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CLINICAL REVIEW

URINARY TRACT INFECTION AND SUBCLINICAL BACTERIURIA IN CATS
A clinical update

Roswitha Dorsch, Svenja Teichmann-Knorrn and Heidi Sjetne Lund

Introduction

Urinary tract infection (UTI) refers to the adherence, multiplication and persistence of an infectious agent within the urogenital system that causes an associated inflammatory response and clinical signs.[1] In the vast majority of UTIs, bacteria are the infecting organisms; fewer than 1% of UTIs are due to parasitic, fungal or viral infections.

Adherence to treatment guidelines for urinary tract infections, and confinement to a few first-line antimicrobial agents, is imperative to avoid further deterioration of the antimicrobial resistance situation.

In addition to cats with typical clinical signs of feline lower urinary tract disease (FLUTD) or upper UTI, many cats have asymptomatic or subclinical bacteriuria. In human medicine, asymptomatic bacteriuria is defined as the isolation of a specified number of bacteria in a urine specimen from a patient without symptoms referable to UTI.[2] In veterinary medicine, use of the term subclinical UTI has been suggested for these cases, because clinical signs might be too subtle to be detected.[3] In humans and most of the studies on dogs and cats, the terms asymptomatic bacteriuria (in humans) and subclinical bacteriuria (in dogs and cats) are also used if there is evidence of inflammation (pyuria, haematuria) in the urine sediment.

Terminology

- **Urinary tract infection** Adherence, multiplication and persistence of an infectious agent within the urogenital system that causes an associated inflammatory response and clinical signs
- **Subclinical bacteriuria** Presence of a significant number of bacteria ($\geqslant 10^3$ colony-forming units [CFU]/ml in a cystocentesis-derived urine sample), with or without signs of inflammation in the urine sediment, in an animal that has no clinical signs referable to UTI

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Practical relevance: Urinary tract infection (UTI) is an important cause of feline lower urinary tract disease (FLUTD), particularly in female cats older than 10 years of age. In addition to cats with typical clinical signs of FLUTD or upper UTI, many cats have subclinical bacteriuria, but the clinical relevance of this is currently uncertain. UTIs are one of the most important indications for antimicrobial use in veterinary medicine and contribute to the development of antimicrobial resistance. Adherence to treatment guidelines and confinement to a few first-line antimicrobial agents is imperative to avoid further deterioration of the antimicrobial resistance situation. The decision to treat with antimicrobials should be based on the presence of clinical signs, and/or concurrent diseases, and the results of urine culture and susceptibility testing.

Clinical challenges: Distinguishing between cats with bacterial cystitis, and those with idiopathic cystitis and concurrent clinical or subclinical bacteriuria, is challenging, as clinical signs and urinalysis results may be identical. Optimal treatment of subclinical bacteriuria requires clarification as there is currently no evidence that demonstrates a beneficial effect of routine treatment. Management of recurrent UTIs remains a challenge as evidence for most alternatives used for prevention in cats is mainly anecdotal, and no preventive treatment modality is currently recommended.

Evidence base: This review draws on an extensive literature base in veterinary and human medicine, including the recently updated guidelines of the International Society for Companion Animal Infectious Diseases for the diagnosis and management of bacterial urinary tract infections in dogs and cats. Where published evidence is lacking, the authors describe their own approach; notably, for the bacteriuric cat with chronic kidney disease.

Keywords: Cystitis; feline lower urinary tract disease; FLUTD; pyelonephritis; antimicrobial resistance

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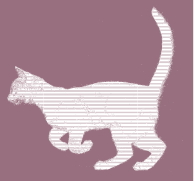
Antimicrobial resistance

UTIs are one of the most important reasons for the use of antimicrobial drugs in veterinary medicine, and contribute to the development of antimicrobial resistance.[4] Over-prescription of antimicrobials in cats with FLUTD is common, and some critically important antimicrobials such as third- and fourth-generation cephalosporins and fluoroquinolones are overused.[5]

A European multicentre study in 2016 documented antimicrobial resistance rates in bacterial isolates from feline and canine urine, and reported various levels of resistance in different countries.[6] Southern European countries (Italy, Greece, Portugal and Spain) generally had higher antimicrobial resistance levels than northern European countries (Denmark and Sweden). For example, 48.2% of *Escherichia coli* isolates from Portugal compared with only 2.9% from Denmark were resistant to amoxicillin–clavulanic acid. A study from Norway[7] identified no feline uropathogens resistant to fluoroquinolones at all, whereas in Italy 32% of *E coli* were resistant.

These differences can be explained by the more restrictive use of antimicrobials in northern European countries. More restrictive use of antimicrobials in other countries is urgently needed to avoid further deterioration of the antimicrobial resistance situation.

More restrictive use of antimicrobials is urgently needed.



Classification

UTIs have traditionally been classified as uncomplicated or complicated.[8] An uncomplicated UTI was defined as a sporadic bacterial infection of the bladder in an otherwise healthy individual with normal urinary tract anatomy and function. UTIs in animals with any anatomic and/or functional abnormalities of the urinary tract, animals with comorbidities that predispose to persistent infection, recurrent infection or treatment failure, or animals experiencing more than three episodes within a 12-month period were categorised as complicated.

The recently updated guidelines of the International Society for Companion Animal Infectious Diseases (ISCAID) for the diagnosis and management of bacterial urinary tract infections in dogs and cats have adopted the following categories: sporadic bacterial cystitis, recurrent bacterial cystitis, pyelonephritis (see box below), bacterial prostatitis, subclinical bacteriuria and cats with indwelling urinary catheters. A new separate category is UTIs in dogs and cats receiving urological surgery, minimally invasive urological procedures and urologic implants.[12] The box on the right defines these categories (with the exception of bacterial prostatitis, which is of little relevance in cats).

Terminology

- **Pyelonephritis (upper UTI)** Inflammation of the renal pelvis and renal parenchyma.[8,9] Most commonly, pyelonephritis is caused by an ascending bacterial infection from the distal urinary tract.[10] The development of renal abscesses as a consequence of ascending infection has also been described in a case series of six cats[11]

Categories of significant bacteriuria[12]

Sporadic bacterial cystitis

Sporadic (fewer than three episodes in the preceding 12 months) bacterial infection of the bladder with compatible lower urinary tract signs in an animal with or without predisposing factors.

Recurrent bacterial cystitis

Three or more episodes of clinical bacterial cystitis in the preceding 12 months or two or more episodes in the preceding 6 months.

- Relapse: infection with the same microorganism that recurs after successful treatment of the initial UTI
- Reinfection: infection with a different microorganism after the initial microorganism responded to therapy
- Persistent infection: persistently positive urine cultures with the same organism during treatment with appropriate antimicrobial agents
- Superinfection: infection with new organisms that develops during antimicrobial treatment for the initial infecting organism

Pyelonephritis

The human classification scheme differentiates:

- Acute pyelonephritis
  - Uncomplicated: no underlying comorbidity
  - Complicated: presence of a predisposing systemic disease or an anatomical/obstructive disorder
- Chronic pyelonephritis

Subclinical bacteriuria

Presence of bacteria in urine as determined by positive bacterial culture from a properly collected urine specimen, in the absence of clinical evidence of infectious urinary tract disease.

Bacteriuria in cats with indwelling urinary catheters

Bacteriuria in cats undergoing urological surgery or minimally invasive urological procedures and/or with urologic implants

Significant bacteriuria in cats undergoing cystoscopy, cystoscopic bladder biopsy, cystoscopic stone removal or laser lithotripsy, voiding urohydropropulsion or placement of ureteral stents or subcutanous ureteral bypasses.

Emphysematous, encrusting and polypoid cystitis are rare forms of complicated lower UTIs. Emphysematous cystitis is characterised by gas accumulation within the bladder wall and lumen secondary to infection with glucose-fermenting bacteria, mainly *E coli*.[13] Animals with diabetes mellitus are predisposed because of their high urinary glucose concentration.[14,15] The hallmark of encrusting cystitis is adherent bladder mucosal plaques. Urea-splitting bacteria, such as *Corynebacterium urealyticum*, may lead to mineral precipitation, resulting in bladder wall encrustation.[16–18] Treatment of encrusting cystitis can be challenging and long-term antimicrobial therapy, urine acidification and surgical debridement of plaques is often required.[16] Polypoid cystitis refers to mass-like proliferations or diffuse thickening of the bladder mucosa induced by chronic inflammation, and is most commonly associated with *Proteus* species infections.[19] Although adequate antimicrobial treatment can lead to complete resolution, surgical intervention may be required.[19,20]

Prevalence

Urinary tract infections

Bacterial UTIs occur much less frequently in cats than in dogs, with only 1–2% of cats suffering from UTIs in their lifetime.[21] In cats with clinical signs of FLUTD, such as pollakiuria, macroscopic haematuria, stranguria, periuria or urethral obstruction, the proportion of cases with a UTI ranges from 2–19%.[22–26] A low prevalence of UTI, <3%, has been identified in referral populations of cats of younger ages in the USA.[24] European studies incorporating higher proportions of primary cases and cats of all ages revealed higher rates of UTIs. While UTI is less common in younger cats, it is an important cause of FLUTD in cats older than 10 years, affecting 40–45% of the latter population.[22,27]

Subclinical bacteriuria

The reported prevalence of subclinical bacteriuria depends on the study population; for example, it was low (0.9%) in a cohort of 108 healthy cats from Norway with a mean age of 4 years.[28] In other studies, 6.2%[29] and 29%[30] of cats were affected. The median age of culture-positive cats in these three studies was 14 years. A prospective observational study that included 67 non-azotaemic cats that were at least 7 years old and tested on five occasions revealed a prevalence of 10–13%.[31] The most recent study, which included 179 cats over 6 years of age, revealed a prevalence of 6.1% for subclinical bacteriuria, with no significant difference between healthy cats and cats with different diseases.[32] In all of these studies, female cats were significantly more likely to be affected.[28–32]

Risk factors

A large case-controlled epidemiological study involving 22,908 cats with clinical signs of FLUTD revealed that UTIs were significantly more common in spayed female cats, Abyssinian cats and cats older than 10 years.[33] Other studies investigating cats with clinical signs of FLUTD or with subclinical bacteriuria have also identified female sex and age as risk factors.[29,31,34] An increased risk for Abyssinian cats or Persian cats has only been identified in one study each.[33,35] Possibly the Persian and Abyssinian cats' longer hair and decreased grooming in cases of systemic illness could result in contamination of the fur in the anogenital area, allowing faecal bacteria to colonise the lower urinary tract.

A predisposing comorbidity can be identified in 75–87% of cats with a UTI or subclinical bacteriuria (see box below).[30,34,35,44]

The most common systemic comorbidities in affected cats are CKD and endocrine diseases (diabetes mellitus and hyperthyroidism). In two studies, approximately one-third of all culture-positive urine specimens were derived from cats with CKD.[37,44]

The most common systemic comorbidities in affected cats are chronic kidney disease and endocrine diseases.

Predisposing factors for bacterial UTIs and subclinical bacteriuria in cats

Systemic factors

- Age[28,31]
- Female gender[29,31]
- Chronic kidney disease (CKD)[34,36–38]
- Diabetes mellitus[34,36,37,39]
- Hyperthyroidism[34,36,37]
- Gastrointestinal disease[38]

Local factors

- Previous perineal urethrostomy following obstructive FLUTD[37,40–42]
- Indwelling urinary catheter[37,43]
- Other transurethral procedures[44]
- Incontinence[44]
- Urocystoliths, nephroliths[27,45]
- Bladder neoplasia[46]
- Ureteral stents and subcutaneous ureteral bypass[47,48]

The reported prevalence of positive urine cultures in cats with CKD, diabetes mellitus and hyperthyroidism is 22–29%, 12–13% and 12%, respectively.[36,38,39] Only 8–28% of cats with CKD displayed clinical signs of FLUTD; 20% of cats had clinical signs and haematological findings compatible with pyelonephritis (abdominal pain, pyrexia, renomegaly, neutrophilia with left shift).[36,38] In cats with diabetes mellitus and hyperthyroidism, clinical signs of FLUTD were seen in 14–44% and 33% of cases with a positive urine culture, respectively.[34,36,39]

Impaired local defence mechanisms also predispose to the presence of positive urine cultures. One retrospective study investigating clinical features and risk factors predictive of positive urine cultures (defined as any growth of bacteria in cystocentesis samples or $\geqslant 10^3$ CFU/ml in catheter-derived urine samples) in cats, included 155 culture-positive cats and 186 control cats. Clinical signs of FLUTD were documented in 65% of cats with a positive urine culture, and 35% had subclinical bacteriuria. Factors associated with an increased risk of positive urine cultures in this study were urinary incontinence, transurethral procedures and urogenital surgery, gastrointestinal disease, decreased urine specific gravity (USG) and decreased body weight.[44] However, a low USG does not appear to be a consistent risk factor for positive urine cultures.[33]

Hugonnard and colleagues investigated the incidence of catheter-associated UTIs in 18 cats with obstructive FLUTD.[43] In these cats, a transurethral catheter was placed using a standardised protocol and aseptic technique. The catheter was connected to a closed urine collection system. After 24 h and 48 h, urine culture was positive in 3/18 (17%) and 6/18 (33%) cats, respectively.[43] Another study reported that 8/37 (22%) cats had positive urine cultures after 48 h with an indwelling urinary catheter.[49]

Perineal urethrostomy (PU) is a well-recognised risk factor for UTI, with 22–53% of affected cats having undergone the procedure.[40–42] Bass et al reported that 23% of cats with a PU suffered from a bacterial UTI, and 15% of cats had up to 10 recurrent episodes of UTI.[40] In another study,[42] nine cats with recurrent or persistent urethral obstruction and 10 healthy castrated male cats underwent PU.

A predisposing comorbidity can be identified in 75–87% of cats with a urinary tract infection or subclinical bacteriuria.

Two of the nine cats with recurrent or persistent urethral obstruction developed recurrent UTIs after surgery, but none of the healthy castrated males did. Therefore, PU does not appear to predispose to UTI, but cats with an underlying uropathy undergoing surgery have an increased risk of infection.[42]

In addition to obstructing the urinary outflow and injuring the renal parenchyma, nephroliths can predispose cats to pyelonephritis.[45] The reported prevalence of positive urine cultures in cats with ureteral obstructions before surgery is 2–33%.[50–52] Bacterial UTIs are also among the most common complications after subcutaneous ureteral bypass and ureteral stent placement, with infection rates reaching 31%.[47,48] Most culture-positive cats with a subcutaneous ureteral bypass have lower urinary tract signs and/or clinical signs of pyelonephritis.[52]

To date, little evidence exists to suggest that feline immunodeficiency virus or feline leukaemia virus infection and immunosuppressive drug treatment are predisposing conditions for significant bacteriuria. In one study, long-term treatment of 32 cats with glucocorticoids and ciclosporin was not associated with subclinical bacteriuria or UTI.[53]

Development of urinary tract infection and subclinical bacteriuria is multifactorial and depends on the interplay between bacterial virulence and alterations in host defences.

Pathogenesis

Development of UTI and subclinical bacteriuria is multifactorial and depends on the interplay between bacterial virulence and alterations in host defences.

Natural host defences

Owing to various host defence mechanisms, the healthy feline urinary tract is a remarkably hostile environment that is not conducive to bacterial migration and colonisation.[54,55] A UTI develops when host defence mechanisms are transiently or permanently breached, allowing virulent microbes to adhere, multiply and persist within the urinary tract.[56] Major host defences against bacterial colonisation include frequent and complete voiding of an adequate urine volume, presence of a normal resident microflora, a physiological urinary tract anatomy, antimicrobial characteristics of the urine and systemic immunocompetence.[54,56–58]

Bacterial virulence factors

Bacterial virulence and fitness factors enable pathogens to colonise and to invade the urinary tract. Virulence factors determine not only the severity of a UTI, but also the infection site. Virulence factors are clustered on pathogenicity-associated islands, which can be easily spread among bacterial populations by horizontal gene transfer.[58]

The virulence of uropathogenic *E coli* (UPEC) is enhanced by adhesins (eg, type 1 and P fimbriae), iron acquisition systems and toxins (eg, haemolysin).[59] P fimbriae are bacterial adhesion molecules found in most (80%) pathogens causing pyelonephritis, in 22% of cystitis strains, and in only 15% of asymptomatic strains in people.[60,61] Bacterial invasion into epithelial cells often triggers the cell to undergo apoptosis and exfoliation. Some *E coli* strains in humans and mice are able to invade deeper tissues, persisting intracellularly, and may also form intracellular biofilm.[61–63] Thus, those pathogens cannot be isolated from urine and can escape antimicrobial treatment.

Pathogens

Most commonly, significant bacteriuria is caused by pathogens from the host's own enteric or distal urogenital flora. The bacteria ascend from the distal urethra into the normally sterile proximal urethra, urinary bladder and upper urinary tract. *E coli* clones causing UTIs can frequently be isolated from the same animal's faeces as well.[62] Haematogenous spread is rare but can cause UTIs, in particular renal abscesses.

Most UTIs (>85%) are caused by a single bacterial pathogen, while two different species have previously been isolated in 13% of cats.[6,23,30,38] Infections with multiple bacterial species are more common in cats with indwelling urinary catheters (27%) or other local comorbidities (20%).[37]

Most commonly, significant bacteriuria is caused by pathogens from the host's own enteric or distal urogenital flora.

In several studies, *E coli* was the most commonly isolated pathogen in feline urine, and was involved in 39–59% of positive cultures (Table 1).

Other frequently documented microorganisms are *Streptococcus* species (2–19%), *Enterococcus faecalis* (5–27%) and *Staphylococcus felis* (17–20%).[6–8,34,35,44,63] *E faecalis* was more likely to be present in cats with subclinical bacteriuria (23%) than in cats with UTIs (11%).[29,34] *Enterococcus* species were previously considered commensal organisms of the gut flora with little clinical significance. Their emergence as leading causes of nosocomial infections worldwide has coincided with increased antimicrobial resistance.[64,65] *E faecalis* has intrinsic resistance to beta-lactams, cephalosporins, trimethoprim/sulfonamide, aminoglycosides, lincosamides and fluoroquinolones.[66] Acquired antibiotic resistance can develop through sporadic mutations within intrinsic genes or through horizontal gene transfer. Great caution is required when interpreting in vitro susceptibility testing results, because cephalosporins, clindamycin and trimethoprim/sulfonamide can appear active against *E faecalis* despite the intrinsic resistance of the pathogen and inactivity of these antibiotics in vivo.[67] Laboratories should not provide the results of drugs to which *Enterococcus* species are inherently resistant. Additionally, *Enterococcus* species form biofilms and can thus evade antimicrobials.[65]

Table 1 Commonly isolated pathogens from feline urine

		Bailiff et al[63]	Martinez-Ruzafa et al[44]	Dorsch et al[35]	Lund et al[7]	Marques et al[6]	Teichmann-Knorrn et al[34]
Study period		1995–2002	1989–2003	2000–2009	2003–2009	2008–2013	2009–2014
Number of cats		NA	155	280	71	NA	150
Number of urine samples		NA	NA	330	72	5963	169
Number of bacterial isolates		101	198	375	82	6282	192
Gram-negative bacteria	*Escherichia coli* (%)	59	50.3	42.3	38.8	59.3	50.5
	Proteus species (%)	3.9	1.3	3.2	2.8	2.0	2.6
	Klebsiella species (%)	2.9	3.9	0.3	1.4	1.5	NA
	Pasteurella species (%)	2.0	1.9	1.3	5.5	NA	1.0
	Pseudomonas species (%)	1.0	5.2	1.6	1.4	1.5	NA
	Enterobacter species (%)	1.0	2.6	NA	2.8	1.8	NA
Gram-positive bacteria	*Enterococcus* species (%)	13.9	21.3	6.6	9.7	12.1	15.1
	Staphylococcus species (%)	7.8	17.4	16	15.3	16.8	22.9
	Streptococcus species (%)	5.9	12.9	19.2	4.2	2.0	3.6
	Lactobacillus species (%)	NA	3.2	NA	NA	NA	NA
	Corynebacterium species (%)	NA	1.9	2.1	1.4	NA	NA

NA = not assessed

Clinical signs

Clinical signs should not be relied on alone for diagnosis. Rather, the presence of clinical abnormalities indicates that further work-up is needed.

Lower UTI

Clinical signs of lower UTI include pollakiuria, gross haematuria, periuria, dysuria and stranguria. These are non-specific and can be seen in any disease of the lower urinary tract, of which idiopathic cystitis is the most common in cats.

Upper UTI

Pyelonephritis can have an acute or chronic clinical presentation and is commonly suspected in hospitalised patients. The diagnosis remains challenging and information in the literature is limited to a small number of case reports.[68,69]

Acute pyelonephritis may be associated with distinct clinical signs such as fever and painful kidneys, as well as anorexia, lethargy, polyuria and polydipsia, vomiting and diarrhoea.[70] According to one study of 17 histopathologically confirmed cases of pyelonephritis, the most common clinical signs were non-specific, such as anorexia, lethargy and vomiting;[71] renal pain and pyrexia were only observed in 3/17 and 2/17 cats, respectively. Azotaemia (11/11 cats with available serum chemistry), hyperphosphataemia (8/11 cats) and non-regenerative anaemia (7/10 cats with available complete blood count) were the most common clinicopathological abnormalities.[71] In addition, an inflammatory leukogram can be present.[72]

In dogs, chronic pyelonephritis is considered to produce only mild or absent clinical signs.[9,70] In cats, there is a lack of knowledge regarding this disease entity.

Clinical signs should not be relied on alone for diagnosis. Rather, the presence of clinical abnormalities indicates that further work-up is needed.

Positive urine cultures are indispensable for a reliable diagnosis in cats, as other causes for clinical signs of lower urinary tract disease are common.

Diagnosis

UTIs are diagnosed based on clinical signs, urinalysis findings and quantitative bacterial cultures. Distinguishing between cats with bacterial cystitis, and those with idiopathic cystitis and concurrent clinical or subclinical bacteriuria, is challenging, however, as clinical signs and urinalysis results may be identical.[35,73] Particularly in cats, where other causes for clinical signs of lower urinary tract disease are common, positive urine cultures are indispensable for a reliable diagnosis. To select an effective antimicrobial, in vitro susceptibility testing should be performed on all isolates. Diagnostic imaging can help assess for complicating conditions (eg, upper urinary tract involvement) (Figure 1).

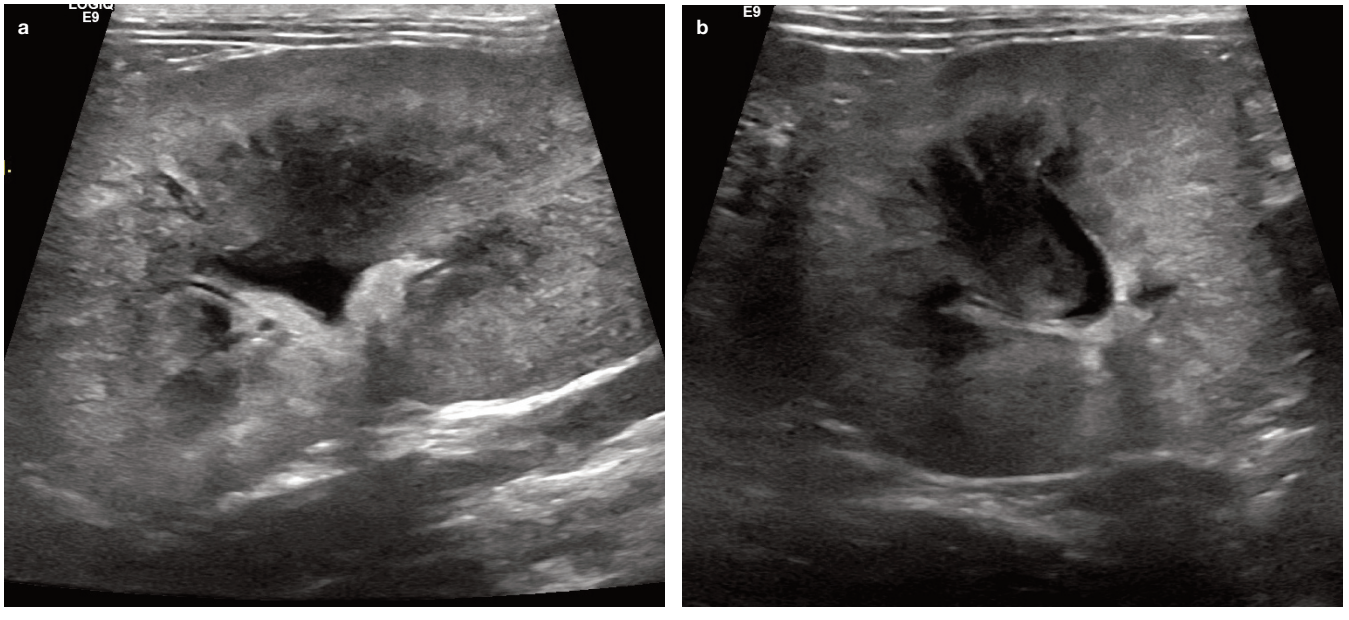


Figure 1 Longitudinal (a) and transverse (b) ultrasound images of the left kidney of a cat with bilateral renomegaly and acute (grade V) kidney injury. The kidney is enlarged, there is poor corticomedullary differentiation, the cortex is patchy hyperechoic and the medulla has lost its typical hypoechogenic to anechoic appearance. The renal pelvis is dilated to 4 mm. Post-mortem examination of this cat revealed severe pyelonephritis

Urinalysis

When possible, urine specimens should be obtained by cystocentesis and before initiating antimicrobial treatment (Figure 2). Urine can be sampled by catheterisation, but the risk of contamination is higher and catheter placement requires sedation or anaesthesia. Free-catch samples (mid-stream voiding) are frequently contaminated and should not be used for bacterial cultures.[8] Note that manual expression is no longer recommended.

Storage of urine specimens can influence the test results owing to altered pH, lysis of casts, leukocytes and epithelial cells, precipitation of substances and in vitro crystal formation. Furthermore, inadequate storage can lead to bacterial contamination and proliferation as well as bacterial death.[74]

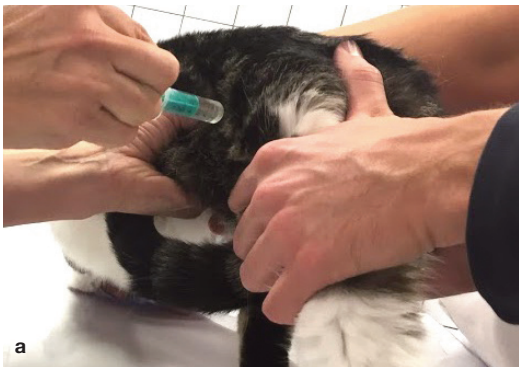
USG is variable in cats with UTIs. Gram-negative-infected specimens are reported to have a lower USG than Gram-positive-infected specimens and culture-negative specimens.[30] USG is higher in specimens infected with *S felis* and lower in specimens infected with *E coli* than in those infected with other uropathogens.[75] Dipstick analysis often reveals haematuria and proteinuria. Importantly, the leukocyte field is often falsely positive in cats, and the nitrite field is unreliable.[76]

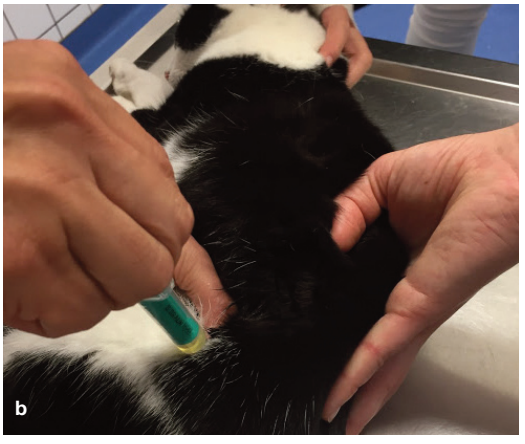
Urine sediment

Examining the urine sediment is an important diagnostic. There is, however, a large overlap between sediment findings in cats with UTIs and cats with other diseases of the lower urinary tract (Table 2). Haematuria (>5 red blood cells/high-power field [HPF]) and pyuria (>3–5 white blood cells/HPF) are seen in 28–77% and 35–100% of cats with subclinical bacteriuria or UTIs, respectively.[29,31,73]

Haematuria is also present in more than 70% of cats with feline idiopathic cystitis, and in most cats with urolithiasis and bladder neoplasia.[23,35,78] Pyuria is likewise a non-specific finding and has been reported in up to 77% of cats with feline idiopathic cystitis and more than 50% of cats with urocystoliths.[73]

Figure 2 Cystocentesis performed with palpation of the urinary bladder in the standing cat (a) and the cat in lateral recumbency (b) through the lateral abdominal wall





When possible, urine specimens should be obtained by cystocentesis and before initiating antimicrobial treatment.

In feline urine samples, bacteriuria identified on unstained or stained wet urine sediments is poorly correlated with positive culture results, whereas examination of air-dried Wright-stained urine sediments is much more reliable.[73,77,79] In a study by Swenson et al, 29/472 urine specimens were culture-positive and 443 were culture-negative.[77] Considering the culture-positive samples as true positives and the culture-negative samples as true negatives, the wet unstained sediment had a sensitivity of 75.9% and a specificity of only 56.7%. Air-dried Wright-staining of the urine sediment improved sensitivity and specificity to 82.8% and 98.7%, respectively.

Quantitative bacterial cultures

Storage at room temperature leads to rapid increases in bacterial numbers.[74] Therefore, urine samples for culture/susceptibility

Table 2 Urinalysis findings in cats with positive urine cultures

Reference	n	Population of cats	Culture positive	Urinary tract infection	Subclinical bacteriuria	Haematuria	Pyuria	Bacteriuria
Gerber et al[23]	77	Signs of FLUTD	5	5	0	5/5	3/5	3/5
Bailiff et al[39]	141	Diabetes mellitus	18	8/18	10/18	4/16	12/16	14/16
Swenson et al[77]	472	No selection	29	NA	NA	NA	10/29	24/29
Lund et al[73]	111	Signs of FLUTD	14	14	0	13/14	14/14	NA
Dorsch et al[22]	302	Signs of FLUTD	57	57	0	51/57	44/57	44/57
Puchot et al[29]	500	No signs of FLUTD	31	0	31	10/30	20/30	18/30

FLUTD = feline lower urinary tract disease; NA = not assessed

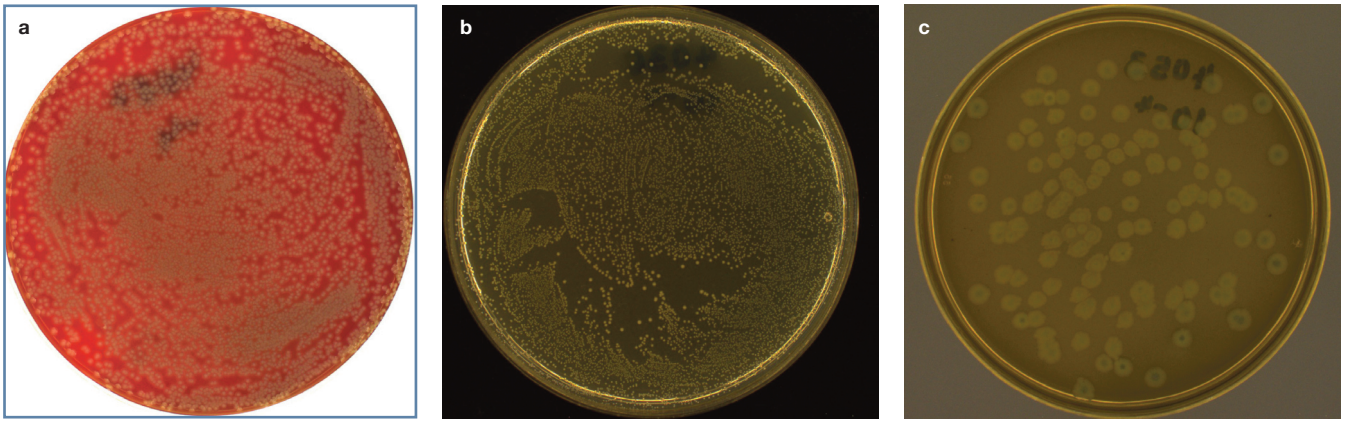


Figure 3 **Positive aerobic urine cultures: (a) *Escherichia coli* on nutrient agar with 5% sheep blood; (b) *Enterococcus faecalis* on Mueller Hinton agar; and (c) *Proteus mirabilis* on Gassner agar.** *Images courtesy of Dr Georg Wolf, Institute for Infectious Diseases and Zoonoses, LMU Munich*

testing should be refrigerated as soon as possible and processed in a microbiology laboratory within 24 h.[80] Growth of $\geqslant 10^3$ CFU/ml in urine specimens obtained by cystocentesis or catheterisation is considered significant in cats (Figure 3; Table 3).[81–83]

Most uropathogens can be cultivated over an 18–24 h incubation period. However, some slow-growing pathogens, such as *Corynebacterium* species, may require a longer time to appear in cultures.[16] This should be considered if bacteriuria was diagnosed on sediment analysis but bacteria cannot be cultivated. In these cases, incubation periods should be extended to at least 5 days.

Pyelonephritis

Culture of urine obtained by pyelocentesis is ideal for identifying the bacteria involved in pyelonephritis.[70,72,81] Otherwise, cystocentesis (repeated cultures may be needed) or blood cultures may be used depending on the assumed infection route. Blood cultures should be considered in immunosuppressed cats, and in the presence of fever and azotaemia in cats with negative urine cultures and no abnormalities in the urine sediment.[84,85]

Table 3 **Interpretation of quantitative bacterial culture results[81–83]**

Sampling method	Likely contamination (CFU/ml)	Significant growth (CFU/ml)
Catheterisation	$<10^3$	$\geqslant 10^3$
Cystocentesis	$<10^3$	$\geqslant 10^3$

CFU = colony-forming units

Any empirical treatment should always be based on location-specific bacterial prevalence rates and antimicrobial resistance patterns.

Treatment

To prevent treatment failure and the development of antibiotic resistance, antimicrobials should ideally be selected based on in vitro susceptibility testing (see box), and antimicrobials with a narrow spectrum should be used.[8] If true bacterial UTIs are identified, the treatment plan depends on previous UTI history, affected structures, concurrent diseases and, to a lesser degree than in dogs, neutering status.

Empirical treatment is rarely indicated. As bacterial prevalence and antimicrobial resistance have strong regional differences, empirical treatment should be based on location-specific bacterial prevalence rates and antimicrobial resistance patterns.[6,34]

In vitro susceptibility testing

In vitro susceptibility testing informs rational antimicrobial selection and is an important tool for monitoring the development of antimicrobial resistance. Different test methods have been described. Each has advantages and disadvantages; thus, understanding these methods and their limitations is important.

The reference method for susceptibility testing is the broth microdilution method.[86] Serial two-fold dilutions of antimicrobials are inoculated with a standardised bacterial suspension. The tubes are examined for bacterial growth as evidenced by turbidity after an incubation period of 12 h at 35°C.[87] The lowest antimicrobial concentration required to inhibit macroscopic microbial growth represents the minimal inhibitory concentration (MIC). Based on the MIC, microorganisms are categorised as susceptible, intermediate or resistant. The most commonly used test method in veterinary medicine is the simple and cost-efficient disc diffusion method.[88] Other, less commonly used in vitro susceptibility tests are the antimicrobial gradient method and the automated instrument system.

In vitro susceptibility test results predict the expected treatment response, but do not guarantee it.

In vitro susceptibility test results predict the expected treatment response, but do not guarantee it.[86] An organism interpreted as 'susceptible' should be inhibited by antimicrobial treatment using the recommended dose for that infection and species. Conversely, a 'resistant' test result indicates that the patient's organism will likely not respond to antimicrobial treatment with the normal dose of a selected antimicrobial.

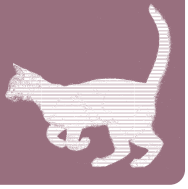
In the recently updated ISCAID guidelines, recommendations for the management of bacterial UTIs in dogs and cats were broadened to cover a more defined range of entities, including first-episode UTIs, recurrent UTIs, UTIs in compromised patients, pyelonephritis, subclinical bacteriuria, catheter-associated UTIs, medical management of infection-induced uroliths, as well as the manangement of dogs and cats with urinary catheters and those that receive urological surgery, minimally invasive urological procedures and urologic implants.[12]

Use of critically important antimicrobials

In veterinary medicine, antimicrobials that are critically important in humans, such as vancomycin, imipenem and other carbapenems, should not be used, or only be used under very limited circumstances. Their veterinary use is only justified if the infection is definitively diagnosed based on clinical signs, culture and cytological abnormalities, and if the pathogen shows resistance to all other reasonable options and is susceptible to the chosen antimicrobial. Critically important antimicrobials are never indicated for subclinical bacteriuria. Additionally, critically important antimicrobials should not be used in untreatable infections or in animals with poor prognoses.[12]

Third- and fourth-generation cephalosporins, such as cefovecin, and fluoroquinolones, such as enrofloxacin and pradofloxacin, also belong in this group and should only be used if an isolate is resistant to other antimicrobials or in cases of pyelonephritis (fluoroquinolones).[12]

Antimicrobials that are critically important in humans should not be used in veterinary medicine, or only used under very limited circumstances.



Antimicrobial treatment of sporadic/uncomplicated cystitis

Owing to the high frequency of comorbidities and an increased incidence of positive urine cultures among older cats, the actual occurrence of uncomplicated or sporadic cystitis in cats has been questioned. The 2019 ISCAID guidelines emphasise that there is no evidence indicating that sporadic cystitis should be more complicated to manage in cats vs dogs, as the presence of comorbidities does not necessarily imply a more complicated infection.[12]

Given the low incidence of UTIs in cats with signs of FLUTD (especially among younger cats), empirical antimicrobial treatment is rarely indicated. To relieve patient discomfort, analgesics can be administered while awaiting culture results. If treatment must be initiated while culture and antimicrobial susceptibility test results are pending, a first-line antimicrobial, such as amoxicillin or trimethoprim/sulfonamide, preferably with a known low local resistance rate, should be administered.[12]

There is a lack of evidence to support the common recommendation for a treatment duration of 7–14 days and growing evidence indicates that shorter treatment periods (3–5 days) may be sufficient in veterinary medicine.[89,90] The 2019 ISCAID guidelines recommend a 3–5 day treatment period in cases of sporadic cystitis.[12]

If clinical signs disappear within the treatment period, and the antimicrobial was appropriate based on susceptibility testing, additional monitoring and diagnostic testing are generally not required. If clinical improvement is lacking and the chosen antimicrobial is insufficient based on susceptibility testing, the original antimicrobial should be discontinued and treatment adjusted as per the susceptibility test results.[12] The guidelines stress the importance of further investigation in cases of treatment failure; empirical changes of antimicrobials should not be performed.[12]

Antimicrobial treatment of recurrent/complicated cystitis

In cases of complicated UTIs, identifying and addressing the primary reason for bacterial colonisation is critical to avoid treatment failure or recurrent infection. While the previous (2011) version of the ISCAID guidelines recommended long-duration treatment for all cases of recurrent cystitis,[8] the 2019 guidelines acknowledge the broad range of conditions encompassed in this category and state that long-term therapy is no longer automatically warranted.[12] Depending on the severity of clinical signs, analgesics could be considered for these patients as well, while awaiting culture results.[12]

If empirical treatment of recurrent cystitis is necessary, the same drugs are recommended as for sporadic/uncomplicated UTIs. A treatment period of 3–5 days should be considered in cases of reinfection, while 7–14 days may be reasonable when treating persistent or potentially relapsing infections.[12] When longer treatment periods are applied, the benefit of urine cultures during treatment is unclear as the clinical outcome is of greater importance than the culture results per se.[12] Urine cultures 5–7 days post-treatment in animals where clinical cure is documented may, if positive, help to differentiate between relapse, reinfection and persistent infection, but do not necessarily indicate the need to continue treatment (see 'Antimicrobial treatment of subclinical bacteriuria' on page 1032).[12]

Longer-term antimicrobial therapy is no longer automatically warranted for cases of recurrent/complicated urinary tract infection.

Antimicrobial treatment of pyelonephritis

If pyelonephritis is suspected (Figures 1 and 4), and empirical treatment is needed, antimicrobials with a good efficacy against Gram-negative bacteria (eg, fluoroquinolones) are recommended. The treatment must be adjusted according to susceptibility test results. Evidence-based recommendations on treatment duration are lacking, and while treatment durations of 4–6 weeks previously were considered reasonable, shorter periods of treatment have been reported to be effective in humans,[91] and the 2019 ISCAID guidelines recommend 10–14 days in veterinary patients.[12] Repeated cultures during the treatment period are no longer automatically warranted, but should be considered in cases of incomplete clinical response, while cultures 1–2 weeks post-treatment are recommended for all cases.[12] As for recurrent/complicated cystitis, consideration must be given to the clinical relevance of possible positive cultures post-treatment. Differentiation between subclinical bacteriuria and persistent infections may be challenging and reasons for potential persistence must be thoroughly investigated.[12]

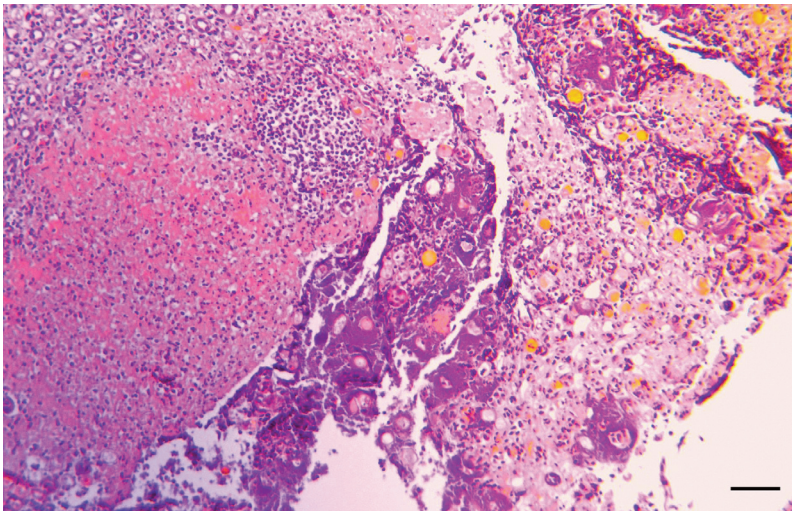


Figure 4 **Severe necrosuppurative pyelonephritis. Haematoxylin and eosin stain of a histological section of the renal papilla of the same cat as in Figure 1, showing severe inflammation with multiple neutrophils and bacterial colonies; bar = 50 µm.** *Courtesy of Dr Monir Majzoub-Altweck, Institute of Veterinary Pathology, LMU Munich*

Antimicrobial treatment of catheter-associated UTIs

Prophylactic antimicrobial treatment is never warranted and no evidence supports routine urine cultures after catheter removal. The 2019 ISCAID guidelines recommend bacterial cultures only in cats with ongoing clinical signs of FLUTD after the catheter has been removed.[12]

Cats with indwelling urinary catheters and clinical signs of UTI may be difficult to identify as many will have been catheterised for signs of FLUTD initially. Routine cytological evaluation of urine is not recommended as haematuria, pyuria and bacteriuria can occur in the absence of cystitis. Urine cultures should be performed in all cases with suspected bacterial cystitis, in the presence of fever and bacteraemia, and if a sudden change in urine character is seen.[12] Because treatment is more likely to be effective if the catheter is removed prior to treatment, the catheter should be removed if possible and urine for culture should be collected by cystocentesis. If the catheter must remain in place, it should be replaced and urine for culture should be obtained through the new catheter.[12]

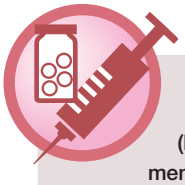
Prophylactic antimicrobial treatment is never warranted.

No evidence supports routine urine culture after catheter removal. Bacterial culture is only recommended once the catheter is removed in cats that have ongoing clinical signs of lower urinary tract disease.

Antimicrobial treatment of subclinical bacteriuria

Currently, the clinical relevance of subclinical bacteriuria is uncertain, and its optimal treatment requires clarification.[12] In healthy women, and in women and men with comorbidities, asymptomatic bacteriuria is common.[92] Several randomised clinical trials and meta-analyses with high numbers of patients have shown that antimicrobial treatment does not benefit asymptomatic individuals but is instead associated with negative effects, such as adverse drug reactions and increased antimicrobial resistance.[93–95] Therefore, guidelines for antimicrobial use in human medicine contain strong recommendations against screening for and treating asymptomatic bacteriuria. In one study of older cats, subclinical bacteriuria was not adversely associated with survival despite withholding antimicrobial treatment.[31]

The current recommendation for cats and dogs is to consider treatment of subclinical bacteriuria only in animals with suspected pyelonephritis, patients undergoing surgical procedures of the urinary tract, patients undergoing endoscopic procedures of the urinary tract with associated bleeding, in patients where the bladder is thought to be the focus of extraurinary tract infection, and in diabetic animals if subclinical bacteriuria is thought to be the reason for insulin antagonism or ketosis.[12] Treatment should also be considered in cats with *C urealyticum* bacteriuria[96] because this has been associated with encrusting cystitis in cats (see earlier)[17] as well as an increased risk of obstructive uropathy in human transplant patients.[97] The presence of multidrug-resistant bacteria should not affect the decision of whether or not to treat subclinical bacteriuria.[12]



Authors' approach to the bacteriuric cat with CKD

Routine culture for cats without clinical signs and without evidence of infection in the urine sediment (haematuria or pyuria ± bacteriuria) is not recommended, as most cats with positive urine cultures also have evidence of inflammation in the urine sediment.

If a cat with CKD shows lower urinary tract signs or if there is a suspicion of pyelonephritis, this would be a clear indication to culture the urine and, in cases of significant bacterial growth, to treat the cat based on culture/susceptibility test results.

In CKD cats without any clinical signs but with haematuria or pyuria ± bacteriuria in the stained urine sediment, the authors would typically perform urine culture. If the culture comes back positive, the decision to treat is a difficult one and depends on the totality of clinical signs, laboratory parameters, diagnostic imaging findings, the identified bacterial isolate, and whether this was the first positive culture or there had been previous unsuccessful attempts to eliminate bacteriuria. Subclinical bacteriuria always requires an individually tailored approach. For example, if subclinical bacteriuria with *E coli* is identified in a cat with CKD that has never been treated, the authors typically make one attempt to eliminate bacteriuria and treat the cat for 2 weeks with an antimicrobial determined to be effective based on culture/susceptibility testing. If instead it is a cat with recurrent subclinical bacteriuria that has been treated previously and the cat has stable renal function, then the authors' decision would be not to treat at this stage and make the owners aware of possible clinical signs of cystitis and pyelonephritis. If the same cat presents again with clinical signs of UTI, urine culture should be performed again as it cannot be concluded that the isolate causing clinical signs is the same as the one previously cultured. The treatment should then be based on the new culture/susceptibility test results. If immediate treatment is warranted, an antimicrobial that was shown to be effective based on the last susceptibility testing can be selected. Treatment of subclinical bacteriuria is typically not warranted if the urine culture reveals growth of *Enterococcus* species.

Preventive therapy

Currently, no preventive treatment modality is recommended by ISCAID.[12] Evidence for most of the alternative approaches used to prevent recurrent UTIs in cats, as discussed below, is mainly anecdotal.

- Preventive therapy in the form of pulse or chronic low-dose antimicrobial administration is, at best, controversial.[12,98,99]
- Proanthocyanidin from cranberry inhibits UPEC adherence to human uroepithelium and can reduce the prevalence of recurrent UTIs.[100–102] Cranberry extracts have demonstrated in vitro efficacy in preventing bacterial attachment to the uroepithelium of dogs and cats in a dose-dependent way, but evidence of a clinical effect is inconsistent.[103–106] D-mannose may disrupt bacterial adhesion to the urothelium, but evidence of a clinical effect in cats and dogs is lacking as well.[107]
- Based on positive results for preventing recurrent UTIs by orally and vaginally administering probiotics in women,[108,109] probiotics have also been recommended for cats and dogs. One prospective controlled clinical study in dogs, however, demonstrated no benefit from orally administered *Lactobacillus*, *Bifidobacterium* and *Bacillus* species.[110] In cats, no clinical studies have, to date, provided data on the efficacy of this therapy.
- There is no evidence for a clinical effect of direct instillation of various components such as antimicrobials, antiseptics or dimethyl sulfoxide into the feline urinary bladder.[111–114] Urinary antiseptics in the form of methenamine salts require acidic urine to convert methenamine to bacteriostatic concentrations of formaldehyde.[113,114] No evidence-based recommendations for this treatment exist in veterinary medicine.
- Intravesical application of non-pathogenic *E coli* strains reduced symptoms of UTI in humans with urine retention by approximately 50%.[115,116] In similar studies in healthy dogs, consistent establishment of bladder colonisation was less successful.[117,118] However, a recent pilot study applying non-pathogenic *E coli* intravesically in dogs with recurrent UTI showed promising results.[119] To the authors' knowledge, use of non-pathogenic bacteria has not been examined in cats.
- Possible future treatment strategies include the introduction of bacteriophages able to lyse UPEC. This has been studied in both feline and canine UPEC isolates.[120]

KEY POINTS

- UTI and subclinical bacteriuria are most common in older, female cats.
- Most culture-positive cats have underlying predisposing diseases, principally CKD and endocrine diseases.
- Urine sediment analysis alone is inadequate for diagnosing UTI because urine sediment findings largely overlap with findings in cats with other diseases of the lower urinary tract.
- Antimicrobial treatment while culture and susceptibility test results are pending is only indicated in selected cases, such as cats with suspected acute pyelonephritis.
- Adherence to treatment guidelines and confinement to a few first-line antimicrobial agents is imperative to avoid the development of antimicrobial-resistant bacteria.
- Antimicrobials with a narrow spectrum should be used as first-line drugs.
- Screening selected populations for bacteriuria, such as cats with diabetes mellitus or hyperthyroidism, without clinical signs of UTI is questionable, as no evidence demonstrating a beneficial effect of routine treatment in culture-positive cats exists.

Case notes

Bella, a female neutered domestic shorthair cat, exhibited recurrent episodes of UTI over 4 years, having first been presented at 10 years of age in June 2014 with signs of haematuria, periuria, pollakiuria and stranguria.

Initial case work-up On physical examination, Bella was alert and responsive. Heart rate was 180 beats/min and respiratory rate was 30 breaths/min. Rectal temperature was 38°C. Mucous membranes were pink and moist. Bella was mildly uncomfortable on palpation of the caudal abdomen.

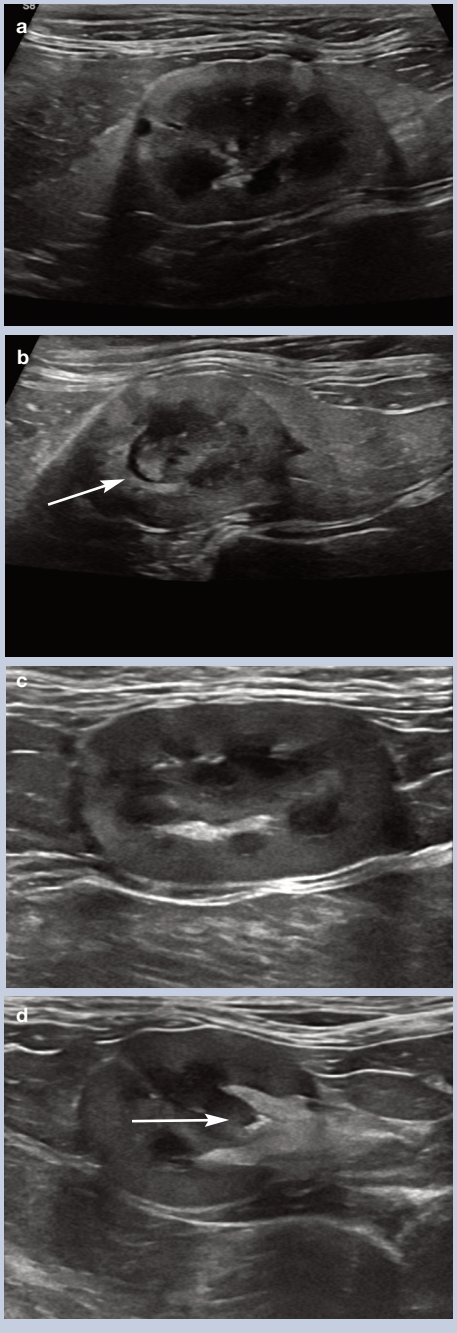


Figure A Ultrasonographic appearance of Bella's kidneys. (a,b) The left kidney has a slightly irregular outline due to mild indentations caused by multifocal triangular-shaped hyperechoic cortical lesions. There is one round, anechoic cortical lesion causing distal enhancement in the cranial pole. The definition between cortex and medulla is slightly reduced and there is mild pyelectasia (arrow in [b]). (c,d) The right kidney is larger than the left kidney. The right cranial pole is slightly misshapen due to decreased cortical thickness. There is a focal hyperechoic region in the right cranial pole and one small hyperechoic structure identified in the renal pelvis (arrow in [d]). These findings are consistent with bilateral nephropathy and a nephrolith in the right renal pelvis. *Images courtesy of Dr Nina Ottesen, Section for Anaesthesia and Radiology, Department of Companion Animal Clinical Sciences, Norwegian University of Life Sciences*

Otherwise, the physical examination was unremarkable. Blood samples were collected for haematology and biochemistry, and a urine sample was obtained by cystocentesis for complete urinalysis and culture/susceptibility testing. Blood pressure measurement was not possible due to Bella's fractious nature. Ultrasound examination revealed chronic changes to the kidneys bilaterally, small nephroliths in the right kidney and no ureteral dilation (Figure A).

Laboratory parameters (Table A) and results of urinalysis (Table B and Figure B) and susceptibility testing (Table C) are shown. Urine culture revealed growth of *E coli* (10^7 CFU/ml) (Figure C).

Table A Laboratory parameters

Parameter	June 2014	April 2018	Reference interval
Creatinine (µmol/l)	152	174	75–180
Urea (mmol/l)	7.7	8.5	5.0–10
Total protein (g/l)	64	61	61–86
Albumin (g/l)	32	33	32–45
Phosphate (mmol/l)	1.2	1.8	1.0–2.8
Total calcium (mmol/l)	2.2	2.2	2.2–2.9
Sodium (mmol/l)	152	150	150–165
Potassium (mmol/l)	4.5	4.2	3.7–5.8
Haematocrit (l/l)	25	24	24–45

Table B Urinalysis*

Parameter	June 2014	April 2018
USG	1026	1035
pH	6.4	6.0
Protein	+	+
Glucose	Negative	Negative
Ketones	Negative	Negative
Bilirubin	Negative	Negative
Blood	+++	++
RBCs/HPF	>10	1–3
WBCs/HPF	4–10	4–10
Epithelial cells	Negative	Negative
Casts	Negative	Negative
Bacteria	Rods on dried stained sediment (Figure B)	Rods on dried stained sediment

*Urine was obtained via cystocentesis
USG = urine specific gravity; RBCs = red blood cells; WBCs = white blood cells; HPF = high-power field

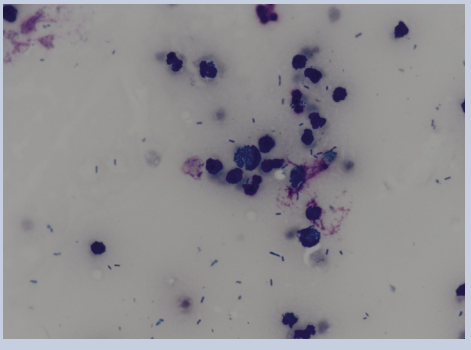


Figure B Modified Wright stain of an air-dried sediment of Bella's urine, showing numerous leukocytes and intra- and extracellular rod-shaped bacteria

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Continued from page 1034

Table C Susceptibility testing

Erythromycin	Intermediate
Clindamycin	Resistant
Penicillin	Resistant
Trimethoprim/sulfonamide	Susceptible
Tetracycline	Susceptible
Cephalexin	Intermediate
Ampicillin	Susceptible
Amoxicillin/clavulanic acid	Susceptible
Enrofloxacin	Intermediate
Spiramycin	Resistant
Neomycin	Susceptible
Nitrofurantoin	Susceptible
Trimethoprim	Susceptible

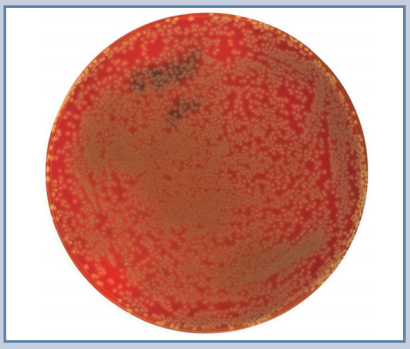

Figure C Quantitative aerobic urine culture on nutrient agar with 5% sheep blood. The plate was inoculated with 0.1 ml of a 10^3 dilution of Bella's urine. Culture revealed heavy bacterial growth of 10^7 colony-forming units/ml. The colony type was identified by mass spectrometry as *Escherichia coli*. *Courtesy of Dr Georg Wolf, Institute for Infectious Diseases and Zoonoses, LMU Munich*

Diagnosis and treatment

Bacterial cystitis was diagnosed based on the combination of clinical signs of lower urinary tract disease and a positive culture from a cystocentesis-obtained urine sample.

Bella was treated with intravenous (IV) fluid therapy and amoxicillin 15 mg/kg PO q12h for 2 weeks. The clinical signs resolved within hours of the initiation of treatment. After 10 days of treatment, serum creatinine concentration was 148 µmol/l. Based on a combination of persistent increases in serum creatinine concentration and an inappropriate urine concentration (urine specific gravity <1035), chronic kidney disease was diagnosed (International Renal Interest Society stage 2 without proteinuria, urine protein:creatinine ratio 0.11).

Recurrent episodes

Bella had a second episode with identical clinical signs 7 months later. Pyuria and bacteriuria were present on urinalysis, and urine culture again revealed a significant growth of *E coli*. Bella was treated with amoxicillin 20 mg/kg q8h PO for 4 weeks. Urine cultures 10 days and 1 month after the end of treatment were negative.

Clinical signs recurred again 5 months later. Results of physical examination and laboratory investigations were identical, urine culture was positive, with growth of *E coli*, and Bella was treated with IV fluid therapy and ampicillin 25 mg/kg IV q8h for 3 days, followed by 4 weeks of amoxicillin PO. Cultures were once again negative during treatment, and 7 days and 1 month after completed treatment.

Bella went on to have four subsequent episodes 5–7 months apart (the most recent in April 2018, Table A) with clinical signs of lower urinary tract disease (all with positive urine cultures, *E coli* with identical susceptibility profiles). For the latter episodes, Bella was treated only with analgesic drugs (primarily buprenorphine) for 3–5 days with or without 2–3 days of IV fluid therapy. Since the clinical signs resolved while awaiting culture and susceptibility test results, further treatment with antimicrobials was postponed.

Bella's creatinine was monitored every 4 months and she remained at stage 2 CKD.

What this case demonstrates: Bella's renal disease remained stable despite the presence of significant bacteriuria over a period of 4 years. Moreover, treatment consisting of analgesics and fluid therapy proved as effective as treatment including antimicrobials in terms of improvement of clinical signs in this patient. It is open to debate whether a change of antimicrobial type should have been tried instead. In cases of recurrent UTIs, the decision to treat should be based on the likelihood of successful elimination of bacteria.[14] In Bella's case, there was the possibility that the nephroliths were acting as the nidus for recurrent/persistent infection; antimicrobial treatment may thus be ineffective regardless of type and treatment duration. The consistent use of ampicillin and amoxicillin in this case was based on the susceptibility results and the limited range of antimicrobials available for use in cats in Bella's home country. Patient compliance further limited the range of potential antimicrobials that could be used in this patient.

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Conflict of interest

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