–1.33	**0.00**	1.24	1.15–1.34	**0.000**
Microorganism						
Carbapenemase other than single OXA-48-like [a]	1.33	0.78–2.26	0.30	…	…	…
MLST type (reference other)						
ST2096	2.47	1.25–4.86	**0.01**	1.94	0.95–3.96	**0.07**
ST101	1.92	0.88–4.22	**0.10**	1.92	0.84–4.38	**0.12**
ST14	2.91	1.33–6.36	**0.01**	1.96	0.88–4.44	**0.10**
Treatment						
Active treatment	0.75	0.46–1.22	0.25	0.71	0.42–1.21	0.21

[a]OXA-48/MBL ($n=29$), MBL ($n=11$), KPC ($n=4$), KPC/MBL ($n=2$), [b]excludes those who died within 48 h. p value < 0.2 in bold

(HR 1.24, 95% CI 1.15–1.34, $p<0.001$), whereas the association between ST2096 and ST14 clonal types and mortality did not reach statistical significance (HR 1.94, 95% CI 0.95–3.96, $p=0.07$; HR 1.96, 95% CI 0.88–4.44, $p=0.10$; respectively). Mortality rates for OXA-48-like/MBL coproducers and single OXA-48-like producers within the ST14 group were 58% and 57%, respectively ($p=0.97$).

This study demonstrated the emergence of an OXA-232 harbouring ST2096 lineage associated with high mortality and antibiotic resistance rates. OXA-232 was characterized in 2012 from French patients returning from India [7]. It remains endemic in India, with cases and hospital outbreaks reported from several countries around the world [12]. ST2096 is a single locus variant of ST14 and is an emerging clone with limited data available outside India [13, 14]. In a single-centre study of 65 colistin-resistant CRK isolates from India, ST2096 was one of the three main clonal types ($n=9$) and was associated with OXA-232 carriage (7 of 9 isolates harboured OXA-232) [15]. OXA-232 carrying ST2096 CRK isolates were recently reported from the Arabian Peninsula. A collection of 235 MDR *K. pneumoniae* isolates from a single hospital outbreak in Saudi Arabia, registered on the bioproject database, demonstrated that there were 80 (34%) ST2096 isolates and 51/80 (64%) harboured OXA-232. These isolates are thought to be associated with high mortality rates, but no further details (e.g., number of patients, number of isolates per patient, infection versus colonization status) were available (https://www.ncbi.nlm.nih.gov/bioproject/?term=prjeb36683). The Arabian peninsula may serve as the source for Turkish CRK isolates given the increasing number of Arab visitors to Turkey in recent years [16].

In a genomic surveillance study from South Asia, ST2096 was one of the clonal types with AMR-virulence convergence and local expansion [14]. The risk of global spread of this clone poses a significant threat given limited treatment options due to extremely high resistance rates to last line antibiotics. Reliable susceptibility to ceftazidime-avibactam is promising. However, ceftazidime-avibactam resistance development is a concern.

Another important finding of this study is the high number of isolates harbouring dual carbapenemases in the form of OXA-48 and NDM and their association with ST14. Interestingly, the presence of a second carbapenemase did not increase the mortality within the ST14 group with similar mortality rates between the OXA-48/NDM coproducers and single OXA-48 producers. In an epidemiologic analysis of OXA-48/NDM co-harbouring *K. pneumoniae* from 10 European countries, ST14 was the main clonal type after ST307 associated with dual carbapenemases [17]. This may have originated from the Arabian Peninsula as similar findings were reported from a recent study in the United Arab Emirates, where 24% of the CRK strains carried OXA-48/NDM and half of those belonged to the ST14 clone [18]. It was hypothesized that ceftazidime-avibactam use may be contributing to the expansion of dual carbapenemases as it lacks activity against MBLs while inhibiting non-MBLs [19]. However, larger genomic surveillance studies are needed to investigate this further. Aztreonam-avibactam is a new beta-lactam/beta-lactamase inhibitor with activity against both MBLs and OXA-48-like carbapenemases currently being tested in phase clinical trials, which provides hope for the treatment of dual carbapenemase producers [20].

This study demonstrated that in a setting where most CRK strains belong to high-risk clones with high AMR rates, in vitro active treatment was not associated with survival. However, the majority of active treatment regimens in this cohort consisted of monotherapy with either tigecycline or colistin, which may provide some explanation for the poor outcomes observed given both of these antibiotics are associated with unfavourable PK/PD properties [21, 22].

To our knowledge, this is the largest cohort of OXA-48-like CRK BSI. The emerging high-risk clone ST2096 with OXA-232 is the predominant clonal type among Turkish CRK BSI isolates and remains susceptible to ceftazidime-avibactam. We note an increase in the number of OXA-48-like/NDM coproducers, carried on high-risk clones, which is a major concern in the context of extremely high colistin resistance rates and lack of ceftazidime-avibactam activity against these isolates. Therefore, the development of newer antimicrobials with activity against these highly resistant isolates is important.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Burcu Isler, Berna Özer, Güle Çınar, Abdullah Tarık Aslan, Cansel Vatansever, Caitlin Falconer, İştar Dolapçı, Funda Şimşek, Necla Tülek, Hamiyet Demirkaya, Şirin Menekşe, Halis Akalin, İlker İnanç Balkan, Mehtap Aydın, Elif Tükenmez Tigen, Safiye Koçulu Demir, Mahir Kapmaz, Şiran Keske, Özlem Doğan, Çiğdem Arabacı, Serap Yağcı, Gülşen Hazırolan, Veli Oğuzalp Bakır, Mehmet Gönen, Mark D. Chatfield, Brian Forde, Neşe Saltoğlu, Alpay Azap, Özlem Azap, Murat Akova, David L. Paterson, Füsun Can and Önder Ergönül. The first draft of the manuscript was written by Burcu Isler and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by Pfizer Global Medical Grants (grant number 56644459).

Data availability The genomic dataset generated during the current study will be available shortly in the public database [i.e., US National Library of Medicine (NLM) National Center for Biotechnology Information (NCBI), PRJNA789336]. The data are available from the corresponding author in the interim.

Declarations

Competing interests Dr. Paterson reports research grants from Merck, Pfizer and Shionogi. David Paterson has received honoraria for advisory board membership from Merck, Pfizer, Shionogoi, GSK, QPex, Entasis, VenatoRx, BioMerieux and Accelerate. All other authors declare that they have no conflicts of interest.

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