Randomized, Controlled, Crossover trial of Prevention of Clindamycin-Induced Gastrointestinal Signs Using a Synbiotic in Healthy Research Cats

J.E. Stokes, J.M. Price, and J.C. Whittemore

Background: Synbiotics often are prescribed to limit antibiotic-associated gastrointestinal signs (AAGS) in cats, but data to support this recommendation are lacking.

Objective: To determine whether synbiotic co-administration mitigates AAGS in healthy research cats treated with clindamycin.

Animals: 16 healthy research cats.

Methods: A randomized, double-blinded, placebo-controlled, 2-way, 2-period, crossover study with a 6-week washout was performed. Each study period consisted of a 1-week baseline and a 3-week treatment period. Cats received 75 mg clindamycin with food once daily for 3 weeks, followed 1 hour later by either 2 capsules of a synbiotic or placebo. Food consumption, vomiting, fecal score, and completion of treatment were compared using repeated measures split plot or crossover designs with covariates, with P < 0.05 considered significant.

Results: Cats that received the synbiotic were more likely to complete treatment in period 1 (100% vs. 50%; P = 0.04). Cats vomited less when receiving the synbiotic but this was not significant, but there were significant period effects (F-value = 11.4, P < 0.01). Cats had higher food intake while receiving the synbiotic (F-value = 31.1, P < 0.01) despite period effects (F-value = 8.6, P < 0.01). There was no significant effect of treatment on fecal scores, which significantly increased over time (F-value = 17.9, P < 0.01).

Conclusions and Clinical Importance: Administration of a synbiotic 1 hour after clindamycin administration decreased hyporexia and vomiting in healthy cats. Additionally, significant period effects suggest that clinical benefits of synbiotic administration persist for at least 6 weeks after discontinuation, decreasing the severity of AAGS in cats that subsequently received clindamycin with placebo. Unlike in people, synbiotic administration did not decrease antibiotic-associated diarrhea.

Key words: Antibiotic-associated diarrhea; Antibiotic-associated gastrointestinal signs; Diarrhea and vomiting; Probiotic.

Antibiotic-associated gastrointestinal signs (AAGS) occur in 1–44% of people;1–3 the prevalence of AAGS varies by the antibiotic administered. Antibiotics that are poorly absorbed from the colon or secreted in bile, including clindamycin, are associated with high rates of antibiotic-associated diarrhea in people,1,4 and clindamycin is commonly associated with AAGS in people.1 Adverse drug effects, including AAGS, are a common cause of noncompliance,5–9 resulting in premature antibiotic discontinuation in 6–60% of people and increased hospitalization and complications,7,10,11 as well as community-acquired antibiotic resistance.12–15 Co-administration of probiotics with antibiotics is associated with up to a 3-fold decrease in AAGS in people.2,3,14,16 Clindamycin and other antibiotics cause AAGS in cats,17–19 and the prevalence likely varies by antibiotic. The incidence of noncompliance with antibiotic administration in cats is unknown, but 26% of dog owners failed to administer at least 1 antibiotic dose in 1 study of short-term administration.20 Reasons for noncompliance were not determined, but noncompliance with dosing instructions to administer antibiotics on an empty stomach suggests that 1 possible cause was concerns regarding AAGS. Prevention or mitigation of AAGS in animals might increase owner compliance and, thus, decrease patient morbidity and development of community antibiotic resistance.

High-dose clindamycin (26–44 mg/kg/d) was shown to induce AAGS in 100% of healthy research cats in 1 recent study.21 Vomiting was less common in cats concurrently given a synbiotic (a commercial mixture of probiotics and prebiotics), but differences were not statistically significant, potentially because of the antibiotic dosage used, concurrent administration of the antibiotic with the synbiotic, or interindividual variability in susceptibility to AAGS. The purpose of our study was to determine the incidence of AAGS in healthy research cats.
cats treated with a clinically-relevant dose of clindamycin, followed by either a placebo or synbiotic, in a blinded, randomized crossover trial. It was hypothesized that PO administration of clindamycin to healthy cats would cause AAGS, but administration of a synbiotic 1 hour after clindamycin would lessen the severity of, or prevent development of, AAGS.

Materials and Methods

Animals

The study protocol was approved by the Institutional Animal Care and Use Committee at the University of Tennessee, College of Veterinary Medicine (Protocol number 2375). Sample size calculation, performed using data from a previous study, was performed for each of 3 variables: food intake, vomiting, and fecal score. These calculations indicated that 7 cats per group would need to complete each study period to detect a 10% difference in food intake, 10% difference in vomiting, or a 1-point difference in fecal score between groups with an alpha of 0.05 and beta of 0.2, in the absence of period effects. To accommodate potential exclusion of cats from enrollment because of potential health conditions and removal as a consequence of severe AAGS during treatment, 19 overtly healthy, purpose-bred, domestic short-haired research cats initially were enrolled in the study. After completion of physical examination and laboratory assessment (CBC, plasma biochemistry, urinalysis), 3 cats were eliminated from the study: 1 each because of aggression, abnormal physical examination findings, and abnormal laboratory test results.

One week before the start of the study, the 16 remaining cats were moved from group housing to individual cages. No other changes were made to the cats’ husbandry during the study. Cats were maintained on their individual maintenance diet plans and portion-fed during both individual and group housing. During the week of acclimation, daily food intake was quantitated, cats were monitored daily for the presence of vomiting, and photographs of daily voided feces were taken by an independent observer for scoring using a published fecal scoring system by 1 investigator (JCW). Based on appropriate caloric intake relative to current weight and body condition score, lack of vomiting, and normal fecal scores (median, 2; range, 1–3), all 16 cats were considered healthy and were retained in the study. Based on review of their medical records, 14 cats had received antibiotics during their lifetime, each cat received either 2 capsules of the synbiotic after being fed 2 mL of water after each treatment. If a cat vomited an intact capsule within 1 hour of administration, a new capsule was fed 2 mL of water after each treatment. If a cat vomited an intact capsule within 1 hour of administration, a new capsule was administered.

Study Periods

A randomized, double-blinded, placebo-controlled, 2-way, 2-period, crossover study with a 6-week washout period was performed. Each study period was 4 weeks long, comprised of a 1-week baseline followed by a 3-week treatment period. For the first 5 weeks of the washout period, cats were returned to group housing, after which they underwent 1 week re-acclimation to individual housing in order to identically match the 2 treatment periods.

Treatments

Each cat received 75 mg clindamycin PO once daily (median dosage, 18.0 mg/kg/d; range, 12.1–22.7 mg/kg/d) after being fed its daily ration of commercial food. One hour after antibiotic administration, each cat received either 2 capsules of the synbiotic or placebo PO. Cats in Group A received placebo in period 1 and synbiotic in period 2. Conversely, cats in Group B received synbiotic in period 1 and placebo in period 2. All cats were syringe fed 2 mL of water after each treatment. If a cat vomited an intact capsule within 1 hour of administration, a new capsule was administered.

Animal Observations

An observer blinded to the treatment group quantitated daily food intake and vomiting (present or absent). Any vomiting, including vomiting of hairballs, was considered true vomiting for the purposes of the study. Feces also were photographed daily by the blinded observer. Body weight was measured every 7 days. Cats were removed from a treatment period if they had <50% of baseline food intake for 3 consecutive days, vomited on 3 consecutive days, or lost ≥6% of body weight.

After completion of each treatment period, photographs of daily voided feces were randomized so that investigators were blinded to cat identity, time point, and treatment group. Investigators independently scored photographs of feces with a published fecal scoring system after completion of each treatment period, instead of after completion of the study, as a consequence of the performance of an interim analysis after the conclusion of the first treatment period (see Results below).

Statistical Analysis

Descriptive statistics were calculated for each variable. Samples were analyzed for normality using the Shapiro-Wilk test and for the presence of outliers using box-and-whisker plots. Age and weight for the 2 sequence groups were compared using an independent 2-sample Student’s t-test. Mean percent food intake, percent days of vomiting, and mean fecal scores were determined for each week of each study period (baseline and treatment weeks 1, 2, and 3). Mean food intake for each week in each study period was calculated as a percentage of food intake during the acclimation week. Inter-rater correlation coefficients were calculated for fecal scores. The mean of fecal scores assigned by the 2 investigators was used for all further statistical analyses. Successful completion of treatment was defined as completion of a treatment period (e.g., not being removed from treatment because of excessive hyporexia, vomiting or weight loss). Cats that did not complete a treatment period were censored from data analyses at the point of removal from treatment.

Because there was a marked difference in successful completion of treatment of the first study period between the 2 groups (see Results below), an interim analysis was performed during the washout period to confirm that continuation of the trial was necessary and, thus, ethically appropriate. For the interim analysis, successful completion of treatment, mean food intake, percent days vomiting per week, and mean fecal score were compared between groups using a repeated measures split plot design with covariates. Treatment (A or B), week, and cat were included as categorical variables. Treatment, week, and the treatment-by-week interaction were included as fixed effects. Week was included as a repeated measure with subject as cat. Age, weight, and sex were included as covariates. Cat nested within treatment was included as a random effect. A 1-sided Fisher’s exact test was used to compare completion of treatment between groups. Although the treatment completion percentage of sequence Group B was significantly higher than Group A (Group A, 50%; Group B, 100%, P = 0.04), no other statistically significant differences were found. The second treatment period therefore was performed.

For the final analysis, a 2-treatment, 2-sequence, 2-period AB/BA crossover design with repeated measurements within periods
was performed that included fixed effects of treatment (A or B), order of treatment, week, and treatment-by-week interaction. Age, weight, and sex were included as covariates in the analysis. The repeated measure of time period was accounted for in a repeated statement. Cat nested within sequence group was included as a random effect. A compound symmetry variance/covariance structure was incorporated into each model to account for the inclusion of constant covariates over time (age and weight). The Shapiro-Wilk test of normality of the residuals was evaluated for each marker to confirm that the assumption of normally distributed residuals had been met. Model assumptions regarding equality of variances were verified using Levene’s test for equality of variances. Differences in least squares means were determined for markers with significant main effect or interaction terms.

Commercial statistical software packages were used for all analyses. \( P < 0.05 \) was considered significant.

**Results**

**Animals**

There were 5 female spayed (FS) and 3 male castrated (MC) cats in Group A and 2 FS cats and 6 MC cats in Group B. Median age was 7 years (range, 7–10 years) for Group A and 9 years (range, 5–10 years) for Group B. Median weight was 3.9 kg (range, 3.3–6.2 kg) for Group A and 4.3 kg (range, 3.4–5.3 kg) for Group B. There were no significant differences in age (\( P = 0.35 \)) or weight (\( P = 0.91 \)) between sequence groups. Weight did not differ between first and second baseline for cats in either group. No cat vomited any of the administered capsules during the study. Weight, and thus antibiotic dose, was not associated with any of the analyzed outcome variables.

**Successful Completion of Treatment**

The percentage of cats in each group completing each week of treatment is summarized in Figure 1. During period 1, 4 cats (50%) from Group A were removed from treatment because of vomiting on 3 consecutive days; 1 cat had concurrent hematemesis on the third day of vomiting. In contrast, all cats in Group B successfully completed treatment. Completion of treatment differed significantly (\( P = 0.04 \)) between groups based on interim analysis, with more cats completing treatment in the group that received the symbiotic.

During period 2, 1 cat in Group A was removed from treatment because of vomiting for 3 consecutive days, and 1 cat in Group B was removed because of weight loss. The cat from Group A that was removed in period 2 was 1 of the cats that failed to complete treatment in period 1. Based on analysis of the crossover data, successful completion of treatment period was not significantly associated with treatment (F-value = 3.0, \( P = 0.09 \)) or any other analyzed variable.

**Vomiting**

Vomiting increased in both groups with treatment (Table 1) and differed significantly over time (F-value 6.9, \( P < 0.01 \)). Order of treatment was significantly associated with vomiting (F-value 11.4, \( P < 0.01 \)), but treatment (placebo versus symbiotic) was not (F-value 2.1, \( P = 0.15 \)). Increasing age (F-value 10.7, \( P < 0.01 \)) and female sex (F-value 14.6, \( P < 0.01 \)) were significantly associated with vomiting.

**Food Intake**

Food intake (Table 2) decreased significantly over time (F-value 5.7, \( P < 0.01 \)), and food intake was significantly higher when cats received symbiotic versus placebo (F-value 31.1, \( P < 0.01 \)). There also was a significant effect of period on food intake (F-value 8.6, \( P < 0.01 \)), primarily reflecting 3 cats that initially received placebo and had markedly higher food intake during the second baseline period.

**Fecal Scores**

The inter-rater correlation coefficient for fecal scores was 0.72 (95% confidence interval [CI], 0.66–0.77) in period 1 and 0.69 (95% CI, 0.64–0.74) in period 2.
Table 1. Mean (± standard deviation) percent days vomiting per week for 16 healthy cats, 8 per group, that received 75 mg clindamycin PO once daily for 21 days, followed 1 hour later by 2 capsules of either placebo or synbiotic PO. Cats in Group A received placebo during period 1 and synbiotic in period 2, whereas cats in Group B received synbiotic during period 1 and placebo during period 2.

|               | Period 1 |               | Period 2 |
|---------------|----------|---------------|----------|
|               | Baseline | Week 1        | Week 2   | Week 3   | Baseline | Week 1        | Week 2   | Week 3   |
| Group A       | 8.9 ± 13.0 | 23.7 ± 26.2   | 38.4 ± 30.6 | 29.2 ± 26.3 | 1.8 ± 5.0 | 26.8 ± 33.7   | 10.2 ± 10.8 | 2.0 ± 5.4 |
| Group B       | 5.4 ± 10.6 | 21.4 ± 21.6   | 16.1 ± 11.9 | 16.1 ± 14.2 | 1.8 ± 5.0 | 17.9 ± 18.3    | 8.9 ± 10.6  | 7.1 ± 7.6 |

Table 2. Mean (± standard deviation) percent food intake per week for 16 healthy cats, 8 per group, that received 75 mg clindamycin PO once daily for 21 days, followed 1 hour later by 2 capsules of either placebo or synbiotic PO. Cats in Group A received placebo during period 1 and synbiotic in period 2, whereas cats in Group B received synbiotic during period 1 and placebo during period 2.

|               | Period 1 |               | Period 2 |
|---------------|----------|---------------|----------|
|               | Baseline | Week 1        | Week 2   | Week 3   | Baseline | Week 1        | Week 2   | Week 3   |
| Group A       | 92.5 ± 12.7 | 80.7 ± 16.1  | 75.1 ± 20.0 | 74.5 ± 17.5 | 112.1 ± 21.8 | 109.4 ± 23.4 | 97.4 ± 24.8 | 94.5 ± 29.6 |
| Group B       | 91.8 ± 8.9  | 92.3 ± 15.3   | 98.0 ± 10.6 | 82.4 ± 16.5 | 89.4 ± 15.0 | 92.0 ± 15.5   | 82.1 ± 15.5 | 72.9 ± 26.8 |

Fecal scores (Table 3) significantly increased over time (F-value = 17.9, P < 0.01). There was no significant effect of treatment group (P = 0.37) or period (P = 0.10) on fecal scores. Three cats that initially received placebo had mean fecal scores >4 during the second baseline. Interestingly, these cats were not the same cats that had markedly increased food intake during the same time period.

**Discussion**

Veterinarians often recommend prophylactic administration of probiotics to minimize AAGS in cats and dogs receiving antibiotics, although objective data to support this recommendation are lacking in veterinary medicine. In our study, administration of a synbiotic 1 hour after antibiotic administration significantly decreased hyporexia in healthy cats receiving clindamycin, although it did not prevent development of diarrhea. Symbiotic administration was associated with increased likelihood of completion of antibiotic treatment as a result of decreased frequency of vomiting on multiple sequential days based on interim analysis, although statistical significance was not maintained after completion of the crossover. Cats initially treated with the synbiotic had a significantly lower frequency of vomiting when treated with antibiotics in conjunction with placebo, compared to cats that initially received the placebo, despite a prolonged washout period. If decreased vomiting reflected habituation to repeated antibiotic administration, then both groups should have experienced equivalent decreases in the frequency of vomiting during the second period of the study. Thus, the presence of significant period effects suggests a prolonged protective effect of prior synbiotic administration against future development of AAGS, even in the absence of repeated synbiotic administration. This finding likely confounded the analysis of successful completion of treatment. Review of the data indicated significantly increased food intake in the absence of weight change 6 weeks after discontinuation of antibiotics for 37.5% (3/8) of cats that initially received

Table 3. Mean (± standard deviation) fecal score per week for 16 healthy cats, 8 per group, that received 75 mg clindamycin PO once daily for 21 days, followed 1 hour later by 2 capsules of either placebo or synbiotic PO. Cats in Group A received placebo during period 1 and synbiotic in period 2, whereas cats in Group B received synbiotic during period 1 and placebo during period 2.

|               | Period 1 |               | Period 2 |
|---------------|----------|---------------|----------|
|               | Baseline | Week 1        | Week 2   | Week 3   | Baseline | Week 1        | Week 2   | Week 3   |
| Group A       | 1.7 ± 0.3 | 3.5 ± 1.1     | 4.5 ± 1.3 | 4.8 ± 0.9 | 3.2 ± 1.3 | 2.6 ± 1.0     | 4.0 ± 1.8 | 3.6 ± 1.6 |
| Group B       | 1.7 ± 0.3 | 3.6 ± 1.2     | 4.4 ± 1.6 | 3.3 ± 1.5 | 2.1 ± 1.0 | 2.6 ± 1.0     | 3.3 ± 1.9 | 3.1 ± 1.9 |
In a double-blind study, 22 and mean fecal scores significantly decreased in diarrhea in cats admitted to an animal shelter. The lack of mitigation of diarrhea after synbiotic administration differs from most previous reports in cats.21–23 Probiotic administration was associated with a significant decrease in diarrhea in cats treated with the placebo, but not in cats that initially received the synbiotic. These results are consistent with results of a recently completed study that identified persistent antibiotic-induced dysbiosis in cats treated with clindamycin.4

Although a single-agent administration of the synbiotic significantly decreased hyporexia and increased the likelihood of successful completion of antibiotic therapy, it did not prevent development of diarrhea. The observed lack of mitigation of diarrhea after synbiotic administration differs from most previous reports in cats.21–23 Probiotic administration resulted in increased weight gain and decreased diarrhea (a common cause of death) after tylosin treatment of dogs with enteropathogenic species).28,29 Because no studies had been published regarding the effects of different antibiotics on the microbiome of cats at the time of study development, the washout period was chosen after review of the literature regarding antibiotic effects on the microbiome of dogs, as well as the effects of probiotics and synbiotics on markers of gastrointestinal health and immune function in healthy cats and dogs. In 1 study, healthy dogs treated for 4 to 7 days with amoxicillin had changes to the microbiome and antibiotic-resistant patterns that lasted up to 14 days after antibiotic discontinuation.30 Similarly, administration of tylosin for 14 days to healthy dogs resulted in persistent changes to the microbiome 14 days after discontinuation.30

Furthermore, clearance of the probiotic bacteria was demonstrated 3 days after discontinuation of supplementation in that study. Because we anticipated immunomodulatory effects after probiotic administration, we elected to use an extended washout period compared to that used in previous studies. Despite this, significant period effects were identified. Cats treated with the synbiotic in period 1 were significantly less likely to have AAGS when receiving placebo in the second period, compared to cats that received the placebo initially. Additionally, 75% of cats that received placebo in period 1 developed evidence of antibiotic-induced chronic enteropathy, which was not anticipated. Prior antibiotic exposure increases the risk of AAGS in people,32 suggesting that AAGS should have been more common or severe during the second treatment period. As a result, our study likely underestimates the beneficial effects of synbiotic administration on prevention of AAGS.

Evidence-based guidelines regarding probiotic use for prevention of AAGS are lacking in veterinary medicine. Several ideal bacterial strains, overall colony-forming units (cfu), and benefits of concurrent prebiotic inclusion likely vary by indication, and some effects appear to be dose-dependent.33–34 Higher dosages of probiotics currently are recommended for management of active gastrointestinal disease in animals.35–38 Therefore, we elected to use a dose of 2 capsules of synbiotic per cat. It is unknown
whether similar results would be obtained using lower 
cfu or a different balance of pro- and prebiotics.

Conflicting positions have been taken regarding the 
benefits versus risk of inclusion of antibiotic-resistant 
bacterial strains in probiotics.36–39 Antibiotic-resistant 
bacteria might improve protection against AAGS36,37 but 
they also could serve as a source of antibiotic-resis-
tant genes for normal flora.38,39 As a result, the use of 
resistant strains in probiotics generally is discouraged,
and it is explicitly banned by the European Food Safety 
Authority.38,39 Given this information, results of the 
prior study using high-dose clindamycin,40 and anecdotal 
experience with improved efficacy by a staged adminis-
tration protocol (JCW, personal experience), we chose 
to administer the synbiotic 1 hour after clindamycin 
administration. Although the synbiotic was adminis-
tered PO to assure complete ingestion, many probiotics 
and synbiotics are formulated to allow administration 
on or mixed with food without compromising efficacy,
eliminating the need for pet owners to directly adminis-
ter each medication.

As has been found in people, the incidence and sever-
ity of AAGS have been shown to vary by antibiotic in 
dogs.30,40,41 Adverse gastrointestinal effects were not 
noticed during or after amoxicillin or tylosin therapy in 
healthy dogs.30,40 but a high incidence of diarrhea 
(poorly, commercial capsules were used for our study. 
Clindamycin is available in liquid and capsule formulations. 
Because many cats tolerate the taste of the liquid formulation 
poorly, commercial capsules were used for the study. 
Variability in the size of subjects resulted in a wide dos-
ing range, but weight (and, thus, antibiotic dosage) was 
not significantly associated with the frequency of 
AAGS. However, the value of synbiotic administration 
in mitigating AAGS might differ for cats receiving 
antibiotics other than clindamycin.

A few other limitations to this study should be 
noted. The first was the use of healthy cats as subjects. 
Although cats in our study had fewer AAGS while 
receiving clindamycin during or after synbiotic adminis-
tration, results might differ in systemically ill cats. 
Additionally, most of the cats had received antibiotics 
previously, although only 2 within the previous 
2.5 years. Administration of antibiotics, such as 
macrolides, can cause dysbiosis that persists for up to at least 
4 years in people,41 and we recently have demonstrated 
that risk of microbiome alterations >600 days after 
clindamycin administration in cats.42 Given associations 
between prior antibiotic administration and increased 
risk of AAGS in people, AAGS might have been more 
severe for cats in our study than would be identified in 
antibiotic-naïve cats. Age was positively associated with 
AAGS, but no interaction between age and response to 
treatment was identified. Significant differences previ-
ously have been demonstrated between the microbiome 
of older cats (ages 8–15 years) compared to kittens.42,43

Some studies11,44 have found that probiotics do not 
decrease AAGS in older people (>65 years), although 
other studies suggest strong benefits45 and several meta-
analyses have confirmed their efficacy in adults and 
children.16,32,33,46 The lack of collinearity between age 
and treatment effect in our study suggests that synbi-
oitics have prophylactic effects independent of age in 
cats. Confirmation of these findings in a study popula-
tion with a greater percentage of geriatric cats is war-
ranted, however, because the majority of the cats in 
our study were middle-aged, with a median age of 
9 years. The association between female sex and vomiting 
also warrants further scrutiny. No association was 
found between sex and AAGS in a previous study per-
formed in cats.46 The majority of studies of AAGS in 
people employ sex-matching. However, 1 prospective 
study in which patients were not sex-matched to con-
trols found no association between sex and develop-
ment of AAGS.47 Human females, however, have been 
found to be at increased risk of community-acquired,
but not hospital-acquired, C. difficile infection.48 Patien-
ts with community-acquired infection were less 
likely to have prior antibiotic exposure (78%) than 
those with hospital-acquired infection (94%), although 
the prevalence of antibiotic exposure was extremely 
high in both groups. Finally, cats were maintained on 
their individual maintenance diets, instead of being 
placed on 1 or more standardized diets. Although this 
design improves the applicability of results to clinical 
pactice in which there is marked heterogeneity in 
patient diets, it unknown whether results would differ 
in cats that received concomitant alterations in their 
diets.

In conclusion, concurrent synbiotic administration 
significantly increased the likelihood of completion of a 
3-week course of clindamycin in healthy cats, and it 
was associated with improved food intake and 
decreased frequency of vomiting during antibiotic 
administration. Initial administration of clindamycin 
with placebo instead of the synbiotic was associated 
with persistence of clindamycin-induced chronic 
enteropathy 6 weeks after antibiotic discontinuation in 
75% (6/8) of cats. Mitigation of AAGS has the poten-
tial to improve patient outcome and decrease commu-
nity-acquired antibiotic resistance by increasing owner 
compliance in completing antibiotic treatment. Further 
evaluation of the impact of synbiotic administration in 
ameliorating AAGS in clinically ill cats and dogs receiv-
ing antibiotics is warranted.

Footnotes

a Whittemore JC, Stokes JE, Laia N, Price JM, Suchodolski J. Short and long-term effects of a synbiotic on clinical signs, fecal microbial diversity and metabolomic profiles in healthy research cats receiving clindamycin: a randomized, controlled trial. 2017 ACVIM Forum Research Abstract Program. J Vet Intern Med, 31. https://doi.org/10.1111/jvim.14778
b Proviable-DC, Nutramax Laboratories Veterinary Sciences, Inc., Lancaster, SC
Stokes, Price, and Whittemore

Acknowledgments

Conflict of Interest Declaration: Dr. Whittemore has received honoraria from Nutramax Laboratories for development of educational materials and public speaking.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials in this study.

References

1. McFarland LV. Antibiotic-associated diarrhea: Epidemiology, trends, and treatment. Future Microbiol 2008;3:563–578.
2. Lenoir-Wijinkoop I, Nuijten MJ, Craig J, et al. Nutrition economic evaluation of a probiotic in the prevention of antibiotic-associated diarrhea. Front Pharmacol 2014;5:13.
3. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: A systematic review and meta-analysis. J Am Med Assoc 2012;307:1959–1969.
4. Bartlett JG. Antibiotic-associated diarrhea. New Engl J Med 2002;346:334–339.
5. Llor C, Hernandez S, Bayona C, et al. A study of adherence to antibiotic treatment in ambulatory respiratory infections. Int J Infect Dis 2013;17:e168–e172.
6. Pechere JC, Hughes D, Kardas P, et al. Non-compliance with antibiotic therapy for acute community infections: A global survey. Int J Antimicrob Agents 2007;29:245–253.
7. Chan YH, Fan MM, Fok CM, et al. Antibiotics nonadherence and knowledge in a community with the world’s leading prevalence of antibiotics resistance: Implications for public health intervention. Am J Infect Control 2012;40:113–117.
8. Muñoz EB, Dorado MF, Guerrero JE, et al. The effect of an educational intervention to improve patient antibiotic adherence during dispensing in a community pharmacy. Aten Primaria 2014;46:367–375.
9. Kardas P, Devine S, Golenbesky A, et al. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. Int J Antimicrob Agents 2005;26:106–113.
10. Jefferds MD, Laserson K, Fry AM, et al. Adherence to antimicrobial inhalational anthrax prophylaxis among postal workers, Washington, D.C., 2001. Emerg Infect Dis 2002;8:1138–1144.
11. Jafarnejad S, Shab-Bidar S, Speakman JR, et al. Probiotics reduce the risk of antibiotic-associated diarrhea in adults (18–64 years) but not the elderly (>65 years): A meta-analysis. Nutr Clin Pract 2016;31:502–513.
12. Perez-Gorricho B, Ripoll M, Group PS. Does short-course antibiotic therapy better meet patient expectations? Int J Antimicrob Agents 2003;21:222–228.
13. Larson E. Community factors in the development of antibiotic resistance. Annu Rev Public Health 2007;28:435–447.
14. Selinger CP, Bell A, Cairns A, et al. Probiotic VSL#3 prevents antibiotic-associated diarrhoea in a double-blind, randomized, placebo-controlled clinical trial. J Hosp Infect 2013;84:159–165.
15. Omotosho BA, Adebayo AM, Adeniyi BO, et al. Tuberculosis treatment outcomes and interruption among patients assessing DOTs regimen in a tertiary hospital in semi-urban area of south-western Nigeria. Nige J Med 2014;23:51–56.
16. Goldenberg JZ, Lyytyni, Steurich J, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea (Review). Cochrane Database Syst Rev 2015;(12):CD004827.
17. Suspected drug adverse reactions reported to the Bureau of Veterinary Drugs. Can Vet J 1995;36:246–249.
18. Hunter RP, Lynch MJ, Ericson JF, et al. Pharmacokinetics, oral bioavailability and tissue distribution of azithromycin in cats. J Vet Pharmacol Ther 1995;18:38–46.
19. Albarelos GA, Landoni MF. Current concepts on the use of antimicrobials in cats. Vet J 2009;180:304–316.
20. Adams VJ, Campbell JR, Waldner CL, et al. Evaluation of client compliance with short-term administration of antimicrobials to dogs. J Am Vet Med Assoc 2005;226:567–574.
21. Hart ML, Suchodziolki JS, Steiner JM, et al. Open-label trial of a multi-strain probiotic in cats with chronic diarrhea. J Feline Med Surg 2012;14:240–245.
22. Bybee SN, Scora AV, Lappin MR. Effect of the probiotic Enterococcus faecium SF68 on presence of diarrhea in weanling kittens. 2015 ACVIM Forum Research Abstract Program. J Vet Intern Med, 29. https://doi.org/10.1111/jvim.12609
32. Ouwehand AC, Forssten S, Hibberd AA, et al. Probiotic approach to prevent antibiotic resistance. Ann Med 2016;48:246-255.
33. Szajewska H, Konarska Z, Kołodziej M. Probiotic bacterial and fungal strains: Claims with evidence. Dig Dis 2016;34:251–259.
34. Pagnini C, Saeed R, Bamias G, et al. Probiotics promote gut health through stimulation of epithelial innate immunity. Proc Natl Acad Sci USA 2010;107:454–459.
35. Rossi G, Pengo G, Caldin M, et al. Comparison of microbiological, histological, and immunomodulatory parameters in response to treatment with either combination therapy with prednisone and metronidazole or probiotic VSL#3 strains in dogs with idiopathic inflammatory bowel disease. PLoS ONE 2014;9:e94699.
36. Strompfová V, Lauková A, Ouwehand AC. Selection of enterococci for potential canine probiotic additives. Vet Microbiol 2004;100:107–114.
37. Tian P, Xu B, Sun H, et al. Isolation and gut microbiota modulation of antibiotic-resistant probiotics from human feces. Diagn Microbiol Infect Dis 2014;79:405–412.
38. EFSA Panel on Additives and Products or Substances used in Animal Feed Scientific. Opinion on the safety and efficacy of Prostora Max (Bifidobacterium animalis) as a feed additive for dogs. EFSA Journal 2012;10:2964–2978.
39. Sharma P, Tomar SK, Goswami P, et al. Antibiotic resistance among commercially available probiotics. Food Res Int 2014;57:176–195.
40. Suchodolski JS, Dowd SE, Westermarck E, et al. The effect of the macrolide antibiotic tylosin on microbial diversity in the canine small intestine as demonstrated by massive parallel 16S rRNA gene sequencing. Microbiology 2009;9:210.
41. Jakobsson HE, Jernberg C, Andersson AF, et al. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS ONE 2010;5:e9836.
42. Jia J, Frantz N, Khoo C, et al. Investigation of the faecal microbiota of geriatric cats. Lett Appl Microbiol 2011;53:288–293.
43. Jia J, Frantz N, Khoo C, et al. Investigation of the faecal microbiota of kittens: Monitoring bacterial succession and effect of diet. FEMS Microbiol Ecol 2011;78:395–404.
44. Wright K, Wright H, Murray M. Probiotic treatment for the prevention of antibiotic-associated diarrhoea in geriatric patients: A multicentre randomised controlled pilot study. Australas J Ageing 2015;34:38–42.
45. Hickson M, D’Souza AL, Muthu N, et al. Use of probiotic Lactobacillus preparation to prevent diarrhea associated with antibiotics: Randomized double blind placebo controlled trial. BMJ 2007;335:80–85.
46. Lau CSM, Chamberlain RS. Probiotics are effective at preventing Clostridium difficile-associated diarrhea: A systematic review and meta-analysis. Int J Gen Med 2016;9:27–37.
47. Wiström J, Norrby SR, Myhre EB, et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: A prospective study. J Antimicrob Chemother 2001;47:43–50.
48. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired Clostridium difficile infection: A population-based study. Am J Gastroenterol 2012;107:89–95.