American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 805-809
DOI: 10.12659/AJCR.903992

Received: 2017.02.23
Accepted: 2017.05.01
Published: 2017.07.18

New Delhi Metallo-Beta-Lactamase (NDM-1)-Producing *Klebsiella Pneumoniae* Isolated from a Burned Patient

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Data Interpretation D
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Conflict of interest: None declared

Patient: Male, 32
Final Diagnosis: NDM-1-producing *Klebsiella pneumoniae* • bacteremia
Symptoms: Fever
Medication: —
Clinical Procedure: None
Specialty: Infectious Diseases

Objective: Diagnostic/therapeutic accidents

Background: Infections affecting burn patients are frequently caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* species. Infections with these pathogens have become increasingly difficult to treat due to evolving antibiotic resistance mechanisms, including the production of carbapenemases.

Case Report: The present case report describes the evolution of a burn patient with polymicrobial healthcare-associated burn infections, including a bloodstream infection due to an emergent multidrug-resistant New Delhi metallo-beta-lactamase (NDM-1)-producing *Klebsiella pneumoniae*. During hospitalization, initial antibiotic treatment eradicated some of the infecting species. Newer isolates were found to be multidrug-resistant and required unique antibiotic combinations. The patient's condition continued to deteriorate after the isolation of multidrug-resistant *P. aerug*inosa and NDM-1-positive *K. pneumoniae* from the blood.

Conclusions: This case report illustrates the need for adequate antibiotic therapies in burn patients with subsequent infections due to a carbapenemase-producing multidrug-resistant bacteria. The potential danger of new bacterial pathogens should be considered in this group of susceptible patients.

MeSH Keywords: Bacteremia • Burn Units • Genes, MDR • *Klebsiella Pneumoniae*

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903992

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Background

After pneumonia, wound infections are the second leading cause of morbidity and mortality in burn patients with an increased outcome severity, a prolonged stay at the hospital, and increased costs [1–4]. Within the first 72 h after a burn incident, most infections are caused by Gram-positive bacteria like Staphylococcus aureus, but afterward, common etiologic agents include antibiotic-resistant Gram-negative bacteria that are associated with other types of hospital-acquired infections [4–7]. Therefore, effective treatment of infected burns requires knowledge of both the evolution of the infecting bacteria and antibiotic resistance patterns [4,6]. The presence of multidrug-resistant bacteria, including *Klebsiella pneumoniae* with resistance to carbapenems as a consequence of a new metallo-beta-lactamase, represents a treatment challenge [8–10]. The following case report illustrates the follow-up and outcome of a burned patient with an infection caused by a carbapenemase-producing, multidrug-resistant bacteria in a third-level hospital in Guadalajara, Mexico.

Case Report

A 32-year-old male patient without previous comorbidities was admitted to the hospital after suffering second-degree burns. Initially, the patient was stabilized in an emergency unit at another hospital, with intravenous fluids, but without antibiotics. After stabilization, the patient was transferred to our hospital. On admission, the burn areas affected 60% of the body, mainly the face, neck, anterior and posterior chest wall, abdomen, and right arm and leg. On admission, his temperature was 38.0°C, heart rate was 110 beats per minute, respiratory rate was 32 breaths per minute, and blood pressure was 110/64 mmHg. Blood values included: hemoglobin, 18.8 g/dL; hematocrit, 56%; platelets, 206 000/mm^3; leukocytes, 28 200/mm^3; glucose, 57 mg/dL, and creatinine, 0.66 mg/dL. After surgical debridement, the patient was admitted to the intensive care unit. Although no damage to the respiratory tract was found during a bronchoscopy, the patient developed respiratory fatigue that was attended with tracheostomy. However, the respiratory fatigue continued and was accompanied by bronchospasms and wheezing. At a PaO2 of 58 mm Hg, the patient received supplemental oxygen, but the PaO2 persisted below 60 mm Hg and bilateral rales were documented; therefore, mechanical ventilation was initiated.

Blood cultures taken within the first 24 h were negative. Because of the extensive burns, empirical intravenous (IV) moxifloxacin (400 mg every 24 h) was initiated. During the next 96 h, the patient remained stable, but on the fifth day of hospitalization, the patient's temperature rose to 39°C. Moxifloxacin was discontinued and antibiotic treatment was substituted with empirical IV cefepime (1 g every 8 h) and tigecycline 50 mg every 12 h after a loading dose of 100 mg.

On day 10 of hospitalization, when the patient was at the plastic surgery service, a burn lesion culture was positive for *Escherichia coli* and *Enterococcus faecalis*. Species identification and drug susceptibility studies – results of the minimum inhibitory concentration (MIC) expressed in µg/mL – were performed using the VITEK automated system (bioMérieux, Marcy-l'Étoile, France). *E. coli* was susceptible to amikacin (MIC ≤1), ertapenem (MIC ≤.25), cefepime (MIC=2), and tigecycline (MIC ≤.25), but resistant to aztreonam (MIC=4), ceftriaxone (MIC=32), ciprofloxacin (MIC >4), and trimethoprim/sulfamethoxazole (MIC >320). *E. faecalis*, on the other hand, was susceptible to most of the antibiotics tested (MICs in µg/mL: ampicillin <1, linezolid=1, tigecycline ≤.06, and vancomycin 1) and only resistant to levofloxacin (MIC >8).

On day 20 of hospitalization, the temperature again rose to 39.0°C, procalcitonin (PCT) level was 10 ng/mL (normal value, 0.5 ng/mL), and simultaneous blood cultures from the central venous catheter and a venous site were positive for *P. aeruginosa* and *K. pneumoniae*. The MICs (µg/mL) for *P. aeruginosa* were as follows: cefepime, 8; colistin <.025; levofloxacin, 1; piperacillin, 8; cefixime >4; chloramphenicol >64; and trimethoprim >16; the MICs (µg/mL) for *K. pneumoniae* were: aztreonam >64, cefepime >64, ceftriaxone >64, cefixime >4, levofloxacin >8, meropenem >16, minocycline >16, piperacillin >128, tetracycline >16, and trimethoprim >16. A routine Carba NP test was positive in the *K. pneumoniae* isolate [11].

A 300-mg IV loading dose of colistin was initiated, followed by 150 mg every 12 h, in combination with IV amikacin (1g every 24 h) and rifampin 600 mg every 24 h via a nasogastric tube. Nevertheless, *P. aeruginosa* and *E. faecalis* were recovered from a burn lesion culture on day 27. The resistance patterns were similar to the ones that had been observed before from burn lesion isolates.

The patient's condition continued to deteriorate; a serum creatinine level of 8 and an alanine transaminase/aspartate transaminase ratio of 250/375 was registered, which indicate renal and hepatic damage, respectively. The patient died on day 30 of hospitalization while on colistin, amikacin, and rifampin.

The *K. pneumoniae* isolate was further identified at an associated research laboratory in Monterrey, Mexico. Identification and sensitivity examination using the Sensititre method (TEK Diagnostic Systems Inc., Cleveland, OH, USA) confirmed the initial description. Antimicrobial susceptibility tests, performed with the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI), confirmed the sensitivities reported for *K. pneumoniae* on day 20 of hospitalization.

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Polymerase chain reactions for the detection of genes encoding carbapenemases were positive for New Delhi metallo-beta-lactamase (NDM-1) and negative for Verona integron-encoded metallo-beta-lactamase (VIM), Imipenem-hydrolyzing beta-lactamase (IMP), *K. pneumoniae* carbapenemase (KPC), and oxacillin-hydrolyzing beta-lactamase (OXA-48) [12,13].

Discussion

Colonization of burned tissues is unavoidable, but if it leads to local infection and evolves to a systemic infection the costs and mortality rises significantly. The use of prophylactic antibiotics or early empirical therapy for burn patients is controversial [14]. We initiated an empirical quinolone monotherapy considering local microbiology data. After clinical failure of preventive therapy, quinolone was substituted by cefepime and tigecycline because of the possibility of a Gram-negative infection.

The selection of an appropriate empirical antimicrobial therapy is based on colonization rates reported for burned tissues during hospitalization [4]. During the first 7 days of hospitalization, Gram-positive bacteria are often isolated, including methicillin-susceptible *S. aureus* (MSSA), coagulase-negative staphylococci, *Streptococcus* spp., and *Enterococcus* spp. [4,15]. Isolation rates of Gram-positive species decrease with time (e.g., the isolation rate of *S. aureus* dropped from 3.04 in week 1 to 0.11 in week 4; in the same period, the isolation rate of coagulase-negative staphylococci diminished from 2.43 to 1.99 for, the one of *Streptococcus* spp. from 3.12 to 0.18, and the one of vancomycin-resistant *Enterococcus* sp. from 1.45 to 0.50 ($P<0.001$ for all) [4]. In contrast, after 1 week of hospitalization, drug-resistant Gram-negative species predominate; e.g., the colonization rates for carbapenem-resistant Enterobacteriaceae increased from 0.004 in week 1 to 0.82 in week 4. Likewise, *P. aeruginosa* increased from 0.04 to 1.85, while isolation rates of both *P. aeruginosa* and *K. pneumoniae* increased from 1.27 to 2.26 ($P<0.001$ for all) [4]. In our study, Gram-negative bacteria were detected in the fourth week, with the presence of *P. aeruginosa* and *K. pneumoniae* in the blood stream. As the hospitalization lengthens, the risk of bacteria becoming drug resistant increases [4]. The 2 bacteria responsible for the bloodstream infection were multidrug-resistant.

The epidemiological evolution of various resistance mechanisms in Gram-negative bacteria has significantly impacted healthcare-associated Enterobacteriaceae infections. Carbapenem-resistant Gram-negative bacteria emerged after the introduction and widespread use of extended-spectrum beta-lactamases (ESBL) in cases of Enterobacteriaceae infections [16]. Until the turn of this century, ESBL resistance was mainly limited to *K. pneumoniae*, but as of 2001, other Enterobacteriaceae began producing novel metallo-beta-lactamases with versatile hydrolytic capacities [16,17]. Before 1992, the isolation of carbapenem-resistant Enterobacteriaceae (CRE) was rare in certain countries, but as of 2000, CRE prevalence increased from 0.6% in 2004 to 5.6% in 2008 in the United States [16]. Since then, many other metallo-beta-lactamases (including IMP, VIM, and NDM) have emerged, disseminated, and caused outbreaks [18,19]. A survey among 202 medical centers from 40 countries revealed that 471 metallo-beta-lactamases positive isolates have been recovered, mainly from *P. aeruginosa* (65%), *K. pneumoniae* (18%), and *Enterobacter* spp. (8%). The metallo-beta-lactamase variants included VIM (14), IMP (14), and NDM (4) [20].

In a network of long-term acute-care hospitals, the overall carbapenem-resistant rate among 3846 *K. pneumoniae* isolates was 25%. The isolation sites included the respiratory tract (54%), urine (37%), and blood (9%). The median age of the patients was 73 years and 40% of the patients had respiratory failure. Prominent risk factors included tracheostomy (65%) and the presence of a central venous line (51%) [21]. In another setting, the prevalence of carbapenem-resistance was 10%; 90% of the carbapenem-resistant Enterobacteriaceae were *K. pneumoniae* and 92% produced KPC; 50% of the patients had cancer or transplants [22]. In other countries, the isolation of KPC-positive Enterobacteriaceae continues to predominate; for example, 65% in China and in 4 of 6 countries in Latin America [23,24].

The treatment of carbapenem-resistant bacteria is complex. Usually, it requires antibiotic combinations and the application of antimicrobials like flomoxef, cefoxitin, cefmetazole, cefepime, piperacillin-tazobactam, ceftolozane-tazobactam, or ceftazidime-avibactam [25,26]. To prevent future problems with this type of resistance, the Gram-Negative Committee of the Antibacterial Resistance Leadership Group aims to advance knowledge and improve patient outcomes. The observational study CRACKLE (Consortium on Resistance Against Carbapenems in *K. pneumoniae* and other Enterobacteriaceae) has described risk factors and patient outcomes in sentinel US hospitals [27]. Carbapenem-resistant *K. pneumoniae* infections cause severe acute illness in patients with chronic comorbidities, and causes prolonged hospitalization, high mortality, and frequent readmissions [27].

Our *K. pneumoniae* isolate produced the novel metallo-beta-lactamase, NDM-1. An NDM-1-positive strain was first described in 2008 in Sweden from a urinary tract infection due to a *K. pneumoniae* infection acquired in New Delhi, India [8]. In our hospital, the first NDM-1-producing *K. pneumoniae* strain was isolated in September 2014 from a patient with chronic kidney disease treated with hemodialysis and a history of multiple hospitalizations and antibiotic treatments, but no travel history outside of Mexico. Since then, 140 isolates have been collected, mostly from secretions and urine from adult patients.

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The patient of the present case report had no chronic diseases, previous hospitalizations, or travel outside of Mexico.

As with other metallo-beta-lactamases, NDM-1 can hydrolyze all beta-lactam antibiotics except for aztreonam [8]. After, KPC, VIM, and IMP, NDM is one of the most frequent metallo-beta-lactamases identified [20,22,23]. NDM-1-positive isolates have disseminated to more than 9 countries, including India, Pakistan, United Kingdom, the United States, and Mexico [9,19,28–31].

The appropriate treatment of an infection caused by an NDM-1-producing multidrug-resistant bacteria usually requires double or triple antibiotic combinations; the combined use of colistin and rifampin seems more effective than monotherapy with colistin. Other antimicrobial combinations have included colistin and a carbapenem, dual carbapenem like the use of high-dose, and prolonged infusion of doripenem and ertapenem, although for NDM-1, no synergy was observed with the addition of a carbapenem, and the use of newer therapies like the use of ceftazidime with avibactam is not effective against NDM-1-encoded strains [25,26,32,33].

The threat of resistant bacteria, especially those with new resistance mechanisms, has prompted the development of rigorous control and prevention strategies [34]. In an environment with resistant bacteria, strict antimicrobial stewardship measures must be taken to select an adequate antimicrobial therapy during the complete hospitalization period of patients vulnerable to healthcare-associated infections [35,36]. Considering the aforementioned, special infection control measures were taken after this case in our hospital, such as supervising of hand hygiene compliance, environmental cleaning, and antibiotic stewardship [34].

Conclusions

This case of a bloodstream infection due to the presence of an NDM-1 multidrug-resistant *K. pneumoniae* isolate ocurring in a burn patient with prolonged hospitalization emphasizes the importance of early case recognition, early laboratory detection of multidrug-resistant bacteria, the complex selection of the appropriate antimicrobial therapy, the need for burn units with an effective antimicrobial stewardship protocol, the relevance of adequate infection control and prevention, and the importance of implementation of strict control measures [16,21,22,26,27,35,36].

Conflicts of interest

None.

Acknowledgments

The authors thank Casillas-Torres A. for technical assistance.

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