**IncN1 ST7 Epidemic Plasmid Carrying blaIMP-4 in One ST85-Type Klebsiella oxytoca Clinical Isolate with Porin Deficiency**

Mingyue Sun  
Weiqiang Xiao  
Qingxia Xu  
Department of Clinical Laboratory, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, People’s Republic of China

**Purpose:** *Klebsiella oxytoca* is an opportunistic pathogen causing nosocomial infections. This study was designed to characterize the genomic features of a carbapenem-resistant *K. oxytoca* strain and analyze its molecular characteristics.

**Materials and Methods:** The strain wzx-IMP was isolated from the blood of a 2-year-old girl diagnosed with acute myeloid leukemia-M7. Species identification was performed, and the minimal inhibitory concentration of the strain was measured. Multilocus sequence typing was performed to identify the subtypes of *K. oxytoca*. The transfer capacity of the blaIMP-4-harboring plasmid was investigated by conjugation experiments, and the genome characteristics of the strain were examined using whole-genome sequencing.

**Results:** wzx-IMP belongs to the ST85 type and is resistant to imipenem and meropenem, which harbored the blaIMP-4 gene. The blaIMP-4 gene was located in an IS26-associated class 1 integron of pwzx_IMP, which contains conserved IncN1-type backbone regions with a replication gene and its accessory structure for plasmid replication. The blaIMP-4-carrying plasmid in wzx-IMP was successfully transferred to *Escherichia coli* EC600 by conjugation. Whole-genome sequencing showed that the wzx-IMP isolate included the blaOXY-1-1 gene, accompanied by OmpK36 absence.

**Conclusion:** We report an ST85-type carbapenem-resistant *K. oxytoca* strain, which produces blaIMP-4 located in an IncN1-type plasmid and accompanied by OmpK36 porin deficiency.

**Keywords:** *Klebsiella oxytoca*, blaIMP-4, ST85, IncN1, OmpK36

---

**Introduction**

Antimicrobial resistance is a global issue associated with an increased and often unrestricted antibiotic use in clinical settings, which leads to the dissemination of carbapenem-resistant Enterobacterales (CRE) in healthcare facilities (World Health Organization, 2017). CRE constitutes a large group of bacteria with different mechanisms for drug resistance. Among them, carbapenem-resistant *Klebsiella pneumoniae* accounts for approximately 60%, followed by *Escherichia coli* and *Enterobacter cloacae*, but data on carbapenem-resistant *K. oxytoca* are limited. Carbapenemases comprise three of the four Ambler classes as follows: Class A (eg, *K. pneumoniae* carbapenemases and some variants of Guiana extended-spectrum β-lactamases), class B (eg, metallo-β-lactamases (MBLs), including New Delhi MBLs (NDMs), Verona integron-encoded MBLs, and imipenemase (IMP)), and class D (eg, OXA-48-like carbapenemases). Acquired MBLs first appeared in *Pseudomonas*
aeruginosa in the 1980/1990s; soon after, these MBLs spread into Enterobacteriaceae. Unlike NDMs, IMP-type β-lactamases are not often detected in CRE from China; one of the most commonly observed IMP variants is IMP-4, which was firstly detected in Acinetobacter spp. in Hong Kong in 2001. Since then, IMP-4-type carbapenemases have spread globally.5–10 The blalIMP-4 gene is often integrated into broad-host-range conjugative plasmids and carried on IncA/C- and IncN-type plasmids, which are transferred between different Gram-negative bacilli (eg, Enterobacteriaceae, Acinetobacter spp., and Pseudomonas aeruginosa).11–13 The horizontal transfer of blalIMP-4 in these plasmids is frequently associated with class 1 integrons. Plasmids belonging to the IncN incompatibility group are important mobile genetic platforms for disseminating clinically important resistance genes among enterobacterial species.14–19 The IncN group can be further divided into three subgroups: IncN1, IncN2, and IncN3. These subgroups have similar backbone gene organization but with limited nucleotide sequence homology over the backbones. Plasmid-borne blalIMP-4 has been sporadically reported in different Gram-negative bacilli in China. However, only a few studies have reported the complete sequence of blalIMP-4-harboring plasmids, limiting our understanding of the transmission mechanism of blalIMP-4 between different Gram-negative bacilli.13,20–22 In addition to producing carbapenemases, deficiency of outer membrane protein (OMP) combined with high-level AmpC cephalosporinase production also leads to Enterobacteriaceae resistance.23 Still, not many reports on producing MBL in combination with the deficiency of OmpK36 porin in carbapenem-resistant Klebsiella oxytoca strain in China.23

In this study, we characterized the genomic features of an IMP-4-producing accompanied with deficiency of OmpK36 porin K. oxytoca wzx-IMP ST85 strain, a rare sequence type, and the blalIMP-4 gene is carried with an IncN1-type plasmid, isolated from a girl with a bloodstream infection in China. To our knowledge, the blalIMP-4-carrying K. oxytoca ST85 strain identified in this study has not been reported previously.

Materials and Methods

Clinical Case, Bacterial Isolates, and Susceptibility Testing

The patient was a 2-year-old girl admitted to a cancer hospital in September 2019 who was diagnosed with acute myeloid leukemia-M7. The carbapenem-resistant K. oxytoca strain wzx-IMP was isolated from blood specimens on the next 4 days after hematopoietic stem cell transplantation. The patient received intravenous teicoplanin and meropenem, with voriconazole to prevent fungal infections empirically at first. When the child’s condition was still getting worse, the antimicrobial drugs were switched to tigecycline and cefoperazone/sulbactam. The patient condition improved after antibiotic conversion. The antimicrobial susceptibility test results showed sensitivity to tetracycline, which was consistent with the improvement in the patient’s symptoms. The patient was discharged 4 weeks after transplantation.

The species was identified using the Phoenix 100 Automated Microbiology System (Becton-Dickinson, New Jersey, USA), reidentified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) with using a Microflex LT mass spectrometer (Bruker Daltonik), and analyzed using MALDI Biotyper (Bruker Corporation, Massachusetts, USA).

The minimal inhibitory concentrations (MICs) of the CRE strain were measured using the Phoenix 100 Automated Microbiology System and interpreted using the Clinical Laboratory Standards Institute criteria (CLSI, 2019), except for polymyxin, which was interpreted using the European Committee on Antimicrobial Susceptibility Testing criteria (EUCAST, 2019). Nineteen antibiotics belonging to 11 classes of antimicrobials were used for susceptibility tests in this study, including penicillins (ie, ampicillin), β-lactam/β-lactamase inhibitor complexes (ie, amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam), aminoglycosides (ie, gentamicin and amikacin), monooicyclic β-lactams (ie, aztreonam), chloramphenicol (ie, chloramphenicol), cephalosporins (ie, cefazolin, cefotaxime, ceftazidime, and cefepime), carbapenems (ie, imipenem and meropenem), fluoroquinolones (ie, ciprofloxacin and levofloxacin), folate metabolic pathway inhibitors (ie, trimethoprim-sulfamethoxazole), tetracyclines (ie, tetracycline), and colistin.

Bacterial Genotyping

Multilocus sequence typing (MLST) for K. oxytoca was performed using previously described methods.24 The polymerase chain reaction (PCR) products were purified and sequenced, and allelic profiles and sequence types were assigned using the K. oxytoca MLST website (http://pubmlst.org/koxytoca/).
Conjugation Experiment
The transfer capacity of the blaIMP-4-harboring plasmid was investigated by conjugation experiments, which were conducted using previously described methods.25 Rifampin-resistant E. coli EC600 was used as the recipient, and the wzx-IMP strain was used as the donor. Transconjugants were selected on Mueller–Hinton (MH) agar supplemented with sodium rifampin (200 µg/mL) and meropenem (2 µg/mL) and identified by detecting antimicrobial susceptibility and resistance genes using PCR.

Whole-Genome Sequencing
The genomic DNA of the isolate was extracted using a QIAamp DNA Mini Kit (Qiagen, USA). The Illumina NovaSeq 6000 platform (Illumina Inc., San Diego, CA, USA) and a long-read MinION sequencer (Nanopore, Oxford, UK) were used for whole-genome sequencing. The de novo hybrid assembly of both short Illumina reads and long MinION reads was performed using Unicycler. The whole-genome sequence was automatically annotated by the Prokaryotic Genome Annotation Pipeline server (NCBI, Maryland, USA).

Plasmid Analysis
We used the oriTfinder to quickly detect the origins of transfer (oriTs) and three other transfer-associated modules, such as relaxase, type IV coupling proteins (T4CP), and type IV secretion system (T4SS), in the blaIMP-4-carrying plasmid. The graphical circular map of the blaIMP-4-carrying plasmid was converted using the CGView Server.26 Comparisons of the blaIMP-4-carrying plasmid with similar plasmids were performed using the BRIG and Easyfig tools.27,28

Nucleotide Sequence Accession Numbers
The sequences of the blaIMP-4-carrying plasmid were submitted to the GenBank database (NCBI, Maryland, USA) with the following accession number: pwzx_IMP (MW590809). All relevant data are available from the corresponding author upon reasonable request.

Results
Bacterial Identification and Susceptibility Testing
The isolate was identified as K. oxytoca using the Phoenix 100 system and MALDI-TOF-MS. Regarding antimicrobial susceptibility profiles, as shown in Table 1, the wzx-IMP strain was susceptible to amikacin, aztreonam, chloramphenicol, levofloxacin, trimethoprim-sulfamethoxazole, tetracycline, and colistin (MICs, ≤0.5 µg/mL), intermediate susceptible to gentamicin and piperacillin-tazobactam, and resistant to ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, cefazolin, cefotaxime, ceftazidime, cefepime, imipenem, and meropenem.

MLST and Conjugation Experiments
MLST was performed for the wzx-IMP isolate. Based on the MLST results, the K. oxytoca isolate belongs to the ST85 type, which has not been reported previously in carbapenem-resistant K. oxytoca. We analyzed the genome data in the GenBank database (accessed on June 10, 2021) and found that no ST85-type K. oxytoca sequences are currently available in the database. The blaIMP-4-carrying plasmid in the wzx-IMP strain was successfully transferred to E. coli EC600 by conjugation. Transconjugants exhibited phenotypes resistant to imipenem and meropenem. PCR assays showed that the transconjugants under study were positive for the blaIMP-4 gene.

Table 1 Antimicrobial Susceptibility Testing

| Antimicrobial Agent | MIC (µg/mL) | MIC Breakpoint (µg/mL) |
|---------------------|-------------|------------------------|
|                     | S | I | R                  |
| Amikacin            | ≤8/S         | ≤16                     | 32          | ≥64         |
| Aztreonam           | ≤2/S         | ≤8                      | 16          | ≥16         |
| Chloramphenicol     | ≤4/S         | ≤8                      | 16          | ≥32         |
| Levofloxacin        | ≤1/S         | ≤0.5                    | 1           | ≥2          |
| Trimethoprim-sulfamethoxazole | ≤0.5/5/5 | ≤2/5                    | 16          | ≥4/76       |
| Tetracycline        | ≤2/S         | ≤4                      | 8           | ≥16         |
| Polymyxin           | ≤0.5/S       | ≤2                      | >2          | ≥4          |
| Gentamicin          | ≤8/I         | ≤8                      | 16          | ≥16         |
| Piperacillin-tazobactam | ≤64/4/I | ≤16/4                    | 32/4–64/4   | ≥16/4       |
| Ampicillin          | >16/R        | ≤8                      | 16          | ≥32         |
| Amoxicillin-clavulanate | >16/8/R   | ≤8                      | 16          | ≥32/16      |
| Ampicillin-sulbactam| >16/8/R      | ≤8                      | 16          | ≥32/16      |
| Cefazolin           | >16/R        | ≤2                      | 4           | ≥8          |
| Cefotaxime          | >32/R        | ≤2                      | 4           | ≥8          |
| Cefazidime          | >16/R        | ≤2                      | 4           | ≥8          |
| Cefepime            | >16/R        | ≤2                      | 4           | ≥8          |
| Imipenem            | >8/R         | ≤2                      | 4           | ≥8          |
| Meropenem           | >8/R         | ≤2                      | 4           | ≥8          |

Notes: *CLSI guideline for MIC breakpoints of Enterobacteriaceae except polymyxin. **EUCAST guideline for MIC breakpoints of polymyxin.

Abbreviations: S, susceptible; I, intermediate; R, resistant; –, missing breakpoints.
WGS and Molecular Characterization

The wzx-IMP isolate had a chromosome and two plasmids (PlasmidA and pwzx_IMP), which were 6013415 bp, 140577 bp, and 62892 bp in length, had guanine–cytosine content of 55.91%, 51.90%, and 52.50%, respectively.

WGS showed that the isolate included blaOXY-1-1, a chromosomally encoded gene. Concerning the chromosomal outer membrane proteins OmpK35 and OmpK36, we did not find OmpK36 porins, and analysis of Ompk35 sequences did not reveal any nonsense point mutation insertion and/or deletion causing a reading frameshift with a premature stop codon or gross disruption by an insertion sequence.

Plasmid Analysis and Comparisons

pwzx_IMP was a 62,892-bp circular plasmid and was identified as an IncN1 group structure. It contains 45 predicted open reading frames. Through the oriTfinder server, we found that pwzx_IMP had a complete set of oriTs, relaxase, T4 cP, and T4SS (Figure 1), indicating that the plasmid has a strong self-transfer ability, which was consistent with the results of the conjugation experiments.

The blaIMP-4-carrying plasmid belonged to the IncN1 ST7 lineage. Four genes were involved in antimicrobial resistance, including the carbapenemase-encoding gene blaIMP-4, the qnrS1 gene for quinolone resistance, the

![Figure 1](https://doi.org/10.2147/IDR.S330362)
sulfonamide resistance gene *sul1*, and the *aac* gene (Figure 2).

The pwzx_IMP plasmid contained conserved IncN1-type backbone regions, containing a replication gene and its accessory structure for plasmid replication (Figure 2). The *blaIMP-4* gene mapped to pwzx_IMP was located at the proximal end of a truncated integrase gene, which included *Δintl1* and *blaIMP-4* and was designated In823, preceded by IS26 in the upstream region, followed by another IS26 sequence in the downstream region.

A BLAST search of the pwzx_IMP plasmid sequence against the GenBank database showed that several similar previously published IncN1 plasmids were found (Figure 3): pIMP-HZ1 (accession no. KU886034) from the *K. pneumoniae* strain Kp1, pIMP-HK1500 (accession no. KT989599) from the *Citrobacter freundii* strain CRE1500, and pIMP-GZ1517 (accession no. KT982618) from the *E. coli* strain CRE1517, which are all found in China with an 84% query coverage and overall 100% nucleotide identity. However, the plasmid with the *C. freundii* strain ECL-14-57 (accession no. MH727565) exhibited an 84% query coverage and overall 99.89% nucleotide identity; the plasmid from the *K. oxytoca* strain pKOX3 (accession no. KY913900) exhibited an 81% query coverage and overall 99.90% nucleotide identity; the plasmid from the *K. pneumoniae* strain BKP19 (accession no. VWRO01000005) exhibited a 62% query coverage and an overall 99.95% nucleotide identity. The structural characteristics of pwzx_IMP compared to pIMP-HZ1, pIMP-HK1500, pIMP-GZ1517, and p24854-IMP, pECL-14-57, pKOX3 and pBKP19 are presented in Figure 4. KT982618, KT989599, and VWRO01000005 carry *blaIMP-4* only, whereas KU886034, KY913900, and MH727565 carry both *blaIMP-4* and *qnrS1*; however, pwzx_IMP harbors the *blaIMP-4*, *qnrS1*, *sul1*, and *aac* resistance genes. Both the *sul1* and *aac* genes are absent in similar plasmids.

![Figure 2 Backbone structure of the pwzx_IMP.](https://www.dovepress.com/doi.org/10.2147/IDR.S330362)
Discussion

The chromosome of *K. oxytoca* encodes a class A β-lactamase-designated OXY (previously called K1 or KOXY). The β-lactamase OXY group comprises the OXY-1, OXY-2, OXY-3, OXY-4, OXY-5, and OXY-6 subgroups. Strains that overproduce the chromosomally encoded β-lactamase OXY are resistant to all β-lactamase inhibitors. In this study, the isolate included *blaOXY-1-1*, a chromosomally encoded gene, which is the most common OXY gene type. IMP-4 carbapenemases, first identified in Hong Kong and China in the 1990s and initially restricted to Asia and the Pacific, have since become the predominant carbapenemase type worldwide; however, unlike NDMs, IMP-type β-lactamases are not often detected in CRE from China. The *blaIMP* genes are often found together
with other resistance genes in the variable gene cassette arrays of class 1 integrons, and these integrons are further associated with mobile elements, such as transposons and plasmids, leading to the easily mobilization of cassette-borne resistance genes across various bacterial species. IncN plasmids have been reported globally but are mainly prevalent in China and the USA. In the study by Hao et al, examining IncN1 plasmids in China (including the mainland and Taiwan, China), the most common carbapenemase type was \$\textit{bla}\text{IMP}$ (63.9%; 23/36), followed by \$\textit{bla}\text{NDM}$ (19.4%; 7/36) and \$\textit{bla}\text{KPC}$ (19.4%; 7/36), and among the 25 IncN1 plasmids reported in the USA, \$\textit{bla}\text{KPC}$ was the most common carbapenemase type, which accounted for 88% (22/25). In China, Chen et al have reported a Chinese \textit{Klebsiella oxytoca} strain ZC101 with \textit{IMP}-4 and OmpK36 porin deficiency, the OmpK36 loss of strain was due to the IS5 insertion to OmpK36. However, the strain wzx-IMP has a large number of points mutations and deletions. In short, we report for the first time an ST85-type \textit{K. oxytoca} strain in China, which carried an IncN1-type plasmid, producing \textit{IMP}-4-type MBLs along with OmpK36 porin deficiency.

Note that the backbone structures of \textit{pwzx_IMP} identified in this study have been reported in other members of the \textit{Enterobacteriaceae} family, including \textit{E. coli}, \textit{Klebsiella} species, \textit{C. freundii}, and \textit{Enterobacter cloacae}, along with \textit{Pseudomonas} species. Based on the data reported in this study, it is reasonable to hypothesize that these resistance-encoding genes may have been recruited into a variable genetic locus flanked by IS elements.
by transposons and insertion sequence elements, while conserving the remaining plasmid scaffold. The successful transmission of these related episomes among various bacterial species challenges people with an interest in public health, which should be a cause of concern for clinicians, microbiologists, and administrators for infection control measures.

Conclusion
In summary, this study reports the first *K. oxytoca* ST85 strain harboring the class B β-lactamase blaIMP-4 in an IncN1-type plasmid recovered from a child with a bloodstream infection in China. This work highlights the important role played by mobile plasmids identified in *K. oxytoca* and other bacteria as a modern threat to the successful treatment of infections.

Ethical Approval
This study obtained permissions from the Bioethics Committee of Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital and participants (consent to participate was obtained from participants) to review patient records and use the data.

Consent Statement
All authors reporting this patient’s details of the manuscript “IncN1 ST7 epidemic plasmid carrying blaIMP-4 in ST85-type Klebsiella oxytoca clinical isolate with porin deficiency” state that publication of their clinical details was obtained from the parent of the patient.

Funding
This study was supported by the Hospital Nursery Fund (Grant No. 20170111).

Disclosure
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References
1. Sekizuka T, Matsui M, Takahashi T, et al. Complete genome sequence of bla IMP-6-positive Metakosakonia sp. MRY16-398 isolate from the ascites of a diverticulitis patient. *Front Microbiol*. 2018;9:2853. doi:10.3389/fmicb.2018.02853
2. ZHOU H, ZHANG K, CHEN W, et al. Epidemiological characteristics of carbapenem-resistant Enterobacteriaceae collected from 17 hospitals in Nanjing district of China. *Antimicrob Resist Infect Control*. 2020;9 (1):15. doi:10.1186/s13756-019-0674-4
3. Perez-Vazquez M, Otle-Iglesias J, Sola-Campoy PJ, et al. Characterization of carbapenemase-producing Klebsiella oxytoca in Spain, 2016–2017. *Antimicrob Agents Chemother*. 2019;63(6):e02529–18. doi:10.1128/AAC.02529-18
4. Miao M, Wen H, Xu P, et al. Genetic diversity of carbapenem-resistant Enterobacteriaceae (CRE) clinical isolates from a tertiary hospital in eastern China. *Front Microbiol*. 2018;9:3341. doi:10.3389/fmicb.2018.03341
5. Wang J, Yuan M, Chen H, et al. First report of Klebsiella oxytoca strain simultaneously producing NDM-1, IMP-4, and KPC-2 carbapenemases. *Antimicrob Agents Chemother*. 2017;61(9):e09877–17. doi:10.1128/AAC.00877-17
6. Chu YW, Afzal-Shah M, Houang ET, et al. IMP-4, a novel metallo-beta-lactamase from nosocomial Acinetobacter spp. collected in Hong Kong between 1994 and 1998. *Antimicrob Agents Chemother*. 2001;45 (3):710–714. doi:10.1128/AAC.45.3.710-714.2001
7. Lee JH, Bae IK, Lee CH, et al. Molecular characteristics of first IMP-4-producing Enterobacter cloacae sequence type 74 and 194 in Korea. *Front Microbiol*. 2017;8:2343. doi:10.3389/fmicb.2017.02343
8. Lee JH, Lee CH, Bae IK. Emergence of IMP-4-producing Enterobacter aerogenes clinical isolate. *Clin Lab*. 2018;64 (7):1323–1326. doi:10.7754/Clin.Lab.2018.180211
9. Ghaith DM, Zafer MM, Ismail DK, et al. First reported nosocomial outbreak of Serratia marcescens harboring bla IMP-4 and bla VIM-2 in a neonatal intensive care unit in Cairo, Egypt. *Infect Drug Resist*. 2018;11:221–2217. doi:10.2147/IDR.S174689
10. Espedido BA, Partridge SR, Iredell JR. bla(IMP-4) in different genetic contexts in Enterobacteriaceae isolates from Australia. *Antimicrob Agents Chemother*. 2008;52(8):2984–2987. doi:10.1128/ AAC.01634-07
11. Ho PL, Lo WU, Chan J, et al. pIMP-PH114 carrying bla IMP-4 in a Klebsiella pneumoniae strain is closely related to other multidrug-resistant IncA/C2 plasmids. *Curr Microbiol*. 2014;68 (2):227–232. doi:10.1007/s00284-013-0471-x
12. Ho PL, Cheung YY, Wang Y, et al. Characterization of carbapenem-resistant Escherichia coli and Klebsiella pneumoniae from a healthcare region in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2016;35(3):379–385. doi:10.1007/s10096-015-2550-3
13. Lo WU, Cheung YY, Lai E, et al. Complete sequence of an IncN plasmid, pIMP-HZ1, carrying blaIMP-4 in a Klebsiella pneumoniae strain associated with medical travel to China. *Antimicrob Agents Chemother*. 2015;57(3):1561–1562. doi:10.1128/AAC.02298-12
14. Poirel L, Bonnin RA, Nordmann P. Analysis of the resistome of a multidrug-resistant NDM-1-producing Enterobacter aerogenes coli strain by high-throughput genome sequencing. *Antimicrob Agents Chemother*. 2011;55(9):4224–4229. doi:10.1128/AAC.00165-11
15. Chen YT, Lin AC, Siu LK, et al. Sequence of closely related plasmids encoding bla(NDM-1) in two unrelated Klebsiella pneumoniae isolates in Singapore. *PLoS One*. 2012;7(11):e48737. doi:10.1371/ journal.pone.0048737
16. Partridge SR, Paulsen IT, Iredell JR. pJHE137 carrying blaCTX-M-62 is closely related to p271A carrying blaNDM-1. *Antimicrob Agents Chemother*. 2012;56(4):2166–2168. doi:10.1128/AAC.05796-11
17. Netikul T, Sidjabat HE, Paterson DL, et al. Characterization of an IncN2-type blaNDM-(1)-carrying plasmid in Escherichia coli ST131 and Klebsiella pneumoniae ST11 and ST15 isolates in Thailand. *J Antimicrob Chemother*. 2014;69(11):3161–3163. doi:10.1093/jac/dku275
18. Sun F, Yin Z, Feng J, et al. Production of plasmid-encoding NDM-1 in clinical Raoultella ornithinolytica and Leclercia adecarboxylata from China. *Front Microbiol*. 2015;6:458. doi:10.3389/fmicb.2015.00458
19. Tijet N, Muller MP, Matukas LM, et al. Lateral dissemination and inter-patient transmission of blaKPC-3: role of a conjugative plasmid in spreading carbapenem resistance. *J Antimicrob Chemother*. 2016;71(2):344–347. doi:10.1093/jac/dkv356
20. Xu J, Lin W, Chen Y, et al. Characterization of an IMP-4-producing Klebsiella pneumoniae ST1873 strain recovered from an infant with a bloodstream infection in China. Infect Drug Resist. 2020;13:773–779. doi:10.2147/IDR.S247341
21. Feng W, Zhou D, Wang Q, et al. Dissemination of IMP-4-encoding pIMP-HZ1-related plasmids among Klebsiella pneumoniae and Pseudomonas aeruginosa in a Chinese teaching hospital. Sci Rep. 2016;6(1):33419. doi:10.1038/srep33419
22. Zhou K, Yu W, Shen P, et al. A novel Tn696-like composite transposon (Tn6604) harboring bla IMP-4 in a Klebsiella pneumoniae isolate carrying a rare ESBL gene bla SFO-1. Sci Rep. 2017;7(1):17321. doi:10.1038/s41598-017-17641-2
23. Chen LR, Zhou HW, Cai JC, et al. Combination of IMP-4 metallo-beta-lactamase production and porin deficiency causes carbapenem resistance in a Klebsiella oxytoca clinical isolate. Diagn Microbiol Infect Dis. 2009;65(2):163–167. doi:10.1016/j.diagmicrobio.2009.07.002
24. Herzog KA, Schneditz G, Leitner E, et al. Genotypes of Klebsiella oxytoca isolates from patients with nosocomial pneumonia are distinct from those of isolates from patients with antibiotic-associated hemorrhagic colitis. J Clin Microbiol. 2014;52(5):1607–1616. doi:10.1128/JCM.03737-13
25. Liu W, Dong H, Yan T, et al. Molecular characterization of bla IMP-4-carrying enterobacteriae in Henan Province of China. Front Microbiol. 2021;12:626160. doi:10.3389/fmicb.2021.626160
26. Grant JR, Stothard P. The CGView server: a comparative genomics tool for circular genomes. Nucleic Acids Res. 2008;36:W181–184. doi:10.1093/nar/gkn179
27. Alikhan NF, Petty NK, Ben Zakour NL, et al. BLAST ring image generator (BRIG): simple prokaryote genome comparisons. BMC Genom. 2011;12(1):402. doi:10.1186/1471-2164-12-402
28. Sullivan MJ, Petty NK, Beatson SA. Easyfig: a genome comparison visualizer. Bioinformatics. 2011;27(7):1009–1010. doi:10.1093/bioinformatics/btr039
29. Arana DM, Ortega A, Gonzalez-Barbera E, et al. Carbapenem-resistant Citrobacter spp. isolated in Spain from 2013 to 2015 produced a variety of carbapenemases including VIM-1, OXA-48, KPC-2, NDM-1 and VIM-2. J Antimicrob Chemother. 2017;72(12):3283–3287. doi:10.1093/jac/dkx325
30. Gonzalez-Zorn B, Teshager T, Casas M, et al. armA and aminoglycoside resistance in Escherichia coli. Emerg Infect Dis. 2005;11(6):954–956. doi:10.3201/eid1106.040553
31. Hidalgo L, Gutierrez B, Ovejero CM, et al. Klebsiella pneumoniae sequence type 11 from companion animals bearing ArmA methyltransferase, DHA-1 beta-lactamase, and QnrB4. Antimicrob Agents Chemother. 2013;57(9):4532–4534. doi:10.1128/AAC.00491-13
32. Ho PL, Lo WU, Yeung MK, et al. Complete sequencing of pNDM-HK encoding NDM-1 carbapenemase from a multidrug-resistant Escherichia coli strain isolated in Hong Kong. PLoS One. 2011;6(3):e17989. doi:10.1371/journal.pone.0017989
33. Vergara-Lopez S, Dominguez MC, Conejo MC, et al. Lessons from an outbreak of metallo-beta-lactamase-producing Klebsiella oxytoca in an intensive care unit: the importance of time at risk and combination therapy. J Hosp Infect. 2015;89(2):123–131. doi:10.1016/j.jhin.2013.12.008
34. Fevre C, Jbel M, Passet V, et al. Six groups of the OXY beta-lactamase evolved over millions of years in Klebsiella oxytoca. Antimicrob Agents Chemother. 2005;49(8):3453–3462. doi:10.1128/AAC.49.8.3453-3462.2005
35. Partridge SR, Ginn AN, Paulsen IT, et al. pE1157 carrying blaIMP-4, from Sydney, Australia, is closely related to other IncL/M plasmids. Antimicrob Agents Chemother. 2012;56(11):6029–6032. doi:10.1128/AAC.01189-12
36. Goire N, Harnett GB, O’Reilly LC, et al. The implications of endemic IMP-4 carbapenemase for clinical laboratory susceptibility testing. J Microbiol Methods. 2016;124:10–12. doi:10.1016/j.mimet.2016.03.001
37. Zhang R, Liu L, Zhou H, et al. Nationwide surveillance of clinical carbapenem-resistant Enterobacteriaceae (CRE) strains in China. EBioMedicine. 2017;19:98–106. doi:10.1016/j.ebiom.2017.04.032
38. Wang Q, Wang X, Wang J, et al. Phenotypic and genotypic characterization of carbapenem-resistant Enterobacteriaceae: data from a longitudinal large-scale CRE Study in China (2012–2016). Clin Infect Dis. 2018;67(suppl_2):S196–S205. doi:10.1093/cid/ciy660
39. Gillings M, Boucher Y, Labbate M, et al. The evolution of class 1 integrons and the rise of antibiotic resistance. J Bacteriol. 2008;190(14):5095–5100. doi:10.1128/JB.00152-08
40. Hao Y, Shao C, Gong X, et al. Genotypic and phenotypic characterization of clinical Escherichia coli sequence type 405 carrying IncN2 plasmid harboring bla NDM-1. Front Microbiol. 2019;10:788. doi:10.3389/fmicb.2019.00788