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Review

Effect of antibiotic treatment in canine and feline urinary tract infections: A systematic review

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ABSTRACT

Urinary tract infection (UTI) is a major reason for antibiotic prescription in small animal practice. Optimal antibiotic treatment strategies have not been established for veterinary species, especially when considering duration of treatment, which is often considerably longer than for human patients with UTI. The aims of this study were (1) to identify and assess evidence related to the efficacy of antibiotic treatment in canine and feline UTIs; and (2) to compare the efficacy of short (<5 days) and standard (≥7 days) duration of antibiotic treatment for canine uncomplicated UTI. An electronic literature search was conducted for publications to 1 May 2014. Fourteen peer-reviewed prospective and controlled studies were retrieved, 10 of which evaluated antibiotic treatment in dogs and four in cats.

Of the 14 studies, seven were clinical trials and five of those were randomised controlled trials. Most (12/14) studies were not considered to contribute sufficient evidence to evaluate treatment strategies. There were no clinical studies examining the effect of duration of the same drug. Of the short duration regimens evaluated, the efficacy of 3 day antibiotic therapy with trimethoprim-sulphonamide (females only) or high-dose enrofloxacin in dogs with uncomplicated UTIs was supported by fair evidence, as these treatment strategies were non-inferior to medium duration (10–14 days) therapy with β-lactam antimicrobials. In conclusion, there is little published evidence relating to antibiotic treatment of UTIs in dogs and cats. Well-designed clinical trials focusing on the duration of treatment are warranted to create evidence-based treatment protocols.

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Introduction

Urinary tract infection (UTI) is a major reason for antibiotic prescription in small animal practice. Despite UTI being a common condition in dogs, there is great uncertainty regarding optimal treatments for the various forms of UTI. The emerging problem with multidrug resistant bacteria has increased awareness of antibiotic use and misuse in small animals. The International Society for Companion Animal Infectious Diseases (ISCAID) has published guidelines to promote prudent use of antibiotics in canine and feline UTIs (Weese et al., 2011).

Although subject to national and regional variation, the duration of antibiotic treatment for canine and feline UTIs is generally long compared with recommended treatment regimens for human patients with UTI (Grabe et al., 2014). The European Association of Urologists recommends that the duration of antibiotic therapy in women with uncomplicated UTIs should range from 3 to 7 days, depending on the drug used (Grabe et al., 2014). For dogs with uncomplicated UTIs, the advised duration of antibiotic therapy is ≤7 days (Weese et al., 2011), while a 10–14 day course of antibiotics was considered to be the standard of care prior to 2011. For complicated infections in humans, the recommended duration of antibiotic therapy is usually 7–14 days, but it can be extended up to 21 days depending on the underlying condition (Grabe et al., 2014). In comparison, the recommended duration of antibiotic treatment in dogs and cats with complicated UTIs is up to 4 weeks (Weese et al., 2011).

The potential benefits of decreasing the duration of antibiotic treatment are: (1) reduced antimicrobial resistance selection pressure (Singh et al., 2000; Chastre et al., 2003); (2) reduced adverse effects; (3) increased compliance (Claxton et al., 2001); and (4) reduced treatment costs. Although data from humans cannot be translated directly to dogs and cats, the shorter duration of antibiotic treatment in humans does prompt us to question whether medium to long duration treatment is justified in dogs and cats.

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The primary aim of this systematic review was to identify and assess the available evidence related to the efficacy of antibiotic treatment in canine and feline UTIs. A secondary aim was to compare the efficacy of short (<5 days) and standard (≥7 days) durations of antibiotic treatment for uncomplicated canine UTIs, according to the available evidence.

Materials and methods

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al., 2009). A literature search was conducted to identify peer-reviewed publications up to 1 May 2014 comparing in vivo antibiotic treatment in cats and dogs with naturally occurring or induced UTIs. The primary outcome parameters of concern were short term clinical and bacterial cure rates. Secondary outcome parameters were adverse effects and long term clinical and bacteriological cure rates. No limitations to publication year or language, other than a requirement that the abstract should be in English, were imposed.

The electronic databases AGRICOLA, AGRIS, CAB Abstracts, EMBASE, International Pharmaceutical Abstracts and Medline were searched using PubMed[1] and OvidSP.[2] In addition, the Web of Science Core Collection was searched using Web of Knowledge.[3] The search terms used in all search engines were: ([antibiotic$ OR antimicrobial$] AND [treatment$ OR therapy OR therapies OR therapeutic$] AND ['urinary tract' OR urologic* OR UTI$ OR bladder OR cystitis OR prostatitis OR pyelonephritis] AND [infection$ OR infectious]) AND ('small animal$' OR 'companion animal$' OR pet$ OR dog$ OR canine$ OR bitch* OR puppy OR pup$ OR puppies OR hound$ OR mongrel$ OR cat$ OR feline$ OR tom OR tomcat$ OR kitten$). In the PubMed search, all $ were changed to * and in the OvidSP search an addition of (NOT human$) was used.

The reference lists of reviews published after 2000, identified by the electronic searches, were manually screened to identify eligible studies missed by the electronic search. Identified references were imported to reference management software (RefWorks, RefWorks-COS), and duplicates were identified and removed.

Study selection

Screening was divided in two phases. During phase I, papers of relevance were selected based on the following inclusion criteria: (1) original research report; (2) published in peer reviewed journal; and (3) study relating to in vivo systemic antibiotic treatment of spontaneous or induced UTIs in dogs and/or cats reporting on type, dose and duration of antibiotic intervention.

Studies fulfilling the above criteria and those in which fulfilment of the criteria could not be determined from the abstract were retrieved as full texts. Papers in languages other than English were translated into Danish by Google translate or by a professional translator.

Studies identified in phase I were excluded from entry into this systematic review according to the following phase II exclusion criteria: (1) case report or case series; (2) retrospective case control study or retrospective cohort study; (3) single intervention (uncontrolled) prospective clinical studies; or (4) studies lacking both of the primary outcome parameters (clinical and bacterial cure rates).

Data extraction

Data were extracted independently by the first two authors using a purpose-designed extraction sheet. Reviewers were not blinded to author names, institutions or publication titles. For short term outcomes, data were extracted from the point in time defined as the short term evaluation in the original paper. If multiple short term evaluations were available, data were extracted from a time point of 2–4 days post-cessation of treatment. For long term outcomes, data were extracted from the time of the second evaluation after cessation of treatment.

Level of evidence and methodological quality

The studies were graded by level of evidence (LOE) on a scale of 1–3 according to the pyramid of evidence used in the RECOVER and PROVETS guidelines (Boller and Fletcher, 2012; Goggs et al., 2014): LOE 1 for randomised controlled clinical trials (RCTs), LOE 2 for non-randomised controlled clinical trials (NCTs) and LOE 3 for experimental controlled trials (ECT), randomised and non-randomised.

The methodological quality of the studies was evaluated by the following three parameters: (1) risk of bias; (2) size of study groups; and (3) quality of subject enrolment. Risk of bias was evaluated using the Cochrane collaborations tool for assessing risk of bias (Higgins et al., 2011). The studies were categorised as having high, moderate (unclear) or low risk of selection, performance, detection, attrition, reporting and other bias. For non-randomised studies, selection bias was assessed, taking into account the adjustment for confounders (Reeves et al., 2008). Finally, the overall combined risk of bias was defined using a predefined numerical system used in previous veterinary systematic reviews (Olivry and Mueller, 2003; Summers et al., 2012).

Size of study groups was defined as good, moderate, small and very small according to the following criteria used in previous veterinary systematic reviews (Olivry and Mueller, 2003; Summers et al., 2012): > 50 (good), 20–50 (moderate), 10–19 (small) and <10 (very small) animals per group.

The quality of subject enrolment was defined according to the following criteria: (1) good, when the health/disease status of included animals was confirmed by clinical examination and a thorough diagnostic workup, including haematological (complete blood count, CBC) and biochemical (BC) parameters, diagnostic imaging, urinalysis (UA) and bacteriological culture, along with information on age and sex, although diagnostic imaging was not considered mandatory for experimental studies; (2) fair, when the health/disease status of included animals were confirmed by a reasonable diagnostic workup, including UA and bacteriological culture, with or without CBC, BC or diagnostic imaging, along with information on age and sex; and (3) poor, when important information regarding age or sex was not reported, and diagnostic work-up other than culture was not performed or reported.

Definition and classification of urinary tract infections

UTI was classified as uncomplicated UTI (lower UTI in otherwise healthy animals with no underlying anatomic, functional or systemic diseases), complicated UTI (lower UTI in animals with underlying anatomic, functional or systemic diseases and/or recurrent or persistent lower UTI), pyelonephritis (upper UTI) or induced UTI (experimental UTI).

Presentation of qualitative results

The evidence for or against efficacy of a treatment strategy in uncomplicated/complicated/upper UTI was graded as good, fair or insufficient, according to the following criteria modified from Summers et al. (2012) and based upon the definitions of the *US Preventive Services Task Force (USPSTF)*.[4] Evidence was graded according to multiple (good), at least one (fair) or no (insufficient) RCT(s) with a low or low to moderate estimated overall risk of bias reported results for a defined class of UTI. Evidence was also considered insufficient if: (1) interpretation of the results was hampered by limited power of the studies; (2) results of outcome parameters were conflicting; or (3) information regarding important outcome parameters (bacterial or clinical cure rates and/or adverse effects) was lacking. Efficacy of a treatment was defined as superiority or non-inferiority to the comparator, whereas lack of efficacy was defined as inferiority to the comparator or no superiority to placebo/no treatment. Evidence (good or fair) was considered to support a treatment strategy if efficacy was demonstrated. Alternatively, evidence (good or fair) was considered to advise against a treatment strategy if either lack of efficacy was demonstrated or if harmful events associated with use of the treatment were considered unacceptable.

Statistical methods

Fisher's exact test and exact two-sided 95% confidence intervals were calculated when possible, if not already reported in the original studies, using commercially available statistical software (SAS 9.4, IBM). When results of clinical studies that were not originally designed as non-inferiority studies demonstrated no significant difference between groups, a post hoc non-inferiority calculation was applied to the data; the one-sided 95% confidence interval was calculated for the difference in cure rates between study groups and assessed for non-inferiority with $\Delta = 0.2$. If the lower limit of the one-sided 95% confidence interval was above –20%, the study was considered to demonstrate non-inferiority (Jones et al., 1996). In determining the efficacy of intervention and comparing short vs. standard duration treatment, meta-analysis was considered to be inappropriate, since the studies were heterogeneous in terms of study designs, disease definitions, methodologies, outcome measures and treatment interventions tested.

Results

A total of 2142 citations were identified by the literature search strategy, with 167 citations fulfilling the phase I inclusion criteria. Of these, 14 peer-reviewed full-length studies published in English from 1962 to 2014 fulfilled the phase II criteria and entered the systematic review (Fig. 1). Ten studies reported treatment outcomes

[1] See: http://www.ncbi.nlm.nih.gov/pubmed (accessed 1 May 2014).
[2] See: http://ovidsp.uk.ovid.com (accessed 1 May 2014).
[3] See: http://apps.webofknowledge.com (accessed 1 May 2014).
[4] See: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm (accessed 1 May 2014).

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