Pyelonephritis in Dogs: Retrospective Study of 47 Histologically Diagnosed Cases (2005–2015)

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Background: The clinicopathologic aspects of pyelonephritis have not been reported in companion animals.

Hypothesis/Objectives: To evaluate the prevalence of pyelonephritis diagnosed in dogs in a academic referral population, describe the clinical signs and the diagnostic test results in dogs with pyelonephritis, and identify concurrent disorders in order to determine potential risk factors for pyelonephritis.

Animals: Forty-seven dogs with a histopathologic diagnosis of pyelonephritis from the teaching hospitals of three Canadian veterinary colleges.

Methods: Retrospective case series. Review of medical records and renal histologic sections.

Results: Pyelonephritis was diagnosed in 0.4–1.3% of the cases at necropsy. Clinical signs included anorexia or inappetence (n = 27, 57%), lethargy (n = 24, 51%), vomiting (n = 17, 36%), and dehydration (n = 12, 25%). Thirty-five dogs (75%) had concomitant disease(s). *Escherichia coli* was the most common pathogen isolated (37%). Pyelonephritis was classified as acute (n = 12, 26%), subacute (n = 9, 19%), and chronic (n = 26, 55%) disease; and mild (n = 7, 15%), moderate (n = 11, 24%), and severe (n = 28, 61%). Fever was significantly associated with histopathologically subacute pyelonephritis ($P = 0.01$).

Conclusions: In referral hospitals, pyelonephritis has a very low prevalence at necropsy. Nonspecific clinical presentation, concomitant diseases, and high variability in the diagnostic tests results make the antemortem diagnosis of pyelonephritis challenging. Neither the histopathologic stage nor the severity of the pyelonephritis was associated with fever, lumbar pain, or signs of a urinary tract infection (ie, lower urinary tract infection, upper urinary tract infection, or both) except for subacute pyelonephritis which was associated with fever.

Key words: Canine; Complicated urinary tract infection; Subclinical bacteriuria.

Pyelonephritis generally refers to inflammation of the renal pelvis and adjacent renal parenchyma.[1–4] Most cases of pyelonephritis are caused by an ascending bacterial infection from the distal urogenital tract rather than hematogenous spread from a systemic infection.[2,5,6] Surprisingly, there is a dearth of information about pyelonephritis in both the veterinary and human literature. Other than individual case reports, there is only one retrospective study in dogs which

Abbreviations:

UTI(s)	urinary tract infection(s)
WBC	white blood cells
RBC	red blood cells
CKD	chronic kidney disease
USG	urine specific gravity

evaluated the pathologic aspects of pyelonephritis.[1] Other papers have included pyelonephritis cases within reports of other urinary tract infection (UTI) cases.[7]

Pyelonephritis can have an acute or chronic clinical presentation. Dogs with acute pyelonephritis usually show systemic, nonspecific signs of illness such as a fever, lumbar pain, and signs consistent with uremia (eg, anorexia, lethargy, vomiting, and diarrhea).[2,6] By contrast, dogs and cats with chronic pyelonephritis might not show systemic signs making the diagnosis more challenging.[2,6,9] Kidney damage can develop due to the insidious nature of such chronic infections and can ultimately lead to kidney failure.[6,10]

The diagnosis of pyelonephritis is usually presumptive and based on the presence of compatible clinical signs, urinalysis findings, a positive aerobic bacterial urine culture, improvement in degree of azotemia after antimicrobial treatment, and compatible ultrasonographic, excretory urography findings or both modalities.[6,9,11] Ideally, diagnosis should be confirmed by a positive bacterial culture collected by pyelocentesis or by renal biopsies; however, because both are considered invasive, they are rarely performed in cases of pyelonephritis.[2]

The objectives of this retrospective study were to evaluate the prevalence of pyelonephritis in a population of dogs presenting to an academic referral hospital,

to describe the clinical signs and the diagnostic test results in dogs with pyelonephritis diagnosed by histopathology, as well as to identify any concurrent disorders in order to determine potential risk factors for pyelonephritis in dogs. We hypothesized that acute pyelonephritis is associated with distinct clinical signs (fever, back pain, tense abdomen on palpation, polyuria-polydipsia, and signs of UTI) compared to chronic pyelonephritis which we suspected would be relatively clinically silent. We also hypothesized that there is a relationship between the clinical duration of the pyelonephritis and the histopathologic features.

Materials and Methods

Medical records from the teaching hospitals of three Canadian veterinary colleges (The Ontario Veterinary College Health Sciences Centre (OVC-HSC), the Western College of Veterinary Medicine, Veterinary Medical Center (WCVM-VMC), and the Faculté de Médecine Vétérinaire de l'Université de Montréal, Veterinary Teaching Hospital (FMV-VTH)) were searched to identify all dogs with a histologic diagnosis (at necropsy or by renal biopsy) of pyelonephritis between January 1, 2005 and July 1, 2015 at OVC-HSC and WCVM-VMC, and between June 1, 2009 and July 1, 2015 at FMV-VTH (records for 2005–2009 were not available). Histologic sections were reviewed by one board-certified veterinary pathologist (JLC, except for three cases reviewed by PH), and cases were included in the study only if the histologic findings were consistent with bacterial pyelonephritis, specifically, if there was evidence of leukocyte infiltration in the deep medulla, usually with radial streaks extending into the superficial medulla, with or without involvement of the pelvic epithelium. Dogs for which the diagnostic test data were limited (absence of urinalysis, CBC (Complete Blood Count), biochemistry, ultrasonography) were only used to calculate the prevalence of pyelonephritis in referral hospital population and for analysis of the epidemiologic, bacteriologic, and histopathologic results.

Pathology and medical records for the visit where the histopathologic diagnosis of pyelonephritis was confirmed were reviewed for information on histologic findings, signalment (breed, age, sex, and neuter status), presenting complaint, clinical signs, and their duration. Identification of concurrent diseases was based on both the medical records and the pathologic findings. Previous medical treatments including diuretic, anti-inflammatory, immunosuppressive, chemotherapeutic therapy, and any antibiotic treatment within the previous 30 days were documented. In addition, clinicopathologic data (including CBC, serum urea, and creatinine concentration), urinalysis, aerobic urine culture, and abdominal ultrasound findings were included when available at the visit preceding the necropsy or renal biopsy. When laboratory diagnostic tests were not performed at the time of the visit that preceded the owner's decision to euthanize the dog or consent to a renal biopsy, timely laboratory test results from the referring veterinarian were used if available.

For the presenting complaints, dogs were categorized as (1) presenting with only signs of lower UTI, (2) presenting with only signs of upper UTI, (3) presenting with signs of both lower and upper UTI, and (4) presenting with no signs of UTI. Clinical signs compatible with a lower UTI included hematuria, pollakiuria, stranguria, periuria, and dysuria. Signs consistent with an upper UTI included fever, lumbar pain, abdominal pain, polyuria, and polydipsia, whenever these clinical signs were not attributable to a known comorbid disease or to treatment. Incontinence was classified as a sign of either lower or upper UTI. Whenever possible, information in the medical record was used to define whether incontinence was attributable to pollakiuria, overflow from polyuria and polydipsia, or from neurologic or anatomic disease.

Medical records were reviewed to identify potential risk factors associated with the development of pyelonephritis. Identified risk factors were classified into one or more of the following categories: alteration of the urothelium (eg, urothelial carcinoma, urolithiasis, chronic lower urinary tract infections); neoplasia unrelated to the urogenital tract; obstructive uropathy (eg, urothelial carcinoma, urolithiasis); immunosuppressive treatments (eg, chemotherapy, corticosteroids); altered urine composition (eg, chronic kidney disease [CKD], diuretics); incontinence including urethral sphincter mechanism incompetence and neurogenic micturition disorder; neoplasia of the urinary tract; and anatomic defect of the urinary tract (eg, ectopic ureter). Some cases had risk factors in multiple categories.

For statistical analyses, leukocytosis was categorized as mild ($<25 \times 10^3/\mu L$), moderate (25–$50 \times 10^3/\mu L$), and severe ($>50 \times 10^3/\mu L$). Dogs with serum creatinine concentration greater than 1.4 mg/dL (ie, 125 μmol/L) with an accompanying urine specific gravity (USG) less than 1.030 before IV administration of fluid therapy were considered to have renal azotemia. Azotemia was classified as either mild (normal to increased serum urea concentration with serum creatinine concentration ranging from 1.4 to 2 mg/dL (ie, 125–179 μmol/L)), moderate (azotemia and serum creatinine concentration ranging from 2.1 to 5 mg/dL (ie, 180–439 μmol/L)), or severe (azotemia and serum creatinine concentration >5 mg/dL (ie, >440 μmol/L)). For urinalysis, the collection method was documented whenever possible. For dogs that had previously received IV fluids, corticosteroids, or diuretics, their USG data were excluded from statistical analysis. Hematuria was considered relevant when more than 0–5 red blood cells (RBC) per hpf were present in the urine sediment.[12] Pyuria was considered relevant when more than 0–5 white blood cells (WBC) per hpf where present in the sediment of urine samples collected by cystocentesis, and when more than 5–10 WBC where observed in the sediment of urine samples collected by catheterization or voiding.[11] Sediment examination was considered normal when bacteria, hematuria, and pyuria were absent. An active sediment was defined as a sediment in which bacteria, hematuria, pyuria, or any combination of those were present. When there was evidence of hematuria without bacteriuria or pyuria, the hematuria was not considered relevant if it was deemed to result from the method of collection or from an underlying disorder such as neoplasia of the urogenital tract. Culture results where the urine was collected by voiding were excluded for this part of the analysis. Any positive urine culture from a properly collected sample (cystocentesis, urinary catheterization, pyelocentesis, surgical biopsy of a kidney, or from a swabs of the bladder, ureter, or kidney obtained at necropsy) was considered positive.

Histologic sections of kidney were independently evaluated by a single board-certified pathologist. Histologic lesions were classified according to their stage, activity, and severity. For stage, lesions were considered acute if there was little or no newly formed collagen present, and acute lesions typically were dominated by neutrophils with few or no lymphocytes and plasma cells. Lesions were considered subacute if there was immature (ie, lightly eosinophilic) collagen in the areas of inflammation, and in subacute lesions, the neutrophils were typically accompanied by substantial numbers of lymphocytes and plasma cells. Lesions were considered chronic if there was abundant collagen within the areas of inflammation and the collagen showed evidence of maturity (ie, densely eosinophilic collagen, usually forming coarse fibers), and in chronic lesions, the neutrophils were typically accompanied by substantial numbers of lymphocytes and plasma cells. For activity of the lesions, the lesion was considered "active" if there were any histologically visible bacteria or if there were substantial numbers of neutrophils. Inactive lesions had inflammation, but the inflammatory cells were lymphocytes, plasma cells, macrophages, or a combination of those, with few or no neutrophils, and no

histologically observed bacteria. For severity, histologic lesions were scored as mild, moderate, or severe based on the extent of inflammatory cell infiltration in the histologic sections examined (mild, <5%; moderate, 5–30%; and severe, >30%). Finally, the predominant cell type for the inflammatory reaction was also recorded. A corresponding relationship between the clinical duration of the pyelonephritis and the pathologic findings on histologic sections was evaluated (ie, whether clinically acute pyelonephritis corresponded to pathologically acute pyelonephritis, and clinically chronic pyelonephritis corresponded to pathologically chronic pyelonephritis).

Statistics

Descriptive statistics were used for analysis of the epidemiologic data, clinical findings, clinicopathologic data, and comorbidities. A Fisher's exact test was used to evaluate possible associations between urine culture results and the presence or absence of azotemia, leukocytosis, or bacteriuria; between urine culture results and the presence or absence of prior antimicrobial treatment; and between the presence of leukocytosis and whether or not sepsis was diagnosed based on the necropsy or clinical findings. A Fisher's exact test (or Freeman-Halton extension of the Fisher's exact test when applicable)[13] was also used to evaluate for possible associations between a histologic diagnosis of pyelonephritis (acute or chronic, active or inactive and mild, moderate, or severe) and the presence or absence of clinical signs related to a UTI, lethargy, anorexia, fever, back pain or abdominal pain, polyuria and polydipsia, leukocytosis, abnormal serum creatinine concentration, renal azotemia, pyuria, clinical suspicion of pyelonephritis, positive or negative culture results. The association between signs of a lower UTI and the presence of hematuria, pyuria, bacteriuria, or prior antimicrobial treatment was also estimated by the Fisher's exact test. A Mann–Whitney U-test was used to test the association of the duration of clinical signs with pyelonephritis histologic characterization (active versus inactive, acute versus nonacute, chronic versus nonchronic, and mild/moderate/severe). Finally, a Wilcoxon test was performed to compare USG values of dogs that had evidence of bacteriuria, pyuria, hematuria, a history of CKD, or a positive culture (some dogs had more than one finding) versus the USG of dogs that did not have these findings. This test was required as the normality assumption for the USG and WBC data was violated based on the Shapiro–Wilk test. A Wilcoxon test was also used to determine whether a significant difference existed between the mean WBC count of dogs with: a positive versus negative urine culture, presence or absence of azotemia, presence or absence of septicemia, and whether the dog was considered immunocompromised or not. All statistical tests were performed by a commercially available software program.[a] A P value <0.05 was considered significant for all comparisons.

Results

Fifty-three dogs with a histopathologic diagnosis of pyelonephritis were identified. Forty-seven dogs met the inclusion criteria and were enrolled in the study; one dog was excluded because of a concomitant fungal pyelonephritis, and the other dogs were excluded because re-evaluation of the histologic sections did not indicate pyelonephritis. The pathologic diagnosis was based on biopsy in 12 of 47 (25%) cases and on post-mortem samples in 35 of 47 (75%) cases. Among the 12 dogs diagnosed with pyelonephritis based on biopsy, 11 dogs underwent a nephrectomy and one dog had Tru-Cut biopsies taken.

The age of dogs diagnosed with pyelonephritis ranged from 5 months to 15 years (median 7.7 years) with the majority (28/47, 60%) being older than 7 years of age. Thirty-three (70%) of the dogs were female, of which 26/47 (55%) were spayed and 7/47 (15%) were intact. Fourteen (30%) were male, of which 10/47 (21%) were neutered and 4/47 (9%) were intact. The proportion of females was significantly greater than the proportion of male dogs (P = 0.049). The most common breeds represented were Labrador Retrievers (n = 8, 17%), Shi Tzu (n = 4, 9%), Beagle (n = 3, 6%), Shetland Sheepdog (n = 3, 6%), and Doberman Pinscher (n = 2, 4%); 7 dogs (15%) were mixed breed.

Clinical Findings

The median duration of the clinical signs, recorded for 37 dogs, was 7 days (range 1–547). In this study, 8/47 (17%) dogs diagnosed with pyelonephritis showed only signs of lower UTI, 13/47 (28%) showed only signs of upper UTI, 8/47 (17%) showed signs of both lower and upper UTI, and 18/47 (38%) had no signs suggestive of a UTI and only exhibited nonspecific signs. In the latter group, signs possibly related to pyelonephritis were found in less than 20% of the cases. The clinical signs are shown in Table 1.

Predisposing Factors

Of the 47 dogs with pyelonephritis, 35 (75%) had evidence of concomitant disease(s). Potential predisposing factors recognized in this study included alteration of the urothelium (n = 14, 30%), neoplasia unrelated to the urogenital tract (n = 10, 21%), obstructive uropathy (n = 9, 19%), immunosuppressive treatment (n = 8, 17%), alteration of urine composition (n = 11, 23%), incontinence (n = 10, 21%), neoplasia of the urinary tract (n = 3, 6%), and anatomic defect of the urinary tract (n = 3, 6%). Twenty-two dogs (47%) had more than one potential predisposing factors. The precise nature of the predisposing factors of each category is reported in Table 2.

Concurrent Illnesses

Comorbidities included sepsis (n = 7, 15%), defined as the systemic inflammatory response to infection confirmed based on clinical and laboratory findings and the identification of a septic focus microbiologically or histologically.[14] Hepatitis or cholangitis (n = 3, 6%), myocarditis (n = 2, 4%), acute necrotizing pancreatitis (n = 2, 4%), stump pyometra (n = 1, 2%), bacterial

Table 1. Clinical findings in 47 dogs with histologically confirmed pyelonephritis.

Clinical signs	Number of dogs	Percentage of dogs (%)
Anorexia, decreased appetite	27	57
Lethargy	24	51
Vomiting	17	36
Diarrhea	13	28
Dehydration	12	26
Fever	10	21
Polyuria-polydipsia	8	17
Tense on abdominal palpation	8	17
Neurologic signs[a]	7	15
Stranguria	6	13
Hematuria	5	11
Incontinence	5	11
Recumbency	4	9
Dyspnea, cough, or restrictive respiratory	4	9
Paresis/tetraparesis	4	9
Back pain	3	6
Vaginal discharge	3	6
Renomegaly	3	6
Weight loss	2	4
Lameness	2	4
Anuria	2	4
Oral ulceration	2	4
Pollakiuria	1	2
Palpably large bladder	1	2
Heart murmur	1	2

[a]Neurologic signs included Horner's syndrome, strabismus, head pressing, head tilt, circling, vestibular ataxia, seizures. They do not include paresis/tetraparesis stated below.

meningitis (n = 1, 2%), prostatitis (n = 1, 2%), splenitis (n = 1, 2%), and peritonitis (n = 1, 2%) were also noted. Four dogs had more than one comorbidity. Many of these comorbid conditions can also be considered as predisposing factors. In five dogs, based on the necropsy findings, the pyelonephritis was suspected to be the source of sepsis. Outcome and cause of death/euthanasia are listed in Table S1.

Clinical Pathology Findings

Of the 47 dogs with pyelonephritis, eight dogs had limited diagnostic data (ie, no or limited data available from a urinalysis, CBC, biochemistry, and ultrasonography) and were not included in this analysis. Thus, 39 dogs had clinicopathologic data available and were included (Table 3). Among the 28 dogs for whom a serum creatinine concentration and USG value were available, eight dogs (29%) had renal azotemia. The method of collection of the urine was only specified in 14 of 25 (56%) dogs. Sample collection was by cystocentesis in 8/25 (32%), catheterization in 3/25 (12%), and voiding in 3/25 (12%) dogs. Three of 22 (14%) dogs had unremarkable sediment. Three of 15 (20%) of the dogs with pyuria had no clinical signs of UTI. The mean USG value was not different in dogs with or without pyuria ($P = 0.46$), hematuria ($P = 0.75$), abnormal urine sediment ($P = 0.38$), or a history of CKD ($P = 0.66$).

Table 2. Predisposing factors identified in 47 dogs with histologically confirmed pyelonephritis.

Category	Number of dogs	Percentage of dogs (%)
Alteration of the urothelium	14	30
Urolithiasis in the urinary bladder	5	11
Urolithiasis in the kidney	4	9
Urolithiasis in the ureter	4	9
Urothelial carcinoma of the urinary bladder	3	6
Mural irregularity or dystrophic mineralization secondary to previous surgery	2	4
Neoplasia unrelated to the urogenital tract	10	21
Obstructive uropathy	9	19
Ureteroliths	4	9
Urothelial carcinoma of the urinary bladder causing obstruction	2	4
Nephroliths	1	2
Dystrophic mineralization in the trigone of the urinary bladder	1	2
Immunosuppressive therapies	8	17
Chemotherapeutics	3	6
Corticosteroids	7	15
Altered urine composition	11	23
Steroids ± chemotherapeutics	7	15
CKD	4	9
Diuretics	1	2
Anatomical defects of the urogenital tract	2	4
Ectopic ureters	2	4
Incontinence	10	21
Incontinence (unspecified)	5	11
Urethral sphincter mechanism incompetence	1	2
Neurogenic micturition disorder (paralysis/paraparesis)	4	9
Neoplasia of the urinary tract (TCC of the urinary bladder)	3	6
Chronic lower UTI	2	4
Other concurrent conditions	13	28
Sepsis	7	15
Hepatitis/cholangitis	3	6
Myocarditis	2	4
Acute necrotizing pancreatitis	2	4
Stump pyometra	1	2
Bacterial meningitis	1	2
Prostatitis	1	2
Splenitis	1	2
Peritonitis	1	2

CKD, chronic kidney disease; UTI, urinary tract infection.

The difference in mean USG of dogs with and without bacteriuria approached significance ($P = 0.052$).

Imaging Findings

Ultrasound examinations were performed by a board-certified radiologist except for one dog whose

Table 3. Selected clinicopathologic findings in 47 dogs with histologically confirmed pyelonephritis.

Analyte	Number of dogs Abnormal/measured (% Abnormal)	Median (Range)	Reference interval
Hematocrit	14/32 (44)[a]	0.41 (0.20–0.53)	0.39–0.56
Red blood cell count	11/34 (32)[a]	$4.1 \times 10^6/\mu L$ ($1.6–5.1 \times 10^6/\mu L$)	$5.8–8.5 \times 10^9/L$
White blood cell count	19/34 (56)[b]	$22.0 \times 10^3/\mu L$ ($15.6–78.2 \times 10^3/\mu L$)	$4.9–15.4 \times 10^9/L$
Urea	17/37 (46)	81.5 mg/dL (26.9–222.4 mg/dL)	9.8–25.2 mg/dL (3.5–9 mmol/L)
Creatinine	16/37 (43)	4.3 mg/dL (1.5–23.6 mg/dL)	0.23–1.4 µmol/L (20–125 µmol/L)
USG	13/19 (68)	1.014 (1.006–1.028)	<1.030
Hematuria	17/22 (77)	N/A	0–5 cells/hpf
Pyuria	14/22 (64)	N/A	Absent
Bacteriuria	15/22 (68)	N/A	Absent

USG, urine specific gravity; WBC, white blood cells.
[a]All the red blood cell count and hematocrits reported to be abnormal were decreased.
[b]All the WBC counts reported to be abnormal were increased.

report was signed by a non-board-certified clinician who had completed a radiology residency. Ultrasonographic evidence of pyelonephritis[2,15] (see Table 4) was detected in 21 of 29 (72%) cases in which ultrasonography was completed. Two dogs (7%) had a normal urogenital ultrasound. Ultrasonographic signs suggesting a predisposing cause for the pyelonephritis were observed in 14/29 (47%) of the dogs. Four of the 39 dogs were previously diagnosed with chronic kidney disease; thus, some of these findings might have been a consequence of the kidney disease rather than of pyelonephritis.

Bacterial Culture Results

One urine culture performed from urine collected by voiding revealed a *Streptococcus* species (a urinary tract commensal organism),[16,17] which was excluded from the analysis. Culture was performed in 28/45 (62%) of the cases; in 22/28 (79%) dogs, the culture was positive. Nine of the 28 (32%) dogs had cultures done from multiple samples collected using different methods resulting in a total of 38 cultures being collected. The different methods of collection and bacterial isolates are reported in Table 5. Fourteen of the 19 (74%) cultures of samples collected from the lower urinary tract and nine of the 14 (64%) cultures of samples collected from the upper urinary tract were positive. *Escherichia coli* was the most commonly isolated pathogen (37%). Six of the 28 (21%) infections were polymicrobial with 4/28 (14%) involving two isolates and 2/28 (7%) involving three isolates or more. Four of the six dogs (67%) that had a negative culture had previously received antibiotics. Eighteen dogs had both bacteriuria and culture data available. Among them, one dog (6%) had a negative culture in association with bacteriuria.

Table 4. Ultrasonographic findings in 47 dogs with histologically confirmed pyelonephritis.

Observation	Number of dogs Abnormal/measured (% Abnormal)
Signs of pyelonephritis	21/29 (72)
Pyelectasia	19/29 (66)
Hydroureter or ureteral dilation	12/29 (41)
Decreased cortico-medullary distinction	4/29 (14)
Increased renal size	4/29 (14)
Decreased renal size	3/29 (10)
Renal hyperechogenicity	2/29 (7)
Other findings	
Renal cysts or nodules	4/29 (14)
Ascites	2/29 (7)
Evidence of retroperitoneal fluid accumulation	2/29 (7)
Ultrasonographic signs suggesting a predisposing cause for the pyelonephritis	14/29 (47)
Urolithiasis	8/29 (27)
Obstructive uropathy (urolithiasis excluded)	5/29 (17)
Extramural or intramural urogenital masses	3/29 (10)
Ureteral sludge	1/29 (3)
Dystrophic mineralization of the trigone of the urinary bladder secondary to surgery	1/29 (3)
Cystitis[a]	4/29 (14)
Ectopic ureters	None at the time of the consultation

[a]Cystitis is defined as diffuse mural thickening and irregularity of the bladder wall.

Table 5. Bacterial cultures of bladder urine, renal pelvic urine, kidney swab, ureter swab or sample, bladder swab or mucosal biopsy and ascite in 28 dogs.

Method of Collection	Number of Culture	Number of positive Culture	Number of positive Culture/Number of Cultured Samples (% positive) (per method)	Number of positive Culture/Number of Cultured Samples (% positive) (overall)	Number of positive culture of each isolate								
					Escherichia coli	*Staphyloccus* spp.	*Streptococcus* spp.	*Enterococus* spp.	*Proteus mirabilis*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	Mixed Anaerobes	Gram negative Bacillus
Kidney swab	9	5	5/9 (56)	5/26 (19)	3	2	2	2			1	1	
Pyelocentesis	5	4	4/5 (80)	4/26 (15)	1	2			1				
Bladder swab or mucosal biopsy	6	4	2/3 (67)	4/26 (15)	2	1	1						
Ureter swab or sample	2	1	1/2 (50)	1/26 (3)			1						
Bladder urine	13	10	10/13 (77)	10/26 (38)	6	2		1	1	1	1		1
Ascite	3	2	2/3 (67)	2/26 (8)	1		1					1	
Total number	38	26			13	7	5	3	2	1	2	1	1
Percentage isolates (n = 35)					37.1	20.0	14.3	8.6	5.7	2.9	5.7	2.9	2.9
Percentage cultures (n = 38)					34.2	18.4	13.2	7.9	5.3	2.6	5.3	2.6	2.6

Histopathology results

All the dogs were diagnosed histopathologically with pyelonephritis, but data were incomplete in nine dogs (ie, ulceration of the pelvic epithelium or presence of neutrophils in the tubules could not be determined when the pelvic epithelium or the tubules were not visible on the sections examined). Thirty-nine of 47 dogs (83%) had active pyelonephritis. The main inflammatory cells observed were neutrophils (n = 18, 38%); lymphocytes, neutrophils, and plasma cells (n = 18, 38%); lymphocytes and plasma cells (n = 8, 17%); and lymphocytes and neutrophils (n = 3, 6%). Ulceration of the pelvic epithelium was visible in 19 of 40 dogs (48%) and could not be assessed in seven dogs. Neutrophils were visualized in the tubules of 28 dogs (65%) and could not be assessed in four dogs. Bacteria were observed in 16 of 47 dogs (34%), and the presence of bacteria was equivocal in three of the 47 dogs. There was no histopathologic evidence of fungal pyelonephritis in any of the cases included in this study. Pyelonephritis was classified as acute (n = 12, 26%), subacute (n = 9, 19%), and chronic (n = 26, 55%) disease; and lesions as mild (n = 7, 15%), moderate (n = 11, 24%), and severe (n = 28, 61%), respectively, as defined in the Materials and Methods. The severity of the pyelonephritis could not be assessed in one dog. Pyelonephritis was bilateral in 33 of 46 dogs (72%) and unilateral in 13 of 46 dogs (28%) with four dogs affected on the left side, eight affected on the right side, and one case unspecified. The hydronephrosis noted histologically was significantly associated with the hydronephrosis observed on ultrasound ($P = 0.044$).

Overall Results

Thirty-two dogs had bacteria found in at least in one test (urine sediment analysis, culture, histopathology). Among the 32 dogs that had bacteria confirmed, 17 dogs had bacteria found in at least two of the tests (sediment, culture, histopathology). No bacteria were found in 15 dogs.

The mean WBC count of dogs was not significantly different between those with a positive versus negative urine culture ($P = 0.68$) or between those with presence or absence of azotemia ($P = 0.90$), but the mean WBC count was significantly higher ($P = 0.039$) in dogs with immunocompromised status compared to dogs considered immunocompetent.

There was no association between the presence of clinical signs of a UTI and the urinalysis findings (hematuria, leukocyturia, bacteriuria). There was also no association between a positive culture and the presence of azotemia or leukocytosis, nor between a negative culture and the administration of antibiotics. However, a negative culture was significantly associated with the absence of bacteriuria ($P = 0.044$).

The histopathologic severity of the pyelonephritis was significantly associated with anorexia/decreased appetite ($P = 0.024$) (ie, anorexia/decreased appetite was more likely to be present in cases of histopathologically severe pyelonephritis). Fever was significantly associated with histopathologically subacute pyelonephritis ($P = 0.0135$). Histopathologically active pyelonephritis was significantly associated with pyuria ($P = 0.0096$) and shorter duration of clinical signs ($P = 0.046$).

Based on the data in the medical records, as well as the submission documents for laboratory findings, pyelonephritis was not suspected by the clinician working on the case in 21 of 47 dogs (45%). Of 28 dogs with a positive urine culture, 6 (21%) had no clinical signs of UTI.

Discussion

This study evaluated 47 dogs with a histologically confirmed diagnosis of pyelonephritis. Histopathology and renal pelvic culture are recognized as the gold standard methods in the clinical diagnosis of pyelonephritis.[2] However, these methods are rarely utilized for making the diagnosis; therefore, pyelonephritis is often treated when there is a presumptive diagnosis based on consistent clinical signs along with a positive urine culture (collected by cystocentesis or catheter), with or without supportive findings from diagnostic imaging, and improvement of azotemia with antibiotic treatment. Among the dogs that had a postmortem evaluation performed at three veterinary institutions during the study period, pyelonephritis was diagnosed in only 0.4–1.3% of the cases. This is low, but prevalence at necropsy in a referral hospital canine patient population cannot be used as a surrogate to evaluate the prevalence of the disease in dogs in the entire population as many cases of pyelonephritis are successfully treated during the life of affected dogs with appropriate antibiotic treatment and without definitive confirmation by biopsy or at the time of necropsy. However, a low prevalence was also found in two previous studies.[1,7] The first study found a prevalence of 8% of dogs diagnosed with pyelonephritis at necropsy among 178 dogs with nephritis in a British veterinary teaching hospital.[1] The second study, which included cases from a tertiary veterinary medical teaching hospital, found a prevalence of 7.7% of dogs diagnosed with pyelonephritis clinically among dogs with a complicated UTI and a prevalence of 5% among all dogs with a positive urine culture.[7] Indeed, the kidneys have a number of specific anatomic defense mechanisms which prevent ascending infections, and healthy dogs with a normal urogenital tract seem to be highly resistant to the development of experimental pyelonephritis.[3] Only 12 cases of pyelonephritis were diagnosed by renal biopsy in this study and 11 of them were performed after nephrectomy. Renal biopsies are invasive and costly and therefore would likely not be performed if ultrasound findings and a positive urine (ideally collected by cystocentesis or pyelocentesis) culture were supportive of pyelonephritis.

In this study, the majority of dogs with pyelonephritis presented with comorbidities (74.5%). Conversely, potential predisposing factors were not observed in 25.5% of cases. Although uncomplicated pyelonephritis is possible, as occurs with acute nonobstructive (uncomplicated) pyelonephritis in women with an otherwise normal urinary tract and absence of any evidence of a compromised immune system,[18,19] we cannot rule out

the possibility that anatomic or functional abnormalities were present but not identified in the cases where no predisposing cause(s) were identified. As with any UTI, whether or not an infection is established depends on both bacterial virulence factors and host defense mechanisms.[5,11] To the authors' knowledge, uncomplicated pyelonephritis have not yet been described in dogs.

The most common potential predisposing factors for pyelonephritis identified in this study was neoplastic disease unrelated to the urogenital tract. This result, which differs from previous studies of complicated UTIs where nonurogenital neoplasia only accounted for 4.7% of predisposing causes,[7,20] may be inherent to the pathologic nature of the study and the large proportion of necropsied dogs. The relative immunodeficiency associated with neoplasia may also facilitate increased susceptibility to an ascending or hematogenous infection. Indeed, regulatory T cells, which suppress both effector T cells and antigen-presenting cells, have been shown to be systemically increased in dogs with cancer, particularly in dogs diagnosed with carcinoma.[21] Moreover, in this study, four dogs with neoplasia had received immunosuppressive drugs (corticosteroids or chemotherapeutics) which might also have predisposed them to pyelonephritis.

Other common predisposing factors were conditions altering the urothelium, obstructive uropathies, and immunosuppressive treatment. These findings were predictable because urolithiasis is known to alter the host mucosal defense barrier and can be responsible for vesicoureteral reflux or obstructive uropathies.[5,22] Noticeably, immunosuppressive treatment was present in a lower proportion (20.5%) of patients in this study compared to previous reports of complicated UTIs (34.7%).[7] Neurogenic disorders of micturition, urethral sphincter incompetence and altered urine composition were each present in about 10% of the cases in this study. Other studies have also shown that dogs with a neurogenic bladder are predisposed to bacterial colonization secondary to urinary stasis, bladder overdistention, high-pressure voiding, vesicoureteral reflux, and sometimes indwelling catheter placement.[23–25] Four dogs with pyelonephritis were previously known to have CKD (10.6%). This finding is less predominant than in a previous report of dogs clinically diagnosed with complicated UTIs where the percentage of cases of pyelonephritis with underlying CKD was much higher (30.4%).[7] In our study, histologic results showed concurrent renal changes in only two of the four dogs with concurrent CKD and these changes (renolithiasis, glomerular changes, hydronephrosis) could have been secondary to pyelonephritis. Therefore, it seems likely that in those cases the CKD may have resulted from pyelonephritis, instead of CKD causing pyelonephritis. Although pyelonephritis is known to lead to chronic renal failure, several human studies have pointed out that this progression might not be as frequent without another predisposing factor such as obstruction, urolithiasis, ureterovesicular reflux, or diabetes mellitus.[26] Indeed, the number of patients diagnosed with chronic pyelonephritis among human patients with renal failure in several studies is low (10–26%).[26–30] Moreover, a retrospective case controlled study of 99 dogs with acute renal failure showed that only two dogs developed pyelonephritis secondary to the development of acute renal failure.[31]

Interestingly, none of the dogs in this study had diabetes mellitus or spontaneous hyperadrenocorticism which are known to predispose dogs to bacteriuria.[8] Similarly, congenital anatomic defects were uncommon. Ectopic ureters were confirmed in two dogs before the diagnosis of pyelonephritis, but a recessed vulva or other anatomic abnormalities were not observed. However, such anatomic defects could have been overlooked by clinicians in this study in some cases based on the urgency of the dog's presenting complaint which were rarely associated with signs of a complicated UTI.

Many of the clinical signs reported in the dogs in this study were related to concurrent disease(s). The most common presenting signs were nonspecific and included lethargy, anorexia or decreased appetite, vomiting, and dehydration. Fever, polyuria-polydipsia and a tense abdomen on palpation which are considered classic signs for pyelonephritis were present in less than one quarter of the dogs. Therefore, the diagnosis of pyelonephritis should still be considered even in the absence of these signs.

Blood analysis results were nonspecific and based on these findings the absence of azotemia should not preclude the diagnosis of pyelonephritis even when there is severe bilateral involvement. This may not be surprising because azotemia is a late finding and develops only with decreased renal perfusion or when three quarters of the renal mass of nephrons is impaired.[32] Noticeably, about 18% of the dogs with pyelonephritis had a normal CBC.

The urinalysis results from this study were inconsistent. In this study, urine sediment was unremarkable in 13.6% of the dogs. However, two of three dogs with unremarkable sediment were receiving antibiotics at the time of diagnosis. Overall, this result suggests that the majority of dogs with pyelonephritis have abnormal urine sediment, with the exceptions of dogs receiving antibiotics. Hematuria and pyuria were present in 77% and 68% of the dogs with pyelonephritis, respectively. The high proportion of hematuria in this study may be related to concurrent diseases (urolithiasis, urethral carcinoma, genital infection) or the method of urine sample collection (cystocentesis, catheterization). Many dogs (34.8%) with a documented UTI did not have pyuria, which illustrates that the absence of pyuria does not rule out a UTI. This observation is similar to the situation in women where the absence of pyuria does not exclude the diagnosis of a urinary tract infection when there are consistent clinical signs although pyuria has a high sensitivity (95 percent).[18,33]

Bacteriuria was present in 68% of the dogs. The mean USG value did not differ between cases where the urine sediment examination showed the presence or absence of pyuria or hematuria or between cases with an active versus an inactive sediment. Previous publications have reported that bacteria can be difficult to observe when urine is dilute.[9,11] Although not significant ($P = 0.052$) in this study, the mean USG for dogs where bacteriuria was present was lower than in dogs

without bacteriuria. It is possible that significance would have been achieved with a larger sample. It remains unclear why some dogs with pyelonephritis do not have bacteriuria. Previous or concurrent administration of antimicrobial drugs (67% of dogs with negative urine culture), host defense mechanisms with bacteria being well walled off in the kidney and bacterial adherence to the urothelium without shedding are possible explanations.[22,34] In this study, bacterial culture was more sensitive than urinalysis in determining the presence of infection (79% versus 68%). Therefore, performing a urine culture is important for both the diagnosis of pyelonephritis, as well as for guiding the choice of antimicrobial used for treatment in all cases, but especially in those cases where bacteria are not detected with a urinalysis. Although any level of bacterial growth may be significant for samples collected by cystocentesis, quantitative urine culture is strongly recommended because the colony count and the type of the organism identified should be considered before making a treatment decision.[4] It is important to realize that a positive culture result does not necessarily equate to an active infection and overtreating subclinical bacteriuria could be deleterious to animals[35] as it is in humans.[36] Cost, poor compliance in drug administration, adverse drug reactions, and selection for antibiotic resistant bacteria[37–40] are existing issues in veterinary medicine. Current guidelines in veterinary medicine do not recommend treating dogs with subclinical bacteriuria that have no clinical signs of UTI and no evidence of UTI based on examination of urine sediment.[4] In addition, the findings from a previous study do not support the treatment of subclinical bacteriuria in healthy female dogs.[41] However, the true risk for subclinical bacteriuria leading to a UTI, ascending infections, and pyelonephritis remains to be investigated, and other studies question the indication for antibiotic treatment in certain patients at risk for UTI (ie, morbidly obese dogs).[42] The need for treatment in cases with subclinical bacteriuria associated with concurrent immunosuppressive treatment, hyperadrenocorticism, diabetes mellitus, and CKD[43] is more debatable and would be influenced by the colony count, bacterial species identified, past history of the patient including presence of other concurrent diseases, and clinician judgment. In this study, we found a very low prevalence of pyelonephritis at necropsy (0.4–1.3%), and an even lower prevalence of asymptomatic pyelonephritis (38% of dogs did not show classic clinical signs of pyelonephritis). Determination of virulence factors in bacteria isolated in urine samples of asymptomatic patients may in the future help to determine which asymptomatic patients could benefit from antibiotic treatment.[44]

Two third of the dogs in this study showed ultrasonographic abnormalities consistent with pyelonephritis. The most common findings were pyelectasia, hydroureter, and hydronephrosis. These findings are not specific for pyelonephritis and can be related to neoplasia of the urogenital tract, ectopic ureter, obstructive urolithiasis, CKD, prior administration of IV fluids or diuretics.[45] Care should be taken not to overdiagnose pyelonephritis based on such features. Nevertheless, ultrasonography could be useful in detecting occult pyelonephritis, especially because 38% of dogs in this study did not show classic clinical signs of pyelonephritis (ie, no signs of lower urinary tract disease, no abdominal or lumbar pain, and no fever). Interestingly, two dogs had a normal urogenital ultrasonography whereas they had histologically acute, active, and severe pyelonephritis. Therefore, pyelonephritis cannot be ruled out on the basis of a normal ultrasound. Identification of potential predisposing risk factors favoring pyelonephritis by ultrasound was common. For example, urolithiasis was present in almost one third of the dogs. Based on these findings, ultrasonography constitutes a key diagnostic test to support the suspicion of pyelonephritis and to detect potential predisposing causes which have the potential to impact response to treatment.

Bacterial culture results were positive in 79% of the dogs. An equal number of the bacterial isolates identified were Gram-negative and Gram-positive. By contrast, a previous study reported that Gram-negative organisms predominated (81%) in dogs with pyelonephritis.[7] This may reflect the different study designs—retrospective and histologic diagnosis versus clinical diagnosis. Indeed, in this study, bacterial culture was performed in only 28 dogs, so these results may not truly reflect the bacterial distribution in all dogs. *E. coli* and *Staphylococcus* spp. were the two most common isolates which is in accordance with previous reports of bacterial isolates in dogs diagnosed with upper and lower UTIs.[7,40,46]

Overall, a bacterial cause was confirmed in 32 cases based on either urine sediment analysis, culture, or histopathology. In the remaining 15 cases, while suspected to be bacterial in origin, this could not be definitively confirmed. Five of these 15 cases, however, were receiving antibiotics, and in seven of these 15 cases, the patient did not have a diagnostic workup performed antemortem (urine collection), so the diagnosis of pyelonephritis was based entirely on the histopathologic findings. Studies in humans demonstrate that urine often contains bacteria that are not detectable using routine bacterial culture and isolation.[47] Fastidious and anaerobic bacteria were seen in urogenital samples from women[47,48] and for many organisms detected, current cultivation methods are often not diagnostic. Only aerobic bacterial urine cultures were performed in patients in this study; anaerobic bacterial cultures and special cultures for mycoplasma or fungal organisms were not performed but may have been useful in some cases to rule out these rare causes of pyelonephritis. In addition, culture-independent 16S rRNA-based approaches such as fluorescent in situ hybridization (FISH) to look for common isolates causing pyelonephritis might have been useful in these 15 cases, especially the ones not previously receiving antibiotics, for determining whether a bacterial infection was present or not. However, it is important to appreciate that, for example, negative FISH results do not exclude a bacterial infection. Indeed, negative results can occur when bacteria have low metabolic activity[49] to take up an RNA probe,

when the distribution of infection is focal or when the number of bacteria is low. Overfixation of the tissues, the presence of bacteria with thick cell walls and prior antibiotic treatment (sulfasalazine) are other possible causes of negative results. When positive, culture-independent methods do not differentiate if bacteria are alive nor if their presence is related to urinary tract conditions depending on their location.[48] Finally, such testing can be cost prohibitive and its availability is limited to specialized laboratories.

More than two thirds of the cases of pyelonephritis reviewed were characterized histologically as active and the inflammatory infiltrate consisted primarily of neutrophils or neutrophils in association with lymphocytes and plasma cells. About half of the cases of pyelonephritis were histologically considered chronic. The results of this study did not show any link between either the histopathologic features of the pyelonephritis (active versus inactive), the severity (degree of histologic infiltrate), or the histologic chronicity of the pyelonephritis and the cardinal clinical signs (fever, abdominal pain, signs of aUTI [upper UTI, lower UTI, or both]), except fever which was significantly associated with histologically subacute pyelonephritis. There was also no association between the duration, severity, or active versus inactive state and the presence or absence of azotemia or leukocytosis. Therefore, the presence or absence of such cardinal clinical signs, azotemia or leukocytosis, may not provide information to the clinician concerning either the severity or duration of the pyelonephritis. Not only does this observation highlight the challenge of diagnosing pyelonephritis but it also stresses the fact that acute pyelonephritis can also have a subtle presentation.[2,6,9] Active pyelonephritis was significantly associated with pyuria and a shorter duration of clinical signs. Moreover, there was a strong statistical trend between histologically active pyelonephritis and a positive culture ($P = 0.0504$). Although these features are indicative of an active pyelonephritis, they are not specific for the diagnosis of pyelonephritis.

Limitations of this study, as with all retrospective studies, include incomplete medical records and nonstandardized clinical workup. The significance of some of our hypothesis could not be tested as only a small number of dogs without missing values was noted for some parameters. For example, testing an association between a positive urine culture and the site of urine sampling (kidney versus bladder) was not possible. The low number of cases raises the risk for type 2 errors. In addition, a large number of the culture results were not quantitative, but it is very unlikely that bacterial urinary tract infections were overestimated as pyelonephritis was histologically confirmed. Finally, abnormal results did not differentiate between concurrent diseases and pyelonephritis. For example, sediment abnormalities could be mostly related to urolithiasis or urethral carcinoma rather than pyelonephritis. The same limitations occurred for interpretation of blood sample analysis and ultrasonography. However, considering the dearth of information on this type of UTI in dogs and our approach of including only dogs with the diagnosis based on a gold standard diagnosis (histopathology) this study adds important information to the veterinary literature.

Conclusion

This retrospective study found that pyelonephritis was a rare finding among dogs at postmortem examination. Dogs with pyelonephritis in this study had a variable clinical presentation ranging from being asymptomatic to having typical cardinal signs of the disease (fever, lumbar pain, and signs of a UTI [ie, lower UTI, upper UTI, or both]) to very severe clinical signs associated with the development of sepsis. Similarly, we found a high variability in the diagnostic tests results with some of the tests revealing no abnormalities. Therefore, normal diagnostic test results does not preclude pyelonephritis and in a small subset of dogs, an extensive workup would be required to diagnose pyelonephritis and avoid misdiagnosis. Some dogs had concomitant diseases which could predispose them to UTIs and pyelonephritis, in particular neoplasia not involving the urogenital tract, suggesting that these dogs might need to be regularly screened for this complication.

Footnote

Acknowledgment

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Outcome and cause of death/euthanasia in 47 dogs with pyelonephritis.