Neoplasms of the urinary tract are a rare overall tumor type in dogs and cats, but create significant morbidity and mortality when encountered. Like most neoplastic disease, urinary tract tumors usually develop in older dogs and cats. An exception to this generalization is renal lymphoma, which can affect any age. Most urinary tract tumors are aggressive, usually malignant (>90%) and often metastasized at diagnosis (>50%). The typical metastatic pattern for renal tumors is to peritoneal or serosal surfaces, liver, and lungs. The pattern of dissemination for prostatic, urinary bladder or urethral tumors is to lumbar vertebra, regional lymph nodes, liver, kidney and (most commonly) lungs. Three-view thoracic radiographs for metastases are essential for prognostic purposes. With the exception of some transitional cell carcinomas, most urinary tract tumors are poorly responsive to chemotherapy.

**Urinary bladder and urethral neoplasia**

The most common tumor type in the urinary bladder or urethra is the **transitional cell carcinoma**. Squamous cell carcinoma of the urethra is also observed. Other tumor types less frequently encountered include adenocarcinoma, leiosarcomas, rhabdomyosarcoma, and hemangiosarcoma. Note that a non-neoplastic inflammatory condition of the urethra (granulomatous urethritis) in dogs can look very much like neoplasia but is benign, usually related to chronic urinary tract infection. Risk Factors for urinary bladder neoplasia are known for dogs and people. In dogs, obesity, breed (older small breed dogs), sex (females) and exposure to urban environments, organophosphate dips and cyclophosphamide increase the risk for bladder cancer. High risk breeds include the Scottish Terrier, Sheltie, other Terriers and Beagles. In cats, the tumor is slightly more common in male cats than female cats and often arises in the bladder apex or fundus, as opposed to the trigone –the most common location in dogs. Environmental and other risk factors are unknown for cats.

Clinical signs are similar to other lower tract disorders, including chronic hematuria, dysuria, or pollakiuria, recurrent or unresponsive urinary tract infections, or urinary incontinence. **Transitional cell carcinoma is most often diagnosed in dogs or cats presented after multiple suspected urinary tract infections that no longer respond to antimicrobial treatments.** Urinary obstruction is possible with bladder neck or urethral tumors; hydroureter and azotemia are possible if both ureteral orifices become obstructed. Additionally, polyuria and polydipsia (probably psychogenic) are seen in some affected dogs. Respiratory signs or lameness may be seen with metastatic disease.

The **diagnostic approach** for suspected lower urinary tract neoplasia may include:

- **Urinalysis**: inflammatory or neoplastic cells may be observed
- **Abdominal Radiographs**: soft tissue densities, enlarged lymph nodes or a distended urinary bladder may suggest neoplastic disease. Carefully evaluate the bladder neck area.
- **Abdominal ultrasound** is a good tool for detecting tumors > 0.5 cm
- **Contrast cystourethrogram or cystoscopy** further delineates suspicious lesions
- **Cystoscopy**: Very sensitive for detecting subtle urethral lesions, taking biopsy samples, doing laser treatments or placing stents
- **Thoracic radiographs** to screen for metastasis
- **Urinary antigen tests**: These detect tumor antigen in urine; work well in people, but many false positives seen in dogs with other causes of hematuria. Tumor antigen tests may be useful in high risk breeds. Other tests for bladder cancer include flow cytometry and measurement of fibroblastic growth factor.

Cytologic or histopathologic confirmation is required. TCC cells usually exfoliate readily and a reasonably sound diagnosis can be made by combining the imaging findings and cytology findings. A fine needle aspirate, forceps or catheter biopsy, bladder washing, urethral brush, traumatic catheterization or surgical biopsy can be used to gain cells or tissue. **Many oncologists strongly discourage any per abdominal aspirates, including cystocentesis, in suspect patients because of the high possibility of neoplastic cells seeding the abdomen.**

**Treatment options for transitional cell carcinoma**

*Surgical resection* may be considered for an isolated mass in apex of bladder or a benign tumor. Most bladder tumors in dogs develop in the trigone area and are not completely resectable, but many cat bladder tumors develop elsewhere in the bladder and may be more amenable to resection. Margins of approximately 2 cm are suggested; fortunately up to 74% of the bladder can be removed with little impact on urine storage. It is important to recognize that microscopic spread or metastasis may have already occurred, despite the gross appearance of a resectable mass. Additionally, there is some evidence that the entire bladder may be transformed when an
isolated tumor develops, leading to the possibility of spontaneous cancerous transformation in other areas at any time. For this reason, some oncologic surgeons are performing total cystectomy with ureteral diversion in severely affected patients. In most cases, chemotherapy with piroxicam or mitoxantrone/piroxicam is used to reduce clinical signs and modestly prolong survival. Piroxicam (0.3 mg/kg/day PO) is a NSAID with additional antineoplastic activity. The anti-tumor effect may be due to immunomodulation (blocked COX 2 expression) or direct activity on tumor receptors. It is most effective against urinary bladder transitional cell carcinomas. Concurrent antacids (H2 blockers or omeprazole) or misoprostol are administered to protect the gastrointestinal tract. Complete or partial remission is seen in some dogs (about 30%), with survival times of approximately 6 months. Many treated dogs do well for a year or more. Similar results have been observed with Deracoxib (Deramaxx 3 mg/kg PO q 24 hrs). Adjuvant chemotherapy (mitoxantrone, chlorambucil, vinblastine), may be started initially or after NSAID treatment fails to maintain stable disease. The best outcomes have been reported with a mitoxantrone/piroxicam combination protocol. In this report, 17 of 48 dogs (35% had at least partial response) whereas 9 more dogs had stable disease and the median survival time was extended to 10 months. Cisplatin and carboplatin has also been advocated for TCC; cisplatin combinations are more nephrotoxic, however.

Palliative or debulking procedures

The effect of chemotherapy is enhanced when tumor volume can be decreased by debulking procedures. Additionally, debulking may be necessary to temporarily open the trigone and urethral outflow in obstructed dogs. Minimally invasive options for debulking use cystoscopic approaches to reach neoplastic tissue. Using a diode laser, surface tumor can be steadily “burned” off in thin layers. Ultrasound guided endoscopic laser ablation (UGELAB) can be used to debulk TCC if an expert team is available. The sonographer works with the cystoscopist to provide a sonographic view of the bladder, mass, scope and laser tip and guide the overall procedure. Tissue rupture and tumor seeding are potential serious complications. These procedures are easiest to perform in female dogs but can be done in male dogs via a urethrostomy. Other palliative options for obstructed dogs include urethral stent placement or cystostomy tubes for urinary diversion. Many dogs with bladder or urethral neoplasia require antimicrobial treatment for secondary infections as well.

Prognosis

TCC of the urinary bladder is usually slowly progressive; affected patients are usually euthanized when disease causes obstruction of ureters or urethra or when metastases cause clinical debilitation. Depending on the stage of disease at diagnosis, dogs and cats can live months to approximately one year with palliative treatment

Key points

- Urinary tract neoplasms are usually malignant, readily metastasize and respond poorly to chemotherapy.
- Neutered males can be affected with prostatic neoplasia. An enlarged prostate gland in a neutered dog is almost always neoplastic.
- Prostatic neoplasia is diagnosed by the appearance of key “ominous” clinical signs, gross prostatic gland findings and cytological or histopathological confirmation. The main differential diagnosis is chronic prostatitis or atypical BPH. Prostatic tumors will not shrink following castration.
- Lower urinary tract signs that are companied by a negative urine culture, or that do not have a sustained response to antimicrobial therapy, should increase your suspicion of neoplasia, especially in older, female dogs.
- Instrumentation during sampling or surgery of transitional cell carcinomas creates a risk of seeding tumor cells in the abdomen or urethra. Clinician opinion varies regarding the probability and significance of this complication, however.
- Piroxicam is a valuable and usually well tolerated option for long term palliative treatment of TCC and prostatic carcinoma in dogs and cats, with remarkable results in some patients. Gastrointestinal protectants are usually given concurrently.
Prostatic disorders are primarily encountered in intact male dogs and humans and are frequently influenced by androgenic stimulation. Common prostatic diseases include: Benign prostatic hyperplasia/hypertrophy (BPH), Prostatic and paraprostatic cysts, bacterial prostatitis or abscess, and prostatic neoplasia. Diagnostic evaluation of the prostate gland may include: signalment and clinical signs; rectal palpation; diagnostic imaging; cytologic evaluation and culture of prostatic fluid; and biopsy. Evaluation of clinical features, prostatic gross morphology and cellular features is usually sufficient for diagnosis. Treatment of prostatic disease may include hormonal manipulation with either castration or anti-androgenic pharmacologic agents; antimicrobial treatments that penetrate prostatic tissue and glandular fluid; or surgical intervention.

Diagnostic approach

Key clinical findings

Benign prostatic diseases such as BPH and chronic bacterial prostatitis are likely to cause localized signs: hematuria, urethral discharge, hindlimb stiffness and tenesmus. Signs of systemic illness are possible with acute bacterial prostatitis, advanced prostatic neoplasia or abscessation. Urinary incontinence, urinary obstruction, hindlimb tremors and weight loss are ominous signs that suggest neoplasia. Prostatic enlargement in a neutered dog is almost always caused by neoplasia.

Diagnostic imaging

Key clinical findings

Benign prostatic diseases such as BPH and chronic bacterial prostatitis are likely to cause localized signs: hematuria, urethral discharge, hindlimb stiffness and tenesmus. Signs of systemic illness are possible with acute bacterial prostatitis, advanced prostatic neoplasia or abscessation. Urinary incontinence, urinary obstruction, hindlimb tremors and weight loss are ominous signs that suggest neoplasia. Prostatic enlargement in a neutered dog is almost always caused by neoplasia.

Diagnostic imaging

Surveys Radiographs. Signs of disease include: Symmetrical or asymmetrical enlargement; poor contrast of capsule; granular mineralization; enlarged sublumbar nodes (usually metastasis); bony lesions of pelvis or lumbosacral spine (metastasis). Mineralization within the prostate in a neutered dog is highly associated with neoplasia; mineralization in an intact dog usually is associated with non-neoplastic disorders. Contrast radiography is rarely necessary for the evaluation of prostatic disease, but can be useful when the prostatic urethra needs to be identified more clearly, such as when compressed by a large cyst or abscess or disrupted by neoplasia.

Transabdominal Ultrasonography. Sonography is easy and useful for evaluating the prostate gland. The normal gland is homogeneous in appearance with smooth margins. Normal echogenicity is similar to the spleen. Prostate gland size is dependent on dog’s body weight, except for Scottish Terriers who have an unusually large prostate gland. Sonography can be used to identify enlargement, assess homogeneity; evaluate sublumbar lymph nodes (and other abdominal nodes or organs); identify and aspirate or drain cysts; and guide aspirates or biopsies. Occasionally contrast ultrasound or contrast CT is recommended to provide more detail about vascular structures in a diseased prostate gland.

Prostatic sampling

Samples of prostatic cells or fluid are essential to most diagnoses and are usually submitted for cytology and culture (aerobic, anaerobic, Mycoplasma sp.). Normal cytological findings include healthy prostatic epithelial cells, few red blood cells and few inflammatory cells. Normal fluid is sterile. For tissue samples, routine histopathology stains are usually sufficient.

Ejaculate: Easily obtained in young, intact or breeding dogs, but more difficult when the dog has painful prostatic disease such as infection, abscess, or neoplasia. The third fraction of the ejaculate is collected for evaluation of prostatic fluid.

Urethral Brush Sample: An easy, quick and accurate sampling method. A tiny protected urethral brush is passed retrograde into the urethra; then the brush is advanced and exposed at the level of the prostate gland for brushing of the prostatic urethral epithelium. The brush is then retracted and withdrawn from the urethra. Cells are usually captured on the brush and can be placed in a small amount of saline or brushed directly onto a microscope slide.

Fine needle aspirate: Using a long small gauge needle, cyst fluid or tissue can be aspirated with ultrasonographic guidance (avoid the urethra). There is a possibility of seeding the abdomen with bacteria or neoplastic cells. FNA samples are often not as helpful as fluid samples or urethral brushings.

Prostatic massage/wash: Useful for collecting prostatic fluid when an ejaculate is not possible. The procedure is a little cumbersome, requires sedation and at least two people to perform, but includes collecting urine or urethral fluid before and after transrectal massage. Prostatic massage is contraindicated in acute bacterial prostatitis. Inflammation will disrupt prostatic fluid: blood barriers; massage or brushing can force bacteria into the bloodstream. Bacterial cultures of bladder and prostate can be compared using this method.

Prostatic biopsy: Multiple methods are possible, including catheter biopsy, perabdominal, peri-rectal and transrectal or open approaches.
Management of prostatic diseases

Benign prostatic hyperplasia (BPH)

Glandular hyperplasia develops in nearly all intact male dogs with increasing age (especially > 5 yrs). A changing androgen:estrogen hormone ratio with age (and local growth factors) appears to cause the development of BPH, with increased secretion and urethral discharge, cyst formation, increased vascularity and bleeding. The prostate gland is mild to moderately enlarged, usually smooth, symmetric and nonpainful. Large cysts can cause asymmetric enlargement. Diagnostic findings include hematuria, homogeneous prostatic enlargement, small cysts, increased RBCs and hyperplastic prostatic epithelial cells. Definitive diagnosis can be obtained by biopsy but response to treatment (castration) is usually sufficient for diagnosis. Castration is the preferred treatment for BPH. The prostate gland will involute rapidly, decreasing approximately 50% in size within 3 weeks, 70% in size by 9 weeks, with complete involution by 12 weeks. Castration should resolve small cysts, bleeding and chronic bacterial prostatitis. If the prostate gland remains enlarged or clinical signs persist post-castration, then another disease process is likely.

Medical alternatives for management of BPH

- **Finasteride** is a 5-alpha reductase inhibitor that blocks production of DHT from testosterone. Circulating testosterone is maintained at normal levels to preserve libido and semen quality.
  - Dose: 0.1 -0.5 mg/kg/day PO, up to 5 mg/dog
  - Decreases prostate size and clinical signs within 1 – 4 weeks. Treatment usually given for 1 – 4 months.

- **Progestins** exert negative feedback on the pituitary which causes direct suppression of LH release and testosterone production, and are best used for a short period of time in order to maintain breeding dog prior to castration. Progestins are fairly effective in decreasing prostatic size and clinical signs but have more adverse effects than finasteride, including diabetes mellitus, mammary hyperplasia, immunosuppression, and hypothyroidism. Options include:
  - Megesterol acetate 0.1 – 0.5 mg/kg PO q 24 hrs for 3 – 8 weeks (also inhibits 5alpha reductase, facilitates clearance of testosterone and competitively binds testosterone receptors)
  - Medroxyprogesterone injection 0.3 mg/kg SC once (can last up to 10 months)
  - Osaterone acetate is a testosterone receptor inhibitor related to progesterone. Daily treatment for 7 days provides approximately 5 months resolution with fewer side effects (increased appetite, lethargy mild hair loss)

- **Tamoxifen and anastrozole** are anti-estrogen agents that appear to be moderately effective.

- **GnRH superagonist** implants (chemical castration). Decreases glandular size and clinical signs in dogs with BPH for 6 – 22 months. Mild adverse effects included weight gain, transient initial worsening of clinical signs. As expected, sperm quality and ejaculate volume declined 3–5 weeks.

- **Intraprostatic treatments**, including botulinum toxin injection, ethanol and thermal ablation, and histotripsy that disrupt hyperplastic tissue have been investigated in research models.

Acute and chronic bacterial prostatitis

The prostate gland is usually protected from bacterial invasion by host defense mechanisms that protect the urinary tract. Prostatic fluid is also antibacterial in nature, due to locally secreted immunoglobulins and prostatic antibacterial factor. However, prostatic diseases or cysts increase the risk of infection. Bacterial infections are usually caused by pathogens that gain entrance to the urethra and ascend into prostatic tissue. The most common organism is *E. coli*. Other fairly common organisms include Staphylococcus, Klebsiella, Proteus, Pseudomonas, Enterobacter. Rare agents include B. Canis, mycoplasma sp and fungal organisms. Anaerobes may be found in prostatic abscesses.

The prostatic epithelium and a typically acidic prostatic fluid pH (pH 6.4) creates a blood-prostatic fluid barrier that influences antimicrobial penetration and effectiveness. With acute inflammation, the barrier is ineffective; injectable antimicrobials effective against *E. coli* are appropriate initial choices. With chronic bacterial prostatitis (or the prolonged treatment of acute disease), antimicrobials that are lipid-soluble, weakly ionized, poorly protein bound, and weak bases enter prostatic tissue most effectively, and are then ionized (accept a proton) and become “trapped” there. Good empirical choices include:

- Gram negative organisms: enrofloxacin, trimethoprim-sulfa, chloramphenicol
- Gram positive organisms: clindamcin, erythromycin, clindamcin, trimethoprim-sulfa, chloramphenicol
- Mycoplasma: enrofloxacin

Long term antimicrobials (4 – 6 weeks usually, 12 weeks if relapsed) and intensive monitoring are required. Castration is required for complete resolution. Ideal follow-up includes culture of urine and prostatic fluid during initial 2 weeks of treatment then monthly thereafter until completely resolved.

**Treatment of Prostatic Abscesses** generally requires surgical drainage and omentization or marsupialization. Drainage by ultrasound-guided aspiration (along with long term antimicrobials) can be successful in some cases. Subtotal or total prostatectomy may be a salvage procedure.
Prostatic neoplasia

Adenocarcinoma of the glandular tissue or Transitional Cell Carcinoma arising from the prostatic urethra are the most common neoplasms found in the prostate gland (squamous cell carcinoma and sarcomas occur occasionally). Certain common breeds are reported to have increased risk: Beagles, Dobermans, Springer Spaniels, Scotties, Shelties, and Westies. Remember that urinary incontinence, urinary obstruction, hindlimb weakness, tremors and weight loss suggest neoplasia in dogs with prostatic disease. The metastatic pattern extends to regional (sublumbar) lymph nodes, bone and lungs; metastasis is common at the time of diagnosis. Neutering does not protect dogs from prostatic neoplasia; in fact, the relative risk for development of carcinoma increases with the duration of time that the dog has been neutered. Diagnosis is usually straightforward based on imaging and cytology/biopsy findings. Although work on an antibody or antigen assay is ongoing, there is no validated PSA for dogs at this point. No highly successful treatment is available. Advanced surgical methods may be applied to tumors isolated to the prostate, but morbidity is high (urinary incontinence) and significant effect on survival has not been documented. Photodynamic therapy may hold some promise; long term survival has only been reported in a single case report. Generally, dogs are treated palliatively with piroxicam, but prostatic carcinomas are not as responsive to NSAIDs as transitional cell carcinomas of the urinary bladder. Urinary diversion may be necessary if urethral obstruction has occurred.

Key take home points

- Prostatic diseases mostly cause localized lower urinary tract signs; systemic signs usually indicate acute prostatitis, abscess or advanced neoplasia.
- Prostatomegaly or other signs of prostatic disease in a neutered male dog is strongly suggestive of neoplasia.
- Urinary obstruction is rare in dogs with prostatic disease except for neoplasia that disrupts the urethral lumen and paraprostatic cysts that may create extramural compression.
- Castration should resolve all clinical signs and prostatic enlargement associated with BPH.
- Finasteride is the pharmacologic alternative of choice for management of BPH if castration is not possible.
- Long term antimicrobials that penetrate well into prostatic fluid, along with castration, are needed for management of prostatitis.
- The prognosis for dogs with prostatic neoplasia is poor; palliative treatment with piroxicam may minimize clinical signs for short term periods.

Table. Key pharmacologic agents used for prostatic disease in dogs

<table>
<thead>
<tr>
<th>Key Drug</th>
<th>Drug Class</th>
<th>Dose Range</th>
<th>Frequency</th>
<th>Route</th>
<th>Indications/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finasteride</td>
<td>5-alpha reductase inhibitor</td>
<td>0.1 –0.5 mg/kg/day</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>Short or long term management of BPH; Well tolerated</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>Progestin</td>
<td>0.1 – 0.5 mg/kg</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>Short term (3-8 weeks) management of BPH; multiple adverse effects</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Progestin</td>
<td>0.3 mg/kg</td>
<td>Single injection</td>
<td>SC</td>
<td>Short-intermediate term (up to 10 months) management of BPH; adverse effects possible</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>Fluoroquinolone antimicrobial</td>
<td>5 -10 mg/kg</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>Long term treatment of bacterial prostatitis; antimicrobial selection should be based on C&amp;S</td>
</tr>
<tr>
<td>Marbofloxacin</td>
<td>Fluoroquinolone antimicrobial</td>
<td>2.5-5 mg/kg</td>
<td>Q 24hrs</td>
<td>PO</td>
<td>Same as enrofloxacin</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Alpha-antagonist</td>
<td>1 mg/15 kg</td>
<td>Q 12 hrs</td>
<td>PO</td>
<td>Functional urinary obstruction associated with BPH; more effective in humans. Possible sedation or hypotension</td>
</tr>
<tr>
<td>Silodosin</td>
<td>Selective a-1a antagonist</td>
<td>0.1 mg/kg?</td>
<td>Q 24</td>
<td>PO</td>
<td>Same as for prazosin; dosage extrapolated from human dosage; no clinical experience in dogs</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>NSAID</td>
<td>0.3 mg/kg</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>Palliative treatment of prostatic carcinomas; use with gastrointestinal protectants</td>
</tr>
</tbody>
</table>
Little Angrier Bladders:
Options for Refractory FIC
India Lane, DVM, MS, Ed. D, DACVIM
University of Tennessee
Knoxville, TN

Introduction and pathophysiology
Lower urinary tract signs (hematuria, pollakiuria, dysuria and periuria) reflect inflammation and irritation and are similar regardless of the etiology. The most common disorder in cats, a sterile, inflammatory cystitis, is considered idiopathic but may be caused by multiple factors, including viral or other inflammatory triggers, urothelial defects, neurohormonal aberrations, and chronic environmental stresses.

Because of the unusual endocrine, gastrointestinal, neurologic and behavioral findings in affected cats studied over time, a more diffuse syndrome may be at play. Our awareness of comorbid conditions, especially behavioral manifestations, has increased. In a recent review of the evidence available, long term researcher Tony Buffington has proposed an expanded interpretation of idiopathic cystitis as “Pandora” syndrome, as a Pandora’s box of systemic abnormalities are uncovered in these cats.

The lower urinary tract component is characterized by occasional episodes of hematuria, pollakiuria, and inappropriate urination that are not associated with bacterial infection and are self-limiting in nature. However, some cats have more refractory disease, with signs that recur multiple times during a given year or, less commonly, persist for longer than 7 days. Treatments that minimize inflammation, protect the urothelium, or modify neurohormonal or behavioral influences can be useful in decreasing the frequency of recurrence in refractory cats.

Diagnostic evaluation for recurrent non-obstructive feline idiopathic cystitis
Although the diagnostic workup for idiopathic cystitis may reveal little more than a small bladder and hematuria, it is important to do a thorough evaluation for other etiologies in recurrent cases. Urolithiasis must be considered in any cat, and bacterial urinary tract infections may be considered in older cats, cats with perineal urethrostomies or those undergoing recent urinary catheterization. Neoplastic disease is also possible in older cats with progressive signs. In recurrent cases, a complete minimum data base and additional anatomical investigation are recommended.

For a rare recurrence, the diagnostic evaluation should include a problem-specific history and physical examination, urinalysis with sediment examination and culture of a cystocentesis sample. Survey radiographs easily screen for discrete uroliths, which are usually contain radioopaque calcium or phosphate. In older cats, cats with frequent recurrent episodes, or persistent clinical signs a CBC and serum chemistry profile are added to the evaluation as well as ultrasonography or contrast imaging studies. Urethrocystoscopy or exploratory cystotomy with biopsy of bladder or urethral tissue is reserved for cats with severe or persistent hematuria, unexplained lesions observed on imaging studies and other unusual cases.

Practical management strategies for recurrent non-obstructive feline idiopathic cystitis
Short-term relief can be used for 2 to 5 days during acute flare-ups to minimize discomfort and shorten the hematuric phase. Signs will resolve spontaneously in approximately 85% of affected cats within a few days.

- **Analgesics.** For acute flare-ups of lower urinary tract signs, short-term analgesic treatments may be useful to reduce the discomfort associated with bladder and urethral inflammation. Butorphanol (0.5 – 1.25 mg/cat PO q 4 – 6 hrs) has been recommended; longer acting buprenorphine (0.01-0.02 mg/kg q6-12h, IM, SQ) can be considered as well. Both agents can be given as subcutaneous injections (alternatively, fentanyl patches can be used) if less stressful to the cat. Opioids also have some anti-inflammatory effects that may be beneficial in this setting.

- **Anti-spasmodics?** Agents that relax smooth or striated muscle of the urinary tract have been advocated for symptomatic relief of pollakiuria, dysuria, and stranguria in cats with FLUTD. The anticholinergic agents propantheline and oxybutynin (0.2 mg/kg PO q 12 hrs) have been recommended for their antispasmodic effects on the urinary bladder. In one small controlled study, propantheline administration did not affect resolution of clinical signs at 5 days post-treatment when compared with placebo; however, this agent has little direct smooth muscle relaxant properties. If urinary bladder antispasmodic agents are administered, cats should be monitored for urine retention; the loss of a frequent mechanical washout of urine theoretically could delay resolution of inflammation or predispose cats to urinary tract infection.

- **Alpha adrenergic antagonism?** Agents acting on urethral musculature also have been recommended to facilitate urination in dysuric cats and to alleviate functional urethral obstruction in postobstructed cats. Phenoxybenzamine and prazosin (0.25 -0.5 mg/cat PO q 12 – 24 hrs) are alpha-adrenergic antagonists that inhibit urethral smooth muscle contracture. These agents may be helpful in minimizing resistance in the preprostatic and prostatic portions of the
urethra in cats. Diazepam or dantrolene may be more effective in relaxing skeletal muscle in the postprostatic urethra where much of the spasm occurs. Hypotension and sedation are the most common adverse effects of alpha antagonists.

- **Non-steroidal anti-inflammatory agents?** Nonsteroidal anti-inflammatory agents have also been recommended for analgesic and anti-inflammatory effects. No controlled studies are available to demonstrate a response from any of these agents.

- **Note that anti-anxiety treatments such as amitriptyline are not recommended for short term relief.**

**Long term strategies** are employed for frequently recurrent, idiopathic cases after a thorough diagnostic evaluation. Dietary and environmental strategies are usually employed first. Pharmacologic agents may be added if the cat still experiences frequent recurrences. The effects of treatment may take weeks to months to be fully realized; treatment is indefinite to lifelong.

- **Water.** High moisture content is probably the primary key to management of recurrent idiopathic cystitis. Moisture can be provided in wet food, fresh water bowls or fountains, or by adding extra water to food. For cats with urethral plugs or struvite cystalluria, canned diets designed to minimize urolith formation are recommended. Owners should strive to minimize frequent changes in diet, as this may trigger episodes.

- **Dietary management.** Although dietary management can be best advocated for cats with significant crystalline or obstructive disease, many cats with idiopathic disease seem to have reduced episodes of inflammation when fed a food formulated to prevent common feline uroliths. In addition to modified mineral content, these diets also often contain antioxidant or fatty acid profiles designed to be anti-inflammatory. Frequent feeding of small meals with added moisture also may enhance the cat’s acceptance of the food and increases positive owner-cat interactivity.

- **Environmental modifications and enhancements.** Modification of environment and attention to behavioral issues must be done concurrently to minimize the neuroendocrine influences on the disease. Environmental enrichment, reduction in intra-cat conflict or aggression, feeding method and litter box management are included in the potential modifications which are individualized based on a thorough environmental history regarding the cat, other pets and people in the household, and the household routines. Owners can be directed to the OSU indoor cat initiative (www.indoorpet.osu.edu) for general information and for suggestions on managing common stressors (changes in housing, people, pets, schedules, etc.), but will also benefit from consultation about their specific situation.

- **Feline pheromones.** In a recent prospective clinical trial involving 12 cats, feline facial pheromone was compared to a placebo as treatment for iFLUTD. Although there was no statistical difference between the two groups, more of the pheromone treated cats had less severe and fewer episodes of iFLUTD and further studies are warranted.

- **Anti-anxiety medication.** Amitriptyline has been studied for both acute non-obstructive episodes and for longer term usage. This tricyclic antidepressant has anticholinergic, antihistaminic, analgesic and anti-inflammatory effects, and is useful in women with interstitial cystitis. In two controlled trials, short-term administration of amitriptyline did not dramatically reduce the duration or severity of lower urinary tract signs, and may have led to earlier recurrence of clinical episodes. For longer term administration, the drug should be given daily for several months to assess effectiveness. Other tricyclic antidepressants or SSRIs may be useful in cats as well; in the author’s experience, clomipramine is better tolerated by cats than amitriptyline. For cats in which amitriptyline is indicated, a starting dosage of 5 mg/cat every 24 hours is empirically recommended; the dose is adjusted to effect a mild calming behavior in the cat, which is usually achieved with dosages of 2.5 to 12.5 mg/cat per day. The dose of clomipramine is approximately 0.5 mg/kg/day. Others prefer fluoxetine (0.5-1.0 mg/kg PO q24h). If ineffective, these medications should be slowly tapered instead of withdrawn abruptly.

- **Glycosaminoglycans.** Pentosan polysulfate (PPS, Elmiron) is a synthetic polysaccharide that augments the protective glycosaminoglycan layer of the urinary bladder. Orally administered PPS has resulted in good long-term responses (>6 to 12 months) in some women with IC and may be effective in reducing clinical episodes in cats with recurrent or chronic idiopathic disease. GAG have not proven more effective than placebo in two trials in cats, however. The currently recommended oral dosage for cats is 8 mg/kg (usually 50 mg/cat) PO q12 hours. An injectable protocol includes PPS (3 mg/kg) administered subcutaneously on days 1, 2, 5 and 10.

- **Glucosamine and chondroitin sulfate** are the building blocks for formation of glycosaminoglycans. Anecdotally these nutritional supplements have been helpful in some cats with chronic disease. A placebo-controlled trial in cats treated with glucosamine alone, however, had no effect over placebo on severity or recurrence of signs during a 6 month period. Another prospective evaluation of 12 affected cats found slight decrease in signs of pain and hematuria during the short study period (n-acetyl-D glucosamine at 250 mg/cat/24 hrs for 28 days). Plasma GAG concentrations and urine GAG:creatinine ratio increased in the cats as well.

- A variety of other strategies have been advocated, including medications, acupuncture and bladder manipulations/infusions. Although evidence is lacking for any “silver bullet” treatments, individual cats may respond to specific treatments.
Table 1. Environmental checklist for cats with idiopathic cystitis

<table>
<thead>
<tr>
<th>Environmental Checklist</th>
<th>Warning Signs</th>
<th>Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary food source?</td>
<td>Single food</td>
<td>Moist food, possibly with added water</td>
</tr>
<tr>
<td></td>
<td>Dry food</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Competition with other cat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hard to reach</td>
<td></td>
</tr>
<tr>
<td>Conflicts between multiple cats?</td>
<td>Affected cat hides, flees, is quiet</td>
<td>Separate feeding and litter box areas</td>
</tr>
<tr>
<td></td>
<td>Separate resting spots/safe spots</td>
<td>Individual owner attention</td>
</tr>
<tr>
<td>Other Aggressors or tensions?</td>
<td>Kids, dogs, strangers, adults, frequent routine changes, Furniture, etc changes</td>
<td></td>
</tr>
<tr>
<td>Protected private food location?</td>
<td>One water source</td>
<td>Running water</td>
</tr>
<tr>
<td>Adequate water supply?</td>
<td>Partially full water sources</td>
<td>Varied water containers and locations</td>
</tr>
<tr>
<td>Adequate exercise?</td>
<td>Obesity</td>
<td>Short directed play</td>
</tr>
<tr>
<td></td>
<td>Lack of activity</td>
<td>Hunting games</td>
</tr>
<tr>
<td>Adequate enrichment?</td>
<td>No routine</td>
<td>Perches, scratching posts, varied play spots</td>
</tr>
<tr>
<td></td>
<td>No owner-cat time</td>
<td>Individual short play periods</td>
</tr>
<tr>
<td>Adequate vertical space?</td>
<td>Blocked from windows not available</td>
<td>Multiple levels</td>
</tr>
<tr>
<td></td>
<td>In main living areas</td>
<td>View outside (unless outdoor cats are aggressors)</td>
</tr>
<tr>
<td>Protected preferred spaces?</td>
<td>All Noisy rooms</td>
<td>Safe hiding places</td>
</tr>
<tr>
<td></td>
<td>Surprises in rooms</td>
<td>Quiet, low traffic areas</td>
</tr>
<tr>
<td>Adequate Litter boxes?</td>
<td>Undesirable Substrate</td>
<td>Consider fresh step or scoopable litter</td>
</tr>
<tr>
<td></td>
<td>Only one box</td>
<td>Appropriate placement</td>
</tr>
<tr>
<td></td>
<td>Open to “attack”</td>
<td>One per cat plus one for the house</td>
</tr>
<tr>
<td></td>
<td>Scary</td>
<td>Daily scooping</td>
</tr>
<tr>
<td></td>
<td>Difficult to reach</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unclean</td>
<td></td>
</tr>
<tr>
<td>Adequate scratching opportunities?</td>
<td>Away from activity or sleeping areas</td>
<td>Place near resting areas</td>
</tr>
<tr>
<td></td>
<td>Unused</td>
<td>Spray pheromones</td>
</tr>
</tbody>
</table>

**Key take home points**

- Additional diagnostic evaluation, especially imaging, should be performed (or repeated) in cats with frequent recurrences in order to rule out urolithiasis, infection and neoplasia.
- Episodes of flare up are managed primarily with analgesics.
- Diet, water intake and environment are addressed in recurrent cases, with application of environmental enrichment.
- Feline pheromones may reduce episodes, especially when known stressors are anticipated.
- If above strategies are insufficient in controlling recurrences, the cat may benefit from anti-anxiety medication (especially those with inter-cat or significant stress) and/or glycosaminoglycans (especially those with persistent hematuria).

Table 2. Key pharmacologic agents used for refractory idiopathic cystitis in cats

<table>
<thead>
<tr>
<th>Key Drug</th>
<th>Drug Class</th>
<th>Dose Range</th>
<th>Frequency</th>
<th>Route</th>
<th>Indications/ Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Opioid</td>
<td>0.01-0.02 mg/kg</td>
<td>q6-12h</td>
<td>IM, SQ</td>
<td>Short term analgesia during acute episode</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Opioid</td>
<td>0.5 – 1.25 mg/cat</td>
<td>Q 6 – 8 hrs</td>
<td>PO</td>
<td>Short term analgesia during acute episode</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>AnticholinergicAntispasmodic Analgesic</td>
<td>1.25 mg/cat</td>
<td>Q 8 – 12 hrs</td>
<td>PO</td>
<td>Short term analgesia during acute episode; could cause urine retention</td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>Dose</td>
<td>Frequency</td>
<td>Route</td>
<td>Side Effects/Notes</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Alpha-antagonist</td>
<td>0.25 mg/cat</td>
<td>Q 12-24 hrs</td>
<td>PO</td>
<td>Functional urinary obstruction or spasm; Possible sedation or hypotension</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>NSAID</td>
<td>0.1 mg/cat</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>Short term analgesia; caution if renal disease</td>
</tr>
<tr>
<td>Pentosan Polysulfate</td>
<td>GAG</td>
<td>8 mg/kg * OR* 3 mg/kg</td>
<td>Q 12 hrs <em>OR</em> Day 1,2,5,10</td>
<td>PO <em>OR</em> SC</td>
<td>Full effects may take a while</td>
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<tr>
<td>Glucosamine</td>
<td>GAG precursor</td>
<td>250 mg/cat</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Tricyclic</td>
<td>0.5 mg/kg</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>Allow 4 – 8 weeks to assess effect; Taper slowly if withdrawn</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tricyclic</td>
<td>2.5 – 12.5 mg/cat</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>See clomipramine; usually has more adverse effects than clomipramine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>0.5-1.0 mg/kg</td>
<td>Q24h</td>
<td>PO</td>
<td>See clomipramine</td>
</tr>
<tr>
<td>Feli-way pheromone</td>
<td>Environmental application</td>
<td>Multi-ple</td>
<td>Sprays, Diffusers and collars available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Little Angry Bladders: First Steps for Nonobtrusive FIC**

India Lane, DVM, MS, Ed. D, DACVIM
University of Tennessee
Knoxville, TN

**Introduction and differential diagnoses**

Common causes of lower urinary tract disease in cats in young to middle-aged cats include *idiopathic cystitis (obstructive or non-obstructive)* and *urolithiasis*. Bacterial UTI and neoplasia become more likely in older cats (>10 years old). Notice that *bacterial urinary tract infections are not common in cats*, but should be considered in *older cats, cats with concurrent disease (especially those causing dilute urine), cats with perineal urethrostomies or those undergoing recent urinary catheterization*. Recent studies support a larger overall prevalence of bacterial UTI in cats (15-20%) but are complicated by the urine collection method. Neoplastic disease is possible in older cats with progressive signs.

The most common LUT disorders can be related to each other in the following schema (modified from original source: Lulich and Osborne):

**Pathophysiology and clinical presentation**

In cats, a *sterile, inflammatory cystitis* is common and is considered idiopathic (Feline Idiopathic Cystitis or Feline Interstitial Cystitis). FIC is characterized by *occasional episodes of hematuria, pollakiuria, and inappropriate urination that are not associated with bacterial infection and are self-limiting in nature*. However, a subset of affected cats have more refractory disease, with signs that recur multiple times during a given year or, less commonly, persist for longer than 7 days.

Contributing factors to the disorder may include: viral or other inflammatory triggers, urothelial defects, neurohormonal aberrations, and chronic environmental stresses. The disorder in cats is similar to interstitial cystitis in women, which is also a sterile, painful cystitis exacerbated by stress. Other common pathophysiologic features include increased mast cell numbers, decreased urinary glycosaminoglycans, increased bladder mucosal permeability and increased afferent nerve activity.

Affected cats exhibit *neurohormonal abnormalities* including enhanced sympathetic nervous system activation and release of catecholamines and nitric oxide (suspected to increase bladder permeability and to increase pain perception), along with depressed adrenal gland response and small adrenal glands, leading to decreased cortisol production and inability to moderate stress. Because of the unusual endocrine, gastrointestinal, neurologic and behavioral findings in affected cats studied over time, a more diffuse syndrome may be at play. Our awareness of comorbid conditions, especially behavioral manifestations, has increased. In a recent review of the evidence available, long term researcher Tony Buffington has proposed an expanded interpretation of idiopathic cystitis as “Pandora” syndrome, as a Pandora’s box of systemic abnormalities are uncovered in these cats. Treatments that minimize inflammation, protect the urothelium, or modify neurohormonal or behavioral influences can be useful in decreasing the frequency of recurrence in refractory cats.

**Risk factors**

- **Lifestyle**: Indoor cats, most commonly 2-6 years old
- **Diet**: Single brand, dry food or frequently changing in diet
- **Environment**: seasonal, major weather events, change in activity or restriction
- **Voiding Habits**: litter box aversion, urine retention
- **Stress**: Travel, other cats, cat-people stresses
- **Concurrent anxiety disorders** (separation anxiety)

**Diagnostic evaluation for first or rare episode**

The diagnostic workup for idiopathic cystitis may reveal little more than a small bladder and hematuria, but is completed to rule out other disorders, particularly uroliths. A basic plan includes a *problem-specific and environmental history and physical examination, survey abdominal radiographs* to screen for radiopaque urolithiasis and (ideally) *urinalysis with sediment examination* (ideally collected by cystocentesis, but can be difficult to obtain).
Diagnostic evaluation for recurrent episodes or older cats
In recurrent cases, a complete minimum data base, including urine culture, and additional anatomical investigation are recommended, including repeat survey abdominal radiographs and ultrasonography that evaluate that entire urinary tract. Ultrasoundography or contrast imaging studies can help rule out small stones or neoplasia. Urethrocystoscopy or exploratory cystotomy with biopsy of bladder or urethral tissue is reserved for cats with severe or persistent hematuria, unexplained lesions observed on imaging studies and other unusual cases.

Practical management strategies for first or rare episode
Short-term relief can be used for 2 to 5 days during acute flare-ups to minimize discomfort and shorten the hematuric phase. Signs will resolve spontaneously in approximately 85% of affected cats within a few days.

- **Analgesics.** For acute flare-ups of lower urinary tract signs, short-term analgesic treatments may be useful to reduce the discomfort. Opioids also have some anti-inflammatory effects that may be beneficial in this setting.
- **Alpha adrenergic antagonism?** (Phenoxybenzamine and prazosin) Agents that may relax urethral musculature also have been recommended to facilitate urination in dysuric cats and to alleviate functional urethral obstruction in postobstructed cats.
- **Non-steroidal anti-inflammatory agents?** Nonsteroidal anti-inflammatory agents have also been recommended for analgesic and anti-inflammatory effects. No controlled studies are available to demonstrate a response from any of these agents.
- **Antianxiety treatments such as amitriptyline are NOT recommended for short term relief.**

Long term dietary and environmental strategies may be indicated early, especially if the cat is in a high risk home setting.

- **Water.** Moisture can be provided in wet food, fresh water bowls or fountains, or by adding extra water to food. For cats with urethral plugs or struvite crystalluria, canned diets designed to minimize urolith formation are recommended.
- **Dietary management.** Although dietary management can be best advocated for cats with significant crystalline or obstructive disease, many cats with idiopathic disease have reduced episodes of inflammation when fed a food formulated to prevent common feline uroliths. In addition to modified mineral content, these diets also often contain antioxidant or fatty acid profiles designed to be anti-inflammatory.
- **Feeding strategies.** Frequent feeding of small meals with added moisture also may enhance the cat’s acceptance of the food and increases positive owner-cat interactivity. Owners should strive to minimize changes in diet, as this may trigger episodes.
- **Environmental modifications and enhancements.** Modification of environment and attention to behavioral issues must be done concurrently to minimize the neuroendocrine influences on the disease. Environmental enrichment, reduction in intra-cat conflict or aggression, feeding method and litter box management are included in the potential modifications which are individualized based on a thorough environmental history (see Table).

Key take home points
- Evidence based “treatments” for long term prevention and management of FIC are limited to 1) increased moisture intake; 2) environmental modification and stress reduction and 3) specific diet modification.
- Episodes of flare up are managed primarily with analgesics.
- Diet, water intake and environment are addressed in most cases, with application of environmental enrichment.
- Additional diagnostic evaluation, especially imaging, should be performed (or repeated) in cats with frequent recurrences in order to rule out urolithiasis, infection and neoplasia.
- Feline pheromones may reduce episodes, especially when known stressors are anticipated.

<table>
<thead>
<tr>
<th>Table 1. Environmental checklist for cats with idiopathic cystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental Checklist</strong></td>
</tr>
<tr>
<td>Primary food source?</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td>Conflicts between multiple cats?</td>
</tr>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Other Aggressors or tensions?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adequate water supply?</td>
</tr>
</tbody>
</table>

618
Partially full water sources
Varied water containers and locations with full bowls

Adequate exercise?
Obesity
Lack of activity
Short directed play
Hunting games

Adequate enrichment?
No routine
No owner-cat time
Perches, scratching posts, varied play spots
Individual short play periods

Adequate vertical space?
Blocked from windows not available
Multiple levels
In main living areas
View outside (unless outdoor cats are aggressors)

Protected preferred spaces?
All Noisy rooms
Surprises in rooms
Safe hiding places
Quiet, low traffic areas
Blankets, towels or beds, boxes
Radio or tv white noise
Feline pheromones

Adequate Litter boxes?
Undesirable Substrate
Only one box
Open to “attack”
Scary
Difficult to reach unclean
Consider fresh step or scoopable litter
Appropriate placement
One per cat plus one for the house
Daily scooping

Adequate scratching opportunities?
Away from activity or sleeping areas
Unused posts
Place near resting areas
Spray pheromones
Vertical, three D types

Table 2. Key pharmacologic agents used for idiopathic cystitis in cats

<table>
<thead>
<tr>
<th>Key Drug</th>
<th>Drug Class</th>
<th>Dose Range</th>
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<td>Alpha-antagonist</td>
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<td>Meloxicam</td>
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<td>Full effects may take a while</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>GAG precursor</td>
<td>250 mg/cat</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>Allow 4 – 8 weeks to assess effect; Taper slowly if withdrawn</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Tricyclic</td>
<td>0.5 mg/kg</td>
<td>Q 24 hrs</td>
<td>PO</td>
<td>See clomipramine; usually has more adverse effects than clomipramine</td>
</tr>
<tr>
<td>Amitryptiline</td>
<td>Tricyclic</td>
<td>2.5 – 12.5 mg/cat</td>
<td>Q 24 hrs</td>
<td>PO</td>
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<tr>
<td>Feli-way pheromone</td>
<td>Environmental application</td>
<td></td>
<td></td>
<td>Multiple</td>
<td>Sprays, Diffusers and collars available</td>
</tr>
</tbody>
</table>
Most dogs with urinary incontinence are readily diagnosed and respond well to common medications. Phenylpropanolamine and estrogen treatments remain the mainstay of treatment for dogs with simple urethral incompetence, with over 90% of dogs responding to one of these medications, if prescribed and adjusted appropriately. In other dogs, severe urethral incompetence, drug intolerance, complicating factors, or a different cause of urine leakage must be addressed in order to obtain satisfactory clinical outcomes.

Diagnostic evaluation of refractory cases
For dogs that do not respond to treatment, reassessment of the diagnosis and additional investigation is warranted (Table 1).

- Although radiographic imaging is of little use in the diagnosis of functional urethral incompetence, imaging should be pursued in refractory cases and if incontinence is observed in juvenile animals or male dogs, closely follows ovariohysterectomy or other surgical procedure, is continuous or leaks from abnormal anatomic sites, is accompanied by recurrent urinary tract infection, recurrent vaginitis, hematuria, crystalluria or azotemia. Imaging procedures are chosen based on features of the case at hand. Usually, an excretory urogram in combination with CT, contrast cystourethrography or vaginourethrography is completed to fully evaluated urine storage structures. In male dogs, ultrasonographic evaluation of the prostate gland is recommended.

- Direct visualization of urogenital structures by vaginoscopy or cystoscopy is also considered indicated in challenging cases. Vaginal examination to evaluate for vaginal strictures, bands or urine pooling is suggested for female dogs with concurrent vaginitis or with incontinence that fails to respond to trial treatment. Cystoscopic examination also may allow visualization of ectopic ureteral terminations and also may be considered for further evaluation of suspected urethral or bladder neck lesions. Cystoscopic examination has become key for diagnosing intravesicular ectopic ureteral openings, which may cause intermittent, rather than continuous incontinence.

- Urodynamic assessment, including cystometrography and urethral pressure profile, can be done during the same assessment where available. These tests are most useful for 1) confirming or excluding urethral incompetence; 2) diagnosing bladder atony or overactivity, or 3) documenting multiple functional disorders.

Medical treatment strategies for refractory incontinence
Fortunately, most dogs with urinary incontinence will respond to adequate doses of either a drug with alpha adrenergic activity or estrogenic properties. Modifications in standard medications may be required periodically to maintain efficacy. Counterintuitively, a wash out period for alpha agonists and restarting the drug at once a day dosing may restore receptor sensitivity and effectiveness in some dogs. Selective partial alpha agonists targeting the urethral smooth muscle have been under development for some time; it seems unlikely that market availability will happen any time soon. Multiple estrogen products are available; different types can be tried for refractory patients. Estriol appears to be one of the more reliable human products, given once every 24-48 hours. Recommended doses for alpha agonists, estrogen treatments and other medical options are given in Table 2.

Anticholinergic agents, many of which also possess antispasmodic or analgesic properties, have been employed to enhance bladder storage of urine by competitively inhibiting (contractile) muscarinic receptors in the detrusor muscle. These agents are extensively used in human patients, leading to a high level of awareness of the drug among pet owners. Detrusor muscle overactivity, however, is extremely rare in dogs and cats when compared to the incidence of urethral incompetence. Urine leakage with changes in position, walking or jumping, or a pattern that appears behavioral contrasts with the usual resting intermittent incontinence observed in dogs with urethral incompetence. Additionally, bladder storage function has been suspected in juvenile dogs and cats with congenital incontinence, especially those with ectopic ureters or grossly hypoplastic bladders or urethras. Oxybutynin and emepronium bromide have been effective in sporadic cases; similar medications such as dicyclomine, flavoxine and the tricyclic antidepressant imipramine also have been recommended and work in isolated cases. Longer acting preparations, as well as a new antimuscarinic agent, tolterodine, are heavily marketed in the US but the author is unaware of clinical investigations in dogs. One recent report has described botulinum toxin injections into the bladder in an attempt to achieve similar results.

Alternative agents currently under investigation include gonadotropin releasing hormone (GNRH) analogs and duloxetine. Reichler et al (2003) reported their experience with luprolide, buserelin and deslorelin, GNRH analogs that suppress sex hormone release. Their use in incontinence is based on the theory that chronically unsuppressed FSH and LH release (due to lack of negative feedback) in ovarioctomized dogs may contribute to urinary incontinence. Administration of analogs paradoxically results in reduced FSH and LH over time. In 12 of 13 dogs with refractory incontinence, the drug appeared useful, either alone or in combination with alpha agonists. Deslorelin became the preferred treatment in this study but has not been widely used in North America.
Duloxetine, a serotonin and norepinephrine reuptake inhibitor, has proven useful in women with stress incontinence and may improve striated muscle resistance as well as bladder capacity. Adverse effects included nausea, fatigue, insomnia, constipation, diarrhea and headache, but were infrequent and mild. Experience is limited in small animals at this time and anecdotally, has not been highly successful. Selective serotonin reuptake inhibitors which increase urethral pressure modestly in canine models are under development.

Enhanced effectiveness can be obtained by combining medical treatment strategies, as long as the treatment plan does not lead to urinary retention or other unacceptable adverse effects. Most commonly, an alpha agonist is combined with reproductive hormone treatment. Both are started at usual doses, then both can be tapered to the lowest effective combination dosage. Although clinical experience has led to the continued recommendation of this combination, recent urodynamic data failed to support this recommendation. Alpha agonist or estrogen treatment can also be combined with an anticholinergic agent to improve urine storage; urinary retention is a possible hazard with this treatment strategy. Imipramine, a tricyclic antidepressant, possess both urethral adrenergic effects and anticholinergic effects, serving to provide similar “combination” effects. As noted above, dogs treated with GnRH analogs often require added phenylpropanolamine for optimal success.

### Table 1. Potential causes for refractory urinary incontinence

<table>
<thead>
<tr>
<th>Cause or complicating factor</th>
<th>Possible solution(s)</th>
</tr>
</thead>
</table>
| Inadequate dosage or frequency of administration of medication | • Increase dosage within recommended range.  
• Increase frequency of estrogen (up to q 2 days) as tolerated  
• Change product type |
| Desensitization of alpha receptors? | • Consider washout period and restart alpha agonist at q 24 hr administration |
| Inappropriate medication | • Consider change from estrogen to alpha agonist administration  
• Consider addition of estrogen to alpha agonist administration |
| Poor owner compliance | • Consider switch to long-acting alpha agonist or to estrogens to improve compliance (or vice versa) |
| Underlying urinary tract infection | • Monitor for UTI and treat appropriately |
| Underlying polyuria | • Evaluate for common, treatable polyuric disorders (e.g. hyperadrenocorticism, diabetes mellitus) |
| Mixed disorder of micturition | • Consider addition or trial treatment with anticholinergic agent |
| Underlying anatomic abnormality or urine pooling | • Investigate anatomy with contrast radiography and/or cystoscopy  
• Consider endoscopic management of ectopic ureter or vaginal/vulvar abnormality |
| Underlying neurologic lesion | • Investigate for subtle lumbosacral disorder with neurologic examination and imaging studies |
| Behavioral component or senility | • Consider treatments for behavioral disorders or cognitive dysfunction |
| Refractory urethral incompetence | • Consider bulking agents to enhance medical management; consider artificial sphincter in severe, refractory cases |

### Endourological and surgical treatments

**Bulking agents** also can be injected cystoscopically to mechanically improve urethral resistance. Bulking agents not only provide filler but appear to influence the length and strength of smooth muscle fibers. Bulking agents are most effective at improving response to medical treatment in refractory dogs for 6 – 30+ months and can be repeated as needed. Most commonly, good responses are sustained for a year or slightly more than a year. Many dogs will still require adjunct medical management for control of incontinence. Collagen formulations are most commonly used but can be expensive and challenging to obtain. Under general anesthesia and using a cystoscopic approach, two to three blebs of collagen are injected into the urethral submucosa, at circular points just distal to the bladder trigone. The amount and number of injections are titrated to occlude the lumen sufficiently without causing urinary obstruction. Repeated injections can be done as needed (usually within 1 – 2 years). Other agents, including polydimethylsiloxane (silicone) and hyaluronic acid/dextranomer copolymer, have proven effective and nonreactive in women and are being investigated in dogs.

**Episioplasty.** Some incontinent dogs also have vaginal, vestibular or vulvar conformational abnormalities. Although it is not entirely clear how these conformational problems contribute to incontinence, urine retention in the vestibule and vagina may lead to urine pooling, episodic leakage, and recurrent urinary tract infection. In a group of dogs reviewed by Hammel and Bjorling, 19 dogs had refractory urinary incontinence as part of their clinical presentation. Incontinence resolved with surgery alone in 6 dogs, and an additional 9 had improved response to PPA after vulvoplasty. This procedure seems to be most valuable in dogs with a pattern of urine dribbling or spotting after voiding. The procedure can be especially useful in dogs also suffering from recurrent urinary tract infections.
The long-term experience with surgical treatment of urinary incontinence has been less favorable in dogs (with most dogs relapsing by one year post-operatively, so most clinicians now prefer bulking injections rather than surgical intervention for refractory female dogs.

Most recently, experience with an implanted artificial sphincter (hydraulic occlude) device has been reported in male and female dogs. Improved continence can be achieved long term with this device, which provides resistance around the urethra based on how much is infused into a port to expand the luminal pressure of the implanted ring. The device can be cumbersome to manage, however, and post-operative or delayed urethral obstruction is a recognized complication.

Prognosis
The prognosis is good for most adult female dogs with urethral incompetence. Most dogs respond well to one of the commonly used medical treatments. Prognosis is guarded for long term control of incontinence in dogs that develop incontinence at an early age, males or dogs with significant anatomical abnormalities. Prognosis is also guarded for certain breeds affected by urethral incompetence: Doberman pinschers, Retrievers, English Springer Spaniels.

Key points
- Most dogs with urethral incompetence respond well to common medications or combinations of common medications. Modification of drug type, dosage or frequency is usually the first approach to refractory cases.
- When medical treatment fails, a diagnostic reevaluation is in order, considering the diagnosis and investigating concurrent disorders.
- Unusual patterns of urine leakage suggest anatomic abnormalities, urine pooling or bladder overactivity, which may respond to surgical or antimuscarinic treatments.
- Urethral bulking agents are effective in many dogs with confirmed urethral incompetence refractory to medical treatments.

| Table 2. Key pharmacologic agents used in the management of urethral incompetence |
|---|---|---|
| **Agent** | **Classification** | **Recommended Dosage (Dogs)** |
| Diethylestilbestrol (DES), Stilbesterol | Reproductive hormone | 0.1 - 1.0 mg/dog PO q 24 hrs for 5 - 7 days, then weekly or as needed |
| Stilbesterol (Alternate Regimen) | Reproductive hormone | 0.04 - 0.06 mg/dog PO q 24 hrs for 7 days, reduced weekly to 0.01-0.02 mg/dog/day |
| Premarin | Conjugated estrogen | 0.02 mg/kg PO q 24 hrs for 5 - 7 days or until continent, then q 1 - 4 days or as needed |
| Estriol (alternate regimen) | Reproductive hormone | 2.0 mg/dog PO q 24 hrs for 7 days, then reduce daily dose by 0.5 mg each week to establish minimal effective daily dose; then try every other day administration. |
| Phenylpropanolamine | Alpha agonist | 1.5 mg/kg PO q 8 - 24 hrs; some dogs may require less frequent administration |
| Ephedrine or Pseudoephedrine | Alpha agonist | 1.2 mg/kg PO q 8 hrs |
| Imipramine | Antimuscarinic, alpha/beta agonist | 5 - 15 mg PO q 12 hrs |
| Oxybutynin | Antimuscarinic | 0.2 mg/kg PO q 8 - 12 hrs |
| Dicyclomine | Antimuscarinic | 5 - 10 mg/dog PO q 8 hrs |
| Duloxetine | Norepinephrine and serotonin reuptake inhibitor | Undetermined |
| Deslorelin | GNRH analog | 5 – 10 mg depot injection/dog (see references for detail) |
Pathophysiology of micturition and incontinence

Urinary incontinence represents a failure of urine storage. Urine storage normally is maintained by relaxation and accommodation of the urinary bladder and contraction and closure mechanisms of the urethra:

- Sympathetic nervous innervation is provided to the urinary bladder and urethra via the hypogastric nerve
- Beta adrenergic receptors are active in the urinary bladder and alpha adrenergic receptors are active in the smooth muscle of the urethra during storage
- Additional resistance to urine leakage is provided by striated muscle interspersed in certain parts of the urethra and innervated by the pudendal nerve
- Some basal tonic activity maintains closure during alert/awakeness
- Reflex increased contractile activity occurs when intrabdominal pressure increases
- The urethra also is characterized by multiple folds and a rich, moist urethral epithelium that increases closure.

When the urinary bladder extends past a threshold volume or pressure, signals are transmitted to higher centers and the house-trained animal will initiate voluntary urination when appropriate. After complete bladder emptying, the systems “reset” for urine storage. Medical management of urinary incontinence usually is directed at improving smooth muscle or mechanical resistance in the urethra.

Although urinary incontinence can be caused by anatomical disorders (ectopic ureteral termination, or hypoplastic urethra), neurogenic disruption of urethral function (usually lower motor neuron disorders) or urinary bladder storage failure, the most common clinical presentation is urethral incompetence.

Urethral incompetence is a failure of urethral closure mechanisms to prevent urine leakage during storage.

- Urine leakage usually occurs intermittently at rest, with a variable frequency.
- Urethral incompetence is most common in large breed spayed female dogs, but can develop in any neutered dog.
- Onset is usually within 3 years of ovariohysterectomy, but a geriatric onset is also common.
- Possible risk factors include conformation, bladder neck position, tail docking, and obesity. Chronic elevations in FSH and LH as well as changes in collagen content in spayed dogs may play a role.
- Conflicting reports exist regarding whether early ovariohysterectomy affects risk of urinary incontinence. Based on a meta-analysis of available studies, the only well documented impact on risk is very early OHE (risk increases in dogs spayed prior to 3 months of age). Individual risk factors must be considered in each case (genital conformation, breed, etc.) and the benefits of OHE still tend to outweigh the risk of incontinence for most dog owners.
- In a survey study of over 500 spayed dogs in the US, the overall incidence of incontinence was about 5%; body weight was the only significant risk factor increasing the odds of post-spay incontinence. The prevalence in small dogs was quite low (1.4%) whereas it increased in dogs > 20 kg (9%).

Diagnostic approach

Perhaps the most important diagnostic tool is a detailed patient history. Historical questions should be prepared in order to:

- Distinguish leakage of urine from urethral or vaginal discharge;
- Determine if urine leakage is truly involuntary as opposed to behavioral;
- Establish the pattern and frequency of urine leakage;
- Determine onset of urine leakage in relation to age, reproductive status and neutering;
- Establish whether any other signs of neurologic disease, prostatic disease (males) or pelvic disorders are likely;
- Establish whether polydipsia/polyuria is contributing to urine leakage.

Physical examination

- Urinary bladder size to determine whether bladder is small versus distended
- Rectal or vaginal examination to rule out prostatic or urethral disease
- Cursory neurologic examination including tail tone, perineal sensation, vulvar reflexes
Observation of urination and urinary bladder emptying
Urinalysis and urine culture is indicated in all cases in order to detect UTI or polyuria
Imaging if indicated:

- Consider survey radiographs in dogs with UTI and in cats with urinary disorders in order to rule out urolithiasis
- Consider survey radiographs and abdominal sonography in young dogs to further evaluate anatomy and in older dogs to screen for neoplastic lesions
- Perform extended anatomical evaluation in dogs < 1 year of age or in complex, refractory cases
  - May include cystoscopy, contrast radiography
  - Some clinicians advocate cystoscopy in all challenging incontinence work-ups
- Perform extended neurological imaging if indicated for neurologic deficits

Referral for urodynamic measurements may be considered for complex or refractory cases, or if multiple disorders are suspected

Note: Signs that do not usually fit with a diagnosis of urethral incompetence include:

- Continuous urine dripping
- Dribbling after urinating
- Leakage while up and moving
- A large bladder with overflow incontinence
- Frequent urination or urine deposited in odd locations (corners, etc)

Initial medical treatment strategies for urethral incompetence

General management

- Monitor and treat urinary tract infection
- Encourage good training and frequent voiding opportunities to keep bladder small
- Help clients recognize conditions that exacerbate incontinence, including strenuous exercise, inappropriate excessive water intake, medications.

Reproductive hormones

- **Estrogen** administration enhances urethral closure function primarily by increasing the number and responsiveness of alpha receptors in urethral smooth muscle. Estrogen also has effects on urethral mucosa, submucosal blood flow and density of peri-urethral collagen.
- **Diethylstilbestrol** (0.1-1.0 mg/dog q 24 h for 5-7 days followed by once or twice weekly administration) has been utilized for some time with reasonable safety and efficacy.
- **Estriol** has become a favored estrogen product in Europe and is available in the US (Incurin, Merck). Improved to excellent responses were obtained in about 80% of treated dogs in a large group studied in western Europe. Product information for Incurin report improvement or continence in 99% of treated dogs by six weeks of treatment. The starting dose is 2 mg/dog estriol per day for a week, then the dose was reduced at weekly intervals to the minimal effective dose (typically 0.5 - 2.0 mg/dog given daily or every other day). Adverse effects were rare, but included signs of estrus at the initial estriol dose, which resolved in all but one dog after dose reduction. No adverse hematologic effects were observed at day 42 in this study.
- **Premarin**, a conjugated estrogen extracted from pregnant mare urine, was prescribed extensively in the US during the early 2000s when other estrogens were unavailable and appeared effective in some dogs. Unlike DES, a twice to three times weekly dosing seemed necessary based on clinical experience and anecdote. Response to a similar product was followed prospectively in 9 incontinent large breed dogs (reported by Angioletti et al). All dogs responded well to estrogen administration; daily administration was continued until two weeks of continence had been obtained. In seven of nine dogs, maintenance dosages ranged from 0.625 mg to 1.25 mg per dog, administered PO every 12 – 72 hrs. In the remaining two dogs, administration every 4 to 7 days was effective. No adverse hematologic effects of estrogen were observed in treated dogs for up to 49 months.
- **Adverse effects** are rare at maintenance doses but can include signs of estrus, behavioral changes and hair loss. Bone marrow suppression is very unlikely with usual doses.

Sympathomimetic (Alpha) agonists

- Available sympathomimetic agents have an indirect and nonselective effect on the urethral alpha receptors. Sympathomimetic agents can be used in male or female dogs and in dogs for whom reproductive hormones are not advised or not tolerated. Typically, alpha agonist agents are so reliable that they can be used for short trial periods to confirm your diagnosis.
- Excellent responses have been observed in most dogs treated with **phenylpropanolamine** (PPA, 1.5 mg/kg PO q 12 – 24 h), with 90% or greater responding in small studies.
• Frequency of PPA administration required for continence varies from one to three times daily. Some dogs may have acceptable continence with once daily (or less frequent) administration. Some evidence exists that once daily administration may produce effective urethral response and minimize tolerance or receptor fatigue in treated dogs. Urodynamic responses in healthy dogs treated with the drug actually decreased with increased dosing frequency. Although we have previously recommended starting with a high frequency, then tapering down to the minimally effective dose and frequency, an opposite approach may be reasonable in dogs with mild incontinence.

• Ephedrine and pseudoephedrine are alternative alpha agonists with similar effects on urethral function. Their clinical use increases during periods when PPA is difficult to obtain. Nendick and Clark described pseudoephedrine (15 – 30 mg q 8 – 24 hrs) as totally effective in 14/17 (82.4%) dogs in a retrospective study. Arnold found good results with ephedrine (1-2 mg/kg q 12 hrs) in 28 of 38 (74%) female dogs, with some improvement noted in 37 of the 38. In a crossover study of a smaller number of dogs, Byron et al found more adverse effects with pseudoephedrine treatment, including changes in appetite and behavior. In that study, PPA was also slightly more effective than pseudoephedrine, consistent with the earlier reports.

• Adverse effects are fairly rare in treated patients.
  o Most commonly, dogs exhibit other sympathomimetic responses (agitation, panting, tachycardia) although central effects are possible (anorexia, unusual behavior, aggression). Typically, these effects resolve with reduced dosage or frequency although occasional dogs will not tolerate the drug.
  o Systemic hypertension or adverse cardiac effects are the most worrisome potential side effects. Although hypertension has not been reported in clinical reports, healthy beagles had mild increases in blood pressure when administered phenylpropanolamine. Two of these dogs had at least one recording of significant hypertension.
  o Sympathomimetic agents should be avoided or used with careful monitoring in patients with cardiac disease, renal disease or other uncontrolled hypertensive disease.

| Table 1. Comparison of alpha agonists and reproductive hormones for management of urinary incontinence in dogs |
|--------------------------------------------------------|---------------------------------------------------------------|
| **Effectiveness**                                      | **Estrogens**                                                 |
| 75 - 90% excellent results                            | 40 - 65% excellent results (DES)                              |
| 80-90% improved (estriol)                             |                                                               |
| **Indications**                                        |                                                               |
| Males or females, dogs or cats                        | Female dogs                                                  |
| Poor response to estrogen                             | Combination with alpha agonists                               |
|                                                      | Recurrent UTI or vaginitis?                                   |
| **Administration frequency**                          | q 1 - 14 days, depending on preparation                       |
| q 12 - 24 hrs; note tolerance may develop with higher frequency |                                                               |
| **Residual effects**                                  |                                                               |
| Short                                                 | Possibly prolonged                                           |
| **Adverse effects**                                   |                                                               |
| Hyperactivity                                         | Behavioral change                                            |
| Hypertension                                          | Estrus/swollen vulva                                          |
| Anorexia, weight loss                                 | Exacerbation of immune-mediated disease?                     |
| Hypertension?                                         | Bone marrow toxicity? (very rare)                            |

Monitoring and follow up
- All affected dogs should have a urinalysis and urine culture performed once or twice yearly, or if signs worsen.
- Dogs with breed association or clinical signs suggestive of hypothyroidism should have periodic thyroid evaluation.
- Dogs managed with estrogen products should have an initial and then annual CBC.
- Dogs managed with phenylpropanolamine should have initial and periodic follow up blood pressure measurements.
- Additional diagnostic evaluation is indicated if incontinence becomes refractory to medications.

Key points
- Urethral sphincter mechanism incompetence is the most common micturition disorder encountered in practice.
- Intermittent resting urinary incontinence in an otherwise healthy young spayed female dog is most likely due to urethral incompetence.
After ruling out urinary tract infection, most cases will respond to trial treatment with either phenylpropanolamine or estrogen treatment. An acceptable treatment response can be defined as a significant reduction in incontinence; occasional episodes of incontinence still may be observed.

When appropriate formulations and dosing regimens are used, alpha agonist and estrogen treatments are quite safe and effective.

“Bladder Management” is also important – frequent opportunities to urinate, outdoor access, late night walk to void.

Periodic follow up of blood pressure and routine data base (CBC, chemistry, UA and culture) is indicated in treated dogs. Adjustments of medications may be required for relapses.