Case Report

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New Delhi metallo-beta-lactamase-1-producing *Acinetobacter* spp. infection: report of a survivor

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ABSTRACT

New Delhi metallo-beta-lactamase-1 (NDM-1) is a bacterial enzyme that renders the bacteria resistant to a variety of beta-lactam antibiotics. A 20-year-old man was hospitalized several times for surgical treatment and complications caused by a right-sided vestibular schwannoma. Although the patient acquired several multidrug-resistant infections, this study focuses on the NDM-1-producing *Acinetobacter* spp. infection. As it was resistant to all antimicrobials tested, the medical team developed a 20-day regimen of 750mg/day metronidazole, 2,000,000IU/day polymyxin B, and 100mg/day tigecycline. The treatment was effective, and the patient recovered and was discharged from the hospital.

Keywords: Acinetobacter. beta-lactam resistance. microbial drug resistance.

INTRODUCTION

New Delhi metallo-beta-lactamase-1 (NDM-1) is a bacterial enzyme that was first identified in India in 2009 in a strain of *Klebsiella pneumonia*[1]. It was later detected in bacteria isolated in India, Pakistan, the United Kingdom, the United States, Canada, and Japan[2].

The NDM-1 enzyme renders the bacteria resistant to a variety of beta-lactam antibiotics, including the carbapenem class, which is usually reserved to treat infections caused by antibiotic-resistant strains. Such strains are usually susceptible only to polymyxin and tigecycline[3].

A recent systematic review of the global occurrence of NDM-1-positive bacteria described 60 cases of infection, of which 65% were asymptomatic. Many of these bacteria were identified in urine samples, and 28.3% were detected in different anatomical sites. The NDM-1 enzyme was commonly found in *Escherichia coli* and *K. pneumonia*, and most cases occurred in the Indian subcontinent and south-central Asia[4].

In Brazil, the first case was reported in 2013[5], and cases of infection with NDM-1-positive bacteria have been rare since that first case[6]. The mortality rate is estimated at 50%[2].

Here, we describe a case infected with NDM-1 and report the clinical course and outcomes.

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CASE REPORT

A 20-year-old man was first admitted to the Hospital Nossa Senhora da Conceição in Tubarão, Santa Catarina, Brazil, on April 18, 2012 for surgery to remove a tumor resection at the base of the skull that was later identified as a right-sided vestibular schwannoma. At the initiation of anesthesia, 2g Kefazol® (cefazolin sodium, first-generation cephalosporin) was administered as antibiotic prophylaxis; it was continued for 48 hours (4g/day) for postoperative recovery in the intensive care unit (ICU). In that same year, the patient was admitted for three additional surgical procedures due to tumor recurrence, and he had hearing loss as a result of the disease.

In 2013, two additional surgical procedures were performed for cervical tumor excision and ventriculostomy. In the postoperative period, the patient experienced aspiration pneumonia and was transferred to the ICU, where he received 3g/day Claforan® (cefotaxime) and 1.8g/day Dalacin® (clindamycin) for six days. Then, 13.5g/day Tazocin® (tazobactam and piperacillin) was administered for 15 days, which was then changed to 3g/day Meronem® (meropenem) for another 15 days. The diagnosis of pneumonia was based on clinical signs, and empiric antibiotic therapy was administered. The patient clinically improved and was discharged after 35 days of hospitalization.

In November 2013, the patient was readmitted to the hospital with severe protein-calorie malnutrition, anorexia, and vomiting due to intolerance to a nasogastric tube. At that time, the patient weighed 45kg (usual weight, 70kg). He was admitted to the ICU for a decline in general health and worsening

respiratory function, with a drop in oxygen saturation. He was administered 3g/day Meronem® for the pneumonia. After seven days, he underwent a tracheostomy for prolonged intubation, and 1.8g/day Dalacin® was administered. Two days later, the patient was transferred to the infirmary; however, after 13 days, he returned to the ICU because of worsening respiratory function and a drop in oxygen saturation. Polymyxin B (2,000,000IU/day) was administered, in addition to the 3g/day Meronem®. He was placed in hospital isolation on February 7, 2014 because of positive sputum culture with *Proteus mirabilis* producing extended-spectrum beta-lactamase (ESBL) resistant to ertapenem.

On February 10, 2014, the catheter tip culture showed colonization of carbapenem-resistant *Pseudomonas* spp. The patient was administered 3g/day Meronem® and 2,000,000IU/day polymyxin B for 13 days. Venous dissection was required for antibiotic administration.

On April 10, 2014, blood and urine cultures showed *Acinetobacter* spp. infection that was resistant to almost all antimicrobials tested. For treatment of fungal dermatitis, 2,000,000IU/day polymyxin B and 200mg/100mL/day fluconazole were administered for 13 days. On April 26, 2014, blood culture revealed the presence of coagulase-negative *Staphylococcus*. A new antimicrobial treatment was initiated with 600mg/day Zivox® (linezolid), 2,000,000IU/day polymyxin B, and 3g/day Meronem®, in addition to patient isolation. Furthermore, the microbiology sector of the clinical laboratory also isolated a strain of *Acinetobacter* spp. resistant to all antimicrobials tested. Because of infection by gram-negative bacteria resistant to carbepenem, the samples were sent to the Central Public Health Laboratory for investigation of resistant strains using quantitative polymerase chain reaction. As a result, on May 9, 2014, the Hospital Infection Control Committee was notified by the State Coordination of Prevention and Infection Control in Health Care of Santa Catarina that the patient was infected with $bla_{\text{NDM-1}}$ producing bacteria. Because the patient remained febrile, even with the administration of the proposed antibacterial drugs, the administration of 600mg/day Zivox® was suspended and replaced by 1.5g/day vancomycin, combined with 2,000,000IU/day polymyxin B.

Because of venous access difficulty, intramuscular injections of 400mg/day Targocid® (teicoplanin) were initiated on May 13, 2014 and continued until June 4, 2014. On May 22, 2014, 150mg/day fluconazole was initiated because the patient had a severe fungal infection.

Evidence of an NDM-1-producing *Acinetobacter* spp. infection that was resistant to all antimicrobials tested led the medical team to develop a 20-day regimen of 750mg/day metronidazole, 2,000,000IU/day polymyxin B, and 100mg/day tigecycline. The patient responded well to the antimicrobial therapy, which resulted in cure of the infection and patient discharge.

All data related to the microbial culture and sensitivity to antibiotics are shown in **Table 1**. The presence of infection determined the beginning of empirical therapy with antibiotics.

TABLE 1 - Positive microbial culture and susceptibility pattern during hospitalization of a 20-year-old man.

Date	Microbiological culture	Results	Susceptibility pattern
Feb 6, 2014	Sputum culture	*Proteus mirabilis* ESBL	Amikacin: S Ampicillin/sulbactam: R Aztreonam: I Cefotaxime: R Ciprofloxacin: S Ertapenem: R Imipinem: S Meropenem: S Piperacillin/tazobactam: S Sulfamethoxazole/trimethoprim: R
Feb 10, 2014	Catheter tip culture	*Pseudomonas* spp.	Amikacin: R Ampicillin/sulbactam: R Aztreonam: S Cefotaxime: R Cefoxitin: R Cephalexine: R Ertapenem: R Imipinem: R Meropenem: R Piperacillin/tazobactam: R Polymyxin B: S Sulfamethoxazole/trimethoprim: R

Continue...

TABLE 1 - Continuation.

Date	Microbiological culture	Results	Susceptibility pattern
Apr 10, 2014	Blood culture	*Acinetobacter* spp.	Amikacin: I Amoxicillin/clavulanate: R Aztreonam: I Cefadroxil: R Ceftriaxone: R Ciprofloxacin: I Ertapenem: R Imipinem: R Levofloxacin: I Meropenem: R Piperacillin/tazobactam: I Sulfamethoxazole/trimethoprim: R
Apr 12, 2014	Urine culture	*Acinetobacter* spp.	Cefadroxil: R Ciprofloxacin: R Nitrofurantoin: R Sulfamethoxazole/trimethoprim: R Amoxicillin/clavulanate: R Amikacin: R Aztreonam: S Imipinem: R Levofloxacin: R Ertapenem: R Meropenem: R Piperacillin/tazobactam: R
Apr 15, 2014	Blood culture	*Acinetobacter* spp.	Not performed
Apr 26, 2014	Blood culture	*Staphylococcus* coagulase negative	Not performed
Jun 2, 2014	Nasal culture	*Acinetobacter* spp.	Amikacin: R Amoxicillin/clavulanate: R Aztreonam: R Cefadroxil: R Ceftriaxone: R Ciprofloxacin: R Ertapenem: R Imipinem: R Meropenem: R Sulfamethoxazole/trimethoprim: R

ESBL: extended-spectrum beta-lactamase; **S:** sensitive; **I:** intermediate; **R:** resistant.

After identifying the susceptibility pattern, changes in the prescription may occur, based on bacterial resistance. The medications used in the treatment of infections or as prophylaxis are shown in **Table 2**.

This study was approved by the Research Ethics Committee of the University of Southern Santa Catarina, under code number 934 590. The patient and his parents provided written consent.

DISCUSSION

Bacterial resistance is an emerging public health problem[7], especially with the indiscriminate use of antibiotics. To the best of our knowledge, this was the first case of infection with an NDM-1-positive strain in the State of Santa Catarina.

TABLE 2 - Timing of antibiotic administration during hospitalization of a 20-year-old man.

Antibiotics	Prescription	
	initial date	final date
Cefazolin 1g	07/05/2012	08/05/2012
	23/05/2012	24/05/2012
	10/12/2012	11/12/2012
	22/05/2013	24/05/2013
	21/08/2013	25/08/2013
	13/03/2014	17/03/2014
Cefotaxime 1g	26/08/2013	
Clindamycin 600mg/4 mL	26/08/2013	
Tazobactam and piperacillin 4.5g	27/08/2013	09/09/2013
Meropenem 1g	10/09/2013	25/09/2013
	27/12/2013	15/01/2014
	05/02/2014	18/02/2014
	19/03/2014	02/04/2014
	09/04/2014	
	29/04/2014	14/05/2014
Linezolid 600 mg/300mL	05/02/2014	
	29/04/2014	09/05/2014
Polymyxin B 500,000IU	05/02/2014	18/02/2014
	21/03/2014	02/04/2014
	09/04/2014	
	29/04/2014	14/05/2014
	05/06/2014	24/06/2014
Fluconazole 200mg/100mL	10/04/2014	22/04/2014
Fluconazole 150mg	22/05/2014	01/06/2014
Vancomycin 500mg	09/05/2014	14/05/2014
Teicoplanin 400mg	13/05/2014	04/06/2014
Metronidazole 250mg	29/05/2014	22/06/2014
Tigecycline 50mg	04/06/2014	24/06/2014

However, there are reports of carbapenem-resistant *Enterobacteriaceae* in many countries, especially in hospitalized patients, and recent studies have shown the presence of NDM-1-positive strains[8,9].

In addition to the most recent detection of NDM producers in South America, there has been an increase in the number of cases of NDM-producing bacteria. The first detection of NDM in Brazil was described by Carvalho-Assef in 2013 at a hospital in Porto Alegre, Rio Grande do Sul. A patient with diabetes had peripheral vascular disease with a diabetic foot infection. Fragments of the soft tissue from his toe were sent for culture and yielded growth of a carbapenem-resistant *Providencia rettgeri*, in which bla_{NDM-1} was detected[5]. A second case was detected in the same hospital in a retrospective analysis of samples from hospitalized patients[10]. In Londrina, Paraná, the first case of NDM-1-producing *Acinetobacter baumannii* in Brazil was reported; a 71-year-old man was admitted to the intensive care unit with respiratory failure and died on hospitalization day 60[11]. Among 1,137 samples from 17 different hospitals in Porto Alegre, Rio Grande do Sul, 0.97% were NDM-1-positive[6]. In addition, 4 NDM-1 producing *Enterobacteriaceae* clinical isolates have been identified[12].

As of 2011 in Brazil, the National Health Surveillance Agency regulates the dispensation of antimicrobials, requesting a special medical prescription that must be retained at the pharmacy as a way to control medication use. However, due to national and international movement of people and goods, the broad prevalence of NDM producers in Brazil may contribute to the accelerated global spread of bla_{NDM}. However, in the present case, the patient neither traveled nor was hospitalized in any other healthcare center, according to the data collected by the Hospital Infection Control Committee.

Health professionals and caregivers were instructed to be cautious when interacting with this patient and to use personal protective equipment. Intensified hand hygiene with an aqueous solution of 2% chlorhexidine or glycerin alcohol was performed before and after handling the patient as well as in adjacent areas. Upon diagnosis of the NDM-1-producing strain, visitation was prohibited, and the patient was placed in hospital isolation. All patients who were hospitalized in the same sector were monitored, and bacterial cultures were requested to monitor these contacts. The materials used for patient care, such as blood pressure equipment, thermometers, and stethoscopes, were individualized. Both intra- and inter-institutional transfers were prohibited.

These recommendations, collectively with the effective treatment prescribed by the infectious disease experts, were successful, with a positive clinical outcome. Preventive measures were taken to avoid new cases related to the infection with this strain.

Few studies of the prevalence of NDM producers in Brazil have been published, with the findings restricted to case reports. However, data suggest a global distribution of NDM-1-producing *Enterobacteriaceae*. For this reason, the adoption of preventive measures and rational use of antibacterial drugs, especially in hospital settings, are vital to prevent the spread of infections by resistant strains, given the limitations of effective pharmacological treatment and unfavorable outcomes in a number of patients.

This report demonstrated a positive treatment outcome for an NDM-1-producing *Acinetobacter* spp. infection. In contrast to other cases, the patient was young and had no other comorbidities at baseline. His medical history included the presence of an immunosuppressive disease, with numerous relapses and sequels that compromised his immune status. In addition, the long hospital stay, combined with the repeated use of antibiotic prophylaxis and treatment courses, may have contributed to the emergence of resistant strains.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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