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BRIEF REPORT FIDSA

# Case Report of an Extensively Drug-Resistant *Klebsiella pneumoniae* Infection With Genomic Characterization of the Strain and Review of Similar Cases in the United States

**Fiorella Krapp,[1,a] Egon A. Ozer,[1] Chao Qi,[2] and Alan R. Hauser[1,3]**

[1]Division of Infectious Diseases, Department of Medicine, [2]Department of Pathology, and [3]Department of Microbiology-Immunology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Reports of extensively drug-resistant and pan-drug-resistant *Klebsiella pneumoniae* (XDR-KP and PDR-KP) cases are increasing worldwide. Here, we report a case of XDR-KP with an in-depth molecular characterization of resistance genes using whole-genome sequencing, and we review all cases of XDR-KP and PDR-KP reported in the United States to date.

**Keywords.** *Klebsiella pneumoniae*; antibiotic resistance; resistance genes; extensively drug-resistant.

The rapid emergence of carbapenem-resistant Enterobacteriaceae (CRE) worldwide has led to the concern that infections by these bacteria may soon be untreatable. In recent years, cases of extensively drug-resistant and pan-drug-resistant *Klebsiella pneumoniae* (XDR-KP and PDR-KP) infections have been reported around the globe [1–3]. In the United States, the case of a Nevada woman who died of an infection caused by a *K. pneumoniae* strain resistant to all available antibiotics was reported in January 2017 [4]. An investigation for similar cases at our institution revealed a patient infected with XDR-KP in 2011 that subsequently resulted in her death. Here we describe the case and provide an in-depth molecular characterization of this isolate's resistance genes using whole-genome sequencing. In addition, we review all the reported cases of XDR-KP and PDR-KP infections in the United States and analyze the phylogenetic relationships among the strains that caused them.

## CASE

In September 2011, a 76-year-old woman was transferred to our institution from a hospital in Indiana for surgical management of methicillin-sensitive *Staphylococcus aureus* endocarditis. Prior to this admission, she had been residing in a rehabilitation facility for 3 weeks following a recent hospitalization for obstructing nephrolithiasis that required placement of a nephrostomy tube. A few days after transfer to our institution, she developed septic shock requiring intubation and vasopressor support. Blood cultures were negative; however, a urine culture grew *K. pneumoniae* resistant to all routinely tested antibiotics, including aztreonam and all cephalosporins, aminoglycosides, and carbapenems (minimum inhibitory concentration [MIC] >32 μg/mL for meropenem, imipenem, and ertapenem). Additional susceptibility testing showed resistance to colistin (MIC, 4 μg/mL), intermediate susceptibility to gentamicin (MIC, 8 μg/mL), and susceptibility to tigecycline at the breakpoint (MIC, 2 μg/mL) (Table 1). Although the patient clinically improved following empiric treatment with meropenem and tobramycin, XDR-KP continued to be isolated from her urine and nephrostomy tube, only clearing after 1 dose of tigecycline. Her hospitalization was prolonged and further complicated by acute kidney injury and pulmonary hemorrhage. On the 15th day of hospitalization, she experienced a second episode of septic shock with respiratory failure, which led to the patient's death. Cultures from bronchoalveolar lavage, urine and blood obtained at the time of the last decompensation all grew *K. pneumoniae* showing nonsusceptibility to all 16 antibiotics tested except tigecycline.

To determine the mechanisms of resistance, whole-genome sequencing was performed on the first isolate recovered from this patient (designated NU-CRE047, cultured from urine) using both Pacific Biosciences (PacBio) and Illumina HiSeq platforms (GenBank accession numbers: CP025037–CP025042). Assembly yielded a complete circularized chromosome of 5 537 943 bp and 5 plasmids ranging in size from 35 713 bp to 199 686 bp (Supplementary Table 1). In silico multilocus sequence typing (MLST) showed that this strain belonged to the epidemic ST258 MLST group.

Examination of the NU-CRE047 genome identified 18 antibiotic resistance genes or alleles, including the carbapenemase gene *blaKPC-3* and 3 other β-lactamase genes, 3

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[a]Present affiliation: Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru

Correspondence: A. Hauser, MD, PhD, Departments of Microbiology/Immunology and Medicine, Northwestern University, 303 East Chicago Avenue, Ward 6-035, Chicago, IL 60611 (ahauser@northwestern.edu).

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**Table 1. XDR *K. pneumoniae* Cases From the United States Reported as of February 2018**

| Author (Year) | State | Age, Sex | Site of Infection | Presentation | Outcome | AMP | SAM | TZP | CFZ | CRO | FEP | CAZ | CZA | ATM | ETP | MEM | IPM | DOR | AMK | GEN | TOB | CIP | LVX | TGC | NIT | SXT | CST | PMB | FOF | MLST | Carbapenemases |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Elemam (2009) | New York | 70,F | UTI | Nursing home resident, recent treatment of KPC-KP UTI with polymyxin B and tigecycline; recurred as XDR-KP UTI | Survived | >32 | | >128 | >64 | >64 | 32 | | | >64 | >8 | | >16 | | >64 | >16 | >16 | >4 | | >8 | 256 | >320 | | 4 | | NR | *blaKPC* |
| | | 67,M | Hepatic abscess | Previous Whipple procedure, recent treatment with tigecycline for hepatic abscess (CR-KP and CR *Enterobacter cloacae*); recurred as XDR-KP hepatic abscess | Died | >32 | | >128 | >64 | >64 | >16 | | | >64 | >8 | | R[a] | | >64 | >16 | >16 | >4 | | >8 | R | >320 | | >16 | | NR | *blaKPC* |
| Humphries (2010) | California | 49,M | VAP, bacteremia | Respiratory failure due to H1N1, recent treatment with imipenem, tigecycline, and minocycline for VAP (CR-KP); worsening VAP and bacteremia caused by XDR-KP | Survived | >32 | >32 | 512 | >32 | >32 | | | | | >16 | >16 | >16 | | 32 (I) | >10 | >10 | >2 | | 2 | | >4/80 | >8 | | 26mm | ST 258[b] | *blaKPC-2* |
| Bogdanovich (2010) | Pennsylvania | 63,M | Wound | OLTx and cholangitis; CR-KP in urine treated with colistin; isolate acquired colistin resistance during course of treatment, resulting in wound infection by XDR-KP | Survived | | | >128/4 | | | >128 | | | >128 | >128 | >128 | >128 | 128 | 64 | >128 | | 128 | | 2 | | | >128 | | | ST258 | *blaKPC-2* |
| | | 25,F | Wound | Hemorrhagic pancreatitis, multivisceral transplant; CR-KP bacteremia; isolate acquired colistin resistance during the course of treatment, resulting later in wound infection by XDR-KP | Survived | | | >128/4 | | | 32 | | | >128 | 64 | 32 | 16 | 8 | 64 | >128 | | 64 | | 1 | | | >128 | | | ST258 | *blaKPC-2* |
| | | 65,F | Bacteremia | OLTx, cholangitis with bacteremia caused by XDR-KP | Survived | | | >128/4 | | | 32 | | | >128 | 32 | 8 | 8 | 4 | 64 | 8 (I) | | 128 | | 1 | | | >128 | | | ST258 | *blaKPC-2* |
| | | 42,M | Bacteremia | OLTx complicated by intra-abdominal abscess with persistent bacteremia by CR-KP; isolate acquired colistin resistance during the course of treatment, resulting in XDR-KP | Died | | | >128/4 | | | >128 | | | >128 | >128 | 64 | 128 | 64 | 64 | >128 | | 64 | | 0.5 | | | 128 | | | ST258 | *blaKPC-2* |
| | | 41,F | UTI | Traumatic brain injury and UTI caused by XDR-KP | Survived | | | >128/4 | | | >128 | | | >128 | >128 | 64 | 128 | 64 | 64 | 32 | | 128 | | 1 | | | 128 | | | ST258 | *blaKPC-2* |
| Snitkin (2011) | Maryland | 34,M | VAP, bacteremia | Patient with solid tumor, MDR-KP from tracheal aspirate in the setting of a hospital outbreak; isolate acquired colistin resistance during the course of treatment, resulting in bacteremia caused by XDR-KP | Died | >16 | | >64/4 | >16 | >32 | >16 | | | >16 | >4 | >8 | 8 | | 32 (I) | 4 | >8 | >2 | | 2 | | >2/38 | R | | | ST258 | *blaKPC* |

**Table 1.** *Continued*

| Author (Year) | State | Age, Sex | Site of Infection | Presentation | Outcome | AMP | SAM | TZP | CFZ | CRO | FEP | CAZ | CZA | ATM | ETP | MEM | IPM | DOR | AMK | GEN | TOB | CIP | LVX | TGC | NIT | SXT | CST | PMB | FOF | MLST | Carbapenemases |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 72,F | Bacteremia | Patient with solid tumor, with rectal colonization with XDR-KP in the setting of a hospital outbreak, later developed bacteremia caused by XDR-KP | Died | >16 | | >64/4 | >16 | >32 | >16 | | | >16 | >4 | >8 | 8 | | 32 (I) | 4 | >8 | >2 | | 1 | | >2/38 | 4 | | | ST258 | *blaKPC* |
| This report (2011) | Illinois | 76, F | UTI, VAP, bacteremia | MSSA endocarditis with hospital course complicated by UTI, VAP, and bacteremia, all caused by XDR-KP | Died | >32 | >32 | >128 | >64 | >64 | >64 | [d] | 4 | >64 | >32 | >32 | >32 | | >64 | 8 (I) | >16 | >4 | | 2 | 256 | >320 | 4 | 2 | | ST 258 | *blaKPC-3* |
| Chen (2016) | Nevada | 70,F | Infected hip seroma | Femur fracture and hip osteomyelitis treated in India, admitted with infected hip seroma caused by XDR-KP | Died | >32 | | >128/4 | >8 | >32 | >32 | | >16/4 | >64 | >8 | >8 | 32 | >8 | >64 | >16 | >16 | >8 | | 4 | | 8/152 | >8 | >8 | 16 | ST 15[c] | *blaNDM* |
| Mills (2016) | Pennsylvania | 68,F | Intra-abdominal, bacteremia | OLTx andrenal transplant, with intra-abadominal infection caused by XDR-KP; isolate acquired resistance to colistin, tigecycline, and fosfomycin during course of treatment, resulting in bacteremia caused by XDR-KP | Survived | >32 | | >128 | | | 4 | >64 | | >32 | | >16 | | | >64 | 1 | >16 | | >8 | 4 | | 8/152 | >256 | | R | NR | *blaKPC-3* |
| Rosa (2017) | Florida | 35, F | Infected nephrostomy | Gardner syndrome, purulent discharge from nephrostomy tube caused by XDR-KP | Survived | | >32 | >128 | >64 | >64 | >64 | >64 | >256 | >64 | 8 | >16 | | | >64 | >16 | | | >8 | 1 | 256 | >320 | 8 | | 12 | ST14 | *blaNDM-1, blaOXA-48* |

Demographic and clinical characteristics, results of in vitro susceptibility testing, and type of carbapenemase are shown.

Abbreviations: AMK, amikacin; AMP, ampicillin; ATM, aztreonam; CFZ cefazolin; CIP, ciprofloxacin; CR, carbapenem resistant; CRO, ceftriaxne; CST, colistin; CZA, ceftazidime/avibactam; DOR, doripenem; ETP, ertapenem; FEP, cefepime; FOF, fosfomycin; GEN, gentamicin; I, intermediate; IPM, imipenem; KP, *Klebsiella pneumoniae*; LVX, levofloxacin; MEM, meropenem; MLST, multilocus sequence typing; MSSA, methicillin-sensitive *Staphylococcus aureus*; NIT, nitrofurantoin; NR, not reported; OLTx, orthotopic lung transplantation; PMB, polymyxin B; R, resistant; S, susceptible; SAM ampicillin/sulbactam; SXT, trimethoprim/sulfamethoxazole; TGC, tigecycline; TOB, tobramycin; TZP, piperacillin/tazobactam; UTI, urinary tract infection; VAP, ventilator associated pneumonia; XDR, extensively drug-resistant.

[a]Minimum inhibitory concentration (MIC) value was read as susceptible by the automated system, but result was changed to resistant on the basis of a positive polymerase chain reaction for *blaKPC*.

[b]Based on reported pulsed-field gel electrophoresis results showing >80% similarity with the ST 258 MLST group.

[c]MLST group determined by using the publicly available chromosome sequence.

[d]Ceftazidime-avibactam MIC determined by E-test. Susceptibility defined using Food and Drug Administration breakpoints.

fluoroquinolone resistance genes, 5 aminoglycoside resistance genes, and 6 other genes that confer resistance to fosfomycin, trimethoprim, sulphonamides, and chloramphenicol (Table 1; Supplementary Table 1). Except for *blaSHV-11*, *oqxA*, *oqxB*, and *fosA*, which were encoded on the chromosome, all these genes were encoded on plasmids. A pBK30683-like plasmid carried most of the antibiotic resistance genes, including *blaKPC-3*, *blaOXA-9, blaTEM-1A,* and 4 aminoglycoside resistance genes. In addition, point mutations in the *gyrA* and *parC* genes associated with fluoroquinolone resistance were found (Supplementary Table 1).

The potential mechanism of resistance to "last-resort" antibiotics was also assessed. (See the Supplemental Materials for a full description of this examination.) In summary, for colistin resistance, we identified a point mutation in *pmrB* (R256G). The mobilizable colistin resistance (*mcr-1*) gene was not found. Likewise, we found a point mutation in *marR* and an IS5 element integrated in the *kpgABC* operon, suggesting that NU-CRE047 had already acquired early genetic changes that could eventually lead to tigecycline resistance.

KPC-producing *K. pneumoniae* may display a wide range of carbapenem resistance, with MICs ranging from <2 μg/mL to >32 μg/mL [5]. Interestingly, NU-CRE047 displayed a high level of carbapenem resistance, with MIC >32 μg/mL for all 3 carbapenems tested (Supplementary Figure 1). A high number of *blaKPC* copies, defects in porins, and overexpression of efflux pumps have all been associated with high levels of carbapenem resistance [6–8]. For this isolate, we found evidence of all 3 mechanisms: 1) The ratio of the raw Illumina read coverage of the *blaKPC-3*-containing pBK30683-like plasmid relative to that of the chromosome was 6.08, suggesting that there are multiple copies of the plasmid and gene. 2) Characterization of the porin genes showed frameshift mutations resulting in premature stop codons in *ompK35* and *ompK36*; a wild-type ompK37 gene was present, and no mutations were found in the *ompR* regulator gene. 3) A point mutation was found in the efflux pump regulator gene *marR* that could result in overexpression of the AcrAB-TolC efflux pump (see above). Importantly, a high copy number of *blaKPC* in association with OmpK35/36 deficiency has also been linked to decreased ceftazidime/avibactam susceptibility [9]. Although this antibiotic was not available at the time of this patient's presentation, we subsequently tested it against NU-CRE047 and observed borderline susceptibility (MIC, 4 μg/mL). Based on recent evidence suggesting synergy between the combination of ceftazidime/avibactam and aztreonam [10], we evaluated this antibiotic combination using a previously reported MIC test-strip synergy assay [11], which showed a significant decrease of the MIC to <0.016 μg/mL.

Lastly, we performed a literature review during February 2018 and found 13 other reported cases of XDR-KP (but no PDR-KP) in the United States (Table 1) [4, 12–17]. Each of these 13 strains carried at least 1 carbapenemase gene (11 carried *blaKPC,* 1 carried *blaNDM,* and 1 carried *blaNDM* and *blaOXA-48*). Similar to our case, 8 patients were infected with a strain belonging to the ST258 MLST group (the Maryland, California, and Pennsylvania strains), and 2 belonged to the ST14 and ST15 MLST groups (the Nevada and Florida strains, respectively). Whole-genome sequences were available for 3 of these 13 strains: KPNIH6, KPNIH14, and DHQP1605752_NV (GenBank accession numbers: AJZY00000000, AKAF00000000, and CP022125.1–CP022128.1, respectively). We used these genomes to search for antibiotic resistance genes following the approach described above. Many of the resistance genes found in NU-CRE047 were similar to the ones found in the other ST258 strains but distinct from those of the ST15 strain (Supplementary Table 2). Phylogenetic analysis of all publically available global XDR- and PDR-KP genomes showed that NUCRE-047 is most closely related (but nonclonal) to the Maryland strains (Supplementary Figure 2).

## DISCUSSION

Extensive drug resistance has been defined as nonsusceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories [18]. Based on our literature review, as of February 2018, 14 cases of XDR-KP had been reported in the United States since 2009 [4, 12–17], including the current case (Table 1). It is possible that additional reports were missed if they did not include the keywords used for our literature search (see the Supplementary Materials for a full description of the literature search methodology). While none of these met the technical definition of PDR [18], some of them posed the same clinical challenges as treating a PDR *K. pneumoniae* case, as they were resistant to all appropriate antibiotics. Our case illustrates this point. Based on the in vitro susceptibility data at the time, the only active antibiotic—with a borderline MIC of 2 μg/mL—was tigecycline. However, this antibiotic constituted a suboptimal therapeutic option for this patient because it is not indicated for the treatment of ventilator-associated pneumonia and its use in the treatment of bloodstream infections and urinary infections is controversial due to the low serum and urine concentrations achieved with standard dosing [19]. Interestingly, this isolate displayed a borderline MIC to the new antibiotic combination ceftazidime/avibactam, even though it had not been previously exposed to it. However, it was quite susceptible to the combination of aztreonam and ceftazidime/avibactam, supporting recent reports that this combination provides universal coverage against β-lactamase-producing Enterobacteriaceae, including those with XDR profiles [20].

With the use of next-generation sequencing, we have provided the first in-depth characterization of the antibiotic resistance genes of an XDR-KP strain from the United States and have assessed its genetic relatedness to other XDR- and PDR-KP strains reported worldwide. The potential spread of these strains within hospitals is a major infection control concern,

and outbreaks caused by such strains have been reported in Greece (ST258) [1] and China (ST11) [2]. Although the current XDR-KP isolate also belonged to the epidemic ST258 group, a retrospective review at our hospital did not show additional cases of XDR-KP, indicating that the introduction of this strain did not lead to an outbreak. We were not able to investigate whether an outbreak occurred in the Indiana institution from which the patient was transferred and may have initially acquired the strain.

## CONCLUSIONS

Cases of XDR-KP infections have been reported in the United States since 2009. Here we provide an in-depth molecular description of the antibiotic resistance determinants of an XDR-KP strain at a genomic level and assess its homology with other reported XDR-KP and PDR-KP strains from the United States and other parts of the world.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.


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