What is new in the treatment of bacterial urinary tract infections

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Introduction

Urinary tract infections (UTI) are one of the most frequently encountered disorders in companion animals and also one of the most common reasons for prescribing antimicrobial therapy. Most urinary tract infections are caused by pathogenic bacteria, although very rarely, fungi and viruses can be the source. Only infections caused by bacteria will be discussed here. Development of UTI depends on the virulence of the bacteria and alterations in host defences. These host defences include frequent and complete voiding of a sufficient amount of urine, the presence of a normal resident microflora, physiological urinary tract anatomy, and systemic immunocompetence. When these defence mechanisms are breached, for some reason, bacteria can ascend the urethra and then adhere, multiply, and persist within the urinary tract resulting in a UTI. The most common source of these bacteria is the gastrointestinal tract and the skin. Less commonly, bacteria travel through the bloodstream and colonise the urinary tract.

Multidrug resistance can be detected in up to 43% of bacterial UTI. This increase in antimicrobial resistance has led to a change in how different categories of UTI are treated to help minimise the development of antimicrobial resistance. The International Society for Companion Animal Infectious Diseases (ISCAID) has produced guidelines for diagnosing and managing bacterial urinary tract infections in dogs and cats. These guidelines have been updated in 2019 based on new evidence available in veterinary and human medicine and provide information to aid veterinarians in diagnosing and managing upper and lower urinary tract infections in dogs and cats.

UTI can affect more than one anatomical location. Although locations may overlap, it is important to determine whether it is an upper urinary tract (kidneys and ureters) or lower urinary tract (bladder, urethra, and vagina or prostate) infection, as treatments will differ. Several factors can increase the risk of developing UTI, including advancing age, female sex, decreased body condition score, anatomical and functional abnormalities of the urinary tract, and various comorbidities such as kidney and endocrine diseases. Upper urinary tract infections are beyond the scope of this article, and only lower urinary tract infections will be discussed further.

Diagnosis

Animals with Lower UTI usually present with a combination of clinical signs such as pollakiuria, stranguria, dysuria, haematuria and occasionally polyuria/polydipsia. These clinical signs, however, are not pathognomonic for urinary tract infections and could be caused by other non-infectious causes of lower urinary tract disease (especially in young cats); therefore, a presumptive diagnosis of a UTI cannot be made based on clinical signs alone. These patients mustn't get empirically treated with antimicrobials before a UTI has been confirmed, as overuse of antimicrobials can lead to changes in the normal host microbiota and can lead to selection for resistant bacterial strains. Pyrexia is not an expected finding with cystitis, so if present, pyelonephritis or prostatic involvement should be considered, and further diagnostics to rule this in/out should be pursued.

In addition to clinical signs, results of a complete urinalysis, ideally collected via cystocentesis, may provide evidence of a bacterial UTI. The combination of pyuria (>3–5 leucocytes/hpf) and bacteriuria on a urine sediment lead to a high index of suspicion for UTI. Caution must be taken when examining stained urine sediment, as stain precipitates can mimic cocci. Malodorous urine or pyuria without bacteriuria are not sensitive indicators of UTI as they can be the consequence of various other disorders. If a UTI is suspected, aerobic bacterial urine culture and sensitivity should ideally be performed to confirm the diagnosis. A positive urine culture from urine obtained via cystocentesis is the "gold standard" for diagnosing a bacterial UTI. In dogs with suspected sporadic cystitis based on the clinical signs and finding a combination of pyuria and bacteriuria on a urine sediment, empirical therapy may be justified in place of culture, provided that they have had no or limited exposure to antimicrobials previously. However, in all cases of cats with suspected bacterial cystitis, a diagnosis must be confirmed with culture as the probability of bacterial cystitis being the cause of lower urinary tract signs in this species is very low.

Classification

Before delving into the new treatment recommendations, it is necessary to understand the new classification system as it impacts treatment decision-making. Previously, the classification of UTI in veterinary medicine was adopted from human medicine and referred to as either "simple or uncomplicated" and complicated" UTI. The revised classification now has three diagnoses: subclinical bacteriuria, sporadic cystitis, and recurrent UTI.

- Subclinical bacteriuria occurs when bacteria is present in the urine, based on a positive culture, but no clinical signs of lower urinary tract disease.
- Sporadic bacterial cystitis is defined as an infrequent (< 3 per year), symptomatic UTI in a healthy animal without any known anatomic or functional abnormalities to the urinary tract or predisposing comorbidities.
- Recurrent bacterial cystitis is when there are more than three symptomatic UTIs in a 12-month period. Recurrent bacterial cystitis is then further divided into relapsing, refractory/persistent, reinfection and superinfection.

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- Relapsing cystitis is when there is a recurrence of the UTI, with the same organism, within weeks to months of a successfully treated infection
- Refractory or persistent cystitis occurs when bacteriuria is not eliminated during or after treatment of the UTI.
- Reinfections are when there is a recurrence of the cystitis with a different organism to the original infection
- Superinfection is an infection with a different pathogen in the course of the treatment of the original infection.

Treatment recommendations

Subclinical bacteriuria

In patients with subclinical bacteriuria, even patients with systemic disease such as chronic kidney disease (with stable renal function), diabetes mellitus or hyperadrenocorticism, antimicrobial therapy is generally not recommended. There are no indications that these patients will progress to clinical cystitis or that it predisposes them to ascending infections. In human medicine, there is strong evidence that treatment of subclinical bacteriuria (even if they have a multidrug-resistant bacteria) does not change the outcome and may even contribute to selection for resistant bacteria and other adverse outcomes. There is growing evidence that the same is true in veterinary medicine.

The only time treatment of subclinical bacteriuria is recommended is in the following situations:

- When you suspect pyelonephritis along with the subclinical bacteriuria
- When the patient is undergoing surgery of the urinary tract
- To help prevent struvite stone formation in patients with subclinical bacteriuria caused by urease-producing bacteria
- In patients undergoing an endoscopic procedure where bleeding is expected
- If the bladder is suspected to be the site of extra-urinary infection
- If the subclinical bacteriuria is thought to be causing insulin resistance or ketosis in a diabetic patient

A group of patients in which recommendations may be a bit more challenging are the paralysed patients. They may not show clinical signs due to their condition, and those with unperceptive owners who cannot tell you if the patient has lower urinary tract signs or not. When it is unclear whether clinical signs exist, a 3–5-day course of antimicrobial treatment could be attempted in these situations.

Sporadic bacterial cystitis

For sporadic bacterial cystitis cases, it is recommended to prescribe non-steroidal anti-inflammatory drugs to help alleviate discomfort and clinical signs while awaiting the culture results. Sometimes the UTI will spontaneously resolve, and the addition of antibiotics may not be needed. If treatment is needed while results are pending, amoxicillin (11–15 mg/kg orally q12h) or trimethoprim–sulphonamide (15 mg/kg orally q12h) are recommended for initial empirical treatment as both are excreted in the urine at high concentrations. If initial culture results indicate resistance to the chosen empirical antimicrobial, but the animal has shown a good clinical response, the drug should not be changed.

Recently studies in dogs have shown that shorter dosing regimens are effective because the goal of treating a UTI is to decrease the bacterial load enough to control clinical signs with the immune system eliminating remaining organisms. This research has resulted in the changes to the ISCAID guidelines regarding the duration of treatment for UTI. For sporadic UTIs, the treatment duration is 3 to 5 days. If there is a lack of clinical response within 48 - 72 h of starting appropriate antimicrobials, then further investigation should be done to identify the reason for the lack of response. Do not empirically change to a different antimicrobial.

The guidelines also state that it is not indicated to perform intra- or post-treatment urinalysis or culture if there are no ongoing clinical signs of UTI.

Recurrent urinary tract infections:

In all patients with recurrent infections, a urine culture and sensitivity must be performed along with further diagnostic testing to identify possible predisposing factors and comorbidities. Once identified, these should be managed appropriately; it is especially important for preventing reinfections. If this is not achieved and antimicrobials are administered repeatedly, a long-term cure is very unlikely to occur, and there will be an increased risk of developing antimicrobial resistance.

For relapsing, refractory, and persistent infections, one should first determine whether the antimicrobial is actually achieving adequate concentrations in the bladder to clear the infection. Establish if the correct dose and dosing schedule has been used and if the owners have been compliant. If this is not the problem, further diagnostics should be undertaken to identify risk factors and attend to them.

- *Reinfections*
  Treated the same as sporadic bacterial cystitis.

- *Relapsing or persistent UTI*
  A treatment period of 7 to 14 days is indicated for these infections. Urine culture should be considered within 5 to 7 days of treatment. If it is positive and clinical signs have not resolved, further investigation will be needed to determine as to why the bacteria has not been eliminated. Evaluate compliance and proceed with further diagnostic testing to look for underlying predisposing factors. If clinical signs have resolved, i.e., there is now a subclinical bacteriuria, additional treatment might not be indicated.

Various preventative therapies/ strategies for recurrent urinary tract infections have been evaluated, such as using Low-dose or pulse antibiotic therapy, cranberry, D-mannose or urinary antiseptics. Still, unfortunately, there is limited evidence to support their effectiveness, and they are therefore not recommended.

Local therapy

It is not recommended to infuse treatments such as antimicrobials or anti-inflammatories into the bladder at present, as there is no evidence that this is effective. The risk of causing trauma and irritation, as well as potentially introducing an infection to the bladder is high.

Conclusion

Bacterial UTIs are a common finding in small animals. Screening selected populations for bacteriuria, such as patients with diabetes mellitus or hyperadrenocorticism, without clinical signs of UTI, should be avoided, as there is no evidence demonstrating a beneficial effect when treating these animals if they are culture-positive. Identifying and resolving underlying risk factors is an essential part of treating UTIs.

Antimicrobials should only be used when indicated, ideally selected based on culture and sensitivity results and used for the shortest duration possible. If empirical treatment is indicated, choose those with a narrow spectrum as first-line drugs.

Indiscriminate use of antimicrobials leads to the emergence of multidrug-resistant bacteria, which has important implications for both the patient and public health.

Dogs with sporadic UTIs could benefit from using a NSAID while awaiting culture results.

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QUESTION 1

Which one of the following cases (assume the problems listed are the only abnormalities present) would NOT be considered consistent with a UTI?

a. A dog with bacteriuria and gross haematuria
b. A dog with bacteriuria and dysuria
c. A dog with bacteriuria and pyuria on sediment examination
d. A cat with bacteriuria and pollakiuria
e. A dog with bacteriuria, pyuria on sediment examination and gross haematuria

QUESTION 2

Which of the following antimicrobials would be an appropriate first-choice drug for empirical treatment of a UTI in a dog?

a. Enrofloxacin
b. Cephalexin
c. Amoxicillin
d. Chloramphenicol
e. Metronidazole

QUESTION 3

What is the recommended duration of antimicrobial therapy for sporadic cystitis?

a. 3–5 days
b. 6–10 days
c. 10–14 days
d. 14–21 days
e. 21- 28 days

QUESTION 4

In which of the following situations is it recommended to treat a patient with subclinical bacteriuria?

a. Patient where a multidrug resistant bacteria has been cultured
b. Patient with stable chronic renal disease where *E. coli* has been cultured
c. Patient where a urease-producing bacteria has been cultured
d. Patient with hyperadrenocorticism where *Enterococcus spp*. has been cultured
e. Patient with diabetes where E. coli has been cultured

QUESTION 5

Which of the following statements pertaining to urine culture is incorrect?

a. Culture of urine from animals with no evidence of urinary tract disease should not be performed
b. Post-treatment urine culture is recommended for sporadic cystitis when clinical signs have resolved.
c. For relapsing UTI, urine culture should be considered within 5 to 7 days of treatment
d. If initial culture results indicate resistance to the empirical antimicrobial that was chosen, the drug should be changed, unless there has been good clinical response
e. Urine should preferably be obtained via a cystocentesis for culture.

QUESTION 6

For dogs with sporadic bacterial infections, which of the following treatments could be used:

a. Intravesicular administration of a biocide
b. Oral administration of cranberry extracts
c. Oral administration of D-mannose
d. A course of non-steroidal anti-inflammatories
e. Intravesicular administration of a antimicrobials

QUESTION 7

Which statement is correct:

a. Empirical therapy may be justified in place of urine culture for cats with suspected sporadic cystitis.
b. The percentage of male dogs with UTI decreases with advancing age
c. The likelihood of bacterial cystitis being the cause of lower urinary tract signs in cats is low.
d. Haematogenous spread of bacteria is a common cause for UTI in cats and dogs
e. Only about 2 - 5% of bacterial UTI are multidrug resistant

QUESTION 8

Which one of the following cases is less likely to be suffering from a lower UTI and will need further diagnostic test.

a. A 7-year-old female obese Labrador with stranguria and haematuria. Cocci was seen on her urine sediment examination.
b. A 6-month-old female puppy that has a history of having diarrhoea for the past few days that responded fully to anthelminthics and conservative treatment but is now showing signs of stranguria and dysuria.
c. A 12-year-old cat with diabetes mellitus and stage 2 chronic kidney disease that presents with stranguria and bacteriuria on urinalysis.
d. A 5-year-old intact male with pyrexia, stranguria and haematuria
e. A 3-year-old female cross breed with stranguria and haematuria. On clinical examination you notice she has a hooded vulva.

QUESTION 9

When treating a sporadic UTI with antimicrobials, but there is a lack of clinical response within 48 - 72 h, you should:

a. Empirically changing to a different antimicrobial
b. Add a second antimicrobial
c. Investigation the reason for the lack of response
d. Continue the chosen antimicrobial for another 7 days
e. Re culture the urine

QUESTION 10

Shorter antimicrobial dosing regimens are now recommended for UTI because…

A. The antimicrobials used today are more effective against bacteria responsible for UTI
B. Antimicrobials only need to decrease the bacterial load enough to allow the immune system to eliminate the remaining organisms
C. The bacteria have mutated over time and become more susceptible to antimicrobials
D. Urine is culture following cessation of all short courses of antimicrobial therapy, and if it is positive, then the course will be extended
E. All UTI are caused by Enterobacteriaceae which are extremely susceptible to empirical antimicrobial treatments

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