

Session 4:

Recurrent and Resistant Urinary Tract Infections in Dogs

Glossary

MIC (Minimum Inhibitory Concentration): The lowest concentration of antimicrobial that will inhibit growth of a particular microorganism *in vitro*

Breakpoints: The cut-off points based on the MIC used to define a microorganism as susceptible, intermediate, or resistant to a particular antimicrobial drug

Uncomplicated UTI:¹

- Only 1-2 UTIs/year or less
- No immunosuppression
- No underlying anatomic, functional, or medical condition that will predispose the animal to a UTI
- No history or antibiotic use in the past 1-2 months

Complicated UTI:¹

- Immunosuppressed due to illness or medical therapy (i.e. Hyperadrenocorticism or use of cyclosporine or steroids)
- Mucosal damage due to urolithiasis or neoplasia
- Inability to fully empty bladder
- Alterations in urine volume or concentration
- Concurrent disease that may predispose to UTIs (i.e. Diabetes mellitus, neoplasia)
- Anatomic defects of the bladder or urethra

Recurrent UTIs: Repeated UTI which occurs after therapy has been discontinued. Can be relapsing or reinfection.

- Relapsing: UTI recurrence by the same organism. Implies that it was not fully eliminated during treatment. Cause may be related to tissue penetration, duration of therapy, or antimicrobial choice, or the underlying functional or anatomic defects which allowed the bacteria to “hide out”. These may be more difficult to eradicate than reinfections.
- Reinfection: UTI recurrence caused by a different organism of either the same or different genus or species. Implies a defect in the host’s defense mechanisms or anatomic/functional defect. These may occur weeks or months after the previous infection and are usually eliminated with appropriate/standard therapy.

Asymptomatic Bacteriuria: The presence of bacteria in the urine (usually via a positive culture) without clinical signs of infection (straining, pollakiuria, dysuria, etc.).²

Introduction

Recurrent and resistant urinary tract infections (UTIs) are among some of the most frustrating challenges veterinarians tackle in small animal practice. Clients are often distressed at the apparent discomfort and potential house-soiling which occur with UTIs and become frustrated by the need for repeated clinic visits and rounds of antibiotics in the face of perceived treatment failure. It is important for clinicians to recognize recurrent and resistant UTIs and to have a methodical treatment plan and approach to the identification of underlying causes.

Is there a UTI present?

Animals with lower urinary tract signs may have other reasons such as urolithiasis, neoplasia, or feline idiopathic cystitis (FIC) present which can cause signs similar to those of a UTI but with sterile urine. If a dog or cat presents with clinical signs of a UTI, it is important to consider the likelihood of one of these conditions, especially in cats < 10 years of age with Feline Idiopathic Cystitis (FIC). Few of these cats (< 1% in one report) actually have a UTI. This is an important consideration in the rational use of antibiotics and drug stewardship.

Asymptomatic bacteriuria (ASB), has become a controversial topic in recent years. In human medicine, bacteriuria, even with pyuria, is not treated unless there are clinical signs of infection like pain, straining, and dysuria, pregnancy, or impending urologic surgery. Previous recommendations were to periodically culture the urine of dogs and cats with conditions such as diabetes mellitus, hyperadrenocorticism, and those receiving immunosuppressive medications. Current recommendations based on the 2011 ISCAD report are to not culture or treat these patients urine unless there are clinical signs. There is still controversy around the presence of pyuria constituting a clinical sign of active infection. New ISCAD guidelines are due to be released in the Fall of 2018 and may clarify this area further.^{3,4}

A note of caution: The pad on the urine test strip that detects leukocyte esterase is not reliable in dogs and cats. It yields frequent false positives and false negatives. It is important instead to examine a urine sediment to evaluate the presence of WBCs.

Clinical Presentation

Predisposing Factors: There are a number of conditions which will predispose dogs and cats to developing resistant, relapsing, or recurrent UTIs. It is important to search for and identify these patients in order to facilitate successful elimination of the infection as well as to prevent future UTIs if possible.

Medical Therapy: Treatment with drugs such as corticosteroids, cyclosporine, azathioprine, and anti-neoplastic drugs may predispose patients to UTIs which are often asymptomatic or have few WBCs seen in the urinalysis due to immunosuppression. The presence of dilute urine with corticosteroid treatment also impairs the host defense mechanism of high urine osmolality which normally prevents bacterial colonization of the lower urinary tract.

Anatomic and Functional Defects: Urinary incontinence whether from sphincter mechanism incompetence or ectopic ureters leads to changes in the normal cutaneous flora of the perineal skin and wicking of bacteria into the lower urinary tract. Recessed or “hooded” vulva conformation may also lead to increased abnormal flora in close proximity to the external urethral orifice. Mechanical obstruction by uroliths, neoplasia, polypoid cystitis or functional abnormalities which prevent the complete emptying of the bladder will significantly increase the risk of UTI. Urachal diverticulae have been found to contain “micro-abscesses” which, even if the diverticula are small, can lead to relapse of UTI and difficulty in completely eliminating the organism.

Underlying Disease: Hyperadrenocorticism, diabetes mellitus, neoplasia, renal disease, prostatic disease, and stump pyometra should all be considered.

Organisms:

The most common uropathogenic bacteria identified in the dog are *E. coli*, *Enterococcus*, *Staphylococcus aureus/pseudintermedius*, *Proteus*, *Klebsiella*, and *Enterobacter*.

The most common uropathogenic bacteria identified in the cat are *E. coli*, *Enterococcus*, *Streptococcus*, Coag-neg *Staphylococcus aureus/pseudintermedius*, *Proteus*, *Pasteurella*, and Beta *Streptococcus*.

See chart at end of notes. There has been a concern about recent increases in resistance among many uropathogenic bacteria to fluoroquinolones. For this reason we do not advise using a fluoroquinolone as the first line drug in dogs and cats with uncomplicated UTIs.

Corynebacterium urealyticum has also recently become a concern as a uropathogen in dogs and cats. This organism is urease splitting which leads to increased urine pH and “encrusting” of the bladder mucosa with struvite and calcium phosphate crystals which make its elimination challenging. The organism is slow growing so it may not be identified until after 5 days (longer than other bacteria and thus may be missed). It is resistant to amoxicillin, cephalosporins, and potentiated sulfas; treat with tetracycline or chloramphenicol. In some patients surgical debridement of the crystalline plaques may improve outcomes and chance for cure.

Therapeutic Plan:

- Be sure an infection is present
- Perform urine culture via cystocentesis to verify infection and to determine the type of bacteria and sensitivity profile
- Treat with appropriate antibiotic at adequate dose for 10-14 days if reinfection and at least 3-4 weeks if recurrence (do not rely on resolution of clinical signs to determine length of therapy)
- Re-culture urine at 3-5 days after start of antibiotic therapy. If it is not sterile, there is a need to reassess antibiotic choice/dose/compliance.
- Re-culture urine 7-10 days after completion of treatment. If not sterile, consider relapsing infection.
- Evaluate the animal at any time during this process for underlying conditions which may predispose to UTI such as anatomic defects, uroliths, urogenital neoplasia, immunosuppressive disease or therapy, incomplete emptying of

bladder, and metabolic diseases such as hyperadrenocorticism or diabetes mellitus.

If an infection is truly resistant: It is important to remember that the determination of resistance is based on MICs based on *serum* concentrations of antimicrobials, not urine concentrations. Many commonly used antimicrobials such as fluoroquinolones, are excreted in active forms in the urine and achieve much higher concentrations in both renal tissue and the urine than in the serum as long as the animal can concentrate its urine to some degree. It is possible that an organism with intermediate or resistant susceptibility at serum concentrations of drug is susceptible to urine concentrations.

Drugs that may be useful in treating resistant organisms include fluoroquinolones, 3rd generation cephalosporins, chloramphenicol, non-doxycycline tetracyclines, and nitrofurantoin (esp. for *Enterococci*). See the chart at the end of the text for a list of organisms and antibiotics that may be useful in resistant infections.

Strategies for Prevention

Some patients have predisposing conditions or anatomic defects that either the owner is unwilling to correct or are not able to be corrected. Sometimes no underlying predisposing factors are identified after an appropriate search. These dogs and cats may be at a higher risk of developing UTIs and with repeated antibiotic treatment may develop resistant UTIs. It is important to prevent the infections if possible. Prophylactic therapy is controversial since there is risk of development of resistance. For this reason, it is important to demonstrate that the urine is sterile *prior* to beginning prophylactic therapy. The doses used in prophylaxis are not designed to treat an active infection. The medications are given once daily at bedtime after the last urination in order to increase exposure time in the bladder overnight. This is the protocol I use. Pulse dose therapy has also been advocated for prophylaxis, however, there are no studies comparing the two regimens.³

Gram-negative organisms: Nitrofurantoin (my preference), TMS or cephalexin may be used.

Gram-positive organisms: TMS or amoxicillin/clavulanate.

Culture urine every 4-8 weeks to verify that urine is sterile on the prophylaxis. Often the prophylaxis can be stopped after 6 months of sterile urine, but some patients may need medication for life.

Alternative Therapies

The Type A Proanthocyanidins found in cranberry extract have the ability to prevent the adherence of bacterial fimbriae to uroepithelial cells in vitro. Unfortunately, in clinical trials in both humans and dogs there was no difference in recurrence of UTI between patients taking the cranberry extract vs. placebo.^{5,6} Further work needs to be done to determine if higher doses or alternative methods of delivery will improve efficacy.

D-Mannose has been used to prevent bacterial biofilms and reduce bacterial adherence to urothelium by interfering with the FimH portion of the fimbriae. In vitro studies have been

promising. The primary obstacle appears to be bioavailability and tissue delivery of an oral formulation of the product.⁵

There is little evidence that probiotics have an effect on the recurrence of UTIs in dogs and cats.⁵

Common uropathogens of the dog and cat and antibiotic effectiveness patterns (Josh Daniels DVM PhD, personal communication)

	Sulf-onamides	Quinolones	Amino-glycosides	Cephalo-sporines	Amoxi/Clavulanate	Tetra-cyclines (incl. Doxy)	Nitro-furantoin
Hemolytic <i>E. coli</i>	+	+	+	+/-*3 rd gen	+	+	+
<i>Enterococcus</i>	-	+/-	-	-	+		+
Non-hemolytic <i>E. coli</i>	+	+*	+	+/-*3 rd gen	+	-	+
Coag – <i>Staph.</i>	+/-	+/-	+/-	+/-	+/-	+/-	
<i>Staph. aureus/ Pseudintermedius**</i>	+	+	+	+	+	+	+
<i>Proteus</i>	+	+*	+	+	+	-	-
<i>Klebsiella</i>	+	+	+	+	+/-	-	+
<i>Pseudomonas aeruginosa</i>	-	+ at urine conc.*	+	-	-	-	-
<i>Pasteurella multocida</i>		+				+	
Beta- <i>Streptococcus</i>	+	-	-	+	+(amoxi)	+	
<i>Enterobacter</i>	+	+	+	-	-	-	+

**Currently the dominant susceptibility phenotype seen is only sensitive to aminoglycosides, doxycycline, and chloramphenicol. This is the classic MRSP.

References

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