The carbapenemase NDM-1 was initially identified in Escherichia and Klebsiella pneumoniae in 2009, and subsequently in many enterobacterial species worldwide, predominantly from patients hospitalized in India, Pakistan and Bangladesh. While most reports to date have indicated nosocomial acquisition of NDM-1 producers, we have also reported community acquisition of an NDM-1 producer. This case involved a patient who, when hospitalized in France in early 2010, was found to be colonized on her skin by an NDM-1-producing Escherichia coli. Although the patient had been living in Darjeeling, India, there was no prior history of hospitalization in that country. The source of colonization of this patient was not identified, but recent reports have demonstrated the extensive isolation of NDM-1 from tap and environmental water in New Delhi, leading us to speculate that exposure to contaminated water may account for this case.

We report here on the long-term follow-up of this patient over a period of 13 months, from initial hospitalization until her death. Screening of this patient using rectal swabs plated on selective culture medium (ChromID ESBL, bioMérieux, La-Balme-Les-Grottes, France), as described previously, yielded regular positive samples. The patient had received two courses of antibiotics comprising co-amoxiclav (3 g daily) for 10 days at the time of her demise. In our view, those courses of antibiotic treatment are unlikely to have generated sufficient selective pressure to account for the persistence of the NDM-1-positive E. coli in the intestinal flora of the patient for >1 year. Indeed, such long-term persistence of E. coli in the environment and in the intestinal flora is already known. Interestingly, the NDM-1-positive E. coli isolated from this patient was of the ST131 type, which is of the sequence type mainly associated with the dissemination of the prevalent clavulanic acid-inhibited extended-spectrum β-lactamase CTX-M-15 worldwide.

The case we report here indicates the long-term persistence of NDM-1-positive bacteria in the intestinal flora. This sustained level of carriage may be considered as a further risk factor for the dissemination of NDM-1 producers, taking into account that up to 10^6 E. coli per gram of faeces are commonly found in humans.

This observation also further underlines the urgent need to screen for carriers worldwide and the fact that colonized patients should be kept in strict isolation during their entire hospital stay.

Funding
This work was funded by the INSERM (U914), France.

Transparency declarations
None to declare.

References
Sir,

An active intravenous drug-using male presented to the Emergency Department (ED) with 5 days of high-grade fever and rigors. He was found to be febrile and tachycardic on presentation, with a physical exam notable for a holosystolic grade 2 murmur and a large 8 cm x 7 cm ulcer on the extensor surface of his left forearm, where the patient reported injecting heroin. Three sets of blood cultures were collected before empirically starting vancomycin and piperacillin/tazobactam, both renally dose adjusted. A transthoracic two-dimensional echocardiogram (TTE) demonstrated no abnormalities.

On day 3, admitting blood cultures grew methicillin-resistant Staphylococcus aureus (MRSA) (3/3 bottles) and susceptibility tests showed a vancomycin MIC of 2 mg/L, determined using the broth microdilution method. Vancomycin was changed in favour of daptomycin [4 mg/kg (350 mg) intravenously every 48 h; refer to Table 1 for dosing and antimicrobial course]. An Epsilometer test (Etest; AB Biodisk, Solna, Sweden) for daptomycin revealed an MIC of 0.38 mg/L. Piperacillin/tazobactam was discontinued.

On day 4, physical exam revealed paraparesis with power of 4/5 bilaterally. Magnetic resonance imaging (MRI) of the lumbar spine revealed L4–L5 paraspinal fluid collections, which were drained under CT guidance.

On day 7, Etest MICs for the blood culture and paraspinal abscess were 0.38, 2 and 2 mg/L and 0.19, 2 and 2 mg/L for daptomycin, linezolid and vancomycin, respectively. Daptomycin was continued (increased to 6 mg/kg (500 mg) intravenously every 48 h) to cover for MRSA in the blood, paraspinal abscess and wound.

On day 12, blood cultures remained positive for MRSA (3/3). On day 16, repeat Etest MICs (vancomycin, 2 mg/L; linezolid, ≤2 mg/L; and daptomycin, 4 mg/L) prompted discontinuation of daptomycin in favour of linezolid (600 mg orally every 12 h). Blood cultures remained positive until day 19.

On day 20, the patient was noted to have a worsening murmur on examination. Transeosophageal echocardiogram (TEE) revealed a 1.5 cm vegetation on the mitral valve. The patient successfully underwent surgical excision of the vegetation with mitral annuloplasty and remained on linezolid.

The patient’s platelets steadily decreased after linezolid was started. The use of telavancin (Vibativ; Theravance, South San Francisco, CA, USA) was thus considered. Etest revealed an MIC of 0.38 mg/L, and telavancin 900 mg intravenously daily (10 mg/kg) was initiated on hospital day 38. The patient remained on telavancin for 3 weeks without incident. All subsequent blood cultures were negative, platelets were within normal limits and renal function continued to gradually improve. The patient was discharged after 6 weeks of negative blood cultures, which remained negative at follow-up 2 weeks after discharge.

Although the use of linezolid monotherapy resulted in early microbiological response (defined as conversion of positive blood culture to negative within 72 h of antimicrobial initiation) in our patient who had persistent bacteraemia, the development of thrombocytopenia was of concern. In a study by Jang et al.,¹ 75% of patients on salvage linezolid therapy experienced early microbiological response, but 58% also developed thrombocytopenia, necessitating a change in therapy. The use of telavancin was welcome in our patient, who clinically failed daptomycin and could not tolerate linezolid.

Table 1. Antimicrobial course and dosing

<table>
<thead>
<tr>
<th>Hospital day</th>
<th>Antibiotic</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
<th>CLCRE (mL/min)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 2</td>
<td>vancomycin; piperacillin/tazobactam</td>
<td>iv</td>
<td>1 g</td>
<td>every 24 h</td>
<td>11.4</td>
<td>MRSA vancomycin MIC 2 mg/L by broth microdilution</td>
</tr>
<tr>
<td>3</td>
<td>daptomycin</td>
<td>iv</td>
<td>350 mg</td>
<td>every 48 h</td>
<td>10.7</td>
<td>daptomycin renally adjusted, but underdosed at 4 mg/kg; piperacillin/tazobactam discontinued</td>
</tr>
<tr>
<td>6</td>
<td>daptomycin</td>
<td>iv</td>
<td>500 mg</td>
<td>every 48 h</td>
<td>17.3</td>
<td>increased dose to 6 mg/kg secondary to incorrect starting dose (4 mg/kg)</td>
</tr>
<tr>
<td>8</td>
<td>daptomycin</td>
<td>iv</td>
<td>500 mg</td>
<td>every 48 h</td>
<td>25.4</td>
<td>daptomycin MIC (blood) 0.38 mg/L by Etest</td>
</tr>
<tr>
<td>11</td>
<td>daptomycin</td>
<td>iv</td>
<td>500 mg</td>
<td>every 24 h</td>
<td>38.1</td>
<td>increased dose secondary to improved renal function; blood cultures positive, 3/3</td>
</tr>
<tr>
<td>16</td>
<td>linezolid</td>
<td>po</td>
<td>600 mg</td>
<td>every 12 h</td>
<td>42.3</td>
<td>daptomycin stopped secondary to blood MIC of 4 mg/L by Etest</td>
</tr>
<tr>
<td>26</td>
<td>linezolid</td>
<td>po</td>
<td>600 mg</td>
<td>every 12 h</td>
<td>50.8</td>
<td>patient undergoes mitral valve repair</td>
</tr>
<tr>
<td>38</td>
<td>telavancin</td>
<td>iv</td>
<td>900 mg</td>
<td>every 24 h</td>
<td>68.8</td>
<td>linezolid stopped secondary to gradual decline in platelets since initiation (174 K/mm³ → 88 K/mm³); telavancin blood MIC 0.38 mg/L by Etest</td>
</tr>
<tr>
<td>40</td>
<td>telavancin</td>
<td>iv</td>
<td>850 mg</td>
<td>every 24 h</td>
<td>58.2</td>
<td>patient re-weighed and dose adjusted; remained on dose until discharge (day 59)</td>
</tr>
</tbody>
</table>

iv, intravenously; po, orally.
Telavancin is a potent, rapidly bactericidal antimicrobial that has a similar mechanism of action to vancomycin, but also causes bacterial membrane depolarization. To our knowledge, this is the first case using telavancin in mitral valve MRSA endocarditis.

Current expert opinion recommends consideration of alternative therapies for bacterial isolates with a vancomycin MIC of ≥ 2 mg/L, as the required higher doses may lead to an increase in toxicity over efficacy. For this reason, daptomycin was chosen over vancomycin. Initially, daptomycin was dosed (4 mg/kg) at 350 mg intravenously every 48 h—renally adjusted, but not at the recommended dose for endocarditis, 6 mg/kg. Over a period of 8 days, the dose was increased twice (secondary to noticed underdosing and improving renal function) to a final dose of 500 mg intravenously every 24 h. During this period the MIC for the isolate increased from 0.38 mg/L to 4 mg/L [daptomycin-non-susceptible S. aureus (DNSSA)].

Common reasons for daptomycin clinical failure reported in the literature include antecedent vancomycin therapy, exposure of an isolate to suboptimal concentrations of daptomycin and having a large inoculum of infection that is not or cannot be aggressively debrided. Higher doses of daptomycin (10 mg/kg/day) have been suggested for reducing the inoculum from endocardial vegetations, though we ultimately chose against this, as the data are conflicting.

This case demonstrates the efficacy and tolerability of telavancin as well as the importance of proper antimicrobial dosing to prevent the unintended emergence of bacterial resistance. As noted in the literature, prompt surgical intervention should be pursued (if warranted) to optimize clinical outcome. In conclusion, we report successful treatment of a patient with MRSA mitral valve endocarditis. While bacteraemia initially resolved with mitral valve annuloplasty, vegetation excision and linezolid monotherapy, telavancin was successful in completing this patient’s treatment for left-sided endocarditis, paraspinal abscess and forearm wound despite being exposed to vancomycin and subtherapeutic doses of daptomycin that led to development of DNSSA.

Acknowledgements

We would like to thank Drs Ryan Gates, Matthew Dehner, Jeffrey Jolliff and Eric vanSonnenberg for their thoughtful reviews of earlier drafts of this case.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

References


Life-threatening acute generalized exanthematous pustulosis induced by two different protease inhibitors in an HIV-1-infected patient

Myriem Bourkia1, Lucie Charlès1, Olivier Lambotte1, Lupe Orostegui-Giron2, Cécile Goujard1 and Jade Ghosn1*

1 APHP, Department of Internal Medicine and Infectious Diseases, Bicêtre University Hospital, Paris, France; 2 APHP, Department of Drug Safety Surveillance, Bicêtre University Hospital, Paris, France

*Corresponding author. Département de Médecine Interne et Maladies Infectieuses, Centre Hospitalier Universitaire de Bicêtre, 78 Rue du Général Leclerc, 94270 Le Kremlin Bicêtre, France. Tel: +33-1-45-21-27-83; Fax: +33-1-45-21-26-32; E-mail: jade.ghosn@bct.aphp.fr

Keywords: antiretroviral drugs, drug-related cutaneous reactions, adverse events

Sir,

Antiretroviral drugs can cause a variety of cutaneous adverse reactions in HIV-infected persons. To the best of our knowledge, no case of acute generalized exanthematous pustulosis (AGEP) has been reported in HIV-infected patients. We report a case of cross-protease inhibitor-induced life-threatening AGEP in an HIV-1-infected patient.

A patient was admitted for pancytopenia. Exhaustive clinical, biological, radiological and histological (lymph node biopsy) work-up revealed HIV-1 infection and Castleman’s disease. The HIV-1 plasma viral load was 4.4 log10 copies/mL and the CD4 count was 220 cells/mm3. HIV-1 belonged to subtype B with evidence of transmitted primary resistance to thymidine analogues and non-nucleoside reverse transcriptase inhibitors; the virus was CCR5-tropic. The patient was started on tenofovir,