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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<td>Specificity</td>
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<td><strong>Negative Predictive Value</strong></td>
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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 \( \frac{1}{3} \) to \( \frac{1}{2} \) of infections
- Gram positive organisms are second most common cause
  - *Staphylococci* and *streptococci* account for \( \frac{1}{4} \) to \( \frac{1}{9} \) of infections
- Bacteria accounting for remaining \( \frac{1}{4} \) to \( \frac{1}{3} \) 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 breach 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
- 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
  - Breaks in host defenses
    - Local defenses
    - Recessed vulva
    - Deep-seated infection: 18.5% of cases had positive bladder wall or urolith culture with a negative urine culture
      - In our experience, 4% of bladder wall cultures are positive in dogs with negative urine culture who do not have uroliths
    - Anatomic defects (e.g. ectopic ureter)

UTI Antibiotic Therapy

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”
- Indwelling urinary catheter
  - Concomitant antimicrobial administration decreases incidence of UTI
  - However, when UTI develops, it is highly resistant
  - We do not administer antimicrobial agents with an indwelling urinary catheter unless there is another reason
    - Systemic host defenses
    - Associated complicating disease (e.g. diabetes mellitus, hyperadrenocorticism, hyperthyroidism, renal failure)
  - Bacterial factors
    - Multi-drug resistance
    - Unusual organism (e.g. Corynebacterium, methicillin-resistant Staphylococcus)

**Prevention**

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

- Cats with perineal urethrostomies are at high risk for developing bacterial urinary tract infections
- Resistant urinary tract infections

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

- Fluoroquinolones (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
- Potentiated beta-lactams: may be tried if intermediate susceptibility is present. I usually use amoxicillin-clavulanic acid at a higher dosage (22 mg/kg PO q12h). Ampicillin-sulbactam may also be used (cats - 20-30 mg/kg PO q8-12h x 3-7 days; 5-11 mg/kg IM, SQ q8-12h; has been given 20-40 mg/kg IV q6-8h; dogs - 12.5 – 30 mg/kg PO q8-12h x 7 days; 6.6 -40 mg/kg IM, SQ q16-2h x 3-7 days; has been given 20-40 mg/kg IVq6-8h)
- Penems: Meropenem may be useful for highly resistant (8 mg/kg SQ q12h)
- 3rd generation cephalosporins: May be useful. Cefpodoxime (Simplicef) does not have as much activity as parenteral forms and may not be effective even with a favorable sensitivity pattern (5-10 mg/kg PO q24h)
- Cefovecin: A newer parenteral long-acting cephalosporin has been shown to be effective against E coli in dogs and cats; however, effectiveness with resistant organisms is unknown (8 mg/kg SQ q14d)
- 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 urinalysis changes (pyuria, hematuria), no treatment with re-culture in 2 weeks may reveal eradication of the organism. Treatment should be considered for animals with active clinical infection or that are immunocompromised.

- Penicillins: may be sensitive to amoxicillin/ampicillin especially potentiated ones at higher dosages
- Inherently resistant to cephalosporins, flouroquinolones, 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 ½ to ⅓ of daily therapeutic dose and is usually given at night
- Urine should be re-cultured every 4-6 weeks
- If a “break through” infection does not occur during a 6 month period, then antimicrobial treatment can usually be discontinued
- Disadvantages of this approach include development of resistant bacteria and side effects of the antimicrobial agent

**Methenamine is an effective preventative in select cases**

- It is a cyclic hydrocarbon that is hydrolyzed to formaldehyde at pH < 6.5
- It is 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.
o There is really no such thing as a “dog” or “cat” specific probiotic
o Usually want large numbers and multiple organisms
o 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.
Urine Agony: Urolithiasis
Joe Bartges, DVM, PhD, DACVIM, DACVN
Cornell University Veterinary Specialists
Stamford, CT

- 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
- Macrocrystalline 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 ($\text{Mg}_2\text{NH}_4\text{PO}_4^3$), 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

- 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, contra-indicated 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
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
  - **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

- **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**
- 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

**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

**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**
- A cystoscopic-assisted cystotomy is similar to laparoscopic removal
- A small incision is made on ventral midline
  - In male dogs, the incision is made just cranial to the preputial reflection
  - 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
- A stab incision is made and a rigid cystoscope is inserted into the urinary bladder
Stones are retrieved using instruments passed through the cystoscope.
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.
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\textsuperscript{oxl} decreased 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\textsuperscript{oxl} or S/O

Dogs
- Feed a diet that is mineral restricted, diuresing, and alkalinizing
  - 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 alkalinizing
    - 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.
1. 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. Tamsulosin 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. Continence 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 ovariecтомized 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>
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<td></td>
<td></td>
<td>C: 1.25-7.5 mg PO q8h</td>
<td></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></td>
<td></td>
<td>C: 5-7.5 mg PO q8h or 7.5 mg PO q72h</td>
<td></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></td>
<td></td>
<td>C: 0.5-1.25 mg PO q8-12h</td>
<td></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></td>
<td></td>
<td>C: 0.5-1.25 mg PO q6-8h</td>
<td></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></td>
<td></td>
<td>C: 2.5-5 mg PO q12h</td>
<td></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></td>
<td></td>
<td>C: 0.5-1 mg/kg PO q24h</td>
<td></td>
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<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 q24hr 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 q24hr 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>Testosterone propionate</td>
<td>Reproductive hormone</td>
<td>D (males): 2.2 mg/kg SQ or IM q2-3d</td>
<td>Aggression, prostatic disease, perineal hernia</td>
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<tr>
<td></td>
<td></td>
<td>C (males): 5-10 mg IM as needed</td>
<td></td>
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<tr>
<td>Testosterone cypionate</td>
<td></td>
<td>D (males): 2.2 mg/kg IM q30d or 200 mg IM q30 d</td>
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</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>Alpha agonist; urethral smooth muscle contraction</td>
<td>D: 12.5-50 mg PO q8h; 1-2 mg/kg PO q8h</td>
<td>Anxiety, cardiac arrhythmias, anorexia, hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: 1.0-1.5 mg/kg PO q8h</td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Alpha agonist; urethral smooth muscle contraction</td>
<td>D: 1.2 mg/kg PO q8h or 5-15 mg PO q8h</td>
<td>Anxiety, cardiac arrhythmias, hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: 2-4 mg/kg PO q6-12h or 2-4 mg PO q8h</td>
<td></td>
</tr>
<tr>
<td><strong>Agents used to decrease urethral resistance</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Alpha antagonist; urethral smooth muscle relaxation</td>
<td>D: 5-15 mg PO q12h</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: 2.5-10 mg PO q24h</td>
<td>tachycardia, vomiting, diarrhea, increased intraocular pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D, C: 0.25 mg/kg PO q12h</td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>Alpha antagonist; urethral smooth muscle relaxation</td>
<td>D: 1 mg/15kg PO q12-24hr</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: 0.25-0.5 mg PO q12-24hr</td>
<td></td>
</tr>
<tr>
<td>Tamsulocin</td>
<td>Alpha antagonist; urethral smooth muscle relaxation</td>
<td>D: 0.03-0.2 mg/10kg q24h</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Alpha antagonist; urethral smooth muscle relaxation</td>
<td>D: 0.1-1.0 mg/kg PO q24h</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Alpha antagonist; urethral smooth muscle relaxation</td>
<td>D, C: 0.5-5 mg PO q24-24hr</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Drug</td>
<td>Action</td>
<td>Dosage</td>
<td>Adverse Effects</td>
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</tr>
<tr>
<td>Terazosin</td>
<td>Alpha antagonist, urethral smooth muscle relaxation</td>
<td>D: 0.1-1.0 mg/kg PO q24h</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Fiduxosin</td>
<td>Alpha antagonist, urethral smooth muscle relaxation</td>
<td>D: 0.1-3.0 mg/kg PO q24h</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Striated muscle relaxation; central nervous system depressive effect</td>
<td>D: 0.2 mg/kg PO q8h or 2-10 mg PO q8h</td>
<td>Sedation, paradoxical excitation</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Striated muscle relaxation; direct action</td>
<td>D: 3-15 mg/kg PO q24h divided or 0.5-1 mg/kg PO q8h</td>
<td>Weakness, hepatotoxicity</td>
</tr>
<tr>
<td>Acepromazine</td>
<td>Urethral muscle relaxation by neuroleptic effect; alpha antagonism</td>
<td>D: 0.1-2 mg/kg PO q8-12h</td>
<td>Sedation, hypotension, seizures</td>
</tr>
<tr>
<td>Aminopromazine</td>
<td>Smooth muscle relaxation</td>
<td>D, C: 2.2 mg/kg PO q12h</td>
<td></td>
</tr>
</tbody>
</table>
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:
      - $GFR = K_f \times $ 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 (eg penicillin, cephalothin, sulfoxamide, thymol)
• False negative
  • Very alkaline urine
  • Very dilute urine

• Quantitative methods
  • Microalbuminuria
    • Recently, an “early diagnosis of renal disease” (ERD) test has become available
      o Measures micro-albuminuria – range of 1 to 30 mg/dl
      o Less than detectable by dipstick
      o May be useful in detecting early renal disease
        ▪ 19% of healthy dogs have micro-albuminuria
        ▪ 36% of dogs seeking veterinary care have micro-albuminuria
        ▪ 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 (eg “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
    o 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
  - At this level, clinical signs often include polyuria, weight loss, and lethargy
  - With severe or heavy proteinuria, serum albumin is < 1.5 g/dl, and clinical signs are more severe
- In addition to aforementioned signs
  - Muscle wasting
Edema/ascites
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 (eg congenital renal disease, glomerulosclerosis)
    - Many causes that have been described, primarily in dogs:

<table>
<thead>
<tr>
<th>Familial</th>
<th>Neoplastic</th>
<th>Infectious</th>
<th>Inflammatory</th>
<th>Miscellaneous</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>
<td>Lymphosarcoma, mastocytosis, hemangiosarcoma, adenocarcinoma</td>
<td>Bacterial endocarditis, infectious canine hepatitis, brucellosis, dirofilariosis, ehrlichiosis, systemic fungal or bacterial infection, feline infectious peritonitis, feline leukemia virus</td>
<td>Systemic lupus erythematosus, chronic pancreatitis, chronic pyoderma, chronic otitis externa, polyarthritis</td>
<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 tubulointerstial area
  ▪ Amyloidosis is uniformly progressive in nature and animals invariably develop chronic renal failure
  ▪ It may occur:
    • Primary familial disease
      o Primarily described in Shar pei dogs Abyssinian cats
      o In these animals, amyloid may be deposited primarily in the medulla and not glomerulus
      o Proteinuria, therefore, may not be present
      o Amyloidosis develops typically in animals under 5-6 years of age
      o 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)
      o 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.

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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
Getting the Most out of Liquid God: Urinalysis

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Urinalysis is an important laboratory test that can be readily performed in veterinary practice, and is considered part of a minimum database. Collected urine should be evaluated within 30 min. It may be refrigerated for up to 24 hours or submitted to an outside diagnostic laboratory; however, this may alter results.

Urine appearance

Color
Urine is typically transparent and yellow or amber. The intensity of color is in part related to the volume of urine collected and concentration of urine produced; therefore, it should be interpreted in context of urine specific gravity (USG). Significant disease may exist when urine is normal in color. Abnormal urine color may be caused by presence of endogenous or exogenous pigments, but it does not provide specific information. Interpretation of semi-quantitative, colorimetric reagent strips may yield false-positive results because of pigmenturia.

Clarity
Urine is typically clear.

Odor
Normal urine has a slight odor of ammonia; however, the odor is dependent on urine concentration. Some species, such as cats, have pungent urine odor because of urine composition. Bacterial infection may result in a strong odor due to pyuria; a strong ammonia odor may occur if the bacteria produce urease.

Urine chemistries

Semi-quantitative, colorimetric, chemical test pads are usually done prior to centrifugation; however, if urine is discolored or turbid, it may be beneficial to perform these tests on supernatant.

Specific gravity
The USG is determined using a refractometer designed for veterinary samples, which includes a scale calibrated specifically for cat urine. In healthy animals, USG is highly variable, depending on fluid and electrolyte balance. Interpretation of USG depends on clinical presentation and serum chemistry findings. An animal that has prerenal azotemia will have hypersthenuric urine with USG >1.025-1.080. Dilute urine in an azotemic animal is abnormal.

Semi-quantitative, colorimetric reagent strips
Reagent strips can be used to perform semi-quantitative chemical evaluations. They determine urine pH, protein, glucose, ketones, bilirubin/urobilinogen, and occult blood. Some reagent strips include test pads for leukocyte esterase (for detection of WBC), nitrite (for detection of bacteria), and USG; these are not valid in animals and should not be used. Reagent strips are adversely affected by moisture and have a limited shelf life.

Urine pH
Urine pH is typically acidic in dogs and cats, but varies depending on diet, medications, or presence of disease. Reagent strip colorimetric test pads for pH determination are accurate to within ± 0.5 pH units. Urine pH will affect crystalluria.

Protein
The protein test pad uses a color indicator (tetrabromophenol blue), which detects primarily albumin in urine. Results range from 30 mg/dL to 3,000 mg/dL. A positive reaction must be interpreted in light of USG, pH, and urine sediment examination. Proteinuria can be measured using sulfosalicylic acid precipitation, which detects albumin and globulins; however, it is not accurate. If proteinuria is present with inactive urine sediment, its significance can be verified and quantitated by dividing the urine protein concentration by the urine creatinine concentration (urine protein to urine creatinine ratio; UPC). A semi-quantitative microalbuminuria test is available to detect urinary albumin in the range of 1 to 30 mg/dL. It uses ELISA technology specific for canine or feline albumin.

Glucose
Glucose is detected by a glucose oxidase enzymatic reaction that is specific for glucose. Glucosuria is not present normally because the renal threshold for glucose is >180 mg/dL in most species and >240 mg/dL in cats. With euglycemia, the amount of filtered glucose is less than the renal threshold and all of the filtered glucose is reabsorbed in the proximal renal tubules. If glucosuria is present, blood glucose concentration should be determined.

Ketones
Ketones are produced from fatty acid metabolism, and include acetoacetic acid, acetone, and β-hydroxybutyrate. The ketone test pad detects acetone and acetoacetic acid, but not β-hydroxybutyrate.
**Bilirubin/urobilinogen**

When hemoglobin is degraded, the heme portion is converted to bilirubin, which is conjugated in the liver and excreted in bile. Some conjugated bilirubin is filtered by the glomerulus and excreted in urine. Male dogs have a higher secretory ability compared with female dogs; bilirubinuria in cats is always abnormal. In dogs with concentrated urine, a small amount of bilirubin can be normal. Urobilinogen, formed from bilirubin by intestinal microflora, is absorbed into the portal circulation and is excreted renally. The test is not clinically useful.

**Occult blood**

The occult blood test pad uses a “pseudoperoxidase” method to detect intact RBC, hemoglobin, and myoglobin. A positive result should be interpreted with microscopic examination of urine sediment.

**Urine sediment**

Microscopic examination of urine sediment should be part of a routine urinalysis. For centrifugation, 3-5 mL of urine is transferred to a conical centrifuge tube. Urine is centrifuged at 1,000-1,500 rpm for 5 minutes. The supernatant is decanted, leaving 0.5 mL of urine and sediment in the tip of the conical tube. The sediment is resuspended by tapping the tip of the conical tube against the table several times. A few drops of the sediment are transferred to a glass slide, and a cover slip is applied. Examination of unstained urine is recommended for routine samples. Microscopic examination is performed at 100X (for crystals, casts, and cells) and 400X (for cells and bacteria) magnifications. Contrast of the sample is enhanced by closing the iris diaphragm and lowering the condenser of the microscope. Stains can be used to aid in cell identification but may dilute the specimen and introduce artifacts such as stain precipitate and crystals. Use of a modified Wright’s stain increases the sensitivity, specificity, and positive and negative predictive values for detection of bacteria.

**Red blood cells**

RBC’s are small, round, have orange tint, and smooth appearance. Normal urine should contain <5 RBC/field at 400X magnification.

**White blood cells**

WBC’s are slightly larger than RBC and have granary cytoplasm. Normal urine should contain <5 WBC/field at 400X magnification.

**Epithelial cells**

Transitional epithelial cells resemble WBC but are larger. They have a greater amount of granary cytoplasm and a round, centrally located nucleus. Occasionally, neoplastic transitional cells may be observed in an animals.

**Cylindruria (casts)**

Casts are elongated, cylindrical structures formed by mucoprotein congealing within renal tubules. Hyaline casts are mucoprotein precipitates, transparent, and have parallel sides and rounded ends. Epithelial cellular casts form from entrapment of sloughed tubular epithelial cells in the mucoprotein. Granular casts are thought to represent degenerated epithelial cellular casts. Waxy casts have a granular appearance. They typically have sharp borders with broken ends. Other cellular casts include erythrocyte casts and WBC casts, and are always abnormal. Fatty casts are not common, but can be observed with disorders of lipid metabolism. A few hyaline or granular casts are considered normal; however, presence of cellular casts or other casts in high numbers indicates renal damage.

**Infectious organisms**

Presence of bacteria in urine collected by cystocentesis indicates infection. Small numbers of bacteria from the lower urogenital tract may contaminate voided samples or samples collected by catheterization and do not indicate infection. Bacterial rods are most easily identified. Particles of debris may be mistaken for bacteria. Suspected bacteria can be confirmed by staining urine sediment with modified Wright’s stain; however, aerobic culture is best for confirmation. Rarely, yeast and fungal hyphae and parasitic ova may be observed in urine sediment. Their presence is not always associated with clinical disease.

**Crystals**

Many urine sediments contain crystals. The type of crystal present depends on urine pH, concentration of crystallogenic materials, urine temperature, and length of time between urine collection and examination. Crystalluria is not synonymous with urolithiasis and is not necessarily pathologic; uroliths may form without observed crystalluria. Struvite crystals appear typically as “coffin-lids” or “prisms”; however, they may be amorphous. Struvite crystalluria in dogs is not a problem unless there is a concurrent bacterial urinary tract infection with a urease-producing microbe. Cats do form struvite uroliths without a bacterial urinary tract infection. Calcium oxalate dihydrate crystals appear as squares with an “X” in the middle or “envelope-shaped.” Calcium oxalate monohydrate crystals are “dumb-bell” shaped. Calcium oxalate crystalluria occurs less commonly in dogs and cats; if persistent, it may indicate an increased risk for calcium oxalate urolith formation. Ammonium acid urate crystals suggest liver disease (e.g., portosystemic shunt). These crystals occur in acidic urine and are yellow-brown spheres with irregular, spiny projections; however, they may also be amorphous. Certain breeds of dogs, e.g., Dalmatians, can normally have ammonium acid urate crystalluria. Cystine crystals are 6-sided and of variable size. They occur in acidic urine. Presence of cystine crystals represents a proximal tubular defect in amino acid reabsorption. Bilirubin crystals occur with bilirubinuria; however, they may be normal in dogs.– Lipid, spermatozoa, and plant material may occasionally be seen.
Bladder tumor antigen test (VBTA)
The VBTA can be used as a screening test for transitional cell carcinoma in dogs. The results are not specific and non-neoplastic disease (e.g. urinary tract infections, hematuria, etc) can give positive results. A negative test; however, is meaningful in that a transitional cell carcinoma is not likely to be present. This test may be useful for routine screening of dogs at higher risk of developing transitional cell carcinoma (e.g. Scottish terriers) that do not have other signs or laboratory findings of lower urinary tract disease.

Point-of-care testing for urinary tract infections
There are several point-of-care tests for evaluating a patient for a urinary tract infection. They suffer from either a low level of sensitivity or specificity or both. As mentioned before, staining the urine sediment with a modified Wright’s stain is effective in determining whether a urinary tract infection is present or not, but urine culture is still the most reliable if performed correctly.

References
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.

**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

**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 \( \times \) BWkg = L for rehydration
  - Maintenance:
    - Typically 1 ml/lb/hour (2.2 ml/kg/hour)
  - On-going losses:
    - Measure or estimate
    - Some recommend \( \frac{1}{2} \) 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 \( > 8 \text{ mEq/L} \).
  - Death occurs with potassium concentration exceeds 12-13 mEq/L.

- 3 ways to decrease plasma/blood potassium concentration:
  - Dilute and excrete – fluid therapy or dialysis
  - Transcellular shift:
    - Glucose
    - Insulin
    - Insulin and glucose
    - Bicarbonate
  - 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.

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
  - 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; phenoxymenzamine: 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 and if added back in – no difference between diet groups
  - In another study, there was a dramatic decrease in recurrence of clinical signs when cats with idiopathic cystitis were fed a diet that contained higher levels of omega 3 fatty acids and anti-oxidants

- **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](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
Obesity is the most important malnutrition of companion animals. It can be a disabling medical condition when moderate to severe in scope. At prevalence rate estimates of 10-40%, obesity must be considered a significant hazard to dogs and cats. Increased emphasis on pet health and preventative health programs makes obesity prevention an important aspect of health maintenance programs in dogs and cats. Treatment for obesity varies from frustrating to rewarding and evaluating and prescribing for successful, long term weight loss and maintenance usually requires management of multiple, inter-related patient and client factors. Diagnosis of disease secondary to obesity and the major task of client education and motivation is the provenance of the veterinarian.

The American Animal Hospital Association released the Guidelines for Nutritional Assessment (July/August JAAHA 2010). Utilizing the two-step iterative process, a screening assessment is made and if concerns are found, then a more detailed assessment is made. Following assessment, data are analyzed, a plan formulated and initiated, and repeated evaluation and modification of the plan is made. The importance of nutrition is emphasized by it being considered one of the “5VA’s” (5 vital assessments): temperature, cardiac function, respiratory health, pain, and nutrition (http://www.everypeteverytime.com/index.html).

The American College of Veterinary Nutrition recommends a two-step process in making nutritional recommendations. The process is iterative in that it should be re-evaluated periodically and changes made as deemed necessary.

The first step is ASSESSMENT. During this step, assess the ANIMAL, the DIET, and the FEEDING factors.

**ANIMAL FACTORS** assessed include gathering historical information, performing physical examination, body condition scoring, and evaluating laboratory and imaging results if indicated. Gather information on any health or disease-related conditions, medications (including over-the-counter and nutraceuticals/supplements), reason for visit, and other household members. A thorough physical examination is performed and a body condition score assigned. There are 5- and 9- point body condition scoring systems; either can be used. In either scale, the middle number of the scale (3 out of 5 or 5 out of 9) represents ideal body condition and a body fat content of 15-25%; numbers lower than this correspond to lower body condition and less body fat (0-15%) while numbers higher than this correspond to higher body condition and greater body fat (≥ 35%). Assigning a body condition score provides more information than body weight alone and can be used with a muscle condition scoring system where 3 = adequate muscle mass, 2 = decreased muscle mass, and 1 = severe muscle wasting (sarcopenia).

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Description</th>
<th>5 point</th>
<th>9 point</th>
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</thead>
<tbody>
<tr>
<td>CACHETIC</td>
<td>Ribs are easily palpated with no fat cover; bony structures are prominent and easy to identify; muscle tone and mass often decreased; little to no subcutaneous fat; hair coat often poor; pronounced abdominal tuck</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>UNDERWEIGHT</td>
<td>Ribs are easily palpated with little fat cover; abdominal tuck present; bony structures are palpable but not prominent; hair coat may be poor; muscle tone and mass may be good or slightly decreased</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>IDEAL</td>
<td>Ribs are easily palpated, but fat cover is present; hourglass shape present and abdominal tuck is present, but not pronounced; bony prominences are palpable but not visible some subcutaneous fat, but no large accumulations; muscle tone and mass good; hair coat quality is good</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>OVERWEIGHT</td>
<td>Ribs are difficult to palpate due to overlying fat accumulation; hourglass shape is not prominent and abdominal tuck is absent; subcutaneous fat obvious with some areas of accumulation; muscle tone and mass good; hair coat quality may be decreased; cannot identify bony prominences</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>
**DIETARY FACTORS** include gathering information on dietary intake and inspection of the food, if needed. Take the dietary history from the person that actually feeds the pet(s) asking for type of food, amount fed, frequency of feeding, table food or treats, access to other food (garbage, outside, etc), supplements, and medications (including over-the-counter). If necessary, inspect a sample of the food or send a sample for analysis (i.e. Cornell Animal Health Diagnostic Center, Woodson Tenent Laboratories, EMSL Food and Consumer Products Testing Lab, etc). Pet foods can be purchased in a variety of forms – dry, canned, semi-moist, semi-dry, liquid, and frozen.

Reading the food label is also beneficial. The food label can be roughly divided into a principal display panel and an information panel. The PRINCIPAL DISPLAY PANEL contains information directed towards the consumer including the product name, species for which the food is intended, net weight of product, and descriptive words and/or pictures (e.g. “new and improved”, picture of a famous cat, etc). The INFORMATION PANEL contains the important information including ingredient list, guaranteed analysis, feeding guidelines, contact information, and the nutritional adequacy statement. Although often maligned and not as complete as labels for human foods, there is useful information to be found. Ingredients are listed in descending order according to pre-processing weight and names are set by AAFCO (e.g. by-product, etc); this means that ingredients containing moisture that weigh more will be listed first. Unfortunately, this does not give information as to the quality or exact amount of each ingredient; also, different forms of the same type of ingredient are listed separately. Chemical sounding ingredients are typically vitamins, minerals, and preservatives. Feeding guidelines are provided that are suitable for most, but not all, dogs or cats that consume the diet. The manufacturer’s or distributor’s name and address is required and questions regarding the food should be directed to them; they should be able and willing to provide answers.

When contacting them, several questions should be asked:

1. Do you have a Veterinary Nutritionist or some equivalent on staff in your company? Are they available for consultation or questions?
2. Who formulates your diets and what are their credentials?
3. Which of your diet(s) is AAFCO Feed Trial tested? Which of your diets have been AAFCO Nutritional analyzed?
4. What specific quality control measures do you use to assure the consistency and quality of your product line?
5. Where are your diets produced and manufactured? Can this plant be visited?
6. Can you provide a complete product nutrient analysis of your bestselling canine and feline pet food including digestibility values?
7. Can you give me the caloric value per can or cup of your diets?

The **guaranteed analysis** provides information regarding the 4 major components of a pet food as percentages of the diet as fed including minimum amount of crude protein, minimum amount of crude fat, maximum amount of crude fiber, and maximum amount of moisture. “Crude” refers to the analytical procedure and does not refer to the quality of the ingredient.

The **nutritional adequacy** statement must be included and is designed to ensure that the product, when fed as the sole source of nutrition, is complete and balanced for one or more life stages, including how this adequacy was verified. The four recognized life stages by AAFCO are pregnancy, lactation, growth, and adult maintenance, and nutritional adequacy can be determined by feeding trials or by calculation. The calculation method involves determining the amount of nutrients in the diet and comparing to AAFCO nutrient profiles for that/those life stage(s). Feeding trials are performed by feeding the diet to the animals in that/those life stage(s) following AAFCO protocol. Feeding trials, while not perfect, provide indirectly information on bioavailability of nutrients and is preferred method for validation of nutritional adequacy. Therapeutic diets, supplements, and treats often do not carry a nutritional adequacy statement. Therapeutic diets are formulated for specific non-healthy conditions, which are not recognized by AAFCO and for which no nutrient profiles exist (e.g. renal failure, liver failure, etc); they usually carry a statement such as “intended for intermittent use” or “use only under the supervision or direction of a veterinarian”. Snacks and treats are not formulated or intended to be the sole source of nutrition; therefore, they are not required to carry a nutritional adequacy statement.

The label often contains other information, much of which do not have official definitions. According to AAFCO, “natural” is “…only acceptable in reference to the product as a whole when all of the ingredients and components of ingredients meet the definition.…the use of ‘natural’ is false and misleading if any chemically synthesized ingredients are present in the product; however, AAFCO recommends that exceptions be made in the cases when chemically synthesized vitamins, minerals, or other trace nutrients are present as ingredients in the product, provided that the product is not a dietary supplement and that a disclaimer is used to inform the consumer that the vitamins, minerals, or other trace minerals are not natural. For example, ‘Natural with added vitamins, minerals, and other trace minerals.’” AAFCO defines “natural” as “a feed or ingredient derived solely from plant, animal, or mixed sources,
either in its unprocessed state or having been subject to physical processing, heat processing, rendering, purification, extraction, hydrolysis, enzymolysis, or fermentation, but not having been produced by or subject to a chemically synthetic process and not containing any additives or processing aids that are chemically synthetic except in amounts as might occur unavoidably in good manufacturing processes.” “Organic” does not have a specific AAFCO definition other than in reference to processing, “organic (process): a formula or a specific ingredient within a formula feed that has been produced and handled in compliance with the requirements of the USDA national Organic Program (7 CFR Part 205).” The USDA National Organic Program (NOP) “develops, implements, and administers national production, handling, and labeling standards for organic agricultural products. The NOP also accredits the certifying agents (foreign and domestic) who inspect organic production and handling operations to certify that they meet USDA standards.” There is no definition of “human grade” food and many ingredients used in pet foods are suitable for human consumption. “The U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine has taken the position that if every ingredient in a product is edible, meaning that it was processed according to rules of sanitation required of food sold to people, then the product may be labeled “human grade”. However, an edible ingredient becomes inedible when you add it to other inedible ingredients.” - Dr. William Burkholder, veterinary medical officer for the FDA CVM (January 2009). Other designators such as “premium” and “gourmet” also have no official definitions. Such designators are arbitrary and subject to interpretation.

**FEEDING FACTORS** to be assessed include how the nutrition is provided and must take into account owner and animal factors. Simply filling a bowl within reach of the animal is not enough; the appropriate diet must be provided in the appropriate amount. Obesity is the most common nutritional disorder of dogs and cats and, in part, is due to overfeeding. “One cup” of food refers to the amount of food contained in one 8-ounce measuring cup. Ask specifically for the size of the cup used and the size of the bowl that is filled up. Many owners feed free choice – “drive-by feeders” - without regard to amount. The amount of energy required by the pet can be determined using one of two formulae:

- **Linear:** \[ (30 \times BW_{kg}) + 70 \]
- **Exponential:** \[ 70 \times (BW_{kg}^{0.75}) \]

This provides the RESTING ENERGY REQUIREMENT and this result is multiplied by a life stage or activity factor depending on the individual.

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Canine Factor</th>
<th>Feline Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation</td>
<td>1.0 – 3.0</td>
<td>1.6 – 2.0</td>
</tr>
<tr>
<td>Dogs – first 1/2 - 2/3</td>
<td>1.0 – 2.0</td>
<td></td>
</tr>
<tr>
<td>Dogs – last 1/3</td>
<td>2.0 - 3.0</td>
<td></td>
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<tr>
<td>Lactation</td>
<td>2.0 – 8.0</td>
<td>1.0 – 2.0</td>
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<tr>
<td>Growth</td>
<td>2.0 – 3.0</td>
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<tr>
<td>Work – light</td>
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<tr>
<td>Work – heavy</td>
<td>4.0 – 8.0</td>
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<td>Obese prone</td>
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<td>Weight loss</td>
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<td>Critical care (usually)</td>
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The second step is FORMULATION AND INITIATION OF A FEEDING PLAN. The nutritional plan is formulated based on the assessment phase and initiated. It is important that this plan is re-evaluated periodically (iterative process) and adjustments made based on what is found during assessment. Recommendations for the feeding plan are made based on life stage and physiological or pathological condition of the pet as well as the life style of the owner. Working within the constraints placed by the owner helps to ensure compliance; otherwise, recommendations will not be followed. There is no “one best” diet available for healthy pets or for pets that suffer from a disease. Oftentimes, many options exist including homemade diets.

Today’s health care providers, veterinarians and technicians, need to be able to assess a pet, evaluate diets, and make recommendations on diets and feeding. Knowledge of assessment and formulation of a nutritional plan should be part of a patient’s health care. Use body condition scoring in addition to weight to assess nutritional status.

**Types of diets**

There are basically 3 types of diets available for pets: (1) commercial, over-the-counter diets, (2) therapeutic diets, and (3) homemade including raw food diets. These arbitrary designations are becoming somewhat blurred as there are commercial raw food diets and commercially available feed mixes that provide all nutrients except for the protein source, which the pet owner adds a protein source whether cooked or raw. Over-the-counter (OTC) diets are regulated through several different agencies. The Association of American Feed Control Officials (AAFCO) is not a regulatory agency but sets nutritional standards for life stages (of which there are basically two: adults and reproduction (pregnancy, lactation, and growth) and defines ingredients. The FDA specifies and regulates health
claims in addition to ensuring safety. The USDA regulates ingredients and inspects facilities. The State Department of Agriculture enforces animal food regulations. AAFCO sets nutritional standards so that if the food is fed as a sole source of nutrition it meets or exceeds known nutritional requirements.

OTC foods are convenient and can be cost effective and they are easy to feed especially dry foods. There are potential disadvantages, though, including the minimal regulatory requirements, lack of additional AAFCO lifestages (e.g. is a 15 year old Chihuahua the same as a 3 year old Great Dane?), pet food labels provide a minimal amount of information and give no indication of food quality, and there is a wide range of diets available that vary in composition and ingredients.

Therapeutic diets have more defined formulations and are primarily produced by larger companies who maintain better control over formulation, production, and distribution. Therapeutic diets are formulated primarily for non-healthy states (e.g. chronic kidney failure and obesity); however, some can be fed to healthy pets. Larger companies actively pursue and support research. These companies maintain control of the process and so have better quality control and formulations are more defined. Therapeutic diets are available for food elimination, but OTC diets may claim to contain “novel” ingredients. There is one study of 4 OTC venison dry dog food diets that showed that none of the diets would be suitable for an elimination food trial because they contained common pet food proteins some of which were identified on the label while others were not but were detected in the diet. If these diets represent a majority of OTC products then OTC diets should not be used for a diagnostic elimination trial. In another study of “soy free” diets, 4 of 4 OTC diets contained soy while 1 of 7 therapeutic diets contained soy. There are some disadvantages of therapeutic diets including public perception of large pet food companies, some of the therapeutic diets have been recalled (especially the melamine/cyanuric acid recall in 2007 due to specialized formulated diets containing wheat gluten), often pets are transitioned onto therapeutic diets when they are sick and so do not eat, and many therapeutic diets are formulated for specific disease states and so may not be suitable for all pets in the household (e.g a weight reduction diet for an obese pet would not be advisable for a lean healthy pet and an alkalinizing renal diet would not be suitable for a pet during growth). Some joint diets, dermatology diets, and GI diets are suitable for healthy pets including large breed growth (e.g. some joint diets).

Some owners prefer to prepare homemade foods – feel less guilty and have impression of preparing a “real meal” that is “more natural” and “more traditional”. Nearly all dogs and cats in the US consume table foods at some time in their lives. Majority of dogs and cats in US receive >90% of calories from commercial foods. When a client wants to prepare pet foods at home, it is important for veterinarians to understand the client’s reasons and motivation. In many cases it is possible to address their concerns and to recommend an appropriate commercial food. If they still wish to cook, then proper guidance can be provided.

Some owners wish to cook homemade diets in order to provide a natural or organic food. Remember, there is no legal definition for the terms “natural” and “organic”. Pet owners may also want to prepare vegetarian food for their dog or cat because they are vegetarian or vegan. Because cats are true carnivores, vegetarian cooking should be discouraged. Other owners wish to prepare homemade diets including cooked and raw diets in order to avoid additives, preservatives, and contaminants. Pet food labels may be difficult to read and understand and they do not contain as much information as human food labels; therefore, some choose to home cook because they are more comfortable with being in control. Some pets will only eat table foods because it has become a habit. Lastly, homemade diets may be used for dietary elimination trials and for medical situations where a commercial diet is not available (e.g. a dog with chronic kidney disease and pancreatitis). Homemade diets are often very palatable and so may be useful with sick patients.

It is possible to achieve the same nutrient balance with a homemade food as with a commercially prepared food. However, this largely depends on the accuracy and competence of the person formulating the food, and on the compliance and discipline of the owner. Unfortunately, some homemade recipes are flawed even when followed exactly and consistently. IN one survey, 90% of homemade elimination diets prescribed by 116 veterinarians in North America were not nutritionally adequate for adult dog or cat maintenance. Few of the recipes available in books, magazines, and on-line have been tested to document the nutritional adequacy of the diet. Preparing homemade diets take time and some owners cannot afford the time.

There are common nutrient problems in many homemade foods. Many formulations contain excessive protein, but are deficient in calories, calcium, vitamins, and micro-minerals. Commonly used meat and carbohydrate sources contain more phosphorous than calcium resulting in inverse calcium: phosphorous ratio. Foods designed by clients are commonly deficient in fat and energy density or contain an unpalatable fat source (vegetable oil). Homemade foods are rarely balanced for micro-minerals and vitamins because veterinary vitamin-mineral supplements are not complete nor are the nutrients well balanced within the product.

People are taught that eating a variety of foods is nutritionally sound. Clients often extend this principle to their pet’s nutrition. Pet owners perceive that feeding a variety of foods is their best defense against malnutrition. Likewise, many owners feed a homemade diet because they can use a variety of ingredients. Some owners choose meat and carbohydrate sources for their pet’s food based on their own preferences, product availability, or affordability. Other pets are fed “leftovers” such as fat trimmings, bones, vegetable skins, crusts, and condiments. Some owners feed their pets according to guidelines for humans not realizing that dogs and cats have different requirements. A common problem with homemade diets is that the vitamin-mineral supplement is left out because

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of inconvenience, expense, or failure to understand its importance – after all, many humans do not take vitamins. Lastly, some
homemade diets use raw ingredients – we will talk more about these in a little bit
Veterinarians encounter a wide variety of pet food recipes from breeders and the popular press. Some owners want an opinion as
to whether the recipe is good and others want to alter the recipe. Homemade formulations can be checked for nutritional adequacy
and adjusted using the “quick check” guidelines:
1. Do five food groups appear in the recipe?
   a. Carbohydrate/fiber source from a cooked cereal grain
   b. A protein source, preferably of animal origin, or if more than one protein source is used, one source should be of animal origin
   c. Fat source
   d. Source of minerals, particularly calcium
   e. Multivitamin and trace mineral source
2. Is the carbohydrate source a cooked cereal and present in a higher or equal quantity than the meat source?
   a. Carbohydrate to protein ratio should be at least 1:1 to 2:1 for cat foods and 2:1 to 3:1 for dog foods
   b. Sources are cereal such as cooked corn, rice, wheat, potato, or barley
   c. These sources have similar caloric contributions, but some carbohydrates contribute a substantial amount of protein, fiber, and fat
3. What is the type and quantity of the primary protein source?
   a. Overall protein quality of the diet can be improved by substituting an animal-derived protein source for a vegetable protein
   b. Skeletal muscle protein from different species have similar amino acid profiles
   c. Final food should contain 25-30% cooked meat for dogs (1 part meat to 2-3 parts carbohydrate) and 35-50% cooked meat for cats (1 part meat to 1-2 parts carbohydrate)
   d. Providing some liver in the meat portion is recommended once a week or no more than ½ of the meat portion on a regular basis – corrects most potential amino acid deficiencies and contributes fatty acids, cholesterol, energy, vitamins, and microminerals
   e. If owner requests an ovo-lacto-vegetarian food, eggs are best
   f. If vegan food is requested, soybeans are the next best, but incomplete, amino acid profile
4. Is the primary protein source lean or fatty?
   a. Lean protein sources require addition of an animal, vegetable, or fish fat source at 2% of the formula weight for dogs and 5% of the formula weight for cats
   b. If a homemade food lacks sufficient caloric density, addition of cooked beef or chicken fat, poultry skins, vegetable or fish oils can markedly increase caloric density without adding other nutrients
5. Is a source of calcium and other minerals provided?
   a. An absolute calcium deficiency is common
   b. Many owners erroneously assume cottage cheese, cheese or milk added in small quantities provides adequate calcium
   c. Most foods require a specific calcium supplement
      i. When the protein fraction equals or is greater than the carbohydrate fraction, usually only calcium carbonate is added (0.5 g/4.5 kg cat/d and at least 2.0 g/15 kg/dog/d).
      ii. Calcium and phosphorous supplementation may be necessary when the protein fraction is less than the carbohydrate fraction. Steamed bone meal, dicalcium phosphate, and certain proprietary mineral supplements contain @ 27% calcium and 16% phosphorous (about 2:1) and micro-minerals
6. Is a source of vitamins and other nutrients provided?
   a. A human adult over-the-counter vitamin-mineral tablet that contains no more than 20% of the recommended daily allowances for people works well for both dogs and cats at ½ to 1 tablet per day (@ 1 gm/tablet).
   b. One tablet per day of a human adult product will not over-supplement pets with calcium, phosphorous, magnesium, vitamins A, D, and E, iron, copper, zinc, iodine, and selenium according to AAFCO maximum allowances for canine and feline foods.
   c. In general, veterinary supplements provide between 0-300% of vitamin-mineral requirements of dogs and cats

Substitution of ingredients can be done, but should be researched as to the equivalent amounts. One protein source is not the same as another. Other instructions that should be given owners include those for preparation, storage, and feeding. Emphasis should be
made to not eliminate an ingredient or indiscriminately substitute ingredients. Owners that wish to use raw eggs and meats should be informed that there is a risk for infectious diseases. Animal ingredients should be cooked for at least 10 minutes at 180F. Vegetables should be washed or rinsed and cooked if increased digestibility is desired. Since antioxidants are not usually added to homemade diets, storage in airtight containers at refrigeration temperature can be done for 7 day stretches. Large quantities can be frozen. Owners should check appearance and odor daily to make sure rancidity or contamination has not occurred. Starches should be cooked to increase digestibility; however, they should be cooked separately from the protein source. Carbohydrate sources require a longer cooking time; meat and liver should not be overcooked or protein denaturation will occur.

Pets should be evaluated routinely whether they are being fed commercial food or homemade food. Stools should be formed although they may contain more water. Body condition and weight should be maintained. If problems are encountered, then either the homemade diet should be re-evaluated and modified or use of a commercially available diet should be encouraged.

**Definition**

Obesity is a condition of positive energy balance and excess adipose tissue accumulation with adverse effects on quality and quantity of life. Obesity literally means increased body fatness, but measurement of fat fractions of body composition is difficult in practice. Therefore, obesity can be defined as body weight in excess of 15 to 20% of ideal, due to the accumulation of body fat. Negative health manifestations often begin at this level of weight excess and are a virtual certainty at a 30% excess over ideal weight.

**Pathogenesis of body fat composition**

Pathogenesis of obesity is not as simple and direct as uncontrolled gluttony. The idea of human obesity as a syndrome caused by being “weak in will” has yielded to observations and reasoning that obesity is a complex disorder of metabolism and satiety control with significant genetic components. Multiple genetic and environmental factors control regulation of food intake, resting metabolic rate, thermic effect of food, and energy expenditure and efficiency during work. Three causes of initial obesity in pets are overeating, decreased exercise, and lower metabolic rate; however, genetic influence cannot be overlooked.

**Risk factors for obesity**

Gender is important in the development of adult obesity; females or neutered animals are more frequently affected with obesity than males or intact animals. In addition to gender, certain breeds are predisposed to developing obesity while other breeds appear to be resistant. Pet owner lifestyle is important, as overweight human beings are more likely to own an overweight pet. Apparently overweight owners provide opportunities that override normal internal and external satiety control signals for both themselves and their pets. Ad libitum feeding, improper meal feeding, inappropriate diet selection, supplementation, provision of home cooking, and the conditioning of abnormal feeding behavior all cause excess calorie consumption. Begging, competitive eating with other pets and specific food addictions are problems in some homes and are identifiable risk factors. In addition to these factors, there are metabolic diseases such as hypothyroidism and hyperadrenocorticism that are associated with obesity.

**Body fat deposition**

Body composition of 1-2% fat at birth increases rapidly to 10-15% by weaning at 4-6 weeks, and is 15-20% in normal dogs during the first year of maturity. Females have increased levels when compared with males. Twenty-five to 30% fat is normal in dogs 8-10 years of age as there is lower lean body mass and increased adiposity with ageing. The initial phase of obesity occurs during chronic, positive energy balance. A phase of static obesity follows when caloric expenditure equilibrates with intake and the animal maintains a stable, but altered body composition of increased adipose tissue. These phases may repeat many times during an animal’s life leading to a gradual step-wise increase in body weight and body composition. Because fat-free mass appears to be an important determinant of resting energy, as more fat mass is acquired and as lean mass is lost, less energy intake is required to maintain the increased body weight (increasing fat mass). This explains why many obese animals do not appear to be eating “too much” or why owners often say “but my dog only eats a half of a cup of food a day”.

**Detrimental effects of obesity**

Obesity is associated with many diseases and has been shown to decrease life span in dogs and cats. In many respects, obesity-associated conditions could be considered metabolic syndrome. In human medicine, metabolic syndrome is often defined as “a cluster of conditions — increased blood pressure, a high blood sugar level, excess body fat around the waist and abnormal cholesterol levels — that occur together, increasing risk of heart disease, stroke and diabetes.” While these are not necessarily the manifestations observed in human beings, the etiopathogenesis of metabolic syndrome is similar.

Obese pets generally appear less healthy and have a less pleasing appearance. Furthermore, obese animals have less tolerance to heat and environmental changes. With added weight in obesity, physical activity is often decreased. This may not only make for an acceptable pet, but inactivity may also potentiate the weight gain because of decreasing the resting energy requirement. Obesity is associated with increased risk for musculoskeletal disease such as degenerative osteoarthritis, intervertebral disc disease, and anterior...
cruciate rupture, and in growing large breed dogs, excessive energy intake and obesity may lead to developmental musculoskeletal disease such as hip dysplasia, osteochondrosis desiccans, and joint laxity and deformity. In dogs, obesity has been shown to be associated with increased blood pressure. Excess thoracic fat and increased liver size may impair ventilation, decrease respiratory efficiency, and result in alveolar hypoventilation. Treatment of collapsing trachea is improved with weight reduction. With increasing adiposity, lipid infiltrates the liver and in cats may result in liver failure due to hepatic lipidosis if a stressful event resulting in anorexia occurs. In breeding animals, obesity causes decreased sperm viability due to decreased testosterone production, and in females, it predisposes them to dystocia. Bacterial infections were also more severe in obese dogs than in dogs of normal weight. Obesity has been associated with increased skin and gastrointestinal disease in dogs and cats. It may represent overall decrease in body condition, decrease in general health, decrease in immunocompetence, and intake of an unbalanced diet. When surgery is necessary in obese animals, a compromised surgical approach, general difficulty in dissection, and increased incidence of intraoperative and postoperative complications can be expected. Obesity predisposes to local infection and some surgeons consider using antibiotic prophylaxis even in clean surgical procedures performed on obese animals. Obese animals are more difficult to achieve an adequate anesthetic state because of decreased hepatic metabolism, compromised respiratory and cardiovascular function, and because of redistribution of drugs into adipose tissue. Obesity not only interferes with surgical procedures, but diagnostic procedures as well such as thoracic auscultation and abdominal palpation. Obesity is associated with an increased risk of certain types of cancer. Obesity is associated with insulin receptor defect(s) and decreasing sensitivity to insulin fat, muscle, and liver. Insulin resistance and hyperglycemia occur concurrently as fatty acids displace glucose as the preferential fuel source. While the obese, type II diabetic animal is not dependent on exogenous insulin for maintaining the non-ketotic state, there is both a fasting hyperglycemia and abnormal glucose tolerance test response. Non-insulin dependent diabetes mellitus caused by obesity may be reversible by weight loss in some cats. Obesity decreases longevity in pets.

**Diagnosis of obesity**

The diagnosis of obesity is often obvious on clinical inspection and palpation of the patient. The differential diagnosis for obesity includes pregnancy, peripheral edema, intra-abdominal organomegaly, abdominal masses, ascites, hypothroidism, and hyperadrenocorticism. Quantification of obesity requires the use of objective methods, but the convenient measurement of body composition is not practical in practice settings. Therefore, indirect methods are substituted and their limitations accepted.

**Body weight**

Body weight can be an indirect measurement of obesity in pets and it is a procedure that is familiar, easily determined, and universally available. The dog’s weight at its first birthday or during the first year of maturity probably reflects the “ideal” adult weight if skeletal development and juvenile nutrition are normal. Another useful generalization from weight measurement is that the mature domestic cat weighs 3.5-5.0 kg (8-11 lb) at a normal body composition. The major disadvantage of using body weight as a standard for body composition is that “overweight” may not mean “overfat”. This is true in athletic or working animals. Breed weight tables serve as guidelines for diagnosis in individual patients. Normal intra-breed body weight and height variability, determining ancestry in mixed breed animals, and the lack of statistically validated age- and gender-specific adjustment factors to the purebred dog averages are the major limitations in using weight tables too literally.

**Body condition score**

Subjective clinical observations for obesity assessment are the loss of an “hourglass” shape when viewed from above, protuberant or draped accumulations of fat around the tailhead and neck, and the inguinal “udder” in cats. Different fat accumulation patterns are specific for men versus women and are predictive for cardiovascular disease risks in human beings. Such patterns are of attenuated diagnostic importance in the companion animal. Inability to easily distinguish the individual ribs by palpation means that excess subcutaneous fat is present. This is a practical means of physical diagnosis, but may under-diagnose obesity if there are substantial, localized fat accumulations elsewhere. A 5-point and 9-point scale have been published. The middle of the scale represents optimal condition; lower values represent various degrees of under-conditioning and higher values represent various degrees of ‘over-conditioning’. The problem with these scales is that the highest condition score (5/5 or 9/9) equates to an estimated body fat content of 45%; however, morbidly obese pets may have 65-70% fat. Thus, the upper end of the scale underestimates body fat content.

**Treatment of obesity**

Treatment of obesity requires a team effort and convincing the client to be a part of the solution and not part of the problem. Set a goal for the clients and stick to it. Giving positive feedback even if the success is small is very important and helps to support the client in their effort to not only change habits, perhaps long-standing, in their pets, but in themselves as well. When possible, a combination of dietary therapy and exercise is effective. This is difficult in dogs that have pre-existing orthopedic problems and in cats.

**Diet**

There are basically five dietary options available for the management of obesity. The first option is feed lesser amounts of the same diet. While this has the advantage of allowing the owner to purchase and feed the same diet, many times the pet will develop habits of...
begging or of scavenging for food. It is thought that the pet experiences a feeling of hunger because of this technique. Furthermore, owners often feel guilty because their pet appears to be constantly hungry, and many times their perception is that a “healthy pet is a full pet”. The second option is starvation. Starvation results in rapid weight loss; however, initial losses are often due to changes in water content of the body. This is a very dangerous technique and requires the animal to be hospitalized. As a result, owners are not part of the effort. This is an especially dangerous technique in cats because obese cats that suddenly stop eating are at risk for developing hepatic lipidosis and failure. The third option is to feed a low carbohydrate containing diet. The idea is that by limiting carbohydrate intake and providing protein, vitamins, minerals, and fat, the body begins to mobilize peripheral fat for energy. This strategy works in some cats, but not all, and has not been shown to be effective yet in dogs. The fourth option utilizes a high protein diet. In human beings, this is usually a liquid diet. This type of weight loss diet is not utilized any more because of fatalities associated with electrolyte and mineral imbalances. Lastly, substituting “empty calories” for digestible calories can decrease the caloric content of the diet. A safe and effective formulation must provide for complete nutrition and nutrient balance in relation to dry matter intake. There must be complete bioavailability of all nutrients except energy. Using unbalanced diets in weight reduction programs may produce deficiency states that can be dangerous or lethal. Replacing dietary fat with indigestible fiber creates a hypocaloric diet. Fiber reduces the caloric density of the diet by physically insulating nutrients from digestive enzymes, and reducing food transit time. The reduced total and energy digestibility of a high fiber diet requires offsetting increases in protein and micronutrients to compensate for the diet’s reduced digestibility. Because the patient is treated with a low fat, high fiber diet, it is able to ingest familiar volumes of dry matter and dietary bulk and neuroendocrine responses to mechanical and chemical gastrointestinal fullness are retained as contributory signals to the satiety center. Hyperphagia and begging are less frequent. Whether high fiber diets in fact induce satiety is controversial. There are also “low fiber” diets available for weight management. Although the crude fiber content is perhaps low, the types of fiber that are used in these diets are not analyzed by the crude fiber method; therefore, the unmeasured fiber is reported as part of the carbohydrate (NFE) fraction. Dietary fiber is defined as chemically and morphologically diverse plant substances resistant to hydrolysis by digestive enzymes including plant cell wall substances (cellulose, hemicellulose, pectin, and lignin) as well as intracellular polysaccharides (gums and mucilages). Fiber can be classified based on solubility or fermentability, and each imparts different physiological effects. There are several diets that are manufactured and marketed for weight reduction. Usually these diets are higher in fiber.

There are two techniques that are available for weight reduction in pets. The first uses an estimation of the ideal weight, and the second uses a target goal of weight loss per week and monitoring and adjusting dietary intake to meet this goal (iterative approach).

Using ideal weight
Using this technique, an ideal weight for the animal is estimated. The maintenance energy requirements for that animal are estimated using the ideal weight. In order to induce weight reduction, it is necessary to restrict caloric intake further, to approximately 60-75% of the maintenance energy requirement calculated using the ideal body weight. Different pet food companies recommend different percentages, and they range from 40% to 80%. At least 2 studies show that in dogs, using 75% of maintenance energy requirement results in a 1-2% rate of weight loss per week and minimizes rebound weight gain once the target weight is reached and the diet is changed to a maintenance diet.

A weight reduction diet is chosen, typically a high fiber/low fat diet or a low carbohydrate diet if a cat, and the amount to feed to meet this calculated weight loss goal is determined by dividing the MER for weight reduction by the caloric content of the diet. The diet is gradually changed over 5-7 days to avoid inducing gastrointestinal upsets such as vomiting, diarrhea, and inappetence. Following this period, the pet should be weighed every 2 weeks and the body weight charted. This accomplishes several things. First, it provides graphical representation of the weight loss period. Secondly, it provides encouragement for the owner. Once the target weight is reached, the diet can be switched from a weight loss diet to a diet designed for weight maintenance.

Iterative process
Using this technique, the ideal weight is not estimated. Rather, a target rate of weight loss is estimated, and a weight loss diet is fed to achieve this rate. For example, a target rate of 2% loss of body weight per week may be chosen. The amount of a weight loss diet to feed in order to induce this 2% loss of body weight is then calculated, and the diet is slowly switched. The pet is returned every 2 weeks and the food intake is adjusted to continue this controlled rate of weight loss. A computer program developed by Ralston Purina Company is available to facilitate using this technique.

Pharmacologic treatment
Dehydroepiandrosterone (DHEA) is an agent that has been evaluated in dogs, and is not effective. Slentrol (dirilotapide), a selective microsomal triglyceride transfer protein inhibitor that blocks assembly and release of lipoproteins into the bloodstream, has been approved by the FDA to decrease weight in dogs. Its primary mechanism of action is decreasing appetite; however, a slight decrease in fat absorption also occurs. The drug is given to the dog in varying amounts over the course of the treatment. The dog is given an initial dose for the first 14 days. After that, assess the dog's progress at monthly intervals, adjusting the dose depending on the dog's weight loss. After the dog has achieved the goal weight, the drug is continued during a three-month period, while the the optimal level of food intake and physical activity needed to maintain the dog's weight is established. Adverse reactions associated with treatment
with Slentrol include vomiting, loose stools, diarrhea, lethargy and loss of appetite. Unfortunately, while this drug was very effective, it has been removed from market and is no longer available.

There are two groups of approved drugs that can be used to manage weight in obese humans: medications approved for obesity per se and medications that affect body weight for obese patients who have complications from their obesity and are receiving these medications for chronic disease management. For obesity per se, treatment is with one of the three drugs currently approved for long-term treatment of obesity or one of a few others that can be used for short-term treatment. Among these, orlistat partially blocks intestinal digestion of fat and produces weight loss of 5-8 kg but major limitations are associated gastrointestinal symptoms; lorcaserin, a serotonin-2C agonist with few side effects, produces a mean weight loss of 4-7 kg; and the combination of phentermine and topiramate (extended release) produces a mean weight loss of 8-10 kg, but should only be used after verifying a woman is not pregnant. Failure to lose more than 3% of body weight within 3 months with any of these agents should lead to reevaluation of therapy. The short-term drugs for treating obesity per se are sympathomimetics, with phentermine being most widely used. The second group of drugs is for weight-centric prescribing for patients with a chronic disease such as diabetes, depression, or psychiatric disorders. For each disorder, some drugs produce weight gain, others are weight neutral, but the best choice for these patients is the combination of drugs that treat the underlying condition and also produce weight loss.

Prevention
In order to prevent obesity, it is necessary to modify risk factors that led to obesity in the first place. This involves altering behaviors of not only the pet, but of the owners as well. In animals that have difficulty in keeping weight off, diets are available that are less calorically dense, contain higher fiber content, and are complete and balanced for maintenance (see table of diets). Animals that are high risk for recurrence of obesity should be evaluated periodically. Examination should involve not only a good physical examination, but also measurement of body weight, and estimation of body condition using a body condition score. This can be accomplished as part of an overall health maintenance plan. This allows the veterinarian to recommend changes that may aid in preventing obesity from recurring. Also, it establishes a good patient-client-doctor relationship. Owners require positive reinforcement for doing a good job and a gentle “push in the right direction” if their pet is beginning to gain weight back.

Snacks may be an important part of development and maintenance of obesity. Therefore, they should be used sparingly. If used, they should not represent more than 5% of energy intake, and they must be accounted for in estimation of dietary intake necessary to meet maintenance energy requirements. Because “snacking” is a large part of human existence, it is difficult to break owners of this habit. Instead of punishing owners for giving snacks to their pets, in which case they may be dishonest about providing such treats, it is better to counsel them on what treats and what amount is acceptable.