European Network for Optimization of Veterinary Antimicrobial Therapy (ENOVAT) Guidelines for Antimicrobial Use in Canine Acute Diarrhoea

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Abstract

Acute diarrhoea is a common presentation in dogs, and a common reason for antimicrobial prescription and nutraceutical use. This evidence-based guideline provides recommendations for antimicrobial and nutraceutical treatment of canine acute diarrhoea (CAD). A multidisciplinary panel developed the recommendations by adhering to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The opinions of stakeholders (general veterinary practitioners and dog owners) were collected and incorporated to ensure the applicability of this guideline. Four strong recommendations informed by high certainty evidence, and three conditional recommendations informed by very low or low certainty evidence, were drafted by the panel, along with an ungraded section on diagnostic work-up of dogs with acute diarrhoea. The ENOVAT guidelines initiative encourages national or regional guideline makers to use the evidence presented in this document, and the supporting systematic review, to draft national or local guidance documents.

Keywords

Antimicrobial stewardship; antibiotics; enteritis; evidence based; GRADE

67 **Executive summary** (recommendations and remarks without full rationale)

Recommendation 1
In dogs with mild disease and acute non-hemorrhagic diarrhoea (dogs in good general condition, with no signs of dehydration or systemic illness), we recommend against treatment with antimicrobials.
Strong recommendation, high-certainty evidence.

Recommendation 2
In dogs with mild disease and acute diarrhoea with hematochezia (dogs in good general condition, with no signs of dehydration or systemic illness), we recommend against treatment with antimicrobials.
Strong recommendation, high-certainty evidence.

Recommendation 3
In dogs with acute non-hemorrhagic diarrhoea, and moderate disease (dogs with impaired general condition and varying degrees of dehydration/hypovolemia. Dogs may have signs of systemic disease related to the deficit of body fluids, that will resolve with adequate fluid therapy), we recommend against treatment with antimicrobials.
Strong recommendation, high-certainty evidence.

Recommendation 4
In dogs with acute hemorrhagic diarrhoea, and moderate disease (dogs with impaired general condition and varying degrees of dehydration/hypovolemia. Dogs may have signs of systemic disease related to the deficit of body fluids that will resolve with adequate fluid therapy), we recommend against treatment with antimicrobials.
Strong recommendation, high-certainty evidence. **Remarks:** Dogs with laboratory values indicative of severe or overwhelming inflammation, such as severe neutrophilia (> $25x10^9$/L), neutropenia and/or degenerative left-shift, represent an exception.

Recommendation 5
In dogs with hemorrhagic and non-hemorrhagic diarrhoea, and severe disease (dogs with impaired general condition and varying degrees of dehydration/hypovolemia, and signs of systemic disease despite adequate fluid therapy), we suggest systemic treatment with antimicrobials.
Conditional recommendation, very low-certainty evidence.

Recommendation 6
In dogs with severe disease, we suggest parenteral (intravenous or intramuscular) administration of antimicrobials that are expected to be effective for treatment of bacterial translocation and bacteraemia or sepsis. Drug choice depends on how critical the clinical status of the dog is, as well as regional prevalence of antimicrobial resistance (AMR) and drug availability. In dogs with non-critical illness (Table 1) living in a region with low AMR prevalence, we suggest ampicillin or alternatively amoxicillin-clavulanic acid or trimethoprim/sulfonamides as first line drugs.
In dogs with critical illness (Table 1) or where antimicrobial resistance is more likely (e.g. based on geographic trends or the patient's antimicrobial exposure history) we suggest administration of a four-quadrant protocol providing gram positive, gram negative, aerobic and anaerobic coverage (Table 5). Dogs with non-critical illness that do not respond to first line antimicrobials and supportive care should also receive this protocol.
Conditional recommendation, very low-certainty evidence/expert opinion. Level of agreement 100 %
*Antimicrobial drug combinations with four-quadrant spectrum (aerobic, anaerobic, gram positive and gram negative spectrum) include aminopenicillins or clindamycin combined with fluoroquinolones or aminoglycosides (gentamicin, amikacin).

Recommendation 7
The duration of antimicrobial treatment is dependent on the treatment response and the panel suggests daily assessment of animals while hospitalized. Antimicrobial therapy should not extend beyond clinical resolution. For the majority of dogs, treatment of 3-7 days is likely adequate to obtain clinical resolution
Conditional recommendation, very low-certainty evidence. Level of agreement 100%

Recommendation 8
In dogs with acute diarrhoea we do not recommend either for, or, against use of probiotics.
The trade-offs are closely balanced. Moderate certainty evidence.

Introduction

Acute diarrhoea in dogs is a common presenting complaint in veterinary practice ((Jones et al., 2014). The vast majority of dogs with acute diarrhoea have mild and self-limiting disease (Hubbard et al., 2007), while a small proportion of dogs become more profoundly sick and require intravenous fluid support and hospitalization (Singleton et al., 2019). A study of over 3000 dogs with acute diarrhoea presented to primary practice showed that 84% of consults had mild clinical signs, 15 % had moderate clinical signs, and less than 1% had severe clinical signs, as defined by the attending veterinarian (Singleton et al., 2019). Only 2.3% of all dogs were admitted and 0.2% were referred to secondary practice in the same study. While the aetiology of acute diarrhoea often remains unknown, the prognosis in most cases is excellent. Most cases resolve within one week (Hubbard et al., 2007) and fatalities are rare, with an all-cause mortality/euthanasia in hospitalized dogs of approximately 2– 4 % (Mortier et al., 2015; Dupont et al., 2021). Despite the mild biological course of disease and favorable prognosis, acute diarrhoea remains one of the more common indications for antimicrobial use in dogs (De Briyne et al., 2013). It has been documented that 50-65% of dogs with acute diarrhoea are prescribed antimicrobials (Jones et al., 2014; Singleton et al., 2019; Lutz et al., 2020). According to a UK study, metronidazole is most frequently administered drug followed by amoxicillin-clavulanic acid (Singleton et al., 2019). Antimicrobial resistance (AMR) is one of our times most pressing health problems, it affects humans and animals alike, and is mainly driven by the selection pressure created by antibiotic usage (WHO, 2024). Canine acute diarrhea represents a highly common condition associated with inappropriately high antimicrobial prescription rates, and as such, is of high priority for antimicrobial stewardship in companion animal practice. Presently there are no international antimicrobial use guidelines available for treatment of acute diarrhea in dogs.

Scope and purpose

The purpose of this document is to provide guidance on antimicrobial use in dogs with acute diarrhoea, based on the best available evidence and transparent reasoning. The target audience is veterinary practitioners managing dogs with acute diarrhoea, in either out-patient or hospital settings. The guideline is intended to help practitioners direct antimicrobial treatment towards those dogs that are most likely to benefit from it, while reducing unnecessary use in the remaining dogs. As with all guidelines, this document is not intended to be a substitute for good clinical judgement, and recommendations should not be viewed as diktats. Even strong recommendations may not apply to all dogs in all circumstances.

The recommendations in this guideline are informed by the systematic review previously published by the group (Scahill et al., 2024). The ENOVAT guidelines initiative encourages national or regional guideline makers to use the evidence presented in this document, and the supporting systematic review, to draft

national or local guidance documents. Translation and dissemination of ENOVAT guidance documents is encouraged.

This guideline is produced in collaboration with the European Society of Clinical Microbiology and Infectious Disease (ESCMID) Study Group for Veterinary Microbiology (ESGVM).

Methods

This guideline was produced following the ENOVAT operating procedure (ENOVAT, 2024). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence and draft recommendations (Guyatt et al., 2008).

Composition of the Guidelines Drafting Group

The guidelines panel was established in 2020, and is composed of 18 members representing the veterinary fields of gastroenterology (MW, SU, CRB, KA), internal medicine, (LRJ, FA, EL, CA, CP), infectious diseases (SW, KS), general medicine (TB), microbiology (LG), pharmacology (AF), epidemiology (MB, DS) and public health (UW). One panel member (FF) represents the field of guidelines methodology in human medicine. The work was chaired by an oversight committee (LRJ, DS) and a methodology taskforce (KS, MW, CP, MB, FF) was established as a subset of the group. Two members of the methodology taskforce were non-voting members (MB, FF).

Conflict of interest

This article is based upon work from the COST Action European Network for Optimization of Veterinary Antimicrobial Treatment (CA18217), supported by COST (European Cooperation in Science and Technology). The panel members did not have any substantial conflicts of interest at the time of drafting recommendations. However, it should be noted that most of the panel members are involved in antimicrobial stewardship activities. Two panel members (MW and SU) were authors of trials included in the systematic reviews and did not participate in the risk of bias assessment or any other individual quality assessments for these publications.

Generation of Guidelines content and involvement of veterinary practitioners and dog owners

An overview of the guidelines process is depicted in Figure 1. In brief, the content of the guidelines and the clinical questions were generated by the panel in an iterative process involving electronic Delphi questionnaires and on-line meetings. The panel defined the target population as dogs with acute (less than 7 days duration) diarrhoea, regardless of aetiology, and categorized this population into three sub-populations of dogs depending on the severity of their clinical state. Each sub-population was further sub-

grouped, based on the presence or absence of blood in the stools. Three clinical questions concerning the effect, choice and duration of antimicrobial therapy, were selected for systematic reviews. Furthermore, three clinical questions concerning the effect of nutraceuticals were selected for systematic review, of which only the question on probiotics was included in the guidelines.

Clinical questions were phrased using the Population Intervention Comparator Outcome (PICO) format. To ensure the relevance of the guidelines content, and integrated the perspectives of guideline end-users, panel members conducted structured interviews with veterinary practitioners (n=41) and dog-owners (n=33) from across Europe and Israel. From this process, five outcomes (duration of diarrhoea, progression of disease, duration of hospitalization, mortality and adverse effects) were prioritized for evaluation. Outcomes were classified as critical if deemed so by the majority of either the veterinary practitioners, dog owners and/or panel members.

To evaluate the effect of treatment, thresholds for clinically relevant treatment effects were established for all outcomes. Thresholds for a relevant reduction in the duration of diarrhoea, and a relevant reduction in the duration of hospitalization, were established prior to conducting the systematic review, and were based on the opinion of the majority of interviewed veterinary practitioners, dog owners and panel members. The thresholds for a clinically relevant effect of treatment on the risk of mortality, and the risk of disease progression, were established after conducting the systematic review, following GRADE's updated guidance of the imprecision domain (Zeng *et al*., 2022). These thresholds were derived by surveying a different group of veterinary practitioners (n=23) and panel members from the clinical field (n=11) and calculating the 25-percentile value of the risk-effects selected by the survey participants. Outcomes and thresholds for a clinically relevant treatment effect are listed in Table 1. Subgrouping of dogs are described in table 2.

Table 1. Critical outcomes and treatment effect thresholds in dogs with acute diarrhea

Outcome (subgroup)	**Threshold for a clinically relevant effect of treatment**
Duration of diarrhea	At least 1 day reduction
Duration of hospitalization (dogs with moderate and severe disease)	At least 1 day reduction
Mortality (dogs with severe disease)	3 % risk increase/decrease
Progression of disease (dogs with mild disease)	30 % risk increase/decrease
Progression of disease (dogs with moderate – severe disease)	10 % risk increase/decrease

Systematic review and judging the certainty of evidence

The systematic reviews, meta-analyses (MA), and evidence assessment were conducted by the methodology taskforce and oversight committee. The results of the systematic reviews, and a description of the methods applied, are available in the supporting systematic review (Scahill et al., 2024). In brief, the certainty of evidence was assessed for each outcome using the GRADE methodology, and was based on the risk of bias, imprecision, indirectness, inconsistency and publication bias (Guyatt et al., 2008). The partially contextualized approach was used to assess imprecision for separate outcomes (Zeng et al., 2022). The certainty of the body of evidence was based on the certainty of evidence of the outcomes deemed critical, and could not be graded higher than the critical outcome with the lowest certainty.

Generation of recommendations

Recommendations were drafted by the panel in May 2022 in a face-to-face hybrid meeting in Copenhagen. Prior to the meeting, panel members were presented with a video summary of the systematic review and meta-analyses, as well as a written evidence summary report prepared by members of the methodology taskforce (KS, MW). Panel members were also provided with a narrative summary of the harmful effects of antimicrobial therapy on the canine gastrointestinal residual flora (MW, SU, LG), and a summary of the stakeholder interviews (LRJ, CP). Finally, panel members were provided with links and asked to familiarize themselves with video material from the McMaster University on the guidelines formation process following the GRADE approach. Drafting of recommendations followed the GRADE Evidence to Decision (EtD) framework, and for each recommendation the following factors were discussed: certainty of the overall evidence, the balance of desirable and undesirable effects, preferences and values of dog-owners and veterinary practitioners, equity, acceptability and feasibility (Alonso-Coello et al., 2016). The panel defined consensus as 80% agreement prior to drafting recommendations. Agreement was calculated based on the 16 voting members. The panel drafted four strong and three conditional recommendations. Strong recommendations were informed by moderate or high certainty evidence, conditional recommendations were informed by low or very low certainty evidence. The definitions of certainty and the implications of strong and conditional recommendations are described in Table 3. Two recommendations (6 and 7) were elaborated and modified after the meeting and subjected to two more processes of agreement. All recommendations received 100 % agreement.

Generation of the diagnostic (ungraded) section.

The diagnostic section was generated by an iterative process involving several Delphi rounds and a final approval of considerations by the voting panel members.

Consultation phase

Guidelines were available on the ENOVAT website from 26/02/2024 to 26/03/2024 for public consultation (ENOVAT, 2024). The public consultation phase was announced by the ENOVAT newsletter and members from ESGVM, ENOVAT and the European Society of Comparative Gastroenterology (ESCGE) were contacted by email/newsletter and encouraged to participate.

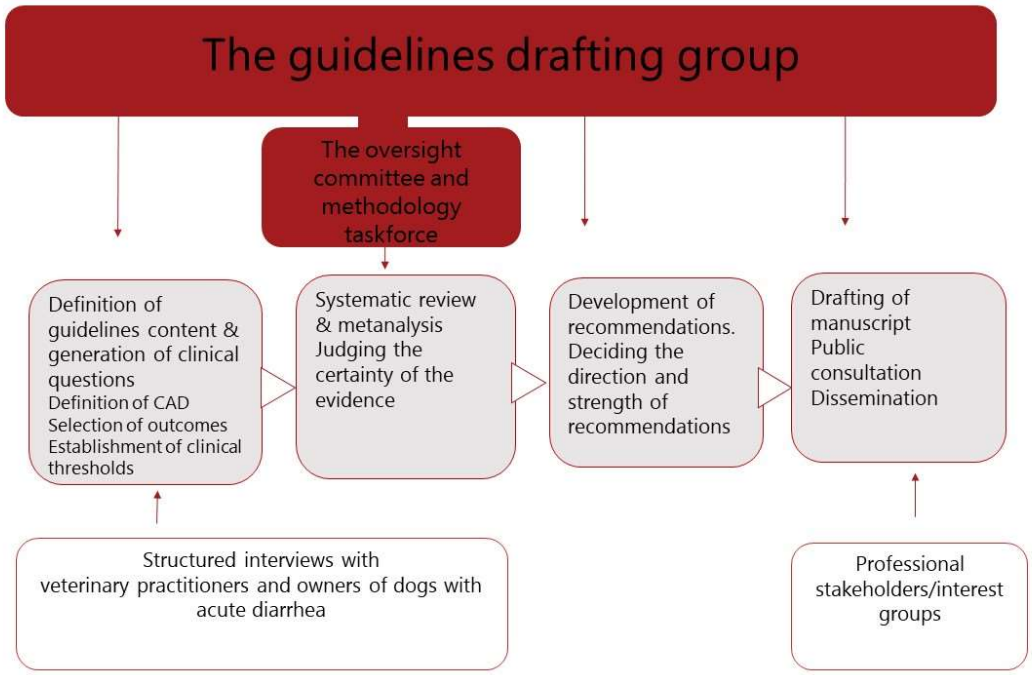

Fig 1. Overview of the guidelines process.

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203 Table 2. Sub-populations of dogs with acute diarrhea.

Sub-population	Presence/absence of blood in the stools	Definition
Mild disease	Non-hemorrhagic diarrhea Hematochezia.	Dogs with mild disease are bright, alert and responsive. They have no clinical signs of dehydration or hypovolemia and there is absence of fever. These dogs are managed as out-patients.
Moderate disease	Non-hemorrhagic Hemorrhagic	Dogs with moderate disease have mild to moderately depressed mental status, and are dehydrated or hypovolemic. Dogs in this category may present with signs of systemic disease, typically tachycardia. When present, systemic signs are due to dehydration/hypovolemia, and resolve rapidly with adequate fluid replacement. There is absence of fever. Dogs with moderate disease warrant fluid therapy and supportive care, and are often hospitalized.
Severe disease	Non-hemorrhagic Hemorrhagic	Dogs with severe disease have moderately to severely depressed mental status and signs of dehydration or hypovolemia. Dogs with severe disease warrant fluid therapy and supportive, sometimes intensive care. These dogs are hospitalized. Dogs in this category may present in different ways: • Dogs with critical illness (severely depressed mental status and severe vascular compromise/shock) • Dogs with non-critical illness e.q., dogs presenting with moderate disease but systemic signs do not resolve or progress or relapse despite adequate fluid replacement; or dogs that present with or develop overwhelming inflammation (severe neutrophilia or neutropenia) or fever (>39.3)

204 *Dogs with acute diarrhea are sub-categorized according to the severity of clinical disease.*
205 *Categorization is not based on volume or frequency of diarrhea.*

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207 Table 3. Definition of the certainty of evidence and implications of strong versus conditional
208 recommendations.

Certainty of evidence [a]	
High	The authors have a lot of confidence that the true effect is close to the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Very low	The true effect is probably markedly different from the estimated effect

Recommendations		
Implications for:	Strong Recommendation	Conditional Recommendation
Animals	Most animals in this situation would benefit from the recommended course of action and only a small proportion would not.	The majority of animals in this situation would benefit from the suggested course of action, but many would not.
Clinicians	Most animals should receive the recommended course of action.	Evidence is inadequate to make a strong recommendation, and/ or different choices might be appropriate for different animals. Be prepared to help animal owners make a decision that is consistent with their own values/preferences.
Policy makers	The recommendation can be adapted as policy in most situations.	Policy making may require substantial debate and involvement of many stakeholders. Policies are also more likely to vary between regions.

Modified from (Guyatt et al., 2008)

Results

Recommendations on antimicrobial use in dogs with acute diarrhoea and mild disease

Recommendation 1

In dogs with mild disease and acute non-hemorrhagic diarrhoea we recommend against treatment with antimicrobials.

Strong recommendation, high-certainty evidence.

Level of agreement 100%

Recommendation 2

In dogs with mild disease and acute diarrhoea with hematochezia we recommend against treatment with antimicrobials.

Strong recommendation, high-certainty evidence.

Level of agreement 100%

Rationale for recommendations 1 & 2

Evidence of therapeutic effect

There is high certainty evidence that antimicrobials do not confer a clinically relevant effect in dogs with acute diarrhoea and mild disease, whether or not blood is present in the stools. Based on the enquiries among dog owners and veterinarians, the main concern in dogs with acute diarrhoea and mild disease is the duration of diarrhoea (critical outcome), and for dogs with hematochezia, the risk of disease progression is also a concern (critical outcome). To investigate the effect of antimicrobials in dogs with diarrhoea, we conducted a systematic review, and included outcome data from 232 dogs from six randomized controlled trials in a metanalysis (Scahill et al., 2024). Dogs with mild disease were represented in four trials (Shmalberg et al., 2019; Langlois et al., 2020; Werner et al., 2020; Rudinsky et al., 2022), two of which also included dogs with moderate disease and non-hemorrhagic diarrhoea receiving intravenous fluid therapy as out-patients(Shmalberg et al., 2019; Langlois et al., 2020). Dogs with hematochezia were represented in one study (Rudinsky et al., 2022). The remaining two trials were conducted in dogs with moderate disease and hemorrhagic diarrhoea (Unterer et al., 2011; Israeloff, 2009). Antimicrobials investigated were metronidazole (3 studies), amoxicillin clavulanate (2 studies) or a combination (1 study).

The mean duration of diarrhoea in dogs with acute diarrhoea ranged from 1.7 to 9.3 days in dogs receiving antimicrobials and from 1.9 to 6.68 days in the control group. When looking at the pooled mean difference between treated and untreated dogs, duration of diarrhoea was reduced by 0.28 days or approximately 7 hours (95% CI -0.77-0.21) in dogs receiving antimicrobials. The mean difference was below the 24 hours threshold for a clinically relevant reduction in the time of diarrhoea, as predefined by dog-owners and veterinary practitioners, and was therefore considered trivial. Likewise, subgroup analysis of the 126 non-hospitalized dogs (dogs with mild disease, and dogs with moderate disease and non-hemorrhagic diarrhoea) and the 106 hospitalized dogs (dogs with moderate disease and hemorrhagic diarrhoea) showed only trivial reduction in the duration of diarrhoea in response to antimicrobials. The mean reductions in days of diarrhoea were 0.07 days (95% CI -1.19-1.05) and 0.38 days (95% CI -0.81-0.04), respectively. No dogs with mild disease included in the systematic review suffered progression of disease. The certainty of evidence for dogs with mild disease was high. The systematic review included the six trials in a network meta-analysis to make an indirect comparison between metronidazole and beta-lactams. Amoxicillin-clavulanic acid was marginally more efficient in shortening the duration of diarrhoea (MD -0.29 days, 95% CI -2.24, 1.65) in comparison to metronidazole but the difference was considered clinically trivial (below 24 hours), and did not change the overall conclusion (Scahill et al., 2024).

The balance between desirable and undesirable effects

From the perspective of the individual dog and society, avoidance of antimicrobial use, where there is no benefit of therapy, is preferred to avoid harmful effects of antimicrobial treatment (Table 4). Harmful effects could include adverse drug effects, antimicrobial resistance, impacts on the gut microbiota, and problems relating to drug administration (e.g., bites, disruption of the human-animal bond).

The six studies included in the systematic review did not report adverse effects, or exacerbation of clinical signs, in association with antimicrobial administration. However, adverse effects may go undetected in dogs with acute diarrhoea as the most common manifestations are indeed gastrointestinal upset. Impacts on the microbiota were investigated in dogs with acute diarrhoea and mild disease in two of the trials included in the systematic review. The PCR based dysbiosis index was altered, indicating dysbiosis following antimicrobial therapy with metronidazole (Rudinsky et al., 2022) but not in dogs treated with amoxicillin-clavulanic acid (Werner et al., 2020). Selection for antimicrobial resistance was investigated in the latter study, which documented selection of amoxicillin-resistant *Escherichia coli* (*E. coli*), persisting up to 3 weeks following cessation of therapy (Grock et al., 2021).

When balancing the desirable against undesirable effects of antimicrobials in dogs with mild disease, the panel finds that undesirable effects clearly outweigh the desirable effects, for which documentation is lacking.

Recommendations on antimicrobial use in dogs with acute diarrhoea and moderate disease

Recommendation 3

In dogs with acute non-hemorrhagic diarrhoea, and moderate disease, we recommend against treatment with antimicrobials.

Strong recommendation, high-certainty evidence.

Level of agreement 100%

Recommendation 4

In dogs with acute hemorrhagic diarrhoea, and moderate disease, we recommend against treatment with antimicrobials.

Strong recommendation, high-certainty evidence.

Level of agreement 100%

Remarks: Dogs with laboratory values indicative of severe or overwhelming inflammation, such as severe neutrophilia (> $25x10^9$), neutropenia and/or degenerative left-shift, represent an exception.

Clinical monitoring of dogs with moderate disease while hospitalized is imperative as some dogs will experience worsening of clinical signs hours or days after initial improvement.

Rationale for recommendations 3 & 4

Evidence of therapeutic effect

There is high certainty evidence that antimicrobials do not confer a clinically relevant effect in dogs with acute diarrhoea and moderate disease, whether or not the diarrhoea is hemorrhagic (Scahill et al., 2024)., 2023). Based on the enquiries among dog owners and veterinarians, the risk of disease progression and the duration of hospitalization are the main concerns in dogs with acute diarrhoea and moderate disease, thus these are considered critical outcomes. Other outcomes deemed important in this group of dogs are duration of diarrhoea and risk of mortality. The effect of antimicrobials on duration of diarrhoea in dogs with acute diarrhoea is described in the prior paragraph (see evidence summary for dogs with mild disease) and the same conclusion applies for dogs with moderate disease. Disease progression, duration of hospitalization and mortality were investigated in the same systematic review of 232 dogs with acute diarrhoea as discussed earlier (Scahill et al., 2024). Disease progression occurred in two out of 106 dogs with moderate disease and hemorrhagic diarrhoea, one was described as clinically worsened and one developed leukopenia. The pooled risk difference between treated and untreated dogs was 0.02, which translates into a risk of 21 more dogs per 1000 dogs suffering progression of disease without antimicrobials (95% CI from 70 more dogs to 30 less dogs per 1000 dogs). This risk difference was below the threshold for clinical relevance predefined by panel members and veterinary practitioners, and therefore considered trivial. The mean duration of hospitalization in dogs with acute diarrhoea ranged from 3.59 to 3.61 days in dogs receiving antimicrobials and from 3.22 to 3.36 days in the control group. When looking at the pooled mean difference between treated and untreated dogs, there was a trivial (< 24 hours) prolongation of time of hospitalization in dogs receiving antimicrobials by 0.37 days (95% CI 0.04-0.69). Likewise, for mortality there was no detectable benefit of antimicrobial therapy, and the odds ratio of 1.43 (95% CI 0.24-8.54) was in favour of the untreated control group. Mortality occurred in 5 out of 106 dogs with moderate disease and hemorrhagic diarrhoea, three of which were treated with antimicrobials and two of which were not treated. The certainty of evidence for dogs with moderate disease was high.

The balance between desirable and undesirable effects

When balancing the desirable against undesirable effects of antimicrobials in dogs with moderate disease, the panel finds that undesirable effects clearly outweigh the desirable effects, for which documentation is lacking. The readers are referred to the prior paragraph for dogs with mild disease and to Table 4 for a description of the harmful effects of antimicrobials in dogs with acute diarrhoea.

Recommendations on antimicrobial use in dogs with acute diarrhoea and severe disease

Recommendation 5

In dogs with hemorrhagic and non-hemorrhagic diarrhoea, and severe disease we suggest treatment with systemic antimicrobials.

Conditional recommendation, low-certainty evidence

Level of agreement 100%

Rationale for recommendations 5

Evidence of therapeutic effect

Dogs with severe disease constitute a minor proportion of dogs with acute diarrhoea (Singleton et al., 2019) and they are not represented in any of the randomized controlled antimicrobial treatment trials (Scahill et al., 2024). Observational studies in dogs with acute diarrhoea and severe disease provide data on treated individuals only and baseline rates for progression of disease and mortality in untreated dogs with severe disease are lacking. The overall certainty of the evidence informing the recommendation is low, due to very serious indirectness of data.

The balance between desirable and undesirable effects

When balancing the desirable against undesirable effects of antimicrobials in dogs with severe disease, the panel finds that the potential desirable effects outweigh the undesirable effects. Dogs with severe disease are dogs with impaired general condition and persistent signs of systemic disease. Some dogs in this group may directly present critically ill with overt signs of sepsis, while others have more subtle disease, yet have not responded to - or have progressed despite - adequate fluid therapy. The panel finds that discriminating between animals that will, and will not, benefit from antimicrobials in dogs with severe disease is challenging, and that withholding antimicrobials may pose a risk of the disease progressing to sepsis or other infectious consequences in some dogs. A beneficial effect of antimicrobials, though not investigated in any trial, should be considered likely. Harmful effects of antimicrobials are

described in Table 4 but are considered of lesser importance to the animal's health when considering the potential risk of sepsis in dogs with severe disease.

Recommendation 6

In dogs with severe disease, we suggest parenteral (intravenous or intramuscular) administration of antimicrobials that are expected to be effective for treatment of bacterial translocation and bacteraemia or sepsis. Drug choice depends on how critical the clinical status of the dog is, as well as regional AMR prevalence and drug availability.

In dogs with non-critical illness (Table 1) living in a region with low AMR prevalence, we suggest ampicillin or alternatively amoxicillin-clavulanic acid or trimethoprim/sulfonamides as first line drugs.

In dogs with critical illness (Table 1) or where antimicrobial resistance is more likely (e.g. based on geographic trends or the patient's antimicrobial exposure history) we suggest administration of a four-quadrant protocol providing gram positive, gram negative, aerobic and anaerobic coverage (Table 5). Dogs with non-critical illness that do not respond to first line antimicrobials and supportive care should also receive this protocol.

Conditional recommendation, very low-certainty evidence/expert opinion

Level of agreement 100%

Rationale for recommendation 6

Evidence of therapeutic effect

We did not identify any randomized controlled trials comparing treatment with different antimicrobials in dogs with acute diarrhoea and severe disease. Some low certainty evidence can be derived from a retrospective study of dogs with acute haemorrhagic diarrhoea syndrome (AHDS) in which a proportion of dogs were treated with antimicrobials, the majority with intravenous ampicillin, and the prognosis was favourable (Dupont et al., 2021). However, dogs included in that study were not classified into moderate and severe disease and likely represented a mix of severities. The most severely ill dogs were treated with a four-quadrant protocol, for the most part consisting of ampicillin and a fluoroquinolone. Indirect evidence of the effect of amoxicillin clavulanic acid can be derived from the network meta-analysis performed to compare the effect of metronidazole and amoxicillin clavulanic acid in dogs with mild and moderate disease, in which no difference in efficacy was found (Scahill et al., 2024). However, as dogs with mild and moderate disease have no benefit of treatment with antimicrobials, the value of this evidence in dogs with severe disease is limited. Overall, the certainty of evidence informing the

recommendation on choice of treatment is very low and the recommendation is mainly based on the opinion and experience of the panel members.

The balance between desirable and undesirable effects

In dogs with severe disease the purpose of antimicrobial administration is prevention or treatment of bacterial translocation, bacteremia or sepsis, and treatment is aimed at achieving efficient systemic concentrations. Parenteral administration is therefore preferred over oral therapy. De-escalation to an oral equivalent can be performed once there is confidence that an oral antimicrobial will be properly absorbed.

When balancing benefits and harms of different antimicrobials the panel has taken into considerations the limited evidence summarized above, the critical illness of the animal and the risk of developing life threatening complications of infection as well as the antimicrobial spectrum and the categorisation of antimicrobials for use in animals from the European Medicines Agency (EMA). EMA categorizes antimicrobial drugs into four categories from D to A with D being the more prudent group ((EMA), 2024).

Based on experience from the North European countries, dogs that are not critically ill (Table 1) may benefit from treatment with intravenous ampicillin (EMA cat.D) alone, or parenteral administration of either amoxicillin clavulanic acid (EMA cat. C) or trimethoprim/sulphonamide (EMA cat. C).

For dogs with critical illness immediate administration of antimicrobial therapy with four-quadrant coverage is indicated. The suggested drug combinations in Table 5 represent common combinations for treatment of sepsis caused by unknown agents, it is not an exhaustive list of antimicrobial combinations providing four-quadrant coverage. The panel finds that though use of fluoroquinolones (EMA cat. B) should generally be restricted, their use in critically ill dogs with severe disease and acute diarrhea is justified, to provide immediate coverage against gram negative *Enterobacterale*s. Aminoglycosides (gentamycin, amikacin) are EMA category C drugs with a gram negative spectrum similar to fluoroquinolones. There is some concern over nephrotoxicity when aminoglycosides are administered to animals with compromised renal blood flow, limiting their use in dogs with hypovolemia and/or reduced urine production. Aminoglycosides can be administered in dogs once they are euvolemic and have adequate urine production.

Recommendation 7

The duration of antimicrobial treatment is dependent on the treatment response and the panel suggests daily assessment of animals while hospitalized. Antimicrobial therapy should not extend beyond clinical resolution. For the majority of dogs, treatment of 3-7 days is likely adequate to obtain clinical resolution.

Conditional recommendation, very low-certainty evidence.

Level of agreement 100%

Rationale for recommendation 7

Evidence of therapeutic effect

There are no studies comparing the effect of short (7 days or less) vs long (greater than 7 days) duration of antimicrobial treatment in dogs with acute diarrhoea. Some low certainty evidence can be derived from a retrospective observational study of hospitalized dogs with AHDS, representing a mix of dogs with moderate and severe disease. Of those dogs treated with antimicrobials, the majority was treated for less than 7 days and up to one third of dogs were released from hospital without further antimicrobial treatment (Dupont et al., 2021). Likewise, indirect evidence derived from trials in dogs with moderate disease indicates that most dogs are treated for less than seven days, and that clinical resolution of disease occurs prior to cessation of therapy (Scahill et al., 2024). There is currently no consensus on the optimal duration of treatment in dogs with bacteraemia, or in dogs with sepsis. In people there are several RCTs demonstrating that short duration (5-7 days) of antimicrobial therapy is non-inferior to long duration 10-14 days) of antimicrobial therapy for gram negative bacteraemia (Runyon et al., 1991; Montravers et al., 2018; Tansarli et al., 2019; Yahav et al., 2019). For suspected or established sepsis in people, recent international guidelines from the Society of Critical Care Medicine (Evans et al., 2021) recommend shorter over longer duration antimicrobial therapy, and daily evaluation to decide when to discontinue antimicrobial therapy.

The balance between desirable and undesirable effects

Antimicrobial use should not be used long beyond clinical resolution to avoid harmful effects of prolonged antimicrobial exposure (Table 4). It is the experience of the panel that most animals with acute diarrhoea and severe disease experience resolution of disease well within 7 days of treatment, and thus will not require extended treatment.

Common considerations for recommendations on antimicrobial use in dogs with acute diarrhoea

Feasibility, cost and equity

Recommendations are feasible and are unlikely to have important impact on equity or costs. There is a cost-saving effect of not prescribing antimicrobials; however, the expenses for antimicrobial therapy vary with the size of the dog and the specific product, in some cases it may constitute a relatively minor part of

the total cost of a veterinary consult. Antimicrobial therapy does not impact duration of hospitalization and recommendations against antimicrobial therapy will not increase overall costs in hospitalized dogs.

Preferences and values of dog-owners

The panel considered values and preferences of veterinary prescribers and dog-owners when selecting the treatments and outcomes to investigate in the systematic review (Scahill et al., 2024). Our enquiries suggest that owners of dogs with acute diarrhoea have specific expectations for medication and these expectations could be used to assess if therapeutic effects were clinically relevant or not (clinical effect thresholds). The panel acknowledges that there may be a preference for antimicrobials when diarrhea is disruptive to the owners (e.g. house soiling, waking up in the night to defecate) and that there may be pressure from owners to take an approach other than watchful waiting. However, the panel believes that most dog-owners would wish to avoid the cost and effort of medication if they are made aware that there are no clinically relevant therapeutic effects of treatment, and in particular, if informed of the potential harms of antimicrobial treatment. The panel believe that in the case of dogs with severe disease, most dog owners would prefer antimicrobial treatment if informed of the potential benefits.

Acceptability and implementation

The panel recognizes that acceptance of a non-antimicrobial treatment strategy may vary among dog owners in the European region. In some regions, guidelines will require a greater effort to implement, and implementation strategies should take into account national values and preferences. Client pressure, perceived or true, may pose a barrier to antimicrobial stewardship, and video animations targeting owners can be downloaded, in 12 different languages, from the websites of (ENOVAT, 2024). The short video animation explaining the consequences of unnecessary antimicrobial use has been tested in a population of dog owners in the UK and was found to significantly impact owners' perceptions of antimicrobial use (Wright, 2022)

Recommendations for future research on antimicrobial use in dogs with acute diarrhea.

The panel considers investigation into non-antimicrobial treatments a priority in dogs with acute diarrhoea and mild or moderate disease. When investigating the effect of a given treatment one should consider not only the effect on the duration of diarrhea, but also the risk of disease progression. This risk is a concern of dog-owners and practitioners that was not addressed in earlier studies. Antimicrobial trials are relevant in dogs with severe disease and should aim to elucidate optimal choice of drug and duration of treatment. Other knowledge gaps to fill include long-term consequences of antimicrobial use and diagnostic markers to identify dogs that will benefit from antimicrobial treatment.

468

469 Table 4. Harmful effects of commonly used antimicrobials in dogs with acute diarrhea

Harm	Description
Adverse effects	Adverse effects of antimicrobial therapy has been investigated in healthy dogs receiving metronidazole. The most common adverse effects were hyporexia, vomiting and diarrhea. Diarrhea was reported in 56% to 100% of healthy dogs following administration of metronidazole alone (Pilla et al., 2020) or in combination with enrofloxaxin (Whittemore et al., 2019).
Dysbiosis	Antibiotics can lead to an alteration of the intestinal microbiota and metabolites. The severity depends on the type of antibiotic, the duration of the application, and individual factors. These changes can persist for months to years, depending on the antibiotic used and the species. Several studies in healthy dogs found that the commonly used antibiotics for canine diarrhea, tylosin and metronidazole, resulted in dysbiosis, which was present in some dogs even weeks after therapy. Moreover, typical for these antibiotics was a severe reduction in the number of *Clostridium hiranonis* (Manchester et al., 2019; Pilla et al., 2020), a bacterium that is thought to play a role in maintaining a healthy intestinal metabolism in dogs .Similarly, dysbiosis associated with metronidazole treatment in dogs with acute diarrhea was recently documented (Rudinsky et al., 2022). The alterations of the canine intestinal microbiota induced by amoxicillin or amoxicillin clavulanic acid seem to be fewer and less long lived (Gronvold et al., 2010; Espinosa-Gongora et al., 2020), and a recent study in dogs with acute diarrhea could not document dysbiosis using the PCR based dysbiosis index (Werner et al., 2020). Alterations found in other populations of dogs include reductions in microbial richness and diversity during treatment. In addition, the abundance of beneficial taxa is reduced by addition of clavulanic acid (Espinosa-Gongora et al., 2020), suggesting that clavulanic acid may broaden the impact of amoxicillin on the gut microbiota, with potential negative consequences on gut health.
Antimicrobial resistance	Selection of antimicrobial resistant bacteria is a well-documented effect of antimicrobial therapy in humans and animals, and has been documented in various populations of dogs ((Damborg et al., 2011; Espinosa-Gongora et al., 2020). In dogs with acute diarrhea, selection for antimicrobial resistance has been investigated in dogs receiving amoxicillin-clavulanic acid (Werner et al., 2020). Treatment with amoxicillin-clavulanic acid favored development of amoxicillin-resistant *E. coli*, which *increased* from 0.2% before antibiotic administration to 100% during antibiotic administration. Three weeks after discontinuation of the antibiotic, the

	percentage of amoxicillin-resistant *E. coli was still* significantly higher (10%) than in the control group (0.1%).

Table 5. Antimicrobial combinations with four-quadrant spectrum (aerobic, anaerobic, gram positive and gram negative spectrum).

Gram positives aerobes and Anaerobes	+	**Gram negative Aerobes**		**Comments**
Aminopenicillin (e.g. amoxicillin EMA D, ampicillin EMA D) or Clindamycin EMA C		Fluoroquinolone* EMA B or Aminoglycoside** EMA C (gentamycin, amikacin)		*avoid in young growing animals ** nephrotoxicity, avoid in dogs with compromised renal function or reduced renal blood flow (hypovolemia).

Each drug is assigned a category from the European Medical Agency (EMA): category D = Prudence, category C = Caution, category B = Restrict, category A = Avoid.

Recommendations on probiotic use in dogs with acute diarrhoea

Recommendation 8

In dogs with acute diarrhoea, we do not recommend either for or against use of probiotics.

Level of agreement 100%

Rationale for recommendations 8

Evidence of therapeutic effect

A recent systematic review conducted by this group did not identify a clinically relevant effect associated with probiotic administration in dogs with acute diarrhoea (Scahill et al., 2024). The systematic review included four trials of probiotic administration in dogs with acute diarrhoea, all prospective, randomized, and controlled (Herstad et al., 2010; Gomez-Gallego et al., 2016; Ziese et al., 2018; Shmalberg et al., 2019). The total number of dogs assessed was 149, all privately owned dogs (probiotic group = 75; placebo = 74) presenting for spontaneous idiopathic acute diarrhoea. Only one study (Shmalberg et al., 2019) showed a small beneficial effect of probiotics on the duration of diarrhoea (shortening of the duration of diarrhea by >1 day), the effect in the other three trials was trivial, as was the effect when looking at all studies combined (reduction of diarrhoea by 0.68 days). There were no clinical adverse effects or mortality reported in any of the studies. Two studies showed a shift in the microbiome towards the microbiome of healthy animals

in the dogs receiving probiotic (Gomez-Gallego et al., 2016; Ziese et al., 2018). Risk of bias was generally low, and the certainty of the combined evidence considered moderate.

The balance between desirable and undesirable effects

There are two major considerations leading to the panel making a non-recommendation (neither for nor against). The first consideration concerns the diversity of probiotic products. Probiotics are highly diverse and the biological effects are considered to be dependant not only on the specific strains, but also on the dose (McFarland et al., 2018). It is unclear how the results of the systematic review apply to other probiotic organisms, combinations or doses, limiting the relevance of a general recommendation for or against all probiotics. The second consideration concerns the trade-offs that are closely balanced. While we could not document a clinically relevant effect of treatment in dogs with acute diarrhoea, probiotics did result in what was assumed to be improvements in the microbiota in two studies. However, understanding of what constitutes clinically relevant beneficial changes in the gut microbiota is still limited. Probiotics are considered safe in veterinary medicine. When practitioners and dog owners were questioned, we identified a clear preference for probiotic prescribing among veterinary practitioners and a high degree of acceptance among dog owners. However, the cost of the product, which can be considerable, and the stress of medication, may not be justified. In conclusion, the panel decided not to make any recommendation concerning probiotics at present, and the use of probiotics in dogs with acute diarrhoea remains a matter of preference for the attending clinician and client.

Diagnostic work up in dogs with acute diarrhoea.

The following considerations on diagnostic work-up represent the professional opinion of the panel. The panel has not conducted systematic reviews to inform the statements included in this section, and the guidance provided is ungraded.

Complete blood count (CBC) and Biochemistry

CBC and biochemistry are indicated in dogs with acute diarrhoea and moderate or severe disease. In dogs with azotemia, measurement of urine specific gravity is indicated to distinguish prerenal from renal causes of azotemia.

Rationale

Dogs presenting with acute diarrhoea and mild disease often have self-limiting disease and do not warrant extensive work up (Hubbard et al., 2007; Schwartz and Newman, 2013; Berset-Istratescu et al., 2014). For dogs presenting with depressed mental status and systemic response to disease (moderate and/or severe disease), a minimum database including CBC and biochemistry will help detect signs of overwhelming inflammation (severe neutrophilia, neutropenia, degenerative left shift) and/or bacterial sepsis (hypoglycaemia, hyperbilirubinemia), which may influence the decision to treat with an antimicrobial (Purvis and Kirby, 1994; Hauptman et al., 1997). CBC and biochemistry will help assess the degree of dehydration (hemoconcentration, relative hyperproteinemia, prerenal azotæmia) and detect electrolyte abnormalities which may influence the amount, type and rate of fluid therapy. Lastly, it will help rule out obvious metabolic or endocrine causes of acute diarrhoea.

C-reactive protein (CRP)

CRP may be considered in dogs with moderate or severe disease to help assess the degree of systemic inflammation and monitor disease progression/regression.

Rationale

In dogs presenting with depressed mental status and systemic response to disease, CRP may be helpful to monitor disease progression in the individual dog. It is uncertain if CRP at admission can be used for antimicrobial therapy decision making, or to what extent it offers additional information compared to the clinical assessment. CRP has been investigated in dogs with moderate and severe disease, more specifically in dogs with parvovirus enteritis and in dogs with AHDS (McClure et al., 2013; Dupont et al., 2021; Sanger et al., 2022). In dogs with AHDS, CRP correlates with clinical and laboratory scoring systems (Dupont et al., 2021; Sanger et al., 2022), and concentrations decrease gradually with disease regression (Sanger et al., 2022), indicating CRP might be useful as a monitoring tool. However, its benefit over routine clinical monitoring remains unclear. The correlation with antimicrobial therapy has not been established, and CRP did not correlate with antimicrobial therapy in a recent, prospective study in dogs with AHDS (Sanger et al., 2022). In another retrospective study of dogs with AHDS (Dupont et al., 2021), CRP at admission was higher in dogs that received antimicrobials compared to those receiving supportive care alone. However, a causal relationship could not be established due to the retrospective nature of the study, and CRP might have influenced the choice of treatment. Also, values were overlapping and high CRP concentrations were also found in dogs that did not receive antimicrobials. CRP did correlate to prognosis in puppies with parvovirus enteritis (McClure et al., 2013), but this was not found in dogs with AHDS (Dupont et al., 2021).

Testing for hypoadrenocorticism

Testing for hypoadrenocorticism (e.g., adrenocorticotropic hormone (ACTH) stimulation test/basal cortisol) is indicated in dogs with acute diarrhoea presenting with either depression/weakness/lethargy/collapse, and/or a history of recurrent episodes of acute diarrhoea, and/or presence of laboratory abnormalities compatible with hypoadrenocorticism (Hanson et al., 2016).

Rationale

The clinical picture of hypoadrenocorticism ranges from mild disease to severe life-threatening vascular collapse. In dogs with acute diarrhoea and mild disease a history of waxing and waning and recurrent episodes may justify further work up. Typical abnormalities include hyponatemia, hyperkalemia, hypercalcemia, hypoglycemia, azotemia with concurrent inability to produce concentrated urine, reverse stress leukogram, lymphocytosis, eosinophilia and hypocholesterolemia (Kintzer and Peterson, 1997).

One should keep in mind that dogs with atypical Addison's disease do not have electrolyte abnormalities. (Hauck et al., 2020). The CBC abnormalities are due to cortisol deficiency and can be found in animals with both typical and atypical hypoadrenocorticism. An ACTH stimulation test may be preceded by basal cortisol measurement, as values greater than 55 mmol/L (2 mcg/dL) can be used to rule out hypoadrenocorticism (Lennon et al., 2007; Bovens et al., 2014). Dogs with values below 55 mmol/L should undergo ACTH stimulation testing to rule the disease in or out.

Diagnostic Imaging

Diagnostic imaging (ultrasound/radiology) of the gastrointestinal tract is not routinely indicated in dogs with acute diarrhoea. It should be considered in dogs with concomitant, non-transient, vomiting and in dogs with marked or progressive abdominal pain or distension.

Rationale

Diagnostic imaging is generally unrewarding in dogs with diarrhoea. It is mainly relevant in dogs with acute diarrhoea when gastrointestinal obstruction and/or involvement of other organ systems, such as pancreatitis, is suspected (Finck et al., 2014; Mapletoft et al., 2018; Holzmann et al., 2023).

Testing for Parvovirus

Testing for canine parvovirus (CPV) enteritis (e.g., Point of Care ELISA, PCR) is indicated in young dogs (< 6 months of age) with acute diarrhoea; in young dogs (<12 months of age) with acute hemorrhagic diarrhoea; in unvaccinated/inadequately vaccinated dogs of any age, and should be considered in dogs with neutropenia. CPV testing is also indicated whenever there is an outbreak of

diarrhoea in a group of (unvaccinated/inadequately vaccinated) dogs. Given the lower sensitivity of the POC test for parvovirus, in cases of a negative result coupled with a strong clinical suspicion, it is advisable to perform a confirmatory PCR test.

Rationale

Commonly, CPV infects 4–12-week-old puppies that are prone to acquiring the virus in concomitance with waning maternally derived antibodies. Adults are thought to be less prone to CPV infection due to the age-reduced susceptibility and presence of specific immunity induced by vaccination or previous (often subclinical) infections. There are some reports of the occurrence of parvovirosis in adult dogs, but they are rare (Cavalli et al., 2001, Decaro et al., 2008a, Decaro et al., 2009a). The most characteristic clinical form induced by CPV is represented by hemorrhagic enteritis. Leukopenia is a consistent finding, with white blood cell (WBC) counts dropping below 2000–3000 cells/µL (2.0-3.0 x 10^9 cells/L) of blood (Cavalli et al., 2001, Decaro et al., 2008a, Decaro et al., 2009a).

Testing for bacterial enteropathogens

Testing for bacterial enteropathogens is not routinely recommended in dogs with acute diarrhoea. Faecal testing can potentially be indicated in dogs with severe disease that are of increased risk of pathogen transmission (e.g., fed a raw diet) or when several individuals in a household, including dog owners, or in the local region show similar clinical signs. Testing for *Clostridium difficile* (PCR combined with ELISA for toxin A/B), *Campylobacter jejuni/coli* (PCR or culture), and *Salmonella* spp. (PCR or culture) could be considered in these cases. However, antimicrobial treatment is not recommended beyond the resolution of clinical signs even when test results prove positive for enteropathogens. Bacterial culture of blood, abdominal fluid or lymph node aspirates should be considered if sepsis or bacteraemia/bacterial translocation is suspected.

Rationale

Canine acute diarrhoea is self-limiting, and faecal testing is thus unlikely to change treatment recommendations (Cave et al., 2002). Dogs that are fed a raw diet are at increased risk of transmitting antimicrobial resistant bacteria, as well as *Salmonella* spp and *Campylobacter* spp (Viegas et al., 2020). Testing in these animals can be considered to elucidate the zoonotic risk, a positive test result is not an indication to treat with antimicrobials. *Clostridium perfringens* is part of the microbiota in healthy dogs (Werner et al., 2021), and although strains encoding for NetF-toxin might play a role in acute haemorrhagic diarrhoea syndrome, testing is still not recommended since a positive result does not change treatment recommendations (Sindern et al., 2019). If testing for *C. difficile* is performed, an

ELISA for toxin A/B should be included as this could be part of the aetiology in a small number of individuals (Rainha et al., 2022). Haemolytic *E. coli* is found in the gastrointestinal microbiota in healthy dogs, as well as in dogs with diarrhoea, and testing is not recommended (Werner et al., 2021).

Fecal flotation and testing for *Giardia*

Testing for *Giardia* should be considered in young dogs with acute diarrhoea and is particularly indicated in those with non-self-limiting or relapsing disease.

Rationale

Protozoa or parasites are infrequently the primary cause of diarrhoea and might be a coincidental finding with a prevalence of 7-17 % (Drake et al., 2022) in healthy dogs and somewhat higher prevalence in hunting or shelter dogs (Uiterwijk et al., 2019). Most cases are not associated with clinical signs. Nevertheless, parasites are thought to lower the threshold for diarrhoea caused by other factors and are typically treated in dogs with clinical disease. qPCR is by far the most sensitive test for Giardia detection and might be useful to assess the zoonotic risk, but may not reflect a clinically relevant protozoal load causing diarrhea (passage of ingested cysts through the intestine). Fecal antigen testing and fecal flotation are probably the most widely used tests in veterinary practice for *Giardia* detection. Antigen testing is more sensitive than fecal flotation (Uiterwijk et al., 2018) and the combined use of both methods improves detection (Drake et al., 2022).

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