Use of intermittent bladder infusion with clotrimazole for treatment of candiduria in a dog

Zoe A. Forward, DVM; Alfred M. Legendre, DVM, MS, DACVIM; Hari Dharm Singh Khalsa, DVM

- Urinary tract infection with *Candida albicans* is often associated with a predisposing factor such as diabetes mellitus or prolonged antimicrobial or glucocorticoid administration.
- When fluconazole and other orally administered antifungal agents are ineffective in eliminating candiduria or when the patient cannot tolerate orally administered antifungal drugs, bladder irrigation with an antifungal agent may offer a viable alternative method of treatment.

A 14-year-old diabetic hypothyroid spayed female Miniature Poodle that weighed 4.3 kg (9.5 lb) was evaluated because of frequent urination and a mucoid vaginal discharge filled with tiny yellow granules. The dog had a history of recurrent bacterial urinary tract infections for 4 years and hind limb paresis of 3 years' duration attributed to lumbar intervertebral disk disease. Despite the intervertebral disk disease, the dog was able to control urination and void voluntarily; however, incomplete bladder emptying was suspected. The lower urinary tract bacterial infections decreased in frequency substantially when the dog was treated with the urinary antiseptic methenamine mandelate. This drug is bactericidal when the urine pH is maintained between 5.0 and 5.5.[1] Therefore, the dog was exclusively fed a prescription diet[a] to maintain an acidic urine pH. A urinalysis was performed every other month to monitor pH, and urine pH remained between 5.5 and 6.0. Diabetes was monitored closely by twice daily determination of urine glucose concentrations and periodic use of glucose tolerance curves. At the time of evaluation, daily medications included methenamine mandelate[b] (10 mg/kg [4.5 mg/lb], PO, q 8 h), levothyroxine sodium[c] (0.01 mg/kg [0.005 mg/lb], PO, q 12 h), and lente insulin[d] (3 units, SC, q 12 h). There were large numbers of oval budding yeast and WBC in the urine sediment. Urine pH was 6.0. A fungal culture of urine was performed, and *Candida albicans* (> 100,000 **colony-forming units [CFU]**/ml) was isolated.

While awaiting results of fungal culture, the dog was administered fluconazole[e] (5 mg/kg [2.3 mg/lb], PO, q 12 h). This treatment was continued for 3 weeks. The dog continued to receive methenamine mandelate (10 mg/kg, PO, q 8 h). Weekly urinalyses revealed that fluconazole had little to no effect in diminishing the number of *C albicans* organisms in the urine. The dog continued to have a mucoid discharge associated with frequent urination. Urine pH remained between 6.0 and 6.5 during fluconazole treatment. Treatment with fluconazole was discontinued. The values of a serum chemistry panel were within reference ranges. Ultrasonography revealed that the kidneys were normal, but the bladder wall was thickened.

The dog was then treated with terbinafine hydrochloride[f] (5.5 mg/kg [2.5 mg/lb], PO, q 12 h) for 3 weeks. After 3 weeks, the dog remained polyuric and had a large number of budding yeast, coccoid bacteria, and WBC in the urine, with urine pH of 5.0 and urine glucose concentration of 5 g/L. Terbinafine treatment was discontinued. A second fungal culture reconfirmed the presence of *C albicans* (> 100,000 CFU/ml), and determination of the **minimum inhibitory concentration (MIC)** for flucytosine was requested. An aerobic culture for bacteria was not performed at this time. Fructosamine concentration was 361 µmol/L (reference range, 175 to 400 µmol/L), which was indicative of adequate long-term glycemic regulation. While awaiting the results of the MIC determination, the dog was treated with enrofloxacin[g] (5 mg/kg, PO, q 12 h) for 3 weeks to control the bacteria detected via urinalysis, and with itraconazole[h] (5 mg/kg, PO, q 12 h). Methenamine mandelate treatment was discontinued. After 2 days of itraconazole treatment, the dog developed anorexia and lethargy, which resolved upon discontinuation of administration of the drug.

The *C albicans* isolate was susceptible to flucytosine, as judged by results of the MIC determination.[i] Flucytosine[j] was administered (50 mg/kg [23 mg/lb], PO, q 8 h) for 5 weeks. Flucytosine is potentially toxic to rapidly proliferating normal tissues such as bone marrow, skin, and gastrointestinal tract mucosa[1,2]; to monitor for bone marrow suppression, a CBC was performed every 2 weeks during flucytosine treatment, and results remained within reference ranges. A urinalysis was performed every 2 weeks, and urine pH ranged from 5.0 to 6.0. By the fourth week of flucytosine treatment, no yeast were seen in the urine sediment. However, during the fifth week of treatment, there was a recurrence of large numbers of budding yeast, coccoid bacteria, and WBC in the urine. The dog also developed a diffuse cutaneous skin eruption during the fifth week of treatment that was attributed to a drug reaction. Administration of flucytosine was discontinued. Results of a serum chemistry panel and CBC were within reference ranges. Bacteriologic culture of urine was not performed.

From the Timberlyne Animal Clinic, 110 Banks Dr, Chapel Hill, NC 27514 (Forward); the Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37901 (Legendre); and the Fountain City Animal Hospital, 3630 N Broadway, Knoxville, TN 37918 (Singh Khalsa). Address correspondence to Dr. Forward.

At this time, amphotericin B was considered as an antifungal treatment but was deemed unsuitable because of the potential for renal toxicity in this geriatric dog. Direct infusion or irrigation of the bladder with an antifungal agent was considered as a potential treatment for the candiduria. Clotrimazole was chosen because of its cost and availability as a sterile solution.

The bladder was infused with clotrimazole[k] (1% topical solution) via ultrasonographically guided cystocentesis every other day for 3 treatments and in 1 final treatment 2 weeks after the first infusion. Cystocentesis was chosen as the route of administration of the clotrimazole, because the owner requested that bladder catheterization not be performed.

For administration of the drug, urine volume in the bladder was estimated, and approximately the same volume of clotrimazole was infused; ≤ 30 ml of clotrimazole was infused during any single treatment. The clotrimazole was infused slowly through a 22-guage 1.5-in needle attached to a 2-way stopcock and catheter extension tube. The risk of bladder perforation and extraluminal infusion was minimized by vigilant ultrasonographic monitoring throughout the infusion. If bladder volume was > 30 ml before infusion, urine was removed until approximately 30 ml remained. The dog was monitored closely for 1 hour after treatment and usually retained the solution in the bladder for at least 5 minutes before urinating.

After the second treatment, the owner noticed a substantial improvement in the dog's overall attitude. The mucoid discharge associated with urination resolved, and polyuria decreased. No yeast were seen in the urine sediment prior to the third infusion. Urinalysis prior to the final infusion revealed a substantial number of β-hemolytic *Streptococcus* organisms that were susceptible to enrofloxacin. No yeast were cultured at that time. The dog was treated with enrofloxacin (5 mg/kg, PO, q 12 h) for 3 weeks and administration of methenamine mandelate was again performed (10 mg/kg, PO, q 8 h). No yeast organisms were seen in the urine sediment 4, 8, and 12 weeks after the final infusion treatment. A fungal culture of urine 12 weeks after the final infusion revealed no growth. Bacteria were detected in the urine sediment 8 weeks after the final infusion, and the dog was treated with orbifloxacin[l] (5 mg/kg, PO, q 24 h) for 3 weeks. An aerobic bacterial culture performed 12 weeks after infusion treatment revealed *Escherichia coli* and *Enterococcus* sp, the latter of which was resistant to ciprofloxacin, levofloxacin, and tetracycline.[2] The dog was treated with clavulanic acid-amoxicillin[m] (13.75 mg/kg [6.25 mg/lb], PO, q 12 h) for 2 weeks.

Urinary tract infections with *Candida* spp are uncommon in dogs but when detected are often associated with a predisposing factor such as diabetes mellitus, prolonged antimicrobial or glucocorticoid administration, aciduria (pH of 5.4 to 6.1), an indwelling urinary catheter, or systemic immunosuppression.[2-5] In the dog reported here, predisposing factors included diabetes mellitus, aciduria, and incomplete voiding attributed to lumbar intervertebral disc disease. In human medicine there is much controversy regarding the importance of candiduria, but patients are usually treated if the infection is persistent because of concern of systemic dissemination or that candiduria represents a systemic infection with secondary renal involvement.[2,4,6] There are no studies in animals that evaluate the extent of infection represented by candiduria or determine the best modality of treatment.

On the basis of recommendations for humans, orally administered antifungal agents are the treatment of choice in dogs and cats. Specifically, fluconazole is preferred because it can be given orally and is the only azole compound that is mainly eliminated through the kidneys; approximately 70% of the dose is excreted unchanged in the urine.[6-8] In human medicine, oral administration of fluconazole for candiduria has been associated with a mean eradication rate of 85% when used for 2 to 8 weeks.[8] In the dog reported here, fluconazole may not have been effective in eliminating the *C albicans* because of drug resistance or because duration of treatment may have been insufficient.

Flucytosine is also primarily eliminated by the kidneys and has been associated with a success rate of approximately 70% in human medicine to eradicate candiduria. However, the limitation of flucytosine is that as many as 25% of strains of *C albicans* are resistant, and it is potentially toxic to rapidly proliferating tissues such as bone marrow.[8] In the dog reported here, *C albicans* was susceptible to flucytosine, but development of drug resistance may have occurred, resulting in recurrence of the infection.

When oral administration of fluconazole and other antifungal agents is ineffective in eliminating candiduria, as in this dog, or when the patient cannot tolerate orally administered antifungal agents, there is no recommended alternative treatment for animals. In human medicine, bladder irrigation with an azole compound or amphotericin B has been used for the past 2 decades to treat candiduria either independently or in conjunction with oral administration of antifungal agents.[3,7] The bladder irrigation technique in humans usually involves use of an indwelling suprapubic bladder catheter for 2 to 14 days. The antifungal agent is infused either continuously or intermittently.[6,7,9] When intermittent treatment is done, the antifungal agent is placed directly into the bladder via the urinary catheter, and the catheter is clamped, or the patient is asked to withhold urination for a period of time in order to retain the solution in the bladder.[6] Neither the continuous infusion method nor a long-term indwelling urinary catheter was deemed suitable for this dog; therefore, clotrimazole was placed directly into the bladder via cystocentesis. Despite the fact that the dog urinated soon after each infusion treatment, candiduria was successfully eliminated with this method of treatment. The incomplete voiding noticed in this dog may have aided in treatment. Intermittent bladder infusion with an antifungal agent may, therefore, offer a viable alternative or conjunctive treatment to oral administration of antifungal drugs for the treatment of candiduria.

[a]Prescription diet w/d, Hill's Pet Nutrition Inc, Topeka, Kan.
[b]Mandelamine, Warner Chilcott Lab, Rockaway, NJ.

[c]Soloxine, Daniels, St Louis, Mo.
[d]Humulin L, Eli Lilly Co, Indianapolis, Ind.
[e]Fluconazole, Pfizer Inc, New York, NY.
[f]Lamisil, Novartis, Summit, NJ .
[g]Baytril, Bayer Corp, Shawnee Mission, Kan.
[h]Sporanox, Ortho Biotech, Raritan, NJ.
[i]Fungus Testing Laboratory, Department of Pathology, University of Texas Health Science Center, San Antonio, Tex.
[j]Flucytosine, ICN Pharmaceuticals, Costa Mesa, Calif.
[k]Clotrimazole 1% topical solution, Schering Corp, Kenilworth, NJ.
[l]Orbax, Schering-Plough Corp, Union NJ.
[m]Clavamox, Pfizer Animal Health Group, Exton, Pa.

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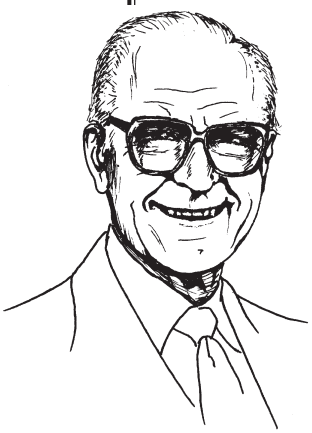
From My Armchair: W. W. Armistead



Best Friends

Mankind's best friend is also its oldest. Dogs were domesticated about 12,000 years ago—at least 2,000 years before other animal species.

Early humans valued dogs for their help in hunting and herding. But, because of their remarkable capacity for expressing love, loyalty, and heroism, dogs also became valuable as companions and guardians. In many homes today, dogs have been elevated to the status of family members, qualifying them for the kind of consideration and care accorded to human children.

Mark Twain said, "If you pick up a starving dog and make him prosperous, he will not bite you. This is the principal difference between a dog and a man." The decision to live with and serve mankind was made by the dog eons ago. In return, man through the ages has treated his friend the dog on the whole better than he has treated his fellow man.

W. W. Armistead