EVERYBODY HURTS SOME TIME: URINARY TRACT INFECTIONS
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INTRODUCTION

• Urinary tract infection refers to colonization of one or more parts of the urinary tract with an infectious agent.
• Urinary tract infection (UTI) can induce urethritis, prostatitis (in intact male dogs), cystitis, and pyelonephritis and all of the urinary tract is at risk of colonization once UTI is established.
• Most UTI is caused by bacteria emanating from the gastrointestinal tract crossing the perineum and colonizing the external genitalia prior to retrograde invasion of the urethra and bladder against the flow of urine.
• A lesser number of lower UTI’s go on to further ascend with colonization of the ureters and kidneys.
• Hematogenous renal infection, e.g., from bacterial endocarditis, can induce septic infarcts and pyelonephritis although this is relatively uncommon.
• In addition to bacteria, UTI may occur due to infections with fungal, viral, or parasites

ETIOPATHOGENESIS

• Urinary tract is in contact with external environment and bacteria normally reside in the distal urogenital tract
  • Development of UTI depends upon the balance between infectious agents and host resistance.
  • Although UTI can occur when a very virulent organism invades a normal urinary tract, many times UTI develops when there is a disturbance of anatomical or functional host resistance factors that normally prevent microbial invasion.
• Urinary tract has many defense mechanisms to prevent bacterial urinary tract infection
  • Anatomically
    • Length of urethra
    • Presence of high pressure zones in urethra
    • Urethral and ureteral peristalsis
    • Vesicoureteral flaps
    • Extensive renal blood supply and flow
  • Mucosal defense barriers
    • Glycosaminoglycan layer
    • Antibody production
    • Intrinsic mucosal antimicrobial properties
    • Exfoliation of cells
    • Commensal non-pathogenic microbes in distal urogenital tract
  • Composition of urine
    • Concentration/osmolality
    • High urea nitrogen concentration
    • Organic salts
    • Low molecular weight carbohydrates
    • Tamm-Horsfall mucoprotein
    • Cell-mediated and humoral-mediated immunity
    • Frequent and complete voiding
• A UTI also requires a pathogenic bacterial organism
  • Not all bacteria are pathogenic
  • For UTI, bacteria must possess 1 or more urovirulence factors for motility, adherence, invasion, production of enzymes, and production of toxins
• Uropathogenic bacteria invade primarily from ascension from the lower urogenital tract
PHYSICAL EXAMINATION FINDINGS AND CLINICAL SIGNS

- May be symptomatic or asymptomatic
- Bacterial infection of the lower urinary tract is often associated with signs similar to other lower urinary tract diseases including hematuria, pollakiuria, dysuria, stranguria, and inappropriate urination
- Bacterial of the upper urinary tract may be associated with hematuria
  - If sepsis develops, systemic illness may occur
  - May be associated with recurrent lower urinary tract infection and clinical signs
- Bacterial urinary tract infections occur in 2-3% of dogs and in female dogs more often than male dogs
  - It is more common in older dogs
- **Bacterial urinary tract infections occur in <1% of cats**
  - It is uncommon in cats <10 years of age
  - It occurs in >40% of cats >10 years of age

**DIAGNOSIS**

- Urinalysis and urine culture
  - **IT’S GOLD FOR A REASON !**
    - Urine should be collected by cystocentesis
      - Urine in the bladder is normally sterile or contains very low numbers of bacteria
      - The more distal in the urogenital tract, the larger the numbers of bacteria
      - Even if a single organism is cultured from a voided sample, it does not mean that a UTI is present or that is the offending organism
    - Always examine urine sediment
      - Pyuria (>5 WBC/hpf) is often present, unless animals are immunosuppressed
      - Identification of bacteria is helpful, but not accurate
        - Staining urine sediment improves predictive value
        - | Unstained | Stained |
          |-----------|---------|
          | Sensitivity | 82 % | 93 % |
          | Specificity  | 76 % | 99 % |
          | Positive Predictive Value | 40 % | 95 % |
          | Negative Predictive Value  | 96 % | 99 % |
    - Urine specific gravity should be normal; however, dilute urine may be a risk factor for development of bacterial urinary tract infection or may indicate infection of the upper urinary tract
    - Urine sediment examination may reveal struvite crystalluria associated with UTI
      - Struvite crystalluria, however, can be normal
      - We will discuss further with urolithiasis
    - Cylindruria may be present with upper urinary tract UTI
      - Cellular casts are always abnormal
    - **Urine culture** is most definitive means of diagnosing a bacterial urinary tract infection
      - Urine should be collected by cystocentesis and transported in a sealed container and processed as soon as possible
        - If processing is delayed, refrigerate the sample
      - Point-of-care bacteriological testing. Several in-house of point-of-care bacteriological testing is available.
        - In-house culture plates. Blood agar and MacConkey's agar plates may be inoculated and incubated for 24-48 hours. A calibrated bacteriologic loop or a microliter mechanical pipette that delivers exactly 0.01 or 0.001 mL of urine to the culture plates should be used to estimate cfu/mL, and urine should be streaked over the plates by conventional methods. Blood agar supports the growth of most aerobic bacterial uropathogens, and MacConkey's agar provides morphologic information that aids in the identification of
bacteria and prevents “swarming” of *Proteus* spp. Plates are incubated or placed under an incandescent light. If bacterial growth is noted within 48 hours, the plates may be submitted for identification and determination of antimicrobial sensitivities

- **Flexicult.** An agar plate with one compartment for quantitative analysis using a chromogenic substrate allowing for bacterial identification and 5 antibiotic impregnated compartments: ampicillin, amoxicillin plus clavulanate, cephalothin, enrofloxacin, and trimethoprim-sulfamethoxazole. Accurately excludes urinary tract infection but less reliable for diagnosing infection, especially with Gram-positive cocci. Most of the antimicrobial susceptibilities had only fair concordance with standard microbiological culture technique

- **EZ-PZ.** A rapid catalase based urine-screening test. Screens for bacteriuria, hematuria, pyuria and the presence of other somatic cells. A positive result indicates that urine requires further diagnostic evaluation

- **Indicator RX.** This is a 24 hour test that detects the presence of bacteria in canine or feline urine samples. Identifies bacteria as one of the primary gram-negative uropathogens (i.e., *Escherichia coli*, *Klebsiella*, *Enterobacter spp.*, and *Proteus spp.* that are responsible for feline and canine urinary tract infections (UTI). Predicts the antibiotic resistance pattern for the UTI-related gram-negative bacteria found in canine and feline urine samples. Device is composed of 5 test wells, labeled “BAC” (bacteria), “GM(-)” (Gram negative), “FQ” (fluoroquinolone), “AMO” (amoxicillin), “CEP” (cephalosporins – first generation) and 2 control wells labeled “POS” (positive) and “NEG” (negative)

- **Uricult Vet.** A UTI screening by providing a semi-quantitative colony count along with a presumptive identification of many common uropathogens. Product consists of a two sided paddle containing selective and non-selective media that fits securely into a screw cap plastic vial to maintain sterility. One side contains C.L.E.D. agar that changes color in the presence of various organisms including *E. coli*, *Proteus*, *Pseudomonas*, *Enterobacter*, and others. The opposite side contains EMB (Eosin Methylene Blue) agar, a selective medium that will support the growth of most Gram negative organisms while providing additional information regarding the suspected pathogen

- **Antimicrobial susceptibility testing**
  - **Kirby-Bauer agar diffusion test**
    - After an organism is isolated and identified, it is transferred to an agar plate
    - Antimicrobial discs are placed on the plate
    - Zone of inhibition around the antimicrobial discs are measured to determine susceptibility of the bacterium
    - This is an inexpensive and readily available technique
    - However, concentration of antimicrobial on most discs are not similar to concentration of antimicrobial achieved in urine
  - **Minimum inhibitory concentration**
    - More sensitive and specific than Kirby-Bauer method
    - More expensive and more time consuming technique and not widely available
    - Lowest concentration required to inhibit bacterial growth
    - Performed using a series of dilutions of each antimicrobial in a multi-well plate to which a standard number of bacteria are added
    - When using MIC, choose an antimicrobial agent that achieves a urine concentration at least 4 times the MIC
      - There are published tables of urinary concentration of antimicrobials in dogs and cats; however, data are unavailable for many antimicrobials that we use
    - Kirby-Bauer technique is acceptable for most bacterial urinary tract infections
Dosage and mean urinary concentration of the drugs commonly used to treat UTI

<table>
<thead>
<tr>
<th>Mean Urine Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Concentration (±S.D.) µg/ml</th>
<th>MIC µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>25 mg/kg tid</td>
<td>P.O.</td>
<td>309 (±55)</td>
<td>77</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>11 mg/kg tid</td>
<td>P.O.</td>
<td>202 (±93)</td>
<td>50</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>2.5 mg/kg bid</td>
<td>P.O.</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>15 mg/kg tid</td>
<td>P.O.</td>
<td>138 (±65)</td>
<td>35</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>33 mg/kg tid</td>
<td>P.O.</td>
<td>124 (±40)</td>
<td>31</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>18 mg/kg tid</td>
<td>P.O.</td>
<td>500 (?)</td>
<td>125</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>22 mg/kg tid</td>
<td>P.O.</td>
<td>1466 (±832)</td>
<td>366</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>5 mg/kg tid</td>
<td>P.O.</td>
<td>100 (?)</td>
<td>25</td>
</tr>
<tr>
<td>Trimethoprim-Sulfa</td>
<td>12 mg/kg bid</td>
<td>P.O.</td>
<td>246 (±150)</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>2.2 mg/kg bid</td>
<td></td>
<td>55 (±19)</td>
<td>14</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>6 mg/kg bid</td>
<td>S.Q.</td>
<td>530 (±151)</td>
<td>132</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1.5 mg/kg tid</td>
<td>S.Q.</td>
<td>107 (±33)</td>
<td>27</td>
</tr>
<tr>
<td>Amikacin</td>
<td>5 mg/kg tid</td>
<td>S.Q.</td>
<td>342 (±143)</td>
<td>85</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1 mg/kg tid</td>
<td>S.Q.</td>
<td>145 (±86)</td>
<td>36</td>
</tr>
</tbody>
</table>

Common bacterial isolates
- *Escherichia coli* is most common in dogs and cats accounting for 1/3 to ½ of infections
- Gram positive organisms are second most common cause
  - *Staphylococci* and *streptococci* account for ¼ to 1/3 of infections
- Bacteria accounting for remaining ¼ to 1/3 of infections
- Laboratory evaluation
  - Should be normal unless associated with septicemia, azotemia due to renal failure or dehydration, or predisposing metabolic disease (e.g. hyperadrenocorticism, diabetes mellitus, hyperthyroidism, etc)
- Radiography, ultrasonography, endoscopy
  - Usually normal unless bacterial infection is associated with a predisposing cause
  - Struvite stones may form secondary to a urease-producing bacterial urinary tract infection
  - Renal pelvic and proximal ureteral dilation may be present with pyelonephritis

TREATMENT
- Treatment of bacterial urinary tract infection is dependent on whether the breech in host defenses is temporary or persistent
  - Antimicrobial agents
  - Supportive care, if necessary
  - Correct or control identifiable predisposing cause(s)
- Bacterial urinary tract infections can be classified as simple/uncomplicated, or complicated
Empiric antimicrobial therapy

**First-line Antimicrobial Options**

### Uncomplicated
- Amoxicillin, trimethoprim-sulfonamide

### Complicated
- Guided by culture and susceptibility testing
- Consider amoxicillin or trimethoprim-sulfonamide initially

### Subclinical Bacteriuria
- Treatment not recommended unless high risk for ascending infection; if so, treat as per complicated UTI

### Pyelonephritis
- Start with a fluoroquinolone (Clavamox)
- Reassess based on culture and susceptibility testing

**Simple/uncomplicated bacterial urinary tract infection**
- Bacterial urinary tract infection with no underlying structural, neurologic, or functional abnormality
- Occurs in most dogs
- Usually successfully treated with a 10-14 day course of the proper antimicrobial administered at appropriate dose and frequency
  - Recent study demonstrated effectiveness of a 3-day course of once-a-day, high dose, enrofloxacin
- Clinical signs should resolve and urinalysis results should improve within 2 days

**Complicated bacterial urinary tract infection**
- Bacterial urinary tract infection associated with a structural, neurologic, or functional abnormality
- Reproductively intact dogs, all cats, and animals with predisposing causes for bacterial urinary tract infections (e.g. renal failure, hyperadrenocorticism, diabetes mellitus, etc)
- In addition, animals that have bacterial urinary tract infections that are relapses, reinfections, or superinfections

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Intact male or female dog?  
Predisposing systemic and/or local factor(s)?  
Recent previous UTI’s?  
Cat?  

**YES**  
→ **NO**

**Treat for 4-6 weeks based on C & S**
→ **Treat for 10-14 days based on:**
  - C & S
  - “Best guess”

Redo C & S  
- 5-7 days after start
- Before stop
- 5-10 days after start
• Pyelonephritis and prostatitis are examples of complicated bacterial urinary tract infections
• Complicated infections should be treated for 3-6 weeks
  • Urine should be evaluated in the first week of treatment
  • Towards the end of therapy
  • 5-7 days after discontinuing antimicrobial treatment
• Relapse
  • Recurrence of a bacterial urinary tract infection with the same organism
  • Usually occur within days to weeks of discontinuing antimicrobial treatment
  • Possible causes include
    • Choice of inappropriate antimicrobial agent
    • Antimicrobial agent given at inappropriate dosage, frequency, or duration
    • Complicating factors
  • A urine culture should be evaluated prior to instituting antimicrobial treatment and further diagnostic testing is indicated
• Reinfestation
  • Recurrence of a bacterial urinary tract infection with a different organism than what was initially present
  • Usually occur weeks to months after cessation of antimicrobial treatment
  • Although predisposing factors may be present, many animals that become reinfected do not have identifiable risk factors
  • If reinfections are infrequent (<3 per year), then each episode may be treated as an uncomplicated bacterial urinary tract infection unless a predisposing cause is identified
  • If reinfections occur with greater frequency (>3 per year), then the animal should be considered as having a complicated bacterial urinary tract infection and treated accordingly
    • Diagnostic testing for predisposing cause(s) should be done if not performed previously
    • Prophylactic antimicrobial treatment may be warranted in these animals
• Complicating factors for recurrent UTIs
  • Breaks in host defenses
    • Local defenses
      • Recessed vulva
      • Deep-seated infection: In our experience, 1-2% of bladder wall cultures are positive in dogs with negative urine culture who do not have uroliths
      • Anatomic defects (e.g. ectopic ureter)
      • Indwelling urinary catheter
        • Concomitant antimicrobial administration decreases incidence of UTI
        • However, when UTI develops, it is highly resistant
        • We do not administer antimicrobial agents with an indwelling urinary catheter unless there is another reason
    • Systemic host defenses
      • Associated complicating disease (e.g. diabetes mellitus, hyperadrenocorticism, hyperthyroidism, renal failure)
  • Bacterial factors
    • Multi-drug resistance
    • Unusual organism (e.g. Corynebacterium, methicillin-resistant Staphylococcus)
• Failure of an antimicrobial agent to sterilize the urine should alert the clinician to one or more of the following possibilities:
  • Inappropriate drug, dose or duration of therapy. Owner compliance is important in this respect.
Failure of the antimicrobial agent to reach sufficient concentrations in urine despite appropriate drug administration. Intestinal malabsorption, impaired renal concentrating capacity, and development of antimicrobial resistance should be considered.

The presence of a nidus of infection that is capable of recolonizing the urinary tract once antimicrobial therapy is withdrawn. Pyelonephritis, prostatitis, neoplasia, persistent urachal remnant and urolithiasis should be considered.

The presence of anatomical or functional abnormalities of the urinary tract that lower resistance to bacterial colonization. Many defects may be undetectable by available clinical diagnostic methods.

PREVENTION

- Minimize bacterial contamination of the urinary tract and avoid or minimize conditions that impair host defenses
- Catheterization and endoscopy of the urinary tract always carries a risk of inducing a bacterial urinary tract infection
  - Magnitude of risk increases with degree of pre-existing urinary tract disease, amount of any additional injury caused by the procedure, and duration of the procedure
  - Risks can be decreased by being careful to perform invasive procedures only when necessary, by performing the procedure as atraumatically as possible, and by removing the catheter or endoscope as soon as possible
  - Catheter-induced bacterial urinary tract infection
  - Bacteria migrate along outside of catheter
  - Risk of bacterial urinary tract infection increases with pre-existing urinary tract disease
  - Risk is greater in animals with indwelling urinary catheters than in those that are intermittently catheterized
  - Despite the low risk, one study documented bacterial urinary tract infections in 7 or 35 dogs that were catheterized one time
  - Bacterial urinary tract infection occurs in >50% of animals after 4 days with an indwelling urinary catheter
  - Antibiotic treatment while an indwelling catheter is in place decreases the frequency of bacterial urinary tract infection; however, when infection occurs, the organisms exhibit a greater degree of antimicrobial resistance.
    - Therefore, do not give antimicrobials to animals with indwelling urinary catheters unless indicated for some other reason
    - Catheter-induced bacterial urinary tract infection may be minimized by
      - Using intermittent catheterization when possible
      - Removing indwelling urinary catheters as soon as possible
      - Using a closed collection system
      - Avoiding antimicrobial agent administration while catheters are inserted
- Cats with perineal urethrostomies are at high risk for developing bacterial urinary tract infections

RESISTANT URINARY TRACT INFECTIONS

Resistant E. coli UTI – Several options may exist depending on results of culture and sensitivity:

- Fluoroquinolones: May be effective when used at high
- Aminoglycosides: Are often an effective antimicrobial agent. Amikacin appears to be less associated with nephrotoxicity than gentamycin, but should not be given to animals with azotemia. It can be administered by owners at home
- Potentiated beta-lactams: may be tried if intermediate susceptibility is present. I usually use amoxicillin-clavulanic acid at a higher dosage. Ampicillin-sulbactam may also be used
- Penems: Meropenem may be useful for highly resistant
- 3rd generation cephalosporins: May be useful. Cefpodoxime (Simplicef) does not have as much activity as parenteral forms and may not be effective even with a favorable sensitivity pattern
- Cefovecin: A newer parenteral long-acting cephalosporin has been shown to be effective against E coli in dogs and cats; however, effectiveness with resistant organisms is unknown
Staphylococcus UTI (methicillin resistant) – These appear to be more difficult to treat. With resistance to methicillin, beta lactam antibiotics even potentiated ones will not be effective. Staphylococci are inherently resistant to fluoroquinolones (as are most Gram positive coccii) even with a favorable sensitivity pattern.

- Chloramphenicol: monitor liver enzymes as can be hepatotoxic, GI side effects occur commonly
- Linezolid: An oxazolidinone antibiotic with activity against Gram + organisms. It is often effective against methicillin-resistant Staphylococci, but is
- Vancomycin: Standard for treating methicillin-resistant Staphylococci, it is discouraged from being use because of potential for inducing resistance that may spread to human medicine

Enterococcus - Oftentimes Enterococcus UTI is not associated with clinical signs and there is suggestion that not treating may be better than treating. In some animals without clinical signs or urinalysis changes (pyuria, hematuria), no treatment with re-culture in 2 weeks may reveal eradication of the organism. Treatment should be considered for animals with active clinical infection or that are immunocompromised.

- Penicillins: may be sensitive to amoxicillin/ampicillin especially potentiated ones at higher dosages
- Inherently resistant to cephalosporins, fluoroquinolones, trimethoprim-sulfa, erythromycin even if favorable sensitivity results
- Can combine amikacin with a penicillin
- Penems may be effective for E faecalis, but not E faecium infections
- Linezolid and vancomycin may be effective

ASYMPTOMATIC BACTERURIA (ABUTI)
There is evidence that if a UTI is not associated with clinical signs, that it may be better to not treat. In studies, more than 80% of asymptomatic bacteruria will resolve without treatment. The incidence of ABUTI is 10-15% in older cats and up to 25% in morbidly obese dogs.

PROPHYLACTIC ANTIMICROBIAL TREATMENT
- May be indicated in animals with relapses or frequent reinfections
- Antimicrobial agent should be chosen based on urine culture and susceptibility pattern
- The agent is administered at ½ to ⅓ of daily therapeutic dose and is usually given at night
- Urine should be re-cultured every 4-6 weeks
- If a “break through” infection does not occur during a 6 month period, then antimicrobial treatment can usually be discontinued
- Disadvantages of this approach include development of resistant bacteria and side effects of the antimicrobial agent

Methenamine is an effective preventative in select cases
- It is a cyclic hydrocarbon that is hydrolyzed to formaldehyde at pH < 6.5
- It is often given with acidifiers
- It is effective against many organisms, but may cause systemic acidosis because it has acidifying properties
- It should not be used with renal failure

Nitrofurantoin
- Has activity against many organisms
- Is not used much in veterinary medicine; therefore, susceptibility is high
- Complications include GI upset, hepatopathy, peripheral neuropathy

Estrogens
- May be helpful in female dogs with recurrent vaginocystitis
- May increase epithelial turnover keeping bacterial counts down
- No data
- Dose as with incontinence
- Complications are uncommon
**Urinary acidifiers** do NOT work for prevention of bacterial UTI in dogs and cats

- Bacteria can live in pH values of 4.0 to 9.0
- Dogs and cats cannot achieve urine pH values of < 5.5 or > 9.0
- Therefore, it is not physically possible to acidify urine enough to prevent UTI's

**Ecotherapeutics**

- Ecotherapeutics include probiotics (live bacteria) and probiotics (fiber sources that select for certain strains of bacteria)
- The idea is to populate the GI tract with non-pathogenic “healthy” bacteria such as Bifidobacteria spp or non-pathogenic enteric bacteria
- Since bacterial UTI originate from distal urogenital tract bacteria and since these bacteria are primarily enteric bacteria, the premise is that changing the intestinal flora will result in changing of the distal urogenital tract bacteria
- These bacteria are not as “hearty” as the pre-existing normal bacteria; therefore, it is necessary to continue probiotics once you start
- There is minimal evidence that this aids in preventing UTI’s; however, it does seem to help some dogs
- There are several veterinary probiotics (Forti-Flora, Prostora Maxx, ProViable); however, there are many more human probiotics.
  - There is really no such thing as a “dog” or “cat” specific probiotic
  - Usually want large numbers and multiple organisms
  - Visbiome contains most organisms and multiple organisms (450 billion per packet)

**Cranberries** and cranberry extract

- The active ingredient in cranberries are proanthocyanidins
- Proanthocyanidins are found in cranberries, blueberries, and chocolate; however, only the proanthocyanidins found in cranberries are useful with bacterial UTI
- Proanthocyanidins bind to adhesins, primarily PapG pilli, that are virulent factors involved with binding of the bacteria to uroepithelial cells
- PapG pilli are found on 25-50% of canine E coli, but not with other bacteria
- Therefore, proanthocyanidins might be helpful in preventing certain strains of E coli from binding to uroepithelia, but not all E coli and not all bacteria
- There is evidence in human medicine (nearly 2 dozen positive randomized, controlled clinical trials), but one study in dogs failed to show benefit; nonetheless, some dogs may benefit from proanthocyanidins found in cranberry extract

**D-mannose** is a sugar that may prevent bacterial adherence. It is also incorporated into the GAG layer and may prevent bacterial invasion into uroepithelial cells. It has been shown to be beneficial in rodent models and human beings.

**Clarithromycin** is a macrolide antimicrobial agent that has been shown to degrade biofilm thereby exposing the bacterial community to the environment that may include an antimicrobial agent.

**UTI: FUNGAL, VIRAL, PARASITIC**

**FUNGAL UTI**

- Fungal urinary tract infections are a rare cause of lower urinary tract disease in dogs and cats.
- Funguria may be due to primary (confined to the urinary tract and presumptively due to ascending infection) or secondary (systemic infections resulting in shedding of organisms into the urine) infections.
- Organisms of the genus *Candida* are most commonly identified.
- Regardless of the infecting species, fungal urinary tract infections often are challenging to treat because of the strong apparent association with concurrent immunosuppressive diseases or breaches in local immunity that oftentimes cannot be completely resolved.
Candida spp. UTI

- Candida spp. are normal inhabitants of the genital mucosa, upper respiratory tract, and gastrointestinal tract in people, dogs, and cats
  - Candida spp. are yeast, as they reproduce by budding and are capable of fermenting carbohydrates; however this is a morphologic rather than a true taxonomic classification.
  - Yeasts most commonly have a budding, ovate appearance, but they will also occasionally appear filamentous, particularly in biofilms which form on mucosal and catheter surfaces or when tissue invasion has occurred.
  - As with bacterial urinary tract infection, candiduria presumptively occurs in dogs and cats following ascending infection to the lower urinary tract.
  - The majority of infections in dogs, cats and people are due to *C. albicans*, but several other species have been reported.

- Although bacterial urinary tract infections may occur in the absence of predisposing factors, in human and veterinary patients candidal infections appear to be highly associated with breaches in local lower urinary tract defenses or systemic immunocompromise.
  - Approximately 17% of reported cases of candidal urinary tract infections have been in dogs or cats previously or simultaneously diagnosed with diabetes mellitus.
  - In addition, many reported cases in dogs or cats have had concurrent lower urinary tract disease, with permanent stoma formation (urethrostomy or cystotomy tube placement) reported in approximately 40% of cases when the two largest veterinary retrospective studies are combined.
  - As expected, a variety of antibiotics, steroids, and chemotherapeutic agents have been commonly administered to affected animals within one month of diagnosis of *Candida* spp. infections.

- There are no historical or physical examination findings which allow differentiation of candiduria from other causes of lower urinary tract disease.

- The most common reason *Candida* spp. urinary tract infections are first suspected is due to visualization of fungal elements on urine sediment examination.
  - Although cutaneous *Candida* spp. are usually budding, organisms shed in urine may be budding or filamentous in appearance, reflecting shedding from the biofilm that often adheres to the bladder mucosa.
  - Finding fungal elements on routine urinalysis usually suggests that growth of *Candida* spp. is heavy.

- Identification of fungal elements should always be followed by urine culture to determine the infecting species.

Treatment (see algorithm at end of section)

- Treatment of candiduria in people is recommended in all symptomatic patients, patients with systemic immunosuppressive diseases (and who are thus at risk of developing systemic candidiasis), and patients with non-correctable risk factors.
  - Patients with asymptomatic infections and no identifiable risk factors are initially recultured prior to treatment in order to confirm that candiduria is not transient; likewise, treatment is delayed in
asymptomatic patients with correctable risk factors (such as indwelling urinary catheters) until these factors are removed and infection is found to persist.

- Unfortunately, because the most common risk factors in dogs and cats are not easily corrected (e.g. diabetes mellitus, permanent urinary tract stomata, and urinary tract neoplasia), withholding treatment in small animal veterinary patients is not recommended at this time.
- Ineffective treatment may lead to candidal pyelonephritis and/or fungemia.

- Treatment of primary candiduria requires adequate excretion of active drug or metabolites into the urine.
  - Of the antifungal agents widely used in veterinary medicine, only fluconazole and amphotericin B are excreted in significant amounts in active form by this route; in people.
    - Fluconazole is currently recommended as first line therapy in people, dogs, and cats because it can be administered orally and has a high therapeutic margin
    - The majority of *C. albicans* isolates are sensitive to fluconazole, and thus routine antifungal sensitivity testing of this species does not appear necessary at the time of first diagnosis.
    - However other *Candida* spp., particularly *C. glabrata* and *C. krusei*, are more likely to be resistant to fluconazole, and sensitivity testing at first diagnosis is recommended to guide dose of fluconazole (as the MIC and break point may suggest that higher doses could be effective), or to determine if an alternative drug should be used

- Infections should always be considered ‘complicated’ because of the association between candiduria and local or systemic immune system compromise.

  - Treatment should be continued for a minimum of 4 to 6 weeks, with urine sediment examinations and/or cultures performed at 2-3 week intervals to confirm treatment efficacy.
  - Frequency of resolution of infection in dogs and cats with fluconazole is unknown, but is felt to be approximately 50%, likely because predisposing factors in veterinary patients are more difficult to control or resolve.

- For those patients who have persistent candidal urinary tract infections despite appropriate fluconazole therapy or who have recurrent infections, sensitivity testing of isolates should be performed.

- Several alternative treatment options have been reported by others and/or attempted by this author with varying degrees of success; none have been directly compared to fluconazole or each other to determine relative efficacy.

  - Intravenous amphotericin B is primarily used for treatment of systemic candidiasis
  - Of other available antifungal drugs, oral itraconazole or ketoconazole do not result in high concentrations of active drug within urine.
    - Newer parenteral triazole drugs (e.g. posaconazole, voriconazole) are not excreted into urine in active form and have not been used to treat candiduria; the same is true of terbinafine, which may be synergistic with some azole drugs but is not excreted into urine in active form
  - Persistent or invasive candidal urinary tract infections in people have been treated with echinocandins (i.e. caspofungin, micafungin) despite poor urinary excretion of active drug
  - It has been suggested that urine alkalinization may be a useful adjunctive therapy for candiduria in dogs and cats, as *Candida* spp. growth is inhibited at higher pH in vitro.
    - Adequate alkalinization of urine without concurrent dietary therapy often requires high doses of sodium bicarbonate, and urine alkalinization is no longer favored in people with candiduria; as a result I do not manipulate urine pH as part of my standard treatment protocol.
  - Intravesicular infusion of antifungal drugs has also been described
    - Advantages of this modality include direct instillation of large volumes of high concentration drugs, the ability to use drugs whose safety (i.e. amphotericin B) would be limited by pre-existing renal disease, and no need for owner administration of oral medications.
Disadvantages include the need for repeat evaluations by veterinarians to perform drug instillation, difficulties associated with urinary catheterization (particularly in cats and female dogs), and risk of iatrogenic infection or bladder rupture.

Intravesicular infusion of 1% clotrimazole either transurethrally or via needle and syringe using ultrasound-guidance

Modified 1% clotrimazole protocol

- With a minimum of three infusions, success rate for resolution of infection in patients who have failed fluconazole is approximately 50%.
- Unfortunately, because 1% clotrimazole is supplied in polyethylene glycol, it is highly viscous and very difficult to infuse through small diameter urinary catheters.

Intravesicular 1% clotrimazole protocol for treatment of fluconazole-resistant fungal urinary tract infections in dogs and cats

1. Catheterize and empty the bladder. Balloon catheters are preferred in dogs as they prevent premature voiding of drug in non-anesthetized patients; most cats will retain the infused drug if not allowed access to a litter box.
2. Infuse 7.5–10 ml/kg of 1% clotrimazole solution; volume should be determined by bladder palpation during infusion.
3. Infused fluid should be retained for a minimum of 15–30 minutes.
4. Repeat infusion q7 days for 3 treatments.
5. Repeat fungal urine culture 7 days after third treatment to determine whether additional infusions or alternative therapy should be considered.
6. Oral fluconazole therapy should be continued throughout the infusion protocol.

- Despite these various treatment options, approximately 25% of dogs and cats with candiduria will have persistent, asymptomatic infections despite at least two different treatment modalities.
  - In these patients monitor infections, and only reattempt treatment when clinical signs recur,

Non-candidal primary UTI

- Although much rarer than Candida spp., other fungal organisms may also cause primary urinary tract infections in dogs or cats
- Of the common systemic mycoses, Aspergillus spp. and Cryptococcus neoformans rarely may cause primary infection of the lower and upper urinary tract in both dogs and cats.
- Despite these reports, if either agent is isolated from urine, clinicians should initially assume infection is systemic and determine other organ involvement before opting for oral fluconazole or localized intravesicular therapy.
- If organisms are resistant to fluconazole then oral therapy with an alternate agent in conjunction with intravesicular infusion of clotrimazole or amphotericin B should likely be considered.

Secondary funguria

- Although rarer than primary urinary tract infections, Candida spp. and other typically non-pathogenic fungi may occasionally cause systemic infections in both dogs and cats. In most cases the primary source of entry is unknown.
- The kidneys are a common site of involvement in dogs with systemic aspergillosis, and thus fungal hyphae are commonly identified in urine by routine sediment examination or culture
  - Systemic infections are usually treated with itraconazole and/or amphotericin B.
- Dogs with systemic blastomycosis will on rare occasions also have organisms visible on routine urinalysis or concentrated urine sediment examination
  - The blastomycosis serum or urine antigen test detects a surface antigen common to several fungal organisms rather than intact organisms.
Although localized nasal infection in cats is the most commonly encountered form of *Cryptococcus neoformans* infection, systemic infections are uncommonly encountered in cats and rarely in dogs.

Proposed treatment algorithm for fungal urinary tract infections

1. Identify and aggressively correct any concurrent breaks in local immunity or causes of systemic immunosuppression.

2. Identify genus and species of infecting organism via urine fungal culture
   a. If *C. albicans*:
      i. Fluconazole, 5-10 mg/kg PO q12 hrs for 4-6 weeks
      ii. Repeat urine sediment examination and urine culture at 2-3 week intervals to confirm resolution of infection
      iii. Repeat urine sediment examination and urine culture one and two months after stopping therapy
   b. If non-*C. albicans*:
      i. Perform sensitivity testing of isolate against antifungal drugs to guide initial therapy
      ii. Consider penetration of drugs into urine when selecting therapy

3. If initial treatment with fluconazole fails to resolve infection, repeat antifungal drug sensitivity testing and consider:
   a. Intravesicular infusion of 1% clotrimazole (dogs; cats with permanent urinary tract stomata)
   b. Intravesicular infusion of amphotericin B (cats or dogs)
   c. Intravenous or subcutaneous amphotericin B (cats or dogs which have failed intravesicular therapy)
   d. Fluconazole at maximally recommended dose with addition of terbinafine (cats or dogs whose owners decline other treatment options)
   e. Benign neglect and regular monitoring for disease progression

**VIRAL UTI**

- As with all infectious diseases, clinical manifestations of viral UTIs are the cumulative result of the ability of a microorganism to establish infection and compromise host function and, conversely, the host's ability to resist or curtail infection
  - Viral UTIs may be asymptomatic or may be associated with substantial morbidity and mortality.
  - In general, viral pathogens may cause disease by (1) inducing cell injury or death; (2) altering cellular functions; (3) suppressing immune responses; or (4) stimulating systemic or organ-specific pathologic immune responses.
  - It is noteworthy that virus-associated autoimmune diseases may occur in the absence of detectable viruses as a result of persistent non-replicating viral components, virus-induced alterations in antigenic profiles of infected cells, or induction of antiviral antibodies capable of cross-reacting with self-proteins

Upper urinary tract disorders

- Renal injury may be the direct result of virus-induced cytopathic effects on renal vascular, glomerular, tubular, and/or interstitial tissues, the secondary consequence of systemic infection and immune-mediated injury, or the result of both processes.
- Clinical manifestations of viral upper UTIs will be similar to other infectious and noninfectious causes of renal injury and may include varying combinations and degrees of proteinuria, hematuria, isosthenuria, and azotemia.
Several viruses have been associated with canine and feline kidney disorders including:

**Canine adenovirus**
- Canine adenovirus type 1 (CAV-1) is the cause of infectious canine hepatitis and is serologically and genetically distinct from canine adenovirus type 2 (CAV-2)
- CAV-1 is associated with systemic viremia, hepatitis, glomerulonephropathy, interstitial nephritis, and viruria; whereas CAV-2 is largely confined to the respiratory tract

**Canine herpesvirus**
- Canine herpesvirus (CHV) is a member of the alpha herpesvirus subfamily that causes severe, usually fatal, generalized systemic infections in seronegative neonatal puppies or immunocompromised animals; immunocompetent dogs exposed after 2 weeks of age develop only mild or inapparent upper respiratory tract or genital infections
- Neonatal puppies less than 2 weeks of age are uniquely predisposed to CHV systemic infections because of their lower body temperature, inability to mount a febrile response, and poorly developed immune systems
- The hallmarks of generalized systemic infections in affected puppies are disseminated focal necrosis and hemorrhage in multiple organs, especially in the kidney, liver, lung, and spleen
- Grossly, kidneys are mottled in appearance due to multiple subcapsular cortical hemorrhages associated with wedge shaped hemorrhagic lesions radiating outward from the medulla
- In dogs surviving acute infection, CHV is shed in nasal, oropharyngeal, and genitourinary secretions, and in feces for up to 2 weeks; the extent and duration of virus shedding in urine has not been determined
- After an appropriate host immune response, virus shedding ceases and CHV establishes lifelong latent infections of local ganglionic neurons and lymphoid tissues including lumbosacral ganglia, the celiac plexus, and hypogastric lymph nodes
- Reactivation of latent CHV infections and subsequent genitourinary shedding of virus may be induced by stressful situations or by administration of corticosteroids or other immunosuppressive agents; however, the role of latent or recrudescent CHV infections in the development or progression of renal disease has not been determined.

**Feline coronavirus**
- Feline infectious peritonitis (FIP) is a systemic, progressive, and ultimately fatal immunopathologic disease caused by a highly pathogenic feline coronavirus strain derived from a mutation of the more common and less pathogenic enteric strain of feline coronavirus
- The disease principally affects young cats less than 2 years of age
- Renal injury is common and is the direct result necrotizing pyogranulomatous vasculitis/nephritis associated with perivascular localization of activated coronavirus-infected monocyte/macrophages and coronavirus-specific immune complexes
- In addition, glomerulonephritis with or without concurrent vasculitis has been observed in cats with FIP. In one study of 85 naturally occurring cases of FIP, 71% of affected cats had light microscopic lesions of membranous, mesangioproliferative, or membranoproliferative glomerulonephritis

**Feline immunodeficiency virus**
- Feline immunodeficiency virus (FIV) is a member of the lentivirus subfamily of retroviruses that is similar to human immunodeficiency virus (HIV) in structure, biological properties, and clinical manifestations of infection
- Renal abnormalities have been reported in 8% to 24% of naturally infected FIV-positive cats from Japan, The United Kingdom, Australia, and New Zealand
- Abnormalities observed in naturally or experimentally infected FIV-positive cats include varying combinations and degrees of clinical signs consistent with renal failure, uremia, and the nephrotic syndrome, and laboratory findings of azotemia, hypoalbuminemia, and proteinuria
- Renal lesions commonly observed in FIV-infected cats include mesangial thickening, segmental to diffuse glomerulosclerosis, tubular degeneration and/or necrosis, and interstitial mononuclear cell infiltrates; less common lesions include mesangial cell proliferation, glomerular or interstitial amyloid deposition, interstitial fibrosis, and microcystic tubular dilation
Feline leukemia virus

- Feline leukemias virus (FeLV) is a member of the oncornavirus subfamily of retroviruses that has been associated with membranous glomerulonephropathy, interstitial nephritis, proteinuria, nephrotic syndrome, and renal failure in chronically infected cats with or without concurrent lymphosarcoma or other myeloproliferative diseases.
- Glomerulonephropathy was observed in 25% to 37% of necropsy specimens obtained from cats living in households with large populations of FeLV infected cats; however, a substantially lower prevalence of glomerulonephropathy was observed in large necropsy-based surveys of FeLV positive cats from the general population.

Lower urinary tract disorders

- Viruses have long been implicated as causative agents in the etiopathogenesis of some forms of naturally occurring feline idiopathic cystitis.
  - This hypothesis was supported by the isolation of a gamma herpesvirus (aka bovine herpesvirus type 4), retroviruses (aka feline foamy virus), and a calicivirus (aka feline calicivirus; FCV) from urine and tissues obtained from cats affected with lower urinary tract disease.
- Clinical manifestations of viral lower UTIs are often indistinguishable from other infectious and noninfectious urinary tract diseases.
- Although the light microscopic features of acute viral UTIs have not been well characterized, urinary bladder lesions in cats with calicivirus-induced urinary tract infections consisted of urinary bladder mucosal petechial hemorrhages, urothelial ulceration, and submucosal edema and mononuclear inflammation.
- These morphologic features are not unlike those observed in the urinary bladders of a limited number of cats with nonobstructive idiopathic cystitis.

Feline calicivirus

- FCV may have a causative role in the pathogenesis in at least some cases of feline idiopathic cystitis.
- Transmission electron microscopic examination of urethral matrix-crystalline plugs obtained from male cats with urethral obstruction revealed virus-like particles.

**Gamma herpesvirus (bovine herpesvirus type 4)**

- There is considerable evidence that BHV-4 can induce long-term viral UTIs in cats in a laboratory setting and that BHV-4 infection is endemic in the feline population; however, reproducible evidence that gamma herpesviruses cause naturally occurring symptomatic feline lower urinary tract disease is lacking.

Diagnosis of viral UTI

- Exclusion of other known causes of upper or lower urinary tract disease should precede attempts to establish a diagnosis of viral UTI. Generally, diagnostic criteria for viral infections include (1) isolation and identification of viral agents; (2) direct demonstration of virus particles, viral antigens, or viral nucleic acids in tissues or body fluids; and/or (3) detection and quantitation of specific viral antibodies.(Murphy et al 1999b)
- Molecular diagnostic methods, such as PCR or RT-PCR, circumvent many of the difficulties associated with conventional virus isolation methods and are increasingly being used for rapid detection of many viral agents.

Treatment of viral UTI

- The most effective treatment of viral UTIs lies in their prevention through use of appropriate immunization strategies and husbandry practices.
- Although interest in antiviral chemotherapeutics and biologic agents has grown considerably in recent years, antiviral agents available for clinical use are relatively few in number and are accompanied by only limited information regarding their safety and efficacy.
- One exception is feline calicivirus.
  - Parenteral administration of FCV-specific antiviral phosphorodiamidate morpholino oligomers effectively inhibited calicivirus replication, increased survival, decreased virus shedding, and hastened clinical recovery in kittens exposed to a severe virulent strain of FCV.
In the absence of safe and effective antiviral agents, management of suspected virus-induced urinary tract disease in dogs and cats is limited to supportive and symptomatic care to alleviate clinical signs and minimize sequelae of infection.

**PARASITIC UTI**

*Dioctophyma renale*

- Of the nematodes known to affect domestic animals and humans, few can rival the size and appearance of the giant kidney worm
- Adult male and female *D. renale* are typically blood (or vermilion) red in color when they are alive, but become brownish black after they die and degenerate
- The eggs are lemon-shaped and constant in size

- Although the lifespan of *D. renale* apparently has not been determined experimentally, there are estimates that some naturally occurring infections have lasted for 3 to 5 years
- Free-living annelids (*Lumbriculus variegatus*), also called blackworms and mudworms, are related to earthworms and are essential intermediate hosts
- Cases of *D. renale* have been encountered in virtually every part of the world with a temperate climate including Mississippi, Louisiana, Minnesota, Wisconsin, Michigan, and the central and eastern provinces of Canada
- Clinical signs
  - The feeding of *L. variegatus* infected with *D. renale* to dogs typically induces vomiting due to effects of the parasite on the gastric mucosa
  - If only one kidney has been invaded with *D. renale* and the opposite kidney is normal, signs attributable to *D. renale* infestation are often absent
    - Hematuria observed by owners may be the first indication of an abnormality
    - Palpation of the abdomen may reveal an enlarged and/or misshaped hydronephrotic kidney
  - If both kidneys are parasitized, clinical signs attributable to renal failure or uremia may occur; however, the host will die before extensive hydronephrosis of both kidneys has time to develop.
    - The degree of renal dysfunction is influenced by 1) the number of parasites in the kidney, 2) the duration of infection, 3) the number of kidneys parasitized, and 4), and the presence of co-morbid renal diseases.

* Diagnosis
  - If the gravid female parasite is located in the pelvis of a kidney that has a patent ureter, characteristic ova may be found by microscopic examination of urine sediment
  - When the worms are free in the peritoneal cavity, the diagnosis is usually made by ultrasonography, laparoscopy, computed tomography and/or exploratory celiotomy

* Treatment
  - Nephrectomy is usually the treatment of choice when only one kidney is affected and the opposite kidney is capable of sustaining homeostasis
  - In patients with parasites in both kidneys, nephrectomy and removal of the parasites may be indicated if sufficient functional tissue remains in both kidneys to maintain a reasonable quality of life
  - Pharmacologic treatment of adults and/or infective larvae discovered in any species has been virtually nonexistent

**Capillaria Plica, Capillaria Felis-Cati**

- *C. plica* and *C. felis-cati* are lumen dwellers (i.e. they are coelozic)
- *C. plica* and *C. felis-cati* are small, fragile, thread-like yellowish parasites
• The eggs have bipolar plugs, are colorless, and have a slightly pitted shell

- *Capillaria plica* is widely distributed throughout the world
  - It has been found in the urinary bladder, and less frequently in the ureters and renal pelves, of dogs, foxes, coyotes, raccoons, martens, mink badgers, otters, bobcats, skunks, weasels, and wolves
- *Capillaria felis-cati* is found less commonly in the urinary bladder of cats

• Clinical signs
  - Most dogs and cats with urinary capillariasis are asymptomatic; some become pollakiuric, polydipsic, and periuric.

• Laboratory findings
  - Urinalysis may reveal results (hematuria, proteinuria, and pyuria) typical of inflammation
  - Numerous clumps of transitional epithelial cells have also been observed in urine sediment
  - *C. plica* eggs are usually easy to identify, although at times they are difficult to find

• Diagnosis
  - A diagnosis is made by finding typical eggs via microscopic examination of urine sediment

• Treatment
  - Urinary capillariasis is most often asymptomatic and, may be self-limiting. Suggested treatments include:
    1. Several dogs appear to have been cured by single doses of ivermectin, 0.2 mg/kg, administered by subcutaneous injection.
    2. Prolonged treatment with albendazole was effective in 85% of dogs infected with *C. plica*. The urine was negative for eggs 30 days after initiation of treatment. Oral doses of 50 mg/kg of albendazole were given twice daily for up to 30 days
    3. Mebendazole or albendazole (200 mg given orally twice per day) has been reported as the treatment of choice for human intestinal capillariasis
  - Because evidence indicates that in the absence of reinfection, urinary capillariasis may be self-limiting, isolation of dog and cats from earthworms should sufficient to eliminate a Capillaria bladder infection in less than 90 days