

Cystitis in a Bitch with Chronic Kidney Disease Caused by Multidrug-Resistant *Escherichia coli*

Jongchul Yun¹, Taesik Yun¹, Yoonhoi Koo¹, Yeon Chae¹, Dohee Lee¹, Byeong-Teck Kang¹,
Mhan-Pyo Yang¹ & Hakhyun Kim¹

ABSTRACT

Background: In dogs with bacterial cystitis that is resistant to multiple antibiotics, resulting from repeated infections and antimicrobial administration, especially if the dog has impaired renal function and the induction of systemic side effects by intravenous or oral administration is a concern, intravesical instillation of antibiotics might represent an alternative treatment option. In human and veterinary medicine, a number of studies showed intravesical instillation of antibiotics is effective for the therapy multidrug-resistant bacterial urinary tract infection (UTI). This report firstly illustrates successful intravesical meropenem treatment of a UTI caused by multidrug-resistant *Escherichia coli* with no systemic side effects in dog with chronic kidney disease (CKD).

Case: A 15-year-old spayed female Maltese was presented with recurrent bacterial cystitis. The risk factors for the recurrent UTI were spinal cord injury and CKD which had been managed for 1 year. Ultrasound-guided cystocentesis was performed to obtain a urine sample for urinalysis, bacteriologic culture, and antibiotic susceptibility testing. Bacterial cystitis caused by multidrug-resistant *Escherichia coli* was diagnosed on the basis of bacterial culture, and antimicrobial susceptibility testing. Because the dog had CKD, reducing the clearance of meropenem, intravesical instillation of antibiotics was initiated. The intravesical instillation process consisted of the emptying of the urinary bladder, infusion of a diluted meropenem solution (8.5 mg/kg diluted in 20 mL of saline solution) into the bladder through a urethral catheter, and retention of the meropenem solution in the bladder for 1 h, and its removal. The procedure was repeated every 8 h. On day 8 of the intravesical instillation therapy, bacteriologic culture yielded a growth of *E. coli* (50,000 CFUs/mL), which was less than previously obtained. the concentration of the meropenem solution being administered was increased to 17 mg/kg diluted in 20 mL of saline solution, to improve the effectiveness of the therapy. After 21 days of the intravesical meropenem instillation, the bacterial cystitis was resolved. One year after completion of the treatment, the dog is still alive without any recurrence of bacterial cystitis.

Discussion: Because resistant uropathogens can cause zoonotic infections, effective therapy is important with increasing incidence not only for patients, but also for public health. Intravesical instillation of antibiotics can be an effective treatment method for dogs with urinary tract infection in which oral antibiotics are likely to be ineffective and injectable antibiotics cannot be a treatment option. The antibiotics can be administered directly to the affected location, and systemic side effects can be minimized by the impermeability of the bladder wall via intravesical instillation procedure. Meropenem is likely to accumulate in dogs with impaired renal function, leading to systemic side effects and the aggravation of CKD in old dogs. This report describes the successful treatment of multidrug-resistant *E. coli* infection by intravesical instillation of meropenem without any side effects in dogs with CKD. Therefore, clinician should consider the use of intravesical instillation of antibiotics which predominately excreted in the urine for the control of urinary tract infection caused by multidrug-resistant bacteria in dogs showing reduced renal function.

Keywords: canine, intravesical instillation, meropenem, multidrug-resistant organism, urinary tract infection.

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Laboratory of Veterinary Internal Medicine, College of Veterinary Medicine, Chungbuk National University, North Chungcheong Province, Republic of South Korea. CORRESPONDENCE: H. Kim [kimh@chungbuk.ac.kr]. Laboratory of Veterinary Internal Medicine, College of Veterinary Medicine, Chungbuk National University. Cheongju, Chungbuk 28644. Republic of South Korea.

INTRODUCTION

Urinary tract infection (UTI) is a common disease of humans [6] and dogs [4] that may occur when the normal defense mechanisms are compromised. UTI is predisposed to many factors, and develops secondary to interactions between the virulence of an organism and underlying anatomic, functional, immunological, or metabolic abnormalities or comorbidities in the host. In humans, infections, caused by various resistant pathogens are associated with significantly higher morbidity, mortality, and treatment costs. In veterinary medicine, there is still a lack of relevant information, but multidrug-resistant infections are emerging as a significant issue. Antibiotic resistance of uropathogens complicates therapy in dogs and is a public health concern because these pathogens may be zoonotic [4,8,10]. In human and veterinary medicine, a number of studies showed intravesical instillation of antibiotics is effective for the therapy multidrug-resistant bacterial UTI [3,10-12]. This report describes the case of a dog with UTI caused by multidrug-resistant *Escherichia coli* infection, which was successfully managed by intravesical instillation of meropenem for 21 days, without any side effects.

CASE

A 15-year-old spayed female Maltese weighing 3.32 kg was presented with recurrent bacterial cystitis. The dog had a history of paraplegia caused by vertebral fracture and spinal injury, and was unable to voluntarily empty its bladder. The dog had ureteral calculi and chronic kidney disease (CKD), which had been managed for 1 year. The complete blood count (CBC) was within normal limits. Abnormalities detected on serum biochemical analysis included increased activity of alkaline phosphatase (ALP) [212 IU/L; reference interval [RI], 29-97 IU/L], and slightly high blood urea nitrogen (BUN) [28.8 mg/dL; RI, 7-25 mg/dL]. Ultrasonography of the abdomen revealed an irregularly thickened bladder wall, moderate irregularity in the margin of left kidney, and a severe reduction in renal corticomedullary definition.

Ultrasound-guided cystocentesis was performed to obtain a urine sample for urinalysis. Bacteriologic culture of the urine yielded a growth of *Escherichia coli* (>100,000 CFUs/mL), which subsequent testing revealed was susceptible only to imipenem and meropenem, and no growth of other bacteria. Urinalysis

revealed bacteriuria but no bilirubin, glucose, ketone, or urobilinogen, and the urine sediment contained 100 white blood cells (WBCs)/high power field (hpf) and 5 red blood cells (RBCs)/hpf. Therefore, bacterial cystitis caused by multidrug-resistant *Escherichia coli* infection was diagnosed, and the dog was hospitalized.

Because meropenem is predominately excreted unchanged in the urine, it is likely to accumulate in dogs with impaired renal function, leading to systemic side effects and the aggravation of CKD. Therefore, intravesical instillation, instead of intravenous injection, of meropenem¹ was initiated. The intravesical instillation process consisted of the emptying of the urinary bladder, infusion of a diluted meropenem solution (8.5 mg/kg diluted in 20 mL of saline [0.9% NaCl] solution) into the bladder through a urethral catheter, and retention of the meropenem solution in the bladder for 1 h, and its removal (Figure 1). The urethral catheter was changed every other day. No abnormalities in vital signs developed, and there was no hematuria, which can occur when the drug irritates the bladder wall and intravesical instillation was repeated every 8 h. On day 8 of the intravesical instillation therapy, a urine sample was obtained *via* the urethral catheter for bacterial culture and urinalysis. Bacteriologic culture yielded a growth of *E. coli* (50,000 CFUs/mL), which was less than previously obtained, and urinalysis revealed a urine sediment containing 3 WBCs /hpf and 5 RBCs /hpf.

Consequently, the concentration of the meropenem solution being administered was increased to 17 mg/kg diluted in 20 mL of saline solution, to improve the effectiveness of the therapy, which resulted in no detectable side effects. On day 15 of the therapy, a further urine sample was obtained *via* the urethral catheter. Bacteriologic culture yielded no growth of multidrug-resistant *E. coli*. On day 21, a further blood sample was obtained for CBC and serum biochemical analysis, and all of the parameters were within their respective RIs. Therefore, the intravesical instillation of meropenem was discontinued and the dog was discharged. Over the next one year, the dog continued to be routinely re-evaluated, and there has been no recurrence of bacterial cystitis until now.

DISCUSSION

UTI caused by bacteria is common in humans and many domestic animals, and antimicrobial treatment is a risk factor for the development antimicrobial resis-

tance. Because resistant uropathogens can cause zoonotic infections, effective therapy is important with increasing incidence not only for patients, but also for public health.

UTI caused by multidrug-resistant bacteria frequently occurs in dogs with spinal cord injury, which causes incomplete voiding of urine, such as the dog of this report, and it is challenging to manage this effectively. Because the dog described in the present report had a history of paraplegia caused by spinal cord injury, following vertebral fracture, which resulted in incomplete voiding of urine, UTI was a frequent problem, and its history of regular reinfection increased the risk of treatment failure on each occasion.

Intravesical instillation of antibiotics can be an effective treatment method for dogs with UTIs in which oral antibiotics are likely to be ineffective and injectable antibiotics cannot be a treatment option. The drug is administered directly to the affected location, and systemic side effects can be minimized by the impermeability of the bladder wall. In addition, the adverse effects, such as nausea, diarrhea, and colonic superinfection associated with some oral agents passing through the gastrointestinal tract, can be avoided. In a previous study of intravesical instillation of gentamicin sulfate in dogs [7], serum gentamicin sulfate levels were not detectable, and the serum creatinine

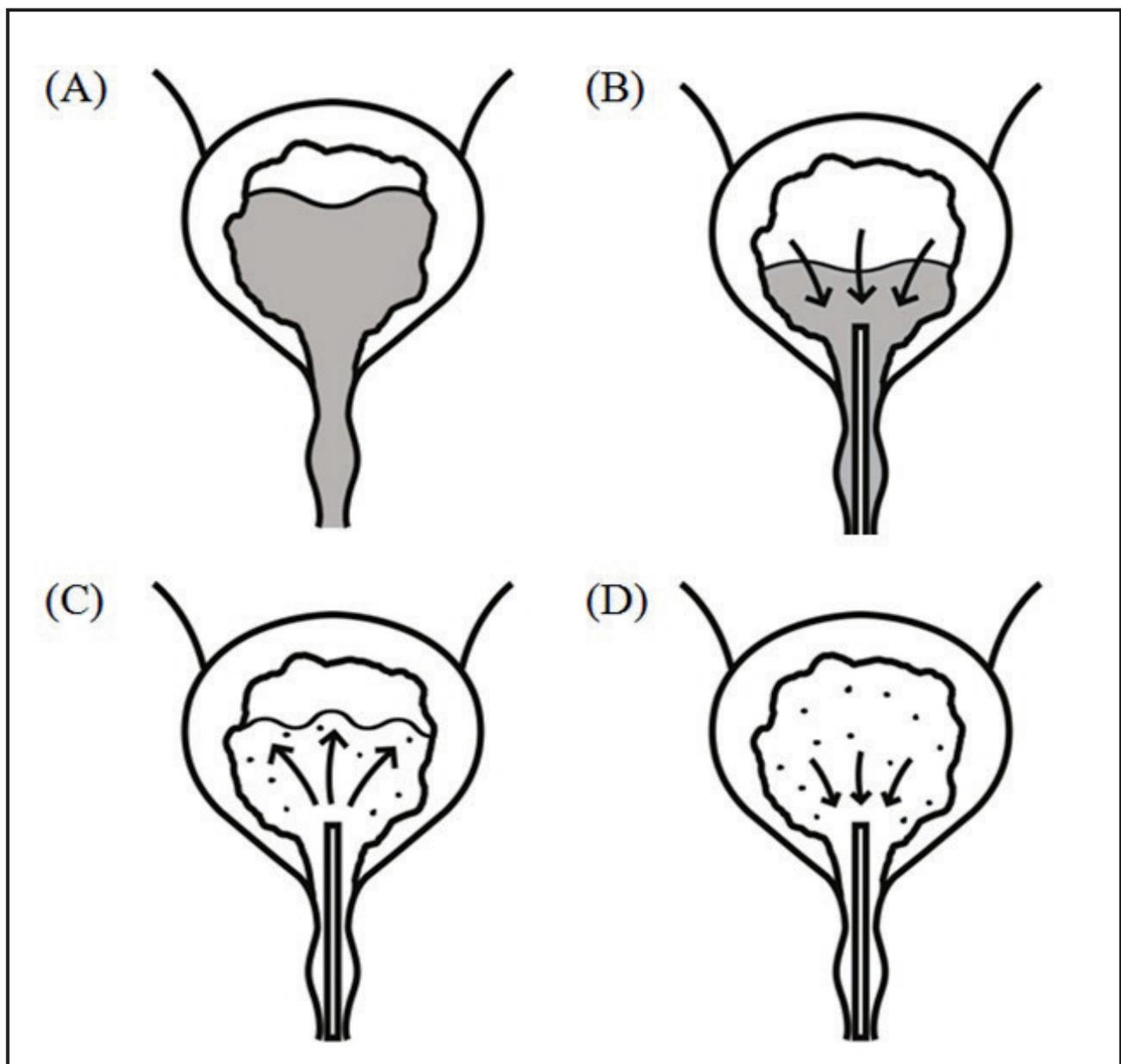


Figure 1. A schematic diagram (created by Dr. Jongchul Yun) of the intravesical instillation of meropenem. Emptying of the urinary bladder (A & B). Infusion of a diluted meropenem solution into the bladder through a urethral catheter (C). Retention of the meropenem solution in the bladder for 1 h and its subsequent removal.

concentration was not affected. These results indicate that intravesical instillation of antibiotics is associated with fewer systemic side effects.

Escherichia coli is one of the main participants in the dissemination of antimicrobial resistance [9], and in both dogs and cats, prior antibiotic administration and recurrent infection are the principal risk factors for the development of multidrug-resistant infections [2,5]. The multidrug-resistance *Escherichia coli* responsible for the UTI in this case was shown to be susceptible to imipenem and meropenem. Compared with imipenem, meropenem is not a substrate for dehydropeptidase-I, a metabolizing enzyme present in renal proximal tubule cells and the brush border, making the concomitant administration of a dehydropeptidase-I inhibitor, such as cilastatin, unnecessary. In addition, meropenem causes less nephrotoxicity and neurotoxicity than imipenem, but the clearance of meropenem from plasma is slower, and therefore the plasma meropenem concentration is maintained for longer, in patients with reduced renal function than in healthy people [1]. Because the dog described herein had CKD, its blood meropenem concentration was likely to remain undesirably high for a long period, which could result in systemic side effects, if the drug was administered by intravenous injection. Furthermore, because meropenem is eliminated largely without having been metabolized, in urine, the dog's CKD was likely to be aggravated by the accumulation of meropenem. Incomplete treated bacterial cystitis may also negatively impact the renal parenchyma, therefore, the dog required more effective treatment of its cystitis. Of the limited treatment options, intravesical instillation of meropenem was chosen because it should be associated with the fewest side effects and have the best therapeutic efficacy.

A previous case report described the successful treatment of a dog with a UTI caused by *Pseudomonas aeruginosa* using intravesical instillation of amikacin for 27 days [11]. In this instance, the dose and frequency of antibiotics used were the same as that recommended for intravenous administration, because information regarding the most appropriate dose and frequency for intravesical instillation was not available. The dog developed hematuria after 27 days of intravesical treatment that resolved within 7 days of the discontinuation of treatment. In the case reported here,

intravesical instillation of meropenem was performed at the same dose as that recommended for intravenous administration (8.5 mg/kg) and repeated every 8 h until day 15, when the dose was increased to 17 mg/kg until day 21. Despite this increase in dose, the dog did not develop any side effects.

The limitations of drug administration by intravesical instillation are the time and labor required to perform transurethral catheterization for each administration, especially in female dogs, or for the maintenance of a sterile indwelling urethral catheter. In addition, if the bladder epithelium is inflamed, it is difficult to predict the circulating concentration of antibiotics that will result, which if high may be associated with adverse effects; therefore, continuous evaluation of the dog is required during therapy. This means that treatment is best undertaken when the dog is hospitalized, and the prolonged stay required may render it too expensive option for owners.

This case report illustrates successful intravesical treatment of a UTI caused by multidrug-resistant *Escherichia coli* over 21 days, with no evidence of systemic side effects. In bacterial cystitis that is resistant to multiple antibiotics, resulting from repeated infections and antimicrobial administration, especially if the dog has impaired renal function and the induction of systemic side effects by intravenous or oral administration is a concern, intravesical instillation of antibiotics might represent a useful treatment option. However, there is a lack of published information regarding the optimal dose, frequency, and duration of intravesical treatment required for a positive outcome. Therefore, further investigation is needed to be established the most ensure effective intravesical protocol and to assess the efficacy of other intravesical protocols for the treatment of UTIs caused by multidrug-resistant bacteria.

MANUFACTURER

¹Meropen Inj. Yuhan Co. Seoul, South Korea.

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