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1 ***In vitro* antimicrobial activity of nitrofurantoin against *Escherichia coli* and *Staphylococcus***
2 ***pseudintermedius* isolated from dogs and cats**

3

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7

8 **Running title:** Nitrofurantoin susceptibility in small animal urinary tract pathogens

9

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13

14 **Keywords:** veterinary medicine, cystitis, antibiotic resistance, rational antibiotic use

15

15 **Abstract**

16 Minimum inhibitory concentrations (MIC) of nitrofurantoin were determined by agar dilution in
17 269 canine and feline isolates of *Escherichia coli* and *Staphylococcus pseudintermedius*, two of
18 the most common bacterial species associated with urinary tract infection (UTI) in small animals.
19 The MIC₉₀ for *E. coli* and *S. pseudintermedius* were 32 and 16 µg/ml, respectively. All isolates,
20 including multidrug-resistant strains of known genetic background, displayed MICs below the
21 drug concentrations reported in canine urine following oral administration of nitrofurantoin.
22 Preliminary data on mutant prevention concentration (MPC) and many years of nitrofurantoin
23 usage in human medicine suggest that emergence of resistant mutants during treatment is not a
24 critical issue for this drug. The study provides species-specific data on nitrofurantoin MIC
25 distribution that can be used for setting dog- and cat-specific breakpoints. Although
26 nitrofurantoin is not an appropriate first-line agent for empirical treatment of canine UTI due to
27 toxicity and poor pharmacokinetic properties, it may be indicated for treatment of UTI caused by
28 multidrug-resistant bacteria, which are otherwise difficult to treat using conventional veterinary
29 antimicrobial agents.

30 **Introduction**

31 Urinary tract infection (UTI) is one of the most commonly diagnosed infectious diseases in small
32 animal practice. The bacterial pathogens most frequently associated with UTI in dogs are
33 *Escherichia coli*, staphylococci, *Proteus*, *Klebsiella*, enterococci and streptococci (Ling et al.,
34 2001). *E. coli* has been reported to account for 33 – 51 % of all cases of canine UTI, while
35 staphylococci, mainly *Staphylococcus pseudintermedius*, are isolated in 12 – 20 % of all cases
36 (Ball et al., 2008; Ling et al., 2001). Beta-lactam antibiotics such as amoxicillin (alone or in
37 combination with clavulanic acid) and cephalosporins are generally regarded as first line agents.
38 However, multidrug-resistant bacteria recently emerged in small animals, namely methicillin-
39 resistant *S. pseudintermedius* (MRSP) (El Zubeir et al., 2007; Kadlec et al. 2010; Loeffler et al.,
40 2007; Perreten et al., 2010; Ruscher et al., 2009) and extended-spectrum beta-lactamase (ESBL)-
41 producing *E. coli* (Carattoli et al., 2005; Ogeer-Gyles et al., 2006; Sanchez et al., 2002; Shaheen
42 et al., 2010; Warren et al., 2001), are per definition resistant to beta-lactams and often
43 additionally resistant to alternative drugs for treatment of UTI.

44 Nitrofurantoin is a synthetic nitrofurane that reaches very high concentrations in urine. This drug
45 has been used for the treatment of uncomplicated UTIs in humans for more than fifty years
46 (Hooper, 2010). In small animal practice, the use of nitrofurantoin has been gradually abandoned
47 due to higher toxicity and lower pharmacokinetic performance in comparison to beta-lactams,
48 fluoroquinolones and trimethoprim-sulfonamides. The objective of this study was to evaluate the
49 *in vitro* antimicrobial activity of nitrofurantoin against *E. coli* and *S. pseudintermedius* isolates
50 from dogs and cats, including strains previously characterized genetically as ESBL-producing *E.*
51 *coli* and MRSP. The results were discussed on the basis of the current knowledge of the
52 pharmacokinetic properties of nitrofurantoin in dogs.

53 **Materials and methods**

54 ***Bacterial strains***

55 A total of 106 *E. coli*, including 6 ESBL- and 9 CMY-producing isolates, and 163 *S.*
56 *pseudintermedius*, including 13 MRSP, were included in the study. All isolates were collected in
57 the time period 1998 to 2010, with the majority of the strains (88%) isolated from 2005 to 2010.
58 The isolates originated from clinical specimens obtained from infected dogs (n=240) or cats
59 (n=29), except 3 MRSP, 5 ESBL- and 9 CMY-producing *E. coli* which had been isolated from
60 healthy dogs or during necropsy. Thirteen *S. pseudintermedius* isolates (including 2 MRSP) and
61 39 *E. coli* isolates (including 1 ESBL-producing strain) were isolated from urine. Nine of the 13
62 MRSP isolates had previously been typed (Perreten et al., 2010) and belonged to seven distinct
63 clonal types (ST54, ST58, ST68, ST69, ST71, ST95 and ST113).

64 ***MIC testing***

65 MIC values were determined by agar dilution in accordance with the Clinical and Laboratory
66 Standards Institute (CLSI 2008). The range of concentrations tested was between 2 and 128
67 µg/ml. The stock solution was prepared dissolving 250 mg nitrofurantoin (Sigma-Aldrich,
68 Germany) in 5 ml of dimethylformamide (DMF) to yield a final concentration of 50 mg/ml.
69 Mueller Hinton agar plates (Oxoid, UK) containing nitrofurantoin were stored at 4°C in dark
70 plastic bags, and used within 9 days after preparation. The following reference strains were used
71 for quality control: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212,
72 *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

73 ***MPC testing***

74 Mutant prevention concentrations (MPCs) of nitrofurantoin were measured in two isolates of
75 each species. MPC testing was performed according to previous studies (Blondeau, 2009;
76 Hansen and Blondeau, 2005). Briefly, for each strain the bacterial content of three 5% blood agar
77 plates displaying confluent growth was transferred to 100 ml of Mueller-Hinton broth (Oxoid,
78 UK) using a sterile swab. Following overnight incubation, 50 ml of overnight culture were
79 centrifugated at 5000 x g for 30 min, and the pellet was resuspended in 2 ml of broth to reach a
80 cellular density of at least 10^{10} CFU/ml. Mueller-Hinton plates containing nitrofurantoin were
81 inoculated using 100 μ l of this bacterial suspension and incubated at 37°C. The lowest drug
82 concentration preventing growth was recorded as the MPC. Bacterial colonies and smears on
83 plates containing nitrofurantoin concentrations higher than the MIC of the wild-type strain were
84 subcultured onto agar plates containing the same drug concentration and subjected to MIC
85 determination.

87 **Results and discussion**

88 The MICs of nitrofurantoin ranged between 8 and 32 μ g/ml in *E. coli* and between 4 and 16
89 μ g/ml in *S. pseudintermedius* (Table 1). The MIC₉₀ was 32 μ g/ml for *E. coli* and 16 μ g/ml for *S.*
90 *pseudintermedius*. The MIC₅₀ values for the two species were 16 and 8 μ g/ml, respectively. As
91 breakpoints for nitrofurantoin resistance have not yet been established for animal *E. coli* and *S.*
92 *pseudintermedius*, only human breakpoints ($S \leq 32$ μ g/ml, $R \geq 128$ μ g/ml) (CLSI 2010) are
93 available as references for interpretation of the MIC results. According to such breakpoints none
94 of the isolates tested was resistant to nitrofurantoin. All isolates, including the multidrug-resistant
95 strains of known genetic background, displayed MICs lower than the concentration of
96 nitrofurantoin achieved in urine following oral administration to dogs. Conklin et al. (1969)

107 reported that four hours after oral administration (4-5 mg/kg body weight) nitrofurantoin
108 concentrations in urine are above 60 µg/ml for the macrocrystalline formulation and above 100
109 µg/ml for the microcrystalline formulation. For both formulations, a slight increase in drug
110 concentration was observed following repeated administration (Conklin et al., 1969). No data are
111 currently available about the urinary excretion profile within four hours after administration. In
112 an absorption and disposition study of nitrofurantoin in dogs performed by Niazi et al. (1983),
113 oral administration of a 100 mg tablet resulted in a peak plasma level ranging from 1.5 to 4.0
114 µg/ml, and an elimination half-life of 32 to 87 minutes, which means that the drug is rapidly
115 distributed and eliminated from plasma. If one assumes that the urinary excretion rate changes
116 according to the plasma levels, these data indicate that urinary concentrations are high shortly
117 after administration but rapidly decrease in parallel with the decrease of the plasma levels. More
118 detailed information on the excretion profiles and on the antibacterial action of the drug (i.e.
119 concentration- vs. time-dependent) are needed in order to optimize dosage regimens in small
120 animals.

121 There are several disadvantages associated with the clinical use of nitrofurantoin in small
122 animals. The drug is a known gastrointestinal irritant and may cause nausea and emesis as side-
123 effects in both dogs and cats. Due to the short plasma half-life (Niazi et al., 1983), nitrofurantoin
124 requires frequent administration (i.e. three to four times daily). Furthermore, it cannot be used for
125 treatment of UTI associated with *Proteus* and *Pseudomonas* as these organisms are generally
126 resistant to this drug (Rohrich et al., 1983). Although better alternatives than nitrofurantoin exist
127 as first-line agents for treatment of canine UTI, the results of this study combined with the
128 current knowledge of the pharmacokinetics in dogs suggest that this drug may be indicated for
129 treatment of UTI caused by ESBL-producing *E. coli* and MRSP. The recent spread of these

120 multidrug-resistant bacteria in dogs and cats represents a serious therapeutic challenge for small
121 animal veterinary practitioners since such bacteria are often resistant to all the conventional
122 veterinary antimicrobial products available for treatment of UTI in small animal medicine
123 (Carattoli et al., 2005; El Zubeir et al., 2007; Loeffler et al., 2007; Ogeer-Gyles et al., 2006;
124 Perreten et al., 2010; Ruscher et al., 2009; Sanchez et al., 2002; Shaheen et al., 2010; Warren et
125 al., 2001). As a consequence, some veterinarians have started to use critically-important
126 antimicrobial drugs such as the carbapenems. Usage of these last-resort antimicrobials is an
127 unwanted practice in veterinary medicine due to public health concerns (Boothe, 2006). This
128 new trend in antimicrobial usage emphasizes the need for alternative treatment options and
129 nitrofurantoin represents an ideal alternative to carbapenems in the treatment of canine or feline
130 UTI associated with multidrug-resistant bacteria. The clinical efficacy of nitrofurantoin has been
131 recently documented in a case of lower UTI caused by MRSP and *Enterococcus faecalis* in a cat
132 with pre-existing and recurrent urethral obstruction (Pomba et al., 2010).

133
134 The MPC values were 128 µg/ml for both *E. coli* strains and 64 µg/ml for both *S.*
135 *pseudintermedius* strains. The MIC was recorded for all presumptive mutants isolated from MPC
136 plates and only one *E. coli* strain had a higher MIC (128 µg/ml) compared with the respective
137 wild type strain (16 µg/ml). The clinical relevance of the MPC data is uncertain since the
138 apparent bacterial growth on MPC plates containing drug concentrations above MIC was not due
139 to the emergence of a subpopulation of resistant mutants but appeared to be an artefact
140 determined by the high density of the inoculum. Resistance to nitrofurantoin in *E. coli* is known
141 to occur as a result of step-wise mutations (Breeze and Obaseiki-Ebor, 1983; Sandegren et al.,
142 2008). Assuming that the drug concentrations achievable in canine urine during therapy

143 approximate 60 to 100 $\mu\text{g/ml}$ depending on the specific formulation (Conklin et al., 1969),
144 nitrofurantoin would not be effective against mutants with high MICs such as that obtained from
145 the MPC test in this study (MIC=128 $\mu\text{g/ml}$). However, it has been shown that the growth rate of
146 first-step mutants is impaired at concentrations well below 100 $\mu\text{g/ml}$, and that second-step
147 mutants have an impaired growth rate at 100 $\mu\text{g/ml}$ (Sandegren et al., 2008). Based on these
148 data, emergence of resistant mutants during therapy does not seem to be a critical issue in the
149 treatment of UTI with nitrofurantoin. It should be noted that after many years of use in human
150 medicine, nitrofurantoin resistance is still uncommon in *E. coli* isolated from human UTI (Garau,
151 2008; Kashanian et al., 2008; Schito et al., 2009; Zhanel et al., 2005).

152 In conclusion, the use of nitrofurantoin for treatment of UTI in dogs is a matter of weighing the
153 risks of toxicity against the benefits of clinical efficacy. Due to its high toxicity and poor
154 pharmacokinetic performance, nitrofurantoin is not a suitable first-line agent for empirical
155 treatment of UTI in small animals. However, the results of this study indicate that the use of
156 nitrofurantoin may be indicated for treatment of UTI caused by MDR *E. coli* or MRSP, which
157 are otherwise difficult to treat using conventional veterinary antimicrobial products. Standard
158 dosage regimens seem sufficient to kill susceptible strains and probably also prevent selection of
159 resistant mutants during therapy. The MIC distribution data generated by this study may be used
160 for setting species-specific epidemiological cut-off values and clinical breakpoints for
161 nitrofurantoin susceptibility testing in UTI isolates from dogs and cats. Setting of UTI-specific
162 clinical breakpoints will require additional data on the PK/PD properties of nitrofurantoin in
163 these animal species and clinical outcome data from perspective clinical studies.

164

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251

251 **Table 1.** Nitrofurantoin minimum inhibitory concentrations (MIC) in *Escherichia coli* and
 252 *Staphylococcus pseudintermedius* isolates from small animals.

Species	No. isolates	MIC ($\mu\text{g/ml}$)						
		2	4	8	16	32	64	128
<i>E. coli</i>	106	0 (0%)	0 (0%)	4 (3,77%)	90 (84,91%)	12 (11,32%)	0 (0%)	0 (0%)
<i>S. pseudintermedius</i>	163	0 (0%)	1 (0,61%)	122 (74,85%)	40 (24,54 %)	0 (0%)	0 (0%)	0 (0%)

253

254