Multidrug-Resistant Urinary Tract Infection in a Dog

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History

A 7-year-old spayed Labradoodle was presented for onset of pollakiuria and dysuria. No other abnormalities were reported. The patient had no history of urinary tract disease.

Examination, Diagnostic Testing, & Treatment

On evaluation, the patient appeared bright, alert, and responsive. BCS was good, and physical examination disclosed no abnormalities.

A urine sample was obtained via cystocentesis for urinalysis with sediment examination and culture and susceptibility testing. Further diagnostic tests (eg, abdominal radiography for uroliths) were discussed, but the owner elected to wait for urinalysis results.

Urinalysis results (***Table 1***) were consistent with UTI. Amoxicillin at 20 mg/kg PO q12h for 5 days was initiated pending culture results. After 2 days, the culture report showed presence of multidrug-resistant *Escherichia coli* (***Table 2***). The owner reported no apparent patient response to amoxicillin.

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TABLE 1

URINALYSIS

Parameter	Result	Reference Range
Color	Orange/brown	Yellow
Clarity	Turbid	Clear
pH	7.20	5.50-7.00
Specific gravity	1.029	1.015-1.050
WBC	25/hpf	0-3/hpf
RBC	>50/hpf	0-3/hpf
Squamous epithelial cells	0	0-3/hpf
Crystals	None seen	/hpf
Casts (per hpf)	None seen	/lpf
Protein	Positive	Negative
Bacteria	Large amount	Negative
Ketones	Negative	Negative
Urine bilirubin	Negative	Negative

hpf = high power field

TABLE 2

URINE CULTURE ANTIMICROBIAL SUSCEPTIBILITY TESTING RESULTS

Isolate	*Escherichia coli*
Amount of growth	100 000 CFU/mL
Antimicrobial	**Susceptible/ Resistant**
Amikacin	S
Amoxicillin	R
Amoxicillin–clavulanic acid	R
Cefovecin	R
Cephalexin	R
Cefpodoxime	R
Doxycycline	R
Trimethoprim–sulfamethoxazole	R
Meropenem	S
Enrofloxacin	R
Marbofloxacin	R
Chloramphenicol	R

ASK YOURSELF

Which of the following is true?

A. The infection may require more time to resolve; because of high amoxicillin levels in the urine, treatment should be continued.

B. Treatment with either meropenem or amikacin should be initiated.

C. Treatment should be withheld because the resistant bacterium might be replaced by a more susceptible strain in the absence of antimicrobial exposure, and that strain could then be more easily treated.

D. The practitioner should ask the laboratory if it has the ability to test susceptibility to additional antimicrobials, including nitrofurantoin and/or fosfomycin.

CORRECT ANSWER

D. The practitioner should ask the laboratory if it has the ability to test susceptibility to additional antimicrobials, including nitrofurantoin and/or fosfomycin.

Urinary tract disease is common in dogs, and UTIs are typically caused by gram-negative bacteria such as *E coli*.[1,2] Most UTIs are readily treated with common antimicrobials such as amoxicillin; however, antimicrobial resistance is increasing among uropathogens,[2,3] and multidrug-resistant infections are becoming more common. The susceptibility profile of this isolate is consistent with an extended-spectrum ß-lactamase (ESBL)–producing *E coli*.

Enterobacteriaceae (eg, *E coli*, *Enterobacter* spp) that produce ESBLs are an increasing problem in veterinary medicine.[4-6] ESBLs are bacterial enzymes that confer resistance to extended-spectrum cephalosporins (eg, cefovecin, cefpodoxime, ceftazidime) and monobactams (eg, aztreonam) but not cephamycins (eg, cefoxitin) or carbapenems (eg, meropenem).

ESBL-producing *E coli* are problematic because they are typically resistant to a wide range of antimicrobials by virtue of their ESBL production and acquisition of other resistance genes, which limits options even further. Production of ESBLs is conferred by a variety of different plasmid-associated genes (eg, CTX-M, SHV, TEM) that can be transferred among bacteria.

ESBL = extended-spectrum ß-lactamase

The types of ESBLs found in bacteria isolated from dogs are often the same as those found in humans,[4,7] which suggests that these may be of human origin. This also raises concerns about the potential for zoonotic transmission,[7-9] which has not been clearly documented.

Treatment of ESBL-producing *E coli* UTIs may require antimicrobials less familiar to many practitioners. Although amoxicillin is actively excreted in urine and high drug levels are achieved, it is not able to overcome resistance. Given the susceptibility results and lack of clinical response, continuation of amoxicillin in this case would be inappropriate.

In some situations, bacteria are present in the bladder without clinical disease—this is known as *subclinical bacteriuria*. Treatment for subclinical bacteriuria is not recommended,[10] and anecdotal experience indicates that resistant bacteria will sometimes be replaced by more susceptible bacteria when antibiotics are withheld. However, the patient presented in this case does not have subclinical bacteriuria because clinical signs are clearly indicative of disease; therefore, treatment is indicated.

As with this patient, ESBL-producing *E coli* are typically susceptible to carbapenems and amikacin but are resistant to most other drugs on the susceptibility panel. Although both carbapenems and amikacin can be used in dogs, they are not ideal because they are injectable, amikacin is potentially nephrotoxic, and carbapenems are critical drugs in human medicine.[11]

Multidrug-resistant infections may necessitate options beyond those ini-

tially reported by the diagnostic laboratory. In this case, susceptibility to nitrofurantoin and fosfomycin was requested from the laboratory, and the isolate was susceptible to both. Nitrofurantoin was prescribed at 5 mg/kg PO q8h for 5 days.

Often referred to as a *urinary antiseptic*, nitrofurantoin is an antimicrobial agent that is rapidly absorbed after oral administration and actively excreted in urine. It is useful for the treatment of cystitis because of its rapid elimination from the bloodstream, but it is also effective against a wide range of bacteria. Acquired resistance is uncommon in clinical isolates.[12,13] It is not a first-line choice for treating UTIs in veterinary medicine[10] but may be a good option in some cases.

Nitrofurantoin efficacy against ESBL-producing *E coli* UTIs has been reported in humans[14]; oral administration is desirable for this patient. Nitrofurantoin is also of limited importance in human medicine, which is desirable when considering the alternative options (eg, meropenem).

One reason that nitrofurantoin is not used as a first-line drug in dogs is the anecdotal incidence of adverse events. Vomiting is not uncommon but typically resolves with cessation of treatment. More serious adverse events such as hepatopathy can occur but are rare. Nitrofurantoin is contraindicated in patients with impaired renal function. The veterinarian should explain to the owner the potential for adverse events but that the benefits likely outweigh the risks in this case.

Further diagnostic testing is never contraindicated and can help identify potential causes of UTI and complications (eg, uroliths). However, because this is the first identified UTI in this dog and no other clinical findings suggest presence of underlying disease, a reasonable initial approach could be assessing the response to treatment and monitoring the patient for subsequent UTI. This should be discussed with the owner; it should be emphasized that further testing will be indicated if the patient develops another UTI or fails to respond to treatment.

The reason this patient developed a multidrug-resistant infection was not apparent. There was no history of recent antimicrobial exposure, no recent hospitalization, and no report of ESBL-producing *E coli* infection in any human contacts—known risk factors for ESBL infection. However, many multidrug-resistant UTIs occur in the absence of identifiable risk factors.[15,16]

Signs improved within 24 hours of nitrofurantoin treatment, and the treatment course was completed without complications. No signs of dysuria were present at the 4-month follow-up evaluation.

THE TAKE-HOME

- Multidrug-resistant UTIs appear to be increasingly common, necessitating the use of alternative antimicrobial approaches.
- Viable treatment options are typically available, even in cases of highly resistant bacteria.
- Nitrofurantoin is a useful drug for treating cystitis in some patients because it reaches high levels in urine and resistance is rare. It is not useful for infections that require adequate tissue drug levels (eg, pyelonephritis) because it is rapidly eliminated from circulation.
- Although useful, nitrofurantoin is not a first-line drug for UTIs because of the potential for adverse events. It can, however, be considered as a second-line option for treating multidrug-resistant infections.

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