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Case report

Treatment of recurrent urinary tract infections in anuric hemodialysis patient, do we really need antimicrobial urinary concentration?

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ABSTRACT

Providing care for patients with chronic kidney disease requires considerations that are unique to this population. Several references recommend the treating urinary tract infections with antibiotics that achieve considerable concentrations in urine however this is not applicable in anuric patients undergoing hemodialysis who are unable to excrete antibiotics significantly in urine. We report successful treatment of several episodes of urinary tract infections in hemodialysis patient highlighting the questionable need for antimicrobial urine concentration.

Infections are one of the leading causes of death among patients with chronic kidney disease stage 5 requiring hemodialysis (CKD-5HD) [1–3]. Urinary tract infections (UTI) are common in this patient population, augmenting the risk of associated complications [4]. These infections are initially a challenge to diagnose, owing to difficulties in obtaining urine samples in anuric or oligouric patients. Patients with CKD-5HD may need up to 2 days to produce a urine sample which is usually done through catheterization. Several factors complicate the treatment of hemodialysis patients, including: compromised immune system, inability to completely void the bladder, chronic comorbidities, and critical need to preserve the patency of intravenous access. A wide array of pathogens that can be implicated in uncomplicated UTIs. However, with the numerous complications hemodialysis patients have, multidrug resistant organisms are more prevalent than in patients with normal kidney function [5,6].

Traditionally, as suggested by the Infectious Diseases Society of America (IDSA) and other infectious diseases organizations, the optimal approach to treatment is to utilize an antibiotic that achieves sufficiently high urinary concentrations. [5,7,8] However, these recommendations are not applicable in anuric patients with CKD-5HD. Due to the lack of consensus to treat UTIs in anuric patients, a multidisciplinary team including a nephrologytrained stewardship pharmacist in making therapeutic decisions, including selection of antibiotic, appropriate dosing using pharmacokinetic/pharmacodynamic data, antimicrobial administration timing and route of administration [9].

We are reporting a case of anuric patient with CKD-5HD repeatedly treated for recurrent UTI, with no significant urine production, highlighting the importance of multidisciplinary team involving a nephrology trained, stewardship pharmacist addressing the unique needs for this group of patients.

Case report: (Table 1) A 69-year old female patient requiring hemodialysis with multiple comorbidities, including: Type-2 diabetes mellitus, hypertension, diabetic nephropathy, hypothyroidism, Sjogren's syndrome, peripheral sensory neuropathy, peripheral vascular occlusive disease, gastroesophageal reflux disease, discoid lupus, fibromyalgia, diverticulitis, seizure disorder, and uterine cancer. Surgical history is significant for tonsillectomy, bilateral cataract surgeries, left renal artery plasty/stent, bilateral Lasik vision correction, right quadriceps tendon repair, total knee replacement, severe lumbar spinal stenosis L2/3 to L4/5. Reported allergies are: sulfamethoxazole, penicillin, sulindac, and norfloxacin but specific manifestations of the allergic reactions are not known.

In the beginning of April 2012, urine culture (catheter collected) yielded $>10^6$ cfu/L *E. coli,* which carried a plasmid-mediated AmpC gene. As per laboratory protocol, the organisms should be considered resistant to all cephalosporins and β-lactamase inhibitors combination drugs and was sensitive to ertapenem, nitrofurantoin and resistant to ciprofloxacin, gentamicin, co-trimoxazole. Additionally, the culture grew 1-10^6 cfu/L *Enterococcus faecium*that was considered a colonizer. The patient was treated empirically with ciprofloxacin which was not substituted due to

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Table 1
Summary of the case.

April 2012 First Episode)	urine culture (catheter collected) yielded $>10^6$ cfu/L E. coli plasmid-mediated AmpC gene	Ciprofloxacin 500 mg po daily - Still symptomatic
		Ertapenem 1000 mg followed by 500 mg post each dialysis for 5 doses total (during last 30 min of dialysis)
May 2012 (One month Later)	Enterococcus faecium (catheter collected) $>10^6$ cfu/L resistant to ciprofloxacin, nitrofurantoin, penicillin, co-trimoxazole and sensitive to vancomycin, linezolid and tigecycline	Vancomycin 2000 mg IV (last 60 min of dialysis) followed by 1000 mg IV after each subsequent dialsysis (6 doses total)
June 2012) 2 months after first episode)	$>10^6$ cfu/L E. coli, a different strain, that was sensitive to cefazolin and nitrofurantoin	Ertapenem for 5 doses (1000 mg IV loading dose followed by 500 mg IV after each subsequent dialysis).
July 2012 (3 months after first episode)	A follow up culture confirmed no significant growth	
September 2012 (5 months after first episode)	$>10^6$ cfu/L Pseudomonas aeruginosa sensitive to ceftazidime, gentamicin, ciprofloxacin, and piperacillin	IV ceftazidime and IV gentamicin for 2 doses after hemodialysis then de-escalated to oral ciprofloxacin 500 mg orally daily for 2 weeks.
October 2012 (6 months later)	E. coli pan susceptible	IV cefazolin 2 g after every dialysis session for 2 weeks (6 doses total)
November 20,120 (7 months later)	$>10^6$ cfu/L *Candida albicans* for which treatment was deferred and 1-10^6 cfu/L *Klebsiella oxytoca*	IV cefazolin 2 g for 6 doses post dialysis session.
December 2012 (8 months later)	confirmatory urine culture was negative for significant growth.	
January 2013 (9 months later)	Enterococcus faecium	IV vancomycin per previously mentioned protocol
February 2013 (10 months later)	Candida albicans and Escherichia coli	fluconazole 200 mg as a loading dose then 100 mg daily for 2 weeks and IV cefazolin 2 g post-dialysis for 2 weeks respectively
April 2013 (12 months later)	Candida albicans	fluconazole 200 mg orally daily for 2 weeks

lack of symptoms. A follow up culture one week after was still growing the identical organisms, thus ertapenem was initiated (1000 mg loading dose) followed by 500 mg for 4 consecutive dialysis sessions given after dialysis and was administered through the central venous catheter which lead to patient self-reported clinical improvement. The patient complained of a recurrence of symptoms around mid-May 2012, triggering a subsequent urine culture that yielded $>10^6$ cfu/L *Enterococcus faecium*resistant to ciprofloxacin, nitrofurantoin, penicillin, co-trimoxazole and sensitive to vancomycin, linezolid and tigecycline. The patient was started on vancomycin loading dose of 2000 mg IV followed by 1000 mg after each subsequent dialysis for 2 weeks (total of 6 doses). Experiencing another episode in early June, a urine culture grew $>10^6$ cfu/L *E. coli*, a different strain, that was sensitive to cefazolin and nitrofurantoin but the physician elected to start ertapenem for 5 doses (1000 mg IV loading dose followed by 500 mg IV after each subsequent dialysis). A follow up culture on July 5th, 2012 confirmed no significant growth. In September 2012, a urine culture collected subsequent to suspected recurrent infection, yielded $>10^6$ cfu/L *Pseudomonas aeruginosa* sensitive to ceftazidime, gentamicin, ciprofloxacin, and piperacillin that was prescribed IV ceftazidime and IV gentamicin for 2 doses after hemodialysis then de-escalated to oral ciprofloxacin 500 mg orally daily for 2 weeks. By the end of October 2012, a urine culture grew $>10^6$ cfu/L *E. coli*pan susceptible that was treated with IV cefazolin 2 g after every dialysis session for 2 weeks (6 doses total). By the end of November 2012, a urine culture grew $>10^6$ cfu/L *Candida albicans*for which treatment was deferred and 1-10^6 cfu/L *Klebsiella oxytoca* that was treated with IV cefazolin 2 g for 6 doses post dialysis session. One month later in December 2012, a confirmatory urine culture was negative for significant growth.

Starting 2013 the patient experienced several recurrent UTIs. In January *Enterococcus faecium* was treated with IV vancomycin per previously mentioned protocol. In February *Candida albicans* and *Escherichia coli*that was treated with oral fluconazole 200 mg as a loading dose then 100 mg daily for 2 weeks and IV cefazolin 2 g post-dialysis for 2 weeks respectively. In April another recurrence with *Candida albicans* treated with fluconazole 200 mg orally daily for 2 weeks. The case requested to be transferred to palliative care and expired in June 2013. Of note, throughout the 14 months period of case follow up the patient was anuric and all antimicrobials used in the succession of recurrence were able to eradicate the targeted infections as evidenced by microbiology reports and clinical course.

Discussion

Antibiotics have been used in the treatment of pyelonephritis, cystitis and urethritis based on the premise of high urine concentrations, where the classical examples being the fluoroquinolones (i.e. norfloxacin, ciprofloxacin, and levofloxacin). [5,7,8] Additionally, low dose trimethoprim monotherapy for is considered an option for the treatment of uncomplicated cystitis as urine concentration remains elevated with varying degrees of deteriorating renal function [4,5]. The commonly used beta-lactams such as ampicillin-sulbactam, cefazolin, ceftazidime, ceftriaxone, ertapenem, meropenem, and piperacillin-tazobactam, achieve a high urine concentration in patients with normal kidney function [5]. However, the combination of sulfamethoxazole-trimethoprim is used cautiously in patients with compromised kidney function; similar caution for nitrofurantoin in patients with creatinine clearance below 60 mL/min are all based on notion of urine therapeutic concentration [5,7,8]. However, there is a paucity of randomized clinical trials specifically investigating the optimal treatment of UTI in patients with CKD-5HD. Of interest, the main source cited by the IDSA and other infectious disease sources to recommend the use of antimicrobials with adequate urine concentration used animal models' data and excluded patients with CKD-5HD and anuric patients [10].

Several antibiotics have approved dosing in patients with CKD-5HD. The approved dose of ertapenem is 500 mg daily in this population. This FDA approved dosing was derived from a pharmacokinetics study in which the authors studied only a single dose of ertapenem for 24 h period in in 7 non-infected patients. [11] After 1 g intravenous infusion post HD, the Cmax was 138.9 ug/mL then declined to 54.9 ug/mL and 27.1 ug/mL, after 12 h and 24 h, respectively. Additionally, the concentrations of free drug were 67 ug/mL and 24.6 ug/mL post infusion and at 12 h. $AUC_{0-\infty}$ of ertapenem in patient with CKD-5D was (1941.5 μg.hr/mL)

summing up to approximately 3 folds of that in patients with mild renal insufficiency (712.2 μg.hr/mL). Furthermore, the free drug concentration $AUC_{0-\infty}$ 252.2 μg.hr/mL in patients with CKD-5D was more than 5-fold higher than the $AUC_{0-\infty}$ of free drug in patients with mild renal impairment (44.2 μ.hr/mL). The authors suggested that 0.5 g IV daily dose was adequate based on extrapolation that it would result in decrease in plasma drug concentration to half of what was observed with 1 g in patients with CrCl < 30 mL/min. [11] However, based on a pilot study including 10 infected patients found that plasma concentration was maintained above MIC for the intradialytic period following 1 gm infused 3 times weekly post-HD [12]. A recent study [13], conducted on 22 patients after multiple doses, found that 500 mg trice weekly after each dialysis is sufficient to maintain ertapenem plasma trough concentration above 2 mg/L.

Although the ertapenem free drug concentration at 24 h remained considerably detectable and exceeded the minimum inhibitory concentration of the studied organisms, the authors suggested the once daily dosing in this population. [11] As detailed above, multiple reports indicated that this dosing strategy is not optimal because of the drug accumulation and increased toxicity namely seizures cases were reported which triggered the experts to suggest a post dialysis dosing in this population would avoid accumulation [12,14]. Our observations in this case support the recommendations that the thrice weekly dosing of ertapenem could be enough to eradicate the bacteria even in anuric patients.

Hemodialysis access is very important in patients with CKD-5HD patients. [15] Multiple nephrology organizations advocate to protect the patients' veins patency by avoiding additional IV access that may affect future fistula or central venous catheter sites due to irreversible damage to the endothelial lining of vascular occurs after inserting central catheters or PICC lines [16–18].

In these situations, the nephrology trained steward pharmacist's pivotal role is clearly needed to select the antibiotics which could be administered through the dialysis access to avoid peripheral and /or PICC lines. [9,16–18] In addition, this contribution would significantly reduce the burden on home health care, potential hospital admissions, and overall cost.

Our case suggests that the infusion of antimicrobials such as cefazolin, ceftazidime, gentamicin, ertapenem, and vancomycin during last 30 min of dialysis or dosed immediately after dialysis through the HD access are as effective as daily dosing and can prevent the unnecessary peripheral or PICC insertion in this population. [9] Second, the outcomes of this case question the current practice of selecting antimicrobials which are readily excreted in the urine in high concentrations. Lastly, the findings underscore the critical need for the nephrology trained stewardship pharmacist at the dialysis units who can select and dose the antibiotics appropriately.

Our observation in this case in conjunction with others, stimulates the interest to rethink the need to select only antimicrobials with high urine concentration to treat UTIs. In addition, to raise the awareness about the essential role of specialized team with stewardship pharmacist to effectively provide care for CKD-5HD patients.

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No budget was associated with study.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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