Clinical Features and Outcomes of Bloodstream Infections Caused by New Delhi Metallo-β-Lactamase–Producing Enterobacterales During a Regional Outbreak

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Limited data about New Delhi metallo-β-lactamase (NDM) bacteremia are available. Blood isolates from 40 patients with NDM bacteremia were studied for antibiotic susceptibility and whole-genome sequencing. NDM bacteremia has high 30-day mortality. In most cases, aztreonam-avibactam is active in vitro. Ceftazidime-avibactam plus aztreonam may represent a feasible therapeutic option.

Keywords. bacteremia; carbapenem-resistant; New Delhi metallo-β-lactamases.

An outbreak of New Delhi metallo-β-lactamase (NDM)-producing Enterobacterales was recently documented in the northwestern area of Tuscany [1]. From November 2018 to May 2019, colonization or infection by NDM-producing Enterobacterales was documented in 350 patients from 9 different hospitals [1]. We retrospectively reviewed the clinical and microbiological characteristics of 40 patients with documented bloodstream infection (BSI).

METHODS

Cases of NDM-producing BSI were identified by reviewing records from the microbiology laboratories of all 9 institutions. Demographics, clinical and laboratory findings, comorbid conditions, source of infection, source control data, treatment regimens, and 30-day mortality rates were collected from clinical charts. Source of infection and source control were defined as previously described [2]. Septic shock was defined according to the Sepsis-3 definition [3]. The study was approved by the local ethical committee.

Blood isolate identification and susceptibility testing were performed by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-ToF MS; Vitek MS, bioMérieux; or MALDI Biotyper, Bruker Daltonics). Carbapenemase determinants were evaluated by either the Allplex Entero-DR Assay (Seegene) or RESIST-3 O.K.N. ICT immunocromatographic assay (Coris BioConcept, Gembloux, Belgium) and confirmed by real-time polymerase chain reaction as previously described [4]. Antimicrobial susceptibility testing was carried out with reference broth microdilution, except agar dilution for fosfomycin, according to the ISO 20776-1:2006 guidelines [5], and interpreted according to the EUCAST clinical breakpoints (v.9.0 2019; http://www.eucast.org/clinical_breakpoints/).

Isolates were subjected to whole-genome sequencing (WGS) with an Illumina MiSeq platform (Illumina Inc., San Diego, CA, USA) and a paired-end approach (2 × 300 bp). Raw sequences were assembled using SPAdes software [6]. In silico analyses using draft-assembled genomes were performed by dedicated tools available at http://www.genomicepidemiology.org/ (eg, MLST v.2.0) and by the BLAST suite (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

Continuous variables were reported as medians and interquartile ranges (IQRs). The Mann-Whitney U test was used to analyze non-normally distributed data. Categorical data were expressed as frequency distributions, and the chi-square test or Fisher exact test was used to determine if differences existed between groups. Factors influencing 30-day survival were examined by univariate analysis. All significant variables at univariate analyses (P < .05) were considered for the multivariate model. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were calculated. Statistical significance was established at P ≤ .05.

RESULTS

Overall, during the study period, 47 patients with BSI caused by NDM-producing strains were initially identified in 9 hospitals in the northwestern area of Tuscany (Italy). Of these, 44 patients...
had a confirmed BSI caused by an NDM-producing strain, whereas 3 patients had an infection caused by strains with a different mechanism of carbapenem resistance (these cases were excluded from further analysis); the data of 4 patients were unavailable. Thus, the final cohort included 40 patients, while 35 strains were available for full microbiological and molecular characterization.

The isolates from bacteremia were identified as *Klebsiella pneumoniae* (31 patients) and *Escherichia coli* (4 patients). Preliminary characterization by WGS revealed that most *K. pneumoniae* isolates belonged to the same clonal lineage, namely sequence type (ST) 147 (n = 30, 96.8%), with a singleton of ST307. The *E. coli* isolates belonged to 2 different clonal lineages, ST8 (n = 2) and ST2 (n = 2). Among the *K. pneumoniae* isolates, all those of ST147 carried the *bla*<sub>NDM-1</sub> gene, whereas those of ST307 carried *bla*<sub>NDM-5</sub> (as did the 4 *E. coli* isolates). All *K. pneumoniae* isolates and the 2 ST8 *E. coli* additionally carried the *bla<sub>CTX-M-15</sub>* extended-spectrum β-lactamase (ESBL) gene. A clonal analysis, based on single nucleotide polymorphisms (SNPs) evaluated on the core genome, revealed that all the ST147 isolates were closely related to each other (SNP range, 0–25), strongly suggesting that the outbreak was due to clonal expansion of a single NDM-1-producing *K. pneumoniae* strain.

Susceptibility patterns determined in vitro for the 35 characterized isolates are detailed in Table 1. All *K. pneumoniae* strains (n = 31) were resistant to expanded-spectrum cephalosporins, carbapenems, and β-lactamase inhibitor combinations, while they were susceptible to aztreonam (ATM)-avibactam (AVI; MIC ≤ 1 mg/L). The *E. coli* isolates (n = 4) showed a similar broad spectrum of β-lactam resistance, but they were more frequently resistant to ATM-AVI, with some differences between the ST8 (n = 2) and ST2 (n = 2) isolates: Whereas the former showed high-level resistance to ATM (MIC > 32 mg/L) and were resistant to ATM-AVI (MIC, 8 mg/L), the latter showed a lower resistance level to aztreonam (MICs, 2 and 8 mg/L) and were not frankly resistant to the AZT-AVI combination (MICs, 2 and 4 mg/L, respectively). Beyond AZT-AVI, the most active antibiotics were colistin and fosfomycin (susceptibility rate of 91.4% and 80.6%, respectively). Almost all strains (97.2%) were resistant to aminoglycosides.

The clinical characteristics of the patient population and comparison between survivors and nonsurvivors are illustrated in Table 2. Half of the bacteremic patients were cared for in medical wards, and 47.5% had malignancy. The majority of patients (67.5%) had previous documented rectal NDM colonization. The overall 30-day mortality rate was 42.5%. Septic shock occurred in 32.5% of patients. The median age and Charlson comorbidity index score were significantly higher in nonsurviving patients than in those who survived. At the same time, primary bacteremia (unknown focus) was more common among patients who died, whereas central venous catheter (CVC)–related bacteremia was more common among survivors.

DISCUSSION

This is the first European report on a relatively large group of patients with bacteremia caused by NDM-producing Enterobacteriales. A preliminary genomic characterization of isolates revealed that the majority of episodes of BSI were caused by an NDM-1-producing strain of *K. pneumoniae* belonging to ST147. Clonal expansion, therefore, appears to be the major mechanism underlying the large outbreak of NDM-producing strains ongoing in this area, although further characterization of other isolates will be necessary to confirm the contribution of this clone and the diversity of circulating strains.

In the Tuscany cluster, BSIs caused by NDM-producing strains involved patients frequently cared for in medical wards, with multiple comorbidities and severe underlying diseases (such as cancer), and were associated with a high 30-day mortality rate. Mortality was greatly influenced by advanced age and by comorbid conditions, calculated by the Charlson comorbidity index. Moreover, mortality was significantly higher among patients not receiving an in vitro active antibiotic therapy. This latter finding underlines the importance of early detection of the molecular mechanism underlying the carbapenem resistance phenotype; it is noteworthy that some patients who died, according to previous local epidemiological data showing a predominance of KPC-producing strains, were empirically treated with CAZ-AVI alone or in combination with aminoglycosides [7].
Data about treatment of BSI caused by NDM-producing *Enterobacterales* are very limited [8, 9]. Treatment regimens used in previous reports include colistin alone or in combination with aminoglycosides or meropenem, and the association of fosfomycin with meropenem [10–13]. In our series, all strains were in vitro resistant to ATM, while full susceptibility was restored when combination ATM + AVI was used. The efficacy of this combination relies on the activity that the monobactam ATM typically retains against MBLs but not against ESBLs (ie, all strains in our study produced CTX-M-15). In vitro studies demonstrated a synergistic effect of the combination of CAZ-AVI plus AZT against NDM-producing isolates [14, 15], and a clinical study including 5 patients with bacteremia caused by NDM-producing *Enterobacterales* showed that combination therapy with CAZ-AVI plus AZT is an effective therapeutic option [16]. Of interest, compared with other regimens, in our study surviving patients were more frequently treated with the combination of CAZ-AVI plus AZT. Although this finding was not statistically significant at Cox regression analysis, this is a potentially interesting finding that should be confirmed in larger, multicentric cohorts.

### Table 1. In Vitro Susceptibilities of 35 NDM-Producing Isolates Collected From Patients With BSI Admitted to 9 Hospitals Across Tuscany in 2018–2019

| Bacterial Species (Isolate No.) and Antimicrobial Agent Tested | MIC, mg/L | Susceptibility Rates, % |
|---------------------------------------------------------------|-----------|-------------------------|
|                                                             | Range     | S  | I  | R  |
| *Klebsiella pneumoniae* (n = 31)                             |           |    |    |    |
| Ceftriaxone                                                  | >4        | -  | -  | 100|
| Cefazidime                                                   | >64       | -  | -  | 100|
| Cefepime                                                     | >16       | -  | -  | 100|
| PIP-TAZ                                                      | >128/4    | -  | -  | 100|
| Ciprofloxacin                                                | >1        | -  | -  | 100|
| Levofloxacin                                                 | >8        | -  | -  | 100|
| Amikacin                                                     | >32       | -  | -  | 100|
| Gentamicin                                                   | ≤0.5 to >8| 3.2| -  | 96.8|
| Meropenem                                                    | 4 to 64   | -  | 3.2| 96.8|
| Ertapenem                                                    | 1 to >2   | -  | -  | 100|
| TMP-SMX                                                      | ≤1/19 to >8/152 | 3.2| -  | 96.8|
| Tigecycline                                                  | ≤0.25 to >4| 80.6| - | 19.4|
| Colistin                                                     | ≤0.5 to >8| 90.3| - | 9.7 |
| Aztreonam                                                    | >32       | -  | -  | 100|
| Fosfomycin*                                                  | 4 to 64   | 80.6| - | 19.4|
| CLZ-TAZ                                                      | >64/4     | -  | -  | 100|
| CAZ-AVI                                                      | >32       | -  | -  | 100|
| MER-VAB                                                      | 4 to >64  | 3.2| -  | 96.8|
| AZT-AVI                                                      | ≤0.25 to 1| 100| -  | -  |
| *Escherichia coli* (N = 4)                                   |           |    |    |    |
| Ceftriaxone                                                  | >4        | -  | -  | 100|
| Cefazidime                                                   | >64       | -  | -  | 100|
| Cefepime                                                     | >16       | -  | -  | 100|
| PIP-TAZ                                                      | >128/4    | -  | -  | 100|
| Ciprofloxacin                                                | >1        | -  | -  | 100|
| Levofloxacin                                                 | >8        | -  | -  | 100|
| Amikacin                                                     | >32       | -  | -  | 100|
| Gentamicin                                                   | >8        | -  | -  | 100|
| Meropenem                                                    | 64 to >64 | -  | -  | 100|
| Ertapenem                                                    | >2        | -  | -  | 100|
| TMP-SMX                                                      | >8/152    | -  | -  | 100|
| Tigecycline                                                  | ≤0.25 to 1| 75 | -  | 25  |
| Colistin                                                     | ≤0.5 to 1 | 100| -  | -   |
| Aztreonam                                                    | 2 to 32   | -  | 25 | 75  |
| Fosfomycin*                                                  | ≤8 to 64  | 75 | -  | 25  |
| CLZ-TAZ                                                      | >64/4     | -  | -  | 100|
| CAZ-AVI                                                      | >32       | -  | -  | 100|
| MER-VAB                                                      | 64 to >64 | -  | -  | 100|
| AZT-AVI                                                      | 2 to 8    | -  | 50 | 50  |

Abbreviations: AZT-AVI, aztreonam-avibactam; CAZ-AVI, ceftazidime-avibactam; CLZ-TAZ, ceftolozane-tazobactam; MER-VAB, meropenem-vaborbactam; PIP-TAZ, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole.

*MIC for fosfomycin determined by agar dilution.*
We used CAZ-AVI at a dosage of 2.5 g every 8 hours and ATM at a dosage of 2 g every 8 hours in all cases (with dose adjustment according to renal function). Recently, therapeutic drug monitoring of CAZ-AVI and ATM performed in a child with BSI caused by KPC and NDM-producing Enterobacter spp. showed adequate serum concentrations of the combination CAZ-AVI plus ATM, both used at a dosage of 50 mg/kg every 8 hours [17]. If we translated this dosage in adult patients, the dose would have to be increased to 3–3.5 g every 8 hours for both ATM and CAZ-AVI. Overall, we observed a good clinical response of this combination therapy at standard dosages. Further pharmacokinetic studies are needed to assess the optimal dosage of ATM and CAZ-AVI in patients with BSI due to NDM-producing strains.

After the identification of the outbreak, several rapid actions were implemented to contain the spread of NDM-producing strains across health care facilities in the northwestern area of Tuscany. The measures included (i) mandatory screening by rapid molecular tests on admission and during hospitalization for all at-risk patients in medical wards and for all patients in ICU, oncology, oncohematology, transplant unit, cardiac surgery, infectious diseases, acute rehabilitation; (ii) adoption of contact precautions in all cases; (iii) collection of data in a regional database and obligatory notification of all cases to a centralized laboratory; (iv) development of practical guidelines for the clinical management of NDM + cases; (v) dedicated medical and nursing staff and, in the tertiary hospital, identification of a dedicated ward for patients with colonization/infection by

Table 2. NDM-Producing Enterobacterales BSI: Comparison Between Survivors and Nonsurvivors (Tuscany, Italy, 2018–2019)

|                             | All Patients (n = 40) | Survivors (n = 23) | Nonsurvivors (n = 17) | P    |
|-----------------------------|-----------------------|--------------------|-----------------------|------|
| Age, median (IQR), y        | 70.5 (55.25–77.75)    | 63 (48–76)         | 74 (67–82.5)          | .018 |
| Male sex                    | 28 (70)               | 17 (73.9)          | 11 (64.7)             | .530 |
| Ward of hospitalization     |                       |                    |                       |      |
| Medical wards               | 20 (50)               | 12 (52.2)          | 8 (47.1)              | .687 |
| ICU wards                   | 13 (32.5)             | 8 (34.8)           | 5 (29.4)              |      |
| Surgery                     | 7 (17.5)              | 3 (13)             | 4 (23.5)              |      |
| Comorbidities               |                       |                    |                       |      |
| Cardiovascular disease      | 20 (50)               | 9 (39.1)           | 11 (64.7)             | .110 |
| Malignancy                  | 19 (47.5)             | 9 (39.1)           | 10 (58.8)             | .218 |
| COPD                        | 12 (30)               | 5 (21.7)           | 7 (41.2)              | .186 |
| Diabetes                    | 12 (30)               | 8 (34.8)           | 4 (23.5)              | .443 |
| Chronic renal diseases      | 7 (17.5)              | 4 (17.4)           | 3 (17.6)              | .983 |
| Charlson comorbidity index, median (IQR) | 4 (2–7)               | 3 (0–5)            | 6 (3–8.5)             | .010 |
| Immunosuppressive therapy,a previous 30 d | 15 (37.5)             | 7 (30.4)           | 8 (47.1)              | .283 |
| Source of infection         |                       |                    |                       |      |
| Unknown                     | 10 (25)               | 3 (13)             | 7 (41.2)              | .067 |
| Urinary tract               | 10 (25)               | 7 (30.4)           | 3 (17.6)              |      |
| Intravascular device        | 9 (22.5)              | 8 (34.8)           | 1 (5.9)               |      |
| ABSSSI                      | 6 (15)                | 3 (13)             | 3 (17.6)              |      |
| Respiratory tract           | 3 (7.5)               | 2 (8.7)            | 1 (5.9)               |      |
| Intra-abdominal             | 2 (5)                 | 0                  | 2 (11.8)              |      |
| NDM-producing strain rectal colonization | 27 (67.5)             | 17 (89.5)          | 10 (62.5)             | .058 |
| Source control              | 20 (50)               | 12 (52.2)          | 8 (47.1)              | .749 |
| SOFA score, median (IQR)    | 4 (2–6)               | 4 (2–6)            | 5 (3–6.5)             | .229 |
| Length of hospital stay, median (IQR), d | 23 (13–38)            | 26.5 (17.25–41.75) | 19 (10–33)            | .187 |
| Septic shock                | 13 (32.5)             | 7 (30.4)           | 6 (35.3)              | .746 |
| Antibiotic regimens         |                       |                    |                       |      |
| No in vitro active antibiotic therapy | 14 (35)               | 5 (21.7)           | 9 (52.9)              | .054 |
| CAZ-AVI + ATM               | 12 (30)               | 10 (43.5)          | 2 (11.8)              |      |
| Colistin-based regimenb     | 9 (22.5)              | 4 (17.4)           | 5 (29.4)              |      |
| Othersc                     | 5 (12.5)              | 4 (17.4)           | 1 (5.9)               |      |

Data are presented as No. (%), unless otherwise indicated. P values < .05 (indicating statistical significance) were reported in bold.

Abbreviations: ABSSSI, acute bacterial skin and skin structures infection; ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range.

aIncluding steroidal and nonsteroidal immunosuppressive therapy.

bColistin was used in combination with meropenem (4 cases), fosfomycin (3 cases), tigecycline (1 case), AZT + piperacillin-tazobactam (1 case).

cOther therapies include: 1 patient treated with fosfomycin + tigecycline + amikacin (death); 1 patient treated with meropenem + tigecycline + fosfomycin; 1 patient treated with fosfomycin alone; 1 patient treated with tigecycline + meropenem; 1 patient treated with tigecycline alone.
NDM-producing Enterobacterales; (vi) educational meetings for all the professionals involved [18].

Our study has some limitations: (i) the number of BSIs is limited, but it is the largest cohort described in Europe; (ii) the multivariate analysis might be affected by the low number of cases; (iii) a high proportion of patients did not receive any active antibiotic therapy, which may have influenced the mortality rate. Nevertheless, this finding reflects clinical practice and the difficulties associated with early identification and appropriate treatment of infections caused by carbapenem-resistant Enterobacterales with multiple mechanisms of resistance.

In conclusion, the epidemiology of carbapenemase-producing Enterobacterales strains is changing over time, and new clones carrying new molecular mechanisms of resistance are emerging in some countries such as Italy. Bacteremia mediated by NDM-producing Enterobacterales is a highly lethal condition and requires prompt recognition and treatment. Although the combination of CAZ-AVI plus AZT appears to be a good therapeutic option in patients with NDM-producing bacteremia, the optimal regimen for the treatment of this infection is not defined and further studies are needed.

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