

Urinary Tract Disorders

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THE UPPER URINARY TRACT

Margie Scherk

The recognition and management of renal disease are important in small animal practice: Cats are popular companions, and the average life expectancy has increased. The purpose of this chapter is not only to explore renal disease in depth but also to remind veterinarians that although the clinical signs may look the same, they should strive to identify specific etiologies insofar as these may have specific treatments.

DIAGNOSTIC METHODS

Various diagnostic methods are available for evaluation of the upper urinary tract, including imaging, renal function tests, urinalysis, urine culture, urine protein: creatinine ratio, and renal biopsy. Table 32-1 describes how diagnostic tests can be used to localize disorders.

Renal Size

Renal size is measured radiographically relative to the length of the second lumbar (L2) vertebra. Although there is no difference between the sexes in this parameter, there is an effect of gonadectomy on kidney size. A significant size difference was determined between intact and neutered cats, with intact cats having larger kidneys. Normal feline renal length ratios range from 1.9 to 2.6 for neutered cats and 2.1 to 3.2 for intact cats, which suggests that reproductive status should be taken into consideration when interpreting renal size.²⁰² Box 32-1 lists the causes of renomegaly in the cat.

Renal Function Tests

Assessment of renal function using the standard measures of urine specific gravity (USG), creatinine (Cr), and blood urea nitrogen (BUN) is extremely crude because these parameters are not altered until significant renal function has been lost (approximately 75%) and because they also reflect nonrenal factors. BUN can be especially

TABLE 32-1 Use of Diagnostic Tests to Localize Lesions within the Urinary Tract

| Diagnostic Test | Renal Function Assessed | Localized to Kidneys? | Localized Distal to Kidneys? |
|--|--|-----------------------|--|
| Blood urea nitrogen | GFR | Not necessarily* | No |
| Serum creatinine | GFR | Not necessarily* | No |
| Iohexol clearance | GFR | No | No |
| IV urography | GFR and crude estimate of renal blood flow | Yes | Yes |
| Urine specific gravity | Tubular reabsorption | Not necessarily* | No |
| Urine osmolality | Tubular reabsorption | Not necessarily* | No |
| Water deprivation and vasopressin response tests | Tubular reabsorption | Not necessarily* | No |
| Ultrasound | No | Yes | Yes |
| Renal biopsy | No | Yes | N/A |
| Renal tubular epithelial cells | No | No, unless in casts | No |
| Hematuria | No | No, unless in casts | Yes, if sample not contaminated by blood |
| Proteinuria | No | Not necessarily† | Not necessarily |
| Pyuria | No | No, unless in casts | Yes, if sample not contaminated by genital tract |
| Significant bacteriuria | No | No | Yes, if sample not contaminated by genital tract or coat |
| Urinary casts | No | Yes | N/A |

GFR, Glomerular filtration rate; IV, intravenous.

*Changes to renal parameters may occur secondary to other nonrenal diseases.

†The presence of large quantities of protein in the absence of red blood cells and white blood cells is suggestive of glomerular disease, and a urine protein:creatinine ratio should be calculated.

Adapted from Osborne CA, Stevens JB: Table 2-3. In *Urinalysis: a clinical guide to compassionate patient care*, 1999, Bayer Corporation.

BOX 32-1

Causes of Renomegaly in the Cat

- Polycystic kidneys
- Perinephric pseudocyst
- Hydronephrosis
- Obstructive nephrosis
- Pyonephrosis
- Pyelonephritis
- Feline infectious peritonitis
- Neoplasia (most common is lymphoma)

difficult to interpret because it reflects ammonia intake, production, and excretion. Urea is a by-product of ammonia metabolism that is excreted in bile, reabsorbed by way of enterohepatic recirculation, and also is eliminated by the kidney. The majority of the ammonia produced in the body is by bacterial fermentation in the gut, with lesser amounts produced by catabolism of endogenous protein and other molecules such as heme and some of the cytochromes that are rich in nitrogen. Because dietary factors can be important—there have

been reports of animals fed organ meats as treats that produced spuriously high urea readings—everything the patient is ingesting must be taken into consideration. Bleeding into the gastrointestinal tract is one of the most common pathologic causes because of the large amount of nitrogen in blood, which is broken down by the bacteria. Other potential causes include factors that could change the amount of ammonia being produced by the bacteria in the gut, such as shifts in bacterial populations and changes in motility and gastrointestinal transit of food. Any metabolic derangement that causes excessive catabolism of protein in the body as an energy substrate has the potential to increase urea levels. Increases in urea (independent of Cr) are common in diabetes mellitus (DM) and hyperthyroidism. Interestingly, urea can be elevated in renal disease when Cr is normal, especially in neonates or animals with muscle wasting insofar as these patients have decreased muscle mass compared with the normal population and therefore correspondingly lower Cr levels. In this situation urea may be more sensitive than Cr for predicting renal disease. In most cases, a diagnosis of renal insufficiency will be made based on elevations in BUN and/or Cr along with a dilute USG.

Numerous tests have been evaluated for the assessment of glomerular filtration rate (GFR) or renal function. The standard 24-hour Cr clearance test is unwieldy, and renal scintigraphy is not widely available.¹²¹ One group evaluated a single injection of either inulin or Cr in normal cats and then compared plasma inulin and Cr clearances. The results showed that inulin may be a better indicator of GFR than Cr.¹⁶⁶ The same researchers subsequently assessed iohexol and found that plasma clearance of this marker not only is a sensitive test for the detection of diminished renal function before changes in either BUN or Cr but also can be performed noninvasively in conscious cats.¹⁶⁷ Another single-injection inulin clearance study compared inulin and iohexol clearance and showed excellent correlation between the two methods in their ability to detect alterations in GFR. The investigators concluded that an “inulin excretion test” sampling blood 3 hours after the administration of 3000 mg/m² body surface area can be used for the assessment of renal function in daily practice.¹⁰⁰ Excretory urography is another method to determine GFR; one study compared iohexol with amidotrizoate and concluded that iohexol was safer and produced better-quality urograms.⁶

Renal hemodynamics (resistance and pulsatility index) of intrarenal arteries has been studied using pulsed-wave Doppler; quantitative scintigraphy (^{99m}Tc-MAG3) was used to study relative renal function and relative renal blood flow. Of clinical relevance is that significant differences were found between awake and isoflurane-anesthetized cats for all pulsed-wave Doppler and quantitative renal scintigraphic measurements.¹⁶⁵ Recently, a group evaluated an enzyme-linked immunosorbent assay (ELISA) test for gadolinium diethylenetriamine pentaacetic acid as a means to determine GFR. This test did not offer a sufficiently accurate estimation of GFR in cats when compared with plasma clearance of iohexol and plasma concentrations of BUN and Cr.²⁰³ Box 32-2 lists additional tests for renal function.

Urinalysis

A complete urinalysis is indicated when disease of the urinary tract is suspected. These include the following:

- Chronic renal insufficiency
- Acute renal failure (ARF)
- Urinary tract infection (kidneys, ureters, bladder, urethra—the last only if urine sample is voided)
- Urolithiasis or crystalluria
- Neoplasia: occasionally exfoliation of neoplastic cells occurs from urinary tract neoplasia

In addition, a voided sample evaluates the urethra, prostate, and vagina.

A urinalysis is indicated as part of a minimum database in any ill cat. For example, pyelonephritis is an occult

BOX 32-2

Diagnostic Tests for Evaluation of Renal Function

Tubular concentration capacity:

Water deprivation test

Pitressin concentration test

Glomerular filtration rate measurement:

Plasma iohexol clearance

Plasma inulin clearance

Renal scintigraphy

Phenolsuphonphthalein (PSP) clearance

Markers:

Blood urea nitrogen (BUN)

Serum creatinine

Amylase, lipase

Excretory urography

condition without necessarily any clinical signs referable to the urinary tract. Urinalysis results reflect the health and function of many body systems because urine is, in essence, filtered blood. Examples of some of the non-urinary tract conditions with significant changes detected through urine evaluation include DM (glucosuria) and ketoacidosis (ketonuria), diabetes insipidus (hyposthenuria), hepatic disease and hemolytic disease (bilirubinuria), prerenal azotemia (concentrated urine), and severe inflammation or multiple myeloma (proteinuria).

Throughout this chapter the term *urinalysis* refers to a complete urinalysis consisting of macroscopic evaluation (e.g., appearance, concentration, semiquantitative urine biochemical dip strip tests for pH and urine constituents: protein, glucose, blood) a USG assessment, and microscopic evaluation of spun urine sediment (e.g., cells, crystals, bacteria).

As with any laboratory test, it is possible to generate invalid and misleading results. The usefulness of a urine specimen is significantly affected by the timing of collection and the way it is collected, handled, stored, and examined. Additionally, the veterinarian should note all the drugs that a patient is receiving because many therapeutic agents affect the results of urinalysis (Box 32-3).¹⁷⁷

Timing of Sample Collection

Samples collected after fasting or in the early morning may show highest concentrating ability and highest yield of sediment. The exception to this is the cat with access at all times to a litter box. This sample is also least likely to show glucosuria. Cytologic quality of the cells will be altered by prolonged exposure to waste products, osmolality, and pH variations.

Recently formed urine provides better cytologic detail, and bacteria are more easily identified. If the sample is dilute, tubular concentrating ability cannot be evaluated. Dilute samples also may distort cells.

BOX 32-3**Effects of Drugs on Urine Sample**

1. Parenteral and oral fluids and diuretics
 - a. Alter urine specific gravity (USG) and osmolality
 - b. Furosemide may acidify urine
 - c. Increased urine volume may dilute biochemical parameters, resulting in false-negative results
 - d. Dilute urine affects cell integrity and promotes lysis
 - e. Glucose-containing fluids may result in iatrogenic glucosuria
2. Antimicrobial agents
 - a. Ideally samples for microbiologic culture should be collected before starting antimicrobial therapy. However, culture of urine while on this class of agent will reflect organisms not susceptible to the antimicrobial being used. To evaluate efficacy of therapy, the patient should be off that treatment for a minimum of 3 days.
3. Acidifying and alkalinizing agents (therapeutic, dietary, or added to urine sample)
 - a. Alter crystal composition of the sample
 - b. Extreme alkalinity may cause false-positive protein reactions on urine strips
 - c. Vitamin C (ascorbic acid) causes false-negative glucose reactions on urine strips, as well as red cells, hemoglobin, and myoglobin
4. Iodinated radiopaque contrast materials
 - a. Given intravenously will increase USG if preadministration USG was <1.040, but will decrease the USG if the preadministration USG was >1.040
 - b. Given by catheter into the lower urinary tract will increase the USG
 - c. Affect cell structure and survival of bacteria in the sample

Collection Technique

The most reliable method for collecting urine from cats is by cystocentesis. Cystocentesis samples reflect prerenal, renal, ureteral, and bladder health. Voided samples reflect the aforementioned, as well as the urethra, prostate, vagina, and perineal fur. Further, voided samples reflect where the cat has urinated (e.g., the litter box, consultation table, or floor). The yield of the sediment must also be interpreted in light of collection technique. The bladder contracts circumferentially; however, sediment depends on gravity. Thus, for a cystocentesis-collected sample, the sediment yield may be improved by gently shaking the bladder just before inserting the needle.¹⁷⁸ Voided samples also do not reflect sediment proportionately because of sediment remaining in the bladder as it contracts; thus samples collected in this manner may underestimate the degree of inflammation, crystalluria, and so on.

Cystocentesis: The bladder must contain a sufficiently large volume of urine for the veterinarian to be able to identify it by palpation and immobilize it manually. The two approaches used are either through the lateral abdominal wall with the cat on its side or ventrally with the cat in dorsal recumbency. Ideally, the hair is shaved and the skin disinfected; however, as this adds to stress for the patient, it is often not performed. After the bladder is agitated, the needle should be inserted in the caudoventral direction on an angle so that the layers of the bladder wall seal the puncture better. By using a smaller-gauge needle (e.g., 23 to 25 G) and not applying pressure to the bladder with the mobilizing hand, the veterinarian can reduce the risk of urine leakage.

If a swirl of blood is seen to enter the hub of the syringe, collection should be discontinued and the blood (an iatrogenic cause for hematuria) should be noted in the medical record. This bleeding is extremely unlikely to result in postcollection complications, however. Iatrogenic hematuria is commonly seen in cystocentesis samples and may be differentiated from true hematuria by comparison with a free catch-voided sample collected by the client at home 24 to 48 hours later. Clients can use a long-handled spoon such as a soup ladle or put clean aquarium gravel or Nosorb in a clean, empty litter box to collect the sample. Penetration of a bowel loop during cystocentesis is unlikely to cause problems other than in the interpretation of bacteriuria (discussed later). The most disconcerting postprocedural complication is the rare occurrence of vomiting and hypotensive collapse. Although the mechanism is unclear, it is believed to be a vasovagal response. With standard fluid therapy (to support volume and systemic blood pressure [BP]) and quiet, patients recover within 30 minutes to 1 hour.

Voided sample: Midstream collection reduces the chance of collecting debris (particulate material including feces and bacteria) from the perineal region; however, a voided sample is never completely free from risk of contamination. Veterinarians often make do with samples collected from the examination table, examination room floor, cage, litter box, or carrier base. These may also be used as long as the veterinarian is aware that the sample is likely to include artifacts (and know which types are most likely).

Catheter collection is another possibility; however, it requires sedation in both sexes to ensure humane treatment and minimize potential trauma to the urethra. In the very young kitten (younger than 3 or 4 weeks of age), a urine sample may be obtained by stimulating the anogenital region with a warm moist cotton ball.

Handling the Urine Specimen

In an ideal world urine should be kept at room temperature and evaluated within 30 minutes of collection. Storage time and temperature alter and affect pH, USG,

and crystal formation.⁷ If it cannot be examined in this time frame, the following suggestions will help preserve the integrity of the specimen.

1. Refrigerate at 41° F (5° C) for 2 to 3 hours or possibly overnight. The sample should be warmed to room temperature before analysis for accuracy of USG and for glucose assessment. Do not freeze the sample.
2. Protect the sample from light. Bilirubin becomes undetectable within 1 hour of exposure to sunlight.
3. Casts and cellular material deteriorate in alkaline urine. Over time, more crystals will develop depending on the pH of the sample; therefore the pH should be determined promptly.
4. Although preservatives for urine are available, each type alters the characteristics of the sample; specific information has been published elsewhere.¹⁷⁸

Examination of the Sample

To minimize interassay variation, a standardized protocol should be used for every sample. Refrigerated samples should be rewarmed to room temperature before evaluation. Urine strips and other reagents should be kept cool but not refrigerated. These and the urine should not be exposed to sunlight or other light for significant amounts of time. It is important to read and interpret the test results at the times designated by the test manufacturer. Centrifugation of urine sediment should be at 1000 to 1500 rpm for 3 to 5 minutes. Most important, the timing and method of collection should be taken into consideration when interpreting the significance of the results relative to the patient.

Urinalysis Interpretation^{177,190}

Volume: The normal 24-hour urine volume production for an adult cat is 20 to 40 mL/kg per day. When the USG is greater than 1.040, polyuria is unlikely. Occasionally, cats with renal insufficiency may paradoxically concentrate their urine above 1.040.

Color: Clarity and color are affected by many things, which, in turn, affect the USG value perceived with an optical refractometer. Conversely, urine color should also be interpreted in light of the USG. The color of the sample may be important insofar as it can affect interpretation of the colorimetric dry chemistries (urine strips). Color comparisons are subjective and are affected by colored urine constituents. Color should be assessed by a trained professional, in a consistently well-lit area and using fresh urine (Figure 32-1). Urine color may provide valuable information, including the following:

- Urine that is colorless is very dilute.
- Normal urine color ranges from transparent to light yellow, medium yellow, and amber. Normally, highly concentrated urine is amber as a result of

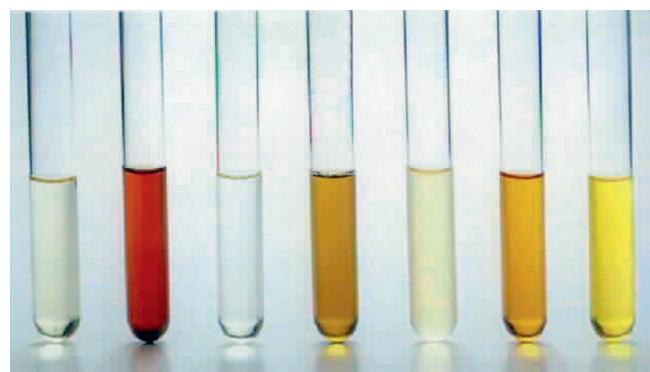


FIGURE 32-1 Urine color is best assessed in good lighting against a white background.

increased urochrome or urobilin. Urochrome levels are also high in states of fever or starvation.

Nitrofurantoin and riboflavin (vitamin B₂) will cause urine to appear deep yellow.

- Orange-yellow color reflects high concentration, or excessive urobilin, bilirubin, or fluorescein (e.g., when used to identify a cat that is urinating inappropriately).
- Red, pink, red-brown, red-orange, or orange color suggests hematuria, the presence of hemoglobin, myoglobin, porphyrin, or warfarin. In humans ingestion of rhubarb, beets, phenothiazines, and other substances may cause this discoloration.
- A brown tint suggests methemoglobin; melanin; and, in humans, several drugs, including bismuth, mercury, and sulfasalazine.
- Yellow- or green-brown discoloration signifies the presence of bile pigment.
- Brown to black discoloration is actually brown or red-brown if evaluated as a thinner layer.
- Milky white urine is a result of chyle, pus, or phosphate crystals.

Turbidity: Transparency is assessed by holding a clear glass tube against a printed page and assessing the legibility of the print. Concentrated urine is more likely to be turbid than dilute urine. Refrigeration changes clarity, as do substances affecting pH. Most commonly, turbidity is caused by sediment—namely, crystals, cells (red blood cells, white blood cells, epithelial cells), bacteria, yeast, semen, or contaminants from the collection container (as well as litter box, carrier, table top, floor) or feces. If there is lipid (from pericystic fat) in the urine, it will rise to the surface of the sample.

Crystal formation is affected by temperature; these may form as urine cools from body temperature to room or refrigerator temperature. Hematuria results in brownish to reddish (rarely black) turbid urine. Myoglobin and hemoglobin create a similarly colored, but clear, urine.

Odor: Cat urine has a characteristic odor that is stronger when the urine is concentrated. Tomcat urine has an

almost pathognomonic smell that helps identify an intact cat or a cat that has been incompletely castrated (e.g., retained testicle) or a cat with a testosterone-secreting tumor. It has been speculated that felinine, the amino acid unique to cats, is responsible for this smell.

Abnormal odors may indicate infection with urease-producing bacteria. Warm temperature facilitates transformation of ammonium $[\text{NH}_4]$ to ammonia $[\text{NH}_3]$, resulting in odor. The odor of urine ketones may be detected by some humans. A putrid smell suggests bacterial degradation of protein.

USG: USG is a measure of the density of the urine relative to the density of water measured at the same temperature. The density of water is 1.000 under set circumstances of temperature and pressure. Temperature affects USG inversely (i.e., increasing urine temperature causes a decrease in its USG, whereas decreasing the urine temperature increases the USG). Solutes affect the density of urine, and each solute may affect it to a different degree, even when each one is present in equal amounts.

The accepted method for determining USG in cats is by using a refractometer. This tool assesses refractive index (ratio of velocity of light in air to the velocity of light in a solution). The refractive index is affected by the type and quantity of solutes present. Although refractometers are calibrated to a reference temperature, they compensate to a certain degree. They should be stored at room temperature. Veterinary refractometers measure a wider range of specific gravity and are therefore best suited for cat urine that may have USG in excess of 1.080. Human refractometers read only to 1.050. Digital refractometers appear to correlate with optical refractometers and have the advantage of less subjectivity.²² Some reagent strips include a pad for USG. Because these are developed for human urine, the highest value they detect is 1.030, which is inadequate for feline urine. Urinometers, devices that float in urine to measure USG, are imprecise. Osmometers assess osmolality rather than specific gravity. Regardless of the method used, all factors that affect refraction still should be taken into consideration.

The normal USG for a cat depends on hydration status and age. By the time a kitten is 4 weeks of age, USG is 1.020 to 1.038; full concentrating ability (up to 1.080) is reached by 8 weeks of age. In a dehydrated cat normal renal function (specifically, concentrating ability), is suggested by USG of 1.040 or above, depending on the diet fed. In cats fed exclusively canned food, a "normal" USG may be 1.025 or greater, whereas in cats fed exclusively dry food, USG should be 1.035 to 1.040 or higher.⁵² In a well-hydrated cat, it may fall between 1.035 and 1.060. *Specific gravity varies within the same individual throughout the day; therefore a single urine sample with a low USG is not reliable evidence of a decline in renal function.*

When nephrons are no longer able to modify glomerular filtrate, a fixed USG of 1.008 to 1.012 develops. USG of 1.007 to 1.039 in a dehydrated cat with or without azotemia is highly suggestive of renal insufficiency (or renal failure, depending on the degree of azotemia once the patient is rehydrated).¹⁷⁶ Hypoadrenocorticism and hyperaldosteronemia are less common causes of such a drop in urine concentration. There is a subgroup of cats with impaired renal function that paradoxically remain able to concentrate urine to greater than 1.045, such that renal azotemia precedes a decline in USG.¹⁷⁷ Because these patients are uncommonly identified, veterinarians must rely on finding USG of 1.045 or greater in the face of azotemia as indicating a prerenal cause for the azotemia.

Urine pH: Urine pH can be used as an index of body acid-base balance; however, this parameter changes so rapidly to provide homeostatic balance to the body that it is a rough guide at best. Obligate carnivores create a great deal of acidic metabolic waste. They regulate their acid-base balance by excreting hydrogen (H^+), ammonium ion (NH_4^+), and phosphates (PO_4^{3-}) in urine (metabolic route) and by exhaling CO_2 (respiratory route). pH is one of the factors affecting crystal formation and may be manipulated to encourage dissolution of some crystal types. Acidic urine inhibits bacterial growth.

Stress affects urine pH. In one study it was reported that the urine pH of a cat increased by 1.4 U when the cat was transported from home to a veterinary clinic. The authors concluded that the most likely cause was anxiety-induced hyperventilation (excessive panting).⁴³ Another study suggested the opposite—namely, that increasing activity of the sympathetic nerves and the adrenal glands will most likely lead to increased metabolism, including catabolic conversion of proteins, which in turn increases sulfuric acid production and lowers urinary pH. This effect can also be seen in the fasted, inappetent, or anorectic cat.⁶⁰

Eating affects urine pH. Postprandial alkaline tide (alkaline urine) is believed to be a result of increased hydrochloride acid secretion after a meal. In their feral state cats eat many (8 to 15) small meals per day rather than two, as are fed in many homes, making the effect of this pH swing much smaller. Frequency of feeding along with quality of food ingested and the composition of the meal will affect urine pH. Higher-protein, meat- and fish-based diets create more acidic urine; lower-protein, grain- and vegetable-based diets create more alkaline urine.

The pH of urine in the healthy "normal" cat generally ranges between 6.0 and 7.5. The pH of urine least likely to result in crystal formation is 6.2 to 6.4. The method used to measure urine pH is critical; pH meters are inexpensive and are most accurate. Hydrogen paper (pH 5.5 to 9.0) is satisfactory. The urine reagent strips most commonly used in clinics are extremely unreliable. pH values

measured with reagent strips are accurate only to within 0.5 units, meaning that the color subjectively translated into a pH value may vary by $+/- 0.5$, resulting in one whole unit variability.

Acidic urine may be a result of an acidifying diet, respiratory or metabolic acidosis, diabetic ketoacidosis, renal failure, starvation or anorexia, pyrexia, protein catabolism, hypoxia, or severe diarrhea. Severe vomiting resulting in chloride depletion may cause paradoxical acidosis.

Alkaline urine is associated with an alkalinizing diet; drug therapy; respiratory or metabolic alkalosis; vomiting; renal tubular acidosis; chronic metabolic acidosis resulting in ammonium ion (NH_4^+) secretion; and infection with urease-producing bacteria, such as *Proteus* and *Staphylococcus*, organisms seen infrequently in the urinary tract of cats.

Drugs may alter urine pH. Acidifiers include DL-methionine, furosemide, ammonium chloride (NH_4Cl), ascorbic acid at supertherapeutic doses, and phosphate salts. Alkalinizing agents include sodium bicarbonate (NaHCO_3), potassium citrate, sodium lactate, and chlorothiazide.

Artifacts affecting urine pH include containers contaminated with detergents or disinfecting agents, CO_2 loss resulting from storing urine at room temperature, and contamination of the sample by urease-producing bacteria from the environment or the distal urethra.

Glucose: The glucose pad on a urine strip is a colorimetric test based on glucose oxidase activity. Although it is easy to use, several points are worth noting. Because the test involves multiple enzymatic steps, it must be performed according to label instructions. The colorimetric indicators can react with substances other than glucose, and some substances may inhibit the test; this means that false-positive and false-negative results are possible. Glucose oxidase is labile, so the expiration date of the strips should be respected. The reaction is also pH dependent. Because the test is temperature dependent, the urine has to be tested at room or body temperature.

Glucose is filtered by the glomerulus and reabsorbed by the proximal tubules. Physiologic or stress glucosuria occurs when serum glucose exceeds the renal threshold for glucose of greater than 260 mg/dL (14 mmol/L). Pharmacologic agents that can result in transient glucosuria include epinephrine, phenothiazines, glucagon, adrenocorticotrophic hormone (ACTH) and morphine. Persistent glucosuria may be a result of DM, hyperprogesteronemia, acromegaly, hyperadrenocorticism, and pheochromocytoma. Renal glucosuria may be caused by acute tubular injury.

Urine glucose monitoring for insulin dose titration in the diabetic cat should not be used because the relationship between serum glucose concentration and that in the urine is variable.¹⁷⁷

Ketones: Ketones (ketone bodies) are produced when metabolism shifts to using stored fat as a source of energy, such as in cellular starvation (unregulated DM or lack of eating) or when excessive fat is ingested. In other species it also occurs with insufficient carbohydrate metabolism. The three ketones produced are acetocetic acid, acetone, and beta-hydroxybutyric acid. The first two are detectable in urine using the reagents in urine strips; beta-hydroxybutyric acid is not. All three types can be measured in blood. Another colorimetric reaction on urine strips, ketone pad color interpretation, is subjective and is affected by colored urine constituents.

Bilirubin: Bilirubin is a by-product of heme (from hemoglobin) catabolism. The portion that is bound to albumin (unconjugated/indirect bilirubin) is removed from circulation by the liver where it is conjugated. Once conjugated, it is water soluble. The majority of the conjugated portion is transported in bile to the intestinal tract, where bacteria convert it into urobilinogen. It is oxidized to urobilin, the pigment that provides the brown color to feces. A small amount of the urobilinogen is reabsorbed into circulation and is excreted into urine. The small quantity of conjugated bilirubin that evades the bile is excreted into glomerular filtrate.

An increase in urinary bilirubin is associated with increased destruction of red blood cells (hemolytic disease), hepatocellular disease preventing normal elimination of this product, or bile duct obstruction (cholestatic disease). Altered selective permeability of glomerular capillaries in glomerulonephropathy can also potentially cause bilirubinuria by changing the renal threshold of affected nephrons. Bilirubinuria may precede clinically recognizable icterus and even bilirubinemia. Unlike in dogs, bilirubinuria is not found in normal cats, even in highly concentrated urine samples, presumably because of a higher renal threshold for bilirubin in this species.¹⁷⁷

Bilirubin is an unstable compound, especially when exposed to room air or light. The degradation products formed under those circumstances (including biliverdin) do not react with the test, causing false-negative test results. To avoid this, urine should be evaluated within 30 minutes of collection or be refrigerated, kept dark, and (for other tests) brought to room temperature just before analysis. This test should also be run before centrifugation (or filtration) because precipitates in the centrifuged (or filtered) sample may absorb bilirubin.

Urobilinogen: The reagent strip test detects normal and increased amounts but not the absence of urobilinogen. Because of this, it cannot be used to detect complete bile duct obstruction. Increased concentration is suggestive of hemolytic disease or decreased hepatic function. For results to be meaningful, a fresh urine specimen is required.

Occult blood, hemoglobin, and myoglobin: Hemoglobinuria (red to brown urine) is suggestive of intravascular

hemolysis; a serum sample from the patient collected concurrently should have a reddish discoloration. Myoglobinuria (brownish urine) is suggestive of muscle disease; the serum from the patient may be clear.

Free hemoglobin and myoglobin, but not intact red blood cells, cause a positive reaction. This urine strip chemical reaction augments and complements the microscopic findings of red cells on urine sediment evaluation. This test must be interpreted in concert with the USG as well as the microscopic sediment evaluation. Very dilute or very alkaline urine may lyse red cells. Serum creatinine kinase should be assessed when a positive reaction occurs and hemoglobinemia has been ruled out to differentiate between myoglobinuria and hemoglobinuria.

Lack of red cells in the sediment with a positive test reaction implies hemoglobinuria, myoglobinuria, low urine concentration, low pH causing red cell lysis, or misidentification of red cells in the sediment. When red blood cells are seen on microscopic examination but the urine test pad is negative, it suggests that the strips are outdated, the sample was improperly mixed or centrifuged, there are too few red cells in the sediment to hemolyze, or red cells have been misidentified in the sediment.

Hematuria indicates blood loss into any part of the urinary tract. Identification of the site of bleeding is the next step. Idiopathic renal hematuria has been recognized in cats and dogs. It is not known whether it is due to a vascular bed abnormality or to an abnormality in podocyte attachment, as occurs in humans.²²⁰

Protein: Numerous types of protein (as many as 40 kinds) may be found in the urine of cats. Hemoglobin and myoglobin have already been mentioned. Protein detected in urine may be prerenal, glomerular, or postglomerular in origin. Small amounts of protein are routinely found in the urine of healthy individuals, but under normal circumstances plasma proteins included in urine are restricted by size and are 66,000 daltons or lower. Because protein loss may be transient, it is essential to verify that proteinuria is persistent before considering appropriate diagnostics and therapeutics. Sample-to-sample variation may be considerable. Centrifugation removes cells that may be causing positive reactions; therefore if protein is detected on an uncentrifuged sample, the test should be repeated on the supernatant after centrifugation.

The aspects of the glomeruli that determine whether protein leaves the glomerular capillaries are size, electrical charge, and hemodynamics. In general, proteins at or below 45,000 daltons with a positive charge are most likely to pass through. Albumin is 66,000 daltons and has a negative charge, which is why there are negligible amounts of albumin in the urine of a cat with normally functioning glomeruli despite high plasma concentrations (Table 32-2). Plasma hemoglobin is normally bound to haptoglobin, making it too large to cross the

TABLE 32-2 Examples of Proteins Found in Urine, Their Relative Size, and Implied Reason for Presence

| Protein | Approximate Molecular Weight (Daltons) | Implication When Found in Urine |
|---|--|--|
| Smaller proteins (e.g., beta ₂ -microglobulin, muramidase) | 11,800-14,400 | Unknown |
| Myoglobin | 17,600 | Ischemic or traumatic injury to muscles (heat stroke, electrocution, severe muscular exertion, snake bite, crush injury) |
| Bence Jones proteins | 22,000-44,000 | Multiple myeloma |
| Alpha ₁ -microglobulin | 27,000 | Unknown |
| Alpha ₁ -acid glycoprotein | 40,000 | Unknown |
| Hemoglobin (unbound to haptoglobin) | 64,500 | Low urine specific gravity, alkaline urine, intravascular hemolysis |
| Albumin | 66,000 | Significant glomerular disease |

Adapted from Osborne C, Stevens J, Lulich J et al: A clinician's analysis of urinalysis. In Osborne C, Finco D, editors: *Canine and feline nephrology and urology*, ed 1, Baltimore, 1995, Williams & Wilkins.

glomeruli. When this binding capacity is exceeded, as may occur in hemolysis, then unbound hemoglobin can enter urine.

Because tubules reabsorb filtered protein, a great deal of protein has to be lost through the glomeruli, exceeding the capacity of the functional or impaired tubules to reabsorb it, for it to be present in the ultrafiltrate. Some proteins originate from the urinary tract. The distal tubules and collecting ducts secrete Tamm-Horsfall mucoprotein. The urothelium secretes immunoglobulins as necessary (e.g., to protect against ascending infection).

Interpretation of the significance of protein in urine depends on the USG. For example, mild 1+ proteinuria with USG of 1.010 implies greater protein loss than 1+ protein in a sample with USG of 1.040. Localization of the protein source requires knowledge of collection technique and the urine sediment constituents (Table 32-3).

Numerous test methods exist to detect urine protein, each having a different specificity and sensitivity. It should be noted that small amounts of protein normally found in urine are not detected by routine methods. When 4+ (approximately 1000 mg/dL) protein is found in the supernatant of a centrifuged specimen, a urine protein:Cr ratio (UPC) should be performed. The UPC should be repeated two to three times at 2-week

TABLE 32-3 Localization, Causes, and Findings in Proteinuria

| Urinary Protein Source | Findings |
|---|---|
| Hemorrhage into urinary tract (trauma, inflammation, neoplasia) | Occult blood test +, TNTC red blood cells + white blood cells in sediment, high protein |
| Inflammation in urinary tract | Variable number of white blood cells in sediment, protein rarely >2+ unless concurrent hemorrhage |
| Infection in urinary tract | Many white blood cells and bacteria in sediment, protein rarely >2+ unless concurrent hemorrhage |
| Glomerular and/or tubular disease | No occult blood, no significant sediment findings, +/- casts, protein higher in glomerular than tubular disease |
| Functional extrarenal causes for transient glomerular changes (e.g., fever, stress, extreme environmental temperatures, seizures, venous congestion of kidneys, exercise) | No occult blood, lack of significant sediment findings, +/- casts, high protein, transient |
| Hemoglobinuria, myoglobinuria | Variable amounts protein, no significant sediment findings |

TNTC, Too numerous to count.

Adapted from: Osborne C, Stevens J, Lulich J et al: A clinician's analysis of urinalysis. In Osborne C, Finco D editors: *Canine and feline nephrology and urology*, ed 1, Baltimore, 1995, Williams & Wilkins.

intervals to verify the persistence of the problem before pursuing additional diagnostics (e.g., biopsy) or therapeutics.

The reader is referred to the ACVIM Consensus Statement¹⁴³ for a comprehensive discussion of causes, significance, identification, and management of proteinuria in dogs and cats. This topic is discussed in greater detail later in this chapter.

Nitrite: In humans this test is used to screen for certain bacterial pathogens. This test is *not* valid in cats (or dogs).

Leukocytes: In humans this test is used to detect the presence of leukocyte esterase and is a semiquantitative assessment for leukocytes in urine. This test is *not* valid in cats (or dogs).

Urine sediment: Microscopic examination of urine sediment is akin to exfoliative cytology of the urinary tract. It is critically important in the interpretation of color, specific gravity, turbidity, protein, pH, occult blood, and so forth. Without this procedure it is not possible to differentiate, for example, proteinuria caused by glomerular disease from that of inflammatory response to bacterial insult at any level of the urinary tract or the genital tract. Conversely, the sediment cannot be interpreted without knowledge of the physical and biochemical characteristics of the sample.

To minimize interassay variation, a standardized procedure should be followed. Centrifugation speed for urine sediment is slow: 1000 to 1,500 rpm for 3 to 5 minutes. Faster or longer centrifugation will lead to artifacts. Normal constituents in urine sediment include a few epithelial cells, red and white blood cells, hyaline casts, some fat, mucus, sperm, and some struvite or oxalate crystals. Yeast bodies are contaminants. Abnormal constituents in urine sediment include more than a few red or white blood cells; hyperplastic or neoplastic

epithelial cells; more than a few hyaline or granular, cellular, hemoglobin, fatty, or waxy casts; a large number of crystals; any parasite ova; bacteria in a properly collected, transported, and prepared sample; or many yeast organisms.

Storage of urine can alter crystalluria dramatically and therefore the clinician's diagnosis and treatment planning. A study performed to look at the effects of storage on the diagnosis of crystalluria and casts in cats with no history of urinary tract disease was performed. Crystalluria was detected in at least one aliquot in 92% of stored samples as opposed to only 24% of samples examined fresh. Regardless of whether the sample was stored or fresh, urine from cats fed an exclusively canned diet did not have crystals.²⁰⁸

Pitfalls of interpretation may be avoided by examining unstained sediment using a reduced microscope light intensity. This can be achieved by either lowering the condenser or closing the iris diaphragm. Stain artifact may include bacteria growing in the stain and foreign material. Stain should be filtered weekly or monthly (depending on the number of samples being examined) and should be kept in the refrigerator. Additionally, staining procedures that require washing and counterstaining may result in loss of sediment in the process. Ideally, some of the sediment should be examined unstained, and if there is enough, some of it should be saved for staining. A lack of bacteria on examination does not mean that bacteria are not present.

Urine Culture and Sensitivity

In cats with chronic kidney disease (CKD), the prevalence of urinary tract infections (UTIs) is 22%; in cats with uncontrolled DM and in cats with hyperthyroidism, it is 12%. Many cats with UTIs have no clinical

BOX 32-4**Factors that May Explain Lack of Growth on Urine Culture when Bacteria Were Identified in the Sediment**

1. Bacteria nonviable in the urine at time of collection (e.g., antimicrobial therapy, immunologic defenses)
2. Urine sample improperly handled or preserved, causing death of bacteria
3. Organisms fastidious, did not survive time between collection and culture outside of the body
4. Improper culture technique (e.g., anaerobic organism processed as an aerobe)
5. Bacteria misidentified in sediment (look-alikes)

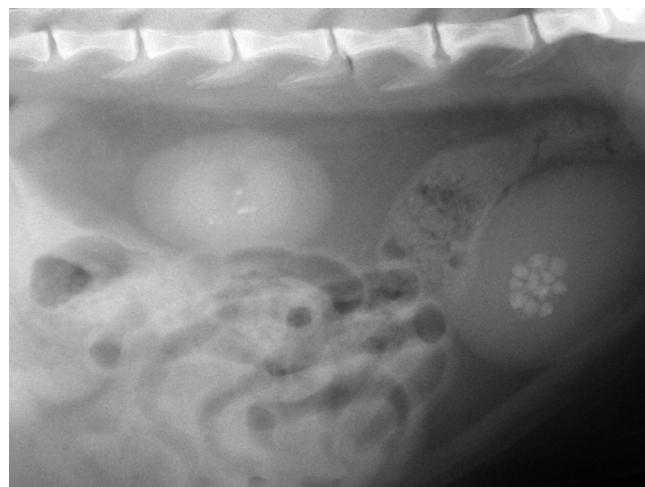


FIGURE 32-2 This radiograph shows a cluster of radio-opaque calculi in the bladder lumen as well as five smaller densities in the kidney. On ultrasound two calculi were also seen in the ipsilateral ureter.

signs of lower urinary tract disease or changes in their laboratory values indicative of infection.¹⁵⁶ Because UTI is so common in cats with hyperthyroidism, DM, and CKD, urine culture and sensitivity is recommended as part of the minimum database for cats with these conditions, especially if the USG is 1.030 or lower regardless of sediment and, in more concentrated samples, if significant numbers of white blood cells or bacteria are seen. **Box 32-4** shows causes of negative growth on urine culture in the face of the detection of bacteria in the sediment.

Urine Protein : Creatinine Ratio

Renal proteinuria occurs by one of two mechanisms. The first is a loss of integrity of the glomerular filtration barrier in excess of tubular reabsorption capacity; this may cause mild to marked proteinuria. The second occurs when the tubules fail to reabsorb normal proteins; this may cause mild to moderate proteinuria. Cr is excreted by the kidneys exclusively by glomerular filtration. Comparing these two urine components gives a measure of protein loss relative to renal function. The equation is simple:

$$\text{Urine protein (mg/dL or mmol/L) divided by} \\ \text{urine Cr (mg/dL or mmol/L)}$$

In cats a UPC below 0.2 is considered nonproteinuric. Values between 0.2 and 0.4 reflect borderline proteinuria and should be reassessed within 2 months and reclassified as appropriate. A UPC above 0.4 is considered clinically significant proteinuria.

Microalbuminuria

In humans microalbuminuria is predictive of future renal health. In cats the predictive significance of microalbuminuria is not understood at present. The

recommendation of the International Renal Interest Society (IRIS; <http://www.iris-kidney.com/>) is to continue to monitor this level of proteinuria.⁹⁶

The reader is referred to the ACVIM Consensus Statement¹⁴³ for a comprehensive discussion of the causes, significance, identification, and management of proteinuria in dogs and cats. (This topic is also discussed later in this chapter.)

Imaging of the Kidney and the Ureters

Imaging studies commonly used in the assessment of the upper urinary tract of cats include survey radiography, contrast excretory studies, and ultrasound. The normal signal intensities have been determined for magnetic resonance imaging (MRI) of the normal feline cranial abdomen.¹⁷³ Each test has a role to play in patient diagnostics. Plain radiographs allow assessment of the number, size, location, and density of the kidneys. The limitations of survey radiography include an inability to visualize kidneys in the thin cat lacking retroperitoneal fat or if retroperitoneal fluid is present. Moreover, survey radiography cannot delineate problems of the renal pelvis or of the ureters unless there is radio-opaque material present (e.g., renoliths or ureteroliths, dystrophic mineralization) (**Figure 32-2**). Fecal material may obscure the outflow tract. Abdominal compression (e.g., using a wooden spoon over the organ of interest or a general abdominal wrap) may help enhance the image of a specific area by eliminating some of the superimposition encountered with survey radiographs.¹¹

Excretory urography is the technique of choice when the renal parenchyma, renal pelvis, or ureters are of concern. This study may be useful to establish the relationship between a renal mass and the pelvis or ureter,

to locate an avulsed or congenitally displaced kidney, to identify and possibly distinguish between acute and chronic pyelonephritis, to detect a nonfunctional kidney, to diagnose hydronephrosis, and to outline radiolucent uroliths.¹¹⁹

Ultrasound has the advantage of being noninvasive and quick. It is safer for the patient because no contrast material is needed and safer for the patient and owner because there is no exposure to ionizing radiation. It can be used to guide renal biopsy should this be indicated. This modality is useful for evaluating renal masses, cysts, diseases of the renal pelvis (calculi, hydronephrosis, pyonephrosis⁵³) and adjacent abdominal structures. Although it is difficult to visualize the normal feline ureters ultrasonographically, various abnormalities associated with ureteral dilation may be revealed, including ectopic ureter, ureterocele, and certain causes of ureteral obstruction. Ultrasonographic evidence of hypoechoic subcapsular thickening in feline kidneys is associated with renal lymphosarcoma.²¹⁵ Ultrasound guidance facilitates certain interventional diagnostic procedures for the ureters.¹³⁵ Its limitations include the inability to visualize structures through abdominal air or bone (i.e., pelvic structures occlude the urethra).

Renal Biopsy

Histopathology of a kidney biopsy sample can provide information by revealing a pathologic process other than chronic interstitial nephritis. Patient selection is important. This procedure should be recommended in those individuals whose treatment will change because of information the results provide. Thus those with proteinuria believed to be of glomerular origin, those with ultrasound evidence of infiltrative disease, or those in ARF are appropriate candidates. The benefits of biopsy in patients with renomegaly outweigh risks; in general, however, for patients with small, scarred kidneys, it is unlikely to be of use. To obtain the best possible results, the veterinarian must be well prepared and understand the laboratory's sample-handling requirements.²¹⁴ The laboratory should ideally be able to perform not just light microscopy but also electron microscopy (EM). The latter requires a specific transport medium, gluteraldehyde, which is available through the laboratory.

Two centers that provide this comprehensive service are the Texas Veterinary Renal Pathology Service (Texas A&M University, College Station, Tex) and the Veterinary Pathology Diagnostic Centre (Utrecht University, Utrecht, The Netherlands). They encourage submission as part of the World Small Animal Veterinary Association (WSAVA) Renal Standardization study in order to increase understanding of glomerular diseases of dogs and cats. EM is needed for complete histologic examinations, especially to define early stages of kidney

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Please refer to the printed publication.

FIGURE 32-3 This drawing depicts the correct way to direct the renal biopsy needle. The needle should remain in the renal cortex and not cross the corticomedullary junction or enter the medulla or the renal pelvis. (From Vaden SL: Renal biopsy: methods and interpretation, Vet Clin North Am Small Anim Pract 34:887, 2004.)

diseases (minimal changes disease, epithelial tubular pathologies, and tubular basement membrane and glomerular basement membrane changes). Along with clinical, histologic, histochemical, and immunologic examinations, it is an essential method for diagnosis and prognosis of renal disease.¹⁹⁸ Because complications after renal biopsy are usually minor, provided the biopsy is performed properly, this tool for diagnostic evaluation should be encouraged.^{164,214}

A sample may be collected by tissue-core biopsy (e.g., Tru-Cut) percutaneously with ultrasound guidance or surgically by laparotomy or keyhole approach. The first technique requires only very good sedation and local analgesia, whereas the latter requires general anesthesia. Regardless of technique, monitoring for postprocedural bleeding is critical. This and other possible complications (e.g., peritonitis, local infection, neoplastic seeding) still occur in fewer than 2% of patients undergoing percutaneous sampling. Unless the procedure inadvertently interferes with significant vasculature, GFR is not substantially affected.⁷⁴ By guiding the biopsy needle through cortex only from pole to pole, the veterinarian is able to avoid the medulla and the medullary-cortical junction and significant vascular supply (Figure 32-3). The patient should be monitored to ensure that adequate analgesia is being used; palpation over and around the biopsy site will be a good guide. Renal biopsy is contraindicated in patients with coagulopathy, those receiving drugs affecting bleeding, and those with cavitated lesions (e.g., vascular lesion, cyst, abscess, hydronephrosis) to avoid leakage of contents or bleeding.²⁶ More information on performing renal biopsy can be found later in this chapter.

INHERITED, CONGENITAL, AND DEVELOPMENTAL RENAL DISEASES

Renal anomalies are rare in cats. The most common familial disorders in cats include renal amyloidosis, renal dysplasia, polycystic kidney disease, glomerular basement membrane disorders, and tubular dysfunction (Fanconi's syndrome).⁹⁸ Errors of embryologic development that have been recognized in cats include agenesis, renal fusion, ectopic kidney, and cysts.

In reports of renal agenesis, the right kidney is more likely to be absent along with its ureter (*in toto* or partially). In affected females the uterine horn on the same side is also partially or completely missing. The ovary, having a different cellular origin, is present. In affected males the vas deferens and epididymis may be lacking, but the ipsilateral testicle will be normal.⁸¹

In the recent literature, two cases with urogenital abnormalities have been reported. The first, a 9-month-old female domestic shorthair, was lacking the right kidney and ureter and a segment of the uterine horn on the same side. The cat was brought in because of acute vomiting, depression, and shivering caused by hydrocephalus of the right uterine horn segment.⁵¹ The second case described was of a 1.5-year-old female Persian with azotemia and inappetence. Like the earlier case, the cat also had renal and ureteral agenesis with segmental aplasia of the uterine horn on the right side; however, in this cat the affected uterine segment was caudal, resulting in cranial uterine horn distention.⁹¹ In a study in which 257 Ragdoll cats were screened for polycystic kidney disease, 0.8% were identified with renal agenesis/aplasia.¹⁷⁹ In a large study of more than 53,000 cats presented for ovariohysterectomy, uterine anomalies were detected in 0.09% of cats ($n = 49$). The kidneys were also evaluated in 34 of the affected cats, and ipsilateral renal agenesis was found in 29% (10 of 34).¹⁵⁸

Crossed renal ectopia with fusion was identified in an adult neutered male cat that was presented for polyuria and polydipsia and shown to have renal disease and hypertension. Imaging revealed an ectopic left kidney fused with an orthotopic right kidney.⁸ Bilateral renal dysplasia was found in a 5-month-old Norwegian Forest Cat; histopathology revealed primary tubular disorganization and changes in the glomeruli.¹⁰

Membranoproliferative glomerulonephritis (GN) was reported in a 9-month-old domestic shorthair cat in Japan.¹⁵ In another report a series of 8 young, related Abyssinian cats of both sexes presented with hematuria and were found to have varying degrees of proteinuria. Six of the eight developed nephrotic syndrome with peripheral edema. Histopathology revealed mild glomerular changes, including mesangial hypercellularity with adhesions between Bowman's capsule and the glomerular tuft consistent with focal proliferative

glomerulopathy. Genetic analysis was not available in this report.²²²

In Norway, 11 Ragdoll cats were evaluated after two unrelated queens were found suddenly dead as a result of oxalate nephrosis with chronic or acute-on-chronic underlying renal disease.¹⁰⁵ Renal abnormalities were found on ultrasound of five cats. Although investigated as an inherited condition, the etiology and mode of inheritance were not elucidated. Primary hyperoxaluria was ruled out by urine oxalate and liver enzyme analysis.

Cystic Diseases

Polycystic Kidney Disease

Polycystic kidney disease (PKD) is found in Persian, Himalayan, and Exotic Shorthair cats around the world and is reported extensively in the United States,⁵⁸ United Kingdom,⁴⁶ Australia,^{17,20} France,¹⁸ Italy,³¹ and Slovenia.⁶⁹ The prevalence rates in these studies are between 40% and 50%. Many young Persian cats are asymptomatic, and renal function may not begin to decline until the cat is 7 or 8 years of age. Other breeds of cats manifest this condition rarely; a case report describing a Chartreux cat was recently published.²¹⁷ It has been shown to have an autosomal dominant mode of inheritance in all of these breeds.^{27,153} All affected individuals are heterozygous for the causative mutation; homozygous individuals die in utero. Concurrent with the renal cysts, unilocular or multilocular cysts may be seen in the liver with or without congenital hepatic fibrosis,³³ as well as other abdominal organs (Figure 32-4).⁶⁹

Cats may exhibit no clinical disease, slowly progressive renal insufficiency as adults, or significant disease as young cats, with marked renomegaly. Because of the variable clinical picture and because of the autosomal dominant inheritance in a pedigreed population,

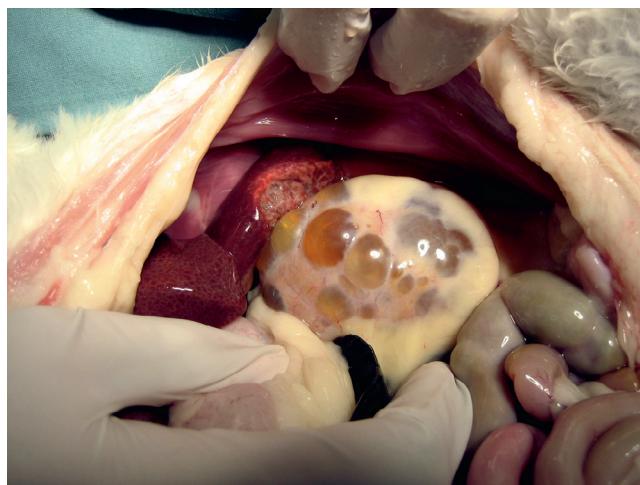


FIGURE 32-4 This necropsy image shows the typical appearance of a polycystic kidney in a Persian cat. (Courtesy Dr. Susan Little.)

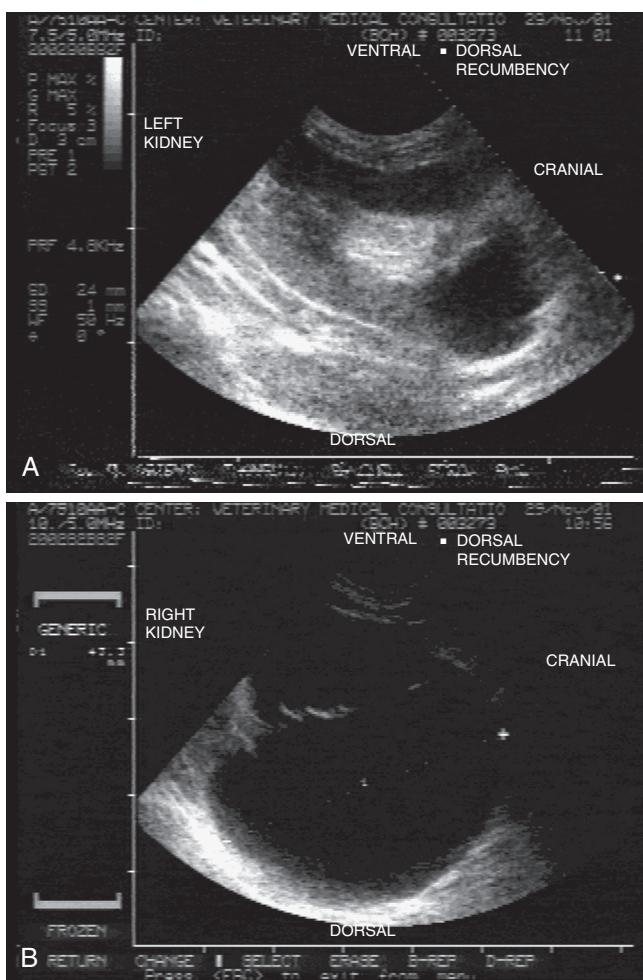


FIGURE 32-5 A, Ultrasound of the left kidney of a cat with polycystic kidney disease. Note the anechoic nature of the cyst. B, This ultrasound is of the right kidney and shows that cysts are of variable sizes within the same cat. (Courtesy Dr. Edward Javinsky.)

screening to identify affected individuals is essential. The condition may be unilateral or bilateral with irregular, enlarged kidney (or kidneys) on palpation. Radiographically, the affected kidney will be irregularly enlarged; on excretory urogram multiple radiolucent areas will be seen. Ultrasound is readily available and may help identify affected cats long before they show clinical signs. Thus sonographic screening is recommended in kittens older than 13 weeks of age; a skilled ultrasonographer can detect cysts in affected kittens as young as 6 to 8 weeks of age. Absence of cysts at a young age does not predict that the kitten will not develop them at a later age. Conversely, a cat with cysts may never show clinical disease. Cysts are located in the medulla or cortex (or both) and are anechoic to hypoechoic, round to irregularly shaped structures of variable size that may grow over time (Figure 32-5). Affected kidneys have indistinct corticomedullary junctions and may have mineralized foci. Further evaluation using intravenous contrast medium allows more

definitive identification of cysts with computed tomography (CT), as well as identification of distortion of the renal pelvis by cysts.¹⁸⁹

Genetic testing has been developed to detect a C→A transversion at position 3284 on exon 29 of the *PKD1* gene, resulting in a stop mutation. A real-time polymerase chain reaction (PCR) assay using fluorescent hybridization probes and melting curve analysis has recently (2009) been developed that may be as reliable but faster than previous methods.⁶³ It is, however, recommended to use both ultrasound as well as genetic testing to improve sensitivity and specificity³² to decrease the prevalence of the disease in the Persian population.⁵⁸ PKD is the leading cause of renal disease in Persian and Persian-related breeds.

Therapy for hepatic and renal cysts is warranted when there is significant compression of adjacent tissue or pain from capsular stretch. Drainage may be performed using ultrasound guidance. In one study of dogs and cats, the drained cysts were infused with alcohol for two periods of 3 minutes. Short-term discomfort was noted in all the patients, with anorexia, lethargy, or vomiting occurring in some.²²⁹

Interestingly, although dogs with renal cysts and humans with PKD have hypertension, cats with PKD are normotensive. One study that looked at the effects of the angiotensin-converting enzyme inhibitor (ACE-I) enalapril on BP, renal function, and the renin-angiotensin-aldosterone system (RAAS) in affected cats compared with healthy controls found that the ACE-I reduced BP in all and resulted in changes in RAAS enzyme activities and hormone concentrations with minimal effects on renal function.¹⁶³

Perinephric Pseudocysts

Much less common than PKD, perinephric pseudocysts (PNPs) surround one or both kidneys, which may be normal or subnormal in size. Not a true cyst, the fibrous sac lacks an epithelial lining; thus the fluid it contains is extravasated rather than secreted. There is no single etiology, and this condition may follow renal trauma (urine leakage resulting in scarification) or perirenal fat necrosis (resulting in inflammation), may be associated with neoplasia (e.g., transitional cell carcinoma¹⁸⁶), or may be categorized as idiopathic. Regardless of the initiating cause, anechoic fluid accumulates between the renal capsule and the parenchyma. The sac is often at a pole, but the fluid dissects between the kidney and its capsule or is extracapsular. Fluid cytology reveals a transudate with urea nitrogen close to that of serum. Because the structure does not communicate with renal parenchyma, contrast does not fill it, and on ultrasound it is seen to envelop the kidney rather than exist within it. One report describes a case in which the pseudocyst communicated with the pleural space, resulting in hydrothorax.

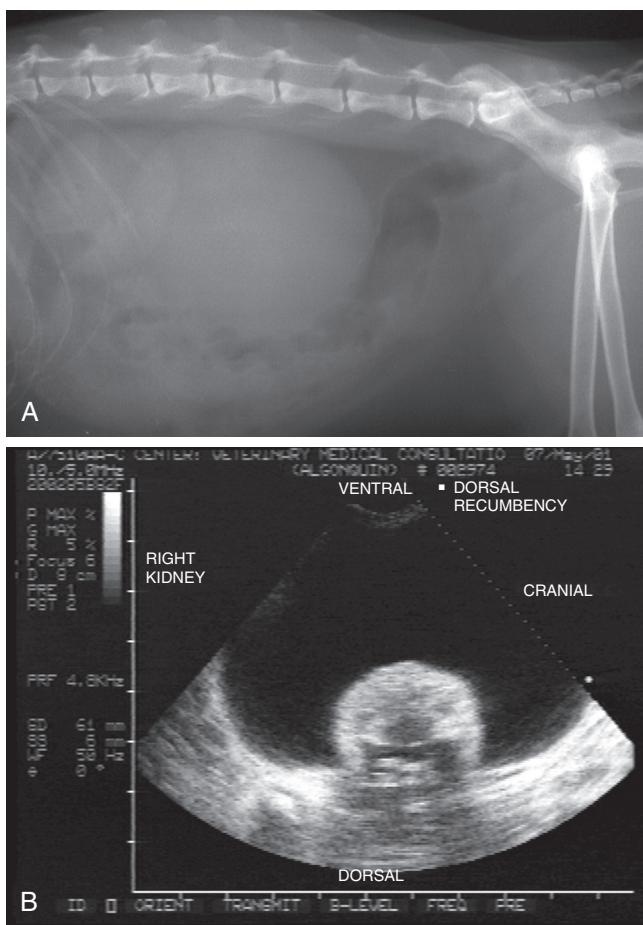


FIGURE 32-6 A, This lateral radiograph shows a soft tissue density in the region of the kidney. B, This ultrasound of the same patient reveals that the mass is a classic perinephric pseudocyst. (Courtesy Dr. Edward Javinsky.)

Unilateral nephrectomy of the affected kidney resulted in resolution of the hydrothorax.¹⁹¹

Affected cats are generally older (older than 8 years of age); there is no sex or breed predisposition.^{21,175} The lesion is initially detected on palpation; renal insufficiency may be diagnosed on the basis of serum biochemistries and urinalysis, either due to associated interstitial fibrosis or the effect of compression. Imaging reveals the nature of the lesion (Figure 32-6).

Surgical resection of cyst walls is recommended, although reduction by drainage may provide temporary relief. There is one report of cyst wall omentalization with good long-term outcome.¹⁰⁸ Another case report describes laparoscopic fenestration of the capsule wall with resulting improvement in GFR of the affected kidney; no relapse was seen.¹⁵⁷ In other cases renal disease progresses, with the outcome being related to the severity of the renal disease.

Acquired Cysts

Cysts may also be acquired as a result of intraluminal obstruction of renal tubules by inflammatory debris or

exudate or because of extraluminal compression associated with interstitial inflammation or fibrosis. Cysts may be unilateral but are more commonly bilateral. Regardless of cause, if cysts enlarge or become more numerous, resulting damage (compression) to parenchyma occurs, function is compromised, and azotemia develops.

RENAL AMYLOIDOSIS

Amyloidosis involves the deposition of insoluble proteins that have a specific pleated conformation. In cats, the condition occurs in the pancreas, where an islet-associated polypeptide form of amyloid is frequently found and is co-secreted with insulin.^{118,152} Another form of localized amyloidosis has been reported in a cat with a plasmacytoma.⁴⁷

Systemic amyloidosis with amyloid deposition primarily in the kidney is seen in Abyssinian cats; however, other breeds may also be affected (e.g., Siamese and other Oriental breeds, in which deposition is primarily in the liver). In the former it appears to be a result of a reactive inflammatory response, as reflected by the presence of amyloid protein AA and identification of concurrent inflammatory lesions in the tissues of approximately half of the examined cats.⁶⁷ Amyloid is deposited in the kidneys between 9 and 24 months of age. Renal insufficiency can progress rapidly, resulting in renal failure within 1 year, or deposits may be so mild that the effect may remain clinically undetected, allowing affected cats to live into old age. The condition affects females to males in a 1.4:1 ratio.³⁵ It is inherited in an autosomal dominant fashion but has a wide spectrum of disease expression because of variable penetrance.

In non-Abyssinian cats, the inflammatory aspect is lacking; a few cases have been associated with hypervitaminosis A.^{55,56} The mean age is 7 years and the male:female ratio favors males 2:1.

Clinical illness reflects renal impairment, with the degree of involvement and location of the amyloid deposits playing a role. If glomeruli are involved, proteinuria will be present, whereas if lesions are restricted to the interstitium, azotemia with decreased urine-concentrating ability will be evoked. Affected cats will be in various degrees of renal insufficiency (uremic ulcers, inappetence, weight loss, dehydration, polyuria, polydipsia, lethargy). Metabolic acidosis, azotemia, hyperphosphatemia, hypokalemia, stress hyperglycemia/glucosuria, nonregenerative anemia, and low USG may all be components.

Definitive diagnosis requires renal biopsy; if the deposits are restricted to the medulla, they will be missed by needle biopsy because the procedure is limited to sampling the cortex (discussed previously).¹⁸⁴ In addition to routine hematoxylin and eosin (H&E) staining, when Congo red is applied to the section and it is viewed

with polarized light, birefringence and an apple-green color specifically represent amyloid. Thioflavine T stain results in a yellow-green stain when visualized with ultraviolet light. Typically, papillary necrosis, chronic tubulointerstitial nephritis characterized by a lymphoplasmacytic infiltrate, and fibrosis with variable degrees of glomerular deposits are present.

In addition to the kidneys, amyloid is found in other organs of affected Abyssinian and non-Abyssinian cats. These may include the tongue, stomach, small and large intestines, liver, pancreas, spleen, heart, and adrenal and thyroid glands.

Treatment goals include supportive care for renal disease, identification and treatment of underlying inflammatory disease if identified, and attempts to mobilize the offending amyloid. Dimethyl sulfoxide (DMSO), by reducing serum amyloid protein A concentrations and through its antiinflammatory effects, could be considered were it tolerated therapeutically by cats. Colchicine is used in dogs and humans with amyloidosis to prevent formation of the amyloid; however, a safe and effective dose has *not* been established in cats.

POLYARTERITIS NODOSA

Polyarteritis nodosa is an extremely rare abnormality in which small and medium arteries undergo segmental inflammation and necrosis. The lesions may be restricted to the kidneys or affect multiple organs. When the kidney is involved, regions supplied by affected vessels become infarcted. There are only a handful of feline cases reported in the literature. Histologic changes were described as fibrinoid necrosis of the tunica media of implicated arteries with concurrent mononuclear cell infiltration. Glomerular lesions are noteworthy. Diagnosis requires biopsy, and therapy centers on supportive care and immunosuppression once cultures prove negative for bacterial infection. Prognosis has been poor in the few documented cases.

FELINE INFECTIOUS PERITONITIS

The dry or noneffusive form of feline infectious peritonitis (FIP) often involves the kidneys, along with other organs (liver, central nervous system [CNS], mesenteric lymph nodes, and eyes). Bilateral, asymmetric renomegaly is common. As might be expected with this disease, vague, nonspecific clinical signs are noted: inappetence, lethargy, muscle wasting, weight loss, and dehydration. Fever may be noted; however, it is also easily missed because of its intermittent nature. Only if, or once, renal involvement is marked, will polyuria and polydipsia become evident. In addition to hyperglobulinemia, a serum albumin:globulin ratio below 0.4; an

inflammatory leukogram; an inappropriate USG of less than 1.040, with or without proteinuria; and cytology of the enlarged kidneys revealing pyogranulomatous inflammation suggest a diagnosis of FIP.¹⁰³ Pyogranulomas (neutrophils, macrophages, lymphocytes, and plasma cells) are generally limited to the renal cortex and may result in lumpy, irregularly enlarged kidneys. Thanks to better diagnostic sensitivity of both biopsy and fine-needle aspirate (FNA) of the liver compared with the kidney, it is advisable to sample both tissues concurrently. Additionally, because false-negative results are not uncommon, use of both Tru-Cut biopsy and FNA together improves diagnostic value.⁸⁸ Lymphoma may manifest in a similar clinical fashion; cytology may be expected to differentiate between the two conditions insofar as cytology will reveal a monomorphic population of lymphocytes in the neoplastic condition. FIP is covered in greater detail in Chapter 33.

RENAL NEOPLASIA

Lymphoma is the most common type of neoplasia affecting feline kidneys; however, primary renal neoplasms that are not hemolymphatic in origin are reported infrequently. Carcinoma and nephroblastoma are less frequent, and mesenchymal tumors (hemangiosarcoma, fibrosarcoma, chondrosarcoma, and leiomyosarcoma) are rare. Metastatic tumors are common in this organ because of the large blood supply.²¹⁶ Evaluation of the records and tissues from four veterinary colleges and one private referral practice over a 6-year period revealed only 19 cases of renal tumors. The majority of these (13 of 19) were renal carcinomas (11 tubular and 2 tubulopapillary), with three transitional cell carcinomas, one malignant nephroblastoma, one hemangiosarcoma, and one adenoma.¹⁰⁶ In addition, the recent literature includes a cat with a renal cystadenoma,¹⁶⁹ one with a transitional cell carcinoma forming a perirenal cyst,¹⁸⁶ and two with renal adenocarcinoma-induced polycythemia.¹²⁶ Lymphoma, in contrast, is very common, with 31% of 118 cats with multicentric lymphoma in one report having renal involvement,⁸⁵ or as high a percentage as 45% according to another source.²¹⁶

Diagnosis of lymphoma is made by FNA or renal biopsy. Cancer staging (I–V) is recommended because treatment planning will be affected. This involves palpation, hematology, serum biochemistry, survey abdominal radiographs or ultrasonography, and bone marrow aspiration (see Chapter 28). The presence of ultrasonographic evidence of hypoechoic subcapsular thickening in feline kidneys is associated with renal lymphosarcoma. In one study the positive predictive value of this finding was 80.9%, and the negative predictive value was 66.7%. This resulted in a sensitivity of 60.7% and a specificity of 84.6%.²¹⁵

Surgical management is generally not recommended for lymphoma. In cats with renal or multicentric lymphoma, chemotherapy is recommended. Numerous induction and maintenance protocols using multiple chemotherapeutic drugs have been described. These agents include vincristine, cyclophosphamide, L-asparaginase, doxorubicin, methotrexate, and prednisolone. One study evaluated the response to chemotherapy in 110 cats with extranodal lymphoma, of which 35 had renal lymphoma. The conclusions of this retrospective study were that cats with extranodal lymphoma respond to chemotherapy and achieve survival times comparable to those with disease in other locations. Corticosteroid pretreatment reduced survival time in cats achieving complete remission.²¹² The prognosis for a cat with renal lymphoma depends on the stage of the tumor, existing renal function, responsiveness to chemotherapy, and retrovirus status.²¹⁶ More information about lymphoma can be found in Chapter 28.

PYELONEPHRITIS

Pyelonephritis refers to bacterial infection of one or both kidneys. Resulting inflammation may be centered in the pelvic region and adjacent medulla, which suggests ascending infection. Alternately, if the route of infection is hematogenous, a more generalized distribution of lesions may be expected (Figure 32-7). The clinical presentation in either case may be vague (lethargy, inappetence, anorexia, and dehydration) or may include more marked but still poorly specific signs of weight loss, vomiting, polyuria, and polydipsia. Fever may remain undetected because of its tendency to wax and wane. Clinical signs may be brief with self-resolution or may persist over time.

Because of the infrequent use of biopsy as a diagnostic tool in feline medicine and the less common prevalence of infection of the urinary tract in cats compared with dogs, it is unclear how often infection by either route (ascending versus hematogenous) occurs. In humans ureteral obstruction by casts or ureteronephroliths contributes to risk of infection; this occurs at least experimentally in cats. Pyelonephritis potentially predisposes to ongoing inflammation and may contribute to chronic interstitial nephritis. However, it is unlikely that this is the originating cause of chronic interstitial nephritis, the most common histopathologic form of chronic renal disease in the majority of cats.

Urine culture and renal imaging are required for definitive diagnosis. Minimum database tests (hematology, biochemistries, urinalysis, and BP assessment) yield results that point to renal infection. Neutrophilia with a left shift may be present in acute disease. A stress leukogram may reflect inflammation and chronicity along with a nonregenerative anemia. Biochemistry findings

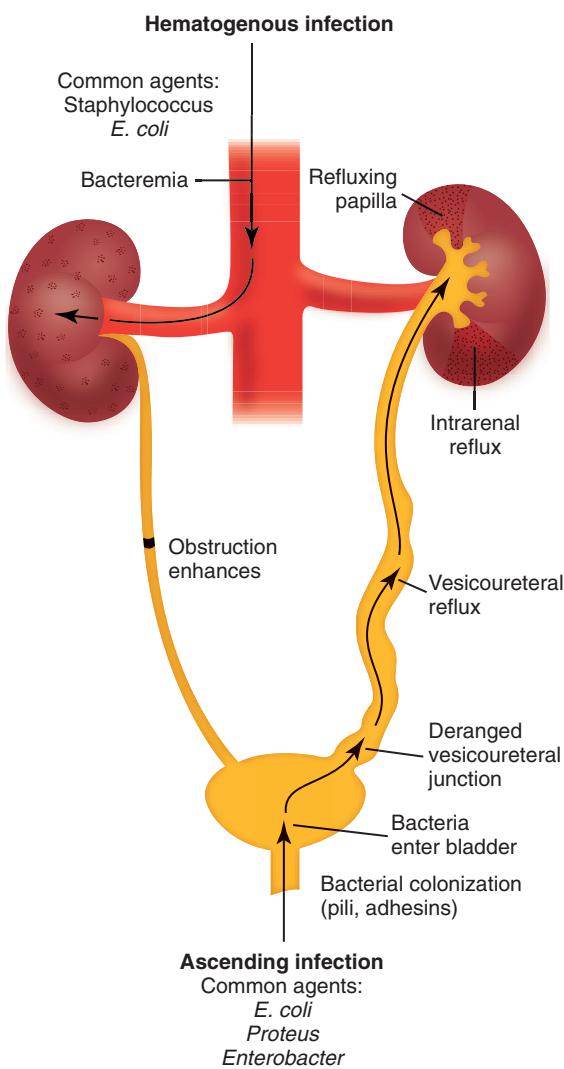


FIGURE 32-7 Infection of the kidney resulting in pyelonephritis may occur by either the hematogenous spread of bacteria or from ascending infection. (Adapted from Cotran RS, Kumar V, Robbins SL: *The kidney*. In Cotran RS, Kumar V, Robbins SL, editors: *Robbins pathologic basis of disease*, ed 5, Philadelphia, 1994, Saunders.)

include azotemia, hyperphosphatemia, and metabolic acidosis. Urinalysis shows proteinuria, bacteriuria with pyuria, and hematuria indicative of infection, but imaging (ultrasound or a contrast radiographic study) is needed to determine what part of the urinary tract is affected. Although it might be expected that concurrent typical signs of stranguria and pollakiuria, with or without perirenia (inappropriate urination), indicate lower urinary tract involvement, a remarkable 29% (38 of 132) of cats with positive urine cultures lacked these clinical signs in one study. There was a significant predisposition to being female among these patients, and *Enterococcus faecalis* was the most commonly isolated bacteria, ahead of *Escherichia coli* phylogenetic group B2.¹⁵¹ Finding leukocyte casts in the urine localizes the disorder to the kidneys; however, because casts are

infrequently reported, a diagnosis of pyelonephritis should not rely on this finding.

Either ultrasound or an excretory urogram may be used to suggest a diagnosis of pyelonephritis. Ultrasound findings suggestive of this condition include a dilated renal pelvis with hyperechoic, edematous mesentery and peritoneal or retroperitoneal effusion reflecting inflammation of these tissues. In contrast, the far more common hydronephrosis may be characterized by a similarly dilated renal pelvis, but with anechoic contents and no findings indicative of peritonitis.⁵³

Older cats with low USG associated with CKD or glucosuria caused by poorly controlled DM are more prone to upper or lower UTI. A study was performed to ascertain whether antibiotic sensitivity profiles can be used to distinguish between relapsing (or persisting) UTIs from reinfection by different clones of uropathogenic *E. coli*. Results showed that they cannot be relied on for this purpose in the cat.⁸⁴

Similar to lower UTI, antimicrobial therapy should be continued for 4 to 5 weeks for an initial episode of pyelonephritis; subsequent occurrences require a 5- to 8-week course of antibiotic therapy, as determined by sensitivity spectrum. Follow-up urine culture after and possibly during therapy is required to document eradication of infection. Culture during therapy may be considered with the intention of verifying that no additional organisms have become apparent as a result of treatment. Given the potential for infection-instigated inflammation favoring chronic renal insufficiency and interstitial nephritis, complete and thorough treatment with documentation of cure is extremely important.

GLOMERULONEPHRITIS

GN occurs as a sequela to one of two instigating pathways for immune-mediated damage of the glomeruli. In the autoimmune form antibodies react with glomerular basement membrane antigen; in the other form soluble circulating immune complexes become entrapped in the glomerular capillary wall. Any infectious, inflammatory, neoplastic, or degenerative processes capable of sustained antigenic stimulation can induce immune-mediated glomerular injury.¹⁷⁴ It is this latter form that is seen in cats. Because the underlying cause for antigen production is so varied and generally not associated directly with the kidney itself, it is important to try to identify and treat the underlying cause. Most cases are deemed to be idiopathic in cats because the cause is not usually apparent.^{93,94} Box 32-5 lists causes of GN in cats.

Cats with GN tend to be young adults (mean age 4 years, range up to 12 years) and male (intact or altered). They present with either classic nephrotic syndrome (subcutaneous edema, ascites, muscle wasting) or variable degrees of clinical signs associated with chronic

BOX 32-5

Causes of Glomerulonephritis in Cats

Idiopathic: most common

Infectious: e.g., feline infectious peritonitis, bacterial, feline leukemia virus, *Mycoplasma gatae*

Inflammatory: e.g., systemic lupus erythematosus?, chronic progressive polyarthritis

Neoplastic: e.g., lymphoma, myeloproliferative disorders

Toxicity: e.g., hydrocarbons?¹⁸⁸, mercury?

Familial: Abyssinians²²²

renal insufficiency. These may include inappetence; anorexia; weight loss; lethargy; polyuria; polydipsia; vomiting; pale mucous membranes; and small, firm kidneys.

Proteinuria is certainly a hallmark finding for glomerular disease. It must, however, be remembered that proteinuria may also be a result of prerenal inflammation or tubular or interstitial disease, as well as originating in the urinary tract distal to the kidney. Thus proteinuria itself is not pathognomonic for GN. In the cat with nephrotic syndrome, proteinuria, hypercholesterolemia, and hypoalbuminemia with mild azotemia may be expected and the USG may remain between 1.030 and 1.050. In the cat with clinical signs of renal insufficiency, the azotemia is more moderate to severe in degree, the USG is lower, and a nonregenerative anemia may be present. The other laboratory findings reflect CKD. In addition to a complete blood count (CBC), serum biochemistries, urinalysis, and BP evaluation, retroviral serology is indicated. If joints are affected, joint fluid analysis should be considered. Antinuclear antibody titer and lupus erythematosus cell preparations may also be considered. Urine or blood culture (or both) may be warranted.

On the basis of light microscopy, immunofluorescence, transmission electron microscopy, and scanning electron microscopy, there are a number of types of GN that have been reported in cats. The following definitions or descriptions are in order:

- Membranous GN has a thickened glomerular basement membrane.
- Proliferative GN (mesangioproliferative GN) is characterized by glomerular hypercellularity with accumulation of mesangial matrix.
- Membranoproliferative GN has a thickened glomerular basement membrane but also is hypercellular.
- Glomerulosclerosis is characterized by both an increase in mesangial matrix and glomerular scarring.

- “Minimal change disease” is characterized by minimal increases in mesangial cell proliferation, abnormal podocyte foot processes, and a lack of immunoglobulin deposition when stained with immunofluorescent preparations.

Eleven cases of membranous nephropathy,²²⁵ two types of membranoproliferative,^{15,113} nonamyloidotic fibrillary glomerulonephritis,⁴⁹ and glomerular fibrosis (“collagenfibrotic glomerulonephropathy”)¹⁷⁰ have been reported in cats. The GN of six related Abyssinians was not characterized beyond light microscopic evaluation.²²² Experimentally, immune-complex proliferative GN (more similar to the disease in humans than other feline forms) has been induced using intravenous injections of cationic bovine or human serum albumin.^{28,29,30,171} In this model cats develop hypoalbuminemia before signs of clinical disease occur. However, the appearance of proteinuria may be misleading insofar as it occurred in some of the control cats without GN as well.²⁹ In a study evaluating histopathology of renal biopsies with clinical data in dogs and cats, higher Cr values were suggestive of (and correlated with) changes of interstitial nephritis. High urinary protein values correlated with glomerular disease. Although no relationship between different types of nephropathy and age were found, in general, cats (and dogs) with chronic tubulointerstitial nephritis were, on average, older than animals with glomerulopathies.¹⁶⁴

In another study of naturally occurring renal disease in dogs and cats, myofibroblast induction was studied. Immunohistochemical expression of myofibroblast markers, alpha-smooth muscle actin (alpha-SMA) and vimentin were evaluated quantitatively. In cats, Cr concentrations correlated with fibrosis, alpha-SMA expression correlated with Cr and fibrosis, tubular vimentin expression correlated with fibrosis, and interstitial vimentin expression correlated with Cr.²²⁷ The relevance is that the correlations found in dogs were different, indicating that the severity of CKD is mediated by different pathways associated with myofibroblast expression in dogs compared with cats.

In a patient with persistent proteinuria of renal origin, a biopsy of the kidney is indicated. Indeed, it is necessary for the accurate diagnosis of GN and may help guide therapy. Indications for renal biopsy are summarized in Box 32-6. When performed correctly (i.e., in a carefully monitored, sedated, or anesthetized cat with no history of a bleeding disorder, using ultrasound guidance and a Tru-Cut biopsy needle or by a surgical keyhole approach, harvesting only cortex [pole to pole] and monitoring for postprocedural bleeding), there is minimal risk even in the face of renal dysfunction. The sample must be handled carefully and submitted in the correct medium to a laboratory able to perform not just light microscopy (standard histopathology and immunofluo-

BOX 32-6

Indications for Renal Biopsy

Acute nephritis: Yes, if injury is recent, active, and ongoing

Acute nephrosis: Maybe; it may help assess severity and reversibility, but it will not direct therapy

Glomerulopathy: Yes, can establish diagnosis and aid in directing therapy

Renal proteinuria: Yes, if higher UPC and lower creatinine; maybe if borderline but not responding to therapy

Chronic kidney disease, IRIS late stage 3 or stage 4: No, generally will not provide clinically useful information

UPC, Urine protein: creatinine ratio.

Adapted from Lees GE, Berridge BR: Renal biopsy—when & why. NAVC Clinician's Brief 7:26, 2009.

BOX 32-7

Centers that Perform Comprehensive Renal Biopsy Evaluations*

Texas A&M University—Texas Veterinary Renal Pathology Service

- Dr. George E. Lees: glees@cvm.tamu.edu; telephone 1-888-778-5523 (toll free) or 1-979-845-2351

Utrecht University—Dept. of Clinical Sciences of Companion Animals, Yalelaan 108, NL 3584 CM Utrecht; mailing address: P.O. Box 80.154, NL 3508 TD Utrecht

- Dr. Astrid M. van Dongen: A.M.vanDongen@uu.nl; telephone +31 (0)30 2537767, fax +31 (0)30 2518126

*At the time of this writing.

rescent staining) but also EM for ultrastructural examination (Box 32-7).

The centers that perform full assessment of renal biopsies provide kits containing detailed instructions along with the materials necessary to collect, properly preserve, and submit the samples to their laboratories. The veterinarian should speak with the person who will be evaluating the tissue sample to obtain complete instructions and ensure that he or she feels comfortable with the technique before proceeding.

Renal biopsy samples should be processed in several ways^{146,147}:

- Using light microscopy, samples are stained with H&E, periodic acid-Schiff (PAS), Masson's

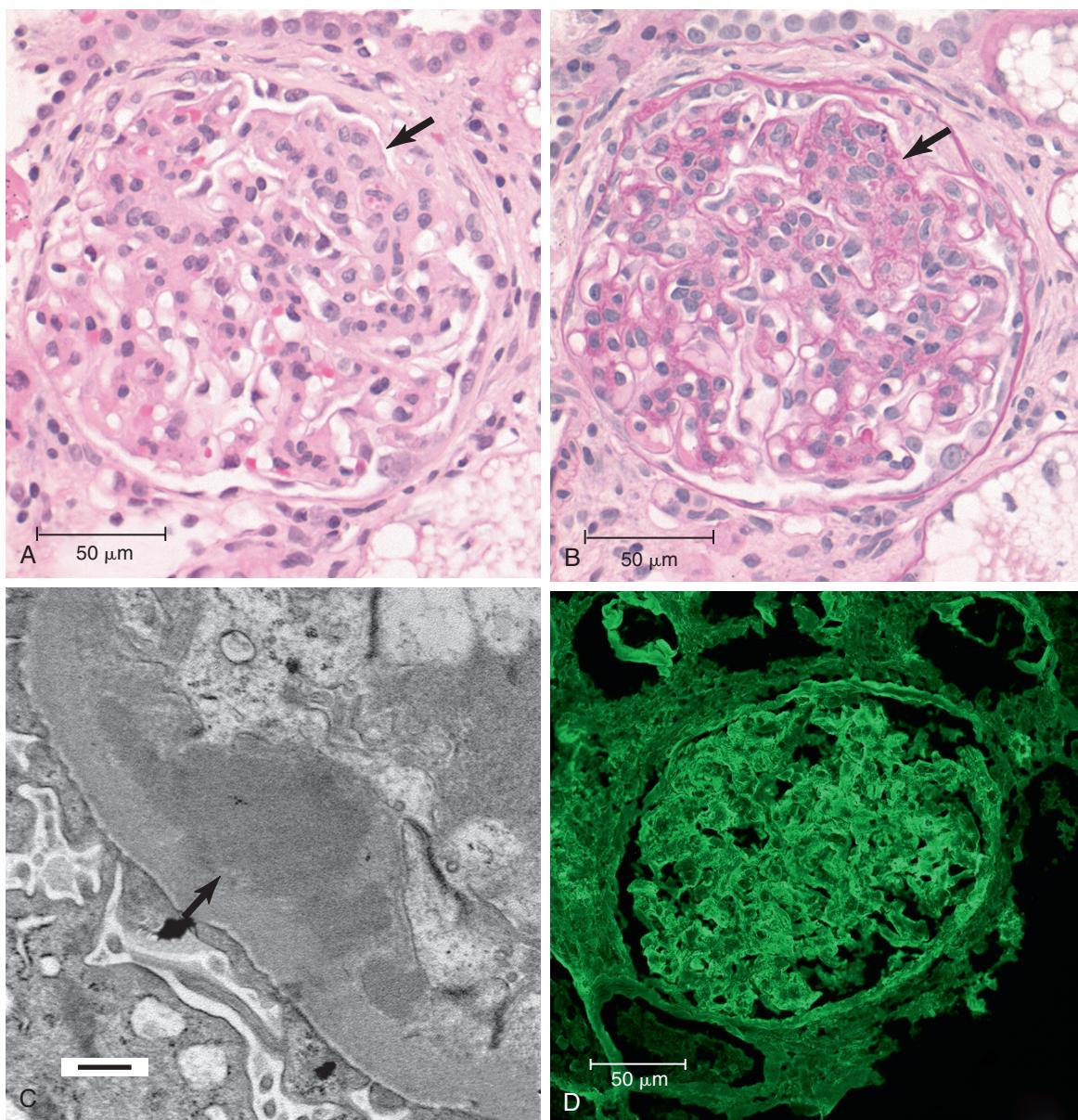


FIGURE 32-8 Pathologic findings in a renal biopsy obtained from a 5-year-old neutered male domestic shorthair cat with glomerular disease. **A** (H&E stain) and **B** (PAS stain), Photomicrographs of a glomerulus that exhibits histologic changes consistent with membranoproliferative glomerulonephritis. The capillary lumens are effaced by mesangial and endocapillary hypercellularity in the marked glomerular lobule (arrows). **C**, Transmission electron photomicrograph of subendothelial electron-dense deposits (arrows) in a glomerular capillary wall (bar = 500 nm). **D**, Immunofluorescence photomicrograph of a glomerulus labeled for immunoglobulin G. (**A**, **B**, and **D** courtesy Dr. George E. Lees, Texas A&M University; **C** courtesy Dr. Fred J. Clubb, Jr., Texas A&M University.)

- trichrome, Jones' methenamine silver (JMS), and Congo red to fully characterize lesions.
2. Immunohistochemical stains are applied to evaluate sections with immunofluorescence.
 3. Lastly, transmission electron microscopy is performed on glutaraldehyde-preserved samples to examine ultrastructural detail.

Figure 32-8 shows renal biopsy samples from a patient with glomerular disease.

Renal biopsies can be performed in two ways¹⁴⁵:

1. Using an automated needle biopsy device and ultrasound guidance
2. By a surgical approach: keyhole needle or wedge biopsies or using laparotomy

All techniques require that the patient be anesthetized rather than sedated for comfort and immobilization. Ultrasound-guided needle biopsy is appropriate when the expected lesions are diffusely distributed in the cortex (e.g., ARF, GN). When the clinician is experienced, this approach is less traumatic for the patient than the surgical

options and can yield adequate to excellent samples. Extensive practice in aspiration and biopsy of other organs is recommended before attempting this procedure because there is little room for error. An automated device, such as a Tru-Cut or similar biopsy needle, is used. The needle throw should be short (e.g., 11 mm, 7 mm specimen notch); an 18G diameter needle is appropriate for cats of most sizes. Patient positioning will depend to some degree on the preference of the ultrasonographer or radiologist. The goal is to present as much of the cortex as possible while minimizing inadvertent damage of hilar blood vessels that could result in bleeding and subsequent infarction or outright fatal hemorrhage. Assuming that both kidneys are affected, the advantage of sampling the right kidney is that it is less mobile than the left. The left kidney, on the other hand, is more superficial and more caudally placed than the right.

The veterinarian should position the cat for an optimal view of the cortex: Ventrodorsal recumbency reveals the lateral cortex, and lateral recumbency exposes the dorsal cortex. Both these positions place the hilus in a less vulnerable, more distal location. An ultrasound guide may be used to position the needle biopsy device alongside the probe once the optimal view is achieved; alternately, the probe and the needle device can be used independently (freehand) of each other. The latter requires excellent hand–eye coordination. Once the direction of the needle placement has been selected, the veterinarian makes a small stab incision with a scalpel blade through the skin and then advances the biopsy needle through the body wall up to and just through the capsule before activating the biopsy device (see *Figure 32-3*).

Next, the veterinarian harvests a minimum of two cortical core samples. Ideal samples are 10 mm in length or longer. If they are shorter than this, a third tissue core should be collected. The veterinarian should use a gentle flow of sterile saline through a 25G needle to flush the tissue from the biopsy needle onto a glass slide to keep the biopsy needle sterile for the next sample and keep from traumatizing the sample. The veterinarian flushes the biopsy needle with more saline and greater force (away from the sample) to dislodge any debris remaining in the cutting channel. This is repeated until two or three good cores have been collected. It is important to check that the samples contain glomeruli using the 10 \times to 40 \times lens on a microscope, a handheld magnifying lens, or an ocular loupe.

Should a surgical approach be preferred over ultrasound guidance, a keyhole incision may be made over the kidney or a celiotomy or laparotomy may be performed. Because it is very easy to penetrate too deeply without the benefit of ultrasound to visualize the difference between the cortical and medullary echos, a wedge biopsy is preferable to using the automated needle biopsy device. The sample is taken by incising the cortex with a small elliptical incision, and the sample is excised

by cutting it off with a flat bottom before the medulla is penetrated. The wedge can then be subdivided into samples, as recommended by the appropriate staff member at the renal pathology center.

It is important to keep the tissue cores moist on saline-soaked swabs. They should never be handled with toothed forceps. They should be placed in the appropriate preservative and fixatives promptly according to the directions provided by the renal pathology service.

On the basis of ultrastructural studies, as well as the type and distribution pattern of the immunoglobulins or complement, clues to the pathogenesis of GN in the individual patient may be determined, thereby allowing a rational and specific treatment plan to be made. Additionally, the clinical problems should be addressed. For the nephrotic, edematous, or ascitic patient with minimal or no azotemia, diuretic therapy is indicated. The patient should be closely monitored to ensure adequate but not excessive diuresis because dehydration and hypovolemia are detrimental to tissue perfusion, including that of the kidneys. An ACE-I is of value in reducing glomerular loss of protein by reducing glomerular pressure and GFR. GFR reduction (and the potential for increased azotemia) is mild and will stabilize. The urine protein:creatinine ratio (UPC) should be monitored for improvement; in patients in which no reduction of proteinuria is noted, the ACE-I should be discontinued. Corticosteroids may be considered to reduce the inflammatory response and production of antibodies for antigen-antibody complexes. Increasing dietary protein by using a growth diet or adding hard-boiled eggs or cooked egg white to the cat's food may be beneficial by countering the hypoalbuminemia caused by the glomerular protein loss. Sodium restriction should be considered if sodium retention is apparent.

For those GN patients with moderate to severe azotemia, corticosteroids and furosemide are not recommended. Instead, treatment is as for the cat with interstitial nephritis (CKD) but with additional dietary protein to offset their urinary losses. In both clinical presentations hypertension should be addressed (discussed later). If urine culture has revealed bacterial involvement, a prolonged course (minimally 5 to 8 weeks) of the appropriate antimicrobial is indicated, with reculture after discontinuation of the antibiotic.

The prognosis is extremely variable and depends on the instigating cause of the immune mechanism. If it is bacterial in origin and the infection is successfully eliminated, cure may occur. If the underlying disease is FIP, the course will be short and the prognosis grim. With nephrotic syndrome or less severe azotemia, good control may be achieved for several years. If azotemia is advanced and multiple components of renal disease are present, such as hyperphosphatemia, hypertension, nonregenerative anemia, and muscle wasting, the prognosis is poor.

URETERONEPHROLITHIASIS

Renal calculi are a significant cause of CKD and hydronephrosis, although urolithiasis occurs less frequently in the cat than the dog. Concomitant UTI is also much less common with feline struvite urolithiasis than it is in dogs.

The first of the two largest retrospective studies of feline and canine ureteronephroliths was published in 1998 (71 cats with *renal* calculi from 1981 to 1993) and reported that 38 of the renal calculi were from female cats and 33 were from male cats. Pedigreed cats were predisposed to renal calculus formation compared with random bred cats. Increased age was identified as a predisposing factor. Somewhat surprisingly, more than 50% of renal calculi were identified in the first known episode of urolithiasis, justifying radiography as part of the minimum database in affected patients (Figures 32-2 and 32-9). Additionally, the risk of forming renal calculi was found to be higher in cats than in dogs compared with other sites of stone formation (approximately 4.95 per 100 stone-forming cats versus 2.88 per 100 dogs). Unilateral disease favors the left kidney; approximately 9% of cats with renal stones had bilateral involvement. Stone composition analysis in this study showed oxalate and apatite as the main contenders, and there was no sex predisposition for stone composition or for concurrent/causative bacterial infection.¹⁵⁰ Struvite stones are more commonly induced by diet in cats; however infection-based stones may occasionally occur as well in cats with conditions predisposing to UTI (e.g., DM, perineal urethrostomy).

The second large study,¹³¹ reported in 2005, reviewed the records of 163 cats with *ureteral* calculi evaluated from 1984 to 2002. Of note was that the number of cats in which ureterolithiasis was diagnosed each year increased progressively during the study period, notably

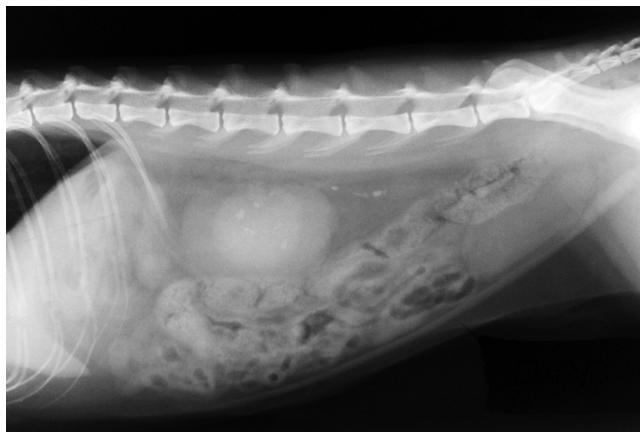


FIGURE 32-9 This lateral radiograph shows numerous radioopacities in the region of the kidney and ureter. A ventrodorsal view or an abdominal ultrasound is required to localize these lesions to the kidney and ureter; however, this is suggestive of urolithiasis.

after the year 2000. The median age of affected cats was 7 years, with a range of 8 months to 16 years. Clinical signs recorded included inappetence and anorexia in 45% of cats, vomiting in 42%, lethargy in 31%, weight loss in 27%, polyuria and polydipsia in only 18%, and the remaining signs (stranguria and pollakiuria, hematuria, pain on abdominal palpation, inappropriate urination, ptalism, urethral obstruction, and obtundation) in fewer than 9%. On laboratory evaluation a surprising 48% of 150 cats tested were anemic. Either renal or pre-renal azotemia (elevation of either BUN or Cr) was found in 83% of the total cats tested (76% of those with unilateral and 96% with bilateral calculi), 54% had hyperphosphatemia (43% if unilateral), 35% were hyperkalemic, and 14% were hypercalcemic. This implies that the function of the contralateral kidney was impaired, the cats were dehydrated, or both. UTI was found in 8% of the cats; crystalluria was reported in 36 of 124 (29%) urine samples.

The sensitivity of ultrasound in identifying ureteral calculi was 77%. Radiography on its own identified 81% of ureteroliths. When ultrasound and radiography were combined, the detection sensitivity rose to 90%. Based on the finding of a dilated renal pelvis or proximal ureter, ureteral obstruction was identified in 143 (92%) of 155 cats that underwent abdominal ultrasound. Interestingly, 73 of the cats had surgical or necropsy confirmation of the diagnosis, yet a combination of radiography and ultrasound revealed only 66 (90%) of those cases. Therefore it seems prudent to pursue both imaging modalities when investigating the possibility of ureteral calculi. In fact, in seven cats the calculi were an incidental finding during ultrasound of the abdomen for another problem. Of additional note is that in this ureterolith population, 101 cats had concurrent renal calculi (62%) and 14 had cystic calculi (<1%). Other imaging modalities that may be considered (and were used in some of these patients) are intravenous urography, antegrade pyelography, nuclear scintigraphy, and CT.¹³²

Clinical signs of renal or ureteral stones may be vague to nonexistent. Cats may present with apparently painless hematuria or with ill thrift associated with infection or azotemia. Excessive grooming over the dorsolumbar region or abdomen has been noted by the author in a few cases. Thus, because clinical signs are so variable and ureteronephroliths are so common, screening radiographs can be justified as part of the workup of an older cat with or without renal insufficiency. In a patient with clinical illness, abdominal ultrasound as well as radiography may well be justified.

Ureteral stones were analyzed in 93 cats in the second study; calcium oxalate (CaOx) was identified in 81 cats, mixed CaOx and calcium phosphate (CaPO₄) in seven cats, CaPO₄ in two cats, and mixed CaOx and urate in two cats, the last being mixed CaOx and amorphous calcium.¹³¹ One paper from Norway reports an oxalate-like

nephrosis in Ragdoll cats.¹⁰⁵ The diagnosis of primary hyperoxaluria types 1 and 2 was excluded in 11 cats tested; both etiology and inheritance remain unknown.

Therapy may initially include IV fluids and diuretics (the goals being to increase urine production and voiding and supportive care for underlying renal insufficiency), but some cats will need additional surgical assistance. Because bilateral chronic interstitial fibrosis is common in cats with ureteroliths or nephroliths, nephrectomy should not be considered unless it has been established that the contralateral kidney has adequate function to support the patient. Renal transplantation may be a feasible option.

In a study of 153 cats with ureteral calculi,¹³² management and outcome were evaluated. After medical therapy for all cats, 66% of the patients received additional treatments. Nephrostomy tubes were placed in a few of these cats to improve urine drainage, and a few patients received hemodialysis. Possible surgical solutions depended on the location of the ureteronephrolith. For proximal ureteral stones, ureterotomy was used; for more distal stones partial ureterectomy and ureteroneocystostomy were the treatment of choice. Postoperative complication rates were 31% in those patients proceeding to surgery (e.g., urine leakage resulting in uroabdomen, persistent ureteral obstruction). The postoperative mortality rate was 18%. Yet the 24-month survival rate of those that received only medical treatment was 66%, and when cats were euthanized, it occurred within 1 month of diagnosis. In the surgical (after medical stabilization) group, 12- and 24-month survival rates were 91% and 88%, respectively.¹³²

Any stones removed surgically or passed during medical treatment should be submitted for quantitative analysis to allow institution of appropriate preventive therapy, when it exists. Similarly, if bacterial infection is identified, antimicrobial therapy based on sensitivity profiles and overall health should be followed for a minimum of 5 to 8 weeks. Subsequent medical care should focus on achieving a moderate urine pH of 6 to 6.5 and USG of approximately 1.035 (should the cat have a higher USG) to reduce the likelihood of recurrence of stones. Recurrence was found in 14 of 35 cats (40%) that were monitored serially with abdominal radiography after medical or surgical therapy.¹³²

A very small case-control study attempted to evaluate whether the presence of nephroliths negatively affected progression of renal disease in cats with IRIS stage II or III disease. It was found that in the 14 cats (7 with nephroliths) there was neither an increase in the rate of progression nor increased mortality from renal disease.¹⁹⁴

Lithotripsy has been evaluated in cats. Compared to canine CaOx stones, feline CaOx uroliths are less susceptible to fragmentation by shock wave lithotripsy. Studies have concluded that the high numbers of shock waves required for adequate fragmentation of the CaOx

nephroliths may cause renal or ureteral injury in some cats.^{3,90} Ureteroliths are often not fixed in location and are capable of spontaneous retrograde movement. In contrast, laser lithotripsy may be more suitable for fragmentation of bladder uroliths—in essence, any urolith that can be accessed using a flexible or rigid cystoscope. A few caveats apply, however. Even when the stones are broken into sandlike fragments, ureteral or possibly urethral obstruction may still occur. Given the anatomic challenges of the narrower male urethra, this technique should be considered in female cats only.

HYDRONEPHROSIS

Hydronephrosis is defined as the distention of the renal pelvis and calices with urine as a result of obstruction of the urinary outflow tract. Obstruction can occur at various places in the urinary tract (Figure 32-10). It usually occurs as a result of ureterolithiasis or urethral obstruction; however, neoplasia, pregnancy, infection, and strictures may also be causes of this condition. Rarely, hydronephrosis may be congenital because of a deformity of, or affecting, the ureter. The condition has been seen in cats of any age and all breeds; a literature search does not reveal a sex predilection.

Depending on the cause, as well as the speed, of treatment, hydronephrosis may be reversible. The condition may be unilateral or bilateral. When it is unilateral, the relative size difference between the affected enlarged kidney and the unaffected normal or fibrosed contralateral organ can be very marked. The patient with unilateral disease may be expected to have a much more gradual onset of illness because the unaffected kidney compensates for the decreased function of its partner. Less commonly, both kidneys are distended concurrently, and these patients will present more acutely in crisis before extensive destruction and remodeling have occurred. If obstruction becomes complicated by infection, pyonephrosis may develop, resulting in lethargy, anorexia, fever, leukocytosis, bacteriuria, and pyuria.

In the case of unilateral hydronephrosis, diagnosis is suggested on finding unilateral renomegaly and verified through imaging. Intravenous urography will show a decreased uptake of contrast material by the kidney, which often has become merely a thin rim of cortical tissue. Ultrasound shows a dilated renal pelvis filled with anechoic fluid and a loss of renal parenchyma.⁵³ Depending on the structural cause, the obstruction may or may not be seen with either form of imaging. Because the fluid is urine, the cytology of a sample will reflect the character of the urine in that patient; it may be unremarkable or may contain renal tubular cells, red blood cells, or white blood cells. Over time it becomes more quiescent. Serum biochemistries and urinalysis results will reflect the patient's disease status (e.g., unilateral,

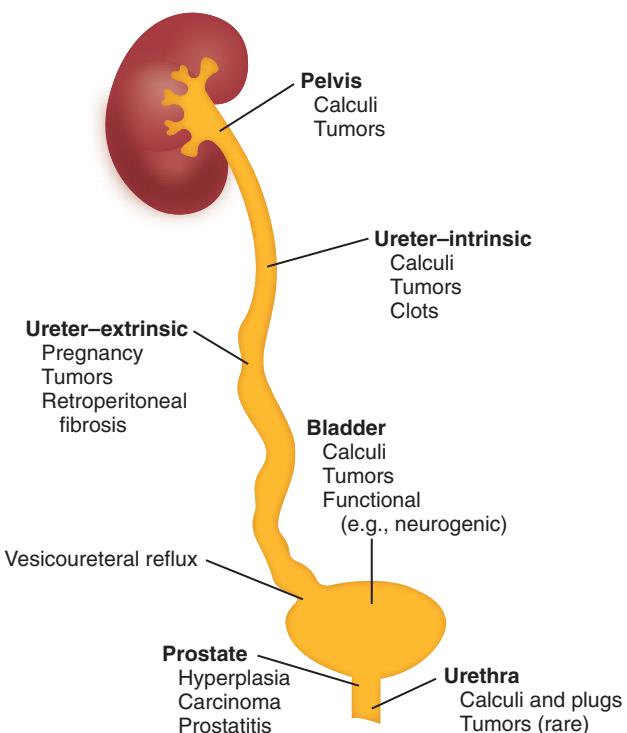


FIGURE 32-10 Although urethral obstruction is frequently recognized, obstruction to the urinary tract may occur at other locations. Calculi are underrecognized. (Adapted from Cotran RS, Kumar V, Robbins SL: *The kidney*. In Cotran RS, Kumar V, Robbins SL, editors: *Robbins pathologic basis of disease*, ed 5, Philadelphia, 1994, Saunders.)

bilateral, duration, concurrent infection). Histopathology of the affected kidney shows a cystic structure with remnants of renal parenchyma, insofar as the kidney is, in essence, an innocent bystander to obstruction.

Treatment, including dialysis and supportive fluid therapy, is aimed at relief of obstruction and optimal restoration of renal function. The longer the obstruction, the poorer the chance of return to function. In some cases renal transplantation may be warranted.

ACUTE RENAL FAILURE

ARF may be a result of ischemia, infectious agents, or toxicity. What appears to be ARF may in fact be an acute decompensation of chronic renal disease. In this case one would expect a long-standing history of polyuria, polydipsia, and weight loss and a finding of anemia, whereas in the case of “true” ARF, exposure to a nephrotoxin or to a potential cause of ischemia (trauma, surgery, and thromboembolism) may precede the onset of acute disease in a previously unaffected individual. Recovery from ARF (but not from CKD) is potentially possible, depending on the type and degree of pathology induced, its location, and the rapidity with which adequate treatment is initiated. The lesions in ARF may be glomerular or tubular.

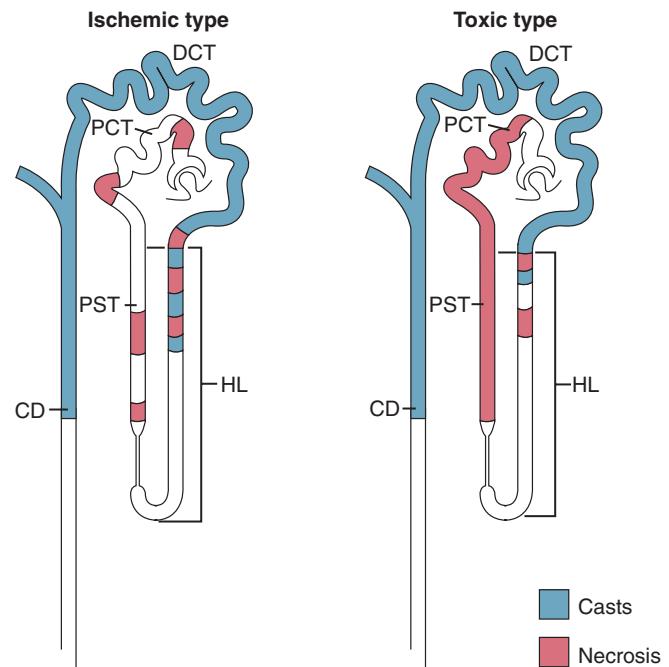


FIGURE 32-11 Acute tubular necrosis (ATN) is the most common cause of acute renal failure. This drawing depicts the two mechanisms by which ATN occurs. With ischemic damage tubular necrosis is patchy, affecting short segments of the proximal straight tubule (PST) and the loop of Henle (HL). When the insult is toxic, the damage is extensive along both the PST and proximal convoluted tubule (PCT), with some damage to the HL as well. Both forms of tubular necrosis result in accumulation of debris in the distal convoluted tubule (DCT) and the collecting duct (CD), resulting in urine casts. (From Cotran RS, Kumar V, Robbins SL: *The kidney*. In Cotran RS, Kumar V, Robbins SL, editors: *Robbins pathologic basis of disease*, ed 5, Philadelphia, 1994, Saunders.)

In general, ischemic damage results in focal tubular necrosis at multiple points in the nephron with unaffected regions in between. Where affected, the basement membrane may be ruptured and the tubules may be occluded by casts. Epithelial regeneration occurs such that, if treated promptly, over time no residual evidence of damage remains.⁵⁹ Toxic insults, on the other hand, tend to predominantly affect the proximal tubules with extensive necrosis, but because the basement membrane often remains intact, tubular regeneration may build on this scaffold.⁶⁴ In the case of ethylene glycol poisoning, in addition to casts, CaOx crystals may plug the lumen (Figure 32-11).⁵⁹

From a therapeutic perspective, it is helpful to think of ARF in three phases:

1. The latent phase describes the period between exposure to insult and onset of renal dysfunction.
2. During the second (maintenance) phase, azotemia and reduction in urine production progress.
3. The final possible phase is that of recovery of as much function as is possible owing to innate mechanisms as well as therapy.

Prerenal ARF is a result of hypovolemia, hypotension, inadequate cardiac output, shock, or hypoxia. Reduced renal perfusion results in local ischemia, which, if sufficiently severe and long in duration, results in renal failure. Hypotension occurring during anesthesia is a common prerenal cause of ARF and may be preventable through careful monitoring. Likewise, hypovolemia can be easily addressed at any time. Hypothermia, another anesthetic risk, should also be avoided and, if noted, treated.

ARF originating from causes directed at the kidney includes ischemia and nephrotoxins. These toxins will be discussed to a limited degree later; the reader should refer to Chapter 31 for more detailed information.

Postrenal causes for ARF may be related to obstruction of urine outflow. Examples of luminal obstruction include plugs, calculi, and sludge in the urethra; however, external compression of the urethra by a mass (e.g., in the prostate, colon, lymph node) or urethral wall thickening from scarring or neoplasia will have the same end effect. Renal failure may occur within 48 to 72 hours of complete obstruction. If the obstruction has been relieved promptly and the cat is supported with fluid therapy, ARF associated with this cause is generally reversible. Uroperitoneum is another potential cause for postrenal ARF.

Although cats may react serologically to *Leptospira* species, they seem remarkably resistant to clinical disease. Cats may become infected and develop bacteremia after 5 to 10 days. The infection localizes in the kidney tubules, where it may cause impairment of renal function, but the clinical significance in this species is questionable. Experimentally infected cats are not usually clinically affected but may have mild to severe nephritis on histology, resulting in gradual chronic renal insufficiency over 1 to 3 years.

There are numerous toxic causes for ARF, however. These may be divided into plant, drug, or chemical toxicities. Cats may be especially predisposed to exposure to topical toxins because of their fastidious grooming behavior; if a toxic material is found on the hair coat or feet, it will be ingested.²⁰⁷

Lilies of many types can cause acute nephrotoxicosis. Easter lilies are not only nephrotoxic but also pancreatic.¹⁹⁷ The dose and species of plant ingested, the part of the plant eaten, and the stage of its life cycle may play a role, as may the efficiency of the cat's gastrointestinal absorption, the preexistence of renal disease (or lack thereof), and the cat's overall health. Not all lilies are toxic and not all plants called lilies are, in fact, lilies. Table 32-4 lists lilies known to be nephrotoxic to cats.⁹

Clinical signs of lily intoxication include peracute gastrointestinal signs (vomiting, ptyalism), neurologic signs (ataxia, tremors, depression, head pressing, and seizures), and ARF. Swelling of face and paws has been reported.²³ The gastrointestinal and neurologic signs

TABLE 32-4 Nephrotoxic Lilies

| Common Name | Latin Name |
|--|----------------------------------|
| Asiatic Lily (Asian lily) | <i>Lilium asiatica</i> |
| Day Lilies (many varieties) | <i>Hemerocallis</i> spp. |
| Easter Lily | <i>Lilium longiflorum</i> |
| Gloriosa Lily (Glory Lily, Climbing Lily, Superb Lily) | <i>Gloriosa superba</i> |
| Japanese Show Lily | <i>Lilium speciosum</i> |
| Red Lily | <i>Lilium umbellatum</i> |
| Rubrum Lily | <i>Lilium speciosum</i> cultivar |
| Stargazer Lily | <i>Lilium orientalis</i> |
| Tiger Lily | <i>Lilium tigrinum</i> |
| Wood Lily | <i>Lilium umbellatum</i> |

Source: American Society for the Prevention of Cruelty to Animals: *Toxic and non-toxic plants* (website): <http://www.aspca.org/pet-care/poison-control/plants/>. Accessed July 23, 2010.

occur within hours of ingestion, but the renal failure develops within 3 to 5 days. Oliguria, anuria, renomegaly, and even renal pain may occur. Azotemia is severe. Urinalysis reveals tubular damage (i.e., casts, glucosuria, and proteinuria). Changes wrought by the as yet unidentified toxic principal consist of acute tubular necrosis with development of polarized crystals in the collecting tubules. Additionally, in the case of the Easter lily, degeneration of pancreatic acinar cells also occurs.

Therapy involves gastrointestinal decontamination, fluid diuresis +/- dialysis. Cats treated within 6 hours of ingestion may be spared from developing ARF; those not treated until after 18 hours are expected to develop ARF. Cats developing anuria or oliguria have a poorer prognosis^{136,224} but may still recover.²³ Cats that survive ARF may have residual damage resulting in chronic renal insufficiency.^{136,207}

In a retrospective evaluation of 32 cases of ARF seen at one institution, the authors reported that the causes included nephrotoxins in 18 cats (56%) (nine from lilies; four from nonsteroidal antiinflammatory drugs [NSAIDs]; two from ethylene glycol; and one each from tulips, tar, and plant food), ischemia in four cats, and 10 cases from other causes. There were 18 oliguric cats. Prognostically, initial BUN and Cr levels were *not* predictive; however, low serum albumin or bicarbonate was negatively correlated to survival. Most significantly, potassium level increases on presentation equated with decreased chance of survival regardless of cause; for every 1 mEq/L increase, chance of survival decreased by 57%. All the nonoliguric cats survived, and all cats that died were oliguric or anuric. There were 17 (53%) cats that survived; azotemia resolved in eight cats, and the other nine were discharged with persistent azotemia.²²⁴

Raisins and grapes have recently been recognized as being nephrotoxic in dogs and cats. The literature includes reports in dogs; cases in cats are reported only anecdotally. The toxic principal is unknown, and the lowest dose known to be toxic in dogs is 0.7 oz/2.2 lb (19.8 g/kg) body weight for grapes and 0.11 oz/2.2 lb (3 g/kg) for raisins. Initial signs are gastrointestinal (vomiting, diarrhea, anorexia, abdominal pain) and lethargy. ARF may develop as soon as 24 hours after ingestion. As with lilies, oliguria and anuria are associated with a poor prognosis. Histopathologic changes in dogs with grape- and raisin-induced ARF include an intact basement membrane; thus with aggressive therapy (diuresis, dialysis), some affected individuals will recover.

Aminoglycoside antibiotics are well known to have a dose- and frequency-dependent potential to be both nephrotoxic and ototoxic in cats. The renal insult occurs in the proximal tubules. Gentamicin has been toxic when administered by the topical,¹⁶⁰ intravenous,¹¹⁷ and intramuscular routes.¹⁰² Orally administered paromomycin, used in the treatment of enteritis from trichomoniasis or cryptosporidiosis, has also resulted in ARF.⁹²

With the growing awareness of pain and increased concern about analgesia in cats, NSAIDs have a significant role to play. A great deal of concern exists regarding the renal safety of NSAIDs both for acute, short-term use as well as longer periods in the patient with an ongoing problem, such as degenerative joint disease. It is certainly possible to cause ARF in the young, renally competent cat when an accidental overdose is administered. However, it is in the older cat, more likely to require long-term analgesia, that the concern regarding preexisting renal disease and the effect of NSAIDs becomes most pertinent. Selective cyclooxygenase (COX)-2 inhibitors spare housekeeping prostaglandins required for renal health. In excessive doses, even this subtype of NSAID may result in COX-1 inhibition and renal damage. Thus dose and frequency, as well as type of NSAID used, play a role in toxicity. Volume depletion or dehydration precipitates renal failure by reducing renal perfusion. Similarly, hypotension, most commonly associated with anesthesia, has adverse effects by itself. In combination with an inappropriate type, dose, or frequency of NSAID, ARF may arise. Nevertheless, there are numerous studies in older cats showing safe use, particularly of meloxicam, over long periods. An extensive review of the subject may be found in the ISFM and AAFP Consensus Guidelines for Long-Term Use of NSAIDs in Cats.²⁰⁴

Vitamin D (as cholecalciferol, vitamin D₃) is well known in rodenticide preparations. Cats can also ingest it by grooming the hair coat or feet if they are exposed to vitamin D-containing human medications (for parathyroid or hypophosphatemic disorders, osteomalacia or osteoporosis, renal failure, and psoriasis) or by eating a diet with excessive levels of vitamin D. In 2006 a

prescription diet manufacturer caused an inadvertent overdose in vitamin D₃ levels in specific feline (and canine) products because of an error originating with the vitamin-mineral premix supplier. In addition to managing the tubular necrosis-based ARF, hypercalcemia must be addressed. Corticosteroids, saline diuresis, furosemide, bisphosphonates, and calcitonin are possible therapies to attempt to keep the calcium × phosphorus product below 60 mg/dL (4.85 mmol/L) in order to prevent soft tissue mineralization.

In 2004 and 2007 there were two outbreaks of ARF in dogs and cats associated with melamine and cyanuric acid contamination of pet food. The site of injury is the distal tubule, with unique polarizable striated crystals found there as well as in the collecting ducts.³⁷ These fan-shaped birefringent crystals are light green to slightly basophilic in color. Additional perivascular and intravascular lesions may also be seen.⁵⁴ In addition to the acute and marked azotemia and crystalluria, severe hyperphosphatemia occurs. Neither melamine nor cyanuric acid on its own was found to cause ARF.^{68,185}

Ethylene glycol may be ingested directly or by the cat grooming the toxic product from the hair coat or feet. There is a well-recognized seasonality in ethylene glycol toxicity cases, with the majority occurring during the fall and winter; however, this agent is found not only in automotive radiator antifreeze but also in lock de-icer, windshield-wiper fluid, some gasoline additives, and film-processing chemicals. The site of damage is the renal tubule. Ethylene glycol is metabolized to several toxic compounds (glycoaldehyde, glycolic acid, glyoxylic acid, and oxalic acid) that cause marked metabolic acidosis and ARF. Characteristic clinicopathologic findings include an increased anion gap, increased osmolal gap, metabolic acidosis, and CaOx crystalluria. If cats are presented in the latent phase (30 minutes to 12 hours after exposure), ataxia, stupor, and muscle fasciculations may be seen, along with relatively nonspecific signs such as anorexia, lethargy, vomiting, dehydration, hypothermia, and oral ulceration. Once the patient becomes oliguric (12 to 72 hours after ingestion), the likelihood of recovery is dramatically decreased. Thus an index of suspicion warrants checking serum or urine (or both) ethylene glycol levels in the clinic. CaOx crystalluria (monohydrates predominate over other forms) may be seen in cats as soon as 3 hours after ingestion. Serum ethylene glycol levels peak 1 to 6 hours after exposure but are no longer detectable after 48 hours.²¹³

The goal of treatment is to block alcohol dehydrogenase (ADH), in order to prevent metabolism of the ethylene glycol into the aforementioned toxic compounds. Ethanol competes with ethylene glycol and has a higher affinity for ADH. It must be given by constant-rate infusion or every 4 hours because of its short half-life. The adverse effects of intravenous ethanol are CNS depression, as well as a worsening of the metabolic acidosis,

osmotic diuresis, and serum hyperosmolality. Whereas fomepizole (4-methyl-pyrazole [4-MP]) is the treatment of choice in dogs, it has only recently been shown to be effective in cats and superior to ethanol only if given within 3 hours of ingestion of ethylene glycol.⁵⁷ The dose used in this prospective study was 125 mg/kg, intravenously as an initial dose, followed by 31.25 mg/kg at 12, 24, and 36 hours; this is higher than doses recommended for dogs. If treatment is delayed until 4 hours after ingestion, mortality rates are high regardless of whether ethanol or 4-MP is used. Intensive physiologic monitoring and aggressive use of intravenous fluids and sodium bicarbonate will be required because electrolyte and fluid shifts are dramatic. The reader should refer to Chapter 31 for more information. Many patients that are already in oliguric renal failure at presentation will require hemodialysis or peritoneal dialysis to survive.^{86,87}

INTENSIVE MANAGEMENT OF RENAL DISEASES

Dialysis

Treatment for all patients with ARF, regardless of the inciting cause, may require peritoneal dialysis or hemodialysis. Although these procedures are not common in feline medicine, they are becoming more readily available, and it is useful to understand the basic indications and contraindications to help with treatment planning and client education. Additionally, as clients become more aware of these treatment options through their own research on the Internet or elsewhere, it is helpful to understand some basic concepts.

Dialysis may be used to reduce azotemia and correct severe electrolyte abnormalities, acid-base imbalances, or overhydration. It is useful for the treatment of ARF associated with intoxication (drug or toxin) or urinary tract outflow obstruction or in the treatment of end-stage chronic renal failure that is nonresponsive to medical therapy and as part of stabilizing the patient in preparation for renal transplantation. Both hemodialysis and peritoneal dialysis have been used for more than 10 years in veterinary medicine and are becoming more widely available and affordable.

The principle underlying dialysis is that solutes diffuse across a semipermeable membrane depending on their concentration, the relative pressure on either side of the membrane (i.e., gradient), and the size of the molecule relative to the pores in the membrane. Solutes move from an area of high concentration or pressure to an area of low concentration or pressure; smaller molecules (e.g., electrolytes, urea, and albumin) move more readily than larger molecules (e.g., blood cells, Cr, and globulins). Applying this clinically, blood flows past a semipermeable membrane (the peritoneal lining or the

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FIGURE 32-12 Blood flows past a semipermeable membrane (the peritoneal lining or the dialyzer in peritoneal dialysis and hemodialysis, respectively), and a dialysate–dialysis fluid flows by or resides on the opposite side of the membrane. (From Fischer JR, Pantaleo V, Francey T et al: *Veterinary hemodialysis: advances in management and technology*, Vet Clin North Am Small Anim Pract 34:935, 2004.)

dialyzer in peritoneal dialysis and hemodialysis, respectively), and a dialysate–dialysis fluid flows by or resides on the opposite side of the membrane (Figure 32-12).

In hemodialysis a dedicated, double-lumen hemodialysis catheter is placed in the jugular vein. Blood is run through an extracorporeal filter (dialyzer) in the opposite direction to the dialysate, resulting in a countercurrent flow pattern. Because the blood is continuously exposed to fresh dialysate, the diffusion occurs more rapidly than in peritoneal dialysis. In peritoneal dialysis the dialysate is infused into the peritoneal cavity and left there for variable amounts of time ("dwell time") before it is drained from the abdomen. Dialysis may be continuous (continuous renal replacement therapy by hemodialysis), or intermittent (hemodialysis or peritoneal dialysis).

Standard dialysate is a solution that mimics normal serum composition. Variations of sodium, potassium, magnesium, phosphorus, and bicarbonate concentrations may be made to adjust the patient's levels as necessary. *Sodium profiling* refers to regular adjustments of sodium concentration during dialysis to reduce the likelihood of complications. The prescription for an individual patient will change as the patient's status changes. To increase water loss in the overhydrated patient, mannitol may be added or the dextrose concentration may be increased. In the hypoalbuminemic patient that is receiving adequate dietary protein, an amino acid dialysate may be considered.

The complication rate for peritoneal dialysis is high but not insurmountable. Peritoneal dialysis requires intensive monitoring of the drain (for obstruction) and the stoma (for subcutaneous leakage, infection), as well as the patient; however, this procedure is more accessible to veterinarians because of the relatively lower cost of

equipment compared with that needed for hemodialysis. Rapid solute removal and electrolyte shifts can result in hypovolemia, hypotension, cramping, nausea, vomiting, and dialysis disequilibrium syndrome.⁸³ In both peritoneal dialysis and hemodialysis, catheters may become obstructed, and prevention of catheter infection requires diligence. The interested reader is referred to the listed references, in particular Dzyban et al and Dorval et al (for peritoneal dialysis) and Fischer (for hemodialysis).*

Another possible method of treatment, diuretic renal scintigraphy using ^{99m}Tc-DTPA plus furosemide, has been evaluated to date as a diagnostic test. This procedure is noninvasive and fast to perform and may have application in patients with significantly impaired renal function and obstructive uropathies.¹⁰⁴

Renal Transplantation

The first successful feline renal transplant was performed in 1987 at the University of California, Davis, by Dr. Clare Gregory. Since that time, the procedure has been performed at numerous centers around the world for cats in chronic renal failure. Clients must understand that this is not a cure; the goal is to provide good quality of life for a cat that otherwise would not survive. Indications are early chronic renal disease (ideally before decompensation) or irreversible ARF. It cannot be a last-ditch effort because the patient must not be too debilitated nor have concurrent conditions. Additionally, the veterinarian cannot ethically justify removing a healthy kidney from a donor cat unless there is a good chance of success for the recipient. Careful screening and early referral of stable cats for renal transplantation improves the likelihood of a successful outcome.^{4,24}

Exclusion criteria include significant cardiac disease, feline leukemia virus infection, active feline immunodeficiency virus infection, UTI, uncontrolled hyperthyroidism, neoplasia, DM, a poor starting body condition score, and a fractious temperament. Some centers will perform transplants on cats with CaOx uroliths.¹⁴ Screening tests that determine suitability as a recipient include a CBC, serum biochemistries including total T₄, urinalysis and urine culture, UPC, thoracic radiographs and echocardiogram, electrocardiogram, abdominal radiographs, heartworm antigen test, and *Toxoplasma* titers. If the cat has positive *Toxoplasma* immunoglobulin IgM or IgG titers, it will be started on clindamycin or trimethoprim sulfa preoperatively and likely kept on the antibiotic for the rest of its life. A renal biopsy for cross-matching and a 2-week cyclosporine challenge will be required, the latter to see if subclinical UTIs or upper respiratory tract infections surface.¹²⁸

Preparation of the successful transplant candidate includes correction of electrolyte and acid-base imbalances, anemia (with appropriate blood products and darbepoietin), and azotemia (may require dialysis) and improvement of nutritional status (may require a feeding tube). Alleviation of preoperative azotemia is essential insofar as this results in a decreased risk of CNS disorders after surgery.⁵

Donors are healthy young adult cats in good body condition with normal CBCs, serum chemistries, and urinalyses. They should also test negative for retrovirus and *Toxoplasma* infections, with no abnormalities found on renal ultrasound. They are blood typed and cross-matched to potential recipients, and renal tissue compatibility is assessed. The kidney size must be relatively similar (not too much larger) to that of the recipient. Computed tomography renal angiography is used in some centers because it is superior to intravenous urography to evaluate the vascular architecture of potential donors.³⁴ Transplantation will not be considered if the client is unwilling to care for the donor and provide it with a home.

The donor's left kidney is harvested because of its greater vein length. The kidney is flushed and then preserved in a solution that can store the organ for 3 to 4 days, allowing a matched donor and recipient to reside in different parts of the world. Several techniques (e.g., renal arterial end-to-end anastomosis to the external iliac artery or end-to-side anastomosis to the aorta) may be employed to anastomose the new kidney to the recipient's renal vessels and ureter.²⁵ The technique used for ureteral attachment is ureteroneocystostomy. Several different techniques have been evaluated; an extravesical technique using a simple interrupted pattern has been found to be most favorable.¹⁶¹

Postoperative care is intensive because several risks exist. Routine care consists of close intensive care unit monitoring and treatment with intravenous fluids, analgesics, antibiotics, gastric protectants, blood products as needed, and enteral nutrition. Ionized (but not total) serum magnesium concentrations are decreased in feline renal transplant recipients in the perioperative period. In addition, ionized serum calcium and potassium concentrations are below normal in many cats as well, although a case of hypercalcemia has been published.¹³ Hence electrolyte monitoring is required. Profound weakness and depression commonly seen in feline renal transplant recipients in the immediate postoperative period may, in part, be a result of these electrolyte disturbances.²²³ Interestingly, in a study of 86 cats with post-transplant hypophosphatemia, survival was unaffected regardless of whether this abnormality was treated.¹⁸⁰

Postoperative malignant hypertension with systolic pressures in excess of 300 mm Hg can result in seizures and neurologic complications, including death. Uncontrolled uremia is believed to cause increased endothelial

*References 70, 75, 76, 83, 137, 138, 149.

catecholamine sensitivity. Additional possible instigating causes include anesthesia and pain. Treatment with subcutaneous hydralazine has been shown to be effective in correcting hypertension and minimizing or preventing neurologic complications.¹³⁴

Other possible postoperative complications directly related to the graft may include torsion, thrombosis, or hemorrhage of the pedicle; this possibility is greatly reduced through pexy of the new kidney to the body wall. Retroperitoneal fibrosis has also been reported.¹² The most likely complication is ischemic injury and ureteral obstruction resulting in delayed graft function.¹⁶² Delayed graft function may be identified through ultrasonographic monitoring of renal blood flow and may occur as late as 21 days postoperatively.¹⁷²

The recipient will require lifelong immunosuppressive therapy (microemulsified cyclosporine or potentially tacrolimus) to prevent graft rejection.¹³⁰ This calls for a dedicated caregiver. Acute allograft rejection initially has minimal clinical signs: a 1° F (<1° C) increase in temperature at 21 days after transplant. Markers of oxidative stress from venous blood were not found to be helpful in one experimental study.¹⁰¹ Cr levels should be monitored routinely in patients as an increase in this parameter is suspicious for allograft rejection; a biopsy of the renal allograft is needed for definitive diagnosis.¹³³ Rejection is a result of a lack of adequate plasma cyclosporine levels. Treatment with intravenous cyclosporine and prednisolone will reverse 60% of rejection cases.

Approximately 20% of the cats undergoing a renal transplant procedure die at the time of surgery or during the first week after surgery. Older cats and cats with severe azotemia, hypertension, and cardiovascular disease may have an increased mortality risk after renal transplantation. For cats that are successfully discharged from hospital, survival rates are approximately 80% for 6-month and 45% for 3-year survival.²⁰¹ Causes of mortality include the following:

- Poor client compliance in giving oral cyclosporine and failure to have cyclosporine trough levels checked routinely
- Infection: In a retrospective study of 169 recipients, infections developed in 25% of the cases, with bacterial causes being most common, viral next most common, and fungal or protozoal least common. Infection was the second most common cause of death after acute rejection of the transplant, accounting for 14% of deaths overall in this study group. Cats with diabetes had a significantly greater risk of developing this complication.¹²⁰
- Acute rejection of the kidney
- Development of cardiac disease, hepatopathy, pancreatitis, neoplasia, diabetes, and other conditions

- Uncommonly, post-transplantation malignant neoplasia may occur, resulting in a shorter survival time. Lymphoma is the most common form; however, a variety of tumor types are reported.^{200,223}

The longest survival time attained after feline renal transplantation was 14 years, as of the autumn of 2009.⁹⁹ The average life expectancy after transplantation is approximately 3 to 6 years, depending on the age of the cat at the time of surgery. All recipients should be considered to have renal insufficiency regardless of how well they do; therefore ongoing monitoring is necessary, just as with any other cat with CKD. In addition, because of the cyclosporine therapy, urine cultures must be performed regularly. Hypertension should be diligently treated.

CHRONIC KIDNEY DISEASES

Despite the tendency to use the terms "chronic kidney disease" and "chronic renal insufficiency" (CKD/CRI) as a single entity, it is helpful to bear in mind that these terms refer to a cluster of clinical signs that may be a result of a number of different etiologies and pathologic entities. Box 32-8 lists recognized causes of CKD in cats. Another term, "chronic renal failure," may also be misleading and should be used judiciously; many patients are far from failure given the wide variability in renal impairment despite the Cr value at initial presentation.^{38,78} Using this potentially inappropriate terminology may distress clients who might believe that the condition is more advanced than it is and may choose not to begin treatment at all (i.e., euthanize) or to discontinue therapy earlier than is warranted.

The most common histopathologic form of chronic disease in the kidneys of cats is tubulointerstitial nephritis characterized by the infiltration of lymphocytes and

BOX 32-8

Causes of Chronic Kidney Disease in Cats

- Chronic tubulointerstitial nephritis of unknown etiology
- Hydronephrosis secondary to ureteronephroliths
- Hypokalemic nephropathy
- Polycystic renal disease
- Neoplasia (primarily lymphoma)
- Hypercalcemia resulting from hypervitaminosis D
- Nephrotoxicoses
- Chronic glomerulonephritis
- Chronic pyelonephritis
- Amyloidosis
- Dry feline infectious peritonitis: pyogranulomatous interstitial nephritis
- Polyarteritis nodosa

plasma cells with concurrent and variable degrees of fibrosis. Retrospective studies evaluating the prevalence of type of renal disease resulting in chronic changes are sparse. A study undertaken in 1987 classified the morphologic category of CKD in 74 cats. 53% were chronic tubulointerstitial nephritis.⁶⁶ The other causes listed in Box 32-8 are less prevalent. What initiates this lymphoplasmacytic inflammatory response is unclear and may not be the same in all individuals. Several studies have been undertaken to investigate the role of antigenic stimulation through routine vaccination. The antigen source that has been evaluated is Crandell-Rees feline kidney (CRFK) cell lysate because this cell line was used to grow many vaccine viruses. Although antibodies to CRFK have been identified in all tissues tested, the only cats in which significant inflammation was detected were those given doses of CRFK cell lysate far in excess of that which any cat could receive in its lifetime.^{140,141} Thus this aspect of routine vaccination does not appear to be a cause of tubulointerstitial nephritis.

An interesting theory is that tubulointerstitial nephritis might, in fact, be a mortality antagonist, meaning that it provides an evolutionary survival benefit. A study evaluated the histopathologic findings from the necropsies of nearly 700 adult cats that were maintained for life as residents of the same colony, over a period of 22 years. The surprising finding was that the cats that died or were euthanized because of renal disease lived longer than those cats dying from other causes. It was also noted that they had higher, but uniform, mean renal histologic scores across ages, compared with cats that had other causes of death. A decline in body condition was a negative prognostic indicator in all cats.¹⁴²

Clinical Findings

Regardless of cause, the clinical presentation of a cat with any CKD is similar. On physical examination a dull, often spiky coat with a delay in skin elasticity and muscle wasting are very common findings. Oral ulcers may be seen; mucous membrane pallor is variable. Although one or both kidneys may be smaller and firmer than normal, renal size cannot be relied on because some cats retain normal size, others have renomegaly, and yet others have small kidneys surrounded by sufficient perirenal fat to obscure the real size. Cats may present in a lethargic or depressed state, with poor or no appetite and concurrent weight loss. Nausea or vomiting is common. Polyuria may go unnoticed unless the cat lives indoors only, without feline housemates, and uses clumping litter and the client pays attention to the size and number of urine clumps in the litter. Polydipsia may likewise be overlooked in this species because, as a result of their desert origin, cats tend to dehydrate and become constipated before they start to drink more.

International Renal Interest Society Classification

Chronic renal insufficiency refers to a gradual decline in renal function and is extremely common in cats. In one retrospective study clinical and laboratory evidence of renal insufficiency from renal disease were present in 7% (11 of 153) of dogs and 20% (27 of 137) of cats.²¹⁹ As in human medicine, this syndrome of chronic renal insufficiency has been divided into stages. The International Renal Interest Society (IRIS; <http://www.iris-kidney.com/>) bases the categories on serum Cr levels once the cat is rehydrated as well as the patient's clinical signs. Substaging is based on the presence or absence of hypertension as well as of proteinuria insofar as both of these parameters are critical in treatment, disease progression, and prognosis for the individual. There are numerous benefits to assigning a stage to an individual patient. Staging ensures that the veterinarian evaluates all the appropriate parameters. The veterinarian then has the information required to focus on cure when possible (e.g., pyelonephritis, early stages 1 and 2), alleviation of factors that affect progression of disease (e.g., hypertension and proteinuria), treatment of clinical uremia, or provision of palliative care. These tools also direct the practitioner to logical monitoring (parameters and frequency) and also provide more information on which to base a prognosis. Having distinctly defined categories allows practitioners to communicate clearly about patients. Table 32-5 and Boxes 32-9 and 32-10 summarize the IRIS definitions. Figures 32-13 to 32-15 are algorithms for staging and substaging patients with CKD.

Patients are classified on the basis of their serum Cr value *once rehydrated* and then substaged on the basis of the presence or absence of hypertension or proteinuria. Thus stage 1 reflects the earliest stage of renal disease with an inappropriate USG for the hydration state of the cat. The Cr is still within normal reference intervals, but proteinuria or hypertension may be present. These cats will not have clinical signs of illness at this time unless significant proteinuria or hypertension are present; this stage is detected by screening cats in an age category at risk (>7 to 8 years of age) and verifying abnormalities as found.

Azotemia may be misleading if a cat is dehydrated. It is not possible to stage, prognosticate, or plan appropriate therapy until the individual has been *rehydrated*. Using the IRIS staging system, stage 1 cats are not azotemic but are classified according to whether they have inadequate renal concentrating ability (a USG ≤ 1.035) in a *dehydrated* state. The diuretic effect of diet (e.g., high sodium, canned versus dry) or drugs will make assessment of USG difficult. Collecting urine after a period of sleep may help counter this effect somewhat.

TABLE 32-5 IRIS Definitions for Classification of Renal Disease

| Stage | 1. Nonazotemic Renal Disease | 2. Mild Renal Azotemia | 3. Moderate Renal Azotemia | 4. Severe Renal Azotemia/ "Chronic Renal Failure" |
|----------------------------|--|--|--|--|
| Creatinine: mg/dL (mmol/L) | <1.6 mg/dL (<140 mmol/L) | 1.6-2.8 mg/dL (140-249 mmol/L) | 2.9-5.0 mg/dL (250-439 mmol/L) | >5.0 mg/dL (>440 mmol/L) |
| Clinical signs | None | +/- inappetence, weight loss, PU/PD | Usually inappetence, weight loss, PU/PD | Uremia, clinically ill |
| Progression | Stable for long periods of time | Stable for long periods of time | May progress | Fragile |
| Therapeutic goals | Identify and treat specific primary kidney disease (e.g., acute pyelonephritis, nephrolithiasis) | Identify and treat specific primary kidney disease (e.g., acute pyelonephritis, nephrolithiasis) | Modify progression: phosphorus restriction, omega 3 fatty acids? | Ameliorate uremic signs: protein restriction, antiemetics, erythropoietin, fluid therapy, appetite stimulation, dialysis, etc. |
| Proteinuria | Classify | Classify | Classify | Classify |
| Blood pressure | Classify | Classify | Classify | Classify |

PU/PD, Polyuria/polydipsia.

Comments: Stage 1: Some other renal abnormality present e.g. inadequate concentrating ability without identifiable non-renal cause; abnormal renal palpation and/or abnormal renal imaging findings; persistent proteinuria of renal origin; abnormal renal biopsy results, progressively elevating creatinine levels. Stage 2: Lower end of the range lies within the reference range for many labs but the insensitivity of creatinine as a screening test means that animals with creatinine values close to the upper limit of normality often have excretory failure.

Adapted from International Renal Interest Society: (website): <http://www.iris-kidney.com/>. Accessed November 28, 2010.

BOX 32-9

IRIS Definitions Regarding Proteinuria

Proteinuria (determined by evaluating sequential urine protein:creatinine ratios)

Nonproteinuric = UPC < 0.25

Borderline proteinuria = UPC 0.25-0.5 Re-evaluate after 2 months

Proteinuria = UPC > 0.4

Adapted from International Renal Interest Society (website): <http://www.iris-kidney.com/>. Accessed November 28, 2010.

Stages 2 to 4 are based on elevation of Cr levels. Again, as with USG, numerous nonrenal factors may affect this parameter. When inadequate protein is available for ongoing needs, cats, being obligate carnivores, catabolize protein stores (e.g., muscle) to fuel metabolic pathways, resulting in an artificially low serum Cr value. Prerenal azotemia associated with dehydration will have the opposite effect. BUN can be especially difficult to interpret insofar as it reflects ammonia intake, production, and excretion (discussed previously).

Regardless of serum Cr concentration, evaluation of BP and urinary protein is required for complete IRIS staging. Hypotension is detrimental to renal perfusion; hypertension, to cardiac output and potentially to renal function. Hypertension increases the risk of vascular damage to target organs (brain, kidneys, and eyes). A persistent UPC higher than 0.4 has been shown to be

BOX 32-10

IRIS Definitions Regarding Classification of Blood Pressure

NH = nonhypertensive = <150 mm Hg with no complications

BP = borderline hypertensive = 150-160 mm Hg with no complications

Hnc = hypertension no complications = consistent systolic blood pressure values >160 mm Hg

Hc = hypertension with extra-renal complications = signs + > 150 mm Hg

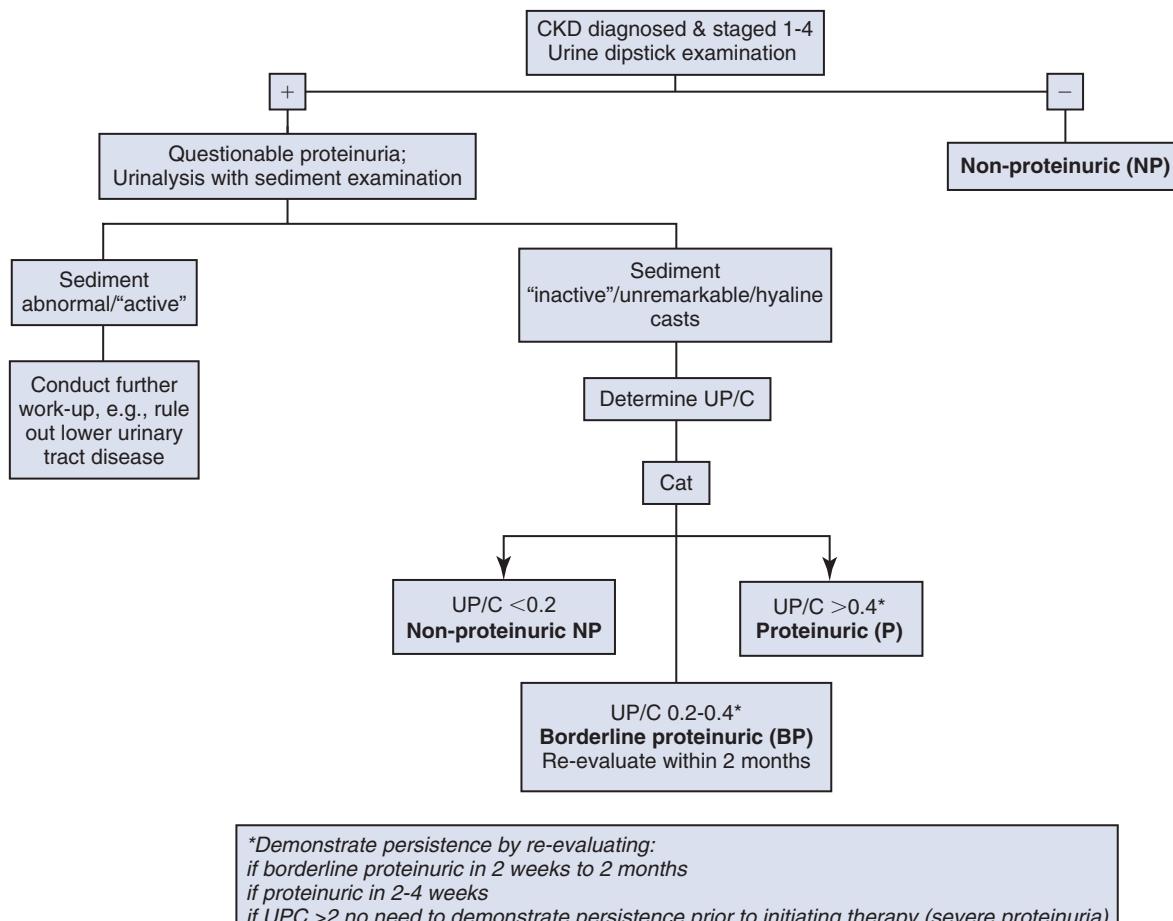
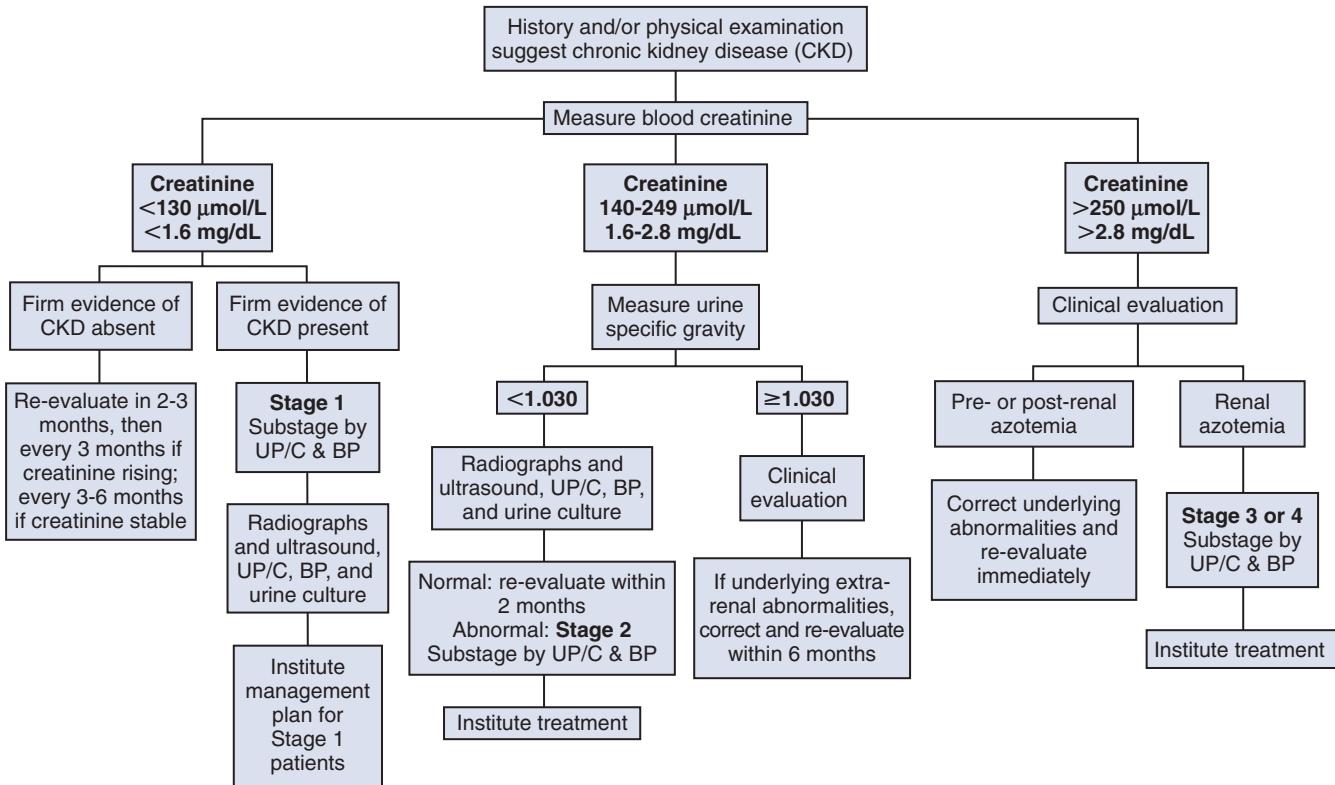
Adapted from International Renal Interest Society (website): <http://www.iris-kidney.com/>. Accessed November 28, 2010.

associated with increased mortality,¹²⁹ as well as progression of renal insufficiency.

Diagnosis

Standard diagnostics for renal disease include the minimum database of CBC and differential, serum biochemistries, BP, and urinalysis with, if significant urinary protein is present, a UPC. It can be argued that radiographs should also be included. Earlier diagnosis could help to blunt pathologic processes and stop progression of CKD.^{96,144}

Azotemia (an increase in either or both BUN and serum Cr) is present and commonly has a prerenal as



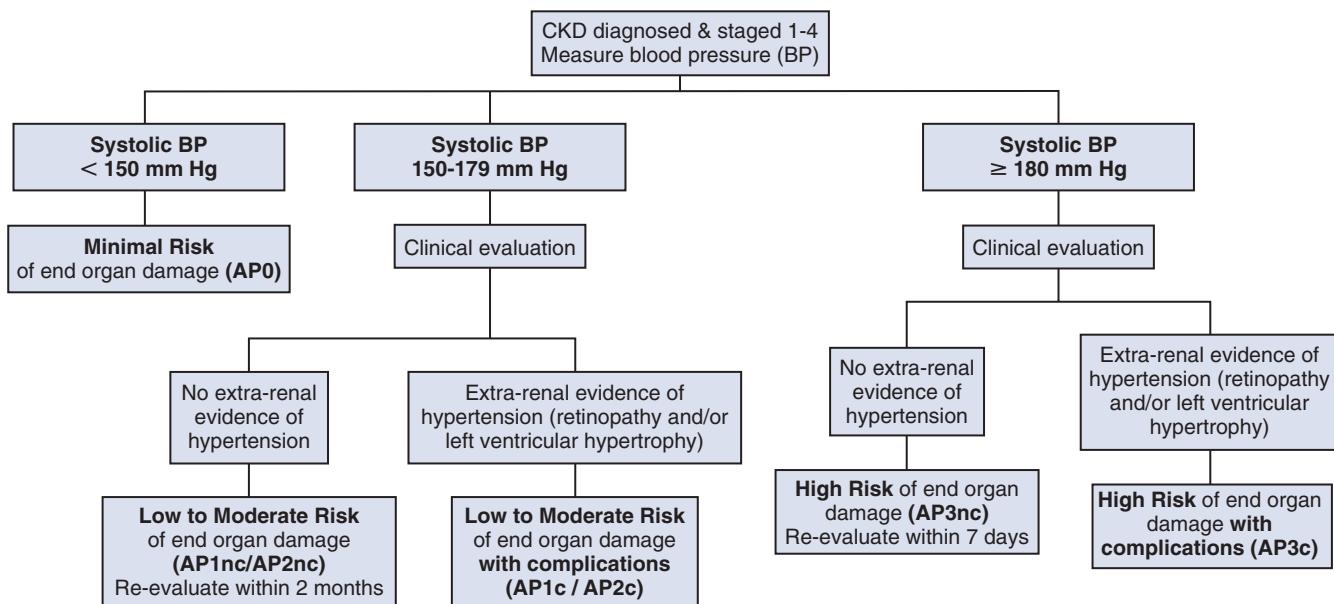


FIGURE 32-15 Algorithm for substaging chronic kidney disease by blood pressure. This is based on the risk of target organ damage due to hypertension. (Adapted from Bonagura JD, Twedt DC: Kirk's current veterinary therapy, ed 14, St Louis, 2008, Saunders/Elsevier.)

well as the defining renal component; variable acid–base and electrolyte changes occur. These are most notably a metabolic acidosis with variable potassium, phosphorus, and calcium levels depending on the mechanism as well as the duration of the problem. A urinalysis reveals a subnormal specific gravity in the face of dehydration (i.e., ≤ 1.035) with or without cellular, bacterial, and cast components. Systolic BP is commonly elevated and has been reported to occur in as many as 60% of cats with CKD.^{127,206} More recently, in a study of 103 cats with CKD, 20 (19.4%) were found to have systolic BP in excess of 175 mm Hg.²⁰⁹ Serum T₄ levels are suppressed in cats with CKD. In a study of 128 cats with CKD, 48% of cats with CKD had low total serum T₄. Total T₄ levels were 12.3 \pm 8.4 nmol/L (0.96 \pm 0.65 µg/dL) compared with healthy, age-matched cats in which the total T₄ range was 27.0 \pm 10.4 nmol/L (2.1 \pm 0.81 mcg/dL).¹⁵⁹ Only a small proportion of cats with CKD have significant proteinuria.

In human medicine numerous biomarkers have been evaluated (Table 32-6) to identify early ischemic or nephrotoxic kidney injury. To date, only a few studies have been published in veterinary medicine that have attempted to find markers that detect a decline in renal function before urine-concentrating ability is lost (approximately 66% nephrons lost) or Cr levels increase (approximately 75% nephrons lost).

In one study USG, proteinuria, and N-acetyl-beta-D-glucosaminidase (NAG) index were evaluated, but only proteinuria at presentation was found to be significantly associated with development of azotemia. Evaluation of NAG index offered no additional benefit.¹¹⁵ The same

TABLE 32-6 Protein Biomarkers Used in Human Medicine for the Early Detection of Acute Renal Injury

| Biomarker | Associated Renal Injury |
|-------------------------------|---|
| Cystin C | Proximal tubule injury |
| KIM-1 | Ischemia and nephrotoxins |
| NGAL (lipocalin) | Ischemia and nephrotoxins |
| Cytokines (IL-6, IL-8, IL-18) | Ischemia, prerenal, postrenal acute kidney injury |
| Actin-actin depolymerizing F | Toxic, delayed graft function |
| a-GST | Ischemia and delayed graft function |
| p-GST | Proximal tubule injury, acute rejection |
| L-FABP | Ischemia and nephrotoxins |
| Netrin-1 | Ischemia and nephrotoxins, sepsis |
| Keratin-derived chemokine | Ischemia and delayed graft function |

Adapted from Ronco C, Haapio M, House AA et al: Cardiorenal syndrome, *J Am Coll Cardiol* 52:1527, 2008.

group attempted to assess the correlation between NAG index, plasma Cr concentration, and proteinuria. They concluded that the NAG index in cats with CKD may be indicative of ongoing lysosomal activity rather than active proximal tubular cell damage. Also, although the NAG activity can be quantified in feline urine using a colorimetric technique, results should be interpreted cautiously because of high interassay variation.¹¹⁶

Another study looked at whether urine NAG might be a predictor for the development of CKD in hyperthyroid cats. Unfortunately, baseline NAG did not differentiate azotemic from nonazotemic treated hyperthyroid cats. It was speculated that it might be of help when combined with USG in adjusting methimazole therapy.¹³⁹

As a matter of interest, although it is specific for myocardial damage or necrosis, cardiac troponin I (cTnI) concentration can be elevated in azotemic renal failure, suggesting that stage 4 renal disease may result in clinically inapparent myocardial injury or possibly altered elimination of cTnI.¹⁸³

In stages 1 and 2 veterinarians have the best chance to identify treatable causes of renal disease. Hence, in addition to the aforementioned basic measures, urine culture, radiographs, abdominal ultrasound, and possibly renal biopsy should ideally be pursued. Urine cultures are worth performing when USG is 1.030 or lower regardless of sediment characteristics and, in more concentrated samples, if significant numbers of white blood cells or bacteria are seen. If a hematogenous source of infection is suspected, blood culture may be considered. Abdominal ultrasound is useful to assess gross renal pathology, guide in collection of intrarenal urine samples, and help with the performance of renal biopsies if indicated. Determination of the cause of CKD should be encouraged in stable patients because this knowledge provides the only chance for accurate treatment of potentially reversible renal disease. When there is concern for primary or secondary cardiac pathology, an echocardiogram and thoracic radiographs should be evaluated. Contributing systemic disease (including electrolyte imbalances) should be identified and stabilized if possible.

Regardless of stage, diagnostics are directed at finding treatable and potentially reversible problems. Thus it is appropriate to try to identify and remove any cause that has compromised renal function, such as a nephrotoxic drug, diet, or plant; prerenal causes of ischemia (hypotension, hypoxia, hypovolemia, hypothermia); postrenal causes of obstruction of urine flow (intraluminal uroliths or sludge, mural or extramural); and UTI (lower tract or upper tract). The veterinarian should evaluate for hypertension and proteinuria.

Therapy

Treatment of CKD in cats consists of etiology-specific and etiology-nonspecific therapy. Specific entities to address include pyelonephritis, nephrotoxicoses, ureteronephroliths, and neoplasia. Problems resulting from these and other causes of CKD requiring therapeutic attention include metabolic acidosis, proteinuria, hypertension, dehydration, electrolyte abnormalities (hyperphosphatemia, hypokalemia, hyperkalemia), renal secondary hyperparathyroidism, inappetence and

anorexia, nausea and vomiting, protein:calorie malnutrition, and anemia.

One paper has recently reviewed the literature regarding treatment modalities for CKD and assessed the quality of the evidence behind each one using evidence-based medicine (EBM) definitions.¹⁹⁵ The grading scheme used was as follows:

Grade I: Evidence based on properly designed, randomized, controlled clinical trials performed in clinical feline patients

Grade II: Evidence from properly designed, randomized, controlled clinical trials of cats with spontaneous disease in a research setting

Grade III: Evidence from appropriately controlled studies without randomization, cohort, or case-control studies; studies using models of disease or simulations in cats; case series; or dramatic results from uncontrolled studies

Grade IV: Evidence from studies in other species, reports of expert committees, descriptive studies, case reports, pathophysiologic justification, and opinions of recognized experts

This comprehensive review elegantly categorizes the studies in the literature using the evidence-based medicine criteria. The therapies evaluated were fluid therapy, calcitriol, antihypertensives, ACE-I, erythropoietin, supplementation with potassium or antioxidants, alkalinization, dietary phosphorus restriction and intestinal phosphate binders, therapeutic renal diets, assisted feeding, dialysis, and renal transplantation. The authors concluded that, with the exception of renal diets, the quality of the evidence is weak for other therapies (Table 32-7). One could argue that it is not possible to design a double-blind, randomized, controlled clinical trial for some of these treatments; for example, not treating hypertension when identified would be unethical and constitute malpractice despite the lack of grade 1 (highest level) evidence. Similarly, it could be argued that if the patient will not take the recommended treatment or the patient-caregiver relationship is negatively affected, the practitioner must adapt the treatment plan accordingly.

Management of Specific Diseases

PYELONEPHRITIS

Antimicrobial therapy must be based on urine culture and sensitivity results. When urine culture and sensitivity is negative despite evidence of bacteria on urinalysis, several possible explanations exist (see Box 32-4). It may be necessary to harvest the urine specimen directly from the renal pelvis using ultrasound guidance to obtain a representative sample.

Antimicrobial therapy should continue for 3 to 5 weeks for the initial episode and for 5 to 8 weeks should

TABLE 32-7 Summary of Evidence Grades Supporting Recommendations for Therapy of Chronic Kidney Disease

| Evidence Grade | Therapy |
|----------------|--|
| Grade I | Some therapeutic diets ACE inhibitors to reduce proteinuria, increase appetite in cats with UPC > 1 |
| Grade III | Some therapeutic diets Antihypertensive therapy with amlodipine Recombinant human/feline erythropoietin Potassium supplementation for cats with hypokalemia Dietary phosphorus restriction for cats in IRIS stages 3 and 4 |
| Grade IV | Long-term SC fluid therapy Potassium supplement for all cats with CKD Intestinal phosphate binders Alkalizing therapy Assisted feeding ACE inhibitors for nonproteinuric cats |

ACE, Angiotensin-converting enzyme; UPC, urine protein:creatinine ratio; IRIS, International Renal Interest Society; SC, subcutaneous; CKD, chronic kidney disease.

Adapted from: Roudebush P, Polzin DJ, Ross SJ et al: Therapies for feline chronic kidney disease. What is the evidence?, *J Feline Med Surg* 11:195, 2009.

re-infection or relapse occur. Urine may be cultured during therapy to verify antimicrobial efficacy and should be repeated 1 week after the end of treatment to ensure that infection has been eradicated.

VITAMIN D NEPHROTOXICOSIS

Nephrotoxicoses generally result in ARF; however, accumulation of vitamin D or overexuberant calcitriol therapy and subsequent hypercalcemia or hyperphosphatemia-induced hypercalcemia cause gradual onset of mineralization. Treatment for hypervitaminosis D may be required in addition to reducing calcitriol dose or addressing hyperphosphatemia. In 2006 an inadvertent error resulted in excess vitamin D addition to several diet formulations.

Appropriate diagnostics are serum ionized calcium and serum 25-hydroxyvitamin D, a marker for vitamin D₃ levels. The half-life of cholecalciferol (vitamin D₃) in the body is about 6 months, and as it is slowly released from the fat stores, it can potentially cause ongoing toxicity. These patients need to be monitored for at least 6 months.

Acute therapy consists of intravenous fluids, corticosteroids, furosemide, and calcitonin. Chronic monitoring and ongoing treatment is necessary because the hypercalcemia can last for months. The use of intravenous bisphosphonates is recommended and has been shown to control hypercalcemia in most cases for at least 3 to 4 weeks after a single dose. Some patients will require

repeated doses; others require only a single dose. A single dose may provide enough time for the hypercalcemia to lessen when the drug wears off. Pamidronate, a second-generation bisphosphonate, has been used intravenously at 1.3 to 2 mg/kg diluted in saline, with intravenous fluid administration before, during, and after the pamidronate infusion. Serum calcium concentration is usually normal within 48 hours.¹¹⁰

HYPOKALEMIC NEPHROPATHY

Hypokalemia is a condition that is known to cause clinical muscle weakness, especially of the cervical muscles. Hypokalemic myopathy is truly a functional disorder insofar as that although electromyographic measurements are abnormal and serum creatine kinase (CK) levels are elevated, on histologic examination the muscle is normal. The feline potassium requirement is related to the dietary protein level; the higher the protein, the more potassium is needed.¹⁰⁹ Potassium depletion results in weight loss and poor hair coat because this electrolyte is required for protein synthesis. In 1993 a paper reported on the development of nephropathy in cats fed a commercial diet that was potassium depleted.⁶⁵ Additionally, acidification of the diet plays a role. Diets that are more extremely acidified may result in metabolic acidosis, and over time this can lead to urinary potassium loss.⁷¹⁻⁷³

Cats with hypokalemia-induced nephropathy may or may not have an increased fractional excretion of potassium (FE_K). Serum potassium levels of less than 3.1 mEq/L, increased CK levels, azotemia, hyperchloremic metabolic acidosis, and isosthenuria with possible hyperphosphatemia are noted. On histopathology morphologic changes in the kidneys include interstitial fibrosis, lymphocytic-plasmacytic interstitial infiltration, tubular dilation, and atrophy with varying glomerular sclerosis.^{65,72}

Treatment of this condition differs from that of chronic tubulointerstitial nephrosis in that diligent attention must be paid to establishing eukalemia by intravenous and oral potassium therapy. It is not unusual for serum potassium levels to decrease initially, despite potassium-supplemented fluid therapy as a result of dilution, increased tubular flow as GFR improves, and cellular uptake of potassium. Clinical improvement should be noticed within 3 to 4 days. Intravenous fluids should not contain more than 40 mEq potassium/L because this can cause vascular pain and damage; the delivery rate of potassium should not exceed 0.5 mEq/kg body weight/hour. Chronic oral potassium gluconate therapy will be required, adjusting the oral dose as needed to achieve normal serum levels. Renal function will stabilize or improve in some cases. Should the hypokalemia be refractory to treatment, serum magnesium should be evaluated, and, if normal, the possibility of hyperaldosteronism should be investigated, especially in the patient with hypertension.

Treatment of ureteronephroliths and renal neoplasia is discussed in an earlier section.

Nonspecific Management Strategies

SLOWING THE INHERENT PROGRESSION OF CHRONIC KIDNEY DISEASE

The IRIS categorization focuses in its staging system on factors that, when managed, slow the rate of inherent progression. These are azotemia, proteinuria, hyperphosphatemia, hypertension, and metabolic acidosis (Box 32-11).

Because azotemia, metabolic acidosis, and (to some degree) hyperphosphatemia are affected by hydration, optimizing hydration by using canned diets, adding water to food, encouraging drinking by use of flavored liquids or a fountain, and administering subcutaneous fluids daily are beneficial to the well-being of the patient. Similarly, for well-being the patient should enjoy the diet offered, regardless of the specific illness. It is always more important that the cat eat, rather than what the cat eats. The amount consumed must be monitored; this requires calculating the caloric requirements for each individual. A reasonable goal is 50 kcal/kg ideal body weight daily. The client should be advised how much food this is equivalent to so that if the cat does not eat that amount, the veterinarian can be notified. It also prevents confusion in that weight loss associated with progressing disease and weight loss associated with inadequate nutrient intake can be more easily distinguished. Inadequate intake results in a negative nitrogen balance; protein:calorie malnutrition; and deterioration of protective mechanisms that affect immunity, red cell hemoglobin content, and muscle mass, as well as tissue healing ability.

HYDRATION

Undoubtedly, rehydration is of critical and key importance to perfuse tissues with oxygen and support nutrient-carrying and waste-scavenging mechanisms.⁹⁵ Rehydration aids in acid-base homeostasis and helps improve renal blood flow, tissue perfusion, and GFR. With an impaired ability to concentrate urine, despite polydipsia, exogenous fluids (isotonic, polyionic fluids administered intravenously or subcutaneously) are

required. Plenty of fresh water should be available at all times. Increasing oral intake of water can be encouraged by provision of a circulating water fountain, flavored water (broth) or ice cubes, milk, and canned foods. Supplementation with water-soluble vitamins should be considered.

In cats with IRIS stage 1 disease, home fluid therapy is generally not yet required; however, in-clinic rehydration as needed may be advisable. See Box 32-12 for an example of how to calculate fluid volume and rate. It is not too early in the progression of chronic renal insufficiency to mention this helpful treatment that the client may consider providing at home in the future, when the disease advances. Many clients are willing to give daily or less frequent subcutaneous fluids at home once they understand how it is done and see the improvement in demeanor that rehydration offers. They can assess the cat's state of hydration by evaluating the character of the feces; feces should be moist and shaped like logs rather than pellets or pieces. Once rehydrated, the goal is to maintain this state; in other words, the skin should not become less elastic, the feces should not become more firm, and so on.

METABOLIC ACIDOSIS

Metabolic acidosis is common in cats with CKD. In one study it was reported in 52.6% of cats with severe renal

BOX 32-12

Example of Subcutaneous Fluid Calculation for a Dehydrated Cat

Ideal healthy hydrated weight: 4 kg

Ill, dehydrated inappetent weight: 3.2 kg

Estimated deficit (firm feces, delay in skin elasticity,

slightly dry oral mucous membranes, normal eye position): 8%

$$\text{Deficit } 8\% \times 4 \text{ kg} = 320 \text{ mL}$$

$$\text{Maintenance } 60 \text{ mL (6\%) } \times 4 \text{ kg/day} = 240 \text{ mL}$$

$$\text{Ongoing losses unknown at present} = ? \text{ mL}$$

$$\text{Fluids needed in first 24 hours} = 560 \text{ mL}$$

The 560 mL can be given intravenously at 23 mL/hour or, were this to be given subcutaneously, for some reason, as 3 boluses of 185 mL over the 24-hour period.

Once rehydrated, the cat should receive maintenance dose of 60 mL/kg ideal weight/day = 240 mL/day. If the cat has not completely absorbed the subcutaneous fluids (e.g., fluid retention in axilla, lower limb), then reduce the dose but not the frequency. If the fluids are completely absorbed and the feces is still passed in firm pieces rather than moist logs, then increase the volume.

After the patient is rehydrated, then a dose of 60 mL/kg per day (6% ideal weight) = 240 mL is needed daily to maintain hydration.

BOX 32-11

Factors That Can Be Managed to Affect Progression of Feline Renal Insufficiency

- Azotemia
- Metabolic acidosis
- Hyperphosphatemia
- Proteinuria
- Hypertension

failure ($\text{Cr} > 400 \text{ mmol/L}$).⁸⁰ It is important because it promotes severe catabolism of endogenous proteins, exacerbates azotemia regardless of diet, promotes wasting (degradation of protein), inhibits protein synthesis, causes a negative nitrogen balance, and enhances hypokalemia. In most cats, however, it is generally mild in degree and readily treated with subcutaneous fluid therapy. When it is persistent, sodium bicarbonate therapy may be required: 160 to 320 mg orally every 8 hours, to be titrated on the basis of serum bicarbonate/ tCO_2 response. Baking soda contains 5 g NaHCO_3 /tsp. Urine pH will be affected, and this treatment may result in struvite crystal formation in a predisposed individual.

HYPERTENSION

What role, if any, *systemic* hypertension plays in the progression of renal disease in the feline species is unknown. However, at any IRIS stage, if a persistent systolic BP higher than 160 mm Hg is detected, treatment for hypertension should be instituted to minimize the risk to target organs (CNS, retina, heart). Should target organ damage already be present, treatment is warranted without re-evaluation for persistence if another cause for this damage is not identified. The suggested schedule for re-evaluation of a questionable systolic BP elevation is as follows:

- A systolic BP of 160 to 179 mm Hg constitutes a moderate risk for target organ damage; BP should be re-evaluated after 2 months.
- A systolic BP of 180 mm Hg or higher constitutes a severe risk for target organ damage; BP should be re-evaluated after 1 to 2 weeks.

The 2007 American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on identifying, evaluating, and managing systemic hypertension is an excellent guide on hypertension in general.³⁹

Reduction of systemic hypertension should be gradual to avoid hypotension and inadvertent activation of the RAAS. Recent publications have looked at the role of dietary sodium in lower urinary tract disease, renal disease, and BP in cats. Increasing dietary sodium has been evaluated as a way to increase urine output and reduce specific gravity, thereby not only increasing frequency of voiding but also reducing the relative supersaturation of solutes to reduce risk of urolith formation.⁵⁰

As far as renal disease goes, there is much conflict in reported results. In one study cats eating a higher-sodium diet had an increase in serum Cr, BUN, and phosphorus compared with cats on a lower-sodium diet.¹²⁵ Another study showed that a low-sodium diet resulted in a reduced GFR, increased urinary potassium loss, and activation of the RAAS.⁴⁴ A third study showed that feeding higher levels of sodium, along with

magnesium, protein, and dietary fiber, resulted in a lower risk for development of chronic renal failure.¹¹² In a different study, feeding a classic restricted-protein, -phosphorus, and -sodium diet to cats in renal insufficiency resulted in fewer renal-related deaths.¹⁹³ Finally, in a study evaluating the effects of increased salt intake on renal function or any other health parameter, no adverse effects were seen.²²⁶

There is no strong evidence that increased dietary sodium increases the risk of hypertension in dogs and cats, and the current recommendation for hypertensive animals is to avoid high dietary salt intake without making a specific effort to restrict it, insofar as restriction may, in fact, activate the RAAS.⁵⁰ Reduction of sodium has not been shown to have an effect on blood pressure (systolic, diastolic, or mean)^{44,125} and may, in fact, result in hypotension in cats, especially if these cats are on an ACE-I.¹⁴⁸

It is important to recognize that these studies vary with respect to diet composition and the definition of what constituted high versus low sodium levels. The studies reported in these six papers are designed differently, so drawing conclusions relative to the other papers is not really possible.

Medical reduction of hypertension is most effectively achieved using the calcium channel blocker amlodipine.¹⁵⁵ After an initial dose of 0.625 mg/cat orally once daily, the BP should be assessed after 3 to 5 days. If this dose is inadequate in controlling the systolic BP at below 160 mm Hg, it may be titrated upwards as needed to as much as 0.5 mg/kg/day, rechecking its effect on systolic BP after 3 to 5 days each time. If this is insufficient, the cat may, in fact, not be receiving the medication or may be hyperaldosteronemic, and serum aldosterone levels should be measured. ACE-I have minimal, if any, effect in reducing systemic hypertension in cats and do not reduce RAAS activation in this species.²⁰⁵ However, they are indicated for cats with proteinuria of glomerular origin. More information on treatment of hypertension is found in Chapter 20.

PROTEINURIA

Several studies have shown that plasma Cr concentration and proteinuria are highly related to survival in cats with naturally occurring renal insufficiency.^{124,211} Preliminary studies also suggest that proteinuria may predict the development of azotemia in normal geriatric cats. It is unclear whether proteinuria is a marker or a mediator of renal injury in the cat, and the pathologic mechanisms remain unclear.²¹⁰ As with Cr, the source of the proteinuria must be determined before attributing significance to the value. Additionally, persistence of proteinuria must be confirmed because transient physiologic events (e.g., fever, excessive physical activity) may cause non-renal proteins to spill into the urine. Other prerenal causes of proteinuria include increases in normal

inflammatory proteins (e.g., from chronic inflammation or infection) or abnormal protein (e.g., from myeloma). Postrenal protein increases are most typically the result of UTI or inflammation. Once persistence and renal origin have been verified, localizing the protein as being glomerular, interstitial, or tubular remains difficult. However, because the latter two are less likely to cause significant proteinuria, the veterinarian can assume that UPC elevations are associated with alterations in glomerular integrity or hyperfiltration associated with a decline in the number of functional nephrons.¹⁴³ Because the significance of microalbuminuria in cats is unclear, UPC remains the test of choice.⁹⁷

Glomerular hypertension promotes urinary protein loss because of a pressure gradient between the preglomerular blood and postglomerular ultrafiltrate. The mechanism of action of ACE-I is a selective dilation of glomerular efferent arterioles. Benazepril has undergone a large, multi-institutional study to assess its effects on CKD in cats. Results of this and other smaller studies show that using benazepril or placebo did not make any significant difference in survival time for all CKD cats unless proteinuria was present.^{123,124,168} However, for cats with urinary protein loss based on UPC, benazepril-treated cats had longer survival times and better appetite than placebo-treated urinary protein-losing cats. Cats with an increased UPC (>0.4) that are started on this medication should be rechecked within 3 to 7 days and have renal parameters, hydration, body weight, appetite, and overall health monitored. Thereafter, re-evaluation should occur every 2 to 4 months in a stable patient. If there is no decrease in UPC, the medication should be discontinued because the possibility of adverse effects on renal function should not be completely discounted.¹⁴⁸

NUTRITION AND DIETARY PROTEIN

There is only one certainty regarding feeding the cat with CKD, and that is that each patient's response to the disease and to nutritional intervention varies dramatically, requiring individualized therapy. The patient must be re-evaluated for response to nutritional therapy.^{42,45,77,182}

In ARF and mild to moderate CKD, restriction of dietary protein may limit the kidney's compensatory response to injury. Protein restriction may lead to protein malnutrition, which impairs immunologic response, decreases hemoglobin production and thus promotes anemia, decreases plasma protein levels, and promotes muscle wasting. Inadequate protein intake also decreases urinary excretion of magnesium; this may result in CaPO₄ precipitation in the kidneys. It is more important for cats with mild to moderate CKD (IRIS stages 1 and 2) to maintain adequate caloric intake and thereby avoid protein-calorie malnutrition. Monitoring for evidence of protein-calorie malnutrition should include monitoring

for weight loss, hypoalbuminemia, poor hair coat quality, and muscle wasting.

Dietary therapy for patients in IRIS stages 3 and 4 ($\text{Cr} > 2.9 \text{ mg/dL} [> 250 \mu\text{mol/L}]$) is not controversial; restriction of both protein and phosphorous is required to prevent uremic complications. Benefits of protein restriction are related to *nonrenal* effects (toxins affect organs other than kidneys). Being obligate carnivores, cats require more of their dietary calories from protein than omnivores do. The minimum daily requirement for cats is 4.5 to 5 g/kg body weight. However, not all proteins are equivalent in bioavailability. Using protein sources of high biological value is important. In addition, should there be concurrent intestinal disease (e.g., inflammation associated with uremic gastritis), there may be alterations in nutrient absorption. Table 32-8 illustrates the differences in protein source as well as quantity of protein in a variety of protein-restricted diets.

Protein restriction may actually be harmful in renal patients that are inappetent, insofar as sustained calorie deficit causes body proteins to be catabolized to supply calories, and the nitrogenous end products of this process will further accentuate uremic signs. Unlike omnivores and herbivores, adult cats are often unwilling to eat a very-low-protein diet. Thus inappetence may be an indication for avoiding protein-restricted diets. Uremia is associated with variable dietary intake, intestinal malabsorption, metabolic acidosis, and comorbid conditions, which independently influence nitrogen balance.

Despite numerous experimental studies^{12,82} and clinical trials,^{79,181,193} questions about feeding protein to the cat with renal disease still remain. These include the following:

1. What is the optimal amount of protein for the cat with renal disease?
2. When should protein restriction be implemented?
3. Does the type of protein make a difference?
4. How much restriction is necessary?
5. Will a cat in IRIS stage 3 or 4 benefit if phosphorus is restricted by other means?

The answer to question 2 is that protein restriction should be considered when moderate azotemia persists in the well-hydrated state (IRIS stage 3). If the cat is unwilling to eat adequate quantities of food, it will have inadequate intake of all nutrients and be receiving even less protein than was intended. Thus it must always be remembered that anorexia and the catabolic state is as or more deleterious to the patient than the higher-protein diet the cat will eat willingly. Increasing fat content provides additional nonprotein calories and may increase palatability.

One of the most recent clinical trials¹⁹³ states that the "renal diet evaluated in this study was superior to an adult maintenance diet in minimizing uremic episodes and renal related deaths in cats with spontaneous stage

TABLE 32-8 Comparison of North American Therapeutic Renal Diets (as of July, 2011)

| Feline (US & Canada) July 2011 | Eukanuba Multi-stage Renal | Hill's k/d Feline Renal Health* | Hill's g/d Feline Early Cardiac-Healthy Aging | Purina NF Kidney Function | Royal Canin† | Royal Canin‡ |
|--------------------------------|---|--|--|---|---|---|
| CANNED | | | | | | |
| Energy kcal/can | 199 kcal/can | 183 kcal/can | 165 kcal/can | 193 kcal/can | 219 kcal/6 oz can | 84 kcal/2.5 oz can |
| Moisture g/100 g as fed | 74.9% | 73.7% | 74.9% | 71.0% | 78% | 80% |
| Protein g/100 kcal ME | 7.2 | 6.5 | 8.2 | 6.7 | 5.2 | 5.6 |
| Source | Beef liver, chicken, beef by-products, corn meal, chicken fat, corn starch, dried egg product, fish oil | Pork liver, chicken, pork by-products, rice, oats, chicken fat | Turkey, pork liver, corn flour, barley, fish oil | Poultry by-products, beef, rice, meat by-products, chicken, fish oil | Pork by-products, chicken, chicken liver, chicken fat, pork, fish oil, rice, rice flour, mackerel | Pork by-products, chicken liver, chicken by-products, corn flour, chicken, fish oil, vegetable oil, dried egg white |
| Fat g/100 kcal ME | 5.1 | 6.1 | 4.6 | 6.4 | 7.3 | 6.7 |
| Carbohydrate g/100 kcal ME | 7.1 | 7.9 | 9.2 | 6.3 | 3.0 | 4.3 |
| Phosphorus mg/100 kcal ME | 128 | 85 | 123 | 120 | 95 | 80 |
| Potassium mg/100 kcal ME | 217 | 264 | 171 | 320 | 189 | 200 |
| Sodium mg/100 kcal ME | 82 | 68 | 76 | 50 | 81 | 50 |
| DRY | | | | | | |
| Energy kcal/cup | 514 kcal/cup | 492 kcal/cup | 297 kcal/cup | 398 kcal/cup | 358 kcal/cup | 428 kcal/cup |
| Moisture g/100 g as fed | 7.9% | 7.5% | 7.5% | 7.4% | 8.0% | 8.0% |
| Protein g/100 kcal ME | 7.1 | 6.8 | 7.9 | 7.2 | 5.7 | 6.2 |
| Source | Corn grits, chicken, corn gluten meal, chicken fat, soy protein isolate, fish oil | Rice, corn gluten meal, pork fat, chicken by-product meal, dried egg, dried chicken, fish meal | Rice, corn gluten meal, pork fat, chicken by-product meal, soybean mill run, pork protein isolate, fish meal | Rice, corn, corn gluten meal, soybean meal, animal fat, fish meal, fish oil | Rice, ground corn, chicken fat, wheat, corn gluten meal, soy protein isolate, fish oil | Pork meal, ground corn, chicken fat, rice, wheat, corn gluten meal, fish oil |
| Fat g/100 kcal ME | 5.6 | 5.3 | 4.5 | 3.0 | 4.3 | 5.1 |
| Carbohydrate g/100 kcal ME | 7.8 | 9.9 | 9.8 | 11.9 | 10.9 | 8.5 |
| Phosphorus mg/100 kcal ME | 94 | 109 | 128 | 100 | 120 | 80 |
| Potassium mg/100 kcal ME | 143 | 175 | 181 | 210 | 240 | 220 |
| Sodium mg/100 kcal ME | 87 | 56 | 77 | 50 | 80 | 70 |

*Hill's k/d canned with chicken.

†Renal LP Modified pate (canned); LP Modified-C (dry).

‡Renal LP Modified in gravy (canned); LP Modified-P (dry).

Note: Manufacturers change diet compositions from time to time, and diets differ in different parts of the world.

II or III CKD" but goes on to acknowledge that "these findings emphasize the value of considering individual dietary components in the overall assessment of the benefits of dietary therapy. Individually or in combination, similar dietary modifications in the present study may have minimized the number of uremic crises and mortality rate." This underscores the difficulties in trying to isolate single factors as being of greatest importance in treating CKD.

Several other studies have attempted to identify what role different dietary components play. Based on natural occurrence as well as experimental study it is known that insufficient dietary potassium in an acidifying diet precipitates the development of renal insufficiency in normal cats and exacerbates pre-existing interstitial nephritis and fibrosis.⁶⁵ Some Burmese cats, primarily in the UK, Australia, and Europe, have been found to be predisposed to hypokalemic nephropathy/myopathy due to a presumed autosomal recessive genetic mutation.¹⁵⁴

Another avenue of research has evaluated the role of oxidative stress in the progression of chronic renal insufficiency in cats.⁴¹ Dietary supplementation of a dry food with the antioxidants vitamins E and C and beta-carotene resulted in significantly reduced oxidative damage to DNA in cats with spontaneous renal insufficiency.²²⁸ This effect may also have been part of the difference noted in the diet effect seen in the Plantinga et al study.¹⁸¹

A survey of cats with CKD was conducted in 2002 to evaluate risk factors for the development of CKD using diet and lifestyle variables. It found that increased levels of dietary protein, sodium, magnesium, and fiber were associated with lower odds of developing CKD, whereas *ad libitum* feeding and increased ash intake were associated with an increased risk of developing CKD.¹¹²

In addition to paying attention to specific nutrients, ultimately with a goal to improve the quality and length of life, the veterinarian must ensure that the patient is receiving an adequate amount of energy (including protein). Uremic gastritis is a common cause of anorexia, nausea, or vomiting in cats with renal disease. This is a result of excessive gastric acid secretion caused by increased plasma gastrin levels. Given that gastrin is metabolized by the kidneys, a decline in renal function may also contribute to increased levels of this hormone.⁸⁹ Histamine-₂ (H₂) receptor antagonists and proton pump inhibitors are important therapies for the reduction of gastric acid secretion. Cats may show only signs of partial anorexia or nausea rather than outright vomiting. The H₂ receptor antagonist famotidine (0.5 to 1 mg/kg orally every 24 to 48 hours) or ranitidine (2 to 3 mg/kg orally every 12 hours) may be tried if inappetence is apparent. The proton pump inhibitor omeprazole may be dosed at 0.7 to 1.5 mg/kg orally every 12 to 24 hours.

Appetite stimulants should be needed as a short-term measure only. Antiemetics can be administered to treat nausea (Table 32-9). If a cat is not eating enough calories

TABLE 32-9 Antiemetics for Use in the Cat

| Generic Name | Brand Name | Dose |
|-------------------|-------------------------|--|
| Chlorpromazine | Thorazine, Largactil | 0.5 mg/kg q8h IM |
| Prochlorpromazine | Compazine | 0.1 mg/kg q6h IM |
| Diphenhydramine | Benadryl | 2.0-4.0 mg/kg q8h PO 2.0 mg/kg q8h IM |
| Dimenhydrinate | Dramamine, Gravol | 8.0 mg/kg q8h PO |
| Metoclopramide | Reglan | 1-2 mg/kg constant rate infusion over 24 hours |
| Ondansentron | Zofran | 0.1-0.15 mg/kg slow push IV q6-12 hours prn |
| Dolasetron | Anzemet | 0.6 mg/kg IV, SC q24h |
| Mirtazapine | Remeron | 1.88-3.75 mg/cat PO q72h |
| Maropitant | Cerenia | 0.5-1 mg/kg SC, IV, or PO q24 hr ≤5 days |

IM, Intramuscular; PO, by mouth; IV, intravenous; prn, as needed; SC, subcutaneous.

BOX 32-13

When to Consider a Feeding Tube

Nutritional support should be considered for the following:

- The severely malnourished cat (e.g., 20% weight loss, body condition score 1-2/9)
- The moderately malnourished cat (e.g., 10% weight loss, body condition score 3-4/9) that also has catabolic disease
- Some cats will benefit from early intervention even at normal weight and condition if they suffer from advanced renal disease, hepatopathy, protein-losing gastrointestinal or glomerular disease, pancreatitis, or bile duct obstruction.

on its own or if muscle wasting and nausea have been addressed, then a feeding tube should be considered proactively to enhance quality of life, rather than considered only as a salvage measure. Box 32-13 lists criteria for the consideration of feeding tube placement.

HYPERPHOSPHATEMIA

It is important to restrict phosphorus in moderately azotemic patients; this is more important than protein restriction to survival in remnant kidney model dogs and has been shown to produce less severe renal lesions in remnant kidney model cats. Suggested serum phosphorus targets are listed in Table 32-10. In an experimental study (using a reduced renal mass model) comparing the effect of dietary phosphorus restriction to a normal

TABLE 32-10 Suggested Serum Phosphorus Targets

| Iris Stage | Creatinine | Target Serum Phosphorus | Method: Adjust on the Basis of Individual Response |
|------------|--------------------------------------|----------------------------------|--|
| 2 | 1.6-2.8 mg/dL (141.44-247.52 µmol/L) | 2.5-4.5 mg/dL (0.81-1.45 mmol/L) | Dietary restriction or normal diet + intestinal phosphate binder |
| 3 | 2.9-4.9 mg/dL (256.36-433.16 µmol/L) | 2.5-5 mg/dL (0.81-1.61 mmol/L) | Dietary restriction ± intestinal phosphate binder |
| 4 | ≥5 mg/dL (>442 µmol/L) | 2.5-6 mg/dL (0.81-1.94 mmol/L) | Dietary restriction ± intestinal phosphate binder |

Adapted from Elliott J, Brown S, Cowgill L et al: Phosphatemia management in the treatment of chronic kidney disease: a roundtable discussion: Vetoquinol, 2006.

phosphorus diet, no difference in renal function was found; however, histopathologic changes (mineralization, mononuclear inflammation, and interstitial fibrosis) were more severe in the cats on the normal phosphorus diet.¹⁹²

When a cat refuses to eat a restricted-protein diet but requires phosphorus restriction, intestinal phosphate binders are an option. To be effective, they must be given within 2 hours of a meal because they act by binding the phosphorus in the lumen of the gastrointestinal tract, preventing absorption of the phosphorus and facilitating its excretion in feces. Aluminum hydroxide, aluminum carbonate, and calcium carbonate are traditional choices. They are dosed at 90 mg/kg per day, divided and given with meals. Many cats object to being given these agents.¹²² Epakin (Vétoquinol, Lavaltrie, Quebec) is designed as an alternative to feeding renal diets as a method to reduce serum phosphorus. It is composed of chitosan and calcium carbonate. There are two published clinical studies of this agent. Serum urea and phosphorus levels were significantly reduced during the treatment period with minimal increase in serum calcium.^{40,218}

Renalzin (lanthanum carbonate with kaolin and vitamin E, Bayer AG) is another option recently introduced in some European countries that has been shown to increase fecal phosphorus excretion in cats with surgically reduced renal mass.¹⁹⁹

HYPERPARATHYROIDISM

Hyperparathyroidism is a common complication of chronic renal disease in cats. As parathyroid hormone (PTH) levels increase as a result of a decrease in calcitriol production and serum ionized calcium levels, intracellular calcium concentrations increase, which can result in cell death. High PTH concentration also affects the cardiovascular system, glucose and lipid metabolism, nerve and brain function, and the gastrointestinal tract.¹⁶ Because phosphorus is retained in CKD, sufficient increases in serum Ca can result in a serum calcium × phosphorus product sufficiently high that soft tissue mineralization occurs.

Along with phosphorus restriction, oral calcitriol therapy has been suggested to enhance gastrointestinal absorption of calcium, providing feedback to the parathyroid glands to reduce PTH secretion. It must not be

used until hyperphosphatemia is corrected. Its use is still controversial.^{111,195}

Advocates suggest that it should be started at 2.5 to 3.5 ng/kg daily in early renal insufficiency when Cr is 2 to 3 mg/dL (175 to 265 mmol/L), USG is compatible with CKD as cause of azotemia, and phosphorus is below 6 mg/dL (<1.94 mmol/L). In these patients the PTH levels are often normal and the calcitriol is used to prevent PTH increase to slow progression of the CKD and prevent symptoms related to PTH toxicity. In patients with a serum Cr higher than 3 mg/dL (>265 mmol/L) and serum phosphorous lower than 6 mg/dL (<1.94 mmol/L) the dose is 3.5 ng/kg per day, administered orally. Good client compliance is critical for ongoing monitoring of ionized calcium and PTH.

ANEMIA

Cats with CKD may develop anemia by several mechanisms, including the following:

- “Anemia of chronic disease” (believed to be associated with iron sequestration)
- Anemia from protein malnutrition (from inappetence or being fed a diet not meeting protein requirements)
- Blood loss (associated with uremic gastritis-induced gastrointestinal bleeding)
- Erythropoietin (EPO) deficiency

EPO is produced in the mesangial cells of the glomerulus in response to hypoxia. When administered parenterally, EPO can cause a rapid correction of anemia by stimulating marrow progenitor cells. In 1994 the first report of the use of human recombinant EPO (r-HuEPO) (Eprex) to treat anemia associated with CKD was published.¹⁰⁷ Subsequently, a multicenter study evaluated the safety and efficacy of using r-HuEPO (Epogen) in cats with anemia caused by CKD. The benefits reported include increased appetite, energy, weight gain, alertness, strength, and playfulness to varying degrees but also that anemia, anti-r-HuEPO antibody production, seizures, systemic hypertension, and iron deficiency occurred, albeit inconsistently, in some of the study subjects.⁶² In 2000 a study reported the development of a recombinant adeno-associated virus vector containing the feline erythropoietin gene (rAAV/feEpo). When

normal healthy cats were given an intramuscular injection, a dose-related increase in hematocrit over a 7-week period was seen.¹⁹ An attempt was made to create recombinant feline EPO (rfEPO) in 2004; unexpectedly, 8 of 26 cats developed anemia that was refractory to additional rfEPO treatments.¹⁸⁷

Despite these setbacks, r-HuEPO therapy should still be considered in the anemic cat with CKD. As with any agent, some patients may experience adverse effects, but no patients can benefit if it is not used.⁶¹ The veterinarian should consider using EPO when the packed cell volume is below 20%; 100 U/kg should be administered subcutaneously three times weekly until the packed cell volume is in the low-normal range (35%), then the dose and frequency should be reduced to 50 to 75 U/kg subcutaneously twice a week. It is important to monitor the packed cell volume every 2 weeks for the first 60 to 90 days to check for development of anti-EPO antibodies (Ab). If they occur, EPO must be ceased immediately. The cat may be transfusion dependent for 2 to 4 months until Ab levels decrease. The veterinarian should administer iron at the start of the treatment regimen and continue until the appetite is good. Iron dextran may be administered at 50 mg intramuscularly every 3 to 4 weeks or ferrous gluconate at 50 to 100 mg per cat orally per day. Although there is a risk of Ab development, the majority of cats will enjoy the benefits of an improved hemogram. Darbepoietin (Aranesp) may be less antigenic than EPO and is administered less frequently at 0.45 µg/kg weekly.

With or without EPO therapy, cats with renal disease may require a transfusion; in one review from a university teaching hospital, 20% of the cats needing blood products had CKD.⁴⁸ With diligent and proper preparation and monitoring, it has been shown that multiple red cell transfusions are well tolerated by cats regardless of underlying disease.¹⁹⁶

HYPOKALEMIA

Hypokalemia is a common problem in renal insufficiency. It is a result of inappetence, muscle wasting, and polyuria. Dietary acidification in cats with or without renal function deficiencies contributes to acidosis, which shifts potassium out of cells, falsely elevating serum potassium. Because 94% of body potassium is intracellular, even small changes in serum potassium concentrations reflect significant intracellular events. Thus even serum potassium levels at the low end of the reference interval should be considered to possibly reflect subnormal cellular potassium levels. Acidosis should be corrected. Intravenous potassium chloride is used therapeutically until the patient is eating; after this, oral supplementation with potassium gluconate should be instituted. The starting dose for potassium gluconate is 2 to 4 mEq orally twice daily; it should be titrated to effect on the basis of serum electrolyte levels.

Some cats have persistently low potassium levels despite therapy. In these patients hypomagnesemia and hyperaldosteronism should be considered. It has been suggested that in the latter, a neoplastic or non-neoplastic endocrine condition may be implicated in the progression of kidney disease.¹¹⁴

Prognosis

Chronic renal disease caused by tubulointerstitial nephritis will progress to eventual renal failure. The prognosis is variable because progression occurs at widely differing times in different individuals. Because amelioration of metabolic acidosis, azotemia, hyperphosphatemia, hypertension, and proteinuria have all been shown to halt or slow this progression, the earlier these are identified and treated, the better. Three studies have profiled cats with naturally occurring chronic renal disease. The first showed the following in a group of 184 cats with CKD²²¹:

- Male cats with CKD were significantly younger than female cats with CKD.
- Younger cats were more likely to be diagnosed at an advanced stage of disease than older cats.
- The age at which cats were diagnosed with CKD was influenced by the veterinary clinic where the cats were treated.
- Breed did not appear to play a significant role in the development of CKD in this survey.

The second, a retrospective review, evaluated the duration of survival of 211 cats with naturally occurring CKD.³⁶ IRIS stage of CKD based on serum Cr at the time of diagnosis was found to be strongly predictive of survival. Median survival for cats in IRIS stage 2b at the time of diagnosis was 1151 days (range 2 to 3107) and was longer than survival in stage 3 (median 778, range 22 to 2100) or stage 4 (median 103, range 1 to 1920).

The third study evaluated 190 cats with stage 2 or higher CKD, half of which were treated with benazepril and half with placebo. Cats were followed for up to 3 years. Compared with cats in the treatment group, increased Cr, increased UPC, and increased blood leukocyte count were significantly ($P < 0.01$) associated with a shorter renal survival time and were independent risk factors. Increased concentrations of plasma phosphate or urea and lower blood hemoglobin concentration or hematocrit were significantly ($P < 0.01$) associated with a shorter renal survival time, but they correlated with plasma Cr concentration at the beginning of the study. Blood pressure was not routinely measured; thus this study was unable to include the effects of hypertension on outcome.¹²⁴

These three studies underscore the need to diagnose this condition early and to treat and correct the aforementioned factors. Cats with CKD have widely variable

and often lengthy survival times depending on when they are identified and how they are treated.

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THE LOWER URINARY TRACT

Susan E. Little

Feline lower urinary tract disease (FLUTD) was described as early as 1925 and remains one of the most common problems encountered in feline medicine. A 1999 survey reported that FLUTD affected 1.5% of cats evaluated in private practice.¹¹⁷ In a 2001 study 8% of cats presented to veterinary teaching hospitals were presented for FLUTD.¹⁰¹ Because inappropriate elimination, often seen in cats with FLUTD, is an important risk factor for relinquishment to a shelter, accurate diagnosis and management are welfare as well as medical issues.¹⁴³

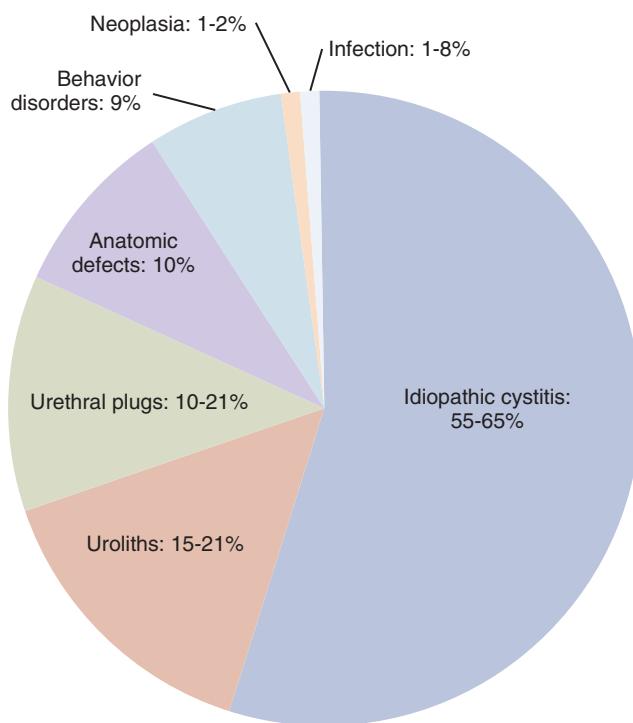


FIGURE 32-16 Prevalence of the causes of feline lower urinary tract disease. (Adapted from Gerber B, Boretti FS, Kley S et al: Evaluation of clinical signs and causes of lower urinary tract disease in European cats, J Small Anim Pract 46:571, 2005; Kruger JM, Osborne CA, Goyal SM et al: Clinical evaluation of cats with lower urinary tract disease, J Am Vet Med Assoc 199:211, 1991; Buffington CA, Chew DJ, Kendall MS et al: Clinical evaluation of cats with nonobstructive urinary tract diseases, J Am Vet Med Assoc 210:46, 1997.)

Over the years various terms such as “feline urologic syndrome” (dating to 1970) and FLUTD (dating to the 1980s) have been used to describe the group of clinical signs related to problems voiding urine.¹³¹ However, these umbrella terms do not identify the underlying etiology. The clinician is encouraged to determine the specific cause for lower urinary tract signs in cats in order to recommend appropriate treatment because FLUTD is not a diagnosis in itself.

A variety of disorders have been implicated as causes of FLUTD, including feline idiopathic cystitis (FIC), urolithiasis, urethral plugs, anatomic defects, neoplasia, infection, and behavioral problems (Figure 32-16). Published studies show general agreement on the relative prevalence of these causes.^{27,60,91} The most common cause is FIC (55% to 65% of cases). Urolithiasis affects about 15% to 20% of cats presenting with FLUTD. Behavioral problems and anatomic defects may account for about 10% of cases. Neoplasia (1% to 2%) and UTIs (1% to 8%) are the least common causes.

Antibiotics are overprescribed for cats with FLUTD, given that bacterial infection is one of the least common diagnoses. In one survey of 301 veterinary practices in the United Kingdom, 47% of practices reported

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FIGURE 32-17 Interactions between urinary tract inflammation and crystalluria to produce common clinical presentations of feline lower urinary tract disease. (Adapted from Gunn-Moore D: Feline lower urinary tract disease, J Feline Med Surg 5:133, 2003.)

providing treatment for cats presenting for the first time with clinical signs of FLUTD without any investigation.⁴⁶ In addition, 68% of practices reported prescribing antibiotics in combination with other options on first presentation. FIC is the most common form of FLUTD and is typically self-limiting. Many cats appear to respond to antibiotic therapy because they have self-limiting disease. This may explain why antibiotics continue to be prescribed in clinical practice despite evidence that they are useless in the majority of FLUTD cases.

Many of the components of FLUTD are not independent factors but instead may be related in a type of unifying hypothesis, leading to the major clinical presentations of FLUTD. In particular, inflammation and crystalluria may be the necessary elements for urolith formation, urethral obstruction, and cystitis (Figure 32-17). This concept was first introduced in the early 1990s by Osborne and colleagues and has since been refined.^{69,136}

Various factors have been associated with risk of FLUTD. In particular, an indoor lifestyle and feeding a diet consisting exclusively of dry food have been implicated.⁸⁴ However, because a great many cats worldwide are confined indoors and fed dry diets but do not have clinical signs of FLUTD, it seems reasonable that some underlying predisposition to FLUTD, as yet uncharacterized, may exist in affected cats.

DIAGNOSTIC METHODS

The underlying causes for FLUTD are varied, and a focused diagnostic plan will help the clinician reach a diagnosis and target treatment (Figure 32-18). A diagnostic evaluation should always include a complete medical and dietary history, physical examination, and urinalysis. Depending on the patient, investigation may

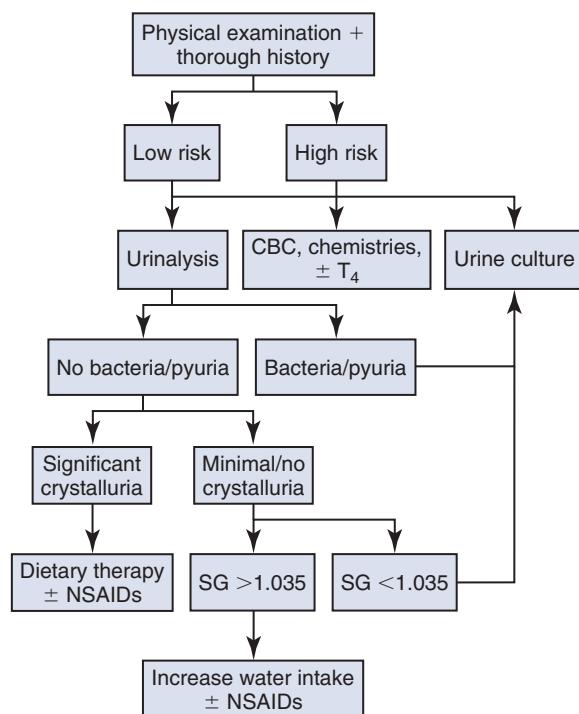


FIGURE 32-18 Decision tree for the initial diagnostic plan for the first occurrence of lower urinary tract signs in a cat without urethral obstruction. Low risk: young to middle-aged cat (<10 years) with no concurrent disease; high risk: older cat (>10 years), with or without concurrent diseases. SG, Urine specific gravity; NSAIDs, nonsteroidal antiinflammatory drugs.

also include urine culture and sensitivity testing, bladder imaging (e.g., plain and contrast radiography, ultrasound, cystoscopy), and other laboratory investigations (e.g., CBC, chemistry profile, total T_4 , retroviral serology). Cats that present with only periuria (urinating outside the litter box) or urine spraying as clinical signs may have a purely behavioral problem or a medical problem with a behavioral component. A behavioral approach to periuria and urine spraying is found in Chapter 13.

Physical Exam and Clinical Signs

It is not possible to determine the cause of FLUTD on the basis of clinical signs alone. Common clinical signs regardless of underlying cause include pollakiuria, dysuria, stranguria, vocalizing during attempts to urinate, hematuria, and periuria. Bilateral ventral abdominal and inguinal alopecia is occasionally seen in cats with bladder pain (Figure 32-19). One of the first steps when evaluating a male cat with FLUTD is to determine urethral patency. Cats with urethral obstruction present with dysuria, stranguria, increased grooming of the penis and perineum, pain, and variable signs of systemic involvement. The bladder may be markedly distended.



FIGURE 32-19 Bilateral ventral abdominal and inguinal alopecia is occasionally seen in cats with bladder pain.

Urinalysis and Urine Collection

A urinalysis should be performed for all cats presenting with signs of FLUTD. Urine samples should be evaluated within 30 to 60 minutes of collection, which means that ideally samples should be analyzed in-house rather than at a referral laboratory. It also means that samples collected at home by the owner and brought to the veterinary clinic for analysis have limited usefulness. Storage for periods of time longer than 60 minutes, especially with refrigeration, may cause in vitro formation of struvite or CaOx crystals.^{2,173} In vitro formation of struvite crystals is especially a risk in stored urine samples from cats fed dry food diets.¹⁷³ Use of a urinalysis preservative tube (BD Vacutainer Plus Urinalysis Preservative Tube; Becton, Dickinson & Co.) may decrease the risk of in vitro crystal formation in stored urine samples.⁸² Urine pH and specific gravity are not significantly affected by storage.² More information on urinalysis is contained in the section on upper urinary tract diseases in this chapter. Although not always a first-line diagnostic test, a urine culture should be performed for any cat with recurrent FLUTD or an identified risk factor. More information on bacterial lower UTI and urine culture is found later in this chapter.

Although urine may be collected in various ways, cystocentesis has become the standard of practice in most situations (Table 32-11).¹⁰⁸ It may be performed blindly using palpation or with ultrasound guidance, especially in obese patients. The benefits of cystocentesis include ease of performance, tolerance by patients, and the collection of samples that are not contaminated by the distal urogenital tract. However, care must be taken with technique to avoid iatrogenic bladder trauma. Because cystocentesis is performed in the veterinary practice, it is helpful if the patient arrives with a full urinary bladder. Owners can be advised to place the cat

TABLE 32-11 Assessment of Urine Collection Methods Based on Patient Safety and Sample Diagnostic Quality

| Purpose of Sample Collection | Cystocentesis | Voided Midstream | Catheterization | Manual Expression |
|-------------------------------|---------------|------------------|-----------------|-------------------|
| Screening test | P | A | N | N |
| Diagnostic urine culture | P | A | N | N |
| FLUTD | P | A | N | N |
| Urolithiasis | P | A | N | N |
| Bladder neoplasia | N | P | N | N |
| Disease distal to the bladder | N | P | N | N |

P, Preferred; A, acceptable; N, not advised, FLUTD, feline lower urinary tract disease.

Adapted from: Lulich J, Osborne C: Cystocentesis: lessons from thirty years of clinical experience, *Clin Brief* 2:11, 2004.

in its carrier or in a room without a litter box for several hours before the veterinary visit. Some cats with FLUTD are pollakiuric as a result of bladder pain; providing analgesia (e.g., buprenorphine, or meloxicam in a well-hydrated patient) can reduce stranguria and may facilitate urine collection. More information on cystocentesis and other methods of urine collection is contained in the section on upper urinary tract diseases in this chapter.

Urethral catheterization is most often performed for diagnostic procedures (e.g., contrast cystography) and for relief of urethral obstruction rather than for collection of urine samples. The procedure for the male cat is described later in this chapter, in the section about the management of cats with urethral obstruction. The procedure for female cats is very similar to that for the female dog and is usually performed under sedation or general anesthesia. Catheterization should always be performed aseptically. The cat is placed in sternal recumbency with the hind legs hanging off the end of the examination table. It is important to keep the body position straight. A 3.5 to 5 French soft catheter with a stylet or a more rigid polypropylene catheter should be used. Because the vaginal vault of the female cat is small, visualization of the urethral opening is not usually possible. Wearing sterile gloves, the veterinarian palpates the urethral papilla on the floor of the vagina with the index finger.¹⁵⁴ The lubricated urinary catheter is then passed under the index finger and directed down and into the urethra. If resistance is felt, the catheter has likely encountered the cervix and must be repositioned.

Imaging

Imaging is recommended for cats with recurrent or persistent FLUTD signs, palpation of a bladder mass, or a history of urolithiasis. Survey radiographs are most useful for detection of radiodense uroliths at least 3 mm in size. The entire urinary tract, including the urethra, should be radiographed. Both lateral and dorsoventral

BOX 32-14

Common Indications for Contrast Cystography

- Suspected bladder rupture
- Bladder tumor
- Chronic cystitis
- Radiolucent calculi
- Bladder diverticuli
- Incontinence
- Congenital anomalies

Adapted from Essman SC: Contrast cystography, *Clin Tech Small Anim Pract* 20:46, 2005.

views should be obtained, and ideally the colon should be emptied with an enema before the procedure to improve visualization of the bladder.

Contrast cystography is relatively easy to perform in clinical practice. The indications are described in Box 32-14. All procedures are performed under general anesthesia and require urethral catheterization. Multiple radiographic views (right and left lateral, ventrodorsal and dorsoventral) have been recommended.⁵⁴ A brief discussion of the techniques follows; more detailed information has been published.⁵⁴ Risks of contrast cystography are few but include urethral trauma or perforation during catheterization, overdistention of the bladder (potentially leading to ischemia, hemorrhage, or rupture), and fatal air embolism.⁵⁴

The simplest technique is negative contrast cystography (pneumocystogram), performed with approximately 10 mL/kg of a negative contrast agent (room air, carbon dioxide, or nitrous oxide) (Figure 32-20). This technique is best for demonstrating the location and size of the bladder and bladder wall thickness but does not provide good mucosal detail, and small bladder tears may be overlooked. When the bladder is distended, normal wall thickness is 1 to 2 mm.



FIGURE 32-20 Negative contrast cystogram with no abnormal findings performed on a 5-year-old neutered male domestic shorthair cat with recurrent signs of feline lower urinary tract disease. (Courtesy Dr. Janet Cohn, Veterinary Information Network.)



FIGURE 32-21 Double contrast cystogram with no abnormal findings performed on the same cat in [Figure 32-20](#). (Courtesy Dr. Janet Cohn, Veterinary Information Network.)

Positive contrast cystography is used for determining bladder size and shape, detecting bladder tears through leakage of contrast, assessment of wall thickness, and identification of small filling defects. It is poor for assessing mucosal detail. It is performed with approximately 10 mL/kg of an organic iodinated contrast medium; barium and sodium iodide are never used.

Double contrast cystography is more involved but is the best technique for detection of most common feline diseases, such as bladder wall abnormalities, mucosal changes, and calculi. First 0.5 to 1 mL of contrast medium is infused into the bladder, followed by approximately 10 mL/kg of a negative contrast agent such as room air. The contrast medium forms a pool in the dependent portion of the bladder; calculi appear as radiolucent objects in the pool ([Figure 32-21](#)).

Ultrasonographic equipment is less expensive than in the past, and image quality has improved, making the procedure affordable and accessible. It has the benefit of being a rapid noninvasive imaging technique that also allows for evaluation of other abdominal organs without sedation or anesthesia in many patients. Another benefit is that veterinary staff is not exposed to radiation. Ultrasonographic examination of the distended bladder may be used to evaluate bladder wall thickness, mass lesions, calculi, blood clots, echogenic debris, diverticula, and ectopic ureters ([Figure 32-22](#)). Although ultrasonography has become a popular diagnostic tool for FLUTD, it is important to understand that it does not replace survey radiography but instead should be considered complementary, particularly for patients with uroliths.¹¹³

One in vitro study concluded that ultrasonography was more sensitive than survey and contrast radiography for detection of canine uroliths.¹⁸⁰ The false-negative

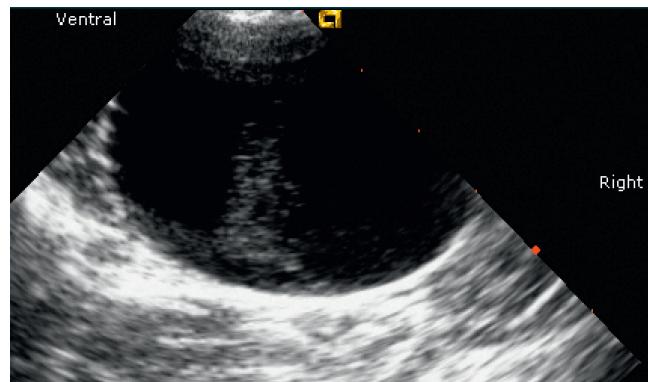


FIGURE 32-22 Ultrasound examination of the bladder of an 11-year-old spayed female domestic shorthair cat with clinical signs of feline lower urinary tract disease. Echogenic debris (cells, debris, +/– crystals), sometimes seen in cats with idiopathic cystitis, is present. (Courtesy Dr. Edward Javinsky.)

detection rate (i.e., the chance of missing the lesion) for CaOx uroliths was lowest with ultrasonography (2%) and highest with double contrast radiography (7%). The false-negative detection rate for struvite uroliths was 0% with ultrasonography, double contrast radiography, and pneumocystography and 2% with survey radiography.

However, ultrasonography does not provide information that may be useful in determining urolith composition. As well as providing an indication of mineral composition ([Table 32-12](#)), radiographs also provide information about urolith number, size, and location.

Cystoscopy

Transurethral cystoscopy, available at some referral centers, is performed under general anesthesia with a rigid endoscope and a balanced electrolyte solution for

TABLE 32-12 Predicting Mineral Composition of Feline Uroliths on the Basis of Radiographic Appearance

| Mineral | Radiographic Opacity Compared with Soft Tissue | Surface Contour | Shape | Usual Number | Appropriate Size |
|------------------|--|-------------------------------------|----------------------------------|--------------------------------|------------------|
| CaOx monohydrate | +++ to ++++ | Smooth, but occasionally bosselated | Commonly round, but also rosette | >5 | 1 mm-5 mm |
| CaOx dihydrate | +++ to ++++ | Rough to smooth | Rosettes | >3 | 1 mm-7 mm |
| Sterile MAP | ++ to +++ | Slightly rough | Round or discoid | Usually 1-3, occasionally many | 3 mm-10 mm |
| Infection MAP | + to +++ | Smooth to slightly rough | Round to faceted | Few to many | 2 to >7 mm |
| Urate | - to ++ | Smooth | Round to ovoid | Usually 1, but up to 5 | 2 mm to 10 mm |
| CaP | +++ to ++++ | Rough | Too rare to comment | Too rare to comment | 1 mm-4 mm |
| Cystine | - to +++ | Rough | Round | Many, but some with few | 1 mm-4 mm |
| Silica | ++ to ++++ | Too rare to comment | Too rare to comment | Too rare to comment | 1 mm-4 mm |
| Xanthine | - to + | Smooth | Round to ovoid | 1-3 | 1 mm-5 mm |

CaOx, Calcium oxalate; *MAP*, magnesium ammonium phosphate; *CaP*, calcium phosphate.

From Lulich JP, Osborne CA: Changing paradigms in the diagnosis of urolithiasis, *Vet Clin North Am Small Anim Pract* 39:79, 2009.

flushing and distention of the bladder. Because of the narrowness of the feline urethra, it is most commonly performed in female cats (or male cats with a perineal urethrostomy), typically using a 1.9-mm diameter, 18-cm long instrument.³⁴ Cystoscopy may be used for diagnosis of bladder diseases through visualization of abnormalities (e.g., ectopic ureters, masses, uroliths, glomerulations) as well as biopsy of masses and calculi removal. In skilled hands the procedure is quick and minimally invasive. Risks include urethral or bladder trauma or perforation as well as overdistention of the bladder.¹⁵¹

IDIOPATHIC CYSTITIS

FIC is a chronic, sterile, inflammatory process causing signs of lower urinary tract disease. The etiology is incompletely understood, and treatment is often frustrating for both clinician and owner. It is the most common diagnosis for young cats with FLUTD (the second most common being urolithiasis). FIC is important not only because of the pain and distress it causes patients, but also because it is highly associated with house soiling, an important cause of relinquishment of cats to shelters.¹⁴³

Terminology can be confusing with this disease. *Interstitial cystitis* is a term best reserved for that subset of FIC patients with chronic or frequent signs and cystoscopic

findings consistent with the National Institutes of Health criteria for humans.⁷³ *Idiopathic cystitis* is a more generic, umbrella term for those cats with acute or chronic signs of FLUTD in which cystoscopy has not been performed or has not revealed changes associated with interstitial cystitis.

Prevalence

FIC appears to be a modern disease, having first been mentioned in the early 1990s when it was discovered that no specific diagnosis could be made in most cats with FLUTD signs.⁹¹ Currently, approximately 55% to 65% of cats younger than 10 years of age with signs of FLUTD have no specific cause identified for their clinical signs and are classified as having FIC.

Patient Signalment and Risk Factors

Most patients are 2 to 6 years of age at diagnosis; FIC is uncommon in cats younger than 1 year of age or older than 10 years of age. FIC is less likely as a new diagnosis in geriatric cats, and other causes of FLUTD should be pursued aggressively in this age group. In one questionnaire-based study of 31 cats with FIC compared with 24 normal housemates and 125 other normal cats, certain risk factors were identified: male sex, being overweight, pedigree breed, and stress factors, especially conflict with another cat in the home.³³ Other studies

have found male and female cats equally affected. Additional risk factors variably reported as associated with FLUTD include an indoor lifestyle, no access to outdoors for elimination (exclusive litter box use), and a predominantly dry-food diet.^{84,187} Outdoor cats may be affected, particularly if the neighborhood cat population is dense. It is important to note that not all studies agree on all risk factors. Studies have been conducted in various locations using different criteria and sample sizes. In addition, concentrating on single risk factors rather than the interplay of factors may be too simplistic an approach. For example, in a study of 238 healthy indoor-housed cats, 157 cats with FLUTD, and 70 cats with other diseases, few differences in lifestyle, environment, or diet were detected among the groups.²⁹ Instead, the authors of this study postulate that an internal predisposition exists in some cats rather than that environmental factors directly cause disease.

An indoor lifestyle protects cats against hazards, such as predation, trauma, and many infectious diseases. However, in some cats the indoor lifestyle may bring unintended health consequences, such as obesity and FLUTD. Undoubtedly, many cats have adapted to indoor living without health problems. A successful adaptation to the indoor lifestyle may depend on the quality of the indoor environment and the ability of the cat itself to adapt.

Some individual cats may be unusually sensitive to features of an indoor lifestyle.²⁴ This is understandable insofar as cats are a less socially interactive species than dogs or humans and free-roaming cats often live in low-density populations. If the home ranges of free-roaming cats overlap, they avoid meeting by using a time-sharing schedule. These natural behaviors are inhibited to greater or lesser degrees with indoor housing. In addition, many indoor environments are boring and predictable, factors considered stressful. Lack of control in an environment and perceptions of threat are also important triggers of stress responses.

The behavioral stress response is accompanied by immunologic, neurologic, endocrinologic, and vascular responses. Comorbid conditions with FLUTD and FIC include obesity, separation anxiety, gastrointestinal tract problems, and hypertrophic cardiomyopathy.^{29,156,160} In one study owners of cats with lower urinary tract disease were more likely to describe their cats as fearful, nervous, or aggressive than healthy cats or cats with other diseases.²⁹ These findings suggest that FIC is a disease process that affects more than the urinary bladder. Even healthy cats may exhibit temporary signs of illness affecting multiple body systems (e.g., anorexia, inappropriate elimination, vomiting, or diarrhea) in response to stressful events.¹⁶⁹ The reader is referred to an excellent review of the stress response and its role in certain feline diseases for more information.²⁴

Clinical Signs

The most common clinical signs in cats with FIC are periuria, pollakiuria, dysuria, vocalizing during attempts to urinate, and hematuria. These clinical signs are not specific to FIC and may also occur in cats with other causes of FLUTD. The clinical signs typically wax and wane and often follow or are exacerbated by stressful events. The episodes are usually self-limiting and of short duration (3 to 7 days). About 50% of cats will have recurrent signs within 1 to 2 years. It appears that recurrent episodes decrease in frequency and severity as the cat becomes older.^{90,92}

Some cats (fewer than 15%) will have more frequent recurrences or chronic persistent clinical signs.^{41,85,92} Whether this represents an extreme on the spectrum of cats with FIC or is an indication that FIC is not a single disease entity remains unknown. Some male cats with FIC will suffer a urethral blockage caused by mucus plugs that include proteins, cells, and debris with or without crystals.

Pathophysiology

Over the years, many theories as to the cause of FLUTD and FIC have been advanced and discarded. In the 1960s and 1970s, bacterial infection was considered to be the main cause of lower urinary tract signs. Many factors contributed to this erroneous theory, such as a high rate of false-positive results on urinalysis and urine culture and extrapolation of information from other species. Various viruses, such as calicivirus, have been associated with FLUTD, but convincing evidence for a causative role is lacking despite decades of investigation. In the 1970s and 1980s, it was thought that vesicourachal diverticula played a role in FLUTD, and surgical correction of the defect was often recommended. However, one case series determined that diverticula resolved within 2 to 3 weeks with medical management to resolve FLUTD signs without surgical intervention and did not recur.¹³⁴

The pathophysiology of FIC is not well understood, although advances have been made in recent years. It seems likely that FIC is a syndrome that may have several underlying causes that may act separately or may be interrelated.⁹² FIC is thought to involve complex interactions among the CNS, bladder, and endocrine system. Cats with FIC are described by Buffington and colleagues as "sensitive cats in a provocative environment." These cats may be unusually sensitive to stressors, such as changes in their environment and diet, weather changes, moving to a new home, holiday activities, and intercat conflict.^{24,29,33,84} FIC has many similarities to nonulcerative interstitial cystitis in humans, although the ulcerative form (Hunner's ulcer) has also rarely been reported in cats.⁴²

Cats with FIC have been shown to have enhanced activation of stress responses, particularly in the sympathetic nervous system (SNS). Stress and pain stimulate increased SNS activity—the “fight or flight” response—that results in release of catecholamines. Tyrosine hydroxylase is the rate-limiting enzyme of catecholamine synthesis and is produced in response to acute or chronic stress. Cats with FIC have increased tyrosine hydroxylase activity in the brain stem and hypothalamus and an increased release of norepinephrine and other catecholamine metabolites during stress compared with normal cats.^{153,182} Moreover, cats with FIC have functional desensitization of central alpha₂ adrenoceptors, probably as a result of chronic stimulation from elevated catecholamine levels.¹⁸³

Activation of the SNS may increase epithelial permeability and permit noxious agents in the urine to access sensory afferent neurons, resulting in pain and inflammation. In support of this hypothesis, cats with FIC are known to have significantly higher bladder permeability than healthy cats, as well as epithelial damage and dysfunction.^{58,97} Biopsies of the bladder of cats with FIC often show submucosal edema, hemorrhage, and vasodilation, sometimes with large numbers of mast cells.^{30,168} Products of activated mast cells could play a role in the pain and inflammation associated with FIC. The exact role of mast cells is difficult to determine insofar as mastocytosis also occurs in the bladders of cats with urolithiasis.¹⁶⁷ In addition, the other histopathologic abnormalities are not specific for FIC and may not correlate well with the presence of clinical signs. It is also unknown if the changes represent primary dysfunction of the urothelium or appear secondary to injury.

Other abnormalities have been found in the bladders of cats with FIC. Neurogenic inflammation is initiated by excitation of C-fiber sensory afferent neurons and mediated by neuropeptides such as substance P. The bladder afferent neurons in cats with FIC show increased excitability to stimuli compared with those of healthy cats.¹⁶² In addition, substance P receptors are increased in the bladder of cats with FIC.³¹ The interaction of neuropeptides with tissue receptors results in many changes, such as vasodilation, increased vascular permeability, and mast cell activation. The combined effects of neuropeptides and mast cell mediators may result in pain, inflammation, tissue injury, and fibrosis.⁹²

A thin layer of glycosaminoglycan (GAG) covers and protects the bladder urothelium. Similar to humans with interstitial cystitis, urinary GAG excretion is decreased in some cats with FIC compared with healthy cats.^{26,144} It has been hypothesized that the low GAG levels in urine reflect qualitative and quantitative changes in the GAG layer and may be associated with increased bladder permeability. The cause of the alterations to the GAG layer is not understood, nor is it known if the changes are a cause of disease or appear secondary to other mechanisms.

Abnormalities are also found in the hypothalamic–pituitary–adrenal axis, which, unlike the SNS, does not appear to be activated. One of the roles of glucocorticoids such as cortisol is to restrain catecholamine synthesis and metabolism, thus balancing the stress response. Cats with FIC have significantly decreased serum cortisol responses compared with normal cats and have smaller adrenal glands with reduced size of the zona fasciculata and zona reticularis.¹⁸⁶ Despite the subnormal cortisol responses in cats with FIC, treatment with prednisolone has not been effective.¹³⁵

Thus the response of the hypothalamic–pituitary–adrenal axis appears to be dissociated from the response of the SNS to stress in cats with chronic FIC. Essentially, FIC is an exaggerated SNS response to stress with an inadequate adrenocortical response, although the cause of these abnormalities is not understood. The complex involvement of the CNS may explain why therapies directed only at the bladder have a high failure rate. In effect, according to this theory, the bladder is an innocent bystander.

An interesting question is why the bladder appears to be the primary target for cats with FIC, although given the presence of comorbid diseases, it is probably not the only target. The SNS is involved in both micturition and sensory arousal, and it is well known that involuntary urination is a response to severe stress. Overlap between micturition and fear pathways may put the bladder at risk during stress responses.²⁵

Diagnosis

There is no gold-standard test for diagnosis of FIC; it is essentially a diagnosis of exclusion. Physical examination of cats with FIC may be unrewarding, or it may reveal a painful thickened bladder. Some cats have bilateral ventral abdominal and inguinal alopecia as a result of chronic overgrooming of the area over the bladder. The minimum initial workup at first presentation calls for a complete history, including environmental and diet history, thorough physical examination, and urinalysis (see Figure 32-18).

A variety of abnormal findings may be revealed on urinalysis, none of which is specific for any particular bladder disease. Hematuria is commonly found, although it may be present in one sample and not in another from the same cat. Hematuria may also be induced by the sample-collection method (i.e., manual expression, cystocentesis, or catheterization). Proteinuria and crystalluria may also be found in some cats. Because mild crystalluria may be found in normal cats, it is important not to overinterpret this finding. Crystals do not damage a healthy urothelium. In fact, it appears likely that crystals form secondary to bladder inflammation rather than being the cause. Neurogenic inflammation of the bladder mucosa leads to leakage of plasma

proteins into urine, thereby increasing the urine pH and allowing struvite crystals to form. USG is often very high with FIC, especially in cats fed exclusively dry foods. A low USG (under 1.035) should prompt investigation for systemic disease. Some normal cats fed only a canned diet may have USG as low as 1.025.

Urine culture is a low-yield test on account of the low prevalence of bacterial UTIs in cats younger than 10 years of age. Urine culture should be performed in cats older than 10 years, cats with recurrent clinical signs (two or more episodes), cats with low USG, cats with concurrent diseases, cats that have undergone perineal urethrostomy, and cats in which a urethral catheter was recently placed.

A survey radiograph of the urinary tract (including the entire urethra) may provide clinically relevant information because 15% to 20% of cats with lower urinary tract signs have urinary calculi. Together urinalysis and survey radiographs are the most commonly used diagnostic tests for cats with lower urinary tract signs. In young cats negative findings on both tests warrant a presumptive diagnosis of FIC and initiation of a treatment plan.

Further imaging studies are indicated in cats with recurrent signs that do not respond to initial treatment as well as in senior cats. Contrast cystography may detect radiolucent calculi and other lesions, such as masses. Double contrast cystography may be useful insofar as certain findings have been associated with FIC in approximately 15% of cases.¹⁶¹ These include focal or diffuse bladder wall thickening and irregularities of the bladder mucosa. Ultrasonography may also be used to evaluate cats for cystic calculi, mass lesions, bladder wall characteristics, and other abnormalities, such as blood clots.

Cystoscopy should be considered for cats with recurrent bouts of FLUTD when available and when other diagnostics have failed to find a cause. Because of the narrowness of the feline urethra, cystoscopy is limited to evaluation of female cats weighing at least 3 kg (6.6 lb) or male cats with a perineal urethrostomy. Cystoscopy allows for visualization of the bladder wall and evaluation for abnormalities associated with FIC, such as increased blood vessel density and tortuosity, edema, and submucosal petechial hemorrhages (glomerulations) (Figure 32-23). However, because these abnormalities have also been seen in otherwise healthy cats, cystoscopy is best performed to rule out other causes for the clinical signs, such as small cystic calculi and ectopic ureters and masses.

Management

Environmental Modification

Given that the etiology of FIC is still unknown, current treatment recommendations are directed at decreasing

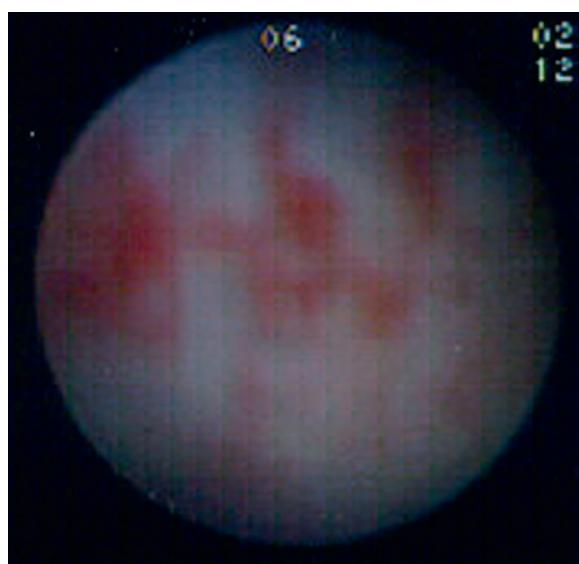


FIGURE 32-23 Cystoscopic appearance of the bladder of a female cat with idiopathic cystitis showing submucosal petechial hemorrhages (glomerulations). (Courtesy Dr. Joseph Bartges.)

the severity and frequency of clinical signs rather than being curative. Perhaps the most important part of the treatment plan is ensuring that the owner understands FIC and is willing to make the recommended changes. FIC is a frustrating disease, one that often requires long-term management, and a strategy that provides owners with ongoing support and information is essential.

Because increased activity of the SNS stress response seems to maintain the chronic inflammatory response, therapy is directed at reducing stressors. Another goal of therapy is to reduce the noxious properties of urine that irritate the bladder mucosa. The recommended standard of care to achieve these goals includes environmental enrichment and stress reduction, increased water intake, litter box management, management of interactions in multiple cat homes, and potentially drug therapy.¹⁸⁵

Environmental enrichment is a tool to help decrease sympathetic overdrive, reduce stress, and prolong time between episodes of FIC. The goal is to increase choices to provide the cat with a sense of control over the environment and allow it to behave in a species-appropriate way. Provisional recommendations have been published that focus on identifying key resources, as well as feeding and litter box management.²⁴ Indoor and high-density cat populations are risk factors for FIC.²⁴ Indoor cats need places to climb, scratch, sleep, perch on high, and hide, in addition to food and water. Many cats find it stressful to compete for these resources daily. Owners often do not understand the importance of resources other than food, water, and a litter box. Box 32-15 is a resource checklist designed to help owners identify and correct problems. In addition, owners are often unfamiliar with the signs of intercat conflict and stress, given

BOX 32-15**A Resource Checklist for Cat Owners**

Enhanced stress response system activity seems to be central in exacerbating clinical signs in cats with feline idiopathic cystitis. Any treatment strategy to decrease sympathetic nervous system outflow may be important in reducing these signs. By altering the environment of a cat that has had previous episodes of feline idiopathic cystitis, the veterinarian can decrease clinical signs and increase the interepisode intervals. The authors provide this list to clients and tailor

these resources on a case-by-case basis. Although most cats do not require all suggestions from this list, a detailed history obtained from the owner will dictate which areas seem to be most relevant for each patient. If drug therapy is necessary in the patient, it should be used in conjunction with appropriate environmental strategies listed in the following.

Litter Box Management

| | Yes | No |
|---|-----|----|
| Boxes are located on more than one level in multilevel houses. | — | — |
| Boxes are located so that another animal cannot sneak up on the cat while it uses it. | — | — |
| Boxes are located away from appliances or air ducts that could come on unexpectedly while the cat uses them. | — | — |
| The litter is kept clean, scooped as soon after use as possible (at least daily). | — | — |
| Boxes are washed regularly (at least weekly) with a mild detergent (e.g., dishwashing liquid), rather than strongly scented cleaners. | — | — |
| Unscented clumping litter is used. | — | — |
| The brand or type of litter purchased is changed infrequently (less than monthly). | — | — |
| If a type of litter is offered, it is put in a separate box so that the cat can choose to use it if it wants to. | — | — |
| Each cat has its own litter box in a convenient, well-ventilated location that still gives the cat some privacy while using it. | — | — |

Food and Water

| | | |
|---|---|---|
| Each cat has its own food and water bowl in a convenient location that provides some privacy while eating or drinking. | — | — |
| Bowls are located such that another animal cannot sneak up on the cat while it eats. | — | — |
| Bowls are located away from appliances or air ducts that could come on unexpectedly while the cat eats or drinks. | — | — |
| Food and water is kept fresh (daily). | — | — |
| Bowls are washed regularly (at least weekly) with a mild detergent. | — | — |
| The brand or type of food purchased is changed infrequently (less than monthly). | — | — |
| If a new food is offered, it is put in a separate dish next to the familiar food so that the cat can choose to eat it if it wants to do so. | — | — |

Environmental Considerations

| | | |
|---|---|---|
| Scratching posts are provided. | — | — |
| Toys are provided, rotated, or replaced regularly. | — | — |
| Each cat has the opportunity to move to a warmer or cooler area if it chooses to do so. | — | — |
| Each cat has a hiding area where it can get away from threats if it chooses to do so. | — | — |
| Each cat has its own space that it can use if it chooses to do so. | — | — |

Rest

| | | |
|--|---|---|
| Each cat has its own resting area in a convenient location that still provides some privacy. | — | — |
| Resting areas are located such that another animal cannot sneak up on the cat while it rests. | — | — |
| Resting areas are located away from appliances or air ducts that could come on unexpectedly while the cat rests. | — | — |
| If a new bed is provided, it is placed next to the familiar bed so that the cat can choose to use it if it wants to do so. | — | — |
| Movement—each cat has the opportunity to move about freely, explore, climb, stretch, and play if it chooses to do so. | — | — |
| Social contact—each cat has the opportunity to engage in play with other animals or the owner if it chooses to do so. | — | — |

BOX 32-16**Recommended Reading and Resources****Techniques**

Essman SC: Contrast cystography, *Clin Tech Small Anim Pract* 20:46, 2005.

Lulich J, Osborne C: Cystocentesis: lessons from thirty years of clinical experience, *Clin Brief* 2:11, 2004.

Reine NJ, Langston CE: Urinalysis interpretation: how to squeeze out the maximum information from a small sample, *Clin Tech Small Anim Pract* 20:2, 2005.

Sabino C, Boudreau A, Mathews K: Emergency management of urethral obstruction in male cats, *Clin Brief*:57, 2010.

Behavior and Environmental Enrichment

Ellis SLH: Environmental enrichment: Practical strategies for improving feline welfare, *J Feline Med Surg* 11:901, 2009.

Herron ME, Buffington CA: Environmental enrichment for indoor cats, *Compend Contin Educ Vet* 32, 2010.

Indoor pet initiative, Ohio State University: <http://indoorpet.osu.edu/>

Overall K, Rodan I, Beaver B et al: Feline behavior guidelines from the American Association of Feline Practitioners, *J Am Vet Med Assoc* 227:70, 2005.

that the signs are typically subtle to the uninformed observer and usually stop short of actual fighting. Cats typically prefer to avoid others rather than engage in fighting, so that sufficient three-dimensional space must be available in multicat homes. Enrichment should also provide mental stimulation through the use of toys, food puzzles, window perches, and so on. The reader is referred to further resources that provide more information on environmental enrichment for cats (Box 32-16). More information is also found in Chapter 14.

Litter boxes should be in a quiet and easily accessible area and should be scooped daily and cleaned weekly. Clumping, unscented litters and those containing activated carbon are preferred by most cats.¹²⁸ Citrus-scented litters should be avoided. It is commonly recommended that owners provide a minimum of one more litter box than the number of cats in the household, although supportive evidence is lacking. Boxes should be located in at least two easily accessible but quiet areas. Cats also seem to prefer large or jumbo-size boxes; commercial cat litter boxes are often too small. Plastic storage bins (e.g., sweater or under-bed storage boxes) or dog litter boxes are good alternatives (Figure 32-24). Further discussion of litter box management is found in Chapter 13.

Feeding is not a social function for cats as it is for humans. In a multicat household, there should be enough



FIGURE 32-24 Large litter boxes can be made by modifying plastic storage bins. (Courtesy Dr. Margie Scherk.)



FIGURE 32-25 Water can be provided in a way that stimulates interest, such as a water fountain. (Courtesy Dr. Emma Thom.)

food and water stations for each cat to eat and drink alone. Some cats may benefit from being fed in a separate room. Food puzzles are mentally stimulating, and hiding food throughout the home allows cats to engage in normal hunting behavior. Water should be provided in large bowls (e.g., dog bowls) or in a more interesting way that stimulates investigation (e.g., pet water fountain) (Figure 32-25).

Unfortunately, published trials that have evaluated the usefulness of the various components of environmental enrichment for cats with FIC are scarce. A recent case report detailed successful management of FIC in an indoor cat living with five other cats using environmental modification.¹⁶³ In an uncontrolled study of 46 client-owned cats, multimodal environmental modification (MEMO) was instituted, and the cats were followed for 10 months.²⁸ The components of MEMO are available for owners and veterinarians on the website of the Indoor Pet Initiative (see Box 32-16). Significant

decreases were documented in signs of FLUTD, fearfulness, nervousness, and aggressive behavior. Moreover, owners reported a reduction in clinical signs referable to the respiratory and gastrointestinal tracts. The results of the study remain difficult to interpret, however, because no controls were included and dietary or drug interventions were used concurrently with MEMO.

Pheromones are fatty acids that induce changes in the limbic system and hypothalamus and appear to alter emotional states in cats.⁶⁷ Feliway (Ceva) is a synthetic analog of a feline facial pheromone, available as both a spray and a plug-in room diffuser. Facial pheromones are deposited on prominent objects (e.g., furniture) by facial rubbing when cats feel comfortable and safe. Use of Feliway has been associated with increased grooming and food intake in hospitalized cats,⁶⁷ decreased urine spraying,¹²⁶ and decreased scratching.¹⁴⁰ Little data are available to evaluate the efficacy of Feliway for cats with FIC. In one pilot study nine cats with FIC completed a randomized, double-blind, placebo-controlled crossover study of the efficacy of Feliway.⁷⁰ Although there were no statistical differences between the treatment groups, there was a trend for cats exposed to Feliway to show fewer days with clinical signs. Current recommendations are that Feliway should be used in conjunction with other management strategies. Further investigation into the use of pheromones in the management of FIC is warranted.

Increasing Water Intake

There is no evidence to suggest that diets designed to prevent urolithiasis or promote “urinary tract health” should be recommended for cats with FIC. Indeed, dietary change is a stress in itself. However, increasing water intake appears to be important in the management of FIC. Increased water intake may dilute noxious components in urine that irritate the bladder mucosa, thereby decreasing pain and inflammation. The treatment goal should be to decrease the cat’s USG until it is below 1.040 and even below 1.030 if possible by feeding canned foods containing at least 60% moisture.⁴⁰ Although cats fed a dry diet drink more water than cats fed canned diets, the total daily water volume ingested is greater in cats fed canned food because of the high water content of canned foods. In addition, feeding the daily food allowance divided into at least two or three meals has been shown to increase water intake in healthy cats.⁸⁸

In a nonrandom prospective study, 54 client-owned cats with FIC were monitored for 1 year.¹¹⁸ The cats were fed either a dry or canned formulation of a diet designed for management of lower urinary tract disease. Signs of FIC recurred in only 11% of cats on the canned diet and in 39% cats fed the dry diet. Cats fed the dry formulation had an average USG of 1.050 compared with 1.030 for cats fed the canned formulation.

To reduce the stress of change, owners should be instructed to offer old and new foods side by side in similar dishes, allowing the cat to become accustomed to the new diet before withdrawing the old diet. Other suggestions for changing diets are found in Box 18-5. If the FIC patient will not change to a canned diet, increased water intake can be accomplished by various other means (see Box 18-16).

A common recommendation to increase water consumption is to use a pet water fountain. One study of 12 healthy cats found that water intake was slightly greater from a fountain than a bowl.⁶⁴ However, urine osmolality was not reduced, which suggests that measurement of water intake from the fountain was falsely elevated. The lowest urine osmolality and specific gravity achieved was only 1901 mOsm/L and 1.044, respectively. One problem encountered during this study was the tendency for cats to play with water in the fountain, thus splashing water out and making assessment of actual intake difficult.

Drug and Nutraceutical Therapy

Many drug therapies have been recommended for FIC, but few controlled studies have been performed. Because FIC is a painful disease, analgesics may be prescribed for acute episodes. It is important to break the pain-inflammation-pain cycle. A common choice is transmucosal buprenorphine (0.02 to 0.03 mg/kg, every 6 to 12 hours) for 3 to 5 days.⁴⁰ Other analgesics that have been recommended include fentanyl transdermal patch, butorphanol (0.1 to 0.2 mg/kg, orally, every 8 to 12 hours), oxymorphone, and NSAIDs. Ease of use is important to decrease the stress associated with administration of the medication.

Dysuric male cats with FIC may benefit from antispasmodics to relax the urethra. Recommended medications include phenoxybenzamine, prazosin, and dantrolene (Table 32-13). Many of these drugs also have sedative properties, which may be beneficial in the short term.

Amitriptyline is a tricyclic antidepressant with anticholinergic, antihistaminic, sympatholytic, antiinflammatory, and analgesic properties and has been recommended for severe FIC cases in which environmental enrichment and diet change have not provided relief. In an uncontrolled study 15 cats with severe recurrent FIC were treated with 10 mg/cat, orally once daily in the evening.⁴¹ Clinical signs were eliminated in 73% of cats for the first 6 months of the study and in 60% of cats for the full 12 months of the study. However, cystoscopic abnormalities persisted despite clinical remission. Side effects noted included weight gain, lethargy, and decreased grooming. Cystic calculi were noted in four cats and resolved spontaneously in three of the cats. Amitriptyline is not effective in the short term and therefore is not useful for acute treatment of FIC insofar as

TABLE 32-13 Drugs Used in the Management of Cats with Urethral Obstruction and Other Lower Urinary Tract Disorders

| Drug | Class | Indication | Dose | Adverse Effects |
|------------------|---|---|--------------------------------|--|
| Acepromazine | Phenothiazine | Sedation, antispasmodic (smooth muscle) | 0.02-0.05 mg/kg, SC, q6-8h | Hypotension |
| Bethanecol | Parasympathomimetic | Detrusor atony | 1.25-5.0 mg/cat, PO, q12h | Vomiting, diarrhea, salivation |
| Buprenorphine | Opiate | Analgesia | 0.01-0.02 mg/kg, SC, q8-12h | Sedation |
| Butorphanol | Opiate | Analgesia | 0.2-0.4 mg/kg, PO/SC, q8-12h | Sedation |
| Dantrolene | Skeletal muscle relaxant | Antispasmodic (striated muscle) | 0.5-2.0 mg/kg, PO, q8h | Hepatotoxicity |
| Diazepam | Benzodiazepine | Antispasmodic (striated muscle) | 2.5-5.0 mg/cat, PO, q8h | Sedation, appetite stimulation |
| Fentanyl | Opiate | Analgesia | 25 µg/hour transdermal patch | Respiratory depression, bradycardia |
| Hydromorphone | Opiate | Analgesia, sedation | 0.02-0.05 mg/kg, IV/IM/SC, q4h | Respiratory depression, hyperthermia, vomiting |
| Phenoxybenzamine | Alpha ₁ -adrenergic antagonist | Antispasmodic (smooth muscle) | 2.5-7.5 mg/cat, PO, q12h | Sedation, hypotension |
| Prazosin | Alpha ₁ -adrenergic antagonist | Antispasmodic (smooth muscle) | 0.25-0.5 mg/cat, PO, q12h | Sedation, hypotension |

SC, Subcutaneous; PO, by mouth; IM, intramuscular.

the drug takes several weeks to exert maximal effect.^{89,90} It appears to be a safe drug, having been prescribed by behaviorists for many years, and may be effective at a lower dose (2.5 to 5 mg/cat daily). Transdermal formulations of amitriptyline have poor systemic absorption and cannot be recommended.¹²² Other drugs have been used for cats with FIC (e.g., clomipramine, fluoxetine, buspirone), but no clinical studies evaluating efficacy have been published. Appropriate monitoring of CBC and serum chemistry profile should be performed before starting any psychotropic medication and repeated periodically during treatment.

GAG therapy is used with short-term success in some human patients with interstitial cystitis. The rationale is to help repair the defective urothelium to decrease permeability, as well as provide analgesic and anti-inflammatory effects. There is one case report in the veterinary literature on the apparent successful use of sodium pentosan polysulfate in a cat with biopsy-diagnosed interstitial cystitis,⁴² although two other clinical studies failed to show any difference between cats receiving placebo and cats receiving treatment.^{38,179}

Glucosamine is a natural substrate for the biosynthesis of GAG and is available combined with chondroitin sulfate as Cosequin (Nutramax). In a recent study oral glucosamine was compared to placebo in a randomized, double-blind, placebo-controlled study of 40 patients with FIC over 6 months.⁷¹ Owners kept a diary of FIC-related events and graded the severity of the cat's

clinical signs at the start and at the end of the trial. There was no significant difference between the two groups when considering the owners' assessment of mean health score, the average monthly clinical score, or the average number of days with clinical signs. Most cats in the study did improve clinically, but this was attributed to a change to a canned food diet in 90% of the cats. The mean USG at the beginning of the study was 1.050; 1 month into the trial, it decreased significantly to 1.036. Despite this, clinical signs recurred in 65% of the cats, so dietary therapy alone was not sufficient. It is difficult to recommend GAG therapy given the lack of any veterinary studies demonstrating efficacy in FIC.

UROLITHIASIS AND URETHRAL PLUGS

Prevalence

Uroliths are organized concretions containing primarily crystalloids with a small amount of organic matrix. The most common components of uroliths are struvite and CaOx,^{35,77} but recently uroliths composed of dried solidified blood have been reported.¹⁸⁴ Urine is commonly supersaturated with crystalloids, so crystalluria itself is not a disease and does not need to be treated unless it is associated with clinical signs. It is important to understand that finding crystalluria in cats with signs of

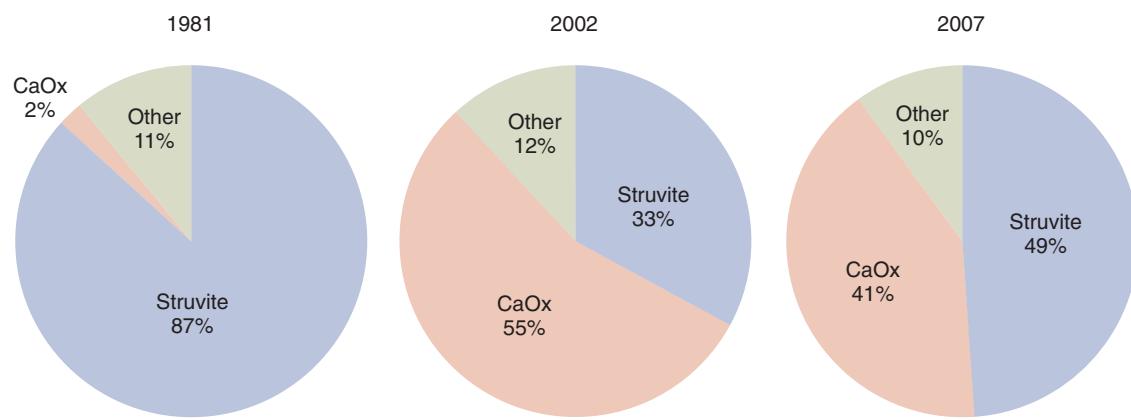


FIGURE 32-26 Composite of changes in feline urolith composition over time (1981-2007) reported by American and Canadian urolith analysis centers. (Adapted from Cannon AB, Westropp JL, Ruby AL et al: Evaluation of trends in urolith composition in cats: 5,230 cases (1985-2004), J Am Vet Med Assoc 231:570, 2007; Houston DM, Moore AEP: Canine and feline urolithiasis: examination of over 50,000 urolith submissions to the Canadian Veterinary Urolith Centre from 1998 to 2008, Can Vet J 50:1263, 2009; Osborne CA, Lulich JP, Kruger JM et al: Analysis of 451,891 canine uroliths, feline uroliths, and feline urethral plugs from 1981 to 2007: perspectives from the Minnesota Urolith Center, Vet Clin North Am Small Anim Pract 39:183, 2009.)

FLUTD does not guarantee that the crystals are actually the cause of the clinical signs.

In the last 25 years, dramatic change in the prevalence of different urolith types has occurred (Figure 32-26). Until the mid-1980s, struvite uroliths made up 78% of submissions to the Minnesota Urolith Center (MUC).¹³⁹ Starting in the mid-1980s, a dramatic increase in the frequency of CaOx uroliths, along with a decrease in struvite uroliths, was noted. By 2002 55% of uroliths submitted to the MUC were CaOx, whereas only 33% were struvite. However, in recent years the prevalence of urolith types has changed again. In 2007 49% of uroliths submitted to the MUC were struvite and 41% were CaOx. The ratio of CaOx to struvite uroliths also increased significantly in submissions to the Gerald V. Ling Urinary Stone Analysis Laboratory from 1985 to 2004.³⁵ But as with the MUC study, by 2002-2004, 44% of uroliths were struvite and 40% were CaOx.

The prevalence of struvite uroliths presented to the Canadian Veterinary Urolith Centre (CVUC) decreased in the 10-year period from 1998 to 2008, whereas that of CaOx uroliths remained constant.⁷⁸ In 2008 49% of uroliths submitted to the CVUC were CaOx and 42% were struvite. In Europe the prevalence of CaOx uroliths also increased from 1994 to 2004.¹⁴⁷ In 1994 77% of uroliths were struvite and 12% were CaOx. By 2003 61% of uroliths were CaOx and 32% were struvite.

Despite these comprehensive data sets, it is important to note that they may not truly reflect the prevalence of urolith types for several reasons. For example, not all cats with uroliths are diagnosed or treated, and not all uroliths are submitted for analysis. It is also possible that CaOx uroliths are more likely to be removed and submitted for analysis than struvite uroliths because there is no medical dissolution option for this type of urolith.

It seems likely that the increase in CaOx uroliths seen in the 1980s was driven by changes in feline diets. The widespread use of diets designed to dissolve struvite uroliths meant that fewer were surgically removed and submitted for analysis. At the same time, the modification of maintenance diets to prevent struvite uroliths may have caused an increase in CaOx uroliths. Some dietary factors that decrease the risk of struvite uroliths can increase the risk of CaOx uroliths. The more recent changes in prevalence of urolith type may be associated with further modification of maintenance diets to minimize the risk of CaOx uroliths and improvements in and increased use of therapeutic diets designed to reduce risk factors for CaOx uroliths.

Methods for Urolith Removal

Various methods for urolith removal are available for cats: surgical removal, basket retrieval by way of cystoscopy, voiding urohydropropulsion (VU), and lithotripsy. Dietary dissolution is available only for struvite uroliths (see Chapter 18). The choice of method will be dictated by patient factors and stone type, as well as the equipment and expertise available (Table 32-14). Regardless of the method used, imaging should be used to confirm complete removal.

Cystotomy is the most commonly used method to retrieve bladder uroliths. The procedure is well known, surgery times are short, and complications are rare.¹⁸⁸ Suture nidus uroliths have been reported to form after cystotomy (discussed later).⁵ Incomplete surgical removal of uroliths occurs in approximately 15% to 20% of patients.¹¹⁶ Several precautions can be taken to reduce this risk.¹¹² If time has elapsed since the original diagnosis, imaging studies should be repeated the day of surgery to confirm the number and location of the

TABLE 32-14 Comparison of Bladder Urolith Treatment Methods

| Technique | Urolith Size/ Number | Urolith Type | Advantages | Disadvantages | Anesthesia Required? | Equipment Required |
|----------------------------|--|-----------------|--------------------------|--|-------------------------|-----------------------------------|
| Voiding urohydropropulsion | <3-5 mm in females <1 mm in males Any number | All | No surgery | Urethral obstruction | Yes | Catheter |
| Cystoscopic retrieval | Small, any number | All | No surgery | Limited to small uroliths | Yes | Rigid cystoscope, stone basket |
| Laser lithotripsy | Small to medium, moderate number | All | No surgery | Limited availability, long procedure times, not well evaluated in cats, limited to females or males with perineal urethrostomy | Yes | Cystoscope, laser lithotripter |
| Cystotomy | Any | All | Rapid, readily available | Invasive, longer recovery time | Yes | Surgical instruments |
| Medical dissolution | Any size, number | Struvite only | Noninvasive | Limited to struvite stones, takes several weeks | No | Prescription diet |

Adapted from Langston C, Gisselman K, Palma D et al: Methods of urolith removal, *Compend Contin Educ Vet* 32, 2010.

uroliths. Urethroliths can be flushed retrograde into the bladder before surgery. The urethral catheter can be left in place during surgery to prevent migration of uroliths into the urethra during the procedure. Finally, the urethra can be flushed before closing the incision in the bladder. The catheter tip is inserted just inside the distal urethra. The urethra is occluded by pinching it around the catheter during retrograde flushing. Postoperative imaging should always be performed to ensure that all uroliths have been removed. Laparoscopy-assisted cystotomy for the removal of bladder uroliths has been described in dogs but has also been used clinically in cats.¹⁵²

VU can be used successfully for removal of uroliths with a diameter smaller than the urethral lumen; in cats this means uroliths smaller than 3 to 5 mm in females and 1 mm in males.^{17,95} Smooth uroliths are more likely to be successfully removed than irregular uroliths or ones with sharp edges. The patient is anesthetized, and a urinary catheter is placed and attached to a three-way stopcock. The bladder is filled with sterile saline until distended. Overdistention is discouraged; the typical volume used is 4 to 6 mL/kg. The patient is then held in a fully upright position with the spine perpendicular to the table. The bladder is gently agitated to loosen any uroliths adhered to the mucosa, and the urinary catheter is removed. The bladder is expressed manually to void the saline and uroliths. The bladder is compressed dorsally and cranially during expression; the bladder should not be compressed into the pelvic canal. The steps are repeated as needed until imaging confirms that all uroliths have been removed. The clinician should be prepared for surgical removal of any uroliths that cannot be removed by VU. Hematuria and dysuria may be expected for 1 to 2 days after the procedure.¹¹⁵ It has been

recommended that antibiotics be administered for up to 5 days to prevent UTI.

Cystoscopic retrieval using a urolith basket is possible in female cats and male cats that have undergone a perineal urethrostomy. It is useful only for uroliths small enough to be withdrawn through the distended urethra (<5 mm). It is a desirable approach for patients with bladders that are too fragile for manual expression, such as patients that have recently undergone cystotomy. Only one urolith is removed at a time, and a large urolith should never be forced through the urethra.

Lithotripsy has been evaluated for stone fragmentation and removal in dogs and cats. Extracorporeal shock wave lithotripsy is best suited for fragmentation of uroliths that are fixed in one location, such as nephroliths. Laser lithotripsy (holmium:YAG) is used for intracorporeal fragmentation of bladder calculi in humans. In veterinary medicine transurethral laser lithotripsy can be performed through small-diameter flexible endoscopes. In cats the small diameter of the male urethra is a limitation, so the procedure is feasible only in females or males that have had a perineal urethrostomy. After lithotripsy the fragments are removed through VU or cystoscopy.

One in vitro study found that holmium laser energy was able to fragment various types of canine uroliths into fragments smaller than 3.5 mm in diameter.¹⁹² Three in vivo studies that evaluated laser lithotripsy in dogs reported bladder urolith removal rates of 83% to 96% in females and 68% to 81% in males.^{1,65,114} Reported complications included bladder and urethral perforation, urethral swelling causing obstruction, and hemorrhage. Most complications were short-lived. Laser lithotripsy has been compared with surgical removal for bladder uroliths in dogs.²¹ The procedures were equally

successful. Laser lithotripsy procedures were on average 23 minutes longer than surgical procedures, but lithotripsy patients were discharged from the hospital about 12 hours sooner. To date, no published studies have evaluated the use of laser lithotripsy for treatment of bladder uroliths in cats.

Struvite Uroliths

Risk Factors

Struvite uroliths have also been called *triple phosphate* or *magnesium ammonium phosphate* uroliths. They most commonly occur in the bladder and usually form in sterile urine in the cat. Infection-induced uroliths may occur in young cats (younger than 1 year of age) and senior cats (older than 10 years of age).¹⁷⁵ Cats with struvite uroliths are generally younger (peak age, 4 to 7 years) than cats with CaOx uroliths. No clear sex predisposition exists. Other risk factors include an indoor sedentary lifestyle, obesity, low water intake, and alkaline urine. Certain breeds appear to be predisposed (e.g., Persian, Himalayan, Ragdoll, Chartreux, Oriental Shorthair), whereas other breeds appear to be at low risk (Rex, Abyssinian, Burmese, Russian Blue, Birman, Siamese).¹⁷⁵

Formation of struvite uroliths is influenced by urine pH, urine concentration, and the presence of calculogenic materials. Early research demonstrated that struvite urolithiasis could be induced in cats by feeding a diet very high in magnesium (3 to 10 times the level found in commercial diets). This led to the erroneous assumption that magnesium was the main cause of struvite urolithiasis in cats. Subsequent research showed that urine pH influences the formation of struvite uroliths and that these uroliths can be dissolved when the urine pH is reduced to less than 6.4. In a study evaluating the association between dietary factors and struvite formation, diets with the highest magnesium, phosphorus, calcium, chloride, or fiber content; moderate protein content; and low fat content were associated with increased risk.¹⁰² However, struvite formation is likely a complex process in which individual dietary factors cannot be considered in isolation but instead interact with one another and with factors such as breed, age, sex, and environment.

Clinical Signs and Diagnosis

Cats with struvite uroliths have the generic signs of lower urinary tract disease: hematuria, pollakiuria, peruria and dysuria. Struvite uroliths are typically round, ellipsoid, or tetrahedral in shape and may be present singly or in large numbers. Survey abdominal radiographs are often sufficient for detection of radiopaque uroliths that are 3 mm or more in diameter. Detection of small uroliths or nonradiopaque uroliths may be improved with double contrast cystography or ultrasonography (Figure 32-27). Urinalysis typically shows an

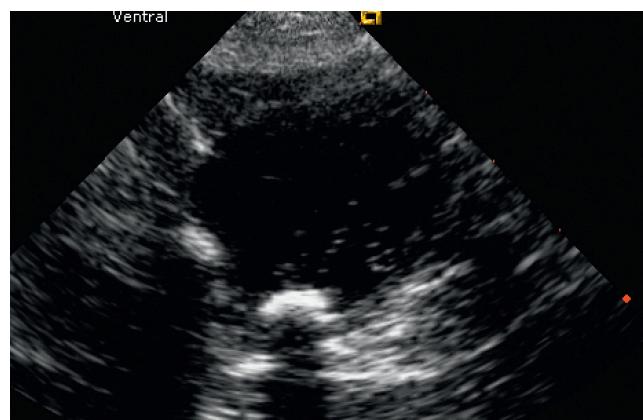


FIGURE 32-27 Ultrasound examination of the bladder of a 2-year-old neutered male domestic shorthair cat with hematuria. A urolith is seen as an echogenic object (6.2 × 3.7 mm) with an acoustic shadow adjacent to the dorsal bladder wall. Some echogenic debris is present in the bladder lumen. (Courtesy Dr. Edward Javinsky.)

alkaline pH; struvite crystals may be present but are not always associated with urolith formation. The index of suspicion for struvite uroliths in patients with lower urinary tract signs is increased in cats younger than 7 years old, those with a prior history, and those with struvite crystalluria and alkaline urine. Definitive diagnosis requires removal and chemical analysis.

Treatment

Both stone dissolution by way of dietary therapy and stone removal are options for cats with struvite uroliths (see Table 32-14). Dissolution therapy is noninvasive but dependent on owner and patient compliance. Treatment failure may occur if the urolith type is misidentified or if the uroliths have a complex composition. Therapeutic diets that reduce urine pH to below 6.4 and contain restricted magnesium levels are used. Dietary therapy is effective; in one study dissolution of sterile struvite uroliths occurred in a mean of 36 days (compared with 44 days for infected uroliths).¹³⁸ In another study using a different diet, struvite uroliths dissolved completely in 31 of 39 cats in an average of 30 days.⁷⁹

Once a dissolution diet is prescribed, owners should feed this diet exclusively and be cautioned against feeding treats, table food, milk, and similar substances. Radiographs should be reassessed once monthly, and the diet should be fed for 2 to 4 weeks after radiographic disappearance to ensure that the smallest uroliths that are not radiographically detectable have resolved.¹⁴¹ If urine culture indicates the presence of a bacterial UTI, antibiotics must be administered or dissolution therapy may not be effective. Antibiotic therapy should be continued for 1 month after radiographic dissolution because bacteria may be released from uroliths as they dissolve.¹³⁸

Struvite dissolution diets should not be used in growing cats, cats with acidemia, or pregnant cats. Some authorities do not recommend use of dissolution diets in male cats because of the risk of urethral obstruction as the uroliths decrease in size.¹⁴¹ However, there is no published evidence to support this concern.

After medical dissolution or stone removal, measures should be taken to minimize urolith recurrence. In one study of 1821 cats with struvite uroliths, 2.7% had a first recurrence and 0.2% had a second recurrence.³ In the past urinary acidifiers (such as DL-methionine and ammonium chloride) were commonly used to reduce urine pH, but they are rarely indicated today. Several struvite-preventive diets are commercially available that acidify urine and avoid excessive magnesium, phosphorus, calcium, and chloride. However, no randomized, controlled studies have evaluated their efficacy. *Ad libitum* feeding may decrease the postprandial alkaline tide, but care must be taken to avoid obesity. Water intake should be increased to encourage diuresis and reduce urine concentration of mineral precursors for urolith formation. This is best accomplished by feeding a canned diet; other methods to increase water intake are listed in Box 18-16. Recommendations on how to change a cat's diet are found in Box 18-5.

Routine monitoring (e.g., urinalysis, radiographs) is recommended for early detection of recurrence. Initially, reassessment should occur every 3 months. Urinalysis should be monitored for crystalluria, pH, and specific gravity. Urine pH should be maintained at less than 6.5 and USG should be less than 1.030. A pH meter is preferable to urine dipsticks for monitoring because meters provide more precise measurement of pH and are not affected by pigments in urine.

Calcium Oxalate Uroliths

Risk Factors

Risk factors for development of CaOx urolithiasis include age (mean age, 7 years) and breed (Persian, Himalayan, British Shorthair, Exotic Shorthair, Havana Brown, Foreign Shorthair, Ragdoll, Scottish Fold).^{35,78,86,100,147}

Some studies suggest male cats are at higher risk than females.^{35,78,100} Diets low in sodium or potassium and those formulated to increase urine acidity increase the risk of CaOx uroliths.¹⁰² The source of drinking water is thought to be an unlikely contributor to the development of CaOx uroliths.⁸⁶

Altered systemic calcium metabolism may play a role in the formation of CaOx uroliths in some cats. Mild hypercalcemia (11.5 to 13.5 mg/dL [2.88–3.38 mmol/L]) was documented in more than one third of cats with CaOx urolithiasis in one study.¹³² Other studies have also reported hypercalcemia in cats with CaOx urolithiasis.^{120,125,158} Many of the cats in these studies had a history of being fed a urine-acidifying diet. Chronic dietary



FIGURE 32-28 Multiple calcium oxalate uroliths surgically removed from the bladder of a 12-year-old spayed female domestic longhair cat with hematuria.

acidification can cause metabolic acidosis, increased serum ionized calcium concentrations, hypercalcemia, and increased bone turnover of calcium. Dietary acidification therefore predisposes cats to hypercalciuria and CaOx urolithiasis. It is important to assess dietary needs throughout all life stages in cats and avoid continuation of a urine-acidifying diet prescribed early in life into the later years. Other factors, such as increased absorption of calcium or oxalate from the gastrointestinal tract or renal tubular dysfunction leading to hypercalciuria or hyperoxaluria, may also be involved but have not been well investigated in cats.¹²⁵

Clinical Signs and Diagnosis

When CaOx uroliths form in the lower urinary tract, clinical signs include stranguria, hematuria, pollakiuria, periuria, and urethral obstruction. CaOx uroliths are radiopaque and usually white and hard, with either an irregular or smooth surface (Figure 32-28). They may be present as either single or multiple stones. Survey abdominal radiographs are often sufficient for detection of CaOx uroliths (Figure 32-29). Detection of small uroliths or nonradiopaque uroliths may be improved with double contrast cystography or ultrasonography, both of which have a false-negative rate of less than 5%.⁹⁴ The index of suspicion for CaOx versus struvite uroliths in the bladder would be higher in male cats, cats over 7 years of age, and in susceptible breeds. Definitive diagnosis of CaOx uroliths requires removal and chemical analysis.

Ruling out concurrent diseases and evaluating for hypercalcemia is important in cats suspected or known to have CaOx uroliths. Cats with CaOx uroliths should have a CBC and serum biochemistry profile performed, as well as a urinalysis and urine culture. Evaluation of hypercalcemia includes assessment of total serum calcium, ionized calcium, and PTH. Because the



FIGURE 32-29 Radiographic appearance of the bladder uroliths pictured in Figure 32-28.

hypercalcemia is usually idiopathic, the total serum calcium and ionized calcium are increased but the PTH concentration is normal or low.

Urinalysis typically shows an acidic pH in cats with CaOx uroliths. These uroliths are not usually associated with infection, although secondary bacterial infections, especially with *E. coli*, may be present in some patients.¹⁷ Although CaOx crystals may be seen on urinalysis, they are not a reliable indicator of whether uroliths are present or of uolith composition. Some cats with uroliths do not have crystalluria, and uncommonly those with uroliths may have urinary crystals that are different from the type in the stone.²³

Treatment

To date, no calculolytic diets for CaOx uroliths exist. The only effective treatment is physical removal of the stones, usually by way of surgery or VU. Lithotripsy is available at some referral centers. Cystotomy must be performed for larger uroliths, but care must be taken to remove all the stones. Uroliths causing urethral obstruction should be retropulsed into the bladder.¹⁷

Recurrence of CaOx uroliths in cats after treatment is common (Figure 32-30). In a study of 2393 cats with CaOx uroliths, 7% had one recurrence, 0.6% had a second recurrence, and 0.1% had a third recurrence (usually, but not always, of the same uolith type).³ Recommendations for the management and prevention of CaOx uroliths include the following (see also Box 18-14):

1. Feed a protein-restricted, high-moisture, alkalinizing diet designed to prevent CaOx uroliths¹⁰⁹; avoid foods high in oxalates, and avoid supplements of ascorbic acid and vitamin D.¹³⁷
2. Reduce the USG to less than 1.025 by feeding canned food (other suggestions for increasing water consumption are found in Box 18-16)

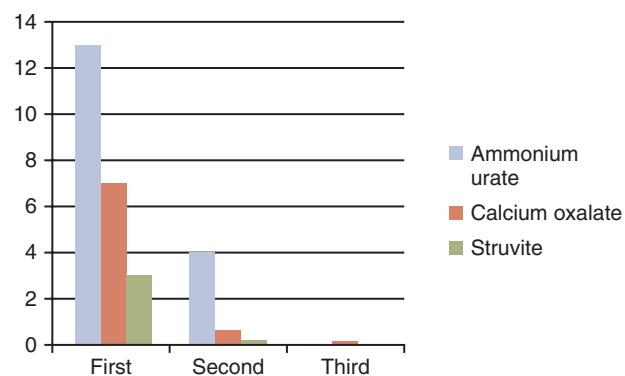


FIGURE 32-30 Percentage of cats with recurrence of uroliths. Recurrence was usually, but not always, with the same uolith type. (Adapted from Albasan H, Osborne C, Lulich J et al: Rate and frequency of recurrence of uroliths after an initial ammonium urate, calcium oxalate, or struvite urolith in cats, J Am Vet Med Assoc 235:1450, 2009.)

3. Maintain a urine pH of 7 to 7.5 by using a therapeutic diet or supplementing with potassium citrate (50 to 75 mg/kg with food, every 12 hours)
4. Other strategies include supplementing with vitamin B₆ (2 to 4 mg/kg, daily to every other day, orally) and administration of hydrochlorothiazide to promote calcium reabsorption (2 to 4 mg/kg, orally, every 12 hours)⁷⁵
5. If hypercalcemia is present, use a high-fiber diet and potassium citrate; other options include glucocorticoids (start prednisolone at 5 mg/cat daily orally for 1 month and reassess) and once weekly oral alendronate (10 mg/cat)³⁹

The appropriate dietary sodium content for prevention of CaOx uroliths is currently a matter of controversy, and guidelines are lacking. For more information, see Chapter 18.

After urolith removal, cats should be re-evaluated within 1 month and then again at 3 months and 6 months. In addition to a physical examination and medical history, a urinalysis should be performed as well as bladder imaging (radiography, ultrasonography, or both). Ideally, bladder imaging should be performed every 6 months. Some cats will require monitoring of total and ionized calcium, and cats receiving diuretics will require monitoring of electrolytes.

Other Urolith Types

Although struvite and CaOx are the most common urolith types in cats, many other mineral types have been identified, including urates (Figure 32-31), apatite, cystine, potassium magnesium pyrophosphate, calcium phosphate, xanthine, and silica.^{35,77,139} Mixed, compound, and matrix uroliths have also been identified.

Uroliths not composed of mineral salts may also form. In one report 49 of 21,784 (0.2%) feline uroliths were



FIGURE 32-31 Uroliths composed of ammonium urate (95%) and calcium oxalate (5%) surgically removed from the bladder of a 5-year-old spayed female Egyptian Mau with pollakiuria, hematuria, and inappropriate elimination.

composed of dried solidified blood (DSB).¹⁸⁴ These uroliths were firm and stonelike and did not resemble blood clots. Almost half had been submitted after 2001. The mean age of affected cats was 9 years. Although they were found throughout the urinary tract, most of these uroliths (57%) were removed from the bladder or urethra. DSB calculi do not appear to be radiodense and may not be detected on ultrasound examination. In another report 60 of 5230 (1.1%) uroliths were determined to be composed of DSB.³⁵ The majority had been submitted in 1999 or later, and male cats were found to be overrepresented.

Foreign objects, such as sutures placed in the bladder during cystotomy, may act as a nidus for urolith formation. From 1999 to 2006, 0.17% of feline bladder uroliths submitted to the CVUC contained a suture nidus.⁵ The most common mineral composition of the uroliths was CaOx, but struvite and compound minerals were also identified. It seems to take an extended period of time, approximately 1 year, for a clinically apparent urolith to form around a suture nidus. The authors of the study recommended certain precautions when closing the bladder after cystotomy, such as avoiding full-thickness bites, long-lasting absorbable sutures, and nonabsorbable sutures.

Urethral Plugs

Most urethral plugs are composed primarily of a proteinaceous matrix (mucoprotein and inflammatory debris) with trapped crystals. They are typically found at the tip of the penis where the urethral diameter is smallest or in other areas of the urethra where a narrowing occurs (i.e., caudal to the bulbourethral gland or between the bladder and prostate gland). Although CaOx uroliths are now at least as common as struvite uroliths, the mineral composition of urethral plugs continues to be predominantly struvite.^{53,77,139} Other urethral plugs are composed almost totally of matrix or sloughed tissue and blood. It is currently not known what causes urethral plugs to form. One theory suggests that urethral plugs form in cats with underlying inflammation.¹⁸¹ Plasma proteins may enter the urine from suburothelial

vascular leakage and may trap crystals in the lumen of the urethra, resulting in obstruction. Oozing of plasma proteins into urine combined with active inflammation may increase the urine pH, thus contributing to the precipitation of struvite crystals.

MANAGEMENT OF URETHRAL OBSTRUCTION

Urethral obstruction is a common feline medical condition, although data on prevalence in the general cat population is lacking. It was diagnosed in 18% of more than 22,000 cats with FLUTD presented to veterinary teaching hospitals¹⁰¹ and in 10% of cats presented to a large urban emergency service.⁹⁹ Little information is available regarding risk factors. In a recent study of 82 cats with urethral obstruction compared with sex- and time-matched controls, the majority of affected cats were between 1 and 7 years old.¹⁶⁴ The proportion of cats consuming exclusively dry food was significantly higher in the cats with urethral obstruction. Increased body weight, which may be a marker for decreased activity, was also associated with increased risk. Cats with access to outdoors were at decreased risk. In another study risk was greatest for cats between 4 and 10 years of age.¹⁰¹

Fortunately, the frequency of urethral obstruction has been declining in recent decades. In veterinary teaching hospitals in Canada and the United States, the hospital proportional morbidity rate for urethral obstruction declined from 19 cases per 1000 cats evaluated in 1980 to 7 cases per 1000 cats in 1999.¹⁰³ This coincides with, and is likely due to, at least in part, the widespread availability of diets designed to minimize struvite crystalluria.

Obstructive uropathy is most common in males because of the small diameter of the male urethra compared with that of female cats. The age at time of castration does not affect the diameter of the urethra and so does not affect risk of urethral obstruction.¹⁵⁵ Typical clinical signs include dysuria, hematuria, frequent attempts to urinate, vocalizing in the litter box, and licking of the penis or prepuce. Owners may not notice that the cat has not voided urine recently, and some cats will be erroneously presented for constipation or for difficulty walking. Some cats will have signs of systemic illness, such as lethargy, anorexia, weakness, and vomiting. Cats suffering from prolonged obstruction may present moribund or dead.

Diagnosis is relatively simple and is accomplished by palpating a large, firm bladder, which seems to be painful for the cat. Palpation of a distended bladder should be performed gently to avoid tears or ruptures. In some cases owners present cats relatively soon after obstruction has occurred, in which case the bladder may not be overdistended but it will not be possible to express

urine. Urethral obstruction should be considered as a differential diagnosis for any young to middle-aged sick male cat.

Obstruction may be caused by an intraluminal object, mural thickening, or compression by an extraurethral mass. Urethral plugs and urethroliths have been identified as the most common causes of obstruction in male cats,^{60,91} although more than 50% of cases were classified as idiopathic in a recent study.⁶¹ Other potential causes include urethrospasm, trauma, congenital defects, stricture, and neoplasia.

Stabilization

Cats with urethral obstruction should be treated as emergencies when presented. Although most patients are stable at presentation, 10% or more have significant physiologic compromise. In particular, cats that have been obstructed 48 hours or more may be severely ill and require crisis management. The initial approach to management should be adapted to the cat's condition because it can make a life-or-death difference to the most severely compromised patients. The most common immediately life-threatening issue is not the obstruction itself but the resulting cardiovascular compromise.

A thorough assessment of the cat's condition should be made before attempting to relieve the obstruction as specific stabilization measures may be necessary, particularly before sedation is provided or anesthesia is induced. Physical evaluation should include mucous membrane color, capillary refill time, pulse quality and rate, cardiac auscultation, and rectal temperature. Hypothermia may occur secondary to circulatory shock. Cats with urethral obstruction would be expected to have a high heart rate on account of stress and pain. The presence of an inappropriately slow heart rate may be associated with hyperkalemia; an electrocardiogram should be performed and serum potassium concentration measured. Supplemental oxygen may be provided by face mask or flow-by delivery.

An intravenous catheter should be placed promptly to administer fluids and medication and obtain blood samples. Blood is collected for a CBC, serum chemistries, and electrolytes. For critically ill cats an emergency database would be packed cell volume, total protein (TP), electrolytes, ionized calcium, blood glucose, BUN, and Cr. Venous blood gases are also useful if available. Analgesia should be provided at the earliest opportunity. Appropriate agents include butorphanol, buprenorphine, hydromorphone, and other opioids. NSAIDs are inappropriate in this clinical setting.

Obstructed cats may have moderate to severe dehydration and varying degrees of electrolyte disturbances and azotemia, so the prompt initiation of fluid therapy is extremely important. In one study 85% of cats with

urethral obstruction were azotemic.¹⁶⁴ A balanced electrolyte solution is recommended for rehydration and stabilization. In two studies metabolic acidosis resolved more slowly in critically ill cats with urethral obstruction treated with 0.9% NaCl than in those treated with balanced electrolyte solutions, but there was no difference in the final outcome between the two treatments.^{45,48} In severely dehydrated or moribund cats, 20 to 30 mL/kg may be administered as an initial intravenous bolus, adjusting the subsequent fluid rate on the basis of initial response.⁴⁷ More information on fluid therapy for cats with postrenal azotemia due to urethral obstruction is found in Chapter 5.

Common electrolyte abnormalities in cats with urethral obstruction that may require correction include hyperkalemia, metabolic acidosis, and hypocalcemia. The measures outlined in subsequent paragraphs have temporary effects but will help stabilize the patient as fluid therapy is instituted and until the inciting cause is corrected. In one study approximately 24% of 199 obstructed cats had mild to severe hyperkalemia (≥ 6.0 mEq/L).⁹⁹ About 12% of the cats in the same study had multiple, life-threatening metabolic derangements (particularly hyperkalemia and concurrent hypocalcemia). In another study hyperkalemia (48%), ionized hypocalcemia (56%), and hyponatremia (55%) were common findings.¹⁶⁴

In most cases metabolic abnormalities resolve with administration of fluids and relief of the obstruction. However, in some cases specific treatment should be considered. Severe metabolic acidosis ($\text{pH} < 7.1$) has profound effects on the cardiac system, respiratory system, and CNS. Treatment with sodium bicarbonate may be required in unstable cats with severe metabolic acidosis. If it is not possible to evaluate blood gases, severely ill cats can be treated with 1 to 2 mEq/kg sodium bicarbonate given slowly and intravenously. It is important to monitor serum calcium because sodium bicarbonate lowers the ionized portion of plasma calcium and some patients are already hypocalcemic at presentation; therefore the hypocalcemia should be corrected first. More information on treatment of metabolic acidosis with sodium bicarbonate is found in Chapter 5.

Potassium is involved in cellular function and neuromuscular transmission. Hyperkalemia may have profound cardiac effects, with characteristic electrocardiographic changes that include bradycardia, peaking and narrowing of the T wave, a shortened QT interval, widening of the QRS complex, and decreased amplitude or loss of the P wave. It is not possible to correlate the electrocardiographic changes with the severity of the hyperkalemia. Some cats have significant hyperkalemia without electrocardiographic changes. The effect of hyperkalemia in cats with severe electrocardiographic disturbances can be countered with calcium gluconate, which directly antagonizes potassium at the cell

membrane level. The veterinarian should administer 50 to 100 mg/kg intravenously over 2 to 3 minutes while monitoring the electrocardiogram for calcium-induced arrhythmias. The effects are almost immediate and will last about 30 minutes.

Plasma potassium can be further decreased if necessary by driving it intracellularly using regular insulin (0.1 to 0.25 U/kg intravenously). The insulin should be followed with an IV bolus of 50% dextrose (0.5 g/kg, diluted) to prevent hypoglycemia. Serum potassium will decrease within 1 hour. Blood glucose should be monitored for several hours after administration of insulin, and intravenous fluids can be supplemented with 2% to 5% dextrose to maintain normoglycemia.

In one study, ionized hypocalcemia (<2.4 mEq/L) was identified in 75% of 24 obstructed male cats, usually associated with high serum phosphorus (caused by decreased renal excretion).⁴⁹ Cats with severe ionized hypocalcemia (<1.6 mEq/L) may have impaired cardiac electrical and mechanical dysfunction, requiring administration of intravenous calcium (as detailed previously).

Cystocentesis is useful to decompress the bladder before attempting to catheterize the urethra.¹⁸¹ This helps relieve pain and distention and makes subsequent attempts to flush the urethra easier by reducing back pressure. The procedure may be performed with a 22- or 23-gauge butterfly needle or a 22-gauge needle attached to an extension set, stopcock, and 20-mL syringe. The veterinarian inserts the needle into the bladder halfway between the apex and the neck of the ventral or ventro-lateral wall while the bladder is stabilized manually. The needle should enter the bladder at an oblique angle and should be directed caudally.¹⁰⁸ The veterinarian should be careful not to apply excessive pressure to the bladder during the procedure to minimize the risk of urine leakage. As much of the urine as possible should be removed, and the samples should be saved for urinalysis and urine culture. The most important complication is damage to the bladder wall or bladder rupture and would be most likely to occur in cats with friable, compromised bladder walls. Bladder rupture could also occur in these patients during attempts to relieve urethral obstruction without prior cystocentesis. Although rupture is an uncommon event, the veterinarian should be prepared for surgical intervention should it occur.

Urinalysis findings in cats with urethral obstruction may include hematuria, proteinuria, pyuria (usually caused by inflammation), alkaluria, crystalluria, and glucosuria (stress induced). In one study 12% of cats also had bilirubinuria, although the cause was unclear.¹⁶⁴

Finally, radiographs provide useful information to direct treatment, such as the presence, location, and number of uroliths. The entire urethra should be radiographed to detect urethroliths that may be lodged distally.

BOX 32-17

Supplies for Urethral Catheterization and Relief of Obstruction

- Sterile lidocaine gel
- Open-end urethral catheter to relieve urethral obstruction
- Intravenous extension set
- Sterile lubricant
- Sterile saline flush
- Sterile gloves
- Several 10-mL syringes
- Indwelling urethral catheter
- Empty intravenous fluid bag and sterile intravenous line

Establishing Urethral Patency

Establishing urethral patency is begun *after* the patient is stable. In particular, severe hyperkalemia and cardiac dysrhythmias should be corrected before anesthesia is induced. The choice of sedation versus anesthesia and the drug protocols employed will vary depending on the condition of the patient and the experience of the clinician. Drugs that require renal excretion should be used with caution. A commonly used combination is ketamine (2 to 5 mg/kg) with diazepam (0.2 to 0.5 mg/kg) or midazolam (0.2 to 0.5 mg/kg) administered intravenously to effect; lower doses may also be adequate. Ketamine should be avoided in cats with cardiac arrhythmia or cardiac disease. Hydromorphone and midazolam is another common choice. Mask induction with isoflurane or intravenous propofol may be used if additional time for procedures is needed. Obtunded patients may not require sedation for urethral catheterization.

The supplies required for urethral catheterization and relieving obstruction are found in Box 32-17. The patient is placed in dorsal or lateral recumbency, and the hair is clipped around the perineal area, especially in longhair cats. Surgical scrub is used to gently cleanse the prepuce and tip of the penis. Wearing sterile gloves, the veterinarian should extrude the penis from the sheath and gently massage it to expel very small calculi and urethral plugs lodged at the tip of the penis. In some cases massaging the urethra through the rectum may dislodge an obstruction. Extrusion of the penis can be difficult in obese cats. Drawing the hind limbs forward may provide better exposure.

Catheters useful for relief of urethral obstruction include the standard open-ended tomcat catheter (3.5 Fr polypropylene, 4.5 to 5.5 inches) or Minnesota olive-tipped urethral catheters (22-G, $\frac{1}{2}$ to $1\frac{1}{2}$ inch) (Figure 32-32), which is the author's first choice for obstructions in the distal urethra. The tip of the catheter is lubricated



FIGURE 32-32 A set of 22-G Minnesota olive-tip catheters ranging in length from 0.5 to 1.5 inches (1.2 to 3.8 cm).

with lidocaine gel and inserted into the external urethral orifice. The tip of the penis can be allowed to retract into the prepuce once the catheter has been inserted. Extending the penis until it is parallel to the cat's spine by pulling the prepuce caudally and dorsally will help straighten the urethra as much as possible and facilitate catheter placement. Alternately, an assistant can apply pressure ventrally through the rectum to help guide the catheter over the pelvic brim. The catheter is gently advanced until the obstruction is reached. Then an intravenous extension set is attached, and a 10-mL syringe filled with saline is used to liberally flush the urethral lumen. It may be helpful to add a small amount of sterile lubricant to the saline flush (shake to form an emulsion). Walpole's solution should never be used because it has an acidic pH and is highly irritating to the already traumatized mucosa; use may result in serious inflammation of the urethra and bladder and even urethral stricture.

It may take several attempts at gentle advancement and flushing to relieve the obstruction. If resistance is felt when saline is injected into the catheter, the catheter should be backed out slightly until the saline can be flushed more easily. Gently massaging the penis during flushing may help dislodge the obstructing material. Occlusion of the urethra may also help distend the urethral lumen and dislodge plugs or uroliths. This can be accomplished in two ways. The urethra can be compressed through the rectum during hydropropulsion. Alternatively, the tip of the penis can be pinched to occlude the urethral lumen and increase pressure by preventing flush from exiting the external urethral orifice. It is important to watch carefully for expulsion

of urethral plugs or calculi during flushing so that the material can be saved for analysis.

Any procedures involving the urethra should be carried out as gently as possible to avoid inflammation and long-term damage. The catheter itself should never be used to push obstructing material into the bladder. One series of 15 cats requiring perineal urethrostomy had sustained urethral trauma during catheterization using inappropriate technique or equipment.⁴⁴ Physical examination abnormalities included perineal hematoma, deviation of the penis, and scrotal swelling. Contrast radiography was performed in 10 cats; urethral stricture (one cat) and urethral rupture (five cats) were found. The other four cats had a stricture at the external urethral orifice.

Once the obstruction has been relieved, any urine remaining in the bladder should be aspirated. The bladder is then flushed and drained repeatedly with saline until the harvested solution appears relatively clear of blood and debris. The catheter used to relieve the obstruction is withdrawn slowly while continuing to flush saline. An indwelling urinary catheter (3.5 to 5 Fr) is not required for all obstructed patients. Factors such as ease of establishing urethral patency, quality of urine stream, size of bladder at presentation, and the presence of systemic illness must all be considered. Marked hematuria is another indication for an indwelling catheter because it represents risk of re-obstruction with blood clots and indicates severe bladder distention, which may impair detrusor contractility. If an indwelling urinary catheter is not used, the bladder should be palpated after natural voiding to assess completeness of emptying. If the cat without a urinary catheter is not voiding regularly or not fully emptying the bladder, the bladder should be expressed manually 3 or 4 times daily.

The best choices for indwelling catheters are made of soft material, such as a polyvinyl red-rubber feeding tube, a silicone tomcat urethral catheter, a polyurethane E-Z-GO urinary catheter (Mila International, Inc.), or a polytetrafluoroethylene Slippery Sam tomcat urethral catheter. These catheters are more flexible than polypropylene catheters and reduce urethral irritation and trauma. Softer catheters are sometimes too flexible to insert easily, especially if a stylet is not included; storing the catheters in the freezer is helpful because they become stiff when cold. The tip of the catheter should be advanced only a short distance into the bladder lumen. Inserting the catheter too far can cause irritation and straining. If the catheter tip lies in the proximal urethra, this will also cause irritation and discomfort. The position of the catheter can be checked radiographically. The catheter should be sutured to the cat's prepuce near the external urethral orifice using a tape "butterfly"; some catheters come with "wings" for this purpose.

Indwelling catheters should be attached to closed collection systems to reduce the risk of ascending

bacterial contamination. A urine collection bag or an empty intravenous fluid bag and intravenous administration set can be used to construct a collection system. After flushing the bladder, the veterinarian should leave 10 to 20 mL of lavage fluid in the bladder lumen. This provides fluid to fill the tubing and immediately indicates that the system is working properly. It is important to check that the intravenous administration line is not clamped closed. The collection bag should be positioned below the level of the cat to provide a siphon effect and prevent retrograde flow of urine. An Elizabethan collar should be used to prevent the cat from biting the catheter or tubing.

Indwelling catheters are generally left in place from 1 to 3 days. Clinical judgment is used to determine the optimal time to remove the catheter. Indications for catheter removal include resolution of clinical signs such as lethargy, weakness, anorexia and vomiting, diminishing hematuria, and resolution of metabolic derangements and postobstructive diuresis. A recovered bladder will feel small and firmly contracted around the tip of the catheter on palpation. When the catheter is removed, risk of postcatheterization voiding problems may be assessed by evaluating the functional status of the urethra. Between 20 and 30 mL of sterile saline may be instilled into the bladder just before catheter removal. As soon as the catheter is removed, the bladder is expressed, and the quality of the urine stream is evaluated.

Whenever possible, antibiotic therapy should not be instituted while an indwelling catheter is in place. Although antibiotics may reduce the risk of postcatheter bacterial infection with short-term catheter placement, infections that do occur may be highly resistant. In addition, prophylactic antibiotic use cannot prevent infection when catheters remain in place for longer than 3 days. Antibiotic use with an indwelling catheter is reserved for cats with evidence of urinary tract or systemic infection at the time of diagnosis. Antibiotics may be required once the catheter is removed. In one study of 13 cats with indwelling urethral catheters, 69% developed bacteruria.⁸⁰ In a study in dogs, culture of the tip of the catheter at removal had poor predictive value.¹⁶⁶ Urine should be cultured on the day of catheter removal or within 24 hours. To culture urine on the day of removal, the clinician should clamp the collection system to allow urine to accumulate in the bladder about 1 to 2 hours before the catheter is removed. Then the collection system is removed, and a midstream urine sample is collected through the catheter; this sample is submitted for culture and sensitivity testing. If an infection is diagnosed, an appropriate antibiotic should be administered for a minimum of 10 days and the urine recultured 1 week after the end of therapy.

Corticosteroids should not be administered to cats with indwelling urinary catheters, insofar as this increases the risk of lower UTI. Furthermore,

corticosteroids predispose these patients to bacterial pyelonephritis and fail to lessen inflammation.¹⁴ In patients with normal renal function and hydration status, NSAIDs may be considered to reduce inflammation.

Reobstruction after catheter removal may be due to various causes, such as incomplete removal of obstructing material (urethral plug or urethrolith) or urethrospasm caused by inflammation. Other causes of reobstruction include obstruction of the proximal urethral opening by a urolith or mass in the bladder or external compression of the urethra by a mass. Additional investigation with imaging should be considered in these cases.

Although the standard of care for cats with urethral obstruction is relief of the obstruction by way of urethral catheterization, treatment often involves extended hospitalization and may be too costly for some owners. Euthanasia or relinquishment is usually the only alternative in such circumstances. Recently, a protocol for managing urethral obstruction without catheterization using medication (acepromazine, buprenorphine, medetomidine); repeated decompressive cystocentesis; subcutaneous fluid therapy as needed; and a quiet, dark, low-stress environment has been described. In one report 15 cats were treated with this protocol.⁴³ Cats with serious metabolic or physiologic derangements were excluded from treatment, and a lateral abdominal radiograph was obtained to rule out cystic or urethral calculi. Treatment was successful in 11 of 15 cats, defined as spontaneous urination within 72 hours and discharge from hospital. Of the 11 cats, 9 urinated spontaneously within 48 hours. In the remaining four cats, uroabdomen or hemoabdomen developed. Necropsy was performed in three cats, but none had evidence of bladder tear or rupture.

Ongoing Medical Management

After stabilization ongoing monitoring should include assessment of hydration, temperature, mentation, and urine output. Any abnormalities on initial assessment should be re-evaluated as needed (e.g., electrolytes, ionized calcium, blood glucose, BUN, Cr, acid-base status).

Cats that were obstructed for longer than 48 hours or that were severely azotemic may experience significant postobstructive diuresis (urine output greater than 2 mL/kg per hour) for a period of 2 to 5 days. In one retrospective study postobstructive diuresis occurred in 13 of 28 cats (46%) within the first 6 hours of treatment.⁵⁵ Cats with acidemia (venous pH less than 7.35) on admission were at greatest risk. Urine output should be monitored and fluid therapy carefully titrated to prevent dehydration. The cat should be carefully monitored for hypokalemia. After azotemia resolves, fluid therapy may be gradually tapered. More information on fluid

therapy for cats with postobstructive diuresis is found in Chapter 5.

In addition to analgesics, other drugs may be used in the management of urethral obstruction (see Table 32-13). Urethral spasms are a common cause for reobstruction once the catheter has been removed, so preemptive therapy with an antispasmodic is warranted starting while the catheter is still in place and once the patient is stable. The proximal (preprostatic) portion of the feline urethra is primarily controlled by smooth muscle, whereas the distal (postprostatic and penile) portion is primarily controlled by striated muscle. Acepromazine may be useful for its antispasmodic effects on urethral smooth muscle. Alternative drugs to decrease urethral smooth muscle tone are the alpha₁ antagonists such as phenoxybenzamine and prazosin. The penile portion of the urethra is the principle portion contributing to excessive outflow resistance in recently obstructed cats. Diazepam may be used to relax the striated muscle component of the urethra, although its clinical efficacy is unclear. Dantrolene may be more effective than diazepam, based on studies in healthy cats.^{171,172} This drug can cause hepatotoxicity and should not be used in patients with preexisting hepatic disease and should be used with caution in patients with severe cardiac or pulmonary disease (e.g., asthma). Some clinicians also find judicious use of NSAIDs (e.g., meloxicam) helpful for management of postobstructive urethral spasms as long as the patient is well hydrated and is not azotemic.

Prolonged distention of the bladder may induce detrusor atony by causing separation of the tight junctions of the detrusor muscle, resulting in weak and ineffective muscle contractions. Patients with detrusor atony may require prolonged urethral catheterization (7 days or more) because the bladder must be kept as small as possible to re-establish tight junction connections. With prolonged catheterization the risk of bacterial infection increases. Frequent urinalyses should be performed and antibiotics prescribed if necessary on the basis of culture and sensitivity testing. The cholinergic drug bethane col may be used in conjunction with prazosin or phenoxybenzamine to stimulate detrusor contractions once the patient is stabilized and there is no outflow resistance.

The survival rate to discharge from the hospital for cats with obstructive uropathy is over 90%.^{22,61,99,164} However, recurrence rates may be high (22% to 36%), particularly if the underlying cause is not identified and corrected or successfully managed.^{22,61,164} Therefore every attempt should be made to identify and treat the etiology while relieving the obstruction. Cats with urethral plugs should be managed the same way as idiopathic cystitis patients. Between 15% and 20% of cats with FLUTD have radiographic evidence of cystic calculi, so bladder imaging is important, especially for

cats with recurrent FLUTD.²⁷ Dietary therapy should be appropriate for the urolith or crystal type. In general, cats with obstruction from urethral plugs or urethroliths should be changed to canned diets to decrease urine concentration and supersaturation with calculogenic precursors.

Surgical Management

Perineal urethrostomy is a salvage procedure that may be indicated for the occasional patient with urethral obstruction (Figure 32-33). Ideally, a decision to perform the surgery should not be based on the number of times the cat has experienced urethral obstruction. Rather, the functional state of the urethra should be the basis of the decision. Indications would include urethral stricture, urethral or penile trauma, and priapism. However, in some cases the frequency and severity of recurrent obstructions, the owner's perception of the cat's quality of life, and the ongoing costs may influence the decision to perform surgery. The procedure, which is described elsewhere, requires thorough knowledge of anatomy and good surgical technique.¹⁸⁸

Data on the frequency with which perineal urethrostomy is performed in cats with urethral obstruction is scarce. In two recent studies perineal urethrostomy was performed in 10% of 82 cats in Israel¹⁶⁴ and 22% of 45 cats in Switzerland.⁶¹ The frequency of perineal urethrostomy performed at veterinary teaching hospitals in North America has been sharply declining. The proportional morbidity rate was reported as 13 cases

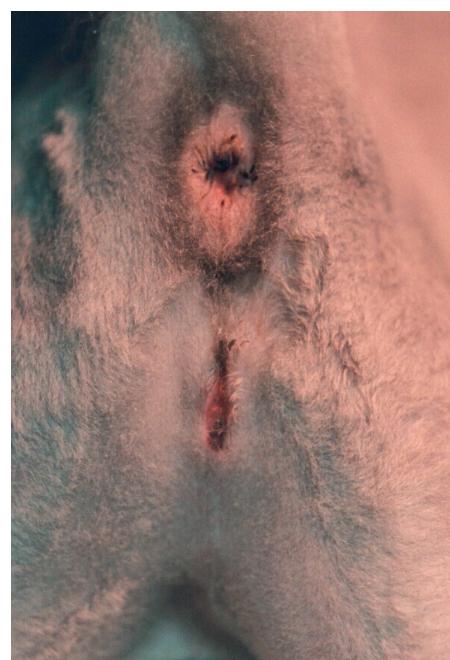


FIGURE 32-33 The 2-week postoperative appearance of a perineal urethrostomy site that is healing normally.

per 1000 cats evaluated in 1980 compared with four cases per 1000 cats in 1999.¹⁰³

Complications of perineal urethrostomy are common and include stricture of the stoma necessitating surgical revision, wound dehiscence, urine scalding, urine leakage into perineal tissue, perineal hernia, and urinary incontinence.^{18,61,130,146} The most common complication is recurrent bacterial UTI, which occurs in 17% to 58% of cases.^{18,44,61,66} However, long-term disease-free outcomes may be achieved with good quality of life.^{18,44,61,164} Clients should be aware that the surgery does not always correct the underlying problem, and recurrent episodes of idiopathic cystitis or uroliths may still occur.

Prepubic urethrostomy is a salvage procedure for cats with failed perineal urethrostomy or stenosis or rupture of the intrapelvic urethra. The complication rate may be high. In one study of 16 cats, six were eventually euthanized because of urinary incontinence, skin necrosis, and unresolved idiopathic lower urinary tract disease.¹¹ Alternate salvage techniques include subpubic or transpelvic urethrostomy. In a study of 11 cats, the post-operative complication rate for transpelvic urethrostomy was low.²⁰ The authors suggested that this surgical technique could be considered as an alternative for perineal urethrostomy.

LOWER URINARY TRACT INFECTION

Prevalence and Risk Factors

The normal feline lower urinary tract has a number of defense mechanisms against infection. These include normal micturition (e.g., frequent and complete voiding), normal anatomy (e.g., length of urethra), uroepithelial mucosal barriers, antimicrobial properties of normal urine (e.g., high specific gravity and osmolality), and a normal immune system.¹⁶ The lower urogenital tract and the perineal area have a resident population of normal flora, a ready source of pathogens for ascending infections in susceptible individuals.

Information on the prevalence of bacterial lower UTI varies with the population of cats studied. Prospective studies of young cats with FLUTD identified bacterial UTIs in fewer than 2% of cases.^{27,91} Higher rates of UTI in cats with FLUTD have been documented (8% to 33%), although the data reported are often not stratified by age or other factors.* Bacterial UTI can also occur in cats without clinical signs. A study of 132 urine specimens from cats without signs of FLUTD collected for routine screening or other diagnostic evaluation found 29% with bacterial infection.¹⁰⁶ Older female cats were at highest risk. Some of the differences in study results may be due

to differences between cats seen as first-opinion cases versus those seen as referral cases.

Persian breed, female sex, increasing age, and decreasing body weight are typically found to be risk factors for UTI.^{9,10,87,101} Urethral catheterization and perineal urethrostomy also increase the risk of bacterial UTI.⁶⁶ Bacterial UTI can develop in healthy male cats with indwelling urinary catheters; risk of infection increases with duration of catheterization.¹⁶ The risk of infection also increases with open indwelling systems, corticosteroid administration, diuresis, and preexisting lower urinary tract disease. The practice of administering antimicrobials while an indwelling urinary catheter is in place is tempting, but this should be discouraged because it may promote the development of multidrug-resistant infections.¹⁶

UTI is an important problem of senior cats (older than 10 years).^{101,106} It is assumed that the decline in immune competence with aging is responsible in part, as well as the increased prevalence of concurrent diseases in this age group. Cats with hyperthyroidism (12% to 22% prevalence of UTI), DM (10% to 13%), and CKD (13% to 22%) are at increased risk.^{8,9,10,87,119} Interestingly, decreasing USG was not associated with a positive urine culture in cats with CKD, DM and hyperthyroidism in one study⁹ although other studies have reported significantly lower USG in cats with UTI.¹⁰⁶

Rarely, lower UTI with fungal organisms has been documented in cats, particularly *Candida* spp.^{83,110,149} In addition to signs of lower urinary tract disease, affected cats may also show systemic signs of illness (e.g., lethargy, anorexia, dehydration, weight loss, pyrexia, and weakness).⁸³ Most affected cats have concurrent problems causing local or systemic immune compromise, such as perineal urethrostomy, lower urinary tract disease (e.g., chronic bacterial cystitis, atonic bladder), DM, neoplasia, and chronic renal disease or have a history of prolonged treatment with antibiotics or glucocorticoids. Treatment options include fluconazole and itraconazole, although resolution of predisposing factors is important for success.

Clinical Signs and Diagnosis

Cats with infections of the lower urinary tract have typical nonspecific signs of FLUTD, including pollakiuria, dysuria, stranguria, hematuria, and periuria. However, asymptomatic infections are also possible.^{8,106,119} Differential diagnosis includes other lower urinary tract diseases, such as idiopathic cystitis, urolithiasis, neoplasia, and behavioral disorders. A full urinalysis (USG, urine chemistries, and microscopic sediment examination) should be performed on all cats with signs of FLUTD and should be part of the routine minimum database for older cats or ill cats. Changes on urinalysis consistently associated with bacterial UTI

*References 51, 60, 89, 101, 142, 176.

include bacteriuria, pyuria (>5 white blood cells/high power field), and hematuria. Proteinuria may also be present. In a dilute urine sample, the magnitude of these changes may be masked. Conversely, there may be no changes on urinalysis or routine laboratory data to indicate UTI.¹¹⁹

Urine culture and sensitivity testing is recommended for cats at increased risk of UTI because of concurrent disease or with recurrent episodes of lower urinary tract disease. Samples for culture should be collected before any therapy is initiated, preferably by cystocentesis.¹⁷⁶ Voided samples or samples collected by catheterization are often contaminated, making interpretation difficult and risking overdiagnosis. Urine samples for culture should be processed as soon as possible. If processing will be delayed for more than 30 minutes, the sample should be refrigerated in a sterile container. A sample collected by cystocentesis may be stored in this way for 6 to 12 hours without additional bacterial growth.¹¹¹ Commercially available urine culture collection tubes containing preservative may be used to refrigerate urine specimens for up to 72 hours.¹⁵ The most commonly isolated organisms are *E. coli* and *Enterococcus*.^{8,10,107,119} Other organisms that have been isolated include *Staphylococcus* spp., *Streptococcus* spp., *Klebsiella* spp., and *Enterobacter* spp. *Corynebacterium* spp. have been identified as a cause of UTI in cats with preexisting lower urinary tract abnormalities and a history of previous UTI with other organisms.^{7,37,150}

Treatment

Administration of appropriate antimicrobials is the main treatment for bacterial UTI. The choice of drug is based on susceptibility testing, but other considerations are important, such as ease of administration, risk of adverse effects, availability, and cost. Most *E. coli* isolates associated with UTI in cats are sensitive to commonly used antimicrobials (e.g., amoxicillin or amoxicillin-clavulanate), and *Enterococcus* is also sensitive to amoxicillin-clavulanate.^{8,68,106,189} Therefore cats with bacteriuria may be started on amoxicillin-clavulanate pending the results of urine culture and sensitivity testing. Uncomplicated bacterial UTIs occur in cats with no underlying structural or functional abnormality. These infections are usually treated with an appropriate antimicrobial for at least 14 days. Clinical signs can be expected to abate within 48 hours.¹⁶ Ideally, a urine culture is performed 1 week after the end of therapy.

Unfortunately, many cats with bacterial UTI have complicated infections with identifiable predisposing factors (e.g., CKD, DM, or hyperthyroidism). These cats should be treated with an appropriate antimicrobial for 4 to 6 weeks. Urine should be recultured 3 to 5 days after the start of therapy, again just before therapy is discontinued, and 1 week after completion of treatment.

Pradofloxacin (Veraflox, Bayer AG) is a third-generation fluoroquinolone antibiotic that is active against a range of feline urinary pathogens, including *E. coli* and *Staphylococcus* spp. It is available as a palatable 2.5% oral suspension that is administered at 0.2 mL/kg once daily. In a recent study 27 cats treated with pradofloxacin all had negative posttreatment urine cultures.¹⁰⁵ Pradofloxacin appears to have no retinal toxic effects in cats.¹²⁴ Cefovecin (Convenia, Pfizer Animal Health) is an extended spectrum semisynthetic cephalosporin with a 14-day dosing interval after a single subcutaneous injection. A recent study of posttreatment urine cultures showed that cefovecin eliminated 76% of *E. coli* infections compared with 62% for cephalexin. However, this is lower than the efficacy of cefovecin for treatment of canine UTI.¹⁴² These newer antimicrobial agents should not be used as first-line therapy but should be reserved for bacterial organisms that are resistant to other drugs on the basis of culture and sensitivity testing or for cats that cannot be treated using other medications.

Relapses are recurrent infections with the same organism that occur for a variety of reasons, such as failure to eradicate the original infection, inappropriate antimicrobial choice (or dose, dose frequency, or length of treatment), or other complicating factors. Re-infections are recurrences caused by a different pathogen than the original infection and typically occur weeks to months after the first infection. Re-infection, as well as persistent and relapsing infection with *E. coli*, has been documented in older cats with chronic renal disease.⁵⁶ Cats with concurrent diseases and other risk factors such as perineal urethrostomy are also likely at risk. Prophylactic antimicrobial treatment for frequent re-infections has not been evaluated in cats.

One strategy employed in human medicine to prevent recurrent bacterial UTIs in women is the use of cranberry products.⁸¹ Cranberry contains proanthocyanidins, which inhibit adherence of *E. coli* to the bladder epithelium.⁷² To date, no data on safety or efficacy of cranberry products for prevention or treatment of UTI in cats has been published.

OTHER LOWER URINARY TRACT PROBLEMS

Neoplasia

Although tumors can occur anywhere in the lower urinary tract of cats, the bladder is the most common location, possibly because the bladder epithelium has prolonged exposure to carcinogenic substances contained in urine. Cats seem to be less susceptible to bladder tumors than dogs and humans. Overall, neoplasia of the lower urinary tract is rare, although data on prevalence is scarce. The most commonly reported

bladder tumor in cats is transitional cell carcinoma (TCC); other tumor types reported include squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, hemangiosarcoma, and lymphoma.* Most feline bladder tumors are malignant and locally invasive. Urethral tumors are very rarely reported; most cases have been TCC.^{12,174}

The mean age of cats with lower urinary tract neoplasia ranges from 9 to 13 years. Compared with cats younger than 10 years old, cats 10 to 15 years old were 6 times more likely and cats older than 15 years were 19 times more likely to have neoplasia of the lower urinary tract in one study.¹⁰¹ The same study showed a slightly increased risk in spayed females (2 times greater) and neutered males (2.5 times greater) than in intact cats. In a study of 25 cats with TCC, neutered males were most commonly affected.¹⁹⁰

Clinical signs of lower urinary tract neoplasia may be general (e.g., lethargy, anorexia, weight loss) or specific to the lower urinary tract (e.g., hematuria, stranguria, dysuria, pollakiuria). Most urinary tract tumors are locally invasive and will eventually interfere with normal function. Inflammation and disruption of the urethral and bladder mucosa cause signs of cystitis. Masses in the urethra or the trigone of the bladder may cause urinary obstruction, as well as abnormalities in the kidneys (hydroureter, hydronephrosis). Metastasis to distant sites (abdominal organs, lungs) is common. Physical examination may be normal, or a palpably thickened urinary bladder may be appreciated.

The differential diagnosis includes other causes of lower urinary tract signs, such as urolithiasis. A thorough diagnostic evaluation including imaging should be performed in cats older than 10 years of age with lower urinary tract signs. Common findings on routine laboratory testing include azotemia, anemia, and hematuria. Hypereosinophilia as a paraneoplastic syndrome was associated with TCC in one reported case.¹⁶⁵ Neoplastic cells may be present on examination of urine sediment, although a definitive diagnosis should not be based solely on these findings.^{59,190} Neoplastic cells often do not exfoliate into urine. Because UTI is common in these patients, urine culture and sensitivity testing should be part of the diagnostic evaluation.

Ultrasonography is a noninvasive, rapidly performed diagnostic tool that is very useful in evaluation of older cats with signs of lower urinary tract disease (Figures 32-34 and 32-35). When available, abdominal ultrasound should be part of the initial evaluation for these patients. In addition to finding bladder masses, ultrasound examination may detect other abdominal abnormalities, such as lymphadenopathy, abdominal effusion, hydroureter, or hydronephrosis.

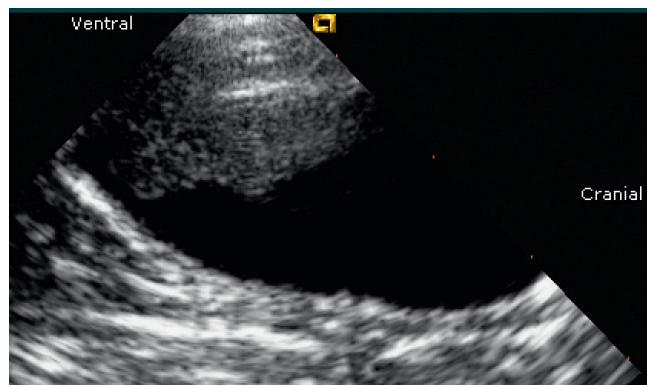


FIGURE 32-34 Ultrasound examination of the bladder of a 12-year-old spayed female domestic shorthair cat with weight loss, anorexia, and azotemia. A 1.5 × 1.0 cm (0.6 × 0.4 in) mass with an irregular surface is present on the caudal ventral bladder wall. Unilateral renomegaly was also found on ultrasonographic examination. (Courtesy Dr. Edward Javinsky.)

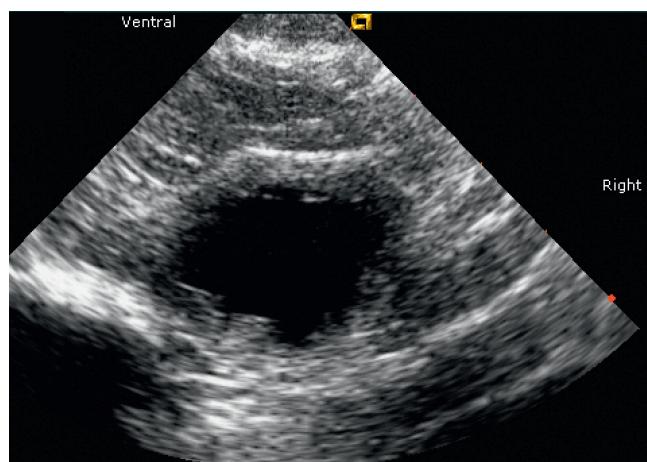


FIGURE 32-35 Ultrasound examination of the bladder of a 15-year-old spayed female domestic shorthair cat with clinical signs of feline lower urinary tract disease. The bladder wall is thickened and irregular. At the thickest point the bladder wall measures 3.9 mm (normal <2 mm). (Courtesy Dr. Edward Javinsky.)

Survey radiographs may detect bladder masses as well as evidence of metastasis. If survey radiographs are unrewarding and ultrasonography is not available, contrast cystography may reveal masses or bladder wall thickening. Other findings associated with neoplasia include decreased bladder distensibility and mineralization of the bladder wall. Contrast urethrography has been used for diagnosis of urethral TCC.¹⁷⁴ Other options for diagnostic imaging include CT, MRI, and cystoscopy.

Definitive diagnosis requires histopathologic examination of biopsy specimens. Biopsies may be collected by way of percutaneous aspiration, traumatic catheterization, cystoscopy, or laparotomy. Ultrasound-guided percutaneous fine-needle aspiration is relatively easy to

*References 19, 59, 145, 157, 178, 190, 191.

perform with minimal complications.¹⁰⁴ Tumor seeding of the needle tract has been reported.^{63,129,177,190}

Clinical staging is important to guide treatment decisions. Imaging of the chest and abdomen should be performed to evaluate for metastasis. The best treatment for tumors of the lower urinary tract is not known and is complicated by the fact that disease is often advanced at the time of diagnosis and many affected patients may have concurrent diseases. Tumors in the apex or body of the bladder can be surgically resected, although risk of recurrence and metastasis is high. TCC is often found in the trigone, where it is not amenable to surgery. In a case report of a cat with urethral TCC, treatment with surgery and radiation produced a survival time of 386 days.¹⁷⁴ Although piroxicam has been associated with clinical improvement in dogs with TCC, no data on safety and efficacy exists for cats. In a series of 25 cats with TCC of the bladder, various treatments were attempted, including surgery, chemotherapy (carboplatin, doxorubicin, cyclophosphamide), and piroxicam.¹⁹⁰ The rate of metastasis at time of diagnosis was 20%. Median survival time regardless of treatment modality was 261 days, and almost all deaths were attributed to advancement of the tumor.

Trauma

The most common lower urinary tract injury is bladder rupture, although urethral rupture can also occur. Causes of lower urinary tract injury include blunt or penetrating abdominal trauma, pelvic trauma, neoplasia, excessive pressure applied to a distended and compromised bladder during palpation or manual expression, repeated cystocentesis of a compromised bladder, urethral calculi, and improper urethral catheterization technique.^{4,6,57} With bladder rupture urine will accumulate in the abdomen or in the tissues of the perineal area. With a urethral rupture urine may accumulate in the perineal subcutaneous tissues, causing swelling and hemorrhage. Physical examination of the cat with lower urinary tract injury may also show evidence of trauma such as bruising, as well as pain and lack of a discrete bladder on abdominal palpation. However, in one report of cats with uroabdomen, the bladder was palpable in some cats with bladder rupture.⁶ Depending on the amount of urine accumulation, cats with uroabdomen may have abdominal distention. Anuria may be present, but the ability to urinate does not exclude a diagnosis of lower urinary tract rupture. As uremia develops, clinical signs appear and worsen, such as vomiting, anorexia, depression, and dehydration. Pain may be caused by inflammation from urine in subcutaneous tissues or chemical peritonitis from uroabdomen. Preexisting UTIs may cause septic peritonitis in cats with uroabdomen.

Diagnosis is based on physical examination findings, evaluation of a minimum database (CBC, serum

chemistries and electrolytes, urinalysis) and radiography. Azotemia and electrolyte disturbances similar to those of cats with urethral obstruction will develop secondary to urinary tract rupture. Uroabdomen can result in third spacing, with volume depletion and hemodynamic compromise. Hematuria is a common finding on urinalysis. Survey radiography may show abdominal fluid, ileus (induced by chemical peritonitis), and loss of the normal bladder shadow. The presence of pelvic fractures in a trauma patient should always prompt investigation of the condition of the bladder and urethra. If abdominal fluid is present, a sample is collected using sterile technique through abdominocentesis, and the Cr and potassium content of the fluid is compared with the serum Cr and potassium. An abdominal fluid:serum Cr ratio of 1:2 (range 1.1:1 to 4:1) and an abdominal fluid:serum potassium ratio of 1.9:1 (range 1.2:1 to 2.4:1) is diagnostic for urine.⁶ A retrograde positive contrast urethrogram or cystogram is used to confirm rupture of the urethra or bladder and determine the location of the lesion. Contrast studies should be performed only once the patient is stable and metabolic disturbances have been corrected.

Initial management and stabilization for cats with lower urinary tract rupture are the same as for cats with urethral obstruction. Trauma patients may require further stabilization measures depending on the type and severity of other injuries. For cats with bladder rupture, percutaneous placement of a peritoneal drainage catheter can be used for drainage of urine from the abdomen to assist in stabilization of the patient. Peritoneal dialysis catheters can be used if available; alternatives include trocar chest tubes and balloon-tip catheters. The reader is referred to other resources for description of peritoneal catheter placement.^{50,57} Placement of a urethral catheter is recommended to keep the bladder decompressed. Bladder wall defects must be repaired surgically once the patient is stable. Small iatrogenic bladder tears may be treated conservatively with good outcomes by placement of an indwelling urethral catheter for continuous bladder decompression during healing in carefully selected cases.¹³³

Treatment options for urethral trauma include surgical repair of the defect and use of a catheter as a stent during healing. In cases not amenable to surgical repair or stenting, urethrostomy is the best option. An important complication of urethral trauma is stricture formation, partly from exposure of the injured tissue to the irritating qualities of urine. Prompt placement of a urethral catheter using appropriate technique protects the tissues from urine. If the urethra is too traumatized to be catheterized, urine can be diverted with a tube cystostomy. The technique for placement of a prepubic cystostomy tube is described elsewhere.^{121,170} In one retrospective case series of 37 dogs and 39 cats with cystostomy tubes, 49% had complications (e.g., inadvertent

BOX 32-18**Some Causes of Urinary Incontinence in Cats**

- Spinal cord lesions: upper motor neuron, lower motor neuron, Manx syndrome
- Detrusor atony: prolonged urethral obstruction, dysautonomia
- Generalized weakness: neuromuscular disorders
- Congenital defects: ectopic ureters
- Associated with feline leukemia virus

tube removal, UTI, inflammation around the exit site, urine leakage around the tube), although most were easily resolved.

Indwelling urethral catheters can also be used to align the urethra during healing. In one study of 11 cats with urethral rupture, placement of a urethral catheter was possible in 10 cats.¹²³ Catheterization was performed retrograde in five cats and normograde by cystotomy in the other five cats. The catheter was left in place for 5 to 14 days. A positive outcome was achieved in 8 of the 10 cats; two cats developed urethral strictures. Primary surgical repair of the urethra may also be performed; in one study risk of stricture formation was reduced in dogs by use of an indwelling urethral catheter during healing.⁹⁸

In a retrospective study of 29 cats with urethral trauma, the outcome was generally good, regardless of the method of treatment. The only poor prognostic factor was the presence of multiple traumatic injuries.⁴

Incontinence

Urinary incontinence is far less common in cats than dogs. The most common causes are neurologic disorders or congenital abnormalities (Box 32-18). Urethral sphincter incompetence is the most common cause in dogs, reported to affect 5% to 10% of spayed females, but is rarely reported in spayed cats.

Micturition disorders are characterized as neurogenic or non-neurogenic. Lesions cranial to the sacral spinal cord cause upper motor neuron dysfunction. Sensory and motor function to the bladder is lost, but urethral resistance is maintained or increased. The coordination of detrusor contraction with urethral relaxation may be disrupted, leading to reflex dyssynergia. Lumbosacral vertebral disk disease affecting L7 to S1 has been associated with urinary incontinence.⁷⁴ One report describes intermittent urinary incontinence in a cat with a spinal arachnoid cyst at T11-12.¹⁵⁹

Lesions of the sacral spinal cord, cauda equina, or peripheral nerves may result in lower motor neuron dysfunction. In this situation sensory and motor input to the bladder is lost, as well as urethral tone, leading to overflow incontinence. This type of micturition disorder may



FIGURE 32-36 Ventrodorsal radiographic view of a stray cat with overflow incontinence. The cat has a Manx phenotype with a shortened tail. Note the severely distended bladder.

be seen in cats with pelvic or sacral fractures. Manx cats or cats with congenital sacral lesions may also be affected with this type of incontinence (Figure 32-36).

Non-neurogenic causes are classified according to whether the bladder is distended. A common non-neurogenic micturition disorder presenting with a distended bladder is detrusor atony, which may be seen after prolonged urethral obstruction and is discussed elsewhere in this chapter. A rare cause of detrusor atony is dysautonomia (see Chapter 27). Non-neurogenic causes of incontinence presenting with a nondistended bladder include congenital defects. Ectopic ureter has been reported in cats and results in dysfunction during the storage phase of micturition.* One or both ureters enter the lower urogenital tract at an abnormal location. Affected cats display intermittent or persistent incontinence from a young age and are at increased risk for UTI. Other urinary tract abnormalities, such as renal hypoplasia, hydronephrosis, and hydroureter may be associated with ectopic ureter. Urinary incontinence with normal bladder size has been reported in cats infected with FeLV.^{13,36,96}

A thorough history is important to determine whether the problem is truly incontinence or another problem (e.g., urine spraying, inappropriate urination, polyuria, pollakiuria). Owners are often unable to distinguish among these various urinary tract signs. Urinary incontinence is characterized by intermittent or constant leakage of urine, usually small volumes. Questions to ask the owner should help establish when the problem occurs, when it was first noticed, if there is a history of trauma, whether the urine appears normal, and whether the cat urinates normally at times. Age at onset is

*References 32, 52, 62, 76, 93, 148.

important because incontinence that manifests during kittenhood is likely to be the result of a congenital defect such as ectopic ureter. Physical examination should include palpation of the bladder and an attempt to manually express urine. Ideally, the cat should be observed while voiding urine. Owners can make a video at home for the clinician to review. The residual volume of urine after voiding should not exceed 0.2 to 0.4 mL/kg.¹²⁷ If the bladder cannot be expressed manually, the urethra should be catheterized to determine if an anatomic abnormality is causing obstruction. A neurologic examination should be performed because neurogenic micturition disorders are accompanied by other neurologic deficits.

A minimum database for the diagnosis of incontinence includes CBC, serum chemistries and electrolytes, complete urinalysis, and retroviral serology. A urine culture should be performed if dictated by findings on examination of the urine sediment. Survey radiography may detect evidence of pelvic or spinal trauma. Contrast radiography (e.g., intravenous urography, positive contrast urethrography) or cystoscopy is useful for diagnosis of congenital defects such as ectopic ureter. Advanced imaging of the spinal cord (e.g., myelography, CT, MRI) may be indicated in some patients. Various procedures for urodynamic and electrodiagnostic testing of bladder and urethral function (e.g., cystometry, urethral pressure profilometry, urethral electromyography) have been described in cats and may be available at referral institutions.

Treatment for urinary incontinence relies on correction of underlying causes whenever possible, as well as pharmacologic therapy. Treatment choices for an ectopic ureter include ureter reimplantation and ureteroovesicular anastomosis. Nephrectomy or ureterectomy may be required when hydronephrosis or hydroureter are present. Few drugs have been evaluated for micturition disorders in cats (see Table 32-13). Bethanechol, a parasympathomimetic drug, is indicated for detrusor atony as long as the bladder is easily expressed and no physical or functional urethral obstruction is present. Relaxation of the urethra may be accomplished with phenoxybenzamine, prazosin, diazepam, or dantrolene. Other management options include frequent manual expression and intermittent urinary catheterization. Cats with lack of urethral tone are at increased risk of UTIs, so urinalysis and urine culture should be performed periodically. Urine scalding of the perineum is common; the affected skin should be kept clean and dry and a nonzinc barrier cream applied.

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