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Successful treatment and digestive decolonization of a patient with osteitis caused by a Carbapenemase-producing *Klebsiella pneumoniae* isolate harboring both NDM-1 and OXA-48 enzymes

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1 **Title:** Successful treatment and digestive decolonization of a patient with osteitis caused by a
2 Carbapenemase-producing *Klebsiella pneumoniae* isolate harboring both NDM-1 and OXA-
3 48 enzymes.

4 **Running title:** double carbapenemase-producing *K. pneumoniae* in osteitis

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24 **Summary**

25

26 **Objectives:** Carbapenem resistance in *Klebsiella pneumoniae* (CRKP) is an increasing
27 problem worldwide and infections caused by this bacterium can be difficult to treat. Here we
28 reported the case of a patient from Romania hospitalized in Bulgaria after an accident trauma
29 that came in France for the treatment of an osteitis caused by a *K. pneumoniae* carrying both
30 *bla_{NDM-1}* and *bla_{OXA-48}*.

31 **Method:** The resistome of this extremely-drug-resistant bacterium was analyzed both with
32 phenotypic (large antibiotic susceptibility testing) and genomic method (genome sequencing).
33 The genetic environment of the two carbapenemases was studied.

34 **Results:** *K. pneumoniae* ST307 carrying both a *bla_{NDM-1}* gene and a *bla_{OXA-48}* gene located on
35 two different plasmids, an Inc L/M and an IncFII. Patient was successfully treated by a
36 combination of intravenous colistin (9 MUI, then 4.5 MUI 2 times/day), intravenous
37 fosfomycin (4 g 3 times/day) and oral doxycycline (100 mg 2 times/day) for 3 months. Fecal
38 microbiota transplantation was successfully conducted for a stool carriage.

39 **Conclusion:** The ST307 type is becoming endemic in hospital environment and is frequently
40 associated with carbapenem resistance. Treatment of infection caused by multi-drug resistant
41 bacteria are a clinical challenge and the use of old antibiotics associated with a screening and
42 decolonization of the reservoirs can be an efficient therapeutic alternative.

43

44 1. Introduction

45 Carbapenemase producing *Enterobacteriaceae* (CPE) have become, in the last decade, a
46 major concern worldwide, particularly in healthcare settings (1). Carbapenemases are the
47 most powerful β -lactamases, being able to hydrolyze almost all β -lactams. Of all the
48 carbapenemases, the OXA-48 carbapenemase is currently the one that is spreading the most
49 rapidly in many European countries (1). In France, the first OXA-48-producing isolate was a
50 *Klebsiella pneumoniae* identified in Paris in 2009 from the sputum of a Tunisian patient (2).
51 Subsequently, OXA-48-producing *Enterobacteriaceae* isolates were found in patients
52 transferred from countries around the Mediterranean sea (1), causing large hospital outbreaks
53 in western-European countries (1).

54 Otherwise, isolates containing New Delhi metallo- β -lactamase (NDM-1) were circulating in
55 India as early as 2006, two years before the first European case was identified (3). Since 2008,
56 there has been repeated import of NDM-1-positive bacteria from the Indian subcontinent to
57 Europe, in addition to being endemic in the Middle East, Northern Africa, and the Balkans
58 (3). The first identification of NDM-1 in France was in 2009, corresponding to an imported
59 *Escherichia coli* isolate from India (4). Two years later, the first reported case of community
60 acquired NDM-1 was identified in southern France, highlighting the risk of autochthonous
61 acquisition (5).

62 We report here the case of a patient who traveled for medical care from Bulgaria to France.
63 This patient had an osteitis caused by a carbapenemase-producing *K. pneumoniae* harboring
64 both *bla_{NDM}* and *bla_{OXA-48}* genes. He also had a stool carriage of a *K. pneumoniae* that was also
65 carrying the two genes. Genome of this extremely-drug-resistant isolate was sequenced and
66 analyzed. The management of the infection included surgical and antibiotic treatment and a
67 fecal microbiota transplantation which are reported here.

68

69 **2. Material and methods**

70 **2.1. Case report**

71 At the end of 2015, a 43-year-old man was admitted to our hospital in the south of France
72 suffering from septic pseudarthrosis of his left arm and left femur. Three years before, in
73 Romania, the patient had had a car accident that resulted in both left humeral and open left
74 femoral fractures. He underwent a humeral plate osteosynthesis and external fixation of his
75 femur. Fifteen days later, the patient was transferred to a tertiary hospital in Bulgaria for fever
76 and suppuration of the leg wound (Figure 1). He then underwent a second surgical
77 intervention for debridement and external fixation replacement. Two months before his
78 admission in France, due to an infection of the pin site, a second external fixation replacement
79 was performed. Despite several lines of empirical antibiotic therapy, the infection persisted,
80 and the patient decided to travel to France for medical care. In our hospital, all osteosynthesis
81 material was removed and bone samples were taken and cultured in the laboratory with
82 standard procedures.

83 **2.2. Microbiological procedures**

84 Samples were inoculated on blood agar medium (Biomérieux, Marcy l'Etoile, France) and
85 chocolate polyvitex agar under aerobic atmosphere at 37°C for 48h. Additionally, one blood
86 agar plate was inoculated under anaerobic conditions for 10 days at 37°C. Screening for stool
87 carriage was done using the ChromeID CARBA SMART medium (Biomérieux, France).
88 Bacterial identification was performed by Matrix Assisted Laser Desorption Ionisation - Time
89 of Flight (MALDI-TOF) as previously described (6). Antimicrobial susceptibility testing
90 testing was performed according the European Committee on Antimicrobial Susceptibility
91 Testing (EUCAST) recommendation. Minimum Inhibitory Concentration (MIC) of
92 tigecycline and minocycline, doxycycline and Imipenem were determined using E-test
93 (Biomérieux, France) while colistin MIC was obtained using the UMIC microdilution method

94 (Biocentric, Bandol, France). Real-time PCR of the carbapenemase genes (*bla_{OXA-48}*, *bla_{NDM}*,
95 *bla_{KPC}*) was performed on every strain. Conjugation test was performed in an azide-resistant
96 *E. coli* J53 strain. Transconjugants selection was done on Luria Bertani agar (Beckton
97 Dickinson, Le Pont de Claix, France) supplemented with 120µg/mL sodium azide and
98 4µg/mL ertapenem. Carbapenemases PCR performed on transconjugants confirmed the
99 presence of the two carbapenemase genes.

100 **2.3. Genome sequencing and analysis**

101 The genome of one multi-drug-resistant (MDR) *K. pneumoniae* KP_DC isolated from the
102 articular liquid (GenBank accession no. NJGM000000000) was sequenced by Miseq
103 technology (Illumina Inc, San Diego, CA, USA) with a paired-end strategy. Genome was
104 assembled with A5 software (7), aligned with Mauve (8) to the reference strain ATCC43816
105 KPRR (genbank accession number CP009208.1) and annotation was performed using Prokka
106 (9) and Arg-annot (10) for the research of antibiotic resistance genes. Plasmid were found
107 using PlasmidSeeker (11) and then reconstitute by mapping the reads of our genome with the
108 reference sequence found with PlasmidSeeker using CLC Genomics Workbench version 7.5
109 (Qiagen, Hilden, Germany). The FAB formula of the IncF plasmid was determined using the
110 Center for Genomic Epidemiology platform (<https://cge.cbs.dtu.dk/>).

111 **3. RESULTS**

112 Both bone biopsies from the humerus and the femur were positive for a carbapenemase-
113 producing *K. pneumoniae*. Screening for stool carriage also found a carbapenemase-
114 producing *K. pneumoniae*. All isolates remained susceptible to fosfomicin, nitrofurantoin,
115 tigecycline, minocycline and colistin (Table 1). All these isolates harbored both NDM and
116 OXA-48 genes, confirmed by PCR (Table 1). We started a treatment combining intravenous
117 colistin (9 MUI, then 4.5 MUI 2 times/day), intravenous fosfomicin (4 g 3 times/day) and

118 oral doxycycline (100 mg 2 times/day) for 3 months (Figure 1). No adverse effects were
119 observed during the treatment. The kidney and liver functions, which were normal before
120 treatment, remained unchanged. Fecal microbiota transplantation (FMT) was performed on
121 day 10 of hospitalization in our ward. In brief, as previously described (12), an anonymous,
122 fully screened, stool donor was used for FMT. The patient was administered a bowel lavage
123 followed by four doses of oral gentamicin (100 mg) and colistin (2.5 MIU) over 24 h prior to
124 FMT. Fifty grams of donor stool was homogenized and diluted in 0.9% NaCl, and 400 mL
125 was administered by nasogastric tube. No adverse events were observed. The patient was
126 placed under contact precaution until three consecutive weekly collected stool samples were
127 negative for carbapenemase-producing isolate. Control stool samples were still negative 12
128 months later. The patient recovered with bone consolidation and wound healing after a 12-
129 months follow-up.

130 The genome of the *K. pneumoniae* KP_DC isolate was assembled into 71 contigs with lengths
131 ranging from 919 to 733,430 bp and a GC content of 57.4 %. 92.3% was found to be genomic
132 DNA but 7.4% of the contig did not map with the reference strain *K. pneumoniae* MGH78578
133 (NC_009648.1). *In silico* Multi Locus Sequence Typing (MLST) showed that this strain
134 belonged to the ST307 type. MLST sequencing of the four other isolates with no available
135 genome shows they also belonged to ST307. An IncFII and an IncL/M plasmids were found
136 using PlasmidSeeker (11). Conjugation tests were positive for the two carbapenemase genes
137 as well as for *bla_{CTX-M-15}* and *bla_{SHV-28}* genes.

138 The IncL/M conjugative plasmid that harbored the *bla_{OXA-48}* gene was 61,682 bp length, with
139 an average G+C content of 51.02% (p2G1140) (Figure 2a). Comparison with the reference
140 plasmid pOXA-48 (accession number JN626286) found 98% identity and 98% query
141 coverage. The genetic environment of the *bla_{OXA-48}* gene includes a *Tn1999*-like transposon
142 inserted within a *tir* gene, flanked on both sides by a direct repeat sequence of 9 bp

143 (CGTTCAGCA). In the 3'-5' direction from the *bla_{OXA-48}* gene, we found the usual *mucB-*
144 *mucA-pemK-pemI* gene pattern. The *Tn1999*-like transposon was flanked on either side by
145 two imperfect insertion sequences (IS): two copies of IS10A on the left and both IS10A and
146 IS1 on the right (Figure 2a).

147 The conjugative IncFII plasmid (p1G1140) was a IncFII Y4:A-:B36 carrying a *bla_{NDM-1}* gene
148 (Figure 2b). This plasmid shared 99% cover and 99% identity with the reference plasmid
149 (pRJF866) for a 110,787 bp length, with an average G+C content of 54.72%. The genetic
150 environment of *bla_{NDM-1}* gene was made by two IS5 genes with several insertion sequences on
151 each extremity. This transposon also carried a dihydropteroate synthase (*Sul1*) involved in
152 sulfonamide resistance, a 16S rRNA methyltransferase (*RmtC*) responsible for
153 aminoglycoside resistance and a *ble_{MBL}* gene leading to bleomycin resistance (Table 1).

154 **4. DISCUSSION**

155 Prior surgery and extended hospital stays in countries with high levels of antimicrobial
156 resistance, as well as the presence of wounds, are recognized as risk factors for MDR
157 organisms acquisition (1,13). Antibiotic selection pressure may be an additional factor that
158 influences colonization with these organisms. In a recent case-control study, prior use of
159 piperacillin-tazobactam, a carbapenem, a quinolone, or metronidazole was significantly
160 associated with infections caused by carbapenemase-producing enterobacteria (14). However,
161 the cumulative number of prior antibiotic exposures appears to be more critical than the use of
162 a specific class of antibiotics (13). This highlights the importance of screening the digestive
163 colonization by MDR organisms directly upon admission to hospitals for high risk patients,
164 especially in patients who have received healthcare in endemic countries or epidemic facilities
165 (13).

166 Old antibiotics (*i.e.*, colistin, fosfomicin, tetracyclines, mecillinam, temocillin, thiamphenicol,
167 pristinamycin...) have been increasingly reused in the last few years, with rising numbers of

168 clinical studies evaluating their efficacy for the treatment of multidrug-resistant bacterial
169 infections, and pharmacokinetic/pharmacodynamic studies reassessing their optimal dosing
170 (15). But despite the evidence that these old antibiotics are still effective, mostly available as
171 generics, they are not universally marketed (16). Our patient was successfully treated with
172 Fosfomycin despite the presence of a fosfomycin resistance gene *fosA* in the genome of the
173 sequenced isolate. The *fosA* gene is widely distributed in the *Klebsiella pneumoniae* species
174 and conferred a Fosfomycin MIC to approximately 24 mg/L, allowing its use in clinical
175 practice (MIC cut-off according to EUCAST guidelines = 32 mg/L)

176 It has been shown that stool carriage of CPE could be extended for as long as 40 months (17).
177 Fecal microbiota transplantation has been proposed as an efficient way of reducing the
178 duration of colonization by CPE, as it has emerged as therapy for MDR bacterial
179 decolonization (12). It was successfully used in our case, since fecal samples were still
180 negative one year later.

181 The ST307 appeared in literature in 2013 from strains isolated from clinical samples between
182 2007 and 2010 in Texas but recent analyzes showed that this clone emerged in the mid-1990s
183 and spread worldwide (18). This clone has been frequently associated with ESBL and
184 carbapenemase genes (18) and is becoming prevalent in hospital environment.

185 Double carbapenemases-producing bacteria have been increasingly reported in the world (19).
186 This acquisition of more than one carbapenemase seems to increase MIC of imipenem (19),
187 limiting its use even in synergistic association with another antibiotic. However, the presence
188 of a double carbapenemase can have no impact on Imipenem MIC (19), as it depends on the
189 expression level of the carbapenemases. This “arm race” is worried to concern and must be
190 detected by microbiological screening.

191

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195

196 **Declarations**

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201 **Competing Interests:** None

202 **Ethical Approval:** Not required

203

204

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TABLES AND FIGURES

Number of tables: 1

Table 1. Antibiotic susceptibility testing of the five strains of *Klebsiella pneumoniae* isolated in the per-operative samples and in stool.

Number of figures: 2

Figure 1. Timeline of osteoarticular infection in our patient.

Figure 2. Representation of plasmids carrying carbapenemase genes compared to plasmids of reference. a. Genetic environment of the plasmid-mediated *bla_{oxa-48}* gene and comparison with the reference plasmid pOXA-48 (accession number JN626286). b. Genetic environment of the plasmid-mediated *bla_{NDM-1}* gene and comparison with the reference plasmid pRJF866 (accession number KF732966).

Table 1. Antibiotic susceptibility testing, resistance genes and MLST results of the five strains of *Klebsiella pneumoniae* isolated in the per-operative samples and in stool.

Isolate number	Strain 1		Strain 2		Strain 3 (genome)		Strain 4		Strain 5	
Date of isolation	14/01/2016		14/01/2016		14/01/2016		14/01/2016		26/01/2016	
Nature of sample	Humeral bone biopsy 1		Humeral bone biopsy 2		Humeral bone biopsy 3		Femoral bone biopsy		Stool	
Antibiotic	Ø (mm)	S/I/R	Ø (mm)	S/I/R	Ø (mm)	S/I/R	Ø (mm)	S/I/R	Ø (mm)	S/I/R
Amoxicillin	0	R	0	R	0	R	0	R	0	R
Amoxicillin/Clavulanic acid	0	R	0	R	0	R	0	R	0	R
Piperacillin/Tazobactam	0	R	0	R	0	R	0	R	0	R
Ceftriaxone	0	R	0	R	0	R	0	R	0	R
Cefepim	9.9	R	9.9	R	9.9	R	10.4	R	10.8	R
Ertapenem	13.3	R	12.3	R	12.3	R	13.2	R	13.6	R
Imipenem	18	I	17.4	I	18	I	18.8	I	17.9	I
Gentamicin	13.6	R	0	R	0	R	13.8	R	0	R
Amikacin	0	R	0	R	0	R	12.7	R	0	R
Ciprofloxacin	10.3	R	16	R	15.9	R	0	R	16.5	R
Trimethoprim/Sulfamethoxazole	0	R	0	R	28.1	R	0	R	0	R
Fosfomicin	21.8	S	19.2	S	20.2	S	20.9	S	22.2	S
Nitrofurantoin	18.8	S	17.8	S	17.5	S	18.1	S	19.3	S
MIC Antibiotic (µg/mL)										
Colistin (microdilution method)	0.25	S	0.25	S	0.25	S	0.25	S	0.25	S
Imipenem (E-test)	8	I	8	I	6	I	1.5	S	8	I
Minocycline (E-test)	2	S	1.5	S	1.5	S	2	S	1	S
Tigecycline (E-test)	1.5	S	1	S	1	S	1.5	S	1	S
Doxycycline (E-test)	16	-	2	-	2	-	16	-	2	-
Resistome										
Carbapenems	<i>bla</i> NDM-1 <i>bla</i> OXA-48		<i>bla</i> NDM-1 <i>bla</i> OXA-48		<i>bla</i> NDM-1 <i>bla</i> OXA-48		<i>bla</i> NDM-1 <i>bla</i> OXA-48		<i>bla</i> NDM-1 <i>bla</i> OXA-48	
Other β-lactams	ND		ND		<i>bla</i> _{CTX-M-15} <i>bla</i> _{CTX-M-132} <i>bla</i> _{SHV-28}		ND		ND	
Aminoglycosides	ND		ND		<i>amp</i> H <i>rmt</i> C <i>str</i> B		ND		ND	
Fluoroquinolone	ND		ND		<i>oqx</i> A/ <i>oqx</i> B		ND		ND	
Sulfamides	ND		ND		<i>Sul</i> I		ND		ND	
Fosfomicine	ND		ND		<i>fos</i> A		ND		ND	
Sequence Type ¹	307		307		307		307		307	

¹ According to the <http://bigsd.b.pasteur.fr/klebsiella/klebsiella.html> database

TREATMENT

3 months

Colistin IV 9 MUI, 4.5 MUI x2/day + Fosfomycin IV 4 g x3/day + Doxycycline PO 100 mg x2/day

MICROBIOLOGY

10/02 Fecal microbiota transplantation

01/26 stool sample CPKP

01/14 per-operative samples CPKP

D3 Negative Stool (NS)

D7 NS

D21 NS

10/10 M6 NS

05/30 M12 NS

PATIENT'S HISTORY

Transfer in Bulgaria for fever and suppuration of the leg wound
Debridement and external fixation replacement. Multiple lines antibiotherapy

Hospitalization in Romania after a car accident
Humeral plate osteosynthesis and femur external fixation

Hospitalization in Bulgaria for an infection in the pin site
External fixation replacement

Transfer in France
Removing of all osteosynthesis material

22/04 Hospital discharge

14 days

2 months



ST307

