CHAPTER 99
UROSEPSIS

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KEY POINTS

- Urosepsis is an uncommonly diagnosed condition in the small animal patient.
- *E. coli* is the most frequently diagnosed uropathogen in patients with urosepsis.
- In most animals with urosepsis, bacteria from the rectum, genital, and perineal areas serve as the principle source of infection.
- Patients with a urinary tract infection and risk factors, including the presence of an anatomic abnormality, a urinary tract obstruction, nephrolithiasis, prior urinary tract disease, renal failure, neurologic disease, diabetes mellitus, hyperadrenocorticism, and immunosuppression, are more prone to the development of urosepsis.
- Causes of urosepsis that have been identified in the veterinary patient include pyelonephritis, bladder rupture, prostatic infection, testicular and vaginal abscessation, pyometra, and catheter-associated urinary tract infections.
- Treatment should be instituted as soon as possible and often includes a combination of intravenous fluid and broad-spectrum antimicrobial therapy, correction of the underlying condition, as well as attempting to correct any predisposing or complicating factors.

Urosepsis, an uncommonly reported condition in veterinary medicine, refers to sepsis associated with a complicated urinary tract infection (UTI). In humans, the source of the infection can be the kidney, bladder, prostate, or genital tract.[1] More specifically, urosepsis in humans has been associated with acute bacterial pyelonephritis, emphysematous pyelonephritis, pyonephrosis, renal abscessation, fungal infections, bladder perforation, and prostatic and testicular infections.[2-5] In addition in human patients, urinary catheter-associated infections also have resulted in sepsis.[6-8] Although many of these conditions often are diagnosed in the veterinary patient, little information currently exists in the veterinary literature regarding the incidence of urosepsis as a complication of these conditions. In one retrospective study looking at sepsis in small animal surgical patients, the urogenital tract was identified as the source of infection in approximately 50% of the cases.[9] Of 61 dogs included in the study, sources of urosepsis included a pyometra (14), prostatic abscessation or suppuration (12), testicular abscessation (3), renal abscessation (3; see Figure 99-1) and vaginal abscessation (1). Of four cats included in the study, one cat had a pyometra and a second cat had a ruptured uterus. This chapter discusses pathogenesis and reviews the current veterinary literature to determine what conditions in veterinary medicine have been associated with urosepsis. Accurate recognition

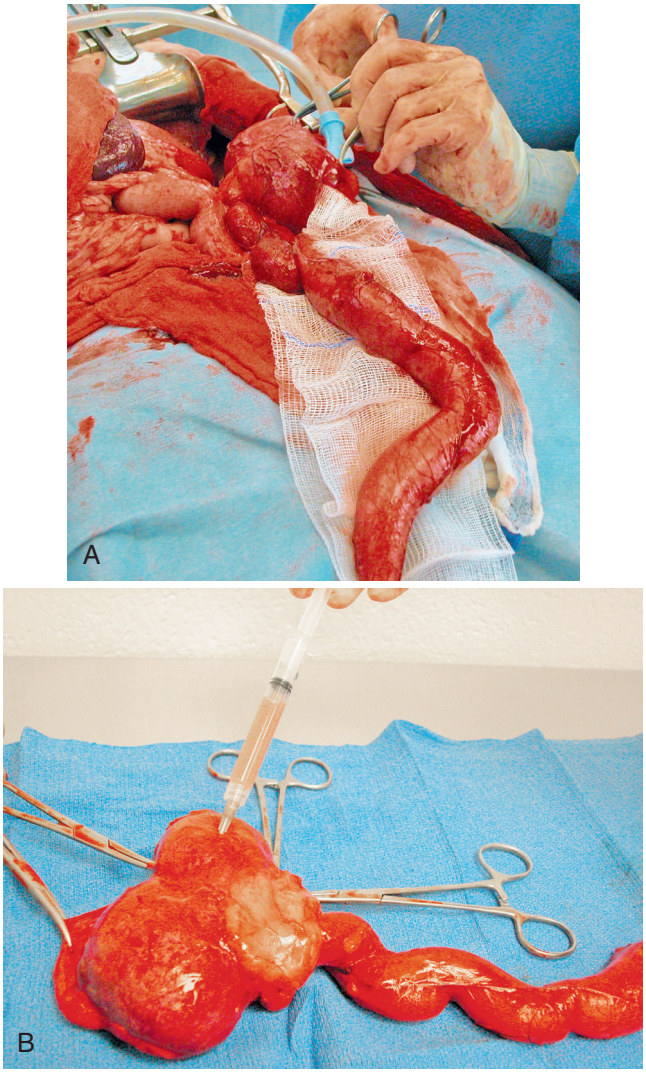

FIGURE 99-1 **A,** Renal and ureteral abscessation in a dog that presented with urosepsis. **B,** The kidney was not salvageable and a nephrectomy was performed. Purulent fluid was aspirated from the kidney.

of these complicated UTIs and appropriate treatment are necessary to prevent morbidity and mortality.

PATHOGENESIS

Urosepsis is a clinical condition that occurs secondary to a systemic bacterial infection originating from the urogenital tract and the associated inflammatory response. In most cases of urosepsis, bacteria isolated from the rectum, genital, and perineal area are the principle source of infection.[10] These bacteria then can migrate from the genital tract to the lower and then upper urinary tract.[10] Similar to human patients, *E. coli* is the most common uropathogen affecting dogs and cats and accounts for up to 50% of the urine isolates.[10-16] Gram-positive cocci, including staphylococci, streptococci, and enterococci account for up to one third of bacteria isolated and, although uncommonly diagnosed, *Pseudomonas*, *Klebsiella*, *Pasteurella*, *Corynebacterium,* and *Mycoplasma* spp. account for the remaining isolates.[12,17-19] In humans, gram-negative sepsis frequently is caused by infections originating from the urinary tract.[6,13]

E. coli is the most common pathogen affecting the urinary tract of human and veterinary patients and consequently the most commonly isolated pathogen in patients with urosepsis; therefore its virulence has been investigated extensively. Most *E. coli* UTIs are caused by pathogenic *E. coli* from the phylogenetic group B2, and to a lesser extent, group D.[20] Although several hundred serotypes of *E. coli* are known, fewer than 20 account for most bacterial UTIs.[21] In dogs and humans, the majority of strains associated with urovirulence belong to a small number of serogroups (O, K, and H; see Chapter 94).[13] Certain properties that may enhance the bacterial virulence include the presence of a particular pilus that mediates attachment to the uroepithelium; the presence of hemolysin and aerobactin; resistance to the bactericidal action of serum; and the rapid replication time in urine.[10-13] In mouse models of human disease, uropathogenic *E. coli* have been shown to possess multiple adaptations, allowing them to survive and persist in the urinary tract.[22-26] In patients with structural or functional abnormalities of the urinary tract or those with altered defenses, infections can be caused by gram-negative aerobic bacilli other than *E. coli*, gram-positive cocci including staphylococci and enterococci, and by bacterial strains that normally lack uropathogenic properties.[5,14] In patients that have a septic peritonitis associated with a urinary tract disorder, the visceral and parietal peritoneum provide a large surface area for absorption of bacteria and endotoxins, resulting in septic shock (see Chapter 91).[27]

The development of a UTI and subsequent urosepsis in human and veterinary patients often represents a balance between the quantity and pathogenicity of the infectious agents and host defenses. The following local host defense mechanisms typically prevent ascending UTIs: normal micturition, extensive renal blood supply, normal urinary tract anatomy (i.e., urethral length and high pressure zones within the urethra), urethral and ureteral peristalsis, mucosal defense barriers, antimicrobial properties of the urine, and systemic immunocompetence.[10,12] Systemic defenses are most important for the prevention of hematogenous spread from the urinary tract.[10] Patients with a UTI and risk factors including the presence of an anatomic abnormality, a urinary tract obstruction, nephrolithiasis, prior urinary tract disease, renal failure, neurologic disease, diabetes mellitus, hyperadrenocorticism, and/or immunosuppression should be considered to have a complicated UTI and are more prone to the development of urosepsis.[2,5,10,28-30] In addition, a UTI diagnosed in pregnant or intact dogs and cats also should be considered complicated.

Clinical and laboratory findings in patients with urosepsis are often similar to patients whose sepsis originated from another source; these may include lethargy, fever, hypothermia, hyperemic mucous membranes, tachycardia, tachypnea, bounding pulses, a positive blood culture, and a leukogram that reveals a leukocytosis or leukopenia with or without a left shift (see Chapter 91).[31] However, patients with urosepsis may display early laboratory changes that identify abnormalities specifically related to the urinary tract, including azotemia, an active urine sediment, and a positive urine bacterial culture. A positive urine culture is extremely important in these patients to confirm the results of the blood culture by isolation of the same organism(s) with identical antimicrobial profiles.[6] In cases of severe sepsis, multiple organ dysfunction can be present along with pale mucous membranes, weak pulses, and a prolonged capillary refill time (see Chapter 7). In addition, in cats, diffuse abdominal pain, bradycardia, anemia, and icterus may be identified.[31]

Aggressive treatment is necessary and typically includes a combination of intravenous fluids and broad-spectrum antimicrobial therapy. However, specific treatment protocols vary depending on the source of the infection and the complications resulting from sepsis. Once the culture and susceptibility testing results are available, antimicrobial coverage should be modified to treat the isolated organism(s). Veterinary professionals have continued concerns regarding the increasing resistance of canine urinary tract isolates to common antimicrobials, including fluoroquinolones, clavulanic acid–potentiated β-lactams, and third-generation cephalosporins.[32-35]

Similar to humans, canine *E. coli* isolates resistant to fluoroquinolones have a lower prevalence for many of the virulence genes and are more likely to be from phylogenetic groups A and B1 and less likely from phylogenetic group B2.[36] Prudent use of antimicrobials is critical to reduce the incidence of antimicrobial resistance. In addition, the clinician should address the underlying condition and attempt to correct any complicating factors.[14] Although different causes of urosepsis in the veterinary patient somewhat overlap, some clinical findings, laboratory results, and treatments are unique to each condition. The rest of this chapter discusses the different causes of urosepsis that have been identified in small animals.

CAUSES OF UROSEPSIS

Pyelonephritis

The kidneys and ureters are affected most commonly by ascending bacteria rather than via hematogenous infections. Renal trauma or the presence of a urinary tract obstruction may increase the incidence of hematogenous spread of infection to the urinary tract because of interference with the renal microcirculation.[37,38] In human patients, hematogenous pyelonephritis occurs most commonly in patients debilitated from either chronic illness or those receiving immunosuppressive therapy.[13] Urosepsis resulting from pyelonephritis has been reported uncommonly in the veterinary literature. In a retrospective study evaluating 61 dogs with severe sepsis, a renal abscess in conjunction with pyelonephritis was the source of the infection in only three dogs.[9] In a second retrospective study evaluating 29 cats with sepsis, pyelonephritis was the cause in only two cats.[31] The author has identified seven cats with obstructive calcium oxalate urolithiasis that also were diagnosed with a pyelonephritis based upon a positive bacteriologic culture result from urine collected by pyelocentesis. None of the cats identified were clinically septicemic, but this can be difficult to diagnose definitively in feline patients. Human patients with infected stones or renal pelvic urine were found to be at a greater risk for the development of urosepsis than those with a lower UTI.[39]

Dogs and cats with pyelonephritis and urosepsis may be febrile, anorexic, lethargic, and dehydrated and have a history of recent weight loss. If the disease is acute, one or both kidneys may be enlarged and painful, and the animal may have signs of polyuria, polydipsia, and vomiting. Azotemia secondary to acute kidney injury may be present, and blood work often reveals a neutrophilic leukocytosis with a left shift and a metabolic acidosis. In acute and chronic cases, abdominal ultrasound and/or intravenous pyelography may reveal mild to moderate pelvic dilation and ureteral dilation. The renal cortex as well as the surrounding retroperitoneal space may appear hyperechoic. Renal enlargement often is identified in cases of acute pyelonephritis; poor corticomedullary definition, distortion of the renal collecting system, irregular renal shape, and reduced kidney size may be seen with chronic cases. The urinalysis may reveal impaired urine concentrating ability, bacteriuria, pyuria, proteinuria, hematuria, and/or granular casts.[10,40]

As previously mentioned, treatment includes the removal of predisposing factors, intravenous fluid therapy, and broad-spectrum antimicrobial administration until a specific organism is identified. Antimicrobial therapy targeted against the isolated organism should continue for 4 to 8 weeks. A urinalysis and bacterial culture should be performed after 1 week of treatment and before discontinuation of antimicrobial therapy to determine whether the infection has resolved. In addition, a urine culture should be performed 2 to 3 days after therapy has been discontinued. In cases of unilateral advanced pyelonephritis, pyonephrosis, or the presence of a renal abscess, a total nephrectomy in addition to antimicrobial therapy is often the preferred treatment.[41] Cases of pyonephrosis have been treated successfully at the author's institution with the temporary placement of a ureteral stent to allow for continued drainage of the kidney. This is done in conjunction with antimicrobial therapy based on culture and susceptibility.

Bladder Rupture

Although rare, urosepsis may result from a bladder and/or a proximal urethral rupture in a patient with a lower UTI.[42] Urosepsis is not identified typically in patients with an intact lower urinary tract.[10] Rupture of the urinary tract in dogs and cats most commonly occurs after blunt trauma resulting from being hit by a car. Other causes include penetrating injuries, aggressive catheterization, rupture secondary to prolonged urethral obstruction, or excessive force during bladder expression. Physical examination may reveal dehydration, lack of a bladder on palpation, fluid accumulation within the peritoneal cavity, and ventral abdominal bruising. Clinical signs are often vague initially but can worsen as the uremia and inflammation/sepsis progress. Signs may include vomiting, anorexia, depression, abdominal pain, and systemic inflammation (see Chapter 6). Abdominocentesis and abdominal fluid to peripheral blood creatinine and/or potassium ratios are often diagnostic of uroperitoneum,[43,44] and the presence of bacteria on cytology confirms a septic peritonitis (for further details, see Chapter 122).[45] Urosepsis after bladder rupture is reported uncommonly in the veterinary literature. In a retrospective study evaluating 23 dogs and cats with septic peritonitis, only one cat had septic peritonitis associated with intestinal herniation and bladder rupture.[46] In a second study evaluating 26 cases of uroperitoneum in cats, five patients had aerobic bacterial cultures performed from the peritoneum or bladder, and of those, three were positive. Organisms isolated included *Enterococcus* spp., *Staphylococcus* spp., and alpha-streptococcus.[43]

If septic peritonitis is confirmed, early repair and/or urinary diversion is recommended to halt continued accumulation of septic urine in the abdominal cavity. The bladder defect is debrided of any devitalized tissue and then closed using a single-layer appositional suture pattern. If the viability of the bladder wall is a concern, a closed indwelling urinary catheter system can be used to maintain bladder decompression postoperatively. Treatment options for patients with urethral trauma include primary urethral repair, placement of a urethral catheter to stent the urethra, placement of a cystostomy tube for urinary diversion until the urethra heals, or the combination of a cystostomy tube and a urethral catheter.

Prostatic Infection

In addition to normal host defense mechanisms previously mentioned, prostatic fluid contains a zinc-associated antibacterial factor, which serves as an important natural defense mechanism. Despite these defense mechanisms, bacterial colonization of the prostate can occur through ascension of urethral flora or by the hematogenous route.[47] Suppurative prostatitis and prostatic abscessation are some of the most common causes of urosepsis in canine surgical patients, with 12 out of 61 cases diagnosed in one study.[9] Dogs with suppurative prostatitis usually have a history of an acute onset of illness. Patients often are presented with signs of anorexia, vomiting, tenesmus, lethargy, fever, dehydration, injected mucous membranes, weight loss, pain upon rectal examination, caudal abdominal discomfort and/or pain in the pelvic and lumbar region, a stiff or stilted gait, and an unwillingness to breed.[48-50] In addition, hematuria, pyuria, stranguria, hemorrhagic preputial discharge, urinary incontinence, or the inability to urinate also may be identified. If the infection is not treated, microabscesses can form and eventually coalesce into a large abscess. A complete blood count often reveals a mature neutrophilia and evidence of a left shift. Septicemia and endotoxemia quickly develop, particularly if the abscess has ruptured into the

abdominal cavity.[51] After rupture of a prostatic abscess, the peritoneal surface provides a large surface area for absorption of bacteria and bacterial by-products, thus leading to the development of septic shock. Hindlimb edema also has been identified in these patients and can result from altered vascular permeability that commonly occurs with sepsis as well as the presence of an abscess interfering with normal lymphatic and venous drainage from the peripheral lymph nodes.

A definitive diagnosis is confirmed after identification of a septic exudate from an ejaculated sample, prostatic wash, traumatic catheterization, urethral discharge, or fine-needle aspirate (although this can be dangerous). Inflammatory changes identified in prostatic fluid are associated with histologic inflammation in more than 80% of the cases.[52] Because of the potential of inducing septicemia during prostatic palpation or rupturing an abscess on fine-needle aspiration, it can be difficult and even clinically dangerous to collect prostatic fluid using some of the above-mentioned techniques from dogs with acute prostatitis.[49] In dogs, similar to humans with acute bacterial prostatitis, bacteremia may result from manipulation of the inflamed gland.[13,49] Because the infectious agent often can be identified on a Gram stain of the urine and bacterial culture collected via cystocentesis, vigorous prostatic palpation generally is avoided.[13] Abdominal radiographs often reveal prostatomegaly; the area near the bladder neck may have poor detail resulting from localized peritonitis. Abdominal ultrasound may reveal varying echogenicity with symmetric or asymmetric enlargement of the gland. Cyst like structures as well as hypoechoic areas also may be present and could represent abscess formation. Rectal examination may reveal fluctuant areas when the abscess is near the dorsal periphery of the gland. Dogs with prostatitis may have a normal ultrasound examination, underscoring the need to make a definitive diagnosis using the previously mentioned techniques.

Suppurative prostatitis and prostatic abscessation are serious life-threatening disorders. In patients with acute suppurative prostatitis, treatment involves fluid therapy to correct dehydration and treat cardiovascular shock and antimicrobial therapy based on culture and susceptibility of urine or prostatic fluid. Because of the risks of obtaining prostatic fluid in this patient population, a urine sample for a urinalysis as well as culture and susceptibility testing should be obtained first to determine if a diagnosis can be made. Antimicrobials should be administered for a minimum of 4 to 6 weeks, then the urine or prostatic fluid should be cultured after discontinuation of antimicrobial therapy and again in 2 to 4 weeks to determine if the infection is eliminated completely.[47-49] If the infection is not eliminated, resistant bacterial infections of the prostate and urinary tract can develop. Castration also is recommended once the infection is controlled and appears to be beneficial in the resolution of chronic bacterial prostatitis in an experimental model.[49,52,53]

In addition to the above-mentioned treatments, surgical drainage or excision is often the treatment of choice in a patient with a prostatic abscess. Antimicrobial therapy in conjunction with castration alone has been ineffective at resolving abscesses.[50] Before surgery, ultrasonography is used to determine the location(s) of the abscess(es). Surgical techniques that have been described to treat prostatic abscessation include prostatic omentalization, placement of Penrose drains, marsupialization of the abscess, ultrasound-guided percutaneous drainage, and subtotal or excisional prostatectomy.[42,54,55] In one study, of the three dogs that were presented with prostatic abscessation, two already had signs of sepsis.[54] In a second study, 15 out of 92 dogs died in the postoperative period because of sepsis. *E. coli* was the most common bacteria isolated.[51] Sepsis and shock were common postoperative complications developing in 33% of the dogs surviving surgery. Absorption of bacteria and toxins from an infected prostate gland and inflamed peritoneal surface contributed to the development of septic shock.[51] Approximately half of the dogs that died had rupture of the abscess and secondary septic peritonitis and shock before surgery.

Pyometra

Pyometra is a serious condition affecting older dogs in the luteal stage of the estrus cycle. It has been associated with neutrophilia and impaired immune function, including a decrease in lymphocyte activity.[56] Urosepsis can occur in dogs and cats diagnosed with pyometra with or without uterine rupture. In the largest retrospective study to date evaluating sepsis in the small animal surgical patient, pyometra was the most common source of urosepsis, with 14 out of 61 dogs reported. Of four cats included in the study, urosepsis occurred secondary to a pyometra in one cat and a ruptured uterus in a second cat.[9] In a review of 80 cases of pyometra, 3 out of 73 dogs developed complications from generalized septicemia and thromboembolic disease in the immediate postoperative period, and one dog died from endotoxic shock resulting from a ruptured uterus.[57] In a second retrospective study evaluating 183 cats diagnosed with pyometra, uterine rupture was present in seven cats. Four of seven cats died of septic peritonitis after uterine rupture.[58] Many aerobic and some anaerobic bacteria have been identified in dogs and cats with pyometra, including *Staphylococcus*, *Streptococcus*, *Pasteurella*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Aerobacter*, *Haemophilus*, and *Moraxella* spp. and *Serratia marcescens*. However, *E. coli* is the most common bacteria isolated. Strains of *E. coli* in cases of canine pyometra display a strong similarity to isolates obtained from UTIs, likely because of the similar pathogenesis (i.e., ascending from the host's intestinal or vaginal flora).[59] UTIs are common complications of pyometra. Although culture results are rarely negative in the dog, aerobic culture results are negative in 15% to 31% of affected cats.[58,60] Dogs diagnosed with a pyometra often are presented systemically sick with signs of anorexia, lethargy, depression, polydipsia, vomiting, diarrhea, and, if the cervix is patent, vaginal discharge. When abdominal pain is present, septic peritonitis is likely.[58] *E. coli* pyometra has been associated commonly with renal dysfunction in dogs, albeit typically transient.[61-65] A recent study evaluating urinary biomarkers in these patients has identified the glomerulus and proximal tubules of the nephron as the main sites of injury.[66] Body temperature may be normal, elevated, or subnormal. Clinical signs in cats are similar but often more subtle.

Clinicopathologic abnormalities in both species can occur to varying degrees and may include anemia, leukocytosis, or leukopenia with a left shift, azotemia, hypoalbuminemia, hypoglycemia or hyperglycemia, hyperglobulinemia, increased alkaline phosphatase, and metabolic acidosis.[58,67-69] Before surgery, medical therapy should be instituted and include intravenous fluid and antimicrobial therapy to correct deficits and concurrent metabolic derangements (see Chapters 60 and 91). Surgery is not postponed in the very sick animals for more than a few hours because of worsening septicemia. Treatment for pyometra is ovariohysterectomy. If the uterus ruptures at surgery, the abdomen is lavaged and the patient treated for septic peritonitis (see Chapter 122).

Catheter-Associated Urinary Tract Infection

In human patients, bacteriuria occurs in up to 20% of hospitalized patients with indwelling urinary catheters and, of these patients, 1% to 2% develop gram-negative bacteremia.[13] The catheterized urinary tract has been demonstrated repeatedly to be the most common source of gram-negative sepsis in human patients[13] and, although rare, the mortality rate in these patients can reach 30%.[13] In human patients, bacteremia can occur immediately as a result of mucosal trauma associated with catheter placement and removal or secondary to mucosal ulceration.[13] Many infecting strains, including *E. coli* and

Proteus, *Pseudomonas, Klebsiella,* and *Serratia* spp., show marked antimicrobial resistance compared with organisms identified in uncomplicated UTIs.

Although nosocomial UTIs after the use of an indwelling urinary catheter in dogs and cats is reported to be a common complication by some authors, the subsequent development of urosepsis is uncommon. Bacterial UTIs developed in 20% of healthy adult female dogs after intermittent catheterization; in 33% of male dogs during repeated catheterization and in 65% of healthy male cats within 3 to 5 days of open indwelling catheterization.[10,70]

A few studies in the veterinary literature have looked at the incidence of UTIs in dogs and cats when a closed catheter system was used. In one study, 11 out of 21 (52%) animals and in a second study, 9 out of 28 animals (32%) developed catheter-associated infections.[71,72] Both of these studies suggested that the risk of infection increased with duration of catheterization and that antimicrobial therapy was associated with increasingly resistant gram-negative organisms. Although the incidence of catheter-associated infections was high in both studies, urosepsis was not identified. In the most recent study looking at the incidence of catheter-associated UTIs in 39 dogs in a small animal intensive care unit, only 4 of 39 dogs (10.3%) developed a UTI.[72] The lower incidence reported in this study was attributed to a shorter duration of catheterization, stricter definition of infection, different indications for catheterization, urine sample collection technique, and the protocol for catheter placement and maintenance. Urosepsis was not a reported complication.

In veterinary and in human hospitals, pathogens can be introduced from the hands of hospital staff, via instrumentation or contaminated disinfectants. The most common location for bacteria to enter the system can occur at the catheter-collecting tube junction or at the drainage bag portal. Intestinal flora also can migrate along the catheter into the bladder from the perineal area of the patient.[13] In a study evaluating multidrug-resistant (MDR) *E. coli* isolates from urine collected from dogs with an indwelling urinary catheter, the electrophoresis pattern of the MDR isolate from one dog was similar to the rectal isolate from the same dog.[73] To prevent or minimize the incidence of catheter-associated infections, clinicians should avoid indiscriminate use of catheters. In addition, catheters should be used cautiously in patients with preexisting urinary tract disease, cats or female dogs with voluminous diarrhea, or those whose immune system is compromised. Appropriate antimicrobial therapy should be instituted rapidly should an infection occur.

Many veterinary hospitals use used intravenous fluid bags as part of their urine collection system, resulting in an open system. In a recent study, 95 properly stored (at least 7 days), used intravenous bags were cultured to see if they were a potential source of contamination for the patient. No aerobic bacterial contamination or growth was identified in the system.[74] Recently, the use of an open versus closed collection system for a short duration of catheterization (at least 7 days) was evaluated with regard to the development of nosocomial bacteriuria. The study included 51 dogs and found an overall incidence of bacteriuria of 9.8%; the type of collection system (open vs. closed) was not associated with the development of bacteriuria. The authors concluded that the low incidence of bacteriuria likely was associated with a strict standard protocol of catheter placement and maintenance as well as the short duration of indwelling catheterization.[75] Another study found that the risk of infection increased by 27% for each 1-day increase in catheterization.[76] Because a longer duration of catheterization has been associated with antimicrobial resistant bacteria and the duration of catheterization is unpredictable, prophylactic use of antimicrobials is not recommended.[72] In addition, diagnostic and therapeutic procedures that may result in the introduction of bacteria into the urinary system also should be minimized.[10,13]

CONCLUSION

Urosepsis is an uncommonly diagnosed but serious problem that can affect dogs and cats. Conditions in veterinary medicine that have been associated with urosepsis include bacterial pyelonephritis and renal abscessation, bladder rupture in patients with a UTI, prostatic suppuration and abscessation, testicular and vaginal abscessation, pyometra, and catheter-associated UTIs. Risk factors that may cause patients to be more prone to the development of urosepsis or complicate treatment include the presence of an anatomic abnormality, a urinary tract obstruction, nephrolithiasis, prior urinary tract disease, acute kidney injury, neurologic disease, diabetes, Cushing's disease, and immunosuppression. Accurate recognition and aggressive therapy addressing the underlying condition, complicating risk factors, and the associated inflammatory response are necessary to prevent significant morbidity and mortality.

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