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Review

Canine bacterial urinary tract infections: New developments in old pathogens

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ABSTRACT

Uncomplicated bacterial urinary tract infections (UTIs) occur commonly in dogs. Persistent or recurrent infections are reported less frequently. They typically occur in dogs with an underlying disease and are sometimes asymptomatic, especially in dogs with predisposing chronic disease. *Escherichia coli* is the organism most frequently cultured in both simple and complicated UTIs. Organisms such as *Enterococcus* spp. and *Pseudomonas* spp. are less common in uncomplicated UTI, but become increasingly prominent in dogs with recurrent UTI. The ability of bacteria to acquire resistance to antimicrobials and/or to evade host immune defence mechanisms is vital for persistence in the urinary tract. Antimicrobial therapy limitations and bacterial strains with such abilities require novel control strategies. Sharing of resistant bacteria between humans and dogs has been recently documented and is of particular concern for *E. coli* O25b:H4-ST131 strains that are both virulent and multi-drug resistant. The epidemiology of complicated UTIs, pathogenic traits of uropathogens and new therapeutic concepts are outlined in this review.

Introduction

Uncomplicated canine bacterial urinary tract infection (UTI) is common and occurs in approximately 14% of dogs that visit a veterinarian in their lifetime (Ling, 1984). In addition, persistent and recurrent UTIs are regularly diagnosed in small animal practice (Norris et al., 2000; Seguin et al., 2003). Norris et al. (2000) suggested that recurrent or persistent UTIs are present in up to 4.5% of dogs with UTI or 0.3% of the canine hospital population. Whilst the majority of simple infections resolve with a 2–3 week course of oral antimicrobials, persistent or recurrent UTIs often involve refractory bacterial isolates and may prove difficult to treat using conventional antimicrobial therapy. A greater understanding of the mechanisms for bacterial persistence and the underlying host factors that make eradication difficult may result in novel, alternative and ultimately more successful therapeutic approaches to bacterial UTIs in dogs.

In this review we discuss the risk factors for complicated and multi-drug resistant (MDR) bacterial UTIs in dogs – in other words those that are resistant to four or more classes of antimicrobials. The major species of bacteria associated with canine UTIs, their likely origins, and the strategies used by these bacteria to circumvent host defences and establish persistent infection are considered, using *Escherichia coli* as the paradigm. Development of antimicrobial resistance by urinary tract pathogens is of growing concern, but other mechanisms used by bacteria to evade elimination from the urinary tract are also discussed. The zoonotic risks and public health implications associated with MDR UTIs in dogs are addressed, including those resulting from the emergence of MDR *E. coli* ST131 strains in humans and their recent detection in dogs. Finally, alternative approaches to antimicrobial agents for the treatment of chronic recurrent canine UTI are considered.

Epidemiology of canine bacterial urinary tract infection

Many reports have shown that UTIs are more common in older female dogs, indicating this is a major risk factor (Kivisto et al., 1977; Bush, 1978; Thomsen et al., 1986; Ling et al., 2001; Cohn et al., 2003). The mean age at diagnosis regardless of sex is approximately 7–8 years (Ling et al., 2001; Cohn et al., 2003). Other risk factors of canine bacterial UTI are listed in Tables 1 and 2. An extensive study on risk factors for recurrent or persistent UTI in dogs was investigated by Seguin et al. (2003) (Table 2). The age and breeds of dogs with recurrent UTIs varies widely (Table 3), which may reflect breed lifespan and changes in popularity of breeds over time (Norris et al., 2000; Ling et al., 2001).

Up to 95% of UTIs in dogs with underlying disease are clinically silent (Forrester et al., 1999; Lulich and Osborne, 1999; McGuire et al., 2002; Seguin et al., 2003) and there is no apparent correlation between the occurrence of stranguria, pollakiuria or pigmenturia and presence of UTI (Forrester et al., 1999). This finding has also been supported by a later study of dogs with recurrent or persistent UTI, where approximately half of the dogs diagnosed with

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Table 1
Risk factors previously identified as associated with increased prevalence of bacterial urinary tract infection (UTI) in dogs.

Risk factor	Reference
Surgically treated intervertebral disc disease	Stiffler et al. (2006)
Intermittent bladder catheterization	Thomas (1979)
Placement of indwelling catheters	Ogeer-Gyles et al. (2006b)
	Bubenik et al. (2007)
Tube cystostomy placement	Stiffler et al. (2003)
	Beck et al. (2007)
Hyperadrenocorticism	Forrester et al. (1999)
Diabetes mellitus	Forrester et al. (1999)
	McGuire et al. (2002)
Chronic corticosteroid use	Ihrke et al. (1985)

Table 2
Possible contributory disorders in dogs with recurrent or persistent urinary tract infection (UTI; Seguin et al., 2003).

Abnormal micturition	Alteration of urothelium
paraparesis	urolithiasis
detrusor dyssynergia	transitional cell carcinoma
prostatic cysts or abscesses	Altered urine composition
Anatomic defects	Hypoadrenocorticism
urethrostomy	Diabetes mellitus
urethral avulsion/rupture	Impaired immunity
ectopic ureters	Corticosteroid therapy
incontinence	Chemotherapy administration
pelvic bladder with incontinence	Systemic lupus erythematosis
vestibular-vaginal stenosis	Hyperadrenocorticism
hooded vulva	

recurrent or persistent UTI were asymptomatic on presentation (Seguin et al., 2003).

Urinalysis findings may yield an unremarkable sediment examination, emphasizing the need for a positive culture result to confirm a diagnosis of UTI (Seguin et al., 2003). Interestingly, like in cats (Bailiff et al., 2008), a low urine specific gravity does not appear to predispose dogs to UTI (Forrester et al., 1999; Seguin et al., 2003).

Bacterial pathogens of the canine urinary tract

As in humans (Krieger, 2002) and cats (Litster et al., 2007), the most common pathogen isolated from the canine urinary tract is *E. coli*, which accounts for 33–55% of isolates obtained from UTI cases (Forrester et al., 1999; Norris et al., 2000; Ling et al., 2001; Cohn et al., 2003; Seguin et al., 2003) (Table 4).

Bacterial species such as *Pseudomonas aeruginosa* and *Enterococcus* spp. have a higher prevalence in persistent or recurrent canine UTIs compared to uncomplicated UTIs (Seguin et al., 2003). In two large retrospective studies of dogs with persistent or recurrent UTIs, the six most prevalent bacteria were *E. coli*, *Klebsiella* spp., *Staphylococcus* spp., *Enterococcus* spp., *Proteus* spp. and *Pseudomonas* spp. (Norris et al., 2000; Seguin et al., 2003). In these cases, multiple bacterial species were often isolated from the urine, which sometimes complicated treatment options (Norris et al., 2000; Seguin et al., 2003).

When managing recurrent or persistent UTIs, it is important to correct any treatable underlying abnormalities as well as to determine whether the same bacterial isolate is involved in subsequent infections (i.e., persistent infection or relapse versus reinfection) and whether any changes in antimicrobial susceptibility pattern have occurred. Seguin et al. (2003) reported that in 100 affected dogs, 42% of isolates from second cultures most likely represented persistence or relapse of infection with the same isolate based on culturing the same bacterial species with an identical susceptibility pattern. However, these results should be interpreted with caution as antibiograms alone are not a reliable test for clonality (Drazenovich et al., 2004). Seguin et al. (2003) also reported that the majority (71%) of isolates were susceptible to at least one commonly prescribed oral antimicrobial, with only a small number (4%) resistant to all tested antimicrobials.[1]

Accurate identification of urinary tract pathogens is critical and requires appropriate sampling technique (i.e., urine collection via cystocentesis) to avoid contamination with faecal bacteria (Comer and Ling, 1981). Multi-drug resistance is increasingly observed in faecal *E. coli* (Johnson et al., 2001; De Graef et al., 2004; De Leener et al., 2005) and unintentional isolation of these organisms during diagnostic workup may result in overuse of reserve antimicrobials.

Table 3
Breed predispositions for recurrent or persistent urinary tract infection (UTI).

Breed	Reference
German Shepherd Dog[a]	Norris et al. (2000)
Miniature/Toy Poodle[a,c]	
Labrador Retriever[a,d]	
Mixed breed dogs[a,c]	
Dachshund[a,e]	
Doberman pinscher[a]	
Springer Spaniel[e]	
Golden Retriever[b]	
Dalmatian[b,d]	
Great Dane[b]	
Bassett Hound[b]	
Alaskan Malamute[b]	
Rottweiler[b]	
Shetland Sheepdog[c]	
Mixed breed dogs[a]	Seguin et al. (2003)
Golden Retriever[a]	
Dachshund[a]	
Cocker Spaniel[a]	
Labrador Retriever[a]	

[a] Breeds accounting for ⩾5% of cases.
[b] Breed identified as having a young (<7 years) average age at first diagnosis in both sexes.
[c] Breed identified as having an old (⩾7 years) average age at first diagnosis in both sexes.
[d] Breed for which males are significantly over-represented.
[e] Breed for which females are significantly over-represented.

Table 4
Prevalence of *E. coli* isolates in bacterial urinary tract infections (UTIs) in dogs.

	E. coli isolates *n* (%)	Total isolates
Forrester et al. (1999)[a]	29 (55)	53
Norris et al. (2000)[b]	891 (41.2)	2165
Ling et al. (2001)	3681 (44.1)	8354
Cohn et al. (2003)	547 (37)	1478
Seguin et al. (2003)[b]	208 (47.2)	441

[a] Dogs with hyperadrenocorticism and/or diabetes mellitus.
[b] Dogs with recurrent or persistent UTI.

Origin of canine uropathogens

Most UTIs are thought to result from ascending infections as opposed to infections from haematogenous/lymphatic spread. The two prevailing theories for the origin of uropathogens in humans are the '*prevalence*' and the '*special pathogenicity*' hypotheses (Plos et al., 1995). The *prevalence* hypothesis argues that bacterial strains

[1] Commonly prescribed oral antimicrobials included trimethoprim-sulfa, amoxicillin/clavulanic acid, amoxicillin, cephalexin and tetracycline. Secondary antibiotics included fluoroquinolones and second and third generation cephalosporins.

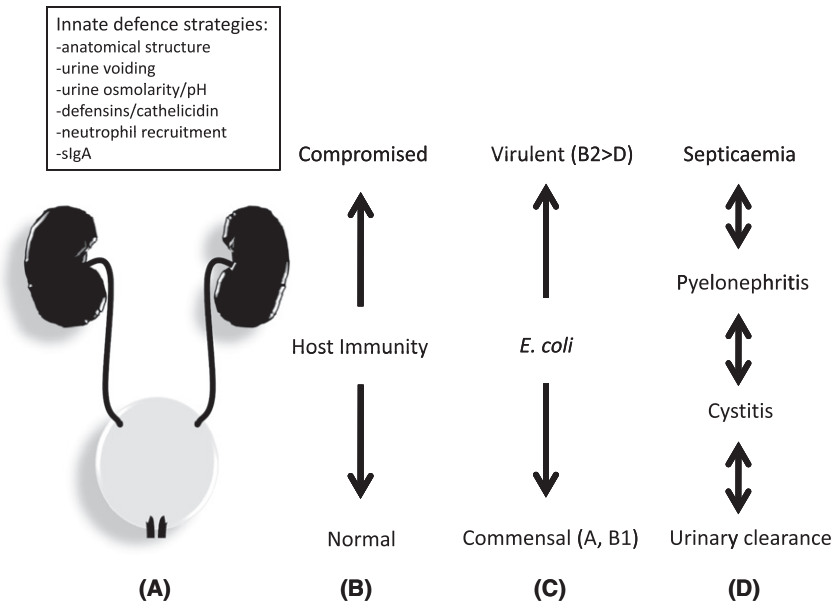

Fig. 1. Schematic diagram of the complex relationship between host and pathogen which affects the outcome of bacterial infection of the canine urinary tract by extraintestinal pathogenic *E. coli* (ExPEC). A number of key innate defence strategies combine to prevent infection of the normal canine urinary tract (A). Impairment of one or more of these host defences tips the balance in favour of infection (B), which is further exacerbated by phylogenetic grouping and virulence characteristics of the *E. coli* strain (C). The possible sequelae resulting from the interaction of these factors include urinary clearance (elimination of bacteria from the urinary tract or bacteriuria without cystitis); uncomplicated cystitis; ascending infection of the urinary tract resulting in pyelonephritis; and occasionally septicaemia (D).

present in the highest numbers in the colonic microbiota are most likely to successfully invade and establish a UTI, whilst the *special pathogenicity* hypothesis suggests that bacteria with the appropriate extraintestinal virulence factors (VFs) are most likely to become uropathogens in spite of their lower prevalence in the colonic microbiota.

Most extraintestinal pathogenic *E. coli* (ExPEC) in humans, including those associated with UTIs, belong to phylogenetic group B2 (generally containing more virulence genes) and to a lesser extent group D (Clermont et al., 2000). These groups of organisms are phylogenetically distinct from commensal and intestinal *E. coli*, which predominantly belong to groups A and B1.

Specific uropathogenic characteristics and VFs are required for bacterial strains to initiate an infection, regardless of the presence of a competitive colonisation advantage in the gut. VFs of importance to uropathogenic *E. coli* (UPEC) include capsular factors, cytotoxins, invasion factors, siderophores and related transport systems, as well as adhesins that mediate binding to the renal tubule (P, S and F1C fimbriae) and bladder urothelium (Type I fimbriae). This is likely to be of particular importance in dogs with intact urinary tract defence mechanisms, since host defences must be overcome by pathogens with specific urinary tract VFs (Fig. 1). However, phylogenetic group A and B1 *E. coli*, whilst generally possessing fewer VFs than group B2 and D *E. coli*, may also initiate UTI in dogs if host defences are compromised (Gibson et al., 2008; Sidjabat et al., 2009).

Increasing antimicrobial resistance in uropathogens and associated potential reservoirs

One recent trend of concern has been the increased prevalence of resistance to antimicrobials observed in canine urinary tract isolates, in particular for fluoroquinolones, third generation cephalosporins, and clavulanic acid-potentiated β-lactams, which are all regarded as second-line veterinary antimicrobial agents (Normand et al., 2000; Cooke et al., 2002; Prescott et al., 2002; Cohn et al., 2003; Gibson et al., 2008). The availability of oral forms and their efficacy against Gram-negative pathogens have resulted in their widespread use in companion animals.

A study of canine urinary isolates over 9 years (1992–2001) demonstrated increasing resistance to fluoroquinolones over time, particularly for *E. coli* (Cohn et al., 2003). However, the efficacy of fluoroquinolones remained high with more than 80% of isolates showing in vitro sensitivity. Another study of canine urinary *E. coli* isolates in a US veterinary teaching hospital (1996–1998) reported a significant increase in the proportion of enrofloxacin-resistant isolates during the second year of the study following an increase use of enrofloxacin the preceding year (Cooke et al., 2002). Molecular fingerprinting of resistant isolates revealed a diversity of DNA macrorestriction profiles, indicating that the growing enrofloxacin resistance was not attributable to a single enrofloxacin-resistant clone, but more likely reflected a collective increase in resistance among several UPEC clonal lineages (Cooke et al., 2002).

When the number of antimicrobials to which recurrent *E. coli* urinary isolates were resistant was examined in a Canadian veterinary teaching hospital (2002–2007), a significant increase was demonstrated over time, whilst this was not the case for non-recurrent *E. coli, Enterococcus, S. intermedius* and *Proteus* spp. isolates (Ball et al., 2008). Gibson et al. (2008) also noted a change in the predominant MDR *E. coli* resistance profile over time (1999–2006). Profiles prevalent in later years demonstrated lower susceptibility to 3rd-generation cephalosporins and cefoxitin.

MDR *E. coli* isolates from canine UTI have been associated with numerous resistance genes (Feria et al., 2002; Sanchez et al., 2002). Similar isolates also carrying several resistance genes were isolated from cases of nosocomial infection, rectal carriers and the environment of a large veterinary teaching hospital in Australia (Sidjabat et al., 2006a,b). The resistant isolates in this study comprised two distinct groups that likely arose through clonal expansion rather than through the transfer and spread of a single MDR plasmid between genetically unrelated isolates (Sidjabat et al., 2006a, 2009). The hospital environment could thus be implicated as a source of

MDR *E. coli* opportunistic infections. A particular concern to spread of resistance is that some resistance genes have been identified on large MDR plasmids that could be readily transferred to other Enterobacteriaceae (Sidjabat et al., 2007).

Increasing antimicrobial resistance in strains isolated from faecal and environmental reservoirs

As ExPEC strains causing cystitis in humans and dogs are predominantly derived from the faecal microbiota, changes in this bacterial population could logically influence the type and severity of UTIs (Johnson et al., 2005). This is another factor to consider in the emergence of the increased number of refractory canine UTIs, with a shift towards faecal carriage of more resistant organisms in some dogs (Johnson et al., 2001; De Graef et al., 2004; De Leener et al., 2005). Canine faecal deposits collected from a suburban neighbourhood were shown to contain *E. coli* strains with similar virulence traits and phylogenetic characteristics to human ExPEC, indicating that dogs may be common reservoirs of these organisms (Johnson et al., 2001). The predominant faecal strain was a *papG*-positive (an adhesion allele) *E. coli* and most isolates correlated with clinical isolates derived from human cases of cystitis, pyelonephritis and bacteraemia.

The proportion of antimicrobial-resistant rectal *E. coli* isolates has been shown to increase in parallel to duration of hospitalisation in an intensive care unit (Ogeer-Gyles et al., 2006a). More specifically, fluoroquinolone administration was associated with a much greater likelihood of colonisation with a quinolone-resistant *E. coli* strain (Ogeer-Gyles et al., 2006a). The majority of dogs with MDR *E. coli* and *Enterobacter* extraintestinal infection in another study had been hospitalised for $\geqslant$3 days and had received prior treatment with antimicrobials (Gibson et al., 2008). Likewise, specimens from hospitalised or kennel dogs are significantly more likely to yield enterococci containing two or more resistance genes compared to non-hospitalised dogs (De Leener et al., 2005). Additionally, the Tn1546 transposon, indistinguishable from that found in vancomycin-resistant human enterococcal isolates, has already been reported in a canine vancomycin-resistant *E. faecium* isolate, demonstrating that exchange of resistance determinants between human and canine enterococcal strains is possible (Simjee et al., 2002).

Consequences of bacterial resistance acquisition

Acquisition of antimicrobial resistance may be associated with loss of VFs, as documented in quinolone-resistant human uropathogenic *E. coli* (Horcajada et al., 2005; Soto et al., 2006). Soto et al. (2006) reported an association between fluoroquinolone resistance and the partial or complete loss of pathogenicity islands, which represent clusters of urovirulence genes, including haemolysin, cytotoxic necrotising factor 1, P fimbriae, and the autotransporter sat.

Potential loss of virulence in fluoroquinolone-resistant UPEC has been investigated in dogs (Johnson et al., 2009). Fluoroquinolone-susceptible and resistant isolates were phylogenetically grouped (A, B1, B2, and D) and the presence of virulence-associated genes were compared. Fluoroquinolone-resistant isolates had a significantly lower prevalence for most virulence marker genes and shifted away from the virulence-associated phylogenetic group B2. Nevertheless, 26% of fluoroquinolone-resistant isolates had still sufficient VFs to qualify as ExPEC. Fluoroquinolone-resistant strains with decreased VFs are common in asymptomatic bacteriuria (ABU), frequently identified in humans with underlying disorders predisposing to UTI (Vranes et al., 2003).

A paradigm shift in the hypothesis that MDR uropathogens are less virulent than their sensitive counterparts occurred recently following the global dissemination of a human *E. coli* clonal lineage (O25b:H4-ST131) that is both MDR and highly virulent. This clonal lineage belongs to phylogenetic group B2 and possesses key ExPEC virulence-associated genes in addition to resistance to several classes of antimicrobial agents, including fluoroquinolones and sometimes third generation cephalosporins (Ewers et al., 2010).

Mechanisms to evade eradication in the canine urinary tract: insight into non-antimicrobial control of chronic, recurrent cystitis

Bacteria have developed additional mechanisms for circumventing host defences, such as long-term persistence in the bladder wall. Long-term UTI caused by a single persistent bacterial strain is an area of increasing interest. Molecular fingerprinting, detection of virulence markers and antibiogram profiling have demonstrated that, despite host defences and appropriate antimicrobial therapy, some uropathogens can persist in bladder epithelial cells, manifesting as recurrent infections (Mulvey et al., 2000; Drazenovich et al., 2004).

One potential mechanism for persistence is invasion of superficial bladder epithelial cells and parenchyma (Mulvey et al., 2000). Whilst it was previously thought that bladder epithelial cells internalized bacteria as a defence mechanism, type-1 fimbriae-mediated invasion of host cells by UPEC is now thought to benefit pathogens by allowing them to evade urinary and bladder defences in a nutrient rich environment ideal for replication or persistence (Mulvey et al., 2000). In mice infected ex vivo, UPEC expressing type-1 fimbriae may induce programmed cell death and exfoliation of bladder epithelial cells, but this defence mechanism can be circumvented by invasion of deeper tissue, thus creating the potential for infection persistence and recurrence despite antimicrobial therapy (Mulvey et al., 1998).

Another potential mechanism for evasion of host defences and medical interventions is the formation of biofilms by sessile adhesive communities associated with the bladder wall. Biofilm formation appears to play an important role in the establishment of ABU; strains with this capability have relatively few adhesins but a significantly better biofilm-forming capacity than UPEC strains (Hancock et al., 2007).

Development of non-antimicrobial treatment/prevention options

The challenge of preventing chronic, recurrent UTI in humans has led to the development of several non-antimicrobial alternatives (vaccines, cranberry juice/extract, probiotics, and adherence/colonisation inhibitors) to low dose daily treatment with antimicrobials (Guay, 2009). Apart from anecdotal reports, the efficacy of these strategies have not been studied in dogs other than identifying bacteriophages from canine and feline UPEC strains (Freitag et al., 2008). Given the problems with resistance development in uropathogens, consideration should be given to the use of low pathogenicity ABU strains to establish long-term colonisation of the canine bladder in chronic recurrent UTI (Thompson et al., 2011). Such strains have been shown to reduce the incidence of UTI in humans with spinal cord injuries, obviating the requirement for repeated courses of antimicrobials (Darouiche and Hull, 2000).

Transmission of uropathogens between humans and dogs: a public health concern

Cross-species transmission may be an important epidemiological factor for UTI in dogs and humans (Yuri et al., 1998). Two MDR

E. coli isolates closely related to canine strains were obtained from rectal swabs of staff working in a veterinary hospital, demonstrating likely transfer of MDR *E. coli* between dogs and humans via the faecal-oral route (Sidjabat et al., 2006b). Similarly, Johnson and Clabots (2006) isolated *E. coli* from the faeces of humans and animals within the same household to determine the level of sharing of bacterial strains between cohabiting hosts. Within-household strain transmission was shown to occur among cohabiting humans and transfer between humans and pets occurred to a similar extent. Hence, rectal carriage of resistant bacteria in either species could provide a risk for the other, especially when physical contact is close. This is particularly significant with the recent detection of the human UTI pandemic MDR *E. coli* strain O25b:H4-ST131 in dogs (Platell et al., 2010). In Australia, the significantly higher prevalence of this clonal lineage among fluoroquinolone-resistant *E. coli* isolates from humans compared to dogs suggests that human-to-dog transmission may currently predominate (Platell et al., 2010).

Conclusions

UTIs in dogs, in particular those that are persistent or recurrent and involve refractory bacterial isolates, represent a growing area of concern. There is a need for further research into the mechanisms for bacterial persistence in the canine urinary tract, especially in dogs with no apparent underlying disorders and during failure of targeted antimicrobial therapy. Likewise, it is desirable to develop a greater understanding of how to minimise resistant isolates with uropathogenic capability in the canine colonic microbiota. Finally, non-antimicrobial therapeutic and/or prevention strategies for recurrent or persistent UTI in dogs warrant further investigations, in terms of reducing the development of antimicrobial resistance and in achieving higher clinical success. Consideration should be given to the recent emergence of highly virulent MDR clones such as O25b:H4-ST131 in UTI cases, their dissemination in humans and dogs, and their possible transfer across species.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

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