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"Double carbapenem" and oral fosfomycin for the treatment of complicated urinary tract infections caused by *bla*$_{NDM}$-harboring Enterobacteriaceae in kidney transplantation

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Abstract

Infections with carbapenemase-producing carbapenem-resistant Enterobacteriaceae represent an emergent problem worldwide. Treatment of infections caused by New Delhi metallo-beta-lactamase (NDM)-harboring Enterobacteriaceae is particularly challenging as it frequently

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involves the use of nephrotoxic agents, which is problematic in kidney transplant recipients and non-renal transplants with marginal kidney function. We present two cases of urinary tract infections caused by NDM-harboring Enterobacteriaceae successfully treated with a combination of “double carbapenem” and oral fosfomycin.

Keywords

carbapenemase; carbapenem-resistant Enterobacteriaceae; fosfomycin; kidney transplant; NDM

1 INTRODUCTION

Treatment of infections with carbapenemase producing carbapenem-resistant Enterobacteriaceae (CP-CRE) represents a growing clinical challenge worldwide. Bacteria harboring these resistance genes usually have an extensively drug resistant phenotype[1] Optimal therapeutic strategies for the management of infections with CP-CRE are not yet clearly defined, and often rely on the use of antimicrobials with narrow therapeutic window profiles such as polymixins.[2] Solid organ transplant (SOT) recipients represent a population particularly vulnerable to infections with multi-drug resistant organisms.[3] In kidney transplantation, avoidance of nephrotoxic medications in order to preserve the integrity of the renal allograft is always a priority, further complicating the choice of antimicrobials in this setting.

We describe our experience with two challenging cases of complicated urinary tract infection (UTI) caused by NDM-harboring Enterobacteriaceae, one in a renal transplant candidate and another in a renal transplant recipient both successfully treated with a combination of “double carbapenem” and oral fosfomycin therapy.

2 CASE REPORTS

2.1 Case 1

A 35-year-old woman had a medical history relevant for Gardner syndrome with familial polyposis and invasive desmoid tumors for which she had previously required multiple bowel resections, leading to small bowel obstruction, intestinal fistulas, and obstructive nephropathy treated with bilateral nephrostomy catheters. The patient was undergoing evaluation for a combined renal and intestinal transplant, when she presented to the hospital with dysuria and right flank pain. The patient was originally from Turkey, and had re-located to Miami, Florida in the month prior to admission. Physical examination showed a temperature of 36.6°C, pulse and blood pressure within normal limits, and copious purulent discharge from the exit site of a nephrostomy catheter. Creatinine clearance was 29 mL/min. Leukocyte esterase levels in the urine were >500 leu/μL; urine culture grew >100 000 colony-forming units/mL of *Klebsiella pneumoniae.* Antimicrobial susceptibility testing performed using the Vitek 2 automated system and interpreted based on the Clinical Laboratory Standards Institute criteria showed resistance to all beta-lactams (meropenem minimum inhibitory concentration [MIC] ≥ 16 μg/mL; ertapenem MIC= not reported), as well as resistance to all fluoroquinolones and aminoglycosides. Susceptibility testing

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performed in cation adjusted Mueller-Hinton broth revealed a colistin MIC of 8 μg/mL. E-test showed a MIC of 12 μg/mL to fosfomycin (susceptible) and a MIC of 1 μg/mL to tigecycline. The isolate was also resistant to the ceftazidime-avibactam (MIC ≥ 256 μg/mL), which raised concerns for the presence of *bla*$_{NDM}$ genes or other metallo-beta-lactamases (MBLs). The Rapid Carb Screen assay suggested presence of a carbapenemase. Colonies from *K. pneumoniae* isolated in the urine were inoculated into blood culture bottles and incubated overnight and subsequently analyzed using the Verigene Gram-Negative Blood Culture Test (BC-GN, Nanosphere, Northbrook, IL USA), which detected the presence of *bla*$_{NDM}$, *bla*$_{OXA,}$ and *bla*$_{CTX-M}$. Polymerase chain reaction (PCR) amplification and DNA sequencing subsequently confirmed the identity of these alleles as *bla*$_{NDM-1}$, *bla*$_{OXA-48,}$ and *bla*$_{CTX-M-15-like}$.

The patient was treated with fosfomycin (3 g by mouth [PO] every 48 hours) for 21 days and combination of extended infusion, renally dosed, meropenem (1 g intravenous [IV], administered over 4 hours, every 12 hours) and ertapenem (1 g IV daily) for a total of 14 days. Both nephrostomy catheters were exchanged. Clinical signs of infection resolved and *K. pneumoniae* was eradicated from the urine on repeat urine culture obtained 2 weeks into therapy. The patient tolerated treatment well.

2.2 Case 2

A 57-year-old man with a history of diabetes mellitus type 1 underwent kidney and pancreas transplantation 15 years before presentation; his post-transplant course was complicated with recurrent UTIs in the setting of urethral strictures; despite multiple surgical corrections, he still experienced difficulty voiding, requiring intermittent self-catheterization. The patient presented with dysuria and acute kidney failure. Creatinine clearance was 33 mL/min.

He was born in the Dominican Republic, and lived in New York City for 3 years and Connecticut for 6 years before moving to Florida in early 1990s. The patient did not have any relevant travel history. On admission, he had a temperature of 36.8°C, blood pressure and heart rate within normal limits, and relevant findings on physical examination were not present. Urine leukocyte esterase was >500 leu/μL. A urine culture grew >100 000 colony-forming units/mL of *Escherichia coli*. Antimicrobial susceptibility testing performed using Vitek 2 showed resistance to all beta-lactams (meropenem MIC ≥ 16 μg/mL; ertapenem MIC = not reported), as well as resistance to quinolones, trimethoprim-sulfamethoxazole, tobramycin, and nitrofurantoin. The isolate was susceptible to amikacin (MIC <2 μg/mL). Fosfomycin was also tested by Etest (bioMérieux Inc, Durham, NC USA) and MIC was 256 μg/mL (resistant). The Rapid Carb Screen assay was performed and suggested presence of a carbapenemase, and resistance to ceftazidime-avibactam (MIC ≥ 256 μg/mL) suggested the presence of *bla*$_{NDM}$ or other MBL genes. Colonies from *Escherichia coli* isolated in the urine were inoculated into blood culture bottles and incubated overnight and subsequently analyzed using the Verigene Gram-Negative Blood Culture Test (BC-GN, Nanosphere, Northbrook, IL USA), which detected presence of *bla*$_{CTX-M}$ and *bla*$_{NDM}$. Presence of these genes was later confirmed by PCR amplification and sequencing and identified the alleles as *bla*$_{CTX-M-14-like}$, *bla*$_{CTX-M-15-like}$, and *bla*$_{NDM-5}$.

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Although the NDM-harboring *E. coli* isolate was susceptible to aminoglycosides and colistin, we opted to use an alternative empiric regimen to avoid nephrotoxicity of such agents in this kidney transplant recipient. The patient received fosfomycin 3 g PO every 72 hours for 21 days, in combination with meropenem 1 g IV administered over 4 hours, every 12 hours, and ertapenem 1 g IV daily for a total of 14 days. Clinical signs of infection resolved, and subsequent urine culture obtained 1 week into antibiotic therapy did not show the presence of *E. coli.* The patient tolerated treatment well.

3 DISCUSSION

Among SOT recipients, infections caused by CRE have an estimated incidence of 3%-10%. In this population, reported mortality rates exceed 30%, with most publications preceding the availability of new antimicrobials with potent activity against carbapenemases.[4] *K. pneumoniae* carbapenemase (KPC) is the most common carbapenemase found in Enterobacteriaceae infecting SOT recipients in the United States. Ceftazidime-avibactam is a novel beta-lactam/beta-lactamase inhibitor combination with *in vitro* activity against strains harboring KPC,[5] but it lacks activity against NDM-producing strains. Thus, in cases of infection caused by NDM-harboring Enterobacteriaceae, therapeutic options are very limited and the few available agents (polymixins, tigecycline, fosfomycin, and aminoglycosides) have not been directly evaluated in randomized clinical trials.

Among patients undergoing renal transplantation, preservation of the kidney allograft is a primary concern; therefore, when clinical stability permits, it is preferable to avoid nephrotoxic medications such as colistin and aminoglycosides. The use of tigecycline is also limited in case of UTI owing to poor renal excretion. Recently, a number of reports have appeared showing that the combination of aztreonam plus ceftazidime-avibactam is synergistic and effective for the treatment of infections caused by NDM-harboring Enterobacteriaceae[6]; however, it is important to note that ceftazidime-avibactam is not available worldwide, and recent shortages of ceftazidime-avibactam have temporarily precluded the use of this combination.[7] Thus, further exploring the role of combination therapy with carbapenems and fosfomycin in these two patients in the pre- and post-renal transplant setting became imperative. The rationale for using “double carbapenem” therapy coupled with fosfomycin, even when one isolate was resistant, is laid out next.

Fosfomycin demonstrates a unique mechanism of action, which is the basis for its proposed synergistic effects with other antibiotics including beta-lactams, aminoglycosides, and fluoroquinolones. Fosfomycin gains access into the bacterial cell through the glycerophosphate transporter and exerts bactericidal activity by interfering with cell wall synthesis by inhibiting the formation of peptidoglycan and by blocking the synthesis of *N*-acetylmuramic acid (the key enzyme target of inhibition is MurA). MurA transfers enolpyruvate from phosphoenol pyruvate to UDP-GlcNAc, thus forming UDP-GlcNAc-enolpyruvate. Fosfomycin alkylates the highly conserved catalytic cysteine of MurA, which is essential for cell survival; this mechanism of action provides fosfomycin with activity against both gram-positive and gram-negative bacteria.[8]

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As a result of inhibiting MurA and cell wall integrity, cells become more permeable. A variety of advanced spectroscopic methods demonstrate that fosfomycin significantly changes the bacterial cell shape and the outer membrane structure responsible for the altered membrane permeability. Atomic force microscopy also shows that “holes” are formed on the cell surface and that the bacterial shape is changed.[9]

In this report, we were challenged by UTI caused by NDM-containing strains. A possible explanation for the effectiveness of our regimen is that fosfomycin enhances cell permeability (“creates holes”) and the “double carbapenem” regimen exceeds the catalytic efficiency of the periplasmic carbapenemase (even NDM-1); the carbapenem remaining in the periplasmic space “bypasses” the hydrolytic action of carbapenemase and allows for inactivation of PBPs. *{Au: what is PBPs?}* Although it is believed that NDM-1, as an MBL, generally hydrolyzes carbapenems faster than KPCs, the overall catalytic activity is surpassed. In the case of the elevated fosfomycin MICs, there apparently were enough permeability changes to achieve efficacy. Essentially, oral fosfomycin acted like an “enhancer” or “sensitizer” despite resistance (MIC > 64 mg/L).

Fosfomycin is approved in the United States for the treatment of uncomplicated UTI as a single-dose oral suspension.[10] The oral formulation has high bioavailability and good tissue penetration. IV administration of fosfomycin is preferred in critically ill patients in whom hemodynamics might preclude the use of oral agents. Our group and others have used IV fosfomycin as part of combination therapy for severe infections caused by carbapenem-resistant *K. pneumoniae* in liver transplant recipients,[11,12] but this is logistically challenging since it requires importing the drug from Europe after an emergency investigational new drug application is approved by the FDA. Thus, considering the absence of bacteremia and the clinical stability of both patients presented here, IV fosfomycin was not considered for these cases; instead, we opted to use oral fosfomycin at doses of 3 g PO every 72 hours for 21 days to treat their UTI. This dose has been suggested for treatment of pyelonephritis and complicated UTI.[13] Based upon previous studies, after a single dose of 3 g of fosfomycin the maximum serum drug concentration ranges between 22–32 mg/L, reached within 2–2.5 hours.[14] Fosfomycin has a serum elimination half-life ($t_{1/2}$) that ranges between 2.5 and 7.5 hours. In cases of renal insufficiency, the half-life is even longer. Importantly, fosfomycin is excreted into in the urine in concentrations of 1053–4415 mg/L 4 hours after administration of the usual 3 g single dose, while concentrations of >128 mg/L can persist for 48 hours. In effect, the *E. coli* and *K. pneumoniae* in the urinary tracts were exposed to high levels of fosfomycin that enhanced the effect of carbapenems.

Clinical data, based on retrospective studies, have suggested that combination therapy is associated with better outcomes than monotherapy in cases of severe infection caused by CP-CRE.[2] Antimicrobial regimens including colistin and a carbapenem, tigecycline, fosfomycin, or an aminoglycoside have been explored, but not directly compared. Furthermore, the majority of *in vitro* and clinical studies have described treatment of infections caused by organisms harboring serine carbapenemases such as KPC.[15]

In exploring a role for combination therapy against MBLs, Tangden et al[15] tested *in vitro* activity of antibiotic combinations against four *K. pneumonia* isolates (two harboring VIM

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and two with NDM-1) and found that the combination of fosfomycin-colistin demonstrated synergy and bactericidal effect against one of the VIM strains, and both NDM strains (despite these two strains being resistant to fosfomycin). Fosfomycin-meropenem-colistin showed a synergistic effect against all strains and a bactericidal effect against three of the four strains evaluated. Regarding double carbapenem combinations, Poirel et al[16] tested *in vitro* combinations of imipenem/meropenem, imipenem/ertapenem, imipenem/doripenem, doripenem/ ertapenem, and ertapenem/meropenem combinations on six isolates of *K. pneumonia* producing NDM-1, including two isolates co-producing NDM-1 and OXA-181, and did not find any of these combinations to be synergistic. In clinical practice, only one other report exists supporting the use of combination therapy with meropenem-fosfomycin.[17] This regimen was successfully used for the treatment of sepsis and bacteremia secondary to complicated UTI with *Morganella morganii* harboring NDM-1 in a renal transplant recipient.[17] Wilkowski et al[18] described a series of three renal transplant recipients with UTI caused by to NDM-1–producing *K. pneumoniae* successfully treated with a variety of regimens: Case 1 was treated with imipenem-colistin-fosfomycin; Case 2 received imipenem-gentamicin, later modified to gentamicin-colistin-fosfomycin; and Case 3 was initially treated with colistin-gentamicin-imipenem, followed by oral suppression with fosfomycin, and a recurrent episode was treated with trimethoprim-sulfamethoxazole-fosfomycin. All regimens achieved eradication of *K. pneumoniae* in urine.[18] The heterogeneity of the aforementioned regimens used in clinical practice reflects the struggles transplant clinicians face when dealing with these extremely drug-resistant organisms.

In summary, the two patients reported here and an additional case from the literature, indicate that combination therapy with (double) carbapenem and oral fosfomycin is safe and effective in the treatment of complicated UTI with NDM-harboring Enterobacteriaceae in kidney transplant candidates/recipients. The role of this combination in treatment of critically ill patients remains to be established; larger studies are needed to evaluate this regimen.

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