Molecular characterization of clinical carbapenem-resistant *Enterobacterales* from Qatar

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**Abstract**

One hundred forty-nine carbapenem-resistant *Enterobacterales* from clinical samples obtained between April 2014 and November 2017 were subjected to whole genome sequencing and multi-locus sequence typing. *Klebsiella pneumoniae* (81, 54.4%) and *Escherichia coli* (38, 25.5%) were the most common species. Genes encoding metallo-β-lactamases were detected in 68 (45.8%) isolates, and OXA-48-like enzymes in 60 (40.3%). *bla*NDM-1 (45; 30.2%) and *bla*OXA-48 (29; 19.5%) were the most frequent. KPC-encoding genes were identified in 5 (3.6%) isolates. Most common sequence types were *E. coli* ST410 (8; 21.1%) and ST38 (7; 18.4%), and *K. pneumoniae* ST147 (13; 16%) and ST231 (7; 18.4%).

**Keywords** CRE · Carbapenemase · KPC · NDM · VIM · OXA · Enterobacterales · Qatar · Middle East

**Introduction**

Considerable variations exist in the epidemiology of carbapenemases in *Enterobacterales* from different parts of the world [1]. Awareness of the locally prevalent carbapenemases is relevant to the appropriate selection of antimicrobial therapy for carbapenem-resistant *Enterobacterales* (CRE) infections [2]. Moreover, the molecular epidemiology of CRE could help guide control efforts. The aim of this study was to identify the predominant carbapenemases in CRE from Qatar and to elucidate their molecular epidemiology.

**Methods**

All carbapenem-resistant *Enterobacterales* isolates from clinical specimens received at Hamad Medical Corporation Microbiology Department during the period between April 2014 and November 2017 were included. The department provides diagnostic microbiology services for all public hospitals in Qatar. Laboratory methods for bacterial identification, antimicrobial susceptibility testing, whole genome sequencing and analysis are described in the supplementary data file.

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Results

A total of 149 non-repetitive CRE clinical isolates from 146 patients were included. The median patient age was 57 years (range, 3 months–97 years), and 77 (52.7%) were males. Diabetes mellitus (73; 50%) and chronic kidney diseases (39; 26.7%) were the most frequent co-existing medical conditions. Nineteen (12.8%) isolates were recovered from samples obtained within the first 24 h of hospitalization. Nearly one-fifth of the patients (25, 17.1%) had entered the country from overseas within 30 days prior to CRE isolation. Further demographic and clinical details are provided in Table 1 and in Table S1 in the supplementary data file.

The most frequent species were *Klebsiella pneumoniae* (81; 54.4%) and *Escherichia coli* (38; 25.5%) (Table 2), whereas urine (41; 27.5%) and blood (33; 22.1%) were the most frequent site of isolation (Table 1). Thirty-four (23.3%) patients died within 30 days of first CRE isolation. The majority of isolates were susceptible to tigecycline (129; 86.5%), whereas urine (41; 27.5%) and blood (33; 22.1%) were the most frequent site of isolation (Table 1). Thirty-four (23.3%) patients died within 30 days of first CRE isolation. The majority of isolates were susceptible to tigecycline (129; 86.5%), fosfomycin (126; 84.6%), and amikacin (108; 72.4%) (Table S2 in the supplementary data file).

Genes encoding Class B carbapenemases (i.e., metallo-β-lactamases [MBL]) were detected in 68 (45.8%) isolates, and Class D carbapenemases in 60 (40.3%). The most frequently identified carbapenemase genes were *bla*~NDM-1~ (45; 30.2%) and *bla*~OXA-48~ (29; 19.5%) (Table 3). KPC-encoding genes were identified in 5 (3.6%) isolates. All 5 patients from whom KPC-producing *K. pneumoniae* were isolated had received medical care abroad within the preceding 30 days (Table S3 in the supplementary data file). No carbapenemase genes were detected in 14 (9.4%) isolates, and 8 (5.3%) carried more than one carbapenemase genes (Table 2).

The included *E. coli* isolates belonged to 16 different sequence types, the most frequent of which were ST410 (8; 21.1%) and ST38 (7; 18.4%). On the other hand, *K. pneumoniae* isolates represented 40 different sequence types, most frequently ST147 (13; 16%) and ST231 (7; 8.6%). *K. quasipneumoniae* belonged mainly to ST196 (9; 56.3%) and ST1416 (4; 25%). Except for *K. quasipneumoniae*, strains with the same sequence type mostly possessed different carbapenemase genes (Table 3).

Discussion

Typical risk factors for multidrug-resistant Gram-negative infections were highly prevalent in the patients from whom the isolates were retrieved [3]. The observed 30-day all-cause mortality of 23.3% is consistent with existing literature describing clinical outcomes in patients with CRE infections [4].

The most common carbapenemase genes in this study were those encoding MBL, especially NDM-1 and NDM-7. Effective antimicrobial therapy options for MBL-producing Enterobacterales are very limited and their management remains particularly challenging [5]. NDM enzymes are established in CRE from the Arabian Peninsula [6, 7]. Given that more than half of the country’s residents originate from the Indian Subcontinent, the high prevalence of NDM in CRE from Qatar is not surprising. NDM genes are commonly co-carried with other carbapenemase genes [5]. In this study, NDM genes were present in all eight isolates that possessed multiple carbapenemase genes.

VIM-producing *Enterobacteriales* are endemic in Greece and Eastern Europe, but are otherwise relatively rare [8]. In this study, VIM genes were present in two *E. cloacae* isolates. VIM carbapenemases have also been reported in *K. pneumoniae* and *E. cloacae* from Turkey, Kuwait, and Saudi Arabia [7, 9, 10]. *bla*~IMP-26~ was detected in a single *E. coli* isolate in this study. IMP-producing *Enterobacteriales* are endemic in Japan, but are rarely detected in CRE from the Middle East [11].

OXA-48-like β-lactamases are wide-spread in the Arabian Peninsula and the Middle East [6]. Likewise, nearly two-fifth of isolates in this study possessed OXA-encoding genes. Some, but not all, Class D β-lactamases have carbapenemase hydrolyzing activity [12]. Notably, 30.2% of our isolates, all of which possessed OXA-48-like genes, were susceptible to meropenem. As previously well-documented, nonsusceptibility to ertapenem is often the most sensitive indicator of carbapenemase production [13]. Similar to previous reports of frequent co-presence of OXA-48-like enzymes with MBL, seven out of eight isolates with multiple carbapenemase genes in this study possessed genes encoding NDM and OXA-48-like enzymes [12, 14].

OXA-181 and OXA-232 are OXA-48-like carbapenemases. OXA-181 differs from OXA-48 by four amino acids and, like NDM, its origin is epidemiologically linked to the Indian sub-continent [12]. In the Middle East region, OXA-181 was previously identified in CRE from Lebanon and Oman [14, 15]. OXA-232 differs from OXA-48 by five amino acids substitutions, and from OXA-181 by one mutation [12]. It was first reported in *K. pneumoniae* from France, but has since been reported from many parts of the world including South Asia and North Africa [16, 17]. Interestingly, OXA-232 is often present in *K. pneumoniae* ST231 [18]. Four out of 10 OXA-232-producing *K. pneumoniae* in our study belonged to this sequence type. One meropenem-susceptible *E. coli* isolate in this report possessed *bla*~OXA-244~. OXA-244 is a single-point mutation derivative of OXA-48, with weaker carbapenem hydrolyzing activity [12]. First described in *K. pneumoniae* from Spain, OXA-244 is now disseminated in *E. coli* in many countries in Western Europe [19].

An important finding in this study is the presence of KPC-encoding genes in five *K. pneumoniae* isolates, all of which were recovered from patients who had recently received medical care in KPC-endemic regions. KPC enzymes have...
historically been rare in the Middle East, except in Egypt and Israel [1]. However, reports have recently emerged of their occasional detection in CRE from Saudi Arabia, and the United Arab Emirates [20, 21]. In common with our report, the isolation of KPC-producing *K. pneumoniae* in Saudi Arabia was associated with recent travel to Egypt, a country where KPC-producing *Enterobacterales* are endemic [1, 20]. Travel generally, and medical tourism in particular, has

| Variable                                              | Number (%)          |
|-------------------------------------------------------|---------------------|
| Demographics                                          |                     |
| Median age in (range)                                 | 57 years (3 months–97 years) |
| Male sex                                              | 77 (52.7%)          |
| Nationality of origin*                                 |                     |
| Eastern Mediterranean Region                          | 96 (65.7%)          |
| South East-Asia Region                                | 41 (28.1%)          |
| European Region                                       | 3 (2%)              |
| Regions of the Americas                               | 1 (0.7%)            |
| Comorbidities                                         |                     |
| Diabetes mellitus                                     | 73 (50%)            |
| Chronic kidney disease                                | 39 (26.7%)          |
| Congestive heart failure                              | 20 (13.7%)          |
| Chronic liver disease                                 | 9 (6.1%)            |
| Chronic airway disease                                | 7 (4.8%)            |
| Solid malignancy                                      | 20 (13.7%)          |
| Hematological malignancy                              | 11 (7.5%)           |
| Solid organ transplant                                | 11 (7.5%)           |
| Hematopoietic stem cell transplant                    | 4 (2.7%)            |
| Active chemotherapy within 30 days of CRE isolation   | 16 (10.9%)          |
| Anti-TNF therapy within 30 days of CRE isolation      | 15 (10.3%)          |
| Corticosteroid therapy within 30 days of CRE isolation| 15 (10.3%)          |
| Carbapenem therapy within 30 days of CRE isolation    | 45 (30.8%)          |
| Invasive procedure within 30 days of CRE isolation    |                     |
| Surgical procedure                                    | 41 (28.1%)          |
| Central line insertion                                | 29 (19.8%)          |
| Urinary catheteration                                 | 29 (19.8%)          |
| Vascular stent insertion                              | 11 (7.5%)           |
| Other risk factors for CRE infection                  |                     |
| Presence of central venous catheter                   | 42 (28.7%)          |
| Total parenteral nutrition                            | 5 (3.4%)            |
| Mechanical ventilation                                | 41 (28.1%)          |
| Travel within 30 days of CRE isolation                | 25 (17.1%)          |
| Site of isolation                                     |                     |
| Urinary tract                                         | 41 (28.1%)          |
| Blood stream                                          | 33 (22.6%)          |
| Lower respiratory tract                               | 17 (11.6%)          |
| Skin and soft tissue                                  | 8 (5.5%)            |
| Others                                                | 14 (9.6%)           |
| Clinical outcome                                       |                     |
| Death within 30 days from CRE isolation               | 34 (23.3%)          |
| Recurrence with 30 days                               | 38 (26%)            |

*World Health Organization Regions. CRE, carbapenem-resistant *Enterobacterales*
frequently been implicated in international importation of multidrug-resistant pathogens [1]. No carbapenemase-encoding genes were detected in 9.4% of the isolates included in this study. It is likely that resistance in those isolates was mediated by non-carbapenemase mechanisms [22].

Tigecycline, fosfomycin, and aminoglycoside were the most active agents against the study isolates. Despite their in vitro activity, these agents’ clinical utility is limited by reduced efficacy in certain infection sites, excessive toxicity, or rapid emergence of resistance [2]. Ceftazidime-avibactam was recently introduced into clinical practice in Qatar. This β-lactam/β-lactamase inhibitor combination is active against most Enterobacterales producing Class A and Class D carbapenemases [2]. However, the introduction of ceftazidime-avibactam to intensive care units in Greece was followed by a change in the pattern of carbapenemases in CRE from blaKPC to blavIM predominance [23]. Given the background high prevalence of MBL in CRE in Qatar, such agents should be used judiciously to minimize the risk of selection of MBL producers.

The study isolates belonged to widely diverse sequence types. Only two international multidrug-resistant high-risk clones were relatively common: E. coli ST38 and K. pneumoniae ST147. However, other important high-risk clones were either infrequent (i.e., E. coli ST131, ST405, and ST648; and K. pneumoniae ST14, and ST258) or absent (e.g., E. coli ST69, ST155, and ST393; and K. pneumoniae ST14) [24]. These observations suggest that rather than clonal expansion, sporadic introductions of CRE and plasmid-mediated dissemination of carbapenemases are the main drivers of CRE epidemiology in Qatar. There are numerous examples of inter-species transmission of carbapenemase genes on mobile genetic elements resulting in in vivo emergence of resistance in individual patients, and also driving

| Carbapenemase genes | All isolates (n = 149) | E. coli (n = 38) | K. pneumoniae (n = 81) | K. quasipneumoniae (n = 16) | E. cloacae (n = 7) | Others* (n = 7) |
|---------------------|-----------------------|-----------------|------------------------|--------------------------|-----------------|-----------------|
| Class A             |                       |                 |                        |                          |                 |                 |
| blaKPC-2           | 4 (2.7%)              | 0               | 4 (4.9%)               | 0                        | 0               | 0               |
| blaKPC-3           | 3 (2.0%)              | -               | 3 (3.7%)               | -                        | -               | -               |
| Class B             |                       |                 |                        |                          |                 |                 |
| blaIMP-26          | 64 (43.0%)            | 14 (36.8%)      | 24 (29.6%)             | 16 (100%)                | 6 (85.7%)       | 4 (57.1%)       |
| blaNDM-1           | 1 (0.6%)              | 1 (2.6%)        | -                      | -                        | -               | -               |
| blaNDM-5           | 45 (30.2%)            | 3 (7.9%)        | 22 (27.2%)             | 14 (87.5%)               | 4 (57.1%)       | 2† (28.6%)      |
| blaNDM-6           | 7 (4.7%)              | 7 (18.4%)       | -                      | -                        | -               | -               |
| blaNDM-7           | 1 (0.7%)              | 1 (2.6%)        | -                      | -                        | -               | -               |
| blaNDM-13          | 5 (3.4%)              | -               | 1 (1.2%)               | 2 (12.5%)                | -               | 2‡ (28.6%)      |
| blaNDM-19          | 1 (0.7%)              | 1 (2.6%)        | -                      | -                        | -               | -               |
| blavIM-2           | 1 (0.7%)              | -               | 1 (1.2%)               | -                        | -               | -               |
| blavIM-4           | 2 (1.3%)              | -               | -                      | -                        | -               | 2 (28.6%)       |
| Class D             |                       |                 |                        |                          |                 |                 |
| blaOXA-48          | 59 (39.6%)            | 21 (55.2%)      | 34 (42%)               | 0                        | 1 (14.3%)       | 2 (28.6%)       |
| blaOXA-181         | 29 (19.5%)            | 10 (26.3%)      | 16 (19.8%)             | -                        | 1 (12.3%)       | 2§ (28.6%)      |
| blaOXA-232         | 19 (12.8%)            | 10 (26.3%)      | 9 (11.1%)              | -                        | -               | -               |
| blaOXA-244         | 10 (6.7%)             | -               | 10 (12.3%)             | -                        | -               | -               |
| Multiple carbapenemases | 8 (5.3%)          | 1 (2.6%)        | 7 (8.6%)               | 0                        | 0               | 1 (14.3%)       |
|blaNDM-1 + blaKPC-3| 1 (0.7%)              | -               | 1 (1.2%)               | -                        | -               | -               |
|blaNDM-1 + blaOXA-181| 2 (1.3%)          | -               | 2 (2.5%)               | -                        | -               | -               |
|blaNDM-5 + blaOXA-48| 3 (2.0%)              | -               | 3 (3.7%)               | -                        | -               | -               |
|blaNDM-5 + blaOXA-181| 2 (1.3%)          | 1 (2.6%)        | 1 (1.2%)               | -                        | -               | -               |
|None                | 14 (9.4%)             | 1 (2.6%)        | 12 (14.8%)             | 0                        | -               | 1▌ (12.3%)      |

*Klebsiella aerogenes (2), Providencia spp. (2), Citrobacter freundii (1), Klebsiella oxytoca (1), and Proteus mirabilis (1)
† Providencia sp. (1), P. mirabilis (1)
‡ C. freundii (1), Providencia sp. (1)
§ K. oxytoca (1), K. aerogenes (1)
▌ K. aerogenes (1)
### Table 3  Study isolates by their sequence type and carbapenemase genes

| Species          | Sequence type (number of isolates) | Carbapenemase-encoding genes (number of isolates) |
|------------------|------------------------------------|--------------------------------------------------|
| E. coli ($n=38$) | ST10 (2)                           | $\text{bla}_{\text{NDM-5}}$ (1), none (1)         |
|                  | ST23 (1)                           | $\text{bla}_{\text{OXA-48}}$ (1)                  |
|                  | ST38 (7)                           | $\text{bla}_{\text{OXA-48}}$ (6), $\text{bla}_{\text{OXA-181}}$ (1) |
|                  | ST58 (1)                           | $\text{bla}_{\text{OXA-48}}$ (1)                  |
|                  | ST101 (2)                          | $\text{bla}_{\text{NDM-1}}$ (1), none (1)         |
|                  | ST131 (1)                          | $\text{bla}_{\text{IMP-26}}$ (1)                  |
|                  | ST167 (3)                          | $\text{bla}_{\text{NDM-1}}$ (1), $\text{bla}_{\text{NDM-13}}$ (1), $\text{bla}_{\text{NDM-19}}$ (1) |
|                  | ST361 (1)                          | $\text{bla}_{\text{NDM-5}}$ (1)                  |
|                  | ST405 (2)                          | $\text{bla}_{\text{OXA-48}}$ (1), $\text{bla}_{\text{NDM-5}}$ (1) |
|                  | ST410 (8)                          | $\text{bla}_{\text{OXA-181}}$ (7), $\text{bla}_{\text{NDM-5}}$ and $\text{bla}_{\text{OXA-181}}$ (1) |
|                  | ST617 (2)                          | $\text{bla}_{\text{NDM-5}}$ (2)                  |
|                  | ST648 (2)                          | $\text{bla}_{\text{OXA-48}}$ (1), $\text{bla}_{\text{OXA-244}}$ (1) |
|                  | ST940 (1)                          | $\text{bla}_{\text{NDM-1}}$ (1)                  |
|                  | ST1487 (2)                         | $\text{bla}_{\text{NDM-5}}$ (1), $\text{bla}_{\text{OXA-181}}$ (1) |
|                  | ST1193 (1)                         | $\text{bla}_{\text{NDM-5}}$ (1)                  |
|                  | ST8346 (1)                         | $\text{bla}_{\text{OXA-181}}$ (1)                |
|                  | Undetermined (1)                   | $\text{bla}_{\text{NDM-6}}$ (1)                  |
| K. pneumoniae ($n=81$) | ST4 (1)                           | $\text{bla}_{\text{NDM-1}}$ (1)                  |
|                  | ST10 (2)                           | $\text{bla}_{\text{NDM-5}}$ (1), none (1)         |
|                  | ST11 (5)                           | $\text{bla}_{\text{NDM-1}}$ (4), $\text{bla}_{\text{KPC-2}}$ (1) |
|                  | ST14 (2)                           | $\text{bla}_{\text{NDM-1}}$ (2)                  |
|                  | ST15 (2)                           | $\text{bla}_{\text{NDM-1}}$ (1), $\text{bla}_{\text{KPC-2}}$ (1) |
|                  | ST16 (3)                           | $\text{bla}_{\text{NDM-1}} + \text{bla}_{\text{OXA-181}}$ (1), $\text{bla}_{\text{OXA-181}}$ (1), $\text{bla}_{\text{OXA-232}}$ (1) |
|                  | ST17 (1)                           | $\text{bla}_{\text{NDM-1}}$ (1)                  |
|                  | ST35 (1)                           | $\text{bla}_{\text{OXA-181}}$ (1)                |
|                  | ST38 (1)                           | $\text{bla}_{\text{OXA-232}}$ (1)                |
|                  | ST39 (3)                           | $\text{bla}_{\text{NDM-1}}$ (3)                  |
|                  | ST101 (1)                          | None (1)                                         |
|                  | ST147 (13)                         | $\text{bla}_{\text{NDM-1}}$ (4), $\text{bla}_{\text{OXA-181}}$ (5), $\text{bla}_{\text{OXA-48}}$ (1), $\text{bla}_{\text{NDM-1}} + \text{bla}_{\text{OXA-181}}$ (1), $\text{bla}_{\text{NDM-5}} + \text{bla}_{\text{OXA-181}}$ (1), none (1) |
|                  | ST220 (1)                          | None                                             |
|                  | ST231 (7)                          | $\text{bla}_{\text{OXA-232}}$ (4), $\text{bla}_{\text{OXA-48}}$ (1), none (2) |
|                  | ST252 (1)                          | $\text{bla}_{\text{NDM-1}}$ (1)                  |
|                  | ST258 (1)                          | $\text{bla}_{\text{KPC-3}}$ (1)                  |
|                  | ST280 (1)                          | $\text{bla}_{\text{OXA-48}}$                     |
|                  | ST307 (2)                          | None (2)                                         |
|                  | ST323 (1)                          | $\text{bla}_{\text{OXA-48}}$                     |
|                  | ST340 (2)                          | $\text{bla}_{\text{NDM-1}}$ (2)                  |
|                  | ST376 (1)                          | $\text{bla}_{\text{OXA-48}}$                     |
|                  | ST383 (4)                          | $\text{bla}_{\text{OXA-48}}$ (1), $\text{bla}_{\text{NDM-5}} + \text{bla}_{\text{OXA-48}}$ (3) |
|                  | ST395 (2)                          | $\text{bla}_{\text{OXA-232}}$ (1), none (1)      |
|                  | ST405 (1)                          | $\text{bla}_{\text{OXA-48}}$ (1)                  |
|                  | ST420 (2)                          | $\text{bla}_{\text{OXA-48}}$ (2)                  |
|                  | ST432 (1)                          | $\text{bla}_{\text{OXA-48}}$ (1)                  |
|                  | ST584 (1)                          | None (1)                                         |
|                  | ST716 (2)                          | $\text{bla}_{\text{OXA-48}}$ (2)                  |
|                  | ST873 (1)                          | $\text{bla}_{\text{OXA-48}}$ (1)                  |
|                  | ST915 (3)                          | $\text{bla}_{\text{NDM-1}}$ (3)                  |
|                  | ST983 (1)                          | $\text{bla}_{\text{OXA-48}}$ (1)                  |
institutional, national, and international CRE outbreaks [24]. Our findings highlight the epidemiological global interconnectedness of bacterial antimicrobial. Given Qatar’s demographics and its position as a major hub for international travel, the findings described here have regional and global implications. The molecular epidemiology of carbapenem resistance in Enterobacterales and its underlying mechanisms should be monitored locally, and interpreted in a global context.

**Conclusion**

The most frequent carbapenemases in CRE from Qatar are NDM and OXA-48-like enzymes. KPC, hitherto rare in the Arabian Peninsula, was present in a minority of the isolates, where all cases were associated with recent overseas medical care. CRE from Qatar belonged to diverse sequence types, suggesting limited local clonal expansion. It appears that the epidemiology of CRE in Qatar is largely driven by a combination of sporadic importation and inter-species transfer of mobile genetic elements.

**Supplementary Information** The online version contains supplementary material available at [https://doi.org/10.1007/s10096-021-04185-7](https://doi.org/10.1007/s10096-021-04185-7).

**Availability of data and materials** The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. The sequencing data are available from the National Center for Biotechnology Information (NCBI) under the accession number PRJNA627583.

**Author contribution** Conceptualization, F.B., A.A.B.; methodology, F.B., C.K.M.T., Y.D, and A.S.O.; data curation, F.B., A.D., K.M., and A.A.; investigation, A.D., C.L.M., W.C.B., and E.L.F.; formal analysis, F.B., C.K.M.T., Y.D., and A.S.O.; resources, M.A.A., A.A., and E.B.I.; writing – original draft, A.S.O., F.B., and C.K.M.T.; writing – review and editing, Y.D. and A.A.B.; all authors read and approved the final manuscript.

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**Declarations**

**Ethics approval** The study was approved with a waiver for informed consent by the Institutional Review Board at Hamad Medical Corporation, Doha (MRC-16134/16).

**Conflict of interest** The authors declare no competing interests.

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