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DIAGNOSIS AND TREATMENT OF ROUTINE AND DIFFICULT URINARY INFECTIONS IN DOGS

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Urinary tract infection (UTI) exists when bacteria have colonized portions of the urinary tract that are normally sterile (kidney, ureter, bladder, and proximal urethra). Urinary tract infections (UTI) result from abrogation of one or more natural defense mechanisms that allow ascent of bacteria from the perineum to the urethra and then to the bladder. In some instances, bacteria will continue to ascend the ureters and enter the kidneys to cause pyelonephritis. Bacteria causing UTI often ascend following contamination with the dog's own fecal flora or from ascent of organisms from the skin. Enteric bacteria, such as the coliforms (*E. coli*, *Klebsiella* spp., *Enterobacter* spp., and *Serratia* spp.) and Enterococci are normal inhabitants of the lower digestive tract and are present in feces in relatively high numbers – usually $>1 \times 10^5$ cfu/gram. Organisms associated with dermatoses and perivulvar inflammation, (e.g., coagulase positive Staphylococci and *Pseudomonas aeruginosa*) are less frequently isolated from UTIs than organisms of fecal origin. UTI rarely results from the hematogenous spread of organisms to the urinary tract. *E. coli* is the most commonly isolated organism as the cause for UTI in both dogs and cats. *E. coli*, *Staphylococcus* spp, and *Proteus* spp. account for most cases of UTI in primary care practices. *Enterococcus* spp. has been isolated in dogs and cats with UTI with increasing frequency at referral centers and is associated with limited treatment options at times due to resistance patterns of this organism.

Defense mechanisms consist of anatomic, metabolic, and functional factors as well as intrinsic properties of normal urine. Normal urine is hostile to growth of bacteria when urine is maximally concentrated. Highly acid urine is inhibitory or toxic to growth of certain bacteria. A healthy urothelium contributes to sterile urine by its ability to kill bacteria when in close apposition to the organisms (local activity of complement and IgA); urethral epithelium can physically trap organisms and then desquamate as another control factor. Compromised urinary anatomy that contributes to the development or persistence of UTI includes poor vulvar conformation (hooding), the presence of an urachal diverticulum, ectopic ureters, urethral stricture, bladder or urethral neoplasia as well as urinary calculi. Infections of the uterus or prostate often contaminate the urinary tract and cause UTI. Metabolic abnormalities that favor the development and persistence of UTI include conditions associated with immunosuppression such as diabetes mellitus, Cushing's disease, some forms of cancer unrelated to the urinary tract, and exogenous administration of glucocorticosteroids. Functional factors favoring UTI include the inability to completely evacuate the urinary bladder

during voiding as well as primary sphincter mechanism incompetence (with or without obvious incontinence) that is associated with low urethral pressure allowing bacteria to more readily ascend. Abnormal urine favoring development of UTI includes sub-maximally concentrated urine from any cause, but especially that encountered in chronic kidney disease, hypoadrenocorticism, and hyperthyroidism. In addition, dogs that are recumbent due to illness or injury are at increased risk for UTI because of decreased hygiene, increased peri-genital moisture, and decreased frequency of walks that promote complete emptying of the bladder. Animals with indwelling urinary catheters frequently acquire UTI since the catheter bypasses many host defense mechanisms against ascent of bacteria.

SPECIES DIFFERENCES

UTI affects dogs far more commonly than cats. This is likely due to the exquisite defense mechanisms for the urinary tract operative in healthy cats. One factor thought to provide this enhanced protection against development of UTI compared to dogs is the higher average urinary concentration (osmolality) in cats with healthy kidneys. UTI is much more commonly encountered in cats that have chronic kidney disease, presumably in association with sub-maximally concentrated urine. UTI is encountered in over 50 % of cats 10 years of age or older that present for signs of lower urinary tract urgency – many of these cats have associated chronic kidney disease. An increased frequency of UTI is expected from cats that have undergone urethral catheterization or that have had perineal urethrostomy performed.

DIAGNOSIS

Urinary tract infections are definitively diagnosed following isolation of bacteria using quantitative culture of urine and reported as colony-forming-units/ml (cfu/ml). We discourage any use of qualitative culture methods that do not report cfu/ml since the number of organisms that are isolated are factored into the decision making as the likelihood that a true UTI exists (see Table 1). The vast majority of UTI are associated with one organism. Isolation of multiple types of organisms suggests the possibility for contamination of the urine sample during collection. The organisms that cause urinary tract infections are almost always facultative or aerobic, therefore anaerobic culture is usually not indicated. However, if there is radiographic evidence of gas in the bladder (emphysematous cystitis), there is a possibility for an anaerobic organism to be involved in the infection; nonetheless, a gas-producing facultative Gram negative organism is much more likely.

Urine may be obtained from dogs and cats using one of three techniques. 1) antepubic cystocentesis, 2) Urethral catheterization, and 3) midstream free catch. Because the bladder should be a sterile site, interpretation of culture results from cystocentesis-acquired urine is the most straightforward as no growth should be identified, though low-magnitude contamination with organisms from the skin is possible (< 1,000 cfu/ml). Rarely, cystocentesis-acquired urine can be contaminated if the needle pierces the dorsal wall of the bladder and enters the colon – large growth of 3 or more organisms is often encountered in these instances. If urine is

acquired via catheterization or midstream free catch, contamination with normal flora from the distal urethra or genital tract is likely that will be isolated during urine culture even of healthy animals. Large quantitative bacterial growth often occurs from voided urine samples collected from healthy female dogs. Consequently, we do not recommend culture of voided urine specimens in dogs because the degree of bacterial contamination can be large and it becomes impossible to know where the organisms arose. Table 1 contains the quantitative interpretive guidelines for bacterial growth from urine samples acquired from dogs and cats. It is never appropriate to culture the tip of an indwelling urinary catheter upon its removal since the tip will likely become contaminated with native flora as the catheter is pulled distally.

SAMPLE HANDLING AND TRANSPORT

In order for quantitative culture results to most accurately reflect the bacteriologic status of a patient's bladder, urine should ideally be cultured as soon as possible following collection. Bacteria continue to divide in urine at room temperature, thus in some instances, a questionably significant number of bacteria could continue to divide, becoming quantitatively significant if urine is kept at room temperature for several hours, leading to a false positive result. It is therefore recommended that urine be plated to culture media within 30 minutes of collection or stored at 4°C until plated. If sending urine to an outside laboratory, use cold packs to keep samples cool. Most bacteria that cause UTIs are nonfastidious and survive several days in refrigerated urine. Quantitative cultures plated more than 6 hours after refrigeration result in less quantitative growth but enough growth is still apparent to make the diagnosis; storage under refrigeration for 24 hours result in substantial decline of bacterial growth (cfu/ml). In true infections, there are sufficiently high numbers of bacteria to permit some cell death during transport while providing diagnostic results.

IN -CLINIC CULTURE

While not all clinics are staffed or equipped appropriately to act as full service microbiology laboratories, it should still be possible to culture urine in some clinical situations. In-house culture as surveillance for occult UTI in Cushing's disease, diabetes mellitus, or CRF (especially cats) may be particularly useful as there is no urgency for culture results. Positive culture plates may be forwarded to external laboratories for organism identification and antimicrobial susceptibility testing.

An in-house culture setup would include some basic supplies (quantitative loops, culture media) and an incubator. A very convenient approach is to use a dipped-paddle culture system, such as the Urocult™. This system is completely self-contained (other than the incubator) and provides quantitative information. In-house urine culture may represent a new revenue "stream" if urine has routinely been sent to outside labs for detection of UTI.

SEVEN CONSIDERATIONS WHEN SELECTING ANTIMICROBIAL THERAPEUTIC AGENTS

Antimicrobial therapy is the mainstay of treatment for UTI. Considerations when selecting an antimicrobial drug are listed below.

1. Relevant spectrum of antimicrobial activity
 - a. Susceptibility data, when available
2. Concentration of drug in urine
3. Route of administration
4. Frequency of administration
5. Any apriori knowledge of likelihood of adverse reactions
 - a. Patient history
 - b. Breed predisposition
 - c. Polypharmacy
6. Availability and cost of drug
7. In addition to the individual patient parameters involved with antimicrobial selection, it is laudable to be mindful of the status of antimicrobial in terms of their importance in population health (i.e. emergence and dissemination of resistant pathogens). Ideally your practice has categorized its antimicrobial formulary into three groups, as recommended by the ACVIM 2005 consensus statement on antimicrobial use.

EMPIRICAL THERAPY

A patient with lower urinary tract signs and a likely UTI can be in considerable discomfort, therefore antibacterial treatment should not be withheld pending susceptibility results. Findings from urinalysis can suggest the likelihood of a true UTI. Pain relief with drugs such as buprenorphine and tramadol can be considered when the diagnosis of UTI is questionable while awaiting results of urine culture. When sediment examination is performed, the finding of excess WBC in combination with bacterial organisms highly suggests that a true UTI exists. When the bacteria are identified as rod-shaped organisms, it is reasonable to choose some antimicrobial agent with Gram-negative coverage. If sediment examination reveals cocci, then it is likely that the infection is due to a Gram-positive organism – notably *Enterococcus* spp. In that case, the animal should be put on amoxicillin or amoxicillin/clavulanate. If there are cocci present, and the urinalysis reveals alkaline pH, then it is likely that the infection is due to a *Staphylococcus* spp. (due to urease production). If *Staphylococcus* spp. is suspected, it is more prudent to use amoxicillin/clavulanate due to the common production of beta-lactamase by Staphylococci. Empirical therapy should not be prescribed for patients with chronic and/or repetitive UTI with history of extensive antimicrobial use. Young cats with urinary urgency have bacterial UTI very infrequently – so treatment with pain relieving drugs as noted above can be given while awaiting return of urine culture results.

INTERPRETATION OF ANTIMICROBIAL SUSCEPTIBILITY REPORTS AND SELECTION OF AGENTS

The drugs chosen for susceptibility testing by individual laboratories is variable, and the methodology used, Kirby-Bauer disc or broth microdilution, is also subject to laboratory preference. The methods of susceptibility utilized by a specific laboratory have direct implications on how laboratory results are reported. If Kirby-Bauer is used, then a simple interpretation of “S” (sensitive), “I” (Intermediate), or “R” (Resistant) is given. If broth microdilution is used, then an interpretive value “S/I/R” is given plus they may additionally report a minimum inhibitory concentration value for each drug. The interpretive values of both methods agree with each other $\geq 96\%$ of the time for a given bacterial isolate, if appropriate performance guidelines and interpretive criteria are followed by laboratories.

SELECTED READING

Ambrose et al in Antibiotics in laboratory medicine 5th ed. Edited by Victor Lorian. Philadelphia, PA : Lippincott Williams & Wilkins, c2005 pp. 1-144

Barsanti, JA in Infectious diseases of the dog and cat 3rd ed. edited by Craig E. Greene. Philadelphia, Pa. ; London : Elsevier Saunders, c2006 pp. 935-961

Table 1

Culture Method	Contamination (cfu/ml)	Infection (cfu/ml)
Midstream voided	$<10^5$	$>10^5$ in cats; cannot distinguish in dogs
Catheterized	$<10^3$ in male dogs and all cats; any number in female dogs	$>10^4$ in male dogs $>10^3$ in cats Any number in animals with indwelling catheters
Cystocentesis	$<10^3$ (be skeptical)	$>10^3$

Table adapted from Greene *et al.* Infectious Diseases of the Dog and Cat, 2006. p. 946