URINE HEAVEN

Joe Bartges, DVM, PhD, DACVIM, DACVN
Professor of Medicine and Nutrition
The Acree Endowed Chair of Small Animal Research
jbartges@utk.edu

Amanda Callens, BS, LVT
Veterinary Nurse, Nephrology and Urology
acallens@utk.edu
Phone: 865-755-3359
FAX: 865-974-5733

The University of Tennessee
Veterinary Medical Center
Knoxville, TN 37996-4544
General Key Points:

• CKD implies irreversible renal failure that remains stable for a period of time, but ultimately progresses.

• Incidence increases with increasing age in dogs and cats.

• Although many things can cause chronic kidney disease, by the time chronic kidney disease is diagnosed the cause(s) is/are not present and not treatable. It can occur as a result of:
  * Congenital renal disease
  * Acquired diseases – hypotension, drugs, toxins, hypotension, infections, cancer
  * Periodontal disease has been linked to renal histologic changes in dogs
  * Feline immunodeficiency virus infection has been linked to renal disease in cats

• Kidneys are involved with whole body homeostasis; therefore, CKD affects general well-being.

• Clinical signs involve primarily:
  * Change in water balance: polyuria / polydipsia (PU / PD)
  * Gastrointestinal signs (vomiting, hyporexia / anorexia, halitosis)
  * Signs of chronic disease (weight loss, loss of body condition, unkempt appearance)

• Laboratory evaluation reveals:
  * Azotemia
  * Inappropriately dilute urine
  * Hyperphosphatemia
  * Metabolic acidosis
  * ± Hypokalemia
  * ± Non-regenerative anemia
  * ± Bacterial UTI
  * Kidneys are often small and irregular on palpation, abdominal radiography and abdominal ultrasonography; however, some causes of chronic kidney disease are associated with renomegaly (ie neoplasia)
  * ± Systemic arterial hypertension occurs in 65-80% of patients
  * ± Proteinuria (microalbuminuria, macroalbuminuria)
  * Progression of CKD
  * The cause(s) of progression of CKD is not completely known
  * It is likely that in typical situation, CKD results from repeated insults over time that result in sequential loss of nephrons
  * The compensatory response is an increase in single nephron GFR in the surviving nephrons
  * This results in maintenance of total GFR despite loss of functional renal tissue (renal reserve)
  * There is dilation of the afferent arteriole
  * Increase in intraglomerular pressure
  * The result is increase in GFR and renal blood flow
  * There are trade-offs, however:
    * Increase in GFR due to increase in renal blood flow and intraglomerular pressure increases likelihood of increased protein loss
    * Increased intraglomerular pressure is transmitted distally
    * There is activation and release of growth factors that promote tubulointerstitial fibrosis and glomerulosclerosis
    * Eventually, these adaptations result in loss of further nephrons and the cycle continues
    * Over time, renal reserve is lost as the threshold of nephron mass loss is surpassed resulting in progression of CKD to end stage

International Renal Insufficiency Society (IRIS) Staging:

• The International Renal Insufficiency Society (http://www.IRIS-kidney.com) has developed staging system for animals with CKD and treatment based on staging.

• The staging system is designed for use with dogs and cats with CKD. A diagnosis of CKD is made first and staging is accomplished by evaluating.
(1) 2 serum creatinine values when patient is well hydrated,
(2) 2 to 3 urine UPC and
(3) 2 to 3 indirect arterial blood pressure determinations.

- Indirect arterial blood pressure is determined by 1 of 2 methods
  - **Doppler**: this utilizes ultrasonographic waves that are transmitted by a piezoelectric crystal and is reflected back to the crystal and then converted to audible sound
    - It utilizes the Doppler shift effect – you know the sound an ambulance or race car makes as it approaches and then drives by you (?)
    - Blood in an artery is moving while surrounding tissue is not
    - It is very good for systolic blood pressure, but is not very accurate for measuring diastolic and mean arterial pressure
    - A cuff is placed over the artery proximal to placement of the piezoelectric crystal
    - The crystal is placed on a shaved area over the artery
    - The cuff is inflated above systolic blood pressure so no flow of blood occurs in the artery
    - The cuff is slowly released until blood flow is re-established, which is the systolic blood pressure
    - A sphygmomanometer (gauge) is used to give a numeric value to the systolic pressure
  - **Oscillometric**: this utilizes the principle of movement (oscillations) and the intensity of vascular wall vibration (movement) from the pressure
    - It can determine systolic, diastolic, and mean arterial pressure
    - Although useful, it is less accurate than Doppler
    - A cuff attached to the oscillometric blood pressure instrument is placed over an artery. No clipping is necessary
    - Pressure in the cuff is increased until it exceeds systolic blood pressure and no flow of blood occurs in the artery
    - The instrument slowly releases pressure from the cuff and detects vascular wall vibrations as blood flow is re-established.
      - The first vibration = systolic
      - The most intense vibration = mean
      - The point where vibrations level off = diastolic
  - Indirect arterial blood pressure is determined over the palmar metacarpal, cranial tibial, or coccygeal arteries
  - It is important to perform when patient is not stressed; therefore, having the owner hold, use minimal restraint, perform away from people and other patients, and perform prior to sample collection and physical examination
  - Systemic arterial hypertension may occur in 65-75% of dogs and cats with CKD

- CKD is staged by magnitude of renal dysfunction and further modified (sub-staged) by presence or absence of proteinuria and/or hypertension. Proteinuria ONLY refers to renal proteinuria and not pre-renal (e.g. hyperglobulinemia) or post-renal (e.g. urinary tract infection, hematuria, etc), and is based on UPC. Blood pressure determination should be performed several times in order to account for a “white coat” effect using a standard protocol.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Plasma creatinine</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mg/dl</td>
<td></td>
</tr>
<tr>
<td>Dogs</td>
<td>Cats</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;125 &lt;1.4</td>
<td>Non-azotemic Some other renal abnormality present e.g. inadequate concentrating ability without identifiable non-renal cause; abnormal renal palpation and/or abnormal renal imaging findings; proteinuria of renal origin; abnormal renal biopsy results</td>
</tr>
<tr>
<td></td>
<td>&lt;140 &lt;1.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>125 - 179 1.4 - 2.0</td>
<td>Mild renal azotemia [lower end of the range lies within the reference range for many labs but the insensitivity of creatinine as a screening test means that animals with creatinine values close to the upper limit of normality often have excretory failure] Clinical signs usually mild or absent</td>
</tr>
<tr>
<td></td>
<td>140 - 249 1.6 - 2.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>180 - 439 2.1 - 5.0</td>
<td>Moderate renal azotaemia Many systemic clinical signs may be present</td>
</tr>
<tr>
<td></td>
<td>250 - 439 2.9 - 5.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;440 &gt;5.0</td>
<td>Severe renal azotaemia Many extra-renal clinical signs present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UPC value</th>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>Cats</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>0.2 to 0.5</td>
<td>0.2 to 0.4</td>
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<tr>
<td>&gt;0.5</td>
<td>&gt;0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic BP mm Hg</th>
<th>Diastolic BP mm Hg</th>
<th>Adaptation when breed-specific reference range is available *</th>
<th>Substage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>&lt;95</td>
<td>&lt;10 mm Hg above reference range</td>
<td>AP0: Minimal Risk (N)</td>
</tr>
<tr>
<td>150 – 159</td>
<td>95 - 99</td>
<td>10 – 20 mm Hg above reference range</td>
<td>AP1: Low Risk (L)</td>
</tr>
<tr>
<td>160 – 179</td>
<td>100 - 119</td>
<td>20 – 40 mm Hg above reference range</td>
<td>AP2: Moderate Risk (M)</td>
</tr>
<tr>
<td>= 180</td>
<td>= 120</td>
<td>= 40 mm Hg above reference range</td>
<td>AP3: High Risk (H)</td>
</tr>
</tbody>
</table>

**Blood pressure not measured**
No complications (nc)
Complications (c)
Risk not determined (RND)
**MANAGEMENT OF CKD**

* Goal of management is to minimize excesses and deficits induced by CKD in order to improve quality and quantity of patient’s life
* Summarized using the acronym NEPHRONS

<table>
<thead>
<tr>
<th>N</th>
<th>Nephrons</th>
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</thead>
<tbody>
<tr>
<td>E</td>
<td>Electrolytes</td>
</tr>
<tr>
<td>P</td>
<td>pH of blood (acid-base status), proteinuria</td>
</tr>
<tr>
<td>H</td>
<td>Hydration status</td>
</tr>
<tr>
<td>R</td>
<td>Retention of wastes</td>
</tr>
<tr>
<td>O</td>
<td>Other renal insults – avoid</td>
</tr>
<tr>
<td>N</td>
<td>Neuroendocrine changes</td>
</tr>
<tr>
<td>S</td>
<td>Serial monitoring</td>
</tr>
</tbody>
</table>

* **NUTRITION**
* Maintain adequate to optimum body condition and adequate muscle condition (lean body mass)
* Body condition scoring (you will learn in nutrition)
* Want a body condition score of 3/5 or 5/9
* There are formulae to estimate daily caloric requirements (you will learn in nutrition)

**Anorexia and nausea** occur commonly with chronic kidney disease. Treatment includes:
* Minimizing excesses and deficiencies
  * Feeding a highly palatable diet or increasing palatability of diet – add water to dog food, use flavoring agents, warm food to near body temperature
  * Modifying feeding patterns – feed frequent small meals, offer rewards, prevent food aversion
  * Treat uremic gastroenteritis
    * Dietary protein induces gastric HCl secretion; therefore, dietary protein restriction is associated with decreasing gastric acid
    * Gastrin levels are increased with CKD
    * Gastrin stimulates HCl production and secretion by gastric parietal cells
    * Results in gastric hyperacidity
    * H2 blockers: decrease HCl secretion by blocking the histamine-2 receptor on parietal cells of stomach. It is reasonable to put all patients with CKD on these (e.g. Ranitidine, Famotidine)
    * Sucralfate: a mucosal protectant that forms a “physiologic band-aid” on active ulcers by binding to exposed submucosal collagen in an acidic environment. May also have cytoprotectant effects via PGE2. Additionally, it is a weak antacid and phosphate binder as it contains aluminum hydroxide.
    * Antacid: are not typically used with CKD although many are available. Usually these are used as phosphate binders.
    * Mirtazapine (Remeron): a noradrenergic and serotonergic antidepressant. It stimulates appetite and is an anti-emetic
    * Maropitant (Cerenia): a neurokinin-1 (NK-1) antagonist that is used for motion sickness and is an anti-emetic.
    * Misoprostol (Cytotec): a prostaglandin E2 analog that increases blood flow to gastric mucosa and increases stir layer on mucosal surface. Not used routinely, but good for prevention of NSAID-induced gastric ulcers
  * Gastrostomy feeding tubes may be used to facilitate nutritional management as well as used for medication administration and fluid support.
  * One theory of progression of CKD involves intraglomerular hypertension in the remaining nephrons. This is beneficial in that it keeps GFR up; however, the intraglomerular hypertension may ultimately result in loss of surviving nephrons and progression.
  * Feeding diets containing omega-3 fatty acids may be beneficial in dogs
  * Omega-3 fatty acids decrease intraglomerular hypertension, maintain GFR, and prolong survival
  * An omega-6 to omega-3 fatty acid ratio of 3:1 to 5:1 appears to be a reasonable intake and is present in many renal failure diets
* **Rubenal**
  * An extract of medicinal rhubarb (*Rheum officinale*)
**RenAvast**
- Proprietary mixture of amino acids and peptides
- Unproven in a controlled, published study

**ELECTROLYTES**

**Potassium**
- **Hypokalemia** may occur especially in cats due to
  - Anorexia
  - Excessive renal and fecal losses
  - Chronic metabolic acidosis (transcellular shift)
  - Activation of renin-angiotensin-aldosterone system (RAAS)
- Clinical signs of hypokalemia include
  - **Polymyopathy** – classic sign is an animal that cannot lift its head while sitting sternally; however, generalized weakness may occur more commonly
  - **Worsening renal failure
  - Anorexia**

**Treatment**
- Potassium (as potassium chloride) may be added to IV or SQ fluids
- Potassium is often present in renal failure diets as potassium citrate
- Potassium may be supplemented orally using potassium gluconate or potassium citrate
- Potassium citrate provides alkalinization as well as potassium
- May cause GI upset – related to formulation not to drug
- E.G. If problems with liquid – try powder, granules, or tablets
- Serum potassium concentrations should be maintained in middle to upper half of normal range

**Sodium**
- Changes in serum sodium concentration occur rarely
- Sodium retention occurs with chronic kidney disease resulting in expansion of extracellular fluid volume and hypertension
- Moderate sodium restriction beneficial
- Decrease fluid retention
- Synergistic with anti-hypertensive medications
- Excessive restriction may activate RAAS promoting urinary potassium excretion
- In one study, high salt intake (1.2%) was associated with increasing azotemia in cats with CKD

**PH OF BLOOD (ACID-BASE STATUS)**

**Metabolic acidosis** occurs commonly
- Occurs because of retention of organic acids, decreased renal ability to regenerate and reclaim bicarbonate, decreased ammoniagenesis (ammonia is a buffer and is renally excreted with acid), generation of acids from catabolism,

**High anion gap metabolic acidosis**
- There is actually no anion gap
- “the body is not a battery” – negative charged ions (anions) must equal the positive charged ions (cations)
- Anion gap = (Na+ + K+) – (HCO3- + Cl-)
- 0 = (unmeasured cations (UC) + Na+ + K+) – (unmeasured anions (UA) + HCO3- + Cl-)
- UA – UC = (Na+ + K+) – (HCO3- + Cl-)
- UA are acids; body cannot tolerate much of a change in UC
- With an increase in unmeasured anions -> decrease in bicarbonate with a subsequent increase in anion gap

(high anion gap acidosis)
- With loss of bicarbonate (base) from body -> decrease in bicarbonate but an increase in chloride to compensate with subsequent normal anion gap (hyperchloremic normal anion gap acidosis)
- Metabolic acidosis may cause anorexia, hypokalemia, muscle weakness; however, it does not appear to directly influence progression
- Serum bicarbonate or total carbon dioxide concentration can be used to estimate blood bicarbonate levels
- Try to maintain a normal concentration
Treatment

Many renal failure diets contain potassium citrate, an alkalinizing agent
Because metabolism of dietary protein results in production of organic acids, dietary protein restriction decreases amount of organic acid that must be excreted by kidneys
Alkalinizing agents (potassium citrate or sodium bicarbonate):
- **Potassium citrate** may be preferred because it provides potassium in addition to its alkalinizing properties
- Sodium bicarbonate administration results in a large sodium load that may worsen hypertension and fluid retention, but has been used

### Proteinuria
- Proteinuria is not just a marker of glomerular disease
- Proteinuria appears to be nephrotoxic
  - Stimulates renal fibrosis and activates inflammation
- Indicated when:
  - CKD IRIS stage 1: UPC > 2.0
  - CKD IRIS stage 2-4: UPC > 0.4 (cats), > 0.5 (dogs)
- Treatment
  - Low protein diet (renal failure diet)
  - ACE-I: decreases intraglomerular pressure
  - Omega-3 fatty acids

### HYDRATION
- Polyuria due to chronic kidney disease is offset by a compensatory polydipsia
- Dehydration occurs if water intake does not equal water loss
- Treatment
  - **Oral**
    - Clean fresh water should be available at all times
    - Water may be added to food or a canned diet may be fed
    - Flavoring agents, such as broth, may be added to food
  - **Intravenous**
    - In a dehydrated animal, address 3 parts of fluid therapy
    - Amount needed for rehydration: %dehydrated x BW\textsubscript{kg} = liters needed for rehydration
    - Maintenance: for healthy animals: 50-70 ml/kg/day
    - Amount necessary to replace fluid lost as vomitus, diarrhea, or third-spaced fluid
    - Animals with chronic kidney disease, especially cats, may require subcutaneously administered fluids to maintain hydration and prevent dehydration
    - Usually 75-150 ml are administered q12-72hr
    - Use a non-glucose containing electrolyte solution such as lactated Ringer’s solution, Ringer’s solution, etc
    - An implantable device is available for long term subcutaneous fluid administration (GIF-Tube); however, many complications

### RETENTION OF WASTES
- Elimination of wastes particularly nitrogen-containing compounds is an important function of the kidneys
- **Reduction of dietary protein** seems logical
- Studies are contradictory whether protein reduction slows progression
- Dietary protein restriction may be associated with
  - Decreased degree of azotemia
  - Decreased serum phosphorous concentration (meat-based protein is also high in phosphorous)
  - Decreased metabolic acids
  - Decreased gastric acidity (protein digestion occurs in stomach and gastric acid secretion is stimulated, in part, by dietary protein)
- Two studies, one in cats and one in dogs, of spontaneously occurring renal failure, demonstrated a beneficial effect from feeding a renal failure diet when compared with feeding a maintenance diet
  - Animals lived longer
  - Episodes of uremia were less frequent and time to onset of first episode was longer
  - Owners perceived quality of life was better
Renal failure diets differ from maintenance in other ways. But, level of dietary protein found in renal failure diets is adequate for maintenance of adult animals is not likely to be associated with protein malnutrition.

**Prebiotics:** Feeding diets that contain soluble fiber may redistribute a small amount of nitrogen into the gut for elimination thus decreasing the amount required by the kidneys to eliminate (“nitrogen trapping”).
- Soluble fiber promotes bacterial proliferation in the colon.
- This proliferation requires nitrogen.
- The major source of nitrogen is blood urea nitrogen.
- Thus, promoting colonic bacterial proliferation may decrease blood urea nitrogen concentration.
- The effect is small and studies are lacking to demonstrate an effect on survival or quality of life.

**Probiotics:** involve administering live bacteria. One formulation, Azodyl, is marketed as “enteric dialysis”. In one study of cats with CKD, there was no benefit and administration of Azodyl was not associated with decreasing the degree of azotemia.

**OTHER RENAL INSULTS – AVOID**
- Dehydration may precipitate an acute renal failure episode making the chronic kidney disease worse.
- Certain drugs may be directly nephrotoxic or may worsen renal failure.
  - Gentamicin
  - Amphotericin
  - Urinary acidifiers
  - Catabolic drugs – glucocorticoids, immunosuppressive drugs
  - Non-steroidal anti-inflammatory drugs
    - May be nephrotoxic if given in high enough dose
    - Are not nephrotoxic when given at recommended dosages, but are a risk factor for renal failure.
    - By decreasing production of prostaglandins, vasodilatory prostaglandins may also be decreased.
    - If hypotension or hypovolemia occurs, blood flow to renal medulla is compromised due to decreased activity of vasodilatory prostaglandins resulting in ischemia and renal tubular necrosis.
- Risk of bacterial urinary tract infection is increased.
  - Concentrated urine is a defense against bacterial urinary tract infection.
  - Dilute urine occurs with chronic kidney disease.
  - Premature apoptosis of white blood cells.
  - Clinical signs may be absent because of polyuria.
  - May worsen chronic kidney disease.
  - Ascending infection from urinary bladder to kidneys.
  - May be part of cause of chronic kidney disease.
  - Prophylactic antibiotics should be avoided.
    - May select for resistant organism.
    - Some antibiotics are nephrotoxic.
    - Most antibiotics are renally excreted and so their kinetics are altered by chronic kidney disease.
    - Administration may have side effects – anorexia, vomiting, diarrhea.
    - Only use antibiotics if a bacterial infection is documented.
    - Because of dilute urine, bacteriuria, pyuria, and hematuria may not be obvious.
    - Urine culture of a sample obtained by cystocentesis is best.

**NEUROENDOCRINE FUNCTION**

**Renal hyperparathyroidism**
- Occurs, in part, because of phosphorous retention and decreased calcitriol (vitamin D3) metabolism by the failing kidneys.
- Hyperphosphatemia may result in renal mineralization and loss of nephrons.
- Fibrous osteodystrophy (rubber jaw).
- Hyperphosphatemia is associated with progression of chronic kidney disease and of shortened survival.

**Treatment**
- Goal is to decrease serum phosphorous concentration to
  - < 4.5 mg/dl with stage 2
  - < 5.0 mg/dl with stage 3
  - < 6.0 mg/dl with stage 3
* Lower is better.
* Serum phosphorous concentration may be decreased by:
  * Feeding a low phosphorous diet (renal failure diets)
  * Administering phosphate binders
    * Administer with food – the idea is to bind phosphorous within the gastrointestinal tract. Side-effects are anorexia and constipation
  * Aluminum hydroxide
    * Phosphorous binder as well as antacid
    * Conventional drug of choice
    * Aluminum toxicity extremely rare and occurs with very high dosing
  * Calcium acetate (PhosLo)
    * Phosphate binder and antacid
    * May induce hypercalcemia
    * No studies in dogs and cats
  * Sevelamer hydrochloride (Renalgel)
    * Non-calcium containing phosphate binder
    * Minimal side effects in dogs and cats
    * Dose is extrapolated but based on toxicity studies
  * Lanthanum carbonate (Fosrenol)
    * Non-calcium containing phosphate binder
    * Appears to be well tolerated
    * Dose is extrapolated
  * Chitosan + calcium carbonate (Ipakitine)
    * Veterinary specific phosphate binder
    * May induce hypercalcemia
    * One study in cats showed decreased phosphorous
  * Vitamin D
    * Hypovitaminosis D has a role in renal hyperparathyroidism
      * Kidneys metabolize 25-hydroxyvitamin D to the active form 1,25-dihydroxyvitamin D (calcitriol) by enzyme, 1-alpha-hydroxylase
      * Calcitriol decreases parathyroid hormone concentration
      * Although recent study in dogs documented decreased vitamin D3 receptors in parathyroid glands
      * Parathyroid hormone may have a role in clinical signs and of progression of chronic kidney disease, but it is controversial
    * Dietary phosphorous restriction decreases parathyroid hormone levels
    * Additionally, oral administration of low doses of calcitriol may decrease parathyroid hormone
    * Serum phosphorous concentration should be normalized before administering calcitriol because of risk of hypercalcemia and increasing the calcium x phosphorous solubility product
    * To date, only dogs in stage III or IV IRIS have been shown to benefit from calcitriol therapy
      * Not been shown to be beneficial in cats at any stage
  * Hypoproliferative anemia
    * Normocytic, normochromic non-regenerative anemia occurs in many animals with chronic kidney disease. May induce progression of disease due to decreased blood flow, stagnation of blood, oxidative stress, decreased oxygen diffusion, and induction of fibrosis
    * Causes of the anemia include
      * Decreased production of erythropoietin
      * Nutritional imbalances because of anorexia
      * Blood loss due to uremic gastroenteritis
    * Treatment includes
      * Maintaining good nutritional status
      * Minimizing gastrointestinal blood loss
      * Stimulating red blood cell production by bone marrow
        * Anabolic steroids have a minimal effect in promoting red blood cell production
          * They may also stimulate appetite
          * They may be associated with hepatopathy
        * Erythropoietin and darbepoetin
Recombinant human erythropoietin (rHuEPO) and its synthetic analog darbepoetin have been used successfully in dogs and cats with chronic kidney disease that are severely anemic.

Many animals receiving rHuEPO feel better even if their anemia does not improve.

Darbepoetin may be associated with fewer incidence of antibody production and is administered weekly and is the hormone replacement of choice.

It is indicated when:

- Packed cell volume is less than 15-20%.

This is based on using rHuEPO where antibody production occurs commonly.

Because antibody production does not appear to occur with darbepoetin, consider use when anemia begins to develop:

- Animal does not feel well because of the anemia.

  - Because uremic gastroenteritis is common, iron should be supplemented to offset the iron deficiency associated with blood loss.
  
  - Infections should also be treated to minimize iron sequestration.

- Target of treatment is to achieve a PCV of 35-45%.

  - Once target is reached, the frequency and amount of dosage can be slowly decreased to find lowest amount necessary to control anemia.

- Complications include:
  
  - Irritation at injection site.
  
  - Systemic arterial hypertension.
  
  - Polycythemia.
  
  - Worsening of anemia after initial response.
    
    - Usually associated with antibody production against rHuEPO.
      
      - Occurs in 20-40% of dogs and cats.
      
      - Anti-rHuEPO antibodies may cross-react with native erythropoietin resulting in more severe anemia than initial.
      
      - Discontinuing rHuEPO usually results in improvement of packed cell volume to value at start of rHuEPO treatment.
      
      - This has not been documented with darbopoietin.

- If an animal initially responds to rHuEPO or darbopoietin, but the packed cell volume begins to decline:
  
  - Cross-reacting antibodies may have developed.
  
  - Iron deficiency may be occurring.
  
  - Treat for uremic gastroenteritis.
  
  - Treat any infections.
  
  - Give iron supplementation if not already receiving.

**Systemic arterial hypertension**

- Occurs in 65-75% of dogs and cats with chronic kidney disease.

  - Pathogenesis includes activation of RAAS, activation of sympathetic nervous system, increased ADH due to hypovolemia.

  - Risks:
    
    - AP0 (sBP < 150 mmHg): minimal risk.
    
    - AP1 (sBP = 150-159 mmHg): low risk.
    
    - AP2 (sBP = 160-179 mmHg): moderate risk.
    
    - AP3 (sBP > 180 mmHg): high risk.

  - Results in diseases associated with organs with small vessels:
    
    - Eyes – retinal vessel tortuosity, hemorrhage, hyphema, blindness.
    
    - Kidneys – proteinuria, progression of renal failure.
    
    - Heart – left ventricular hypertrophy, possible congestive heart failure (left sided).
    
    - Brain – ischemic encephalopathy, seizures, death.

  - Diagnosis is made by measuring arterial blood pressure.

  - Treatment includes:
    
    - Goal is sBP < 150 mmHg.
    
    - Restricting dietary sodium – renal failure diets contain less sodium than maintenance diets.
    
    - Anti-hypertensive drugs:
      
      - Calcium channel blockers.
• Decreases blood pressure by arteriolar vasodilation
  o More effective first line treatment for systemic arterial hypertension in dogs and cats without proteinuria
  o Decreases systolic blood pressure by @ 50 mmHg
• Dilates glomerular afferent arteriole
• Appears to have fewer complications than with ACE inhibitors
  ▪ Hypotension
  ▪ GI signs
• **Angiotensin converting enzyme (ACE) inhibitors**
  • Decreases metabolism of angiotensin I to angiotensin II resulting in vasodilation and decreased aldosterone production
  • Systemic arteriolar dilation (via decrease in angiotensin II) and preferentially dilates glomerular efferent arteriole
  • Complications
    ▪ May worsen azotemia – monitor
    ▪ Hyperkalemia
  • Benazepril has been reported to slow progression of chronic kidney disease in cats
    • 1 study of induced chronic kidney disease has been reported
      ▪ GFR values were not different between benazepril and placebo groups
      ▪ The study lasted only 6 months
    • A long term clinical trial failed to show benefit over placebo except in cats with overt proteinuria
  o Decreases systolic blood pressure by @ 10 mmHg
• **Angiotensin receptor blockers (ARBs)**
  o Inhibit interaction of angiotensin II with receptor
  o Similar effects as ACE-I
    ▪ Decreases systolic blood pressure by @ 10 mmHg
    ▪ Preferential dilation of glomerular efferent arteriole
    ▪ Complications include
    ▪ Worsening of azotemia
    ▪ Hyperkalemia
• **Aldosterone receptor antagonists**
  o Spironolactone
  o Promotes sodium excretion and very mild diuresis
  o Decreases vascular volume
  o Decreases blood pressure – minimal effect
  o Complications
  o Dehydration
  o Hyperkalemia
  o May work synergistically with ACE-I and ARBs to decrease RAAS activation
• **Other drugs** are not as effective and are only used if multiple drugs are required to lower systemic arterial blood pressure
  o Beta-blockers (propranolol, atenolol)
  o Alpha-blockers (prazosin)
  o Direct arteriolar vasodilators (hydralazine)
  o Diuretics (furosemide, thiazides, spironolactone)

  o **Renal transplantation**
    ▪ Renal transplantation can be done
    ▪ More effective and higher success in cats vs dogs
    ▪ Less than 20% one-year survival
    ▪ Cost is > $10,000 and must adopt donor patient

  o **SERIAL MONITORING**
    ▪ Chronic kidney disease is progressive and thus a dynamic disease
Serial monitoring of body condition, body weight, thoracic auscultation, blood pressure, CBC and serum biochemical profile, urinalysis, and urine culture are necessary to adjust treatment.

- How often an animal should be examined depends on
- How rapidly the chronic kidney disease is progressing
- Any non-renal influences that affect renal function
- Owner satisfaction and finances

**How can medical treatment of chronic kidney disease be improved?**
- Early detection and intervention
- Chronic kidney disease is more common in older animals; therefore, geriatric screening blood work may identify animals in early chronic kidney disease
- Minimize or eliminate non-renal influences on renal function
- Individualize treatment
- Avoid over-treatment
- Serial monitoring

**Strategies for diagnosis of CKD using creatinine**
- Normal ranges can be misleading
- Use IRIS recommendations (cats = 1.6 mg/dl; dogs = 1.4 mg/dl)
- Change of 0.2 mg/dl in a hydrated patient is significant
- Marked reductions in kidney function can be associated with “normal” serum creatinine concentrations
- Serial monitoring

**Observations**
- At some point, the disease progresses
- Early modification of rate of progression has marked implication
- Early diagnosis of CKD has profound implications
- Educate owners early
  - Changes in water intake, urine volume, food intake, body weight, activity, behavior
  - Decreased body weight and body condition, small or dissymmetrical kidneys, large urinary bladder (polyuria?), hypertension
  - Urinalysis – an extremely important tool

**When should diet be changed in an animal with chronic kidney disease?**
- Dietary modification can offset many deficiencies and excesses that occur with chronic kidney disease
- Dietary modification includes more than just dietary protein restriction as renal failure diets are more calorically dense, may contain omega-3 fatty acids, may contain soluble fiber, low phosphorous, low sodium, potassium replete, alkalinizing, and water soluble vitamin replete
- I believe diet should be changed when an animal is diagnosed with chronic kidney disease
- Renal failure diets are usually indicated at some point in management of dogs and cats with chronic kidney disease
- Renal failure diets are not associated with deficiencies
- Renal failure diets may be tolerated better if introduced while the animal feels good and is willing to accept a dietary change
- Renal failure diets may decrease uremic episodes and prolong survival
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosage for dogs (D) or cats (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2 blocker</td>
<td>Famotidine</td>
<td>D, C: 1-2 mg/kg PO q12h</td>
</tr>
<tr>
<td>Gastroprotectant</td>
<td>Sucralfate</td>
<td>D: 0.5-1 gm PO q8-12h; C: 0.25-0.5 gm PO q8-12h</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>Omeprazole</td>
<td>D, C: 0.7-2 mg/kg PO q12-24hr</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td></td>
<td>D, C: 0.7 mg/kg PO q12-24hr</td>
</tr>
<tr>
<td>Serotonin antagonist</td>
<td>Mirtazapine</td>
<td>D: 15-30 mg PO q24h; C: 1.875-3.75 mg PO q72h</td>
</tr>
<tr>
<td>Ondansetron</td>
<td></td>
<td>D, C: 1) 0.5 mg/kg IV; then 0.5 mg/kg/hr constant rate infusion 2) 0.1-0.2 mg/kg IV slowly q6-12h prn 3) 0.5-1 mg/kg PO q12-24h</td>
</tr>
<tr>
<td>Dolasetron</td>
<td></td>
<td>D, C: 0.6-1 mg/ kg PO, IV q12-24h</td>
</tr>
<tr>
<td>NK-1 inhibitor</td>
<td>Maropitant</td>
<td>D, C: 2-4 mg/kg PO q24h</td>
</tr>
<tr>
<td>PGE2 analogue</td>
<td>Misoprostol</td>
<td>D: 2-7.5 mcg/kg PO q8-12hr; C: 5 mcg/kg PO q8hr</td>
</tr>
<tr>
<td>Rubenal</td>
<td></td>
<td>D: &lt;3kg: 37.5 mg; 3-6kg: 150 mg; 6-12kg: 150 mg; 13-25kg: 300 mg; 26-45kg: 600mg; &gt;45kg: 900 mg PO q12h C: &lt;2kg: 37.5mg; &gt;3kg: 75mg PO q12h</td>
</tr>
<tr>
<td>Amino acids / peptides</td>
<td>RenAvast</td>
<td>C: 1 capsule with food</td>
</tr>
<tr>
<td>Potassium</td>
<td>Potassium citrate</td>
<td>D, C: initial: 75 mg/kg PO q12h</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Azodyl</td>
<td>D, C: &lt;2.5kg: 1 capsule PO q24h; 2.5-4.5 kg: 1 capsule PO q12h; &gt;4.5kg: 2 capsules PO in AM and 1 capsule PO in PM with food</td>
</tr>
<tr>
<td>VSL#3</td>
<td></td>
<td>D, C: 1/10 packet per 4.5kg PO q24hr with food</td>
</tr>
<tr>
<td>Phosphate binder</td>
<td>Aluminum hydroxide</td>
<td>D, C: 15-45 mg/kg PO q12h with food</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td></td>
<td>D, C: 60-90 mg/kg PO q12h with food</td>
</tr>
<tr>
<td>Sevelamer hydrochloride</td>
<td></td>
<td>D, C: 400-1600 mg PO q12h with food</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td></td>
<td>D: 5-20 mg/kg PO q12h C: 1 ml (1 pump) PO q12h (Renalzin)</td>
</tr>
<tr>
<td>Chitosan + calcium carbonate</td>
<td></td>
<td>D, C: 1 g/kg PO q12h 3-5kg: 1 scoop; 10kg: 2 scoops; 15kg: 3 scoops; 20kg: 4 scoops PO q12h (Ipakitine)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
<td>D, C: initial:2-2.5 ng/kg PO q24h; maximum: 5 ng/kg PO q24h</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Erythropoietin</td>
<td>D, C: 100 ug/kg SQ 3X/week initially</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td></td>
<td>D, C: 1.5 ug/kg SQ 1X/week initially</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Amlodipine</td>
<td>D: 0.1-0.4 mg/kg PO q24h; C: 0.625-1.25 mg PO q24h</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Enalapril</td>
<td>D, C: 0.25 mg/kg PO q12h initially</td>
</tr>
<tr>
<td>Benazepril</td>
<td></td>
<td>D, C: 0.25 mg/kg PO q12h initially</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>Losartan</td>
<td>D, C: 1 mg/kg PO q12h initially</td>
</tr>
<tr>
<td>Irbesartan</td>
<td></td>
<td>D: 5 mg/kg PO q12h initially</td>
</tr>
<tr>
<td>Aldosterone receptor blocker</td>
<td>Spironolactone</td>
<td>D, C: 1-4 mg/kg PO q12h-24h</td>
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</table>
Urine a Losing Situation: Proteinuria
Joe Bartges, DVM, PhD, DACVIM, DACVN
Professor of Medicine and Nutrition
The Acree Endowed Chair of Small Animal Research
The University of Tennessee

Key Clinical Diagnostic Points:
- **Glomerulus** represents a barrier and functions to filter plasma
  - Components include
    - Fenestrated endothelium of glomerular capillary
    - Glomerular basement membrane
    - Podocytes containing negatively-charged slit diaphragms
    - Filtration is limited to molecules that are >68,000 Daltons
  - Function
    - Size and charge determine the “filterability” of a substance from plasma into Bowman’s space
    - Size limit is 68,000 to 70,000 Daltons
      - Albumin is 65,000, but its negative charge precludes filtration
    - From Bowman’s space, the filtrate continues through the tubules
    - For solutes to pass freely through the glomerulus, filtration of a solute is a function of GFR and plasma concentration of the solute:
      - \( \text{GFR} = K_f \times \text{net filtration pressure} \)
      - \( K_f \) is the permeability coefficient, which is a function of surface area and permeability
      - Net filtration pressure is the sum of Starling’s forces (hydrostatic and oncotic) between plasma and Bowman’s space
        - **Hydrostatic pressure** in glomerular capillaries has greatest influence on GFR – it is about 60 mmHg
        - Net filtration pressure is typically about 10 mmHg
- **Diagnosis**
  - Finding of proteinuria should be interpreted in light of other findings on urinalysis
    - Always examine urine sediment to rule-out inflammation, infection, or hemorrhage, which is associated with proteinuria
    - Proteinuria with an inactive sediment may indicate glomerular disease
- Qualitative methods
  - **Dipstick pad**
    - Part of most (perhaps all) urine dipsticks
    - Colorimetric method
      - Amino groups of proteins bind to an indicator in filter paper producing a color change
      - Change is graded subjectively to a standard
      - Most sensitive to presence of albumin
      - Range: 30-3,000 mg/dl
        - Graded as negative, trace, and 1+ to 4+ depending on intensity of color change
      - Recent studies suggest this analytical pad is not very good – many false positives and false negatives – and additional testing for proteinuria should be performed when there is a concern
        - False positives
          - Alkaline urine pH (> 7.5)
          - Contamination of urine with quaternary ammonia compounds (eg some cleaners and disinfectants)
          - Prolonged contact with urine
          - Any pigment in urine may absorb into the pad
        - False negatives
          - Very dilute urine
          - Very acidic urine
          - Presence of some abnormal proteins (eg Bence Jones proteins (myeloma proteins))
          - Sulfosalicylic acid
            - 3-5% sulfosalicylic acid solution is mixed with an equal volume of urine
- Turbidity that results from acid precipitation of protein is evaluated
- Good for albumin and Bence Jones proteins
- Range: 5-5,000 mg/dl
- False positive
  - Radiocontrast agents
  - Certain drugs (e.g., penicillin, cephalothin, sulfonamide, thymol)
- False negative
  - Very alkaline urine
  - Very dilute urine
- Quantitative methods
  - **Microalbuminuria**
    - Recently, an “early diagnosis of renal disease” (ERD) test has become available
      - Measures microalbuminuria – range of 1 to 30 mg/dl
      - Less than detectable by dipstick
      - May be useful in detecting early renal disease
        - 19% of healthy dogs have microalbuminuria
        - 36% of dogs seeking veterinary care have microalbuminuria
        - True with congenital or induced glomerular disease
        - No data (yet) concerning spontaneously occurring non-glomerular renal disease
        - Used in human beings for detection of early renal disease due to diabetes mellitus and hypertension (small capillary (glomerular) damage)
    - Despite inherent issues, there are indications for determining microalbuminuria including
      - Not overtly proteinuric, but clinical disease likely to be associated with proteinuria
      - Not overtly proteinuric, middle-aged or older
      - When conventional tests for proteinuria are equivocal or conflict
      - Dogs and cats known to be at risk for developing a glomerulopathy
  - Verification of significant proteinuria
    - Evaluate urine dipstick in light of urine sediment examination (e.g., “clean” or “dirty” sediment)
      - As little as 10% whole blood (volume/volume) can result in a positive dipstick reaction
      - Inflammation can result in proteinuria even without hematuria
        - If proteinuria is present with a “quiet” sediment and in a dilute urine, consider doing a urine culture
        - A urinary tract infection can result in very large amounts of protein in urine due to exudation
    - Also, evaluate in light of urine specific gravity and urine pH
      - A “trace” amount of protein in a concentrated urine is probably less significant or even an artifact than if it occurs in very dilute urine
      - Likewise, a “trace” amount of protein in a very alkaline urine pH could be an artifact due to the alkalinity of the sample
    - If proteinuria is present with a “clean” sediment and a bacterial urinary tract infection has been ruled-out, then the degree of proteinuria should be verified and quantitated
      - **Urine protein-to-urine creatinine ratio (UPC)**
        - A spot urine sample can be collected by any method (as long as hemorrhage is not induced)
        - Creatinine concentration (mg/dl) and protein concentration (mg/dl) is determined
        - The result is a unit-less number
          - **Normal UPC in dogs is <0.5:1.0 and cats < 0.4:1.0**
          - **Suspect UPC is 0.4/0.5:1.0 to 1.0:1.0**
          - **Significant proteinuria occurs when UP:UC is > 1.0:1.0**
    - With CKD
      - Relative risk of mortality is 3 times higher when UPC > 1
      - Risk of adverse outcome increased by 1.5-fold for every 1 unit increment of UPC above 1

- How is proteinuria investigated?
  - Make sure not artifact
    - False positives: pigment, alkaluria
• Voided sample?
  o If yes – then check cystocentesis (r/o extra-urinary)
• Evaluate plasma proteins and color
  o r/o pre-renal (e.g. hyperglobulinemia, hemolysis, etc)
• Evaluate urine sediment
  o ** Active vs inactive sediment (post-renal) **
    • If active and signs of upper tract dz -> nephritis
    • If inactive -> evaluate further (renal)
• Renal
  o If minimal: re-evaluate in 2 weeks (functional ?)
  o Persistent -> UPC
    • UPC < 2: glomerular or tubular
    • UPC > 2: glomerular

What is the clinical significance of renal proteinuria?
• Proteinuria ≠ renal proteinuria
  • Pre-renal
    • Physiologic proteinuria (exercise, stress, fever, seizures, venous congestion, etc)
    • Overload proteinuria (hyperproteinemia, myoglobinemia, and hemoglobinemia)
  • Post-renal – Most common cause
    • Inflammation
    • Infection
    • Hemorrhage
• When renal proteinuria = renal disease
  • Will the kidney disease lead to morbidity or mortality
  • Is the kidney disease a sign of some underlying condition
  • Is therapy indicated to prevent additional renal or systemic injury
  • Types
    • Glomerular
    • Tubular
    • Interstitial

Renal biopsy
• Indications
  • Renal biopsy is most useful with
    • Nephrotic syndrome/glomerular disease
    • Mass lesions/neoplasia
    • Acute renal failure (for diagnosis and prognosis)
    • Patients with proteinuria
    • Cats with feline infectious peritonitis (diagnosis)
    • Suspected familial or congenital renal disease
    • Perinephric cysts (fine needle aspiration only)
    • Investigation
  • Renal biopsy may be useful with
    • Infectious renal disease (fine needle aspiration of tissue or pelvic urine)
    • Culture of pelvic urine
    • Slowly progressive tubulointerstitial disease
    • Patients with undiagnosed renal hematuria
  • Renal biopsy is not helpful or should not be performed with
    • Chronic renal failure (unless associated with neoplasia)
    • Polycystic kidney disease
  • When performing a renal biopsy, the core of tissue is divided for histopathology (light microscopy = LM), immunofluorescence (IF), and electron microscopy (EM)
• Conservative approach
  • Serially monitor urinalysis, UPC, and renal function
  • Patients with stable or improving mild proteinuria (UPC < 2)
  • If severe or progressive proteinuria – investigate further
    • Identify and treat inciting disorder
    • Limit proteinuria
      • Limits albumin loss and consequences of hypoalbuminemia
    • Renoprotective
      • Proteinuria is nephrotoxic
      • Activates fibrosis and inflammatory pathways

General clinical signs of glomerular disease
• Vary with severity of disease and underlying cause, if any
• Azotemia may or may not be present and is unassociated with the degree of proteinuria and hypoalbuminemia
• Mild to moderate proteinuria results in serum albumin concentrations >1.5 g/dl, but < 2.5-3.0 g/dl
  o At this level, clinical signs often include polyuria, weight loss, and lethargy
  o With severe or heavy proteinuria, serum albumin is < 1.5 g/dl, and clinical signs are more severe
• In addition to aforementioned signs
  o Muscle wasting
  o Edema/ascites
  o Nephrotic syndrome
    • Occurs with severe proteinuria and is characterized by proteinuria, marked hypoalbuminemia, hypercholesterolemia, hyperlipidemia, and edema

Therapy
• Treatment is often frustrating and biologic course is variable
• Goals of therapy are similar to those for CKD with additional goal of increasing serum albumin concentration and minimizing likelihood of nephrotic syndrome
• Treatment includes:
Treat the underlying cause, if it can be identified

- Two major glomerulopathies
  - Glomerulonephritis
    - Glomerulonephritis (GN) is better termed glomerulopathy
    - “-itis” implies inflammation, which typically occurs, but is not always present depending on cause of the glomerular disease (e.g., congenital renal disease, glomerulosclerosis)
    - *Many causes that have been described, primarily in dogs:*

<table>
<thead>
<tr>
<th>Familial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doberman pinscher, Samoyeds (X-linked dominant), Bull terrier (autosomal dominant), soft-coated Wheaton Terrier, Greyhound, Burmese mountain dog, Rottweiler, English Cocker spaniel (autosomal dominant), Norwegian Elkhound, Brittany spaniel (autosomal dominant), Deficiency of C3 results in recurrent bacterial urinary tract infections and membranoproliferative GN</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphosarcoma, mastocytosis, hemangiosarcoma, adenocarcinoma</td>
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<table>
<thead>
<tr>
<th>Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial endocarditis, infectious canine hepatitis, brucellosis, dirofilariasis, ehrlichiosis, systemic fungal or bacterial infection, feline infectious peritonitis, feline leukemia virus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus, chronic pancreatitis, chronic pyoderma, chronic otitis externa, polyarthritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperadrenocorticism, diabetes mellitus, chronic glucocorticoid treatment, systemic arterial hypertension, idiopathic</td>
</tr>
</tbody>
</table>

- Any process resulting in antigenic stimulation may result in GN
- In most cases, underlying cause(s) is/are not identified; therefore, most are classified as idiopathic
- Glomerulopathies may be immune-mediated or non-immune-mediated:
  - Immune-mediated GN:
    - Accounts for @ 48% of renal proteinuria in dogs; amount in cats…?
    - *Etiopathogenesis is related to presence of immune complexes in glomerular capillary walls*
    - Histologically, GN can be classified as:
      - Proliferative:
        - Mesangial and epithelial cell proliferation and infiltration (primarily neutrophils)
        - Cellular proliferation compresses glomerular capillaries resulting in decreased blood flow and GFR
      - Membranous:
        - Thickening of basement membrane due to subepithelial deposition of immune complexes
        - Membranoproliferative:
          - Combination of membranous and proliferative GN
    - Immunofluorescence can be used to document the immune-mediated nature; however, few labs do this technique and even fewer do it well
    - Prognosis is thought to be related to histologic type with membranous having a better prognosis than proliferative or membranoproliferative.
  - Non-immune-mediated:
    - Glomerular disease may occur due to developmental abnormalities in glomerular structure and function
    - Glomerular disease (sclerosis characterized by glomerular thickening and mesangial expansion) has been reported to occur with:
      - Glucocorticoid excess (endogenous or exogenous)
      - Systemic arterial hypertension
      - Diabetes mellitus
      - Renal failure
    - Immunofluorescence studies would be negative
  - Amyloidosis
    - Amyloid is a beta-pleated sheet of serum amyloid A protein
    - Deposits in and around glomerulus, usually beginning in the tubulointerstitial area
    - Amyloidosis is uniformly progressive in nature and animals invariably develop chronic renal failure
• It may occur:
  • Primary familial disease
    • Primarily described in Shar pei dogs Abyssinian cats
    • In these animals, amyloid may be deposited primarily in the medulla and not glomerulus
    • Proteinuria, therefore, may not be present
    • Amyloidosis develops typically in animals under 5-6 years of age
    • Shar pei dogs with amyloidosis often develop an arthropathy associated with fever and joint pain
      (called Shar pei fever, Shar pei swollen hock syndrome, Mediterranean Fever)
    • Has also been described in Siamese cats, Oriental shorthair cats, Walker hound dogs, Beagle dogs, and Collies
  • Secondary to chronic inflammatory diseases (eg infections, inflammatory organ disease, or cancer)
• Clinical signs of amyloidosis include:
  • Proteinuria
  • Edema (depending on degree of proteinuria and hypoalbuminemia)
  • Chronic renal failure
  • Systemic arterial hypertension (and its related clinical signs – see Chronic Renal Failure lectures)
  • Inappetence and weight loss
  • Fever (depending on cause)
  • Arthropathy (depending on cause) – especially in Shar Pei breed
  • Other signs related to inciting cause of secondary amyloidosis
• Diagnosis:
  • Differentiated from other glomerulopathies by renal biopsy
  • On light microscopy, amyloid appears as an eosinophilic substance in the mesangium and/or interstitium
  • Congo red stain using polarized light confirms the presence of amyloid (Congo red gives an “apple green”
    color when viewed under polarized light)
  • Amyloid may occur outside of the glomeruli particularly in the medulla in cats; therefore, it may be missed
    with a renal cortical biopsy

Feed a protein-restricted diet. Studies have shown that dietary protein restriction decreases the degree of
proteinuria and increases serum creatinine concentration. Supplementing dietary protein actually makes the
situation worse.
Decrease sodium intake. This can usually be accomplished by feeding a low protein, renal failure diet. Dietary salt
restriction aids in decreasing fluid retention.

Administer an angiotensin-converting enzyme inhibitor
  Enalapril is the only ACE inhibitor that has been evaluated in dogs with proteinuria although other ACE
  inhibitors have been evaluated in dogs with induced diabetes mellitus (lisinopril) and in human beings
  (captopril, ramipril, etc). Benazepril has been shown to reduce proteinuria in cats. Benazepril is excreted
  more through biliary system than urinary system (although it is renally excreted as well) when compared
  with enalapril; therefore, it may be safer to use in animals with renal azotemia.
Enalapril has been shown in a controlled study to decrease proteinuria, increase serum albumin concentration,
and prolong survival in dogs with GN

  Enalapril in dogs or benazepril may be tried
  There is a potential to worsen azotemia if present; therefore, start with a lower dose in azotemic animals and
  monitor BUN and creatinine
  Indicated when UPC is > 1-2 in IRIS stage 1 or > 0.4 (cats) and 0.5 (dogs) in IRIS stage 2-4
  Initial dose: 0.25 mg/kg PO q12h

Administer anti-inflammatory drugs to decrease platelet aggregation
  Platelet activation and intraglomerular thrombosis occurs with glomerular disease
  Aspirin is usually administered at 0.25-0.5 mg/kg PO q12-24hr in dogs or ½-1 baby aspirin q3d in cats.
  Efficacy is not proven in dogs, but it is in human beings.

Consider omega-3 fatty acids
  Theoretically, diets containing higher levels of omega-3 fatty acids may decrease inflammation. The omega-3
  fatty acid becomes incorporated into plasma lipid membranes instead of arachidonic acid. The
prostaglandins, thromboxanes, and leukotrienes produced from metabolism of omega-3 fatty acids tend to promote less inflammation and coagulation.

In a chronic CKD model, dogs consuming a diet with an omega-6-to-omega-3 fatty acid ratio of 5:1 maintained GFR longer, survived longer, and had less inflammatory prostaglandin excretion than when dogs consumed diets containing higher levels of omega-6 fatty acids. There is no data in dogs with proteinuria. Furthermore, cats with chronic renal failure do not appear to respond to omega-3 fatty acid supplementation.

Most renal failure diets contain an omega-6-to-omega-3 fatty acid ratio of 5:1. Supplementation of omega-3 fatty acid should be done to achieve a ratio of omega-6-to-omega-3 fatty acids of somewhere between 1:1 to 5:1. Therefore, the amount of omega-3 fatty acid supplementation must be done based on the fat content of the diet and type of fat in the diet.

Omega-3 fatty acids can be supplemented with diet with a starting dose of 300 mg of EPA + DHA per 10 lbs per day. Remember, EPA is the 20-carbon long-chain fatty acid and DHA is the 22-carbon long-chain fatty acid.

**Consider immunosuppressive drugs**

Administration of immunosuppressive drugs to dogs with proteinuria is controversial. None have been shown to be effective in controlled studies, although there are sporadic case reports of response. However, biopsies show that 48.7% of glomerular disease in dogs have an immune-mediated basis.

In human beings, glucocorticoids are often administered. Studies in dogs have shown that in most cases of proteinuria, glucocorticoid administration is not beneficial and is often associated with a worsening of the proteinuria. Glucocorticoids appear to promote glomerulosclerosis and intraglomerular hypertension. Therefore, glucocorticoids are not recommended unless the proteinuria is secondary to glucocorticoid-responsive systemic disease.

Cyclosporine was not found to be effective in dogs with idiopathic GN in a controlled, blinded study. Therefore, it cannot be recommended at this time.

Other immunosuppressive drugs that may show benefit, but that have not been evaluated in placebo-controlled, blinded studies are azathioprine (2 mg/kg PO q24h x 2 weeks, then 1 mg/kg PO q24h, then 1 mg/kg PO q48h), cyclophosphamide (50 mg/m² PO q48h), and chlorambucil (2-6 mg/m² PO q24-48h). The most promising are mycophenolate (D: 20 mg/kg PO q12h for 3-4 weeks, then 10 mg/kg PO q12h; C: 10 mg/kg PO q12h) and azathioprine + chlorambucil.

Most immunosuppressive drugs are also cytotoxic; therefore, their administration may be associated with worsening azotemia.

The decision to use immunosuppressive therapy should be based on the likelihood of an immune-mediated cause of proteinuria, the patient’s overall condition, and the ability to monitor the patient.

**Consider diuretics to decrease sodium retention and edema/ascites**

In human beings with nephrotic syndrome, diuretics are often used to decrease ascites/edema. Commonly a combination of a loop diuretic (such as furosemide) and a thiazide diuretic (such as chlorothiazide) are used. These diuretics promote natriuresis thereby decreasing sodium and fluid retention.

Furosemide is often used in veterinary medicine to decrease fluid retention and should be considered in dogs or cats that have nephrotic syndrome. Combination diuretic therapy may be considered in animals that are refractory to single agent therapy.

**Treatment targets**

- **Ideal goal:** reduce UPC to < 0.5 in dogs and 0.4 in cats
- **Realistic goal:** reduce UPC by at least 50%

**Additional therapies**

- If goal is not achieved:
  - Increase dosage of ACE-I and monitor
  - Angiotensin receptor blocking (ARB) agent
    - Some ATII escapes ACE inhibition
    - ARB block ATII interaction at receptor
    - Same tendency for complications as with ACE-I
    - I typically use Losartan (1 mg/kg PO q12h); however, irbesartan has been evaluated in dogs (5 mg/kg PO q12-24h)
Immunosuppression, if not done
- Doxycycline
  - Loose information of decreasing proteinuria in humans
  - Metalloproteinase inhibitor – anti-inflammatory
  - Used with tick-borne disease-associated glomerular disease

**Prognosis**
- Generally poor
- Most patients dead within 1-2 months of diagnosis
- However, can be stable for long time and may resolve with therapy
Etiopathogenesis

- Urinary tract is in contact with external environment and bacteria normally reside in distal urogenital tract
- 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 septicemia 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 very rare 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

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• 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
• Urine should be transported in a sealed container and processed as soon as possible
• If processing is delayed, refrigerate the sample
• Alternatively, a blood agar plate can be streaked and later submitted for identification and antimicrobial susceptibility pattern if bacteria grow
• 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
    • Kirby-Bauer technique is acceptable for most bacterial urinary tract infections

**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 1/5 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

**Intact male or female dog?**

**Predisposing systemic and/or local factor(s)?**

**Recent previous UTI’s?**

**Cat?**

- **YES**
  - Treat for 4-6 weeks based on C & S
  - Redo C & S 5-7 days after start
  - Before stop 5-10 days after start
- **NO**
  - Treat for 10-14 days based on: C & S “Best guess”

- 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
  - 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

- Reinfection
  - 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
  o Breaks in host defenses
    • Local defenses
      o Recessed vulva
      o Deep-seated infection: 18.5% of cases had positive bladder wall or urolith culture with a negative urine culture
        o In our experience, 4% of bladder wall cultures are positive in dogs with negative urine culture who do not have uroliths
      o Anatomic defects (e.g. ectopic ureter)
    • Indwelling urinary catheter
      o Concomitant antimicrobial administration decreases incidence of UTI
      o However, when UTI develops, it is highly resistant
      o 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)
  o Bacterial factors
    • Multi-drug resistance
    • Unusual organism (e.g. Corynebacterium, methicillin-resistant Staphylococcus)

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
  o 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
  o 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
  o Catheter-induced bacterial urinary tract infection
  o Bacteria migrate along outside of catheter
  o Risk of bacterial urinary tract infection increases with pre-existing urinary tract disease
  o Risk is greater in animals with indwelling urinary catheters than in those that are intermittently catheterized
  o Despite the low risk, one study documented bacterial urinary tract infections in 7 or 35 dogs that were catheterized one time
  o Bacterial urinary tract infection occurs in >50% of animals after 4 days with an indwelling urinary catheter
  o 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 (e.g. Enrofloxacin: 5-20 mg/kg PO q24h): May be effective when used at high
• Aminoglycosides: Are often an effective antimicrobial agent. Amikacin (cats: 10-15 mg/kg IV, IM, SQ q24h; dogs: 15-30 mg/kg IV, IM, SQ q24h) 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
Nitrofurantoin

Methenamine

Prophylactic antimicrobial treatment

There is evidence that if a resistant UTI is not associated with clinical signs, that it may be better to not treat. 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 cocci) even with a favorable sensitivity pattern.

Chloramphenicol: monitor liver enzymes as can be hepatotoxic, GI side effects occur commonly (50 mg/kg PO q8h)

Linezolid: An oxazolidinone antibiotic with activity against Gram + organisms. It is often effective against methicillin-resistant Staphylococci, but is expensive (10 mg/kg PO q12h)

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 (15 mg/kg IV q8h)

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 urine analysis 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

There is evidence that if a resistant UTI is not associated with clinical signs, that it may be better to not treat.

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 1/2 to 1/3 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 combined with an acidifying salt either hippurate (D: 500 mg PO q12-24h); C: 250 mg PO q12-24h) or mendelate (D, C: 10 mg/kg PO q6-12h) but additional acidification may be required

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 (4 mg/kg PO q6-8h; prophylaxis: 3-4 mg/kg PO q24h)

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

- Estriol: Start at a dose of 1 mg/dog PO q24h. If treatment is successful reduce the dose to 0.5 mg/dog PO. q24h. If treatment is unsuccessful increase to 2 mg/dog PO q24h. Alternate-day dosing can be considered once a response has been seen. The minimum effective dose is 0.5 mg/dog PO q24-48h. The maximum dose is 2 mg/dog PO q24h

- Premarin: 20 ug/kg/d x 7 days; then q2-3d PO

- DES: 0.1-1 mg/day x 5 days; then q3-7d PO

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 prebiotics (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
  - VSL #3 contains most organisms and multiple organisms (450 billion per packet; 1/10 packet per 4.5kg)

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 pili, that are virulent factors involved with binding of the bacteria to uroepithelial cells
- PapG pili 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. We use Pure Encapsulation d-mannose at 1/8 (1/16 tspn) scoop for small dogs and cats, 1/4 scoop (1/8 tspn) for medium dogs, and 1/2 scoop (1/4 tspn) for large dogs q8h.
Urolithiasis is common in dogs and cats. 99% of uroliths occur in the lower urinary tract. Urolith formation is not a specific disease, but the sequelae to a group of underlying disorders. Urolith formation occurs with sustained alterations in urine composition that promotes supersaturation of one or more substances in urine resulting in precipitation and subsequent organization and growth into uroliths. Urolith formation is erratic and unpredictable emphasizing that several interrelated physiologic and pathologic factors are often involved. Mere presence of uroliths, however, does not necessitate their removal. Approximately 98% of uroliths occur in the lower urinary tract. Composition of uroliths. Approximately 80% of canine uroliths and 90% of feline uroliths are either struvite or calcium oxalate. Calcium oxalate and struvite occur at approximately even frequency although struvite occurs more commonly now (slightly). The third most common type of mineral is urate. Other types – including compound uroliths (uroliths composed of more than 2 minerals) occur less frequently. Urolith formation is dependent on a combination of many factors. Urine pH. State of saturation – related to concentrations of minerals in urine. Inhibitors and promoters of urolith formation. Complexors. Macrocystalline matrix.

**STRUVITE UROLITHIASIS**

Infection-induced struvite are the most common form occurring in dogs; whereas sterile struvite is the most common form occurring in cats. However, any animal that develops a bacterial urinary tract infection with a urease-producing micro-organism can develop infection-induced struvite uroliths. Sterile struvite uroliths have been documented to occur in dogs, but it is very rare.

**Dogs:**

- Struvite uroliths typically, but not always, form in female dogs (because of their higher risk for development of a bacterial urinary tract infection), and in dogs with immunosuppressive diseases or receiving immunosuppressive therapy because of their increased risk for bacterial urinary tract infections.
- They can occur at any age, but are more common in young adult dogs.
- They are the most common type of urolith in puppies (dogs < 1 year of age).

**Cats:**

- Sterile struvite is the most common type of struvite urolith occurring in cats.
- It typically occurs in young adult cats.
- In older cats (>10 years) and in kittens (<1 year), infection-induced struvite urolith formation is more common than formation of sterile struvite uroliths because of their increased risk for development of a bacterial urinary tract infection.
- Remember, crystalluria is not synonymous with urolithiasis.
- In healthy dogs, more than 50% of urine samples will contain struvite crystals without a bacterial urinary tract infection and without subsequent urolith formation.
- Likewise, some animals with active stone disease will not have crystals; however, most animals with active struvite stone disease will be crystalluric.

**“Guesstimation” that is consistent with struvite uroliths**

- Urine pH: alkaline
- Crystals: struvite
- Bacterial urinary tract infection:
  - Yes, if infection-induced struvite uroliths
* Should be a urease-producing micro-organism
  * Typically Staphylococci spp
  * Occasionally Proteus spp
  * Rarely other bacteria such as Klebsiella and Streptococcus
  * Rarely Mycoplasma/Ureaplasma
  * Never Escherichia coli
* No, if sterile struvite
  * Unless a secondary bacterial urinary tract infection has occurred

* Radiographic appearance
  * Density: radiodense
  * Size:
    * Infection-induced: typically variable sized including some fairly large stones
    * Sterile: typically small (<5-10 mm)
  * Surface contour: typically smooth
  * Shape:
    * Infection-induced: often pyramidal shaped, similar to river rocks
    * Sterile: usually round, but can be wafer-like
  * Number:
    * Infection-induced: usually many dozen
    * Sterile: usually small number (perhaps 1-a dozen or so)

* Serum and urine biochemical analysis
  * Often normal, especially in cats
  * In animals with infection-induced struvite, predisposing metabolic causes for bacterial urinary tract infection may be present
    * Cushing’s disease
    * Diabetes mellitus
    * FeLV/FIV

* Signalment
  * Infection-induced:
    * Young to middle-aged adult female dogs
    * Pediatric or geriatric dogs and cats (due to predisposition to bacterial urinary tract infection
    * More common in females than males
  * Sterile:
    * Usually young adult cats (same is true in the few reported cases of dogs)
    * No gender or breed predisposition

Etiologic and Pathophysiologic Points:

* Infection-induced struvite
  * A urinary tract infection with urease-producing bacteria (usually Staphylococci and Proteus spp; rarely other bacteria and Ureaplasma/Mycoplasma) occurs
  * Results in urease-mediated metabolism of urea to ammonium and carbonate
  * Ammonium comes from the ammonia liberated from urea buffering hydrogen ion in urine
  * Results in an alkaline pH
  * Changes ionization state of phosphorous
  * Magnesium is typically present in low amounts in urine
  * Phosphorous is present in high amounts and is a strong and important buffer (in acid-base metabolism) called “titratable acid”
  * These conditions favor formation of uroliths containing struvite (Mg$^{2+}$NH$_4$PO$_4^{3-}$), with some “contaminant” minerals: calcium apatite and carbonate apatite
  * Struvite is less soluble (more likely to precipitate) when the urine pH is > 6.8, and is more soluble (more likely to stay in solution) when the urine pH is < 6.8

* REMEMBER: these are called infection-induced struvite stones
Sterile struvite typically forms in cats; however, it has been reported to occur rarely in dogs. Sterile struvite uroliths are typically composed of 100% struvite and do not contain "contaminant" minerals. The mechanism(s) for sterile struvite formation is not clear, although an alkaline urine pH is necessary. Persistent or recurrent alkaluria is a predisposing risk factor for sterile struvite formation. Because of the carnivorous nature of cats, a “post-prandial alkaline tide” occurs and can be profound. It is thought that with a high protein intake, a large amount of HCl is produced and excreted into the gastric lumen to begin digestion of protein (acid-mediated proteolysis). This results in a metabolic alkalosis. Kidneys respond by excreting less acid and more base. This results in alkaluria. This is the reason most cat foods are “acidifying” – to minimize the post-prandial alkaline tide and prevent struvite formation.

Other factors have a role:
- Highly concentrated urine resulting in retention of urine and concentration of calculogenic minerals
- High levels of magnesium and phosphorous in urine

Therapeutic Points:
- Overview of therapy
- Eliminate existing uroliths
- Eradicate or control bacterial urinary tract infection
- Prevent recurrence of uroliths
- Surgical removal – Will be discussed later
- Minimally invasive procedures – Will be discussed later
- Medical dissolution
  - Infection-induced struvite
    - Can be dissolved medically, or removed physically (surgery or voiding urohydropropulsion) – or combinations
    - Protocol:
      * Control and/or eradicate the bacterial urinary tract infection
      * Choose appropriate antibiotic
      * Must be administered during entire time of medical dissolution. Bacteria are trapped in matrix of urolith and released as the stone dissolves from the outer layers inwards (similar to an ice cube melting in a glass of water)
      * The struvite dissolution diet induces a diuresis, which may decrease efficacy of antimicrobial (although rarely are changes in dosage necessary)
      * Calculolytic diet (struvitolytic diet)
      * Currently, only 1 diet has data documenting its efficacy in medical dissolution of struvite – Hill’s Prescription Diet s/d
    - Diet is:
      * Lower in protein (source of urea and therefore ammonia)
* Lower in magnesium
* Lower in phosphorous
* Acidifying
* Diuresis (to stimulate thirst and urine output)

Although infection-induced struvite stones may dissolve with antibiotic therapy alone, it takes much longer than the combination of antibiotic and struvitolytic diet, and is less successful.

* Average time for dissolution is 8 weeks
  * Monitor animal every 4 weeks
  * Urinalysis – should find aciduria, no crystalluria, no inflammation
  * Urine culture, if necessary
  * Survey abdominal radiography (at least a lateral view) to monitor dissolution

Dissolution therapy should continue for 2-4 weeks beyond radiographic evidence of dissolution of uroliths to ensure all stones are dissolved.

* Complications of medical dissolution
  * Recurrent urethral obstruction
  * Continued clinical signs of lower urinary tract disease (although signs typically resolve, except for polyuria/polydipsia, within 3-5 days of starting dissolution therapy)
  * Reaction to antimicrobial
  * Problems with diet
    * A very low protein diet – protein malnutrition may develop
    * Prolonged feeding of diet – it is not intended for long term consumption
    * Use cautiously if at all in pediatric patients, especially those in rapid growth phase
    * Contra-indicated in pregnant animals
    * Usually see an increase in alkaline phosphatase activity and a decrease in blood urea nitrogen concentration because of the low protein content
    * In addition to pregnant animals, contraindicated in:
      * Hypertensive patients or those that cannot tolerate a sodium load
      * Those with renal failure – acidifying, hypokalemia
      * Animals that cannot tolerate a high fat intake – diet is high in fat

* An alternative dissolution protocol has been shown to be effective in > 80% of dogs
  * In this protocol, the diet is not changed; instead a urinary acidifier (d,l-methionine; D: initial 100 mg/kg PO q12h) is administered in combination with an appropriate antibiotic for the organism responsible for struvite formation (typically Staphylococcus)
  * Dissolution occurs in 4-8 weeks
  * Advantage is that the diet does not require changing and the acidifier is safe
  * Disadvantage is that in the one study, 2 dogs had a shell of calcium phosphate that appeared to impede dissolution – this could be due to “over” acidification

* Sterile struvite
  * Can be dissolved medically or removed physically
  * Protocol:
    * Feed struvitolytic diet
    * Antimicrobials are not necessary unless a secondary infection is present (one that would not be associated with struvite formation)
    * Other aspects are similar to management of infection-induced struvite uroliths
  * Sterile struvite uroliths typically dissolve in 2-4 weeks; therefore, at recheck at 4 weeks, uroliths may no longer be visible on survey abdominal radiographs
  * Feed diet for 2 to 4 weeks beyond medical dissolution

**Prevention of struvite uroliths**

* Successful prevention of struvite uroliths involves modifying risk factors to decrease risk of re-formation

* **Infection-induced struvite:**
  * Most important component of prevention is preventing the bacterial urinary tract infection
  * **REMEMBER: these are called infection-induced struvite**
  * If predisposing risks for recurrent bacterial urinary tract infections cannot be modified, then treat the animal as having a complicated bacterial urinary tract infection, and take appropriate prophylactic steps (see notes on urinary tract infections)
* Dietary modification for prevention of infection-induced struvite uroliths is not warranted, and often not successful
* **Sterile struvite:**
  * Dietary modification is often required to decrease risk of recurrent sterile struvite urolith formation
  * Specific struvite preventative diets are modified to decrease risk

**URATE UROLITHIASIS**
- Urate comprises 5-8% of uroliths retrieved from dogs and cats
  - Most commonly, ammonium urate is the primary salt
  - It is the second most common mineral found in uroliths from dogs and cats < 1 year of age behind infection-induced struvite
- Normally, non-primate mammals have allantoin as end-product of purine metabolism
  - Purines are nitrogen-containing compounds involved in nucleotide bases (adenine and guanine) – y’know DNA and RNA
  - Sources of purines include diet (highly cellular) and endogenous turnover of cells as well as de novo synthesis (production of purines from non-purine precursors)
    - Related compounds are methylxanthine (bronchodilators), caffeine, and theobromine (found in chocolate)
  - The purine pathway eventually terminates in allantoin, which is highly soluble and excreted in urine
    - Hypoxanthine is converted to xanthine and xanthine to uric acid by xanthine oxidase
    - Uric acid is metabolized by hepatic uricase to allantoin

**Clinical Diagnostic Points**
- Ammonium urate is the third most common occurring mineral found in uroliths from dogs and cats
- Urate uroliths may form secondary to liver disease, especially portovascular anomalies, or in genetically predisposed breeds (e.g. Dalmatians).
- Guesstimation that is consistent with urate uroliths
  - Urine pH: acidic
  - Crystals: urate or amorphous urates
  - Bacterial urinary tract infection – secondary to uroliths, if present
  - Radiographic appearance:
    - Density: radiolucent
    - Size: small
    - Surface contour: smooth
    - Shape: round
    - Number: numerous
  - Serum and urine biochemical analysis
    - With liver disease
      - Possibly increased liver enzymes
• Decreased BUN
• Microcytosis (with portovascular anomaly)
• Hyperammonemia
• Without liver disease
  • Usually normal

Signalment
• With liver disease
  • Small breed dogs
  • Usually < 1 year of age
  • Possibly decreased growth and signs of hepatoencephalopathy
• Without liver disease
  • Between 1-4 years of age typically
  • Males > females
  • Dalmatians, English bulldogs

Etiologic and Pathophysiological Points
• Uric acid is a metabolic product of purine metabolism
• Purines originate endogenously from cell turnover (nucleic acids) and exogenously from diet
• In most dogs and cats, the final endpoint of purine metabolism is allantoin
• For urate urolith formation, uric acid is the metabolic endpoint
  • Uric acid is converted to allantoin by hepatic uricase
  • Without liver disease, this conversion does not occur
  • With liver disease, this conversion does not occur
  • Dalmatians have adequate hepatic uricase
  • They lack a necessary transporter encoded by the SLC2A9 gene
    • This results in slightly higher serum uric acid concentrations when compared to most non-Dalmatian breeds of dogs (but lower than found in human beings) and high urine uric acid concentrations
      • Serum uric acid concentrations:
        ▪ Non-Dalmatian dogs: 0.2-0.3 mg/dl
        ▪ Dalmatians: 0.8-1.2 mg/dl
        ▪ Humans: 3.0-6.0 mg/dl
      • Urine uric acid concentrations
        ▪ Non-Dalmatian dogs: 20-30 mg/dl/24h
        ▪ Dalmatians: 600-1200 mg/dl/24h
• High uric acid excreting (HUA) Dalmatians are homozygous recessive for the SLC2A9 gene; therefore, all excrete higher levels of urinary uric acid
  • However, incidence of urate urolithiasis is 10-30%
• The Dalmatian back-cross project, where a Dalmatian was bred to an English setter and then offspring back-bred resulting in dogs that outwardly look like Dalmatians, has resulted in Dalmatians that excrete low uric acid (LUA). These dogs are either heterozygous or homozygous dominant for the SLC2A9 gene
• We have found several other genetic differences between sibling urate urolith forming Dalmatians and non-urate urolith forming Dalmatians

Treatment
• Without liver disease - dogs
  • Dissolution can be attempted with an “ultra low protein”, alkalinizing diet that induces a diuresis and administration of allopurinol
  • Allopurinol is a xanthine oxidase inhibitor that blocks conversion of xanthine to uric acid (D: 15 mg/kg PO q12h)
  • This results in decreased concentrations of uric acid and ammonia in urine and alkaluria
  • Dissolution usually occurs in 4-8 weeks, if it does not occur by then, it won’t
  • Dissolution is successful in approximately 1 out of 3 dogs; in 1 out of 3 dogs, stones decrease in size but do not dissolve and most can be retrieved non-surgically; and in 1 out of 3 dogs, stones increase in size or number associated with xanthine formation
  • Preventative measures include feeding the “ultra low protein” diet – this is successful in > 80% of dogs
    ▪ There is also a “vegetarian” based diet available
- Protein hydrolysate diet has been shown to aid in prevention
- Occasionally, a low dose of allopurinol is also required (5-7 mg/kg PO q12h)
- Want alkaline pH; therefore, a urinary alkalinizing agent such as potassium citrate (75 mg/kg PO q12h) may be required.

- **Without liver disease – cats**
  - No published protocol for medical dissolution exists
  - There is no “ultra low protein” diet available in cats
  - Urate uroliths have been dissolved using “renal failure” diets and administering allopurinol at ½ of dog dose

- **With liver disease**
  - Dissolution therapy is not typically successful (see below)
  - Surgical removal may be required
  - Correction of a portovascular anomaly or medical treatment of underlying liver disease helps with prevention

**Cystine urolithiasis**

- Cystine urolithiasis occurs due to abnormally increased levels of cystine in urine
- In dogs, this occurs as a familial disease
- Represents a proximal renal tubular defect of cystine reabsorption – often in association with loss of other amino acids – COLA (cystine, ornithine, lysine, arginine)
- **Guessimation**
  - Urine pH: acidic
  - Crystals: cystine
  - UTI: none unless secondary infection
  - Radiography: small, round, smooth, marginally radiodense, usually not more than 1-2 dozen
  - Laboratory evaluation: usually normal
  - Signalment
  - Breeds of dogs
  - Young adult
  - Males > females

- **Treatment**
  - **Dietary protein restriction**
    - Dogs: Prescription diet u/d, Royal canin UC, Vegetarian diet
    - Cats: Renal failure diet
  - Thiol-containing drugs
    - 2-mercaptopropionylglycine (2-MPG; 15 mg/kg PO q12h) and D-penicillamine
    - Bond to the individual cysteine molecules at the sulfur groups
    - Prevents di-sulfide bond formation and cystine formation
    - DO NOT use in cats as it causes hemolysis
  - pH
    - Cystine is more soluble in alkaline pH > 7.2
    - Low protein diets are typically alkalinizing
    - May administer an alkalinizing agent as well (e.g. K citrate)
    - Inducing a diuresis decreases concentration of urinary cystine and therefore urinary saturation for cystine

- **Prevention**
  - Low protein or vegetarian-based diet that induces diuresis and alkaluria. Effective in > 90% of dogs
  - Alkaluria
  - ± thiol-containing drugs: Note: some people do not modify diet but only administer thiol-containing drugs at a higher dosage for prevention

**CALCIUM OXALATE**

- Calcium oxalate accounts for 40-50% of all uroliths and > 85% of nephroureteroliths
- **Risk factors** for calcium oxalate formation
  - Increased urinary calcium excretion (hypercalciuria)
May result from hypercalcemia, GI hyperabsorption (excessive absorption of calcium from the GI tract), resorptive (excessive calcium resorption from bone), or renal leak (decreased calcium reabsorption from the distal tubule)

- Increased urinary oxalate excretion (hyperoxaluria)
  - May result from excessive absorption from the GI tract, excessive absorption from the GI tract due to deficiency of Oxalobacter formigenes (an enteric bacterial organism that metabolizes oxalate in the GI tract), and possibly from vitamin B6 deficiency (vitamin B6 is involved with oxalate metabolism)
  - In a small study of Miniature schnauzers, GI hyperabsorption appears to be the most likely cause as urinary calcium excretion decreased with fasting
  - Net result of risk factors is urinary oversaturation with calcium oxalate

**Signalment**

- **Cats**
  - Middle-aged or older
  - Males = females
  - Long-haired cats; Siamese and Ragdolls tend to form at young age
  - Overweight to obese body condition
- **Dogs**
  - Middle-aged or older
  - Males > females
  - Small breed dogs (e.g. Miniature schnauzers, Lhasa apsos, Yorkshire terriers, Bichons). Bichons tend to form at young age
  - Overweight to obese body condition

**Laboratory evaluation**

- **Aciduria**
- **Hypercalcemia**
  - 20-35% of cats – usually idiopathic hypercalcemia
  - 4% of dogs – usually primary hyperparathyroidism
- **Crystalluria – not present in > 50% of cases with active stone disease**
- Renal azotemia – associated with nephroureteroliths

**Management**

- Medical protocols that will promote dissolution of calcium oxalate uroliths are currently unavailable; therefore, uroliths must be removed physically
- **If urethral obstruction** is present, uroliths should be retropulsed into bladder and removed
  - If necessary urethrotomy or urethrostomy may be performed
- **If no clinical signs, then minimize growth** in size and number and monitor for urethral obstruction and clinical signs

**Removal of calcium oxalate uroliths**

- **Surgery** – cystotomy and / or urethrotomy / urethrostomy
- **Catheter-assisted retrieval**
  - Technique can be used to retrieve “sand” or small uroliths
  - Uroliths must be small enough to pass through the internal diameter of the lumen of the urethral catheter
  - It is important to “jiggle” the urinary bladder to get the sand/uroliths “in motion” in order to facilitate retrieval through the catheter

  **Description of technique**

1. Urinary bladder must be distended
2. As cleanly as possible, pass a urethral catheter. The rounded end of the catheter may be cut off to facilitate retrieval of larger uroliths.
3. Infuse sterile fluid if urinary bladder is not distended.
4. In lateral recumbency or in vertical position, agitate the urinary bladder to “put the uroliths in motion”.
5. Aspirate fluid from urinary bladder through urethral catheter.
6. Repeat if necessary.
7. Radiograph if an attempt was made to retrieve all urocystoliths.

**Complications**

- Occur very rarely
- Iatrogenic bacterial urinary tract infection is most likely complication that might occur
- Irritation from catheterization resulting in urethral spasm and lower urinary tract signs may also occur, but they occur rarely
• **Voiding urohydropropulsion**
  
  - Voiding urohydropropulsion is a non-surgical technique for removing bladder stones from dogs and cats
  - The technique is based on the idea of using gravity to assist an animal in voiding out stones
  
  • **Indications**
    
    - The largest diameter stone must be able to pass through the urethra at its narrowest luminal diameter
      
      We have retrieved stones with the following sizes:
      
      - 10 mm - 7.4 kg F / S K9
      - 5 mm - 9 kg M / C K9
      - 5 mm - 4.6 kg F / S Fel
      - 1 mm - 6.6 kg M / C Fel
      
    - It will not work in animals that present with urethral obstruction
  
  - **Description of technique**
    
    1. Sedate or anesthetize the patient
    2. If the urinary bladder is distended, proceed to #4. If the bladder is not distended, distend the bladder with a sterile physiological solution injected through a urethral catheter that is placed as cleanly as possible.
    3. Remove the catheter; if the fluid is expelled prematurely, the vulva or penile urethra can be gently closed.
    4. Position the patient so that the vertebral column is approximately vertical to the ground by supporting the animal under the axillae
      
      - In large dogs, place in dorsal recumbency on a table that can be tilted so that one end of the table is lower than the other
      - Support the dog under the axillae
    5. Gently agitate the urinary bladder by palpation to promote gravitational movement of all urocystoliths into the trigone.
    6. Apply steady digital pressure to the urinary bladder to induce micturition; once voiding begins, the bladder is more vigorously compressed; the object is to sustain maximum urine flow through the urethral lumen to keep it dilated as long as possible. The idea is to induce a micturition reflex, not to squeeze out the stones. Place a collection container under the urethral orifice or vulva to collect voided stones
    7. Repeat steps 2 through 6 if the number of uroliths that are voided is less than that previously detected by radiography; if uroliths detected by radiography were too numerous to count, repeat voiding urohydropropulsion until uroliths are no longer detected in the expelled fluid.
    8. If the number of uroliths retrieved equals the number observed by radiography, recover the patient. If there is a question concerning whether all of the uroliths were retrieved, repeat radiography.
    9. Animals should be treated for 3 to 7 days with antibiotics due to catheterization. It is also a good idea to recheck a urinalysis and if necessary a urine culture 5 to 10 days after discontinuation of antibiotic therapy.
  
  • **Contraindications**
    
    - Animals that present with urethral obstruction due to stones
    - Animals that have urethral outflow obstruction such as strictures, tumors
    - Do not perform in animals that have had a cystotomy in the previous 14 days – the bladder incision may not be strong
    - Use caution when applying pressure on the bladder in animals with a bacterial cystitis as this may cause reflux of infected urine up the ureters into the kidneys
    - Animals with other more serious disease should be stabilized or treated
    - Complications
    - Hematuria occurs commonly
      
      - In dogs, this usually subsides in a couple of hours
      - In cats, this may persist for 12-24 hours
    - Urethral obstruction may occur if one or more stones are larger than the smallest diameter of the urethra
    - Bacterial urinary tract infection occurs uncommonly, but may occur secondary to poor technique and urethral catheterization
    - Bladder and/or urethral rupture could occur, but is very rare
    - Voiding urohydropropulsion can be used in combination with other treatment modalities for bladder stone disease
      
      - Stones amenable to medical dissolution can be dissolved to a size where they can be retrieved using voiding urohydropropulsion
      - Stones that are accidentally left behind at surgery may be retrieved with this technique if they are small enough
• This technique can be done at time of induction for a cystotomy. If all stones are retrieved then the animal can be recovered. If not, then proceed with cystotomy.

• **Cystoscopy and retrieval and laser lithotripsy**
  o Cystoscopy can be performed using rigid cystoscope (in female dogs and cats) or flexible cystoscope (in male dogs)
    ▪ A small “semi-rigid” cystoscope is available for use in male cats; however, due to its size (1 mm) there is no operating channel
      ▪ This permits visualization of the lower urogenital tract
      ▪ Procedures such as biopsy, urolith retrieval, injections, and use of laser can be performed through the operating channel
    ▪ In larger male dogs, a flexible endoscope may be used for visualization
    ▪ In female cats and dogs, a 1.9mm, 2.7mm, or 4.0mm rigid cystoscope is used
    ▪ I perform cystoscopy usually with the patient in dorsal recumbency
      ▪ Requires general anesthesia
      ▪ Fluid for instillation through the scope for distention of the lower urogenital tract and for visualization
  o **Cystoscopic retrieval of uroliths**
    ▪ Baskets and graspers can be inserted through the operating channel of the cystoscope for removal of uroliths
      ▪ They must be small enough to be extracted through the most narrow portion of the urethra
  o **Laser lithotripsy**
    ▪ Laser lithotripsy can be used to manage bladder stones
    ▪ Cystoscopy is performed and a laser fiber – usually a Ho:YAG laser – is inserted through the operating channel
    ▪ The laser energy is used to fragment the stone into small fragments that can be retrieved
    ▪ Complications are rare; however, trauma and perforation of the urinary bladder has been reported

• **Cystoscopic-assisted cystotomy**
  o A cystoscopic-assisted cystotomy is similar to laparoscopic removal
  o A small incision is made on ventral midline
    ▪ In male dogs, the incision is made just cranial to the preputial reflection
  o The urinary bladder is grasped and brought to the incision edge of the linea where it is sutured with a continuous pattern of 2-0 or 3-0 Monocryl
  o A stab incision is made and a rigid cystoscope is inserted into the urinary bladder
  o Stones are retrieved using instruments passed through the cystoscope
  o The urinary bladder is closed with a single layer of 2-0 or 3-0 Monocryl, the linea closed with 2-0 or 3-0 PDS, and the skin and SQ closed with 2-0 or 3-0 Monocryl in a continuous intradermal pattern
  o Patients go home the same day

**Prevention**
• Calcium oxalate uroliths are recurrent; therefore, preventative measures are warranted
  ▪ @ 8% recurrence at 6 months
  ▪ @ 35% recurrence at 1 year
  ▪ Recurrence increases with subsequent years
  ▪ “Pseudorecurrence” refers to leaving uroliths behind after a procedure is performed
    ▪ Occurs in 15-20% of cystotomies
• With hypercalcemia, potential causes should be investigated.
  ▪ 4% of dogs with calcium oxalate uroliths have hypercalcemia – usually due to primary hyperparathyroidism
  ▪ 20-35% of cats with calcium oxalate uroliths have hypercalcemia – usually idiopathic in nature

**Management**
• The goal of prevention is lower the urinary saturation for calcium oxalate by decreasing urinary levels of calcium and oxalate and by increasing urine volume in order to dilute the minerals

• **Cats with hypercalcemia**
  ▪ Feed a high fiber, mineral restricted diet
  ▪ Administer an alkalinizing agent (Potassium citrate)
    ▪ Citrate is an inhibitor of calcium oxalate crystallization and formation
  ▪ In cats with idiopathic hypercalcemia, we have had success feeding a higher fiber diet (Hill’s Prescription Diet Feline w/d) and administering potassium citrate (see below)
• **Cats without hypercalcemia**
  • Feed a diet that induces a diuresis, is mineral restricted, and induces a neutral to alkaline urine pH
  • There are several “multiple use” feline diets formulated to prevent struvite and calcium oxalate
    • Prescription Diet c/d Multicare
    • Royal Canin S/O
    • Purina CNM UR st/ox
  • S/O and UR are higher in sodium than c/d
  • In a study comparing these 3 diets, they each induced a similar degree of urine undersaturation with calcium oxalate albeit by different mechanisms
  • Data from clinical studies is lacking, although in one clinical study of 10 cats with naturally-occurring calcium oxalate bladder stones, consumption of Prescription Diet Feline c/d reduced urinary saturation level to the low end of the metastable range
  • Data from healthy, non-urolith-forming cats have demonstrated decreased urinary saturation with calcium oxalate when cats consumed c/d or S/O

• **Dogs**
  • Feed a diet that is mineral restricted, diuresing, and alkalining
    • Prescription Diet U/d
      • This is an “ultra-low” protein diet originally formulated for “uremic” dogs
      • It is also low in minerals, has increased vitamin D, has increased B vitamins, and is very alkalining
    • Royal Canin S/O
      • Royal Canin s/o has been shown to decrease urine saturation with calcium oxalate but no clinical studies have been done
  • These diets are higher in fat than maintenance foods.
  • Can feed a higher fiber diet and administer the alkalinizing agent, potassium citrate

• **Pharmacologic management**
  • **Potassium citrate** (initial: 75 mg/kg PO q12h)
    • Citrate is an inhibitor of calcium oxalate crystal formation because it forms a soluble salt with calcium
    • Oral potassium citrate may be beneficial in managing calcium oxalate uroliths because it is a calcium oxalate inhibitor and because it is alkalinizing in nature
    • Dosage is titrated to achieve a urine pH of approximately 7.5
    • Calcium oxalate preventative diets contain potassium citrate
  • **Vitamin B6** (2-4 mg PO q24h)
    • Vitamin B6 increases metabolism of glyoxylate, a precursor of oxalic acid, to glycine
    • Whether vitamin B6 deficiency occurs in adult animals, especially cats, with calcium oxalate uroliths is unknown, but unlikely
      • One study in adult calcium oxalate forming dogs showed lower plasma B6 levels when compared with non-urolith forming dogs
      • Vitamin B6 supplementation is inexpensive and safe and should be considered in pets that have difficult to control uroliths
  • **Thiazide diuretics** (hydrochlorothiazide: 1-4 mg/kg PO q12h; chlorothiazide: 20-40 mg/kg PO q12h)
    • By inducing a diuresis and decreasing urinary calcium excretion, thiazide diuretic administration may be beneficial in pets with difficult to control calcium oxalate uroliths
      • Thiazide diuretics decrease urinary calcium excretion in human beings, dogs, and cats
      • In cats, thiazide diuretics have been shown to decrease urinary saturation for calcium oxalate in healthy cats only and they appear safe.
      • One 2-week study in calcium oxalate urolith forming dogs demonstrated decreased urinary calcium excretion
    • Diuretic administration may also be associated with dehydration and electrolyte imbalances and should be used cautiously in animals with renal failure
  • Other agents
    • **Glucocorticoids** have been recommended to decrease blood calcium concentrations in cats with idiopathic hypercalcemia; however, they do so by increasing urinary excretion
    • **Bisphosphonates** have been recommended for cats with idiopathic hypercalcemia; however, no studies have been published.
- **Alendronate** (2 mg/kg PO q7d; most cats respond to 10 mg total dose. Administer at least 6ml of water after administration and butter lips to increase salivation and increase transit as esophagitis and stricture may occur. Beneficial effect usually seen in 3-4 weeks.
Micturition refers to the process of storing and periodically voiding urine.

a. Disorders of urine storage usually lead to urinary incontinence, whereas disruption of urine voiding leads to incomplete emptying, dysuria, or urine retention
b. Micturition is a complex integration of central, sympathetic, parasympathetic, and somatic nervous systems, with resultant muscular activity
c. The two functional units of the lower urinary tract include the reservoir/pump (urinary bladder) and the continence/conduit (urethra).
d. The urinary bladder and proximal urethra are composed of smooth muscle and are thus under autonomic nervous system control while the distal urethra is composed of skeletal muscle and thus under somatic nervous system control

**BOTTOM LINE:**

PARASYMPATHETIC PROMOTES PEEING SYMPATHETIC STIMULATES STORAGE

2. Disorders of micturition

a. Several different ways of classifying
   i. Storage vs voiding
   ii. Full bladder vs empty bladder
   iii. Neurogenic vs myogenic
b. Important to establish status of urinary bladder contractile force and patency of urethral outlet, determine whether disorder is primarily neurogenic or myogenic, and determine underlying etiology or contributing factors
   i. History and signalment
      1. Age
      2. Gender
      3. Reproductive status
      4. Prior neurologic disease
      5. Trauma or surgery to urinary tract or nervous system
      6. Water intake
      7. Urination habit
   ii. Physical examination
      1. Complete examination
      2. Complete neurological examination
         a. Mental status
         b. Gait
         c. Spinal reflexes
         d. Cranial nerve reflexes and responses
      3. Examine external genitalia
      4. Bladder size and tone prior to a voiding urination
      5. Digital rectal exam (all dogs; cats if sedated)
      6. Digital vaginal exam (dogs; cats if sedated)
      7. Observe urination if possible
         a. Does animal sense when bladder is full?
         b. Does it posture appropriately to void?
         c. Is urine stream normal?
         d. Does animal continue to attempt to void after stream has stopped?
         e. How does urinary bladder palpate after voiding?
   iii. Diagnostic testing
      1. Urinalysis and urine culture
2. +/- CBC, serum biochemical panel
3. +/- Infectious disease testing (FeLV, FIV, etc)
4. +/- Imaging
   a. Survey radiographs
   b. Contrast studies
   c. Ultrasound
5. +/- Cystoscopy or exploratory
6. +/- Neurologic testing
   a. Myelogram
   b. MRI or CT
7. +/- Urinary system functional testing
   a. Cystometrogram
   b. Urethral pressure profile

c. Problems with storage
   i. Bladder overactivity
      1. Due to “hyperexcitability” of storage phase -> results in inability to permit adequate bladder filling because of “urgency”
         a. Animals have increased frequency of urination, pollakiuria, inappropriate urination
         b. Often urethral irritation or spasm is present
         c. Examples: cystitis, urocystolithiasis, chemical stimulation (cyclophosphamide)

   2. Treatment: RELAX bladder
      a. Antimuscarinic agents (propantheline, oxybutynin, tolterodine) and antispasmodic agent (oxybutynin, flavoxate, tolterodine)
         i. Decrease detrusor activity and have urethral anti-spasmodic effects
         ii. May help with refractory incontinence by increasing urine storage
      b. Tricyclic antidepressants: imipramine, amitriptyline (?)
         i. May improve bladder storage by several mechanisms including anticholinergic, alpha-adrenergic, and beta-adrenergic effects
   
   ii. Bladder atony
      1. Due to neurogenic or myogenic causes
         a. “Upper motor neuron bladder”
         b. Bladder overdistention
         c. Animal may or may not posture to urinate with a distended bladder

      2. Treatment: STIMULATE bladder (Should almost always relax urethra at same time)
         a. Manage large over-distended bladder with urinary catheterization
         b. Bethanechol
            i. Parasympathomimetic with direct cholinergic activity
            ii. Stimulates or augments smooth muscle contraction
         c. Metoclopramide?
         d. Cisapride?
         e. When pharmacologically stimulating bladder contraction consider relaxing urethra
         f. Manual expression

d. Problems with voiding
   i. Increased outlet resistance
      1. Functional vs mechanical
         a. “Upper motor neuron” lesion
         b. Urethral spasm
         c. Outlet obstruction (mass, stone, etc)
         d. Animal often postures to urinate but cannot void or voids a small amount

      2. Treatment: RELAX urethra
         a. Manage large over-distended bladder with urinary catheterization
         b. Alpha adrenergic antagonists: phenoxybenzamine, prazosin
            i. Sympatholytics
ii. Tamsulocin is used in humans and experimentally in dogs at 1-100 ug/kg IV and PO. Dosage of 1-10 ug/kg produced effect – consider 10 ug/kg PO q24h

c. Skeletal muscle relaxants: diazepam, dantrolene, baclofen
   i. NOTE: external urethral sphincter not as important as internal urethral sphincter
d. Clean intermittent catheterization
e. Chronic catheters (urethral or cystostomy)
f. *Urethral stents

ii. Decreased outlet resistance (urethral incompetence)
   1. Neurogenic or myogenic
   2. Most common cause is urethral sphincter mechanism incompetency in female dogs
      a. Uncommon in male dogs or cats and male dogs
      b. In these animals, search for other causes
   3. Animal “leaks” urine
   4. Treatment: STIMULATE urethra
      a. Alpha agonists – phenylpropanolamine, pseudoephedrine
         i. Continenct in 85-90%
         ii. Once a day treatment may be as effective as three times a day administration with fewer side effects
      b. Reproductive hormones
         i. Estrogens
            1. Increase alpha adrenergic receptor responsiveness and improve urethral vascularity and other mucosal characteristics
            2. Usually given as loading dose and then lowest maintenance dose
            3. Safe and reasonably effective (40-65%)
            4. Estriol (Incurin) is the only approved estrogen for use in dogs and is reported to have a 93% excellent response rate
      ii. GnRH analogs
         1. Chronically unsuppressed FSH and LH release (due to lack of negative feedback) in ovariectomized dogs may contribute to urinary incontinence
         2. Administration of GnRH analogs paradoxically reduce FSH and LH over time
         3. Was found effective in 12/13 dogs in one study and in another study 9/23 dogs were continent from 70-575 days with another 10/23 having partial response; however, the 23 dogs also responded to PPA
   c. Urethral bulking
      i. Involves injection of an agent submucosally in the proximal urethra via cystoscopy
         1. Thought to create artificial urethral cushions improving urethral closure (coaptation)
         2. Also functions as central filler volume increasing length of smooth muscle fibers and closure power of internal urethral sphincter
         3. There are no bulking agents available for use in veterinary medicine. Historically, glutaraldehyde cross-linked collagen was used, but has been withdrawn from market. A study with polydimethylsiloxane has promising results.
   d. Artificial sphincters/urethral occluding devices
      i. A urethral occluding device is similar to a blood pressure or vascular cuff
      ii. It is placed surgically around proximal urethra with a loose fit
iii. A tube connects the device with a subcutaneously implanted injection port, which provides a means to increase pressure within the device and therefore urethral pressure in area of internal urethral sphincter.

iv. Continence rates are high; however, they may require adjustment with time.

v. Urethral obstruction and irritation with clinical signs may occur.

e. Surgical techniques: slings, plication, culposuspension.

iii. Reflex dyssynergia
1. Incoordination between bladder contraction and urethral relaxation.
2. Animal usually postures normally, initiates a good stream, but stream stops yet animal continues to posture and attempt to void.
   a. Treatment involves relaxing urethra.
   b. If bladder does not completely empty despite urethral relaxation, then add bladder stimulant.

iv. Paradoxical incontinence
1. Outflow obstruction resulting in bladder overdistention.
2. Increased bladder pressure results in “leaking” of urine through or around obstruction.
3. Animal dribbles urine with a full bladder and is unable to void.
4. May be due to functional or mechanical outflow obstruction and is often associated with bladder atony.

### TABLE. Drugs used to manage dogs and cats with micturition disorders.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Recommended dosage</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents used to increase urinary bladder contractility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bethanechol</td>
<td>Parasympathomimetic; direct cholinergic activity</td>
<td>D: 5-25 mg PO q8h</td>
<td>Nausea, vomiting, salivation</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Prokinetic; sensitizes to acetylcholine</td>
<td>D, C: 0.2-0.5 mg/kg PO q8h</td>
<td>Behavior changes</td>
</tr>
<tr>
<td><strong>Agents used to decrease urinary bladder contractility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propantheline</td>
<td>Parasympatholytic; acetylcholine blockade</td>
<td>D: 7.5-30 mg PO q8h</td>
<td>Nausea, vomiting, constipation, sedation, increased ocular pressure</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Parasympatholytic; antispasmodic; detrusor relaxation</td>
<td>D: 1.25-5 mg PO q8-12h</td>
<td>Nausea, vomiting, urine retention, diarrhea, sedation</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>Direct smooth-muscle relaxant</td>
<td>D: 100-200 mg PO q6-8h</td>
<td>Weakness</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>Anti-muscarinic</td>
<td>D: 10 mg PO q6-8h</td>
<td>Nausea, vomiting, constipation, sedation, increased ocular pressure</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tricyclic antidepressant with anticholinergic, alpha-and beta- agonist effects, detrusor smooth muscle relaxation and urethral muscle contraction</td>
<td>D: 5-15 mg PO q12h</td>
<td>Seizures, tremors, tachycardia, hyperexcitability</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tricyclic anti-depressant</td>
<td>D: 2.2-4.4 mg/kg PO q12h</td>
<td>Sedation, anticholinergic effects</td>
</tr>
<tr>
<td><strong>Agents used to increase urethral resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estriol (Incurin)</td>
<td>Reproductive hormone</td>
<td>D: 0.5-2 mg PO q24h initially; followed by 0.5-2 mg PO q2-3d</td>
<td>Signs of estrus, bone marrow suppression</td>
</tr>
<tr>
<td>DES</td>
<td>Reproductive hormone</td>
<td>D (females): 0.1-1 mg PO q24h for 5 days (approximately 0.2 mg/kg) followed by 0.1-1 mg PO q7d</td>
<td></td>
</tr>
<tr>
<td>Premarin</td>
<td>Reproductive hormone</td>
<td>D: 20 mcg/kg q24hr x 7-10d; then q1-3d</td>
<td></td>
</tr>
<tr>
<td>Agent</td>
<td>Effect</td>
<td>Dosage Information</td>
<td>Adverse Effects</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Testosterone propionate** | Reproductive hormone                  | D (males): 2.2 mg/kg SQ or IM q2-3d  
C (males): 5-10 mg IM as needed  
D (males): 2.2 mg/kg IM q30d or 200 mg IM q30d  
C (males): 5-10 mg IM q30d | Aggression, prostatic disease, perineal hernia |
| **Testosterone cypionate** | Alpha agonist; urethral smooth muscle contraction | D (males): 12.5-50 mg PO q8h; 1-2 mg/kg PO q8h  
C (males): 1.0-1.5 mg/kg PO q8h | Anxiety, cardiac arrhythmias, anorexia, hypertension |
| **Phenylpropanolamine** | Alpha agonist; urethral smooth muscle contraction | D: 1.2 mg/kg PO q8h or 5-15 mg PO q8h  
C: 2-4 mg/kg PO q6-12h or 2-4 mg PO q8h | Anxiety, cardiac arrhythmias, hypertension |
| **Ephedrine** | Alpha agonist; urethral smooth muscle contraction | D: 5-15 mg PO q12h  
C: 2.5-10 mg PO q24h  
D, C: 0.25 mg/kg PO q12h | Hypotension, tachycardia, vomiting, diarrhea, increased intraocular pressure |
| **Phenoxybenzamine** | Alpha antagonist; urethral smooth muscle relaxation | D: 1 mg/15kg PO q12-24hr  
C: 0.25-0.5 mg PO q12-24hr | Hypotension |
| **Prazosin** | Alpha antagonist; urethral smooth muscle relaxation | D: 0.03-0.2 mg/10kg q24hr | Hypotension |
| **Tamsulocin** | Alpha antagonist, urethral smooth muscle relaxation | D: 0.1-1.0 mg/kg PO q24h | Hypotension |
| **Doxazosin** | Alpha antagonist, urethral smooth muscle relaxation | D, C: 0.5-5 mg PO q12-24hr | Hypotension |
| **Terazosin** | Alpha antagonist, urethral smooth muscle relaxation | D: 0.1-1.0 mg/kg PO q24h | Hypotension |
| **Terazosin** | Alpha antagonist, urethral smooth muscle relaxation | D: 0.1-3.0 mg/kg PO q24h | Hypotension |
| **Fiduxosin** | Alpha antagonist, urethral smooth muscle relaxation | D: 0.1-3.0 mg/kg PO q24h | Hypotension |
| **Diazepam** | Striated muscle relaxation; central nervous system depressive effect | D: 0.2 mg/kg PO q8h or 2-10 mg PO q8h  
C: 2.5-5 mg PO q8h or as needed or 0.5 mg/kg IV | Sedation, paradoxical excitement |
| **Dantrolene** | Striated muscle relaxation; direct action | D: 3-15 mg/kg PO q24h divided or 0.5-1 mg/kg PO q8h  
C: 0.5-1 mg/kg PO q12h | Weakness, hepatotoxicity |
| **Acepromazine** | Urethral muscle relaxation by neuroleptic effect; alpha antagonism | D: 0.1-2 mg/kg PO q8-12h  
C: 0.1 mg/kg IV or 1.1-2.2 mg/kg PO q12h | Sedation, hypotension, seizures |
| **Aminopromazine** | Smooth muscle relaxation | D, C: 2.2 mg/kg PO q12h | |

**Agents used to decrease urethral resistance**

**Phenoxybenzamine**
- **Dosage**: 5-15 mg PO q12h  
- **C**: 2.5-10 mg PO q24h  
- **D, C**: 0.25 mg/kg PO q12h  
- **Adverse Effects**: Hypotension, tachycardia, vomiting, diarrhea, increased intraocular pressure

**Prazosin**
- **Dosage**: 1 mg/15kg PO q12-24hr  
- **C**: 0.25-0.5 mg PO q12-24hr  
- **Adverse Effects**: Hypotension

**Tamsulocin**
- **Dosage**: 0.03-0.2 mg/10kg q24hr  
- **Adverse Effects**: Hypotension

**Doxazosin**
- **Dosage**: 0.1-1.0 mg/kg PO q24h  
- **Adverse Effects**: Hypotension

**Terazosin**
- **Dosage**: 0.1-1.0 mg/kg PO q24h  
- **Adverse Effects**: Hypotension

**Terazosin**
- **Dosage**: 0.1-3.0 mg/kg PO q24h  
- **Adverse Effects**: Hypotension

**Fiduxosin**
- **Dosage**: 0.1-3.0 mg/kg PO q24h  
- **Adverse Effects**: Hypotension

**Diazepam**
- **Dosage**: 0.2 mg/kg PO q8h or 2-10 mg PO q8h  
- **C**: 2.5-5 mg PO q8h or as needed or 0.5 mg/kg IV  
- **Adverse Effects**: Sedation, paradoxical excitement

**Dantrolene**
- **Dosage**: 3-15 mg/kg PO q24h divided or 0.5-1 mg/kg PO q8h  
- **C**: 0.5-1 mg/kg PO q12h  
- **Adverse Effects**: Weakness, hepatotoxicity

**Acepromazine**
- **Dosage**: 0.1-2 mg/kg PO q8-12h  
- **C**: 0.1 mg/kg IV or 1.1-2.2 mg/kg PO q12h  
- **Adverse Effects**: Sedation, hypotension, seizures

**Aminopromazine**
- **Dosage**: 2.2 mg/kg PO q12h  
- **Adverse Effects**: 
Urine a State of Confusion: Feline Lower Urinary Tract Disease  
Joe Bartges, DVM, PhD, DACVIM, DACVN  
Professor of Medicine and Nutrition  
The Acree Endowed Chair of Small Animal Research  
The University of Tennessee

* Prevalence of lower urinary tract disease is more common in cats between 1 and 10 years of age; whereas in dogs, the prevalence increases with advancing age.

![Graph showing prevalence of lower urinary tract disease in dogs and cats](image)

Figure. Prevalence of lower urinary tract disease in dogs (1980-1995) and cats (1980-1990) reported through the Veterinary Medical Database

* In cats >10 years of age, bacterial urinary tract infection is most common
  * In young cats, idiopathic lower urinary tract disease occurs most commonly

![Bar chart showing causes of lower urinary tract disease in cats](image)

Figure. Causes of lower urinary tract disease in cats from 3 studies.

**What is Feline Idiopathic Cystitis (Idiopathic Feline Lower Urinary Tract Disease)?**
* Currently, there are 2 hypotheses concerning FIC
  * **Viral hypothesis**
    * A gamma-herpesvirus, a calicivirus, and a retrovirus have been isolated from urine and tissues from cats with naturally occurring idiopathic lower urinary tract disease
    * Reproducible clinical evidence that viruses cause naturally occurring disease is scarce
    * Viral particles have been observed in plugs recovered from cats with matrix-crystalline urethral plugs
  * **Neurogenic inflammation hypothesis**
• Similar in some respects to hypothesis for interstitial cystitis in women
• Cats with idiopathic lower urinary tract disease have decreased urinary glycosaminoglycan concentration and similar light microscopic changes to interstitial cystitis
• This may represent a central nervous system problem
  • In cats with FIC, there appears to be a dysregulation of the sympathetic nervous system
  • sANS activation w/o activation of hypothalamic-pituitary-adrenal axis for counter-regulation
    • ↑CRF release w/o appropriate ↑cortisol (adrenocortical hypoplasia)
    • ↑ tissue inflammatory response
    • ↑ epithelial permeability
      – Fluorescein studies
    • ↑ neuron firing ->pain (nitric oxide?)
    • “flare-ups” of signs with stress
  • Developmental disorder (Pandora Syndrome)
    • Early age adverse experience (?)
      – Queen stress -> cortisol suppression of adrenal development in kittens
  • Other organ system problems

Clinical signs of feline lower urinary tract disease
• Causes of lower urinary tract disease in cats present with similar clinical signs including, but not limited to:
  • Pollakiuria
  • Hematuria
  • Stranguria
  • Dysuria
  • Inappropriate urination
  • +/- Urethral obstruction

Diagnostic testing for cats with lower urinary tract signs
  ● CBC and biochemical analysis are normal unless urethral obstruction is present
  ● Urinalysis reveals hematuria
    ➢ Pyuria and possibly bacteriuria present, if UTI
    ➢ Crystalluria may be present with plugs or stones
  ● Urine culture is negative unless a UTI is present
  ● Abdominal radiography and ultrasonography may be normal
    ➢ A large bladder may be found with urethral obstruction
    ➢ Uroliths may be observed or “sand”
    ➢ Urinary bladder wall may be thickened on ultrasound
  ● Cystoscopically, small pin-point hemorrhages (glomerulations) are found and occasionally larger mucosal ulceration
    ➢ These can be found with other diseases of the lower urinary tract
  ● Bladder biopsy often reveals submucosal edema, mucosal ulceration, possible submucosal inflammation, possible fibrosis
    ➢ May be observed with other diseases of the lower urinary tract
    ➢ We routinely biopsy the bladder wall for histopathologic examination and aerobic and anaerobic bacterial culture
  ● Idiopathic disease is a diagnosis of exclusion

TREATMENT OF LOWER URINARY TRACT DISEASE
Urethral obstruction
  • Obstruction may occur from uroliths or from matrix-crystalline urethral plugs
    • Matrix-crystalline plugs have been found only in male cats
    • Approximately 84% of matrix-crystalline plugs contain a mineral component
    • Struvite is present in 80% of these
    • Urethral plugs have not been observed to occur in dogs
    • Uroliths occur in both dogs and cats (we will discuss in future lectures)

Consequences of urethral obstruction
  • Consequences of urethral obstruction
    • Early in course of urethral obstruction
      • May not be clinically evident
      • Stranguria, pollakiuria, and inability to urinate may be present
      • Patient may appear uncomfortable and/or have behavior changes
As obstruction progresses, clinical signs increase in severity
• Cat may sit in litter box attempting to urinate or dog may attempt urination and pass only few drops; owners often mistake this sign as constipation
• As urine retention continues, post-renal azotemia and eventually uremia develops
  ▪ Depression, lethargy, moribund state
  ▪ Vomiting due to uremia
  ▪ Bradycardia and collapse due to hyperkalemia
  ▪ Halitosis due to uremia
  ▪ Death will occur in 72-96 hours after complete obstruction
• If urethral obstruction is relieved, cat is likely to recover
• The most common abnormalities associated with obstructive uropathy include: dehydration, hyperkalemia, metabolic acidosis, and post-renal azotemia
  ▪ Dehydration
    • Fluid therapy is very important in obstructive uropathy because of dehydration and for circulatory support
  ▪ Remember the 3 components of fluid therapy
    • Amount for rehydration
      • % dehydrated x BWkg = L for rehydration
    • Maintenance
      • Typically 1 ml/lb/hour (2.2 ml/kg/hour)
    • On-going losses
      • Measure or estimate
      • Some recommend ½ maintenance fluid requirements
  ▪ You should review types of fluid and routes of administration that are acceptable for managing patients with obstructive uropathy
  ▪ Hyperkalemia
    • Management of hyperkalemia with obstructive uropathy is similar to management of hyperkalemia occurring with acute renal failure
    • Re-establishing urethral patency and fluid therapy is often all that is required as long as arrhythmias are not present
      • Arrhythmias (bradycardia -> sinoatrial arrest -> ventricular escape beats) typically do not occur until the serum potassium is > 8 mEq/L
      • Death occurs with potassium concentration exceeds 12-13 mEq/L
    • 3 ways to decrease plasma/blood potassium concentration
      (1) Dilute and excrete – fluid therapy or dialysis
      (2) Transcellular shift
        • Glucose
        • Insulin
        • Insulin and glucose
        • Bicarbonate
      (3) Counteract effect of hyperkalemia at sino-atrial node
        • Calcium gluconate

Re-establishing urethral patency
  ❖ Male cats
    ➢ Male cats may be obstructed with uroliths or matrix-crystalline urethral plugs
    ➢ In male cats, heavy sedation or anesthesia is required
    ➢ Position male cats in lateral or dorsal recumbency – dorsal is best
    ➢ Massage distal urethra while compressing the urinary bladder may dislodge the plug
    ➢ Perform cystocentesis in order to obtain a diagnostic sample and to decompress the bladder. Do not remove all of the urine so that the bladder can be palpated. A potential complication is urine extravasation, which is uncommon if the procedure is performed correctly.
    ➢ Urethral patency can be re-established by retrograde flushing the urethra
  ❖ Make every effort to protect the patient from iatrogenic complications associated with catheterization of the urethra (especially trauma, and urinary tract infection with bacteria).
  ❖ Strive to use meticulous aseptic "feather-touch" technique.
  ❖ Use only sterile catheters.
Perform a cystocentesis for a diagnostic sample and to relieve back pressure.

Cleanse the penis and prepuce with warm water prior to catheterization.

Select the shortest Minnesota olive tipped feline urethral catheter* or a Tom Cat catheter (such as a Slippery Sam) for initial catheterization of the urethra.

Coat the olive tip with sterile aqueous lubricant.

Prior to insertion of the catheter into the external urethral orifice, the extended penis should be displaced dorsally until the long axis of the urethra is approximately parallel to the vertebral column.

Carefully advance the catheter to the site of obstruction. If necessary, replace the short olive tipped Minnesota needle with a longer one. Record the site of suspected obstruction, since this information may be of value when considering use of muscle relaxants, and/or when considering urethral surgery to prevent recurrent obstruction. CAUTION: Do not mistake resistance induced by curvature of the feline male urethra for a site of obstruction. In addition, never use excessive force when advancing the catheter.

Next, a large quantity of physiological saline or lactated Ringer's solution (as much as several hundred ml) should be flushed into the urethral lumen, and allowed to reflux out the external urethral orifice. When possible, the catheter may be advanced toward the bladder. As a result of this maneuver, the obstructed urethral plugs may be gradually dislodged and flushed around the catheter and out of the urethral lumen. Application of steady but gentle digital pressure to the bladder wall after the urethra has been flushed with physiological saline or lactated Ringer's solution may result in expulsion of a urethral plug urolith from the urethral lumen. Excessive pressure should not be used because it may result in: 1) trauma to the bladder, 2) reflux of potentially infected urine into the ureters and renal pelves, and/or 3) rupture of the bladder wall.

If the technique outlined is unsuccessful; it may be necessary to attempt repulsion of suspected urethral plugs or uroliths back into the bladder lumen by occluding the distal end of the urethra around the olive tip of the catheter before injecting fluid into the urethra. By preventing reflux of solutions out of the external urethral orifice, this maneuver will tend to dilate the urethral lumen. If the obstruction persists, an attempt may be made to gently advance the suspected plug or urolith toward the bladder. Excessive force should not be used.

On occasion it is advantageous to allow the reverse flushing solution to soften the obstructing urethral plugs (this technique is ineffective for most uroliths) before attempting to propel them back into the bladder. Allowing lapse of several hours between attempts to remove firmly lodged plugs by reverse flushing has been effective.

Aftercare once urethral patency is re-established

- Re-establishing urethral patency is not the end point
  - Remove as much of the urine as possible once the cat is un-blocked
  - The bladder may need to be “rinsed” if there is a lot of particulate matter and/or mucous present in the urine
    - Use sterile crystalloids or water; do not use glucose containing solutions
    - Do not infuse antibiotics, anti-spasmodics, anesthetics, or acidifiers into the bladder
    - Glucocorticoids are not indicated as they increase risk of infection
    - Systemic antibiotics may be administered if an indwelling urinary catheter is not inserted
  - Anti-spasmodics (urethral relaxants) may help, but there is little data that they in fact do help
    - In order to relax the urethra, an alpha-antagonist is administered
    - Phenoxybenzamine or prazosin can be used
    - Some people administered a skeletal muscle relaxant; however, diazepam has minimal effect on the urinary tract
  - An indwelling urethral catheter may be required
    - Indications for an indwelling urethral catheter include
      - Difficulty in un-obstructing the patient
      - A large amount of particulate matter and/or mucous despite flushing of the urinary bladder
      - When there is a high likelihood of re-obstruction
      - If detrusor atony is present

Management of an indwelling urethral catheter

- An indwelling urethral catheter should be considered on an individual case basis
  - Severely ill patients
  - If difficult to catheterize
  - Poor urine stream post obstruction

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* Minnesota feline olive tipped urethral catheters are available from EJAY International, Inc., P.O. Box 1835, Glendora, California 91740.
Detrusor atony (atonic bladder)

- A urethral catheter should be connected to a **closed collection system**
- **Management**
  - **Systemic antibiotics** should not be administered unless given for some other reason
    - The risk of bacterial urinary tract infection decreases with antibiotic administration
    - However, when an infection occurs, the organism has a high degree of resistance
    - Furthermore, the bacterial organism may invade the upper urinary tract resulting in chronic pyelonephritis
  - **Anti-inflammatory agents** – such as an NSAID – may be beneficial as long as renal function is good
  - With an indwelling catheter, a **urethral relaxing agent** (alpha blocker: prazosin: 0.25-0.5 mg PO q12-24h; phenoxybenzamine: 1.25-5 mg PO q12-24h) is administered to minimize catheter-induced urethral trauma and irritation
  - With bladder atony, a drug to stimulate bladder contraction, a parasympathomimetic (bethanechol: 1.25-5 mg PO q8h; metoclopramide: 0.1-0.2 mg/kg PO q8h), is administered
- **Catheter-associated UTI**
  - Occurs in 50-80% of catheterized patients
  - Prophylactic antibiotics decrease incidence, but increase likelihood of resistance or of an unusual organism
  - Prevention:
    - Use as clean to aseptic technique as possible
    - Physically separate patients with indwelling catheters from others
    - Wear gloves and wash hands between patients
    - Replace catheters when damaged or dirty
- Typically, an indwelling urinary catheter is maintained for 2 to 3 days
  - This is not a hard and fast rule, however
  - Decision to remove the catheter should be based on the progress of the patient, appearance of the urine, and likelihood that the tight junctions of the detrusor muscle have re-established
  - Remove if catheter is non-patent, damaged, or contaminated
- **Post-obstructive diuresis** must be addressed
  - Due to back pressure from the obstructive uropathy being transmitted to the upper urinary tract, a heavy diuresis may develop when the obstruction is relieved
  - This may be as much 2.4 L per day (most cats urinate 30-40 ml per day)
  - It is important to adjust fluid intake to match urine output so that dehydration does not occur
- **Cystostomy catheters** may be inserted and used long term
  - These may be mushroom-tipped catheters or low-profile catheters
  - Allows for long term, indefinite use

**Non-obstructive idiopathic feline lower urinary tract disease**

- There have been dozens of proposed treatments for cats with lower urinary tract disease; very few have undergone evaluation in a randomized controlled clinical trial
- **Antimicrobial agents**
  - Often administered
  - Bacterial urinary tract infection is an uncommon cause of lower urinary tract disease in cats <10 years of age occurring in <1% of such cats
  - If a bacterial infection was present, then the cat would have a diagnosis of bacterial cystitis and not idiopathic lower urinary tract disease
  - Their use is not indicated in cats without a proven bacterial urinary tract infection
- **Urinary tract antiseptics**
  - **Methenamine** and **methylene blue** are not indicated in cats with idiopathic lower urinary tract disease
  - They may cause side effects such as metabolic acidosis (methenamine) or Heinz body anemia (methylene blue)
  - Since bacterial urinary tract infections are uncommon in young cats, they are not recommended
- **Urinary tract analgesics**
  - **Phenazopyridine** is an over the counter preparation available for use by women with recurrent vaginitis/cystitis
  - In cats, phenazopyridine causes Heinz body anemia and should not be used
- **Smooth muscle and skeletal muscle relaxants**
  - Many cats with idiopathic lower urinary tract disease have urge incontinence and inappropriate urination
• **Propantheline**, an anticholinergic agent, minimizes force and frequency of uncontrolled detrusor contractions, but has negligible effect on urethral tone (0.25-0.5 mg/kg PO q12h)
  • It may be beneficial in some cats
  • However, one study could not document a benefit
• **Phenoxybenzamine and prazosin** are sympatholytic agents that decrease urethral tone and spasm
  • Clinical data is lacking as to their efficacy with idiopathic feline lower urinary tract disease
  • I use for a short time in some cats that strain frequently or that had a urethral obstruction especially if an indwelling urinary catheter was inserted
  • prazosin: 0.25-0.5 mg PO q12-24h; phenoxybenzamine: 1.25-5 mg PO q12-24h
• **Diazepam** and **dantrolene** are skeletal muscle relaxants that may decrease tone and spasm of the distal urethra
  • Diazepam has minimal effect on urethral tone (2-5 mg PO q8h)
  • Dantrolene is more effective (0.15-0.6 mg/kg PO q8h)
  • Clinical studies are lacking as to efficacy of these drugs in cats with idiopathic lower urinary tract disease
  • I do not usually use
• **Anti-inflammatory agents**
  • **Glucocorticoids**
    • Have been used historically to decrease inflammation
    • Several studies have shown no benefit
    • They are contraindicated in cats with urethral obstruction or those that have indwelling urinary catheters
      • Risk of urinary tract infection increases in cats with indwelling urethral catheters that receive glucocorticoids
      • Some cats develop pyelonephritis
  • **Non-steroidal anti-inflammatory agents**
    • There are no clinical studies demonstrating safety or efficacy of use of these drugs in cats with idiopathic lower urinary tract disease
• **Amitriptyline**
  • A tricyclic antidepressant
  • May have analgesic properties, stabilize mast cells, and decrease inflammation
  • In one uncontrolled study, 9 of 15 cats with idiopathic lower urinary tract disease improved with amitriptyline
  • One controlled study of cats with active lower urinary tract disease showed no benefit and cats receiving amitriptyline had a higher incidence of recurrence of lower urinary tract signs
  • Goal is to find a dose that will have a calming effect on the cat (begin at 5 mg than increase slowly; most cats require 10-12.5 mg)
• **Glycosaminoglycans**
  • Cats with idiopathic lower urinary tract disease have decreased concentrations of glycosaminoglycans in their urine
  • Glycosaminoglycans may have a protectant role at the mucosal-urine interface
    • Two controlled studies failed to show a difference in clinical signs between a glycosaminoglycan and placebo in cats with idiopathic lower urinary tract disease
    • Pentosan polysulfate sodium, however, may still have effect (50 mg PO q12h)
• **Dietary modification**
  • In cats with matrix-crystalline plugs or with struvite crystalluria, feeding a “struvite preventative” diet may have some benefit
  • In one study of cats with idiopathic lower urinary tract disease, cats fed a canned diet had fewer recurrences than those fed a dry diet
    • However, there were more drop-outs in the canned group for unexplained reasons
    • If added back in – no difference between diet groups
  • These cats were fed “struvite preventative” diets
• **Clomipramine and Fluoxetine**
  • Used for urine spraying / marking behavior
  • Modifies behavior may have some analgesic effects
  • Not studied for FIC
• **Pheromones**
  • Sprays and diffusers
  • May calm a cat down
  • 1 study of cats with FIC – no benefit
• Multi-modal environmental modification (MEMO)
  • Cats do not respond to force
  • Cats are territorial and ‘in control’
  • Litter boxes and food should be away from noise and distractions
  • Cats like to climb, hide, scratch, and hunt – vertical and horizontal space
  • Cats are clean and self-grooming
  • Cats are active at night
  • 1+1 rule – 1 food dish, 1 water bowl, and 1 litter box per cat plus 1 extra
  • Indoor Cat Initiative: http://www.vet.ohio-state.edu/indoorcat.htm
How do I treat cats with lower urinary tract disease?

- **First episode, urethral obstruction, young cat**
  - Unobstruct
  - Radiographs, UA (other lab work?)
  - Indwelling catheter?
  - Torbugesic?
  - Diet change (likely)?
  - Antibiotics (peri-catheterization)
  - Environmental and behavioral modification?
  - If persists or recurs, do additional diagnostics

- **First episode, no urethral obstruction, young cat**
  - Urinalysis (minimum)
  - Torbugesic?
  - Diet change (likely)? – usually crystal-related disease (either stones or plugs)
  - If persists or recurs
    - Do additional diagnostics
    - Consider
      - Diet?
      - Amitriptyline?
      - Pentosan polysulfate?
      - Environmental and behavior treatment

- **First episode, urethral obstruction, older cat**
  - Unobstruct
  - Radiographs, UA (other lab work?)
  - Indwelling catheter?
  - Torbugesic?
  - Diet change (likely)
  - Stones?
    - Struvite: infection vs. non-infection
    - Calcium oxalate
  - Matrix-crystalline plug?
  - Others?
  - Antibiotics (peri-catheterization)

- **First episode, no urethral obstruction, older cat**
  - Diagnostics
  - Torbugesic?
  - Diet change? Most likely – urolithiasis most likely cause (especially calcium oxalate)
  - If persists or recurs
    - Torbugesic as needed
    - Diet?
    - Amitriptyline?
    - Pentosan polysulfate?
    - Environmental and behavior treatment