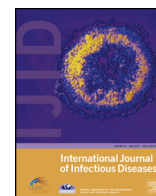


Contents lists available at [ScienceDirect](http://ScienceDirect)

## International Journal of Infectious Diseases

journal homepage: [www.elsevier.com/locate/ijid](http://www.elsevier.com/locate/ijid)

## Sepsis caused by New Delhi metallo- $\beta$ -lactamase ( $bla_{NDM-1}$ ) and $qnrD$ -producing *Morganella morganii*, treated successfully with fosfomycin and meropenem: case report and literature review



Verónica Seija<sup>a,1</sup>, Julio César Medina Presentado<sup>b,1</sup>, Inés Bado<sup>c</sup>, Romina Papa Ezdra<sup>c</sup>, Noelia Batista<sup>a</sup>, Claudia Gutierrez<sup>a</sup>, Mariana Guirado<sup>b</sup>, Macarena Vidal<sup>b</sup>, Marcelo Nin<sup>d</sup>, Rafael Vignoli<sup>c,\*</sup>

<sup>a</sup> Departamento de Laboratorio Clínico, Área Microbiología, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

<sup>b</sup> Cátedra de Enfermedades Infecciosas, Instituto de Higiene, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

<sup>c</sup> Departamento de Bacteriología y Virología, Instituto de Higiene, Facultad de Medicina, Universidad de la República, Alfredo Navarro 3051, CP 11600 Montevideo, Uruguay

<sup>d</sup> Centro de Nefrología Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

## ARTICLE INFO

## Article history:

Received 27 February 2014

Received in revised form 17 September 2014

Accepted 18 September 2014

**Corresponding Editor:** Eskild Petersen, Aarhus, Denmark

## Keywords:

NDM-1

*Morganella morganii*

Sepsis

Meropenem

Fosfomycin

## SUMMARY

**Objectives:** The objective of this study was to describe the microbiological characteristics of an extensively drug-resistant (XDR) isolate of *Morganella morganii* obtained from a patient with sepsis of urinary origin and to describe the patient's clinical characteristics. We further aimed to perform a literature review of the situation in Latin America regarding Gram-negative bacillus (GNB) carriers of New Delhi metallo- $\beta$ -lactamase (NDM-1) and  $qnr$  genes and current reports on the treatment of infections caused by XDR enterobacteria, with particular attention to colistin-resistant isolates.

**Methods:** The patient's clinical data were obtained from his medical history. Microbiological identification and susceptibility testing were done using the VITEK 2 Compact System. Resistance genes were detected by PCR and sequencing.

**Results:** Blood and urine cultures grew an *M. morganii* isolate (Mm4232) harboring NDM-1 and  $qnrD1$ . The patient was treated successfully with fosfomycin and double doses of meropenem. There are no previous reports of the use of fosfomycin and meropenem to treat infections by XDR enterobacteria harboring NDM-1 carbapenemase.

**Conclusions:** This is the first report of  $qnrD1$  in South America. We consider that this report could be helpful to physicians implementing treatments for infections caused by XDR GNB, including colistin-carbapenem-resistant GNB.

© 2014 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

### 1. Introduction

*Morganella morganii* is a Gram-negative rod belonging to the *Enterobacteriaceae* family. It is ubiquitous in the environment and can cause nosocomial outbreaks and serious infections in immunocompromised patients.<sup>1</sup>

This species produces an inducible, chromosomally-encoded AmpC  $\beta$ -lactamase which is responsible for its natural resis-

tance to aminopenicillins, amoxicillin-clavulanate, and first- and second-generation cephalosporins. *M. morganii* mutants with derepressed expression of this AmpC are resistant to third-generation cephalosporins, monobactams, and cephamycin.<sup>2</sup> Additionally *M. morganii* is naturally resistant to tetracyclines, tigecycline, polymyxins, and nitrofurantoin.<sup>3</sup> In this context, the acquisition of additional resistance genes encoding carbapenemases and/or transferable plasmid-mediated quinolone resistance mechanisms significantly reduces the therapeutic options.

The emergence of carbapenemases in *Enterobacteriaceae* is a growing concern, with a high impact on patient health worldwide.<sup>4</sup> Carbapenemases are enzymes that are able to hydrolyze nearly all

\* Corresponding author. Tel./Fax: +598 2487 57 95.

E-mail address: [rvignoli@higiene.edu.uy](mailto:rvignoli@higiene.edu.uy) (R. Vignoli).

<sup>1</sup> Both authors contributed equally to the experimental work and the elaboration of this report.

$\beta$ -lactam antibiotics, including carbapenems. These enzymes can belong to molecular classes A, B, or D: KPC (*Klebsiella pneumoniae* carbapenemase), NDM (New Delhi metallo- $\beta$ -lactamase) or VIM (Verona integron-encoded metallo- $\beta$ -lactamase), and OXA-48 (oxacillinase) are the most representative exponents of each group, respectively.<sup>5</sup>

NDM-1 was first described in 2008 in Sweden from a patient who had previously been hospitalized in New Delhi, India.<sup>6</sup> Rapid worldwide dissemination followed.<sup>5,7,8</sup>

Several plasmid-mediated quinolone resistance (PMQR) mechanisms have been discovered during the past decade, including Qnr proteins, QepA transporters, and the acetyltransferase AAC(6)-Ib-cr.<sup>9</sup> Different lineages of Qnr proteins have been described (QnrA, QnrB, QnrS, and more recently, QnrC and QnrD), with several allelic variants known for some of them. The *qnrD* gene was first described in 2009 in a human clinical isolate of *Salmonella enterica* serovar Kentucky and three *Salmonella enterica* serovar Bovismorbificans isolates from China.<sup>10</sup> In 2011, Mazzariol et al. described the presence of *qnrD* in isolates of *Proteus mirabilis* and *M. morgani*, suggesting that this gene might be closely linked to the Proteaeae tribe.<sup>11</sup>

In this work we present a case report of sepsis caused by an extensively drug-resistant (XDR; according to the definition proposed by Magiorakos et al.<sup>12</sup>) *M. morgani* isolate (Mm4232) co-harboring NDM-1 and *qnrD1*, which was treated successfully with fosfomycin and double doses of meropenem. In addition, we reviewed the literature on plasmid-mediated quinolone resistance and NDM-1 in Latin America, and the experience of therapeutic options for the treatment of invasive infections caused by XDR microorganisms.

## 2. Methods

### 2.1. Patients

The patient's clinical data were collected retrospectively by review of the medical records.

### 2.2. Bacterial identification and susceptibility assays

Bacterial identification and antibiotic susceptibility were determined using the VITEK 2 Compact System (bioMérieux, Durham, NC, USA) and Etest, in accordance with the manufacturer's recommendations. Antibiotic susceptibility to fosfomycin was determined using Etest strips containing this agent and 25 mg/l glucose-6-phosphate, as per the manufacturer's recommendations. Susceptibility was interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (<http://www.eucast.org>).

### 2.3. Metallo- $\beta$ -lactamase screening and carbapenemase screening

The imipenem-EDTA/SMA (ethylenediaminetetraacetic acid 372  $\mu$ g/sodium mercaptoacetic acid 900  $\mu$ g) double disk<sup>13</sup> and Rosco Diagnostica Neo-Sensitabs KPC and MBL confirmation kit were used to detect carbapenemases. Testing was performed in accordance with the manufacturers' instructions.

### 2.4. Detection of antibiotic resistance genes

The presence of *bla*<sub>NDM</sub> and additional  $\beta$ -lactamases such as the *bla*<sub>CTX-M</sub>, *bla*<sub>SHV</sub>, *bla*<sub>TEM</sub>, *bla*<sub>PER-2</sub>, *bla*<sub>OXA-1</sub>, and *bla*<sub>OXA-2</sub> subgroups, was determined using PCR and sequencing, as described previously.<sup>13–16</sup> The presence of other carbapenemases such as *bla*<sub>IMP</sub>, *bla*<sub>SIM</sub>, *bla*<sub>SPM</sub>, *bla*<sub>GIM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>KPC</sub>, and *bla*<sub>OXA-48</sub> was sought by PCR using specific primers (see **Supplementary Material**, Table S1).

In order to identify additional genes responsible for the resistance profile, and associations with mobile genetic elements, we studied the following by PCR and sequencing: (1) the presence of plasmid-mediated quinolone resistance genes (*qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *qepA*, *aac(6)Ib-cr*), (2) the presence of class 1 and 2 integrons, and (3) the presence of insertion sequences *ISEc1*, *IS26*, *IS903*, and *ISCR1*.<sup>17</sup>

### 2.5. Conjugation assays

Conjugation assays were carried out using rifampin-resistant *Escherichia coli* J53-2 (rifampin-resistant, non-motile, and ornithine-negative) as recipient, as described previously.<sup>18</sup> *Salmonella enterica* serovar Typhimurium harboring conjugative plasmid pSTM709 (accession number **HG428759**) was used as the conjugation positive control.<sup>19</sup>

## 3. Results

### 3.1. Case report

A 24-year-old man with a history of hypertension and end-stage renal disease secondary to glomerulonephritis had been on hemodialysis for 7 years. Eight months before presenting to the hospital he underwent a renal transplant, which was complicated by a urinary leak (requiring insertion of a double J ureteral stent) and a urinary tract infection caused by *Enterobacter cloacae*; this infection was treated with piperacillin-tazobactam for 21 days. He had been taking the following medications since then: prednisone (10 mg/day), tacrolimus (4 mg/day), and mycophenolate mofetil (1 g/day).

On admission to the emergency department, the patient presented fever, dysuria, and a decreased urine output. Initial vital signs were as follows: temperature 38.2 °C, normal blood pressure, heart rate 100 beats/min, and arterial oxygen saturation of 96% when breathing air. The patient appeared ill and jaundiced; his abdomen was tender without pain. The rest of the examination was normal.

Urinalysis by dipstick test showed leukocyte esterase, nitrite, protein, and hemoglobin, and urine microscopic examination revealed 15 leukocytes and 7 erythrocytes per high-power field. In addition, laboratory studies on admission showed elements of multiple organ dysfunction such as pancytopenia, renal and hepatic failure, and high values of biomarkers such as procalcitonin (38 ng/ml; according to the manufacturer, procalcitonin values  $\geq 10$  ng/ml can be interpreted as indicating a high likelihood of severe sepsis or septic shock) and C-reactive protein (CRP, 129 mg/l; reference value CRP <3 mg/l). The changes in laboratory results over time are shown in **Table 1**; results from the medical examination done 1 month before admission are included.

Chest radiography was normal. Computed tomography (CT) of the thorax, abdomen, and pelvis showed no alterations except for the presence of the ureteral stent.

In this immunocompromised patient with a diagnosis of sepsis, treatment with meropenem (1 g every 8 h) was initiated and doses of immunosuppressive agents were reduced: tacrolimus 2 mg/day, mycophenolate mofetil 500 mg/day, and prednisone 5 mg/day.

Urine and blood culture results were received after 48 h; both samples grew an *M. morgani* isolate (named in our laboratory as Mm4232), which displayed susceptibility only to fosfomycin. Testing of susceptibility to colistin and tigecycline was not done. Additionally, isolate Mm4232 was resistant to cefepime (FEP), ceftazidime (CAZ), cefotaxime (CTX), piperacillin-tazobactam (PTZ), imipenem (IMP), meropenem (MEM), ertapenem (ERT), ciprofloxacin (CIP), gentamicin (CN), amikacin (AK), and trimethoprim-sulfamethoxazole (SXT) (see results below).

Due to the susceptibility results and considering the presence of sepsis with bacteremia and the potential risk of the emergence of resistance during fosfomycin monotherapy, we decided to use combination therapy based on meropenem, administered by extended infusion (lasting  $\geq 3$  h) at a dose of 2 g every 8 h, along with fosfomycin, 4 g every 8 h with daily natremia control. During hospitalization, the ureteral stent was removed without complications. After 10 days of fosfomycin and 14 days of meropenem treatment, the patient was discharged having made excellent clinical progress and with full renal function recovery (Table 1). A follow-up urine culture on day 14 was negative.

### 3.2. Susceptibility testing

*M. morgani* strain Mm4232 was only susceptible to fosfomycin (minimum inhibitory concentration (MIC) 32 mg/ml). Mm4232 was resistant to cefepime (4 mg/l), ceftazidime ( $\geq 64$  mg/l), cefotaxime ( $\geq 64$  mg/l), piperacillin–tazobactam ( $\geq 128$  mg/l), ertapenem (4 mg/l), meropenem (4 mg/l), imipenem ( $\geq 16$  mg/l), ciprofloxacin ( $\geq 4$  mg/l), gentamicin ( $\geq 16$  mg/l), amikacin (32 mg/l), and trimethoprim–sulfamethoxazole ( $\geq 320$  mg/l).

### 3.3. Carbapenemase screening

The imipenem–EDTA double disk showed an improvement in the inhibition zone in the area between the carbapenems and the inhibitor-containing disk. The Rosco kit displayed a 7 mm difference between the meropenem disk (21 mm) and meropenem + dipicolinic acid disk (28 mm). Both results were interpreted as positive for the detection of metallo- $\beta$ -lactamase.

### 3.4. Antibiotic resistance genes

Mm4232 was positive for *bla*<sub>NDM-1</sub> and *qnrD1*, but was negative for other  $\beta$ -lactamase and plasmid-mediated quinolone resistance genes. In addition, this isolate was IS26-positive but negative for other insertion sequences and integrons. PCRs aimed at connecting IS26 with *bla*<sub>NDM-1</sub> and/or *qnrD1* were negative, suggesting that this IS was not surrounding resistance genes.

### 3.5. Conjugation assays

Results of conjugation assays were negative using *M. morgani* strain Mm4232, but positive using *S. enterica* serovar Typhimurium strain STM709. These findings suggest that both *bla*<sub>NDM-1</sub> and *qnrD1* were codified in non-conjugative elements. More studies are

required to determine if these genes are located in non-conjugative plasmids or the bacterial chromosome.

## 4. Discussion

Reports on NDM-producing isolates in Latin America and Central America are relatively few and have been published only from Mexico,<sup>20</sup> Jamaica,<sup>21</sup> Guatemala,<sup>22</sup> Honduras,<sup>23</sup> Colombia,<sup>24</sup> Paraguay,<sup>25</sup> and Brazil.<sup>26–28</sup> A Pan American Health Organization (PAHO) epidemiological update has also given accounts of the presence of NDM-1 in Costa Rica, Nicaragua, Argentina, and Uruguay.<sup>29</sup> The main characteristics of isolates and clinical cases reported in Latin America, including the one presented in this work, are shown in Table 2.

So far, most of the reported cases have resulted from outbreaks of nosocomial infections (12/17) and have been associated with a low mortality attributable to the infection itself. The treatment was recorded in 11 cases and combinations of antibiotics were used in nine of them; a carbapenem was used in eight of these combinations. Other than the case presented in this paper, fosfomycin susceptibility has only been reported in a work from Guatemala; this has not been used as a therapeutic option at any other time.

In contrast, infections and/or colonization of humans by GNB carrying *qnr* genes in Latin America has been better described. In brief, there are three mechanisms of plasmid-mediated quinolone resistance (PMQR): (1) protection by masking the target *qnr* genes, and (2) modification of the antibiotic enzyme Aac(6′)-Ib-cr and efflux pumps OqxAB and QepA. The *qnr* genes constitute the first mechanism of transferable quinolone resistance described; reports date back to the year 1998.<sup>30</sup> The Qnr protein binds to gyrase, causing the quinolones to recognize the less efficient target enzyme. Variants of this gene have arisen over time. *qnrA* came first, followed by the *qnrB*, *qnrS*, *qnrC*, *qnrD*, and *qnrVC* gene families. Currently, the following variants have been described: *qnrA1–qnrA7*, *qnrB1–qnrB74*, a variant of *qnrC*, *qnrD1–qnrD2*, *qnrS1–qnrS9*, and *qnrVC1–qnrVC6* (<http://www.lahey.org/qnrStudies/>).

A variety of *qnr* genes have been described in Latin America. In Brazil, the first report on *qnr* genes involved *E. coli*, with *qnrA1* associated with *bla*<sub>FOX-5</sub>;<sup>31</sup> *qnrB2*, *qnrB8*, *qnrB19*, *qnrS1*, and *qnrVC32–35* were then detected. In Argentina, *qnrB1*, *qnrB2*, *qnrB4*, *qnrB6*, *qnrB10*, *qnrB19*, and *qnrS* have been found.<sup>36–38</sup> In Bolivia, *qnrS* and *qnrB*;<sup>39,40</sup> in Peru, *qnrB19* and *qnrS*;<sup>40,41</sup> in Uruguay, *qnrA1*, *qnrB1*, *qnrB4*, *qnrB8*-like, *qnrB13*, and *qnrB17*;<sup>14,42</sup> and in Venezuela *qnrB19*,<sup>43</sup> have been reported. The *qnr* genes have been described in a variety of microorganisms isolated either from

**Table 1**  
Main laboratory results

	Control (1 month before admission)	Admission	Day 2	Day 8	Day 13	Day 15
Urea, mg/dl	0.57	0.69	0.51	0.39	0.52	0.52
Creatinine, mg/dl	1.44	2.35	1.74	1.32	1.23	1.23
Hemoglobin, g	13.1	14	12.3	13.2	13	12
WBC count, $\times 10^9/l$	5.800	0.740	4.950	4.740	5.200	4.090
Neutrophils, $\times 10^9/l$	3.300	0.580	3.217	2.700	3.300	2.800
Total lymphocytes, $\times 10^9/l$	1.330	0.130	0.840	1.410	1.180	1.000
Platelet count, $\times 10^9/l$	159	74	83	160	160	186
Total bilirubin, mg/dl	0.46	1.64	0.75	ND	0.18	ND
Direct bilirubin, mg/dl	0.23	0.98	0.45	ND	0.12	ND
AST, U/l	39	132	50	ND	40	ND
ALT, U/l	112	123	122	ND	121	ND
Procalcitonin, ng/ml	ND	38	31.4	2.29	0.13	ND
Na, mEq/ml	140	128	131	134	132	133
CRP, mg/l	ND	129	ND	ND	18	ND
Tacrolimus trough concentration, ng/ml	14	11.4	ND	9.4	ND	8.6

WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ND, not determined.

**Table 2**

Main features of clinical reports of human infections due to New Delhi metallo-β-lactamase-producing Gram-negative bacteria in Latin America

Country	Year	Microorganism <sup>a</sup>	Sex/age (years)	Site of infection	Underlying condition	Antibiotic resistance	Antibiotic susceptibility	Therapy	Microbiological outcome and (observations)	Outbreak (yes/no)	Ref.
Uruguay	2013	<i>M. morgani</i>	M/24	Urosepsis	Renal transplant; on immunosuppressive therapy with prednisone, tacrolimus, and mycophenolate	TGC, CRB, PTZ, CIP, CN, AK, SXT, and natural resistance to TIG, COL and NT	FOS	FOS/MEM	Success	No	This work
Guatemala	2011	<i>K. pneumoniae</i>	ND/1	Nosocomial pneumonia/septic shock	ND	TGC, CRB, PTZ, CIP, CHL, NT	CN, AK, NAL, TIG, FOS, COL	PTZ/AK	Success	Yes	22
Guatemala	2011	<i>K. pneumoniae</i>	ND/ND	Tracheal secretion	Head and neck trauma from gunfire	TGC, CRB, PTZ, CIP, CHL, NT	CN, AK, NAL, TIG, FOS, COL	ND	Death (non-infectious-related cause)	Yes	22
Colombia	2011	<i>K. pneumoniae</i>	F/23 days	BSI	Preterm, placenta abruptio, severe perinatal asphyxia, enterocolitis	TGC, CRB, AK	ATM, CIP, TET, TGC, COL	MEM/RIF	Success	Yes	24
Colombia	2011	<i>K. pneumoniae</i>	M/9 days	NEC	Preterm, chorioamnionitis	TGC, CRB, AK	ATM, CIP, TET, TGC, COL	IPM/CIP	Success	Yes	24
Colombia	2011	<i>K. pneumoniae</i>	M/90 days	BSI	Meconium aspiration syndrome, severe perinatal asphyxia, hypoxic-ischemic encephalopathy	TGC, CRB, AK	ATM, CIP, TET, TGC, COL	IPM/CIP	Success	Yes	24
Colombia	2011	<i>K. pneumoniae</i>	M/10 days	BSI	Preterm, toxemic mother, severe perinatal asphyxia, pneumonia in utero	TGC, CRB, AK	ATM, CIP, TET, TGC, COL	IPM/CIP	Death (non-infectious-related cause)	Yes	24
Colombia	2012	<i>K. pneumoniae</i>	F/1	BSI	Pneumonia in utero with spontaneous pneumothorax, closed thoracostomy (3 days)	TGC, CRB, AK	ATM, CIP, TET, TGC, COL	IPM/CIP	Success	Yes	24
Colombia	2012	<i>K. pneumoniae</i>	F/13	Fulminant NEC	Preterm, chorioamnionitis, pneumonia in utero	TGC, CRB, AK	ATM, CIP, TET, TGC, COL	NT	Death	Yes	24
Mexico	2012	<i>P. rettgeri</i>	M/22	UTI	ND	TGC, CRB, CIP, COL, CN	TIG	ND	Death (non-infectious-related cause)	Yes	20
Mexico	2012	<i>P. rettgeri</i>	M/16	UTI	ND	TGC, CRB, CIP, COL, CN	TIG	ND	Death (non-infectious-related cause)	Yes	20
Mexico	2012	<i>P. rettgeri</i>	F/50	UTI	ND	TGC, CRB, CIP, COL	CN, TIG	ND	Success	Yes	20
Mexico	2012	<i>P. rettgeri</i>	F/53	UTI	ND	TGC, CRB, CIP, COL	CN, TIG	ND	Success	Yes	20
Honduras	2012	<i>A. baumannii</i>	M/76	IAI	Peritoneal dialysis	TGC, CRB, CIP, AK, CN, SXT	COL, TIG	TIG	Success	No	23
Brazil	2013	<i>P. rettgeri</i>	ND/ND	Diabetic foot infection	Diabetic peripheral vascular disease	TGC, IMP, CN, and natural resistance to TIG, COL, and NT	MEM, ERT, AK	AMC	Toe amputation was required	No	26
Paraguay	2012	<i>A. pittii</i>	ND/7	CSF	ND	TGC, CRB, PTZ	CN, AK, NAL, CIP, COL, TIG	SXT, CIP, AK	Death (non-infectious-related cause)	No	25
Paraguay	2012	<i>A. pittii</i>	ND/2	Sepsis	Acute lymphocytic leukemia	TGC, CRB, PTZ	CN, AK, NAL, CIP, COL, TIG	MEM, AK	Success	No	25

AK, amikacin; AMC, Amoxicillin-Clavulanic acid; ATM, Aztreonam; BSI, blood stream infection; CHL, chloramphenicol; CIP, ciprofloxacin; CN, gentamicin; COL, colistin; CRB, carbapenems; CSF, cerebrospinal fluid; ERT, ertapenem; F, female; FOS, fosfomicin; IAI, Intra-abdominal Infection; IPM, imipenem; M, male; MEM, meropenem; NAL, nalidixic acid; ND, not determined; NEC, necrotizing enterocolitis; NT, nitrofurantoin; PTZ, piperacillin-tazobactam; RIF, rifampin; SXT, trimethoprim-sulfamethoxazole; TET, tetracycline; TGC, third-generation cephalosporins including ceftazidime and cefotaxime; TIG, tigecycline; UTI, urinary tract infection.

<sup>a</sup> *Morganella morgani*; *Klebsiella pneumoniae*; *Providencia rettgeri*; *Acinetobacter baumannii*; *Acinetobacter pittii*.

colonization, or from nosocomial and community-acquired infections.<sup>14,38,40,42</sup>

Meanwhile, the association of NDM and PMQR has been reported in Guatemala, Colombia, and Brazil.<sup>22,24,27</sup> In Guatemala, two *K. pneumoniae* ST17 isolates producing NDM-1, *aac(6′)Ib-cr*, and *qnrB1* with the presence of two extended-spectrum β-lactamases (ESBL), CTX-M-15 and SHV-12, have been reported.<sup>22</sup> In Colombia a *K. pneumoniae* isolate (ST1043) carrying *qnrA1*, associated with ESBL CTX-M-15, has been reported.<sup>24</sup> Finally, an *Enterobacter hormaechei* strain carrying NDM-1 in conjunction with *qnrB4* and CTX-M-15 has been described in Brazil.<sup>27</sup>

Most clinical bacteria reported with NDM-1 remain susceptible in vitro only to colistin and to either or both tigecycline and fosfomycin.<sup>44</sup> This was not the case for our isolate.

*M. morgani* is naturally resistant to tigecycline and to polymyxins.<sup>3</sup> In addition, the Mm4232 isolate was resistant to all β-lactam antibiotics, including carbapenems and in combinations with inhibitors, aminoglycosides, and trimethoprim-sulfamethoxazole. Taking into account this antibiotic resistance profile, the Mm4232 isolate was considered to be XDR. This extensive pattern of drug resistance left only fosfomycin as an option for treatment.

There have been no randomized clinical studies on how to treat infections caused by carbapenemase-producing *Enterobacteriaceae*. Evidence comes from non-randomized studies with a retrospective design. The majority of studies refer to KPC-producers, and some to VIM-producers and carbapenem-resistant isolates. NDM-producers are hardly mentioned.<sup>45</sup> The available evidence suggests that infections caused by carbapenemase-producers have better outcomes when combination therapy is used.<sup>46,47</sup>

Tigecycline in combination with colistin, carbapenem in combination with colistin, and tigecycline in combination with gentamicin are the most commonly administered antibiotic regimens among the published studies and might result in lower mortality than other antibiotic combinations.<sup>48–54</sup> In general, carbapenems are administered to patients infected with strains for which the MICs are low (4 mg/l and probably up to 8 mg/l). There are studies that mention an important increase in survival when a carbapenem is administered in combination with another drug. It is important that a high-dose prolonged infusion regimen is administered to drive the pharmacokinetic/pharmacodynamic (PK/PD) profile towards acceptable exposures.<sup>50,51,55</sup>

Fosfomycin represents a potential last-resort treatment option for infections caused by carbapenemase-producers.<sup>47</sup> In vitro studies have demonstrated fosfomycin synergy in combination with imipenem and meropenem in 74% and 70% of KPC-producing *K. pneumoniae* isolates, respectively.<sup>56</sup> Fosfomycin in combination with colistin, gentamicin, or piperacillin-tazobactam has shown a promising clinical success rate (100%) in the treatment of serious infections caused by carbapenem-resistant *K. pneumoniae*.<sup>57</sup> However, the potential emergence of resistance during therapy has been reported.<sup>58</sup>

In a recent study, Pontikis et al. described a series of patients with infections caused by XDR *Pseudomonas aeruginosa* and *K. pneumoniae*, according to the definition used in our work. These patients were treated with fosfomycin in combination with various antibiotics, including meropenem in some cases.<sup>59</sup> However, it is not clear how many cases received the fosfomycin-meropenem combination, or what the cure rate was for this. None of these microorganisms were NDM carbapenemase-producers.

In Uruguay, the surveillance of carbapenemase-producing isolates is done by the Ministry of Public Health (<http://www.msp.gub.uy>), but the dissemination of the results is poor.<sup>29,60</sup> So far, there have been no reports combining the detection of

different resistance genes and the clinical outcomes of infected patients. We recently reported the detection and control of the first outbreak in our country caused by KPC-producing *K. pneumoniae* ST258.<sup>61</sup>

In this paper we reported the successful management of an immunocompromised patient with urosepsis produced by XDR *M. morgani* only susceptible to fosfomycin. The patient was treated with meropenem and fosfomycin and showed a clinical improvement and reduction of acute-phase markers such as procalcitonin and CRP.

Fosfomycin is rarely used in Latin America and there are very few reports on its susceptibility.<sup>22</sup> Similarly, the use of the fosfomycin-meropenem combination for XDR strains is poorly reported and it is not easy to interpret the results of such a therapeutic combination.<sup>59</sup>

To our knowledge this is the first report of severe sepsis caused by *bla*<sub>NDM-1</sub>-producing XDR *M. morgani*. In this context we consider that our report could be helpful to physicians and provides well-documented information on an alternative treatment for infections caused by XDR GNB, including colistin-carbapenem-resistant GNB.

To date *qnrD1* has not been reported in Latin America and more studies will be required to evaluate the dissemination of this PMQR gene in other species of *Enterobacteriaceae*.

## Acknowledgements

This work was supported in part by grants from CSIC (Comisión Sectorial de Investigación Científica, Uruguay) to R.V.

**Ethics:** The study did not interfere with the patient's treatment (clinical or paraclinical). Data were handled and results are presented without disclosing the identity of the patient.

**Conflict of interest:** Nothing to declare.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijid.2014.09.010>.

## References

- O'Hara CM, Brenner FW, Miller JM. Classification, identification, and clinical significance of *Proteus*, *Providencia*, and *Morganella*. *Clin Microbiol Rev* 2000;**13**: 534–46.
- Power P, Galleni M, Ayala JA, Gutkind G. Biochemical and molecular characterization of three new variants of AmpC β-lactamases from *Morganella morgani*. *Antimicrob Agents Chemother* 2006;**50**:962–7.
- Leclercq R, Cantón R, Brown DF, Giske CG, Heisig P, MacGowan AP, et al. EUCAST expert rules in antimicrobial susceptibility testing. *Clin Microbiol Infect* 2013;**19**:141–60.
- Nordmann P, Dortet L, Poirel L. Carbapenem resistance in *Enterobacteriaceae*: here is the storm! *Trends Mol Med* 2012;**18**:263–72.
- Cantón R, Akova M, Carmeli Y, Giske CG, Glupczynski Y, Gniadkowski M, et al. Rapid evolution and spread of carbapenemases among *Enterobacteriaceae* in Europe. *Clin Microbiol Infect* 2012;**18**:413–31.
- Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, et al. Characterization of a new metallo-β-lactamase gene, *bla*(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009;**53**:5046–54.
- Johnson AP, Woodford N. Global spread of antibiotic resistance: the example of New Delhi metallo-β-lactamase (NDM)-mediated carbapenem resistance. *J Med Microbiol* 2013;**62**:499–513.
- Rolain JM, Parola P, Cornaglia G. New Delhi metallo-β-lactamase (NDM-1): towards a new pandemic? *Clin Microbiol Infect* 2010;**16**:1699–701.
- Rodríguez-Martínez JM, Cano ME, Velasco C, Martínez-Martínez L, Pascual A. Plasmid-mediated quinolone resistance: an update. *J Infect Chemother* 2011;**17**: 149–82.
- Cavaco LM, Hasman H, Xia S, Aarestrup FM. *qnrD*, a novel gene conferring transferable quinolone resistance in *Salmonella enterica* serovar Kentucky and *Bovismorbificans* strains of human origin. *Antimicrob Agents Chemother* 2009;**53**:603–8.

11. Mazzariol A, Kocsis B, Koncan R, Kocsis E, Lanzafame P, Cornaglia G. Description and plasmid characterization of *qnrD* determinants in *Proteus mirabilis* and *Morganella morganii*. *Clin Microbiol Infect* 2012;**18**:E46–8.
12. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;**18**:268–81.
13. Nordmann P, Poirel L, Carrer A, Toleman MA, Walsh TR. How to detect NDM-1 producers. *J Clin Microbiol* 2011;**49**:718–21.
14. Garcia-Fulgueiras V, Bado I, Mota MI, Robino L, Cordeiro NF, Varela A, et al. Extended-spectrum  $\beta$ -lactamases and plasmid-mediated quinolone resistance in enterobacterial clinical isolates in the paediatric hospital of Uruguay. *J Antimicrob Chemother* 2011;**66**:1725–9.
15. Vignoli R, Cordeiro N, Seija V, Schelotto F, Radice M, Ayala J, et al. Genetic environment of CTX-M-2 in *Klebsiella pneumoniae* isolates from hospitalized patients in Uruguay. *Rev Argent Microbiol* 2006;**38**:84–8.
16. Vignoli R, Cordeiro NF, Garcia V, Mota MI, Betancor L, Power P, et al. New TEM-derived extended-spectrum beta-lactamase and its genomic context in plasmids from *Salmonella enterica* serovar derby isolates from Uruguay. *Antimicrob Agents Chemother* 2006;**50**:781–4.
17. García-Fulgueiras V, Bado I, Cordeiro N, Algorta G, Vignoli R. First report of the ceftazidimase CTX-M-19 in South America. *New Microbes New Infect* 2013;**1**:44–7.
18. García-Fulgueiras V, Seija V, Aguerrebere P, Cordeiro NF, Vignoli R. First report of a clinical isolate of *Leclercia adecarboxylata* harbouring multiple resistance genes in Uruguay and review of the literature. *J Glob Antimicrob Resist*; 2014;**2**:77–81.
19. Cordeiro NF, Yim L, Betancor L, Cejas D, García-Fulgueiras V, Mota MI, et al. Identification of the first *bla<sub>CMY-2</sub>* gene in *Salmonella enterica* serovar Typhimurium isolates obtained from cases of paediatric diarrhoea illness detected in South America. *J Glob Antimicrob Resist* 2013;**1**:143–8.
20. Barrios H, Garza-Ramos U, Reyna-Flores F, Sanchez-Perez A, Rojas-Moreno T, Garza-Gonzalez E, et al. Isolation of carbapenem-resistant NDM-1-positive *Providencia rettgeri* in Mexico. *J Antimicrob Chemother* 2013;**68**:1934–6.
21. Thoms-Rodriguez CA, Nicholson A, Christian N, Willey B, Didier H, Mataseje L, et al. The detection of the NDM-1 and other carbapenemase genes in multidrug resistant Gram negative bacilli (MDRGNB) in a Jamaican hospital. *Int J Infect Dis* 2012;**16**(S1):e434–5.
22. Pasteran F, Albornoz E, Faccone D, Gomez S, Valenzuela C, Morales M, et al. Emergence of NDM-1-producing *Klebsiella pneumoniae* in Guatemala. *J Antimicrob Chemother* 2012;**67**:1795–7.
23. Waterman PE, McGann P, Snesrud E, Clifford RJ, Kwak YI, Munoz-Urbizo IP, et al. Bacterial peritonitis due to *Acinetobacter baumannii* sequence type 25 with plasmid-borne New Delhi metallo- $\beta$ -lactamase in Honduras. *Antimicrob Agents Chemother* 2013;**57**:4584–6.
24. Escobar Pérez JA, Olarte Escobar NM, Castro-Cardozo B, Valderrama Márquez IA, Garzón Aguilar MI, Martínez de la Barrera L, et al. Outbreak of NDM-1-Producing *Klebsiella pneumoniae* in a neonatal unit in Colombia. *Antimicrob Agents Chemother* 2013;**57**:1957–60.
25. Pasteran F, Mora MM, Albornoz E, Faccone D, Franco R, Ortellado J, et al. Emergence of genetically unrelated NDM-1-producing *Acinetobacter pittii* strains in Paraguay. *J Antimicrob Chemother* 2014;**69**:2575–8.
26. Carvalho-Assef AP, Pereira PS, Albano RM, Berião GC, Chagas TP, Timm LN, et al. Isolation of NDM-producing *Providencia rettgeri* in Brazil. *J Antimicrob Chemother* 2013;**68**:2956–7.
27. Carvalho-Assef AP, Pereira PS, Albano RM, Berião GC, Tavares CP, Chagas TP, et al. Detection of NDM-1-, CTX-M-15-, and *qnrB4*-producing *Enterobacter hormaechei* isolates in Brazil. *Antimicrob Agents Chemother* 2014;**58**:2475–6.
28. Rozales FL, Ribeiro VB, Magagnin CM, Pagano M, Lutz L, Falci DR, et al. Emergence of NDM-1-producing *Enterobacteriaceae* in Porto Alegre, Brazil. *Int J Infect Dis* 2014;**25**:79–81. <http://dx.doi.org/10.1016/j.ijid.2014.01.005>.
29. PAHO/WHO. Epidemiological update. Carbapenemases of type New Delhi metallo- $\beta$ -lactamase (NDM), 7 March 2014. PAHO; 2014.
30. Martínez-Martínez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. *Lancet* 1998;**351**:797–9.
31. Castanheira M, Pereira AS, Nicoletti AG, Pignatari AC, Barth AL, Gales AC. First report of plasmid-mediated *qnrA1* in a ciprofloxacin-resistant *Escherichia coli* strain in Latin America. *Antimicrob Agents Chemother* 2007;**51**:1527–9.
32. Minarini LA, Poirel L, Cattoir V, Darini AL, Nordmann P. Plasmid-mediated quinolone resistance determinants among enterobacterial isolates from outpatients in Brazil. *J Antimicrob Chemother* 2008;**62**:474–8.
33. Minarini LA, Gales AC, Darini AL. First report of plasmid-mediated resistance to quinolones and cefotaxime in an *Enterobacter cloacae* strain isolated from an outpatient in Brazil. *Antimicrob Agents Chemother* 2007;**51**:401–2.
34. Viana AL, Cayo R, Avelino CC, Gales AC, Franco MC, Minarini LA. Extended-spectrum beta-lactamases in *Enterobacteriaceae* isolated in Brazil carry distinct types of plasmid-mediated quinolone resistance genes. *J Med Microbiol* 2013;**62**:1326–31.
35. Fonseca EL, Dos Santos Freitas F, Vieira VV, Vicente AC. New *qnr* gene cassettes associated with superintegron repeats in *Vibrio cholerae* O1. *Emerg Infect Dis* 2008;**14**:1129–31.
36. Cruz GR, Radice M, Sennati S, Pallecchi L, Rossolini GM, Gutkind G, et al. Prevalence of plasmid-mediated quinolone resistance determinants among oxyiminocephalosporin-resistant *Enterobacteriaceae* in Argentina. *Mem Inst Oswaldo Cruz* 2013;**108**:924–7.
37. Quiroga MP, Andres P, Petroni A, Soler Bistue AJ, Guerriero L, Vargas LJ, et al. Complex class 1 integrons with diverse variable regions, including *aac(6′)-Ib-cr*, and a novel allele, *qnrB10*, associated with ISCR1 in clinical enterobacterial isolates from Argentina. *Antimicrob Agents Chemother* 2007;**51**:4466–70.
38. Andres P, Lucero C, Soler-Bistué A, Guerriero L, Albornoz E, Tran T, et al. Differential distribution of plasmid-mediated quinolone resistance genes in clinical enterobacteria with unusual phenotypes of quinolone susceptibility from Argentina. *Antimicrob Agents Chemother* 2013;**57**:2467–75.
39. Bartoloni A, Pallecchi L, Riccobono E, Mantella A, Magnelli D, Di Maggio T, et al. Relentless increase of resistance to fluoroquinolones and expanded-spectrum cephalosporins in *Escherichia coli*: 20 years of surveillance in resource-limited settings from Latin America. *Clin Microbiol Infect* 2013;**19**:356–61.
40. Pallecchi L, Riccobono E, Mantella A, Bartalesi F, Sennati S, Gamboa H, et al. High prevalence of *qnr* genes in commensal enterobacteria from healthy children in Peru and Bolivia. *Antimicrob Agents Chemother* 2009;**53**:2632–5.
41. Riveros M, Riccobono E, Durand D, Mosquito S, Ruiz J, Rossolini GM, et al. Plasmid-mediated quinolone resistance genes in enteroaggregative *Escherichia coli* from infants in Lima, Peru. *Int J Antimicrob Agents* 2012;**39**:540–2.
42. Bado I, Cordeiro NF, Robino L, Garcia-Fulgueiras V, Seija V, Bazet C, et al. Detection of class 1 and 2 integrons, extended-spectrum  $\beta$ -lactamases and *qnr* alleles in enterobacterial isolates from the digestive tract of intensive care unit inpatients. *Int J Antimicrob Agents* 2010;**36**:453–8.
43. Gonzalez F, Araque M. Association of transferable quinolone resistance determinant *qnrB19* with extended-spectrum  $\beta$ -lactamases in *Salmonella* GIVE and *Salmonella* Heidelberg in Venezuela. *Int J Microbiol* 2013;628185.
44. Livermore DM, Warner M, Mushtaq S, Doumith M, Zhang J, Woodford N. What remains against carbapenem-resistant *Enterobacteriaceae*? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomicin, minocycline, nitrofurantoin, temocillin and tigecycline. *Int J Antimicrob Agents* 2011;**37**:415–9.
45. Falagas ME, Lourida P, Poulikakos P, Rafailidis PI, Tansarli GS. Antibiotic treatment of infections due to carbapenem-resistant *Enterobacteriaceae*: systematic evaluation of the available evidence. *Antimicrob Agents Chemother* 2011;**58**:654–63.
46. Lee G, Burgess D. Treatment of *Klebsiella pneumoniae* carbapenemase (KPC) infections: a review of published case series and case reports. *Ann Clin Microbiol Antimicrob* 2012;**11**:32. <http://dx.doi.org/10.1186/1476-0711-11-32>.
47. Levy Hara G, Gould I, Endimiani A, Pardo PR, Daikos G, Hsueh PR, et al. Detection, treatment, and prevention of carbapenemase-producing *Enterobacteriaceae*: recommendations from an international working group. *J Chemother* 2013;**25**:129–40.
48. Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, Cipullo R, Moreira JC, Baia C, et al. Infection with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* in solid organ transplantation. *Transpl Infect Dis* 2012;**14**:198–205.
49. Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M, et al. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. *Clin Microbiol Infect* 2013;**19**:E23–30.
50. Daikos GL, Petrikos P, Psychogiou M, Kosmidis C, Vryonis E, Skoutelis A, et al. Prospective observational study of the impact of VIM-1 metallo- $\beta$ -lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. *Antimicrob Agents Chemother* 2009;**53**:1868–73.
51. Tumbarello M, Viale P, Viscoli C, Treccarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. *Clin Infect Dis* 2012;**55**:943–50.
52. Zarkotou O, Pourmaras S, Tselioti P, Dragoumanos V, Pitiriga V, Ranellou K, et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. *Clin Microbiol Infect* 2011;**17**:1798–803.
53. Souli M, Galani I, Antoniadou A, Papadomichelakis E, Poulakou G, Panagea T, et al. An outbreak of infection due to  $\beta$ -lactamase *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* in a Greek university hospital: molecular characterization, epidemiology, and outcomes. *Clin Infect Dis* 2010;**50**:364–73.
54. Souli M, Kontopidou FV, Papadomichelakis E, Galani I, Armaganidis A, Giamarellou H. Clinical experience of serious infections caused by *Enterobacteriaceae* producing VIM-1 metallo- $\beta$ -lactamase in a Greek university hospital. *Clin Infect Dis* 2008;**46**:847–54.
55. Qureshi Z, Paterson D, Potoski B, Kilayko M, Sandovsky G, Sordillo E, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. *Antimicrob Agents Chemother* 2012;**56**:2108–13.
56. Samonis G, Maraki S, Karageorgopoulos DE, Vouloumanou EK, Falagas ME. Synergy of fosfomicin with carbapenems, colistin, netilmicin, and tigecycline against multidrug-resistant *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* clinical isolates. *Eur J Clin Microbiol Infect Dis* 2012;**31**:695–701.
57. Michalopoulos A, Virtzili S, Rafailidis P, Chalevelakis G, Damala M, Falagas ME. Intravenous fosfomicin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation. *Clin Microbiol Infect* 2010;**16**:184–6.
58. Karageorgopoulos DE, Miriagou V, Tzouveleklis IS, Spyridopoulou K, Daikos GL. Emergence of resistance to fosfomicin used as adjunct therapy in KPC *Klebsiella*

- pneumoniae* bacteraemia: report of three cases. *J Antimicrob Chemother* 2012;**67**:2777–9.
59. Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. *Int J Antimicrob Agents* 2013;**43**: 52–9.
60. Nabon A, García Gabarrot G, Lopez Vega M, Camou T. Carbapenemasas: situación actual en Uruguay. Abstract AbstrMCE-1. *X Encuentro Nacional de Microbiólogos* 2013.
61. Marquez C, Ingold A, Echeverría N, Acevedo A, Vignoli R, García-Fulgueiras V, et al. Emergence of KPC-producing *Klebsiella pneumoniae* in Uruguay: infection control and molecular characterization. *New Microbes New Infect* 2014;**2**:58–63.