Published in final edited form as:

Am J Transplant. 2019 April ; 19(4): 1224–1228. doi:10.1111/ajt.15136.

Transplant tourism complicated by life-threatening New Delhi metallo-beta-lactamase-1 infection

Jenell Stewart¹, Gretchen Snoeyenbos Newman¹, Rupali Jain^{1,2}, Andrew Bryan³, Heather Berger³, Martin Montenovio⁴, Ramasamy Bakthavatsalam⁴, Catherine E. Kling⁴, Lena Sibulesky⁴, Sherene Shalhoub⁵, Ajit P. Limaye¹, Cynthia E. Fisher¹, and Robert M. Rakita¹

¹Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington, USA.

²Department of Pharmacy, University of Washington, Seattle, Washington, USA.

³Department of Laboratory Medicine, University of Washington, Seattle, Washington, USA.

⁴Department of Surgery, Division of Transplant Surgery, University of Washington, Seattle, Washington, USA.

⁵Department of Surgery, Division of Vascular Surgery, University of Washington, Seattle, Washington, USA.

Abstract

Transplant tourism, the practice of traveling to other countries for transplantation, continues to be a major problem worldwide. We describe a patient who traveled to Pakistan and underwent commercial kidney transplantation. He developed life-threatening infections from New Delhi metallo-beta-lactamase-1-producing *Enterobacter cloacae* and *Rhizopus oryzae* resulting in a necrotizing kidney allograft infection and subsequent external iliac artery rupture. He survived after a prolonged course of non-standardized antimicrobial therapy, including a combination of aztreonam and ceftazidime/avibactam, and aggressive surgical debridement with allograft nephrectomy. The early timing of infection with these unusual organisms localized to the allograft suggests contamination and substandard care at the time of transplant. This case highlights the challenges of caring for these infections and serves as a cautionary tale for the potential complications of commercial transplant tourism.

Introduction

Transplant tourism refers to the practice of patients traveling to other countries for transplantation, typically from paid donors under less than optimal circumstances.¹ Despite attempts to deter this following the Declaration of Istanbul, transplant tourism continues to be a major issue with many potential complications and worse short- and long-term outcomes, including graft survival.^{1–3} Due to the clandestine nature of commercial

Corresponding author: Robert M. Rakita, rakita@uw.edu.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

transplantation, it is difficult to quantify the issue. The World Health Organization estimated 5–10% of 60,000 renal transplants world-wide in 2007 were purchased. In Pakistan in 2007, it was estimated that two thirds of renal transplant recipients were foreigners.⁴ Medical tourism comes with multiple risks, but infections are the most common complication, and across all surgeries completed internationally there was a 3-fold greater risk for infections, along with a higher rate of antibiotic resistant pathogens.⁵ We describe the case of a man who traveled overseas for a kidney transplant and suffered rare life-threatening complications, including infection with a New Delhi metallo-beta-lactamase-1 (NDM-1) producing *Enterobacter cloacae*, extended spectrum beta-lactamase (ESBL) producing *Escherichia coli*, and *Rhizopus oryzae*. The early timing and localization of the infections to the allograft were highly suggestive of contamination at the time of transplant under likely substandard conditions. Treatment of infections with NDM-1 producing bacteria is not yet standardized and presents significant management challenges.

Case Report

A sixty-one year old Pakistani-American man with longstanding type 2 diabetes mellitus and hypertension developed chronic kidney disease stage V, approaching the need for dialysis. After learning about the typical, long waiting time to receive a kidney transplant locally in the US, he traveled to Pakistan with the goal of undergoing transplantation more rapidly. He reportedly was seen at a tertiary care academic hospital and was told that the waiting time was several months. Shortly thereafter, he instead paid for and underwent a living unrelated renal transplant in a black market clinic in a converted house. Following transplantation, he had progressive pain at the surgical site, and over the course of the next 1–2 weeks, he developed purulent discharge from his wound, fever, pain, and altered mental status. He flew back to the United States and presented immediately for care, 24 days following kidney transplant surgery.

CT scan of his abdomen revealed a gas-filled fluid collection in the region of the transplanted organ without any remaining renal tissue structure and extensive surrounding involvement of the psoas muscle (Figure 1). Urgent surgical exploration revealed a necrotic kidney allograft (Figure 2) with extension to the psoas muscle and the iliac artery. Transplant nephrectomy was performed and the surrounding nonviable tissue was debrided. Cultures of debrided tissue grew a multi-drug resistant (MDR) *Escherichia coli* (pattern of resistance consistent with an ESBL) and an *Enterobacter cloacae* complex isolate molecularly determined to carry NDM-1 (Cepheid GeneXpert Carba-R platform for genotypic detection of carbapenemases). He was treated empirically with meropenem and vancomycin. Based on the susceptibility testing for the *E. cloacae* (meropenem minimum inhibitory concentration (MIC) of 8 µg/ml, sensitive 2 µg/ml, polymyxin B MIC of 0.25 µg/ml, sensitive 2 µg/ml), polymyxin B was added to prolonged, 3 hour infusions of meropenem. However, on hospital day 9 the patient developed respiratory distress consistent with polymyxin B-induced neuromuscular blockade, and meropenem and polymyxin B were discontinued.

Other NDM-1-producing isolates have been found to be susceptible in vitro to the combination of aztreonam and avibactam despite in vitro resistance to both individually.^{6–8} Susceptibility testing of the *E. cloacae* isolate to aztreonam-avibactam was performed by

agar dilution consistent with CLSI M100 (27th Ed) and M07 (10th Ed) guidelines using a 4 µg/ml fixed avibactam concentration. While the isolate was resistant to aztreonam (MIC 128 µg/ml) and ceftazidime-avibactam (>256 µg/ml) by E-test, the aztreonam-avibactam agar dilution MIC was 0.25 µg/ml. The patient was treated with both aztreonam and ceftazidime-avibactam.

On hospital day 13, he developed acute hemorrhage from the retroperitoneal incision. Emergent exploration demonstrated rupture of the right external iliac artery due to infection and necrotic tissue deep to the iliopsoas muscle and abutting the iliac bone (Figure 3). This required urgent surgical ligation and excision of the external iliac artery, as well as further muscle debridement. Ligation resulted in acute limb ischemia and required a left-to-right femoral-femoral bypass with cryopreserved cadaveric arterial allograft, right superficial femoral artery thrombectomy, and four-compartment calf fasciotomies (Figure 4).

Cultures from the iliac artery grew *E. cloacae* and *Bacillus* species. Fungal hyphae were seen on the initial stain of the resected iliac artery and liposomal Amphotericin B and posaconazole were started. The mould was identified as *Rhizopus oryzae* complex by sequence analysis (University of Washington Clinical Microbiology Laboratory, Molecular Diagnosis Section) and susceptibility testing (University of Texas Health Science Center at San Antonio, Fungus Testing Laboratory) revealed an amphotericin MIC of 0.06 µg/ml, posaconazole MIC of 0.25 µg/ml, and isavuconazole MIC of 2 µg/ml. The patient was continued on dual antifungal therapy with trough posaconazole levels 1 µg/ml, and metronidazole was added for coverage of potential anaerobes in this polymicrobial infection. Throughout his course, all blood cultures were negative, and no evidence for disseminated infection was found.

The patient's renal function worsened on therapy with multiple nephrotoxic agents and on hospital day 48 hemodialysis was initiated. On hospital day 55, the patient completed 6 weeks of antibiotic treatment for the bacterial osteomyelitis, and aztreonam, ceftazidime-avibactam, vancomycin, and metronidazole were discontinued. Liposomal amphotericin B was discontinued on hospital day 71, and posaconazole was continued for a total of 12 weeks of therapy for treatment of intravascular fungal infection. The patient was discharged on hospital day 84. At the time of discharge, he was dialysis dependent and debilitated from his illness. When seen in clinic four months following discharge, the patient remained dialysis dependent with complete wound healing and was otherwise making a good recovery.

Discussion

The shortage of donor organs, growing need for transplants, and resultant long wait times continues to be a major problem.⁹ As a result, patients seek commercial transplants under less-regulated conditions, where the rate of complications is known to be higher.^{10, 11} In our patient, the early timing after surgery, lack of other sources of infection, infection localized to the allograft, and the presence of ubiquitous environmental organisms, such as *Bacillus* and *Rhizopus*, all strongly suggest contamination at the time of the transplant surgery.

While there is a risk of nosocomial infections associated with any transplant, this risk may be higher in other countries where most commercial transplants are performed, such as Pakistan.^{5, 12} This could be expected to be even worse in a black market, unlicensed facility where hygienic measures are likely not standardized or regulated. In addition, the high risk of antibiotic resistant organisms should be considered in patients who return from commercial transplant tourism, in regard to both empiric treatment and infection control measures. Our patient was placed in contact precautions on arrival, even before isolation of a MDR bacteria, based on the high prevalence of antibiotic resistant organisms in international hospitals.⁵

NDM-1 is a metallo-beta-lactamase (MBL) that was originally described in India¹³ and has since spread extensively.¹⁴ Among patients who have undergone solid organ transplantation, MBL producing organisms are a rare cause of postoperative infection in the United States but have increasing prevalence internationally. The clinical experience with successful treatment of MBL-producing organisms is very limited, mortality rates are high, and this case demonstrates many of the challenges. MBL-producing organisms may be treated with a polymyxin, typically in combination with a carbapenem given by prolonged infusion. However, efficacy data are limited, and there may be significant toxicities with polymyxins. Our patient developed respiratory distress due to neuromuscular blockade from polymyxin B. This side effect was thought to have been extremely rare in the modern era. However, with the advent of more MDR infections, increased use of older agents such as polymyxin B has led to a greater appreciation of uncommon side effects, and providers caring for patients with MDR infections need to be aware of these.

If feasible, prompt surgical debridement is a key step in successful treatment, in conjunction with selection of appropriate antimicrobial therapy. A relatively new option for treatment of NDM-1 infections is the combination of ceftazidime/avibactam with aztreonam.^{6, 7} Aztreonam is active against most MBLs, but often the bacteria have other resistance mechanisms (e.g. ESBLs) that inactivate aztreonam. The use of the beta-lactamase inhibitor avibactam enables aztreonam to remain stable against inactivation despite in vitro resistance to both aztreonam and avibactam individually. Resistance to this combination appears to be rare,⁸ but confirmation of activity in vitro should be determined. There is limited clinical experience with this treatment modality, and even less in transplant recipients.^{15, 16} However, the few available reports support our assessment that this combination therapy can be successful in treating NDM-1 infections in this population.

Invasive fungal infections (IFI) have been described after commercial transplant tourism.¹⁷ Treatment of angioinvasive Mucorales infections remains extremely difficult and highly morbid.¹⁸ In renal transplant patients, combined surgical debridement and antifungal therapy is critical for successful treatment.¹⁹ Even with optimal management, mortality rates were 30%, which increased to 56% when the kidney graft was infected and 76% when there was dissemination (infection at 2 or more sites). We found no evidence of dissemination in our patient, he was managed with aggressive local debridement and prolonged antifungal therapy, and he has continued to do well. While combination antifungal treatment was used in our patient, the clinical benefit remains unclear.²⁰

Abbreviations

ESBL	Extended spectrum beta-lactamase
IFI	Invasive fungal infections
MBL	Metallo-beta-lactamase
MIC	Minimum inhibitory concentration
MDR	Multi-drug-resistant
NDM-1	New Delhi metallo-beta-lactamase-1

References

1. Danovitch GM, Chapman J, Capron AM, et al. Organ trafficking and transplant tourism: the role of global professional ethical standards-the 2008 Declaration of Istanbul. *Transplantation*. 2013; 95: 1306–12. [PubMed: 23644753]
2. Prasad GVR, Ananth S, Palepu S, Huang M, Nash MM and Zaltzman JS. Commercial kidney transplantation is an important risk factor in long-term kidney allograft survival. *Kidney Int*. 2016; 89: 1119–24. [PubMed: 27083285]
3. Gill J, Madhira BR, Gjertson D, et al. Transplant tourism in the United States: a single-center experience. *Clin J Am Soc Nephrol*. 2008; 3: 1820–8. [PubMed: 18922987]
4. Rizvi SA, Naqvi SA, Zafar MN, et al. A renal transplantation model for developing countries. *Am J Transplant*. 2011; 11: 2302–7. [PubMed: 21883911]
5. Nelson R Infectious risks of medical tourism. *Lancet Infect Dis*. 2014; 14: 680–1. [PubMed: 25202763]
6. Marshall S, Hujer AM, Rojas LJ, et al. Can Ceftazidime-Avibactam and Aztreonam Overcome beta-Lactam Resistance Conferred by Metallo-beta-Lactamases in Enterobacteriaceae? *Antimicrob Agents Chemother*. 2017; 61: e02243–16. [PubMed: 28167541]
7. Davido B, Fellous L, Lawrence C, Maxime V, Rottman M and Dinh A. Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome beta-Lactam Resistance Conferred by Metallo-beta-Lactamases in Enterobacteriaceae and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2017; 61: e01008–17. [PubMed: 28630191]
8. Karlowsky JA, Kazmierczak KM, de Jonge BLM, Hackel MA, Sahm DF and Bradford PA. In Vitro Activity of Aztreonam-Avibactam against Enterobacteriaceae and *Pseudomonas aeruginosa* Isolated by Clinical Laboratories in 40 Countries from 2012 to 2015. *Antimicrob Agents Chemother*. 2017; 61: e00472–17. [PubMed: 28630192]
9. Hart A and Patzer RE. Equity in kidney transplantation: Policy change is only the first step. *Am J Transplant*. 2018; 18 Suppl 1:18–113. [PubMed: 29292608]
10. Anker AE and Feeley TH. Estimating the risks of acquiring a kidney abroad: a meta-analysis of complications following participation in transplant tourism. *Clin Transplant*. 2012; 26: E232–41. [PubMed: 22487255]
11. Ivanovski N, Masin J, Rambabova-Busljetic I, et al. The outcome of commercial kidney transplant tourism in Pakistan. *Clin Transplant*. 2011; 25: 171–3. [PubMed: 20626425]
12. Rosenthal VD, Richtmann R, Singh S, et al. Surgical site infections, International Nosocomial Infection Control Consortium (INICC) report, data summary of 30 countries, 2005–2010. *Infect Control Hosp Epidemiol*. 2013; 34: 597–604. [PubMed: 23651890]
13. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-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. [PubMed: 19770275]

14. Berrazeg M, Diene S, Medjahed L, et al. New Delhi Metallo-beta-lactamase around the world: an eReview using Google Maps. *Euro Surveill.* 2014; 19.
15. Shaw E, Rombauts A, Tubau F, et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing *Klebsiella pneumoniae* infection. *J Antimicrob Chemother.* 2018; 73: 1104–6. [PubMed: 29272413]
16. Mojica MF, Ouellette CP, Leber A, et al. Successful Treatment of Bloodstream Infection Due to Metallo-beta-Lactamase-Producing *Stenotrophomonas maltophilia* in a Renal Transplant Patient. *Antimicrob Agents Chemother.* 2016; 60: 5130–4. [PubMed: 27551008]
17. Shoham S, Hinestrosa F, Moore J, Jr., O'Donnell S, Ruiz M and Light J. Invasive filamentous fungal infections associated with renal transplant tourism. *Transpl Infect Dis.* 2010; 12: 371–4. [PubMed: 20163566]
18. Chitasombat MN and Kontoyiannis DP. Treatment of mucormycosis in transplant patients: role of surgery and of old and new antifungal agents. *Curr Opin Infect Dis.* 2016; 29: 340–5. [PubMed: 27191199]
19. Song Y, Qiao J, Giovanni G, et al. Mucormycosis in renal transplant recipients: review of 174 reported cases. *BMC Infect Dis.* 2017; 17: 283. [PubMed: 28420334]
20. Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what, and how? *Clin Infect Dis.* 2012; 54 Suppl 1: S73–8. [PubMed: 22247449]

Figure 1. Abdominal computed tomography scan. Arrow indicates the gas-filled area with liquefied transplanted kidney and ureteral stent.

Figure 2.
Intra-operative photograph, showing small size of atrophied, necrosed transplanted kidney.

Figure 3.
Intra-operative photograph, showing the right external iliac artery with a clear degradation of the wall leading to acute hemorrhage.

Figure 4. Computed Tomography reconstruction of the ligated external iliac artery and the left to right femoral-femoral bypass with cryopreserved cadaveric arterial allograft.