

# Impact of the New Delhi metallo-beta-lactamase on beta-lactam antibiotics

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**Abstract:** Since the first New Delhi metallo-beta-lactamase (NDM) report in 2009, NDM has spread globally causing various types of infections. NDM-positive organisms produce in vitro resistance phenotypes to carbapenems and many other antimicrobials. It is thus surprising that the literature examining clinical experiences with NDM does not report corresponding poor clinical outcomes. There are many instances where good clinical outcomes are described, despite a mismatch between administered antimicrobials and resistant in vitro susceptibilities. Available in vitro data for either monotherapy or combination therapy does not provide an explanation for these observations. However, animal studies do begin to shed more light on this phenomenon. They imply that the in vivo expression of NDM may not confer clinical resistance to all cephalosporin and carbapenem antibiotics as predicted by in vitro testing but other resistance mechanisms need to be present to generate a resistant phenotype. As such, previously abandoned therapies, particularly carbapenems and beta-lactamase inhibitor combinations, may retain utility against infections caused by NDM producers.

**Keywords:** carbapenemase, metallo-beta-lactamase, resistance

## The New Delhi metallo-beta-lactamase carbapenemase

Beta-lactamase production is a common mechanism of resistance, particularly among Gram-negative organisms.<sup>1</sup> Carbapenemases are distinct among the beta-lactams; in addition to being able to hydrolyze most penicillins and cephalosporins, they are also able to hydrolyze the carbapenems. There are two biochemically distinct classes of carbapenemases: the serine beta-lactamases and the metallo-beta-lactamases (MBLs). The fundamental difference between these two classes resides in their hydrolytic mechanisms and rate of hydrolysis. The serine beta-lactamases rely on serine residues within the active site for hydrolytic activity, whereas MBLs rely on zinc ions. Because of these mechanistic differences, these enzymes are inhibited differently; serine beta-lactamases can be inhibited by beta-lactamase inhibitors (such as clavulanic acid), whereas MBLs are inhibited by agents that can chelate divalent cations (such as EDTA). Several MBLs have been described in the literature.<sup>2</sup> The imipenemase (IMP) variety of MBLs was among the earlier beta-lactamases in the class to be identified in the 1980s in Japan. Since their discovery, several IMP variants have been described. Verona integron-encoded metallo-β-lactamase (VIM)-type enzymes are another type of MBL with several described variants, and SPM-type enzymes are another example of MBLs that have been discovered. The New Delhi metallo-beta-lactamase (NDM) is the most recently discovered, globally distributed enzyme.<sup>2</sup> This review will focus on the impact of the NDM enzyme on beta-lactam antibiotics.

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NDM was first reported in the literature in 2009 in a *Klebsiella pneumoniae* isolate and was referred to as NDM-1.<sup>3</sup> This particular isolate was found on a urine culture from a male patient in Sweden who had traveled to and had been hospitalized in India. Further investigation of the *bla*<sub>NDM-1</sub> gene found in this isolate revealed that NDM-1 bound and hydrolyzed all beta-lactams, with the exception of aztreonam. To date, there have been 13 variants of NDM that have been identified: NDM-1 to -14 (NDM-11 was not assigned to any unique variant).<sup>4-6</sup> The variants arise from site mutations within the gene encoding the beta-lactamase. The location of the mutation on the gene seems to predict rates of hydrolysis. Many of the variants, such as NDM-2 and NDM-3, share similar hydrolytic activity with NDM-1, as the mutations are not located in the active site of the enzyme. Some variants, such as NDM-4, do have genetic alterations in the active site and have been observed to have increased hydrolytic activity toward carbapenems.<sup>7</sup> As summarized in Table 1, NDM-1 is the most common variant in cases of clinical infections and unless otherwise noted will be the focus of this paper.

NDM was named so after its place of origin: New Delhi, India.<sup>3</sup> Organisms carrying genetic material for NDM have been found to be very capable of transferring genes encoding NDM, as well as any other resistance genes the pathogen may be carrying.<sup>8</sup> The ease with which the genes are transferred is concerning, and the implications for dissemination of NDM are immense. Indeed, since its discovery, it has spread across the globe.<sup>9</sup> The most recently published surveillance study reported a total of 135 NDM isolates from around the world.<sup>9</sup> Despite the fact that about half of the isolates came from India, the study established the presence of NDM-producing organisms in other parts of the world, such as Vietnam, Serbia, the Philippines, the Middle East, Guatemala, and the USA. Reports of NDM-producing organisms have also surfaced from Pakistan,<sup>10</sup> the UK,<sup>10</sup> Japan,<sup>11</sup> the Netherlands,<sup>12</sup> and Australia.<sup>13</sup> Figure 1 depicts the geographical distribution of NDM; the areas where NDM producers are most commonly isolated are located on the Asian continent.<sup>4</sup> Outbreaks have also been reported around the world in areas such as the UK and the Middle East. The clinical cases outlined in Table 1 also help demonstrate the wide spread of NDM producers. A variety of non-beta-lactam antimicrobials are sometimes utilized, including as a part of combination therapy. However, often these organisms producing NDM are resistant to many other antimicrobials, if not all antimicrobials, which may limit non-beta-lactam options. Additionally, the antibiotics that retain activity have high rates of side effects or have limitations in drug delivery, colistin, and fosfomycin, respectively. Given the worldwide spread

and the broad resistance patterns detected, it is important to fully explore all our therapeutic options, including the clinical impact of these enzymes on beta-lactam antibiotics.

## Identification of NDM – microbiological challenges in phenotypic identification

The modified Hodge test was a recommended screening tool by the Clinical and Laboratory Standards Institute (CLSI) for carbapenemase-producing organisms.<sup>14</sup> This test, however, only screens for a phenotype, and therefore will not distinguish between the various types of carbapenemases. MBLs in particular can be difficult to detect using these methods, and as such, pose unique challenges in the laboratory.<sup>15</sup> The Carba NP test has also recently been developed for better carbapenemase detection<sup>16</sup> and is now a preferred method of detection per CLSI standards.<sup>17</sup> Identification methods utilizing chelating agents have also been developed to help better identify MBLs.<sup>14</sup> These methods look for either additive or synergistic effect when a chelating agent is added to a hydrolyzable beta-lactam. The chelating agent, by binding zinc ions that are necessary for hydrolytic activity, prevents MBL from taking action on the beta-lactam. Once an MBL is identified, to further determine which specific MBL is present requires genotypic identification.

## Clinical experience with NDM-producing pathogens

Clinical experience with treating infections caused by NDM producers is limited, making it difficult to fully assess the impact of NDM on clinical outcomes. A study evaluating neonatal sepsis in a level III neonatal intensive care unit (NICU) surprisingly insinuated that infection with an NDM producer did not confer higher mortality as compared to infections caused by other resistant pathogens.<sup>18</sup> The study identified 105 blood cultures from a 5-year time span that were found to have either cephalosporin resistance genes or carbapenem resistance genes. The only carbapenemase identified in this cohort was NDM; all the isolates had various combinations of different extended-spectrum beta-lactamases (ESBLs) and AmpC beta-lactamases. Fifteen isolates were found to produce NDM-1. Cefotaxime combined with either amikacin or gentamicin were the preferred empirical antibiotics within the first year of the 5-year study period, which was switched to piperacillin/tazobactam combined with amikacin. Severe infections warranting broader coverage were treated with combinations of ofloxacin, colistin, and meropenem. This broader therapy was more favored as empirical therapy after

Table 1 Clinical outcomes of case reports for NDM producers

Reference	Patient	Source of culture	NDM-carrying organism characteristics	Initial treatment, duration	Change in therapy reason	Subsequent treatment	Change in therapy	Outcome
52	35-year-old male in Spain – hospitalized in India within previous 9 days	Right iliac fossa abscess	KP S to: COL, TIG, FOS BL present: NDM-1, CTX-M-15, SHV-1	AMX/CLV days 1–3	CF	MER + abscess drainage (duration NR) day 4+	n/a	Survived
21	54-year-old male in Japan – hospitalized in India 1 month prior	Blood (ESBL EC on same culture)	EC S to: MIN BL present: NDM-1	CEF/SUL (duration NR)	n/a	n/a	n/a	Survived
53	7-year-old female in the USA – previously resided in India	Urine	A. EC S to: TIG, FOS, POL, BL present: NDM-1 B. KP S to: FOS BL present: NDM-1	A. CFTX (duration NR) B. FOS + TIG (duration NR)	CF, CR	1A. MER 2A. TIG 3A. FOS (duration NR)	1A. CF, CR 2A. ADE 3A. FOS (duration NR)	A. Survived B. Survived
54	13-month-old male in the USA – recent travel and hospitalization in Pakistan	Lung	KP S to: MIN, TIG BL present: NDM-1	CFTX + AZI days 1–3	CF	1. MER + AZI day 4 2. COL day 5	1. CR	Survived
55	28-year-old female in Australia – recent tooth extraction in India	Urine	EC S to: NTF, FOS, CHL, COL BL present: NDM-3, CMY-6, CTX-M-15	NTF ×7 days	n/a	Received 10-day course n/a	n/a	Survived
55	78-year-old male in Australia – hospitalized in India 3 months prior	Urine (PSA also isolated)	EC L S to: COL BL present: NDM-1	COL + RIF ×14 days	n/a	n/a	n/a	Survived
26	46-year-old male in Ireland – hospitalized in India 1 month prior	Bone (culture also grew VIM-producing PSA)	EC L S to: FOS, COL BL present: NDM-1	COL + TIG days 1–50	CR	COL + AZTR + FOS days 51–92	n/a	Survived
31	3-year-old male in the USA – no travel history	Urine, blood	KP S to: CIP, GEN, SMX/TMP, COL, IMI BL present: NDM-1, CTX-M-15, CMY-4, SHV-11	CIP days 31–45	n/a	IMI + COL days 51–77 + PICC line removal day 56	New infection	Survived
31	2-year-old female in the USA – previously resided in India	Blood, isolated while on MER for non-NDM KP	EC S to: CIP, GEN, SMX/TMP BL present: NDM-1, CTX-M-15, CMY-42	COL + IMI + AMI days 75–89	n/a	n/a	n/a	Expired
33	18-year-old female in France – transferred from hospital in India to France	Blood – urinary source	CFR S to: FOS, COL BL present: NDM-1, CTX-M-15, TEM-1, OXA-1, VIM-4	AMX/CLV ×3 days Urinary catheter removed	n/a	n/a	n/a	Survived
28	65-year-old female in Singapore – previously resided in Indonesia	Blood – source NR	KP S to: POL BL present: NDM-1	POL + AZTR + VAN days 9–10	CR	POL + MER days 11–27 PICC removed	n/a	Survived
56	52-year-old male in Vietnam – no travel history	Urine	EC S to: FOS, COL BL present: NDM-1	FOS (duration NR)	n/a	n/a	n/a	Survived
56	62-year-old male in Vietnam – no travel history	Urine	KP S to: AMI, COL BL present: NDM-1	AMI + CLIN	n/a	n/a	n/a	Survived
57	6-month-old infant in Ireland – resided in India for 4 months	Urine	KP S to: CIP, TET, MIN, CHL BL present: NDM-1	CIP ×10 days	n/a	n/a	n/a	Survived

(Continued)

Table 1 (Continued)

Reference	Patient	Source of culture	NDM-carrying organism characteristics	Initial treatment, duration	Change in therapy reason	Subsequent treatment	Change in therapy	Outcome
35	46-year-old woman in Singapore – previously resided in Bangladesh	Blood, respiratory source	EC S to: TIG, FOS, POL BL present: NDM-1	IMI + VAN days 10–11	CR, CF	TIG + POL day 12 + (duration NR)	n/a	Expired: non-NDM related Survived
24	24-year-old male in Uruguay – no travel history reported	Urine	MM S to: FOS BL present: NDM-1	MER days 1–4	CR	FOS + MER HD/EF days 5–14 US removed	n/a	Survived
58	Diabetic patient in Brazil – no travel history reported	Tissue	PR S to: ERT, MER, AMI BL present: NDM-1	CIP (duration NR)	CF	AMX/CLV + amputation (duration NR)	n/a	Survived
59	76-year-old male in Honduras – no travel history reported	Peritoneal fluid	AB S to: MIN, COL, POL, TIG BL present: NDM-1, OXA-64, CTX-M-15	CFTX (duration NR)	CF	1. CIP + CFTZ (duration NR) 2. TIG × 10 days + PDC removal	1. CF	Survived
22	7-year-old patient in Paraguay – no travel history	CSF	AP S to: TIG; COL BL present: NDM-1	SMX/TMP, CIP, AMI	NR	Treatment duration and chronology NR	NR	Expired: non-NDM related Survived
22	2-year-old patient in Paraguay – no travel history	blood	AP S to: TIG, COL BL present: NDM-1	MER + AMI (duration NR)	NR	n/a	n/a	Survived
29	1-year-old patient in Guatemala – no travel history reported	PICC	KP S to: TIG, FOS, AMI, NAL, LEVO, COL BL present: NDM-1, CTX-M-15, SHV-11, SHV-12, TEM-1, OXA-1	MER + VAN × 14 days	CF	MER + AMI + PIP/TAZ × 14 days	n/a	Survived
23	87-year-old woman in Australia – traveled to India 2–3 months prior	Urine	KP S to: AZTR, CHL, TIG, COL BL present: NDM-1, CMY-6, SHV, DHA	TIC/CLV (duration NR)	n/a	n/a	n/a	Survived
60	56-year-old man in Taiwan – underwent renal transplantation in the People's Republic of China 7 days prior	Pelvic abscess	KO S to: TIG, COL BL present: NDM-1	TIG × 15 days + abscess drainage	n/a	n/a	n/a	Survived
61	32-year-old male in Canada – transferred to Canadian hospital from Indian hospital	Urine	EC S to: TIG, FOS, COL BL present: NDM-1, CTX-M-15	CIP × 5 days	CF	1. ERT × 7 days 2. FOS × 1 day	1. CR	Survived
27	59-year-old male in the UK – traveled to India and Kenya a year prior	A. SSTI biopsy (PSA and MRSA also found) B. Blood – isolated while on TIG	A. EC and KP S to: TIG, COL BL present: NDM-1 B. EC S to: COL BL present: NDM-1	FLU + BPCN (duration NR)	CF	1. PIP/TAZ (duration NR) 2. TIG + CIP × 53 days 3. COL + MER + TEI × 15 days 4. MER + TEI (duration NR)	1. CR 2. CF 3. ADE	Survived

25	A woman in her early 60s in France – recent hospitalization in Serbia	Urine	A, B. PSA S to: PIP, PIP/TAZ, COL BL present: NDM-I	A. AZTR + COL × 21 days B. OFL × 10 days	A. n/a B. CR	A. n/a B. PIP/TAZ × 21 days	Survived
30	23-day-old female – no travel history for child or family	Blood, GI source	KP S to: AZTR, CIP, TET, TIG, COL BL present: NDM-I, SHV	MER + RIFM (duration NR)	n/a	n/a	Survived
30	9-day-old male – no travel history for child or family	Blood, GI source	KP S to: AZTR, CIP, TET, TIG, COL BL present: NDM-I, SHV	PIP/TAZ (duration NR)	CF	IMI + CIP (duration NR)	Survived
30	90-day-old male – no travel history for child or family	Blood	KP S to: AZTR, CIP, TET, TIG, COL BL present: NDM-I, SHV	IMI + CIP (duration NR)	n/a	n/a	Survived
30	10-day-old male – no travel history for child or family	Blood, PICC	KP S to: AZTR, CIP, TET, TIG, COL BL present: NDM-I, SHV	IMI + CIP (duration NR)	n/a	n/a	Expired: non-NDM related
30	1.5-day-old female – no travel history for child or family	Blood, respiratory source	KP on blood culture S to: AZTR, CIP, TET, TIG, COL BL present: NDM-I, SHV	IMI + CIP (duration NR)	n/a	n/a	Survived
30	13-day-old female – no travel history for child or family	Blood, GI source	KP S to: AZTR, CIP, TET, TIG, COL BL present: NDM-I, SHV	Patient expired before therapy could be initiated	n/a	n/a	Expired
62	12-year-old male in Mexico – no travel history reported	Urine	KP S to: none BL present: NDM-I	AMI + CFTX + CLIN + AMP, CEFU (duration, chronology NR)	CR	AMI + CIP	Expired
36	Male patient in his early 40s in Italy – recent hospitalization in Serbia	Blood, source perianal abscess (VRE also isolated)	PSA S to: COL BL present: NDM-I	PIP/TAZ + AMI + VAN for FN (duration NR)	CF	1. MER + AMI + VAN – duration NR, for FN 2. COL + MER + AMI + VAN × 5 days for FN 3. TIG + RIF + COL + MER + AMI + DAPT for NDM	Expired
37	16-year-old male in Turkey – previously resided in Iraq	Blood, respiratory source (OXA-48, CTX-M-15, TEM-1 + EC also isolated)	KP S to: TIG, COL BL present: NDM-I, CTX-M-15, OXA-1, SHV-28, TEM-1	MER + TEI + COL (duration, chronology NR)	n/a	n/a	Expired
63	76-year-old female in Canada – transferred from Indian hospital to Canadian hospital	Urine	KP S to: COL BL present: NDM-I, SHV-1, CTX-M-15, OXA-1, CMY-6	IMI + VAN	CF	1. COL 2. CHL	Expired
34	44-year-old patient in Slovakia – no travel history reported	Blood, (ECF on same culture)	PSA S to: none BL present: NDM-I	PIP/TAZ days 1–6	NR	1. MER + VAN (duration NR) 2. MET + FLUC + MER + VAN (duration NR)	Survived

(Continued)

Table 1 (Continued)

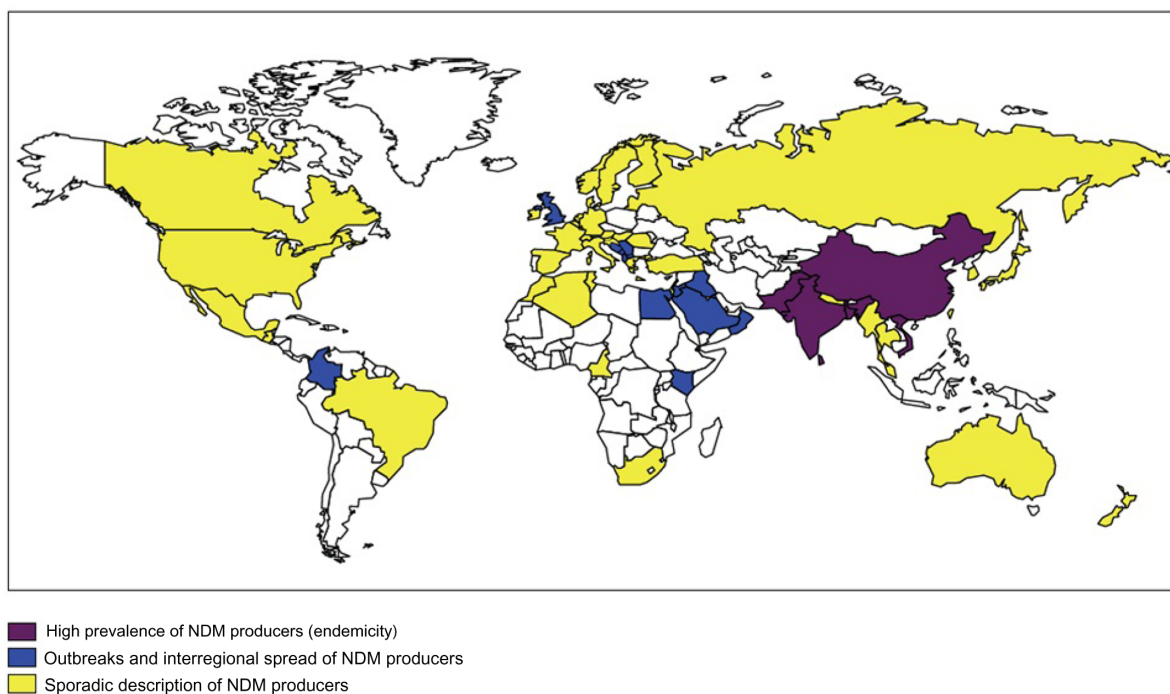
Reference	Patient	Source of culture	NDM-carrying organism characteristics	Initial treatment, duration	Change in therapy reason	Subsequent treatment	Change in therapy	Outcome
32	Elderly male in Norway – previously resided in India, prior hospitalization in India	Blood, urinary source	EC S to: MER, IMI, TIG, COL, SMX/TMP BL present: NDM-1, CMY-6	MER (duration NR)	NR	SMX/TMP (duration NR)	n/a	Survived
64	Elderly male in Morocco – no travel history reported	Urine	KP S to: IMI, DOR, FOS, TIG, COL, NTF BL present: NDM-1, CTX-M-15	NR	CR	AMI + COL	n/a	Survived
64	Female in her 60s in Morocco – no travel history reported	Blood	KP S to: IMI, DOR, FOS, TIG, COL, NTF BL present: NDM-1, CTX-M-15	IMI + MET	n/a	n/a	n/a	Expired
65	77-year-old male in India – no travel history reported	Blood	CI S to: COL BL present: NDM-1	COL × 12 days	n/a	n/a	n/a	Survived

**Notes:** A and B refer to distinct episodes within the same patient that were reported within the same case report.

**Abbreviations:** AB, *Acinetobacter baumannii*; ADE, adverse drug event; AMI, amikacin; AMP, ampicillin; AMX/CLV, amoxicillin/clavulanate; AP, *Acinetobacter pittii*; AZI, azithromycin; AZTR, aztreonam; BL, beta-lactamase; BPCN, benzylpenicillin; CEFU, cefuroxime; CEF/SUL, cefoperazone/sulbactam; CF, clinical failure; CFR, *Citrobacter freundii*; CFTX, ceftazidime; CHL, chloramphenicol; CI, *Chryseobacterium indologenes*; CIP, ciprofloxacin; CLIN, clindamycin; COL, colistin; CR, culture results; CSF, cerebral spinal fluid; DAPT, daptomycin; DOR, doripenem; EC, *Escherichia coli*; ECF, *Enterococcus faecalis*; ECL, *Enterobacter cloacae*; ERT, ertapenem; ESBL, extended-spectrum beta-lactamase; FLU, fluoroquinolone; FLUC, fluconazole; FN, febrile neutropenia; FOS, fosfomicin; GEN, gentamicin; GI, gastrointestinal; HD/IEF, high-dose extended infusion; IMI, imipenem; KP, *Klebsiella pneumoniae*; KO, *K. oxytoca*; LEVO, levofloxacin; MER, meropenem; MET, metronidazole; MIN, minocycline; MIM, *Morganella morganii*; MRSA, methicillin-resistant *Staphylococcus aureus*; n/a, not applicable; NAL, nalidixic acid; NDM, New Delhi metallo-beta-lactamase; NR, not reported; NTF, nitrofurantoin; OFL, ofloxacin; PDC, peritoneal dialysis catheter; PCC, peripherally inserted central catheter; PIP, piperacillin; PIP/TAZ, piperacillin/tazobactam; POL, polymyxin B; PR, *Providencia rettgeri*; PSA, *Pseudomonas aeruginosa*; RIF, rifampin; S, susceptible; SMX/TMP, sulfamethoxazole/trimethoprim; SSTI, skin and soft tissue infection; TEI, teicoplanin; TET, tetracycline; TIC/CLV, ticarcillin/clavulanate; TIG, tigecycline; US, ureteral stent; VAN, vancomycin; VRE, vancomycin-resistant *Enterococcus*.

carbapenem resistance trends were identified. Looking closer at the antibiotics used against NDM-producing isolates, there are a substantial number of patients who received antimicrobials without in vitro activity against the isolate and survived to be discharged from the NICU. Interestingly, mortality rates for neonates with bacteremia caused by an NDM producer (13.3%) versus those with a non-NDM producer were not different. A similar result was seen in another observational study evaluating bloodstream infections caused by *K. pneumoniae* producing VIM, another MBL; production of VIM was not found to be associated with an increase in mortality.<sup>19</sup> These observations are unexpectedly positive, given the additional in vitro resistance that is conferred by these enzymes. However, with mortality rates for *K. pneumoniae* carbapenemase infections being reported from clinical experiences to be between 42% and 53%,<sup>20</sup> the mortality rate seen with NDM seems staggeringly low. These studies call into question the magnitude of impact on clinical outcomes associated with MBL, and particularly, NDM production.

Most data describing clinical outcomes with infections caused by NDM producers are available in various case reports, summarized in Table 1. These case reports also tend to report good outcomes despite mismatches with therapy and susceptibilities. Specifically, there were instances in which appropriate therapy per culture was never reported to be initiated, and the patient's infection resolved.<sup>21–23</sup> There were also cases where therapy was switched to provide antimicrobials to match susceptibility results despite a lack of reported clinical failure on the “inappropriate” antimicrobials.<sup>24–26</sup> Combination therapy at some point during treatment was commonly described and often included a carbapenem in the regimen.<sup>24,27–30</sup> Of the 18 patients with NDM producers identified on blood culture, seven patients had isolates susceptible to antibiotics received during the course of treatment and survived.<sup>27,28,30–32</sup> Five patients had pathogens isolated on blood culture that were not susceptible to any antibiotics received during the course of treatment and survived, three of which received a carbapenem.<sup>21,22,30,31,33,34</sup> Of the six patients with bacteremia who expired,<sup>30,31,35–37</sup> only one had an NDM producer isolated that was not susceptible to any of the antibiotics received during the course of treatment.<sup>31</sup> One of the patients expired before antibiotics were initiated,<sup>30</sup> and the remaining four patients who expired had an NDM-producing pathogen on blood culture that was considered susceptible to antibiotics received during the course of treatment.<sup>30,35–37</sup> Two of these patients expired due to non-NDM related causes,<sup>30,35</sup> and the remaining two patients had undergone stem cell transplantation approximately 2–3 weeks prior to expiring.<sup>36,37</sup>



**Figure 1** Geographic distribution of NDM producers.

**Note:** Reproduced with permission from the Hindawi Publishing Corporation. Copyright © 2014. Dortet L, Poirel L, Nordmann P. Worldwide dissemination of the NDM-type carbapenemases in gram-negative bacteria. *Biomed Res Int.* 2014;2014:249856.<sup>4</sup>

**Abbreviation:** NDM, New Delhi metallo-beta-lactamase.

The cases described in Table 1 ultimately describe a broad range of patients and infection types with surprisingly positive outcomes. Although a trend toward positive outcomes exists, there are many other patient-specific factors that contribute to the patients' success rate, including underlying immune function and disease states, ability to drain/remove abscesses and infected necrotic tissues, and the management of invasive devices that might be colonized with the pathogen. These factors preclude definitive statements from being made about such therapies. However, these results further call into question the repercussions to be expected with NDM producers on patient outcomes and deserve further investigation in a controlled setting to investigate the possible rationale(s) for the discrepancies.

## In vitro susceptibilities

Literature reporting in vitro susceptibility of NDM producers often describes resistance to many antimicrobials and does not offer an explanation for the clinical successes recounted. A surveillance study gathering NDM-carrying clinical isolates from around the world characterized resistance patterns from 135 isolates.<sup>9</sup> Of the varieties of NDM, NDM-1 was most commonly seen, accounting for 96.3% of the isolates. Only levofloxacin (12.7% susceptibility) and amikacin (16.4% susceptibility) had any activity against the isolates; neither

cephalosporins, piperacillin/tazobactam, nor ampicillin/sulbactam displayed any in vitro activity. Based on this study, carbapenems did not appear to offer any substantial activity against these isolates either. Ertapenem minimum inhibitory concentration (MIC) values varied from 1 mg/L to >4 mg/L, with MIC<sub>50</sub> value of >4 mg/L. Imipenem did not look any more promising, with an MIC<sub>50</sub> value >8 mg/L. Of note, 99 of the 135 isolates carried additional genes encoding other ESBLs, with CTX-M being the most common, followed by SHV. Aztreonam is expected to be stable against the MBLs.<sup>9</sup> It is thought that the chemical structure of aztreonam does not allow adequate molecular interaction with the active site of MBLs, and therefore, hydrolysis of aztreonam does not occur.<sup>38</sup> However, because of the additional beta-lactamases and other resistance mechanisms often carried by these organisms, in vitro susceptibility is not always demonstrated to aztreonam.<sup>39</sup> The addition of the beta-lactamase inhibitor avibactam to aztreonam often restores activity of aztreonam against such NDM-carrying organisms. Another study examining isolates from India and the UK confirmed high rates of resistance to carbapenems, cephalosporins, and other beta-lactams (including aztreonam), quinolones, and aminoglycosides.<sup>10</sup> Colistin was reported to have good in vitro activity against these isolates (89%–100% susceptibility),<sup>10</sup> but when tested in a murine lung infection model using susceptible

isolates, it produced variable results.<sup>40</sup> Tigecycline had in vitro activity as well (56%–67% susceptibility)<sup>10</sup> and seemed to have more reliable activity in a murine lung infection against susceptible isolates.<sup>40</sup> However, tigecycline against nonfermenting Gram-negative organisms seems to fall to 15%, as compared to 60% susceptibility against *Enterobacteriaceae*, as reported by Jain et al.<sup>41</sup> Fosfomycin is another antimicrobial to consider; susceptibility of NDM-producing organisms to fosfomycin has been reported in the literature to be 60.5%<sup>41</sup> to 78%.<sup>42</sup> The various pieces published that describe in vitro susceptibility mirror the susceptibilities seen in case reports, thus confirming consistency of in vitro reports, but further highlight the clinical response discrepancies.

Eravacycline is a new fluorocycline antibiotic currently in the development for treatment of infections caused by multidrug-resistant organisms.<sup>43</sup> In a study investigating in vitro activity of eravacycline, five isolates showing nonsusceptibility to third-generation cephalosporins were confirmed to produce NDM. Of these five isolates, two (both *Escherichia coli*) had an MIC  $\leq 0.5$   $\mu\text{g/mL}$  and three (all *K. pneumoniae*) had an MIC of 1–2  $\mu\text{g/mL}$ . Another potential advantage of eravacycline is the availability of both parenteral and oral formulations, which could provide for convenient parenteral-to-oral therapy changes.<sup>44</sup> Despite the small number of NDM-producing isolates evaluated and the lack of clinical data, this study provides hope for another potential drug against NDM.

In vitro efficacy of combination therapy has also been evaluated against two NDM-producing *K. pneumoniae* strains.<sup>45</sup> In a study done by Tangden et al, despite both strains being resistant to fosfomycin, a combination of fosfomycin and colistin was found to have both bactericidal and synergistic activities after 24 hours. Similar activity was seen with a combination of rifampin, meropenem, and colistin despite both strains being nonsusceptible to rifampin or meropenem alone. A combination of fosfomycin, meropenem, and colistin had both bactericidal and synergistic activities against one strain, but lacked bactericidal activity against the other strain. Bacterial regrowth during the 24-hour period was observed for colistin-containing combinations (as well as with colistin alone), but clinical relevance of this is yet to be determined. Another larger study looked for synergistic antimicrobial combination in 28 NDM producers with paired combinations of colistin, fosfomycin, and tigecycline.<sup>46</sup> In this particular study, synergy was rarely observed when colistin was paired with another drug. In this study, no antagonism was observed, and most antibiotic pairs did not have any interaction. However, another study investigating tigecycline and colistin combinations did identify antagonism when the two agents

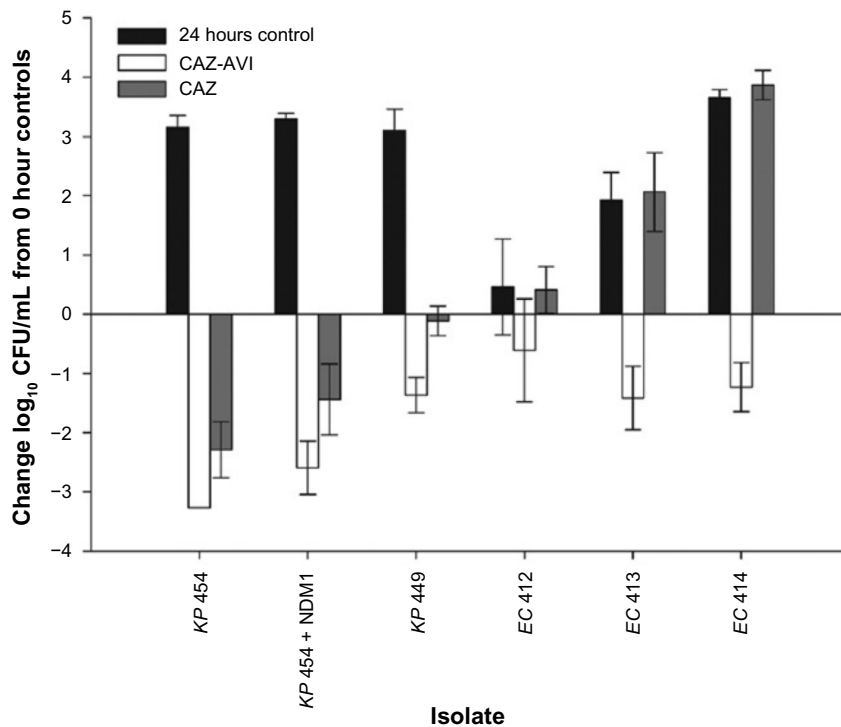
were combined.<sup>47</sup> Further studies are warranted to clarify the clinical significance of the interactions seen in these studies, particularly as it relates to possible antagonism. As it stands, available in vitro data for combination therapy also fails to provide insight into the unexpected good clinical outcomes seen in the literature.

## In vivo studies: reconciling discordance with in vitro findings

Despite the grim outlook on therapy provided by in vitro data, in vivo data from animal studies paints a different picture in terms of antimicrobial options and potentially explains the discordant results of human clinical data. One study compared humanized doses of ceftazidime versus ceftazidime with avibactam against isolates producing NDM, as well as other beta-lactamases.<sup>48</sup> In vitro susceptibility testing to ceftazidime, avibactam, and the combination of ceftazidime/avibactam showed that all NDM-producing isolates were resistant to the tested compounds. Therefore, it was unexpected when humanized exposures of both ceftazidime alone and ceftazidime in combination with avibactam had activity against NDM-producing isolates in a murine thigh infection model (Figure 2). Ceftazidime alone showed a 1.4-log reduction against an isogenic strain harboring NDM-1, whereas only modest to no activity was noted against clinical strains. The addition of avibactam to ceftazidime restored activity against all the tested strains, showing 0.61–1.42-log reductions in bacterial growth. Since ceftazidime was active against the isogenic NDM harboring the single enzyme, it was not surprising that the addition of avibactam essentially eliminated the impact of other beta-lactamases, preserving ceftazidime's activity against the clinical isolates. These data suggest that the magnitude of the in vivo expression of NDM beta-lactamase is not large enough in the context of conventional exposure to ceftazidime as used in the clinical setting. It also highlights that genotypic testing only for NDM may not be sufficient for determining clinical response to therapy.

Carbapenems provide another example of discordance between in vitro data and in vivo data. A murine thigh infection model performed by Wiskirchen et al compared efficacy of humanized, high-dose, prolonged-infusion doripenem, and ertapenem against NDM-producing strains.<sup>49</sup> An isogenic NDM-carrying *K. pneumoniae* strain as well as four clinical NDM-carrying strains all showed  $> 1$ -log reduction in bacterial density with carbapenem therapy in an immunocompetent murine thigh infection model (Figure 3). The exception was one clinical strain with a doripenem MIC  $> 32$   $\mu\text{g/mL}$ , which showed only a modest decrease in bacterial density. This

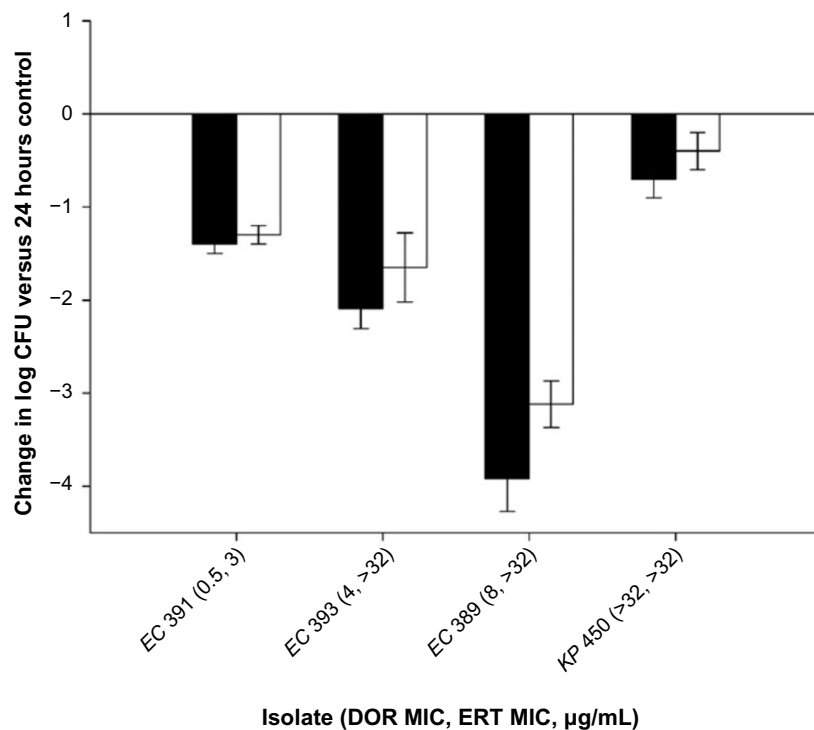




**Figure 2** Comparative efficacies of human-simulated regimens of CAZ-AVI and CAZ alone against NDM-carrying EC and KP, and an isogenic NDM-I pair in the neutropenic murine thigh infection model.

**Note:** Reproduced with permission from the American Society for Microbiology. Copyright © American Society for Microbiology. Wiskirchen DE, Nordmann P, Crandon JL, Nicolau DP. Efficacy of humanized carbapenem exposures against New Delhi metallo-beta-lactamase (NDM-I)-producing Enterobacteriaceae in a murine infection model. *Antimicrob Agents Chemother.* 2013;57(8):3936–3940.<sup>49</sup>

**Abbreviations:** CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; CFU, colony-forming units; EC, *Escherichia coli*; KP, *Klebsiella pneumoniae*; NDM, New Delhi metallo-beta-lactamase.



**Figure 3** Efficacy of human-simulated regimens of doripenem at 2 g every 8 hours as a 4-hour infusion (black bars) or ertapenem at 1 g every 24 hours (white bars) against four clinical NDM-I-producing *Enterobacteriaceae*.

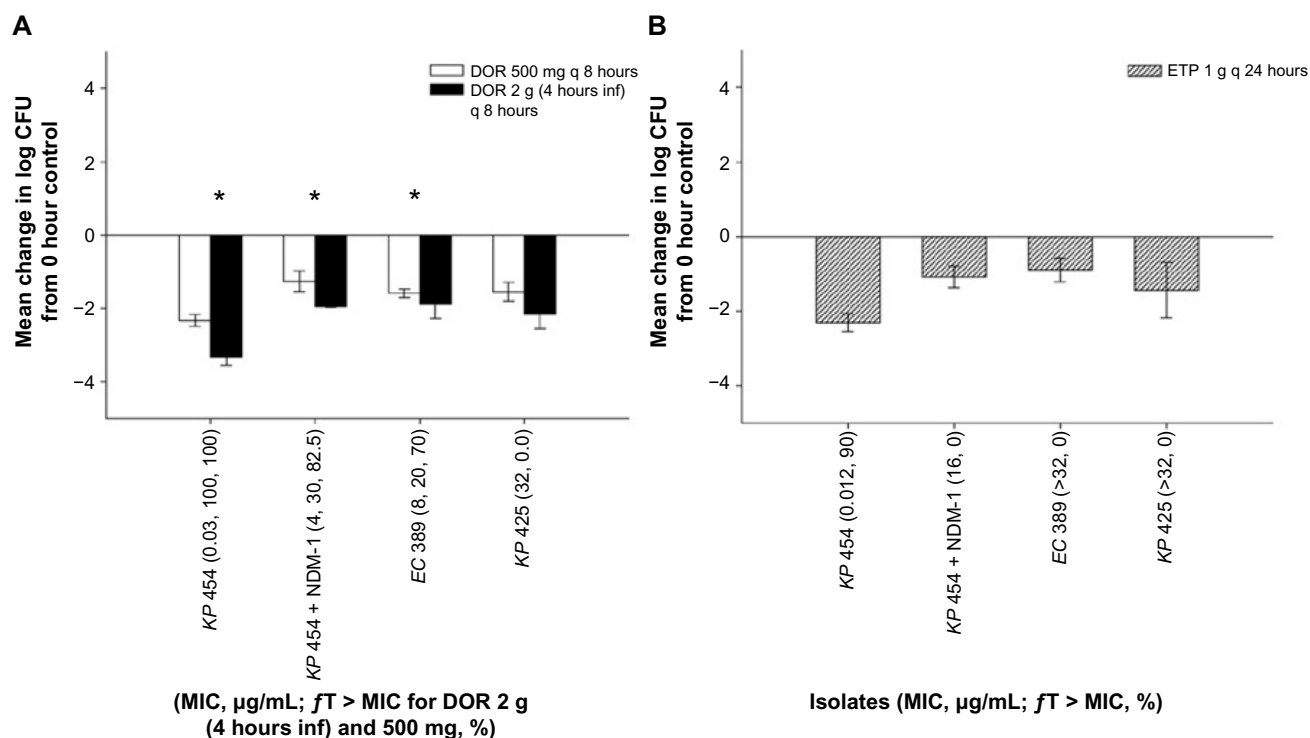
**Note:** Reproduced with permission from the American Society for Microbiology. Copyright © American Society for Microbiology. Bercot B, Poirel L, Dortet L, Nordmann P. In vitro evaluation of antibiotic synergy for NDM-I-producing *Enterobacteriaceae*. *J Antimicrob Chemother.* 2011;66(10):2295–2297.<sup>46</sup>

**Abbreviations:** CFU, colony-forming units; DOR, doripenem; EC, *Escherichia coli*; ERT, ertapenem; KP, *Klebsiella pneumoniae*; NDM, New Delhi metallo-beta-lactamase.

successful reduction in bacterial density was shown again in the same study using two clinical strains in a neutropenic murine thigh infection model, and the effect was shown to be sustained out to 72 hours in an extended immunocompetent murine model. The efficacy of carbapenems against NDM producers was confirmed in a second study done by Wiskirchen et al in both immunocompetent and neutropenic murine thigh infection models (Figure 4).<sup>50</sup> This second study also confirmed the need for higher doripenem doses; a dose providing the human exposure of 2 g every 8 hours infused over 4 hours consistently produced numerically higher bacterial reductions as compared to a standard dose of 500 mg given every 8 hours. This difference in bacterial reductions between the two regimens was statistically different in two of the four tested strains. Both studies also noted efficacy with carbapenems despite high MIC values and unmet pharmacokinetic/pharmacodynamic target for success ( $40\% fT > MIC$ ).<sup>49,50</sup> NDM-producing organisms are not the first MBLs to demonstrate a mismatch between in vitro and in vivo efficacies. *Enterobacteriaceae* carrying the VIM MBL also show in vitro resistance to carbapenems, and yet, meropenem was

able to produce a substantial reduction in bacterial density in a neutropenic murine thigh infection model (American Society for Microbiology, Washington, DC, data on file, 2015). Taken together, these studies suggest that carbapenems may make valuable contributions to fighting infections caused by NDM-producing organisms, and consideration should be given to utilizing these agents, especially when the organism fails to show susceptibility to other agents.

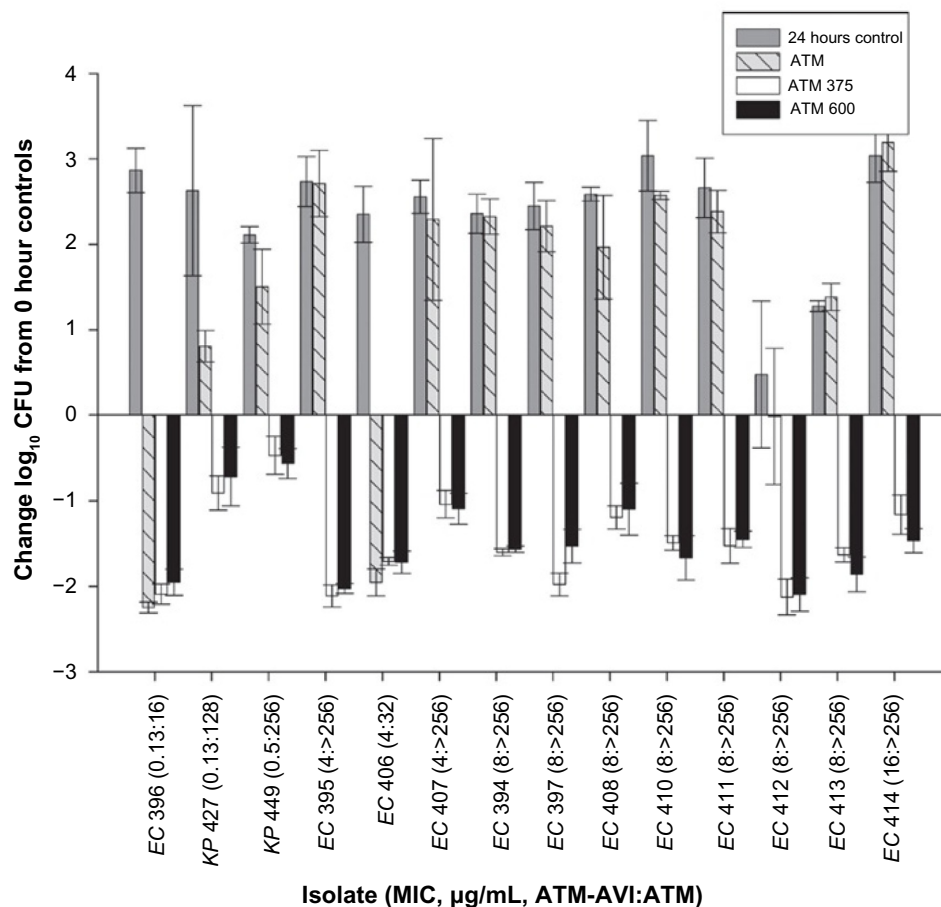
Aztreonam is expected to be stable against NDM-producing organisms, but is often not susceptible in vitro due to the presence of other beta-lactamases.<sup>9</sup> Conversely, the beta-lactamase inhibitor avibactam is protective against most other beta-lactamases, the exception being other MBLs.<sup>39</sup> Activity of the two compounds together has been confirmed both in vitro and in vivo.<sup>39</sup> A neutropenic murine thigh infection model utilizing human-simulated exposures of aztreonam alone and in combination with avibactam was performed.<sup>51</sup> It showed aztreonam alone had poor activity against the 14 NDM-carrying *Enterobacteriaceae* tested, but the combination had excellent antibacterial activity (Figure 5). All the animals in the combination group remained alive, whereas deaths were seen in the aztreonam



**Figure 4** Efficacies of human-simulated regimens of 500 mg of DOR given every 8 hours and 2 g of DOR given every 8 hours as a 4-hour infusion (**A**) and 1 g of ETP given every 24 hours (**B**) in a neutropenic murine thigh infection model.

**Note:** \*Denote a statistically higher efficacy of the higher DOR dose as compared to the lower DOR dose. Reproduced with permission from the American Society for Microbiology. Copyright © American Society for Microbiology. Wiskirchen DE, Nordmann P, Crandon JL, Nicolau DP. In vivo efficacy of human simulated regimens of carbapenems and comparator agents against NDM-I-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother*. 2014;58(3):1671–1677.<sup>50</sup>

**Abbreviations:** CFU, colony-forming units; DOR, doripenem; EC, *Escherichia coli*; ETP, ertapenem; KP, *Klebsiella pneumoniae*.



**Figure 5** Comparative efficacy of a human-simulated dose of 2,000 mg aztreonam q6h (1-hour infusion) as monotherapy or combined with 375 mg avibactam q6h (ATM-AVI 375 mg) or 600 mg avibactam q6h (ATM-AVI 600 mg) against *Enterobacteriaceae* in a neutropenic-mouse thigh infection.

**Note:** Reproduced with permission from the American Society for Microbiology. Copyright © American Society for Microbiology. Crandon JL, Nicolau DP. Human simulated studies of aztreonam and aztreonam-avibactam to evaluate activity against challenging gram-negative organisms, including metallo-beta-lactamase producers. *Antimicrob Agents Chemother.* 2013;57(7):3299–3306.<sup>51</sup>

**Abbreviations:** ATM, aztreonam; AVI, avibactam; CFU, colony-forming units; EC, *Escherichia coli*; KP, *Klebsiella pneumoniae*.

and the control group. Based on these data, the combination of aztreonam and avibactam seems like a viable option for the treatment of infections caused by NDM-producing organisms, particularly when other beta-lactamases may be present.

These animal data match more closely with the observations of clinical outcomes. The mismatch between observed and expected efficacy highlighted by these animal studies brings hope that new therapy options may be uncovered from previously abandoned therapies. These data also underscore the need to further explore and identify potential therapies, whether they are in the form of new antimicrobials or old antimicrobials. It also highlights the need to not only properly identify the presence of NDM but also the presence of other beta-lactamases.

## Conclusion

The current state of evidence demonstrates that in the case of NDM producers, in vitro results do not appear to translate

into clinical results as expected. In the absence of larger trials, numerous case reports demonstrated favorable clinical outcomes despite mismatches between antimicrobials and susceptibility results. Moreover, carbapenems have unexpectedly demonstrated utility both in animal studies and in the clinical setting, despite in vitro hydrolysis. Since most case reports utilize combination therapy with good outcomes, it seems reasonable that combination therapy using sufficient exposure of the selected compound is the preferred strategy against NDM producers. Furthermore, available evidence suggests that carbapenems should continue to be included in the armamentarium against such infections.

## Disclosure

MD Nailor has been involved in consulting/grants and speaker bureaus for Astellas and Merck pharmaceutical

companies. DP Nicolau has been involved in consulting/grants and speaker bureaus for AstraZeneca, Cubist, Merck, Tetrphase, and Actavis pharmaceutical companies. The other authors report no conflicts of interest in this work.

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