

# Critical review on the usage of antimicrobials and on the restoration of the intestinal environment in canine acute and chronic diarrhea



Antimicrobials (AMs) are used in many cases of acute and chronic diarrhea in the dog. The aim of the present manuscript is to critically review the current literature trying to define how frequently bacteria effectively cause acute and chronic diarrhea and which are the most frequent clinical effects of antimicrobials' use. In addition, a brief overview of the main approaches to restore the intestinal environment is given.

It resulted that antimicrobials do not always improve the clinical condition, unless bacteria are an established cause of the observed clinical signs (e.g. diarrhea), as rarely happens, or the related complications (e.g. sepsis). AMs should not be used empirically as a tool in the diagnostic work-up, neither in acute nor in chronic diarrhea and the presence of fresh blood in stools should not necessarily imply the obligation to resort to antimicrobials use.

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## INTRODUCTION

Antimicrobials (AMs) resistance is one of the most complicated and actual worldwide challenge regarding human health (without forgetting the economic implica-

tions), with a lethality due to bacterial infections of around 10 million a year.<sup>1</sup> A condition well known also in Europe, especially in the South-Eastern countries.<sup>2,3</sup> The main widely recognized approaches to the problem are: reduction and rational use of AMs, as underlined by European Medicines Agency,<sup>4</sup> and new therapeutic approaches to antibiotic-resistant bacteria.<sup>1</sup> To be successful in such a challenge, a fundamental role should also be played by veterinarians, in the “One Health” perspective.

AMs employment in veterinary medicine is a common approach,<sup>5,6</sup> both in acute and chronic diarrhea, clinical conditions defined respectively as a short- or long-term increase in fecal water content of stools, and/or increased

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volume and defecation frequency, due to a decreased intestinal absorption and/or increased intestinal secretion and peristalsis (Fig. 1).<sup>7</sup>

In order to apply a rational use of AMs, and therefore to define in which cases they could be really needed, it is important to evaluate first of which clinical conditions the bacteria are responsible for, and/or in which cases their secondary involvement requires AMs, considering that most of bacterial enteropathogens are responsible for self-limiting enteropathies.<sup>8</sup> Exceptions may be represented by mucosally invasive *Escherichia coli* causally associated with the etiopathogenesis of periodic acid-Schiff-positive granulomatous colitis of Boxer dogs, French Bulldogs, and breeds in the mastiff cluster, in which antimicrobial treatment guided by susceptibility profiling is associated with positive long-term outcomes.<sup>9</sup> Further exceptions are represented by novel toxigenic *C. perfringens*<sup>10</sup> enteropathy, or by anecdotal cases such as a recent one by *Clostridium sordellii*.<sup>11</sup>

If we consider cases of acute diarrhea and in particular of canine idiopathic “acute hemorrhagic diarrhea syndrome” (AHDS - previously also called hemorrhagic gastroenteritis)<sup>12</sup>, although the involvement of *Clostridium perfringens* enterotoxin and *Clostridioides difficile* toxin

**In order to reduce the antimicrobial resistance and the related lethality, a fundamental role should also be played by veterinarians with a judicious use of antimicrobials.**

A/B in such conditions has been described as questionable,<sup>13</sup> it has been reported an association with bacterial pathogens (*C. perfringens*),<sup>14</sup> particularly if encoding pore-forming netF toxin.<sup>10,15</sup> However, the use of AMs should be restricted to selected cases, since their routine use in AHDS seems to add no benefit because of disruption of protective intestinal microbiota, stimulation of toxin production, and development of resistant bacteria and long-term dysbiosis.<sup>12</sup> AMs are frequently prescribed in cases considered moderate or severe, in cases associated with hyperthermia (> 39.0°C), and in cases in which weight loss and/or blood in stools are present, reaching a percentage of around 50% of the total as shown in a recent retrospective observational study performed on 3,189 cases.<sup>16</sup> Higher rates of AMs administration (65%) were achieved in a retrospective multicenter study always on acute diarrheic dogs, disregarding in some cases national and international guidelines of prudent AMs use.<sup>17</sup> Such considerations become even



**Figure 1** - Fresh blood and mucus in the stools of a dog with acute diarrhea.

more stringent if talking about the etiologic role of bacteria in chronic diarrheic dogs, which is considered an unlikely event.<sup>9,18</sup> Interestingly, it has been recently reported the presence of *Clostridioides difficile* in feces of chronic diarrheic dogs, which did not respond to AMs but whose clinical signs were solved after dietary changes, allowing the reader to re-consider the causal link between bacterial infections and chronic enteropathies.<sup>19</sup>

In order to better understand the effects of AMs administration on the gastrointestinal and systemic health of a subject, it is important to point out that the maintenance of an eubiosis condition of the gastrointestinal tract is of great importance and associated with local and general health status, and that disorders of such district are associated with dysbiosis and vice versa (Fig. 2).<sup>20-23</sup> Other important factors that may influence microbiota composition are diet (including pre-probiotics) and drugs.<sup>24-29</sup> Among the latter, gastroprotectants and above all AMs are those compounds responsible for major changes.<sup>30-33</sup>

The present critical review aims to analyze the evidence on the real need of using AMs in acute and chronic diarrheic dogs, and on possible alternative approaches that may help in managing the dysbiosis associated to the diarrhea.

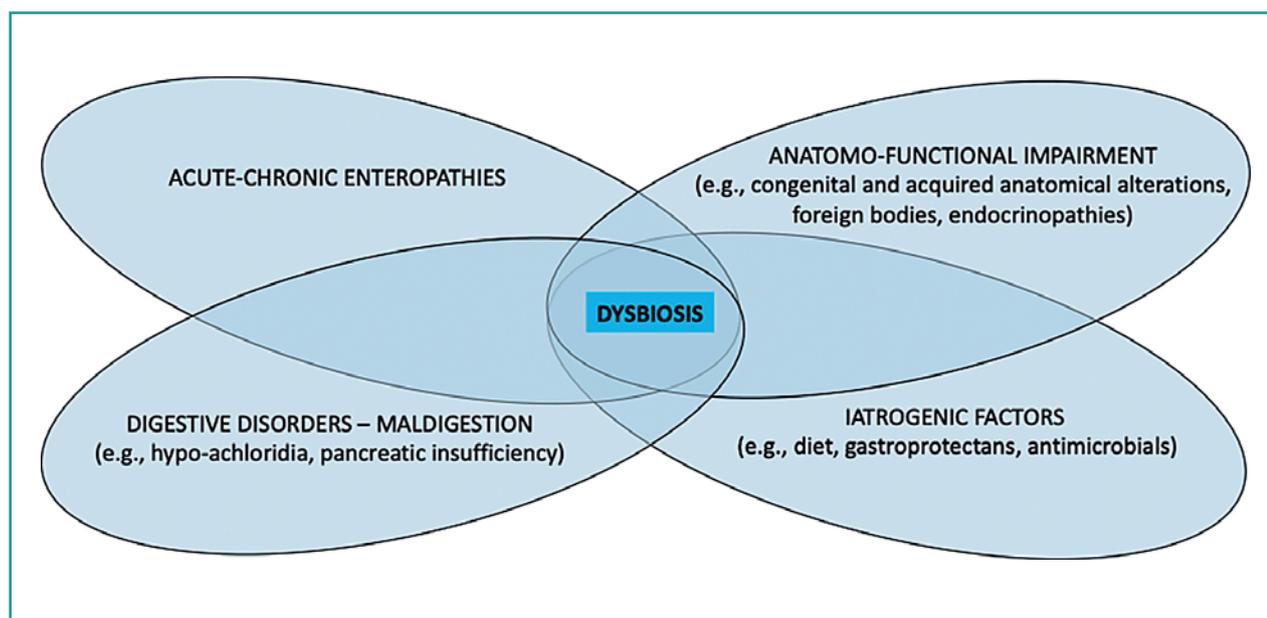
## ANTIMICROBIALS IN ACUTE DIARRHEIC DOGS

As previously reported, AMs are still widely used in dogs presenting acute diarrhea (AD), a pathological condition due to different causes: dietary indiscretion, dietary intolerance, food poisoning, ingestions of drugs (i.e. non-steroidal anti-inflammatory drugs), intestinal parasites/infections, acute liver or kidney failure or hypoa-

**In most acute diarrheic dogs a symptomatic therapy has been demonstrated to be enough to solve the clinical setting.**

drenocorticism.<sup>12</sup> Therefore, since in some cases they have to be considered necessary (e.g., some complicated virosis)<sup>34,35</sup>, much of the most recent literature suggests that their use should be carefully considered in such a way that they can then be effective when needed. Furthermore, diarrhea can be associated with certain “lifestyle risks” (i.e. scavenging habits)<sup>36</sup> reinforcing the concept that specific therapy may not be necessary, being in most cases enough a symptomatic one. Besides, although disease severity markers may be important, supportive treatment has been demonstrated to be enough to solve the clinical settings in a high percentage of dogs with systemic inflammatory response syndrome (SIRS).<sup>37</sup> On the other hand, it has been demonstrated that the amount and the morphological features of band granulocyte neutrophils give important information regarding canine SIRS prognosis, and the presence of degenerative left shift<sup>38</sup> and neutrophilic toxicity<sup>39</sup> has been associated with sepsis and showed as negative prognostic makers, making it necessary, exclusively in these cases, the prescription of antimicrobials.<sup>40</sup>

With regard to AHDS, the lone presence or absence of a left shift seems not to give enough clinical information to establish a prognosis in these patients, and most dogs do not benefit from antibiotic treatment<sup>41</sup>. Moreover, it has been shown that *C. perfringens netE* and *netF* toxins genes can be found with a significantly higher prevalence in diseased than in control dogs, represent-



**Figure 2** - Interlink between dysbiosis and other GI (and non-GI) conditions<sup>85</sup>.

**With regards to the acute hemorrhagic diarrhea syndrome, the use of antimicrobials does not reduce mortality nor length of hospitalization.**

ing an aspect to be considered and further investigated, though its presence alone does not necessarily require recurring to AMs.<sup>42</sup> Parallely, also the role of bacteremia in AHDS has been investigated suggesting this occurrence as not frequent, and not such as to justify the routine use of AMs to prevent sepsis.<sup>34</sup> Nevertheless, despite this evidence, it is important to point out that AMs are quite frequently used in dogs with AHDS, as reported in a large prospective case-control study performed on dogs with such condition, in which AMs were used in 53 out of 108 patients.<sup>41</sup> In a prospective blinded study performed on dogs with hemorrhagic gastroenteritis (now AHDS) treated either with amoxicillin/clavulanic acid or placebo, it has indeed been demonstrated that no significant differences were found between the two groups, concerning mortality and course of the disease (clinical severity and length of hospitalization).<sup>35</sup> Similarly, a further prospective, placebo-controlled, double-blinded study (amoxicillin-clavulanic acid *vs* placebo) showed non clinical differences between two groups of dogs presenting uncomplicated acute diarrhea while, on the other hand, the administration of amoxicillin-clavulanic acid led to an increase of resistant fecal *E. coli*.<sup>43</sup> Furthermore, in cases of hemorrhagic diarrhea, the addition of metronidazole to amoxicillin-clavulanic acid (plus fluid therapy, buprenorphine, and omeprazole) reduced neither the hospitalisation time nor the clinical evolution if compared to dogs treated with a single AM (i.e. amoxicillin-clavulanic acid).<sup>44</sup> Apparently partially in disagree with the above data, are the results of a recent study investigating the effects of metronidazole administered to dogs with acute non-specific diarrhea. In this study, indeed, clinical recovery was achieved slightly before in treated dogs than in controls. However, the authors conclude that such results do not necessarily mean that metronidazole should be used in such cases, as most of them may solve regardless of the treatment instituted.<sup>45</sup> Unfortunately, the exact cause of acute diarrhea is frequently undiagnosed and, as a consequence, the therapeutic approach is often represented by treatment with diet, probiotics, and, in some cases improperly, by AMs (Fig.3).<sup>46</sup>

### INTESTINAL ENVIRONMENT RESTORATION IN CANINE ACUTE DIARRHEIC DOGS

Aside from the debatable use of AMs, the management of the acute diarrheic dog mainly relies on patient sup-

port,<sup>47</sup> but also the microbiota modulation/restoring appears as a fundamental aspect (Fig. 3). With this aim, pre-probiotics have been widely investigated. As example, the administration of a canine derived single-strain probiotic in dogs with acute idiopathic diarrhea allowed a faster resolution of the clinical condition and a lower use of metronidazole with regard to the placebo group.<sup>48</sup> Similarly, in three additional studies performed in dogs with acute self-limiting uncomplicated diarrhea, where single-strain or multi-strain probiotics were used, analogous results were obtained, i.e., reduced time to fecal normalization compared to placebo treated patients.<sup>49-51</sup> Also another multi-strain probiotic mixture led to a faster recovery in dogs presenting with acute hemorrhagic diarrhea without signs of sepsis, a condition however considered to be possibly characterized by rapid and self-limiting course, as already formerly reported.<sup>52</sup> On the

**Probiotics are likely to be beneficial for parvovirus infection or acute hemorrhagic diarrhea syndrome, while in dogs with uncomplicated acute diarrhea their benefits are variable and further studies are needed.**

contrary, the administration of an additional multi-strain probiotic mixture failed to reach statistical significance when compared to metronidazole or placebo with regard to time to fecal improvement.<sup>53</sup> Finally, although many studies refer to possible positive effects resulting from the administration of probiotics, a recent systematic review on the efficacy of probiotics in managing and preventing gastrointestinal disorders concludes that such interventions may allow limited benefits, suggesting that further studies are needed.<sup>54</sup> More specifically, probiotics are likely to be beneficial in some acute or infectious gastrointestinal conditions in dogs and cats, such as parvovirus infection or AHDS, while in dogs with uncomplicated acute diarrhea their benefits are variable, even when similar bacterial strains are used.<sup>48,52,55-59</sup>

As a future promising tool, there is growing interest in the potential of fecal microbiota transplantation (FMT) in the management of gastrointestinal disorders in dogs, both in acute and chronic conditions.<sup>60</sup> However, only few studies are available on the literature both for the former and the latter conditions. The technique consists of administering fecal material from a healthy donor to a patient with the goal of modulating its intestinal microbiome. It has been recommended in human patients with recurrent *Clostridium difficile* infection, but it might also be successful for other types of gastrointestinal diseases.<sup>61</sup> FMT efficacy in treating postweaning diarrhea was evaluated on puppies receiving fecal inoculum from

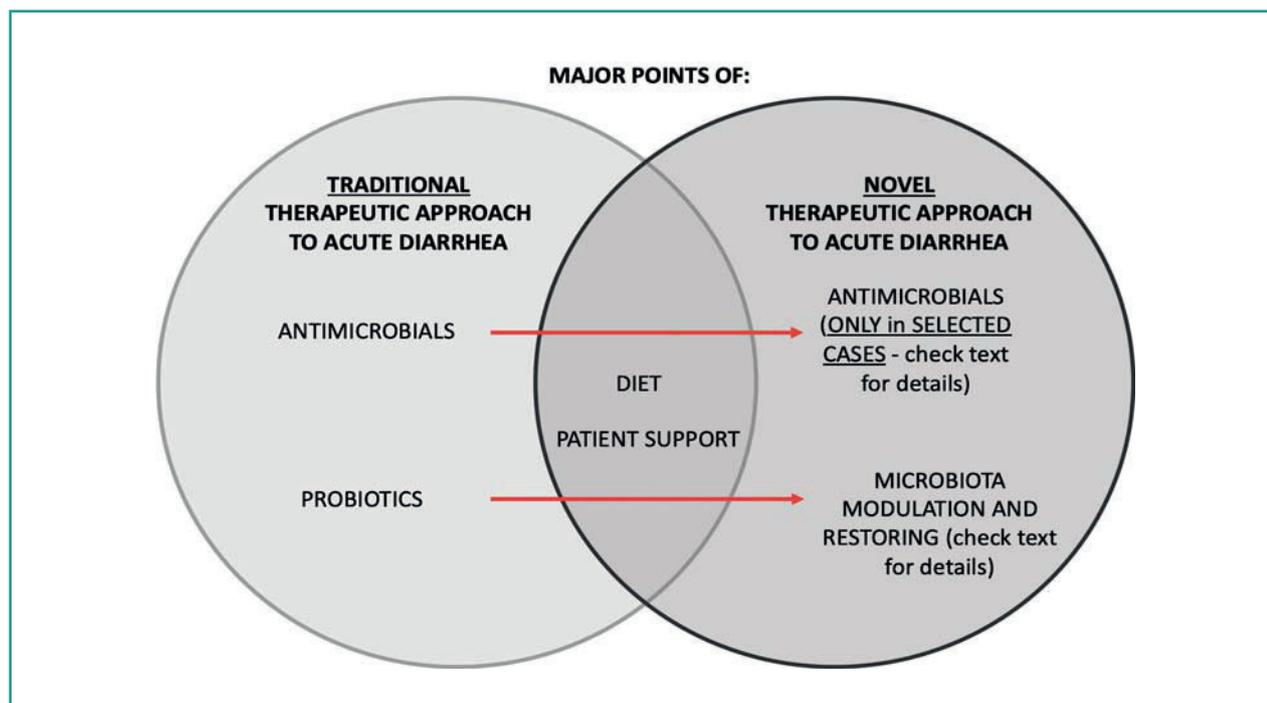


Figure 3 - Changes in the management of acute diarrhea.

their respective dams but, unfortunately, the study did not reach any conclusion on the efficacy of FMT in this disorder as no episodes of diarrhea occurred neither in treated dogs nor in controls.<sup>62</sup> Another study was on the efficacy of FMT (plus standard therapy) during parvoviral infection, and in this case, interesting results were achieved as treated dogs experienced a faster clinical improvement and a shorter length of hospitalizations time, compared with controls treated with standard therapy only.<sup>63</sup> Also noteworthy are data rising from a study comparing FMT and oral metronidazole in acute diarrheic dogs. It showed that although fecal consistency improved in both groups, both at the first time point (7 days from the beginning of the therapy) and at the second one (28 days after the beginning of the therapy), there was a significant difference between the two groups in favor of FMT at the second time point. Interestingly, especially the dysbiosis index (a qPCR-based measure of microbiota changes)<sup>64</sup> behaved differently, as it improved in FMT group while got worse in the metronidazole treated group, at both time points with respect to T0.<sup>65</sup>

**Antimicrobials have been suggested for years as empirical therapy in dogs with chronic diarrhea.**

### ANTIMICROBIALS IN CHRONIC DIARRHEIC DOGS

AMs are widely used not only in dogs suffering from

acute diarrhea but also in dogs presenting chronic diarrhea, often empirically as a tool in the diagnostic work-up, along with parasiticides, dietary interventions, and immunosuppressive drugs (Fig. 4).<sup>66-68</sup> Historically, cases of chronic diarrhea in dogs without detectable underlying causes and that were responsive to antibiotic treatment were termed small intestinal bacterial overgrowth (SIBO).<sup>69</sup> For decades, these treatments have represented a suggested and effective strategy for diagnosing and managing some forms of canine chronic enteropathies (CE),<sup>70,71</sup> so that antibiotic-responsive diarrhea/antibiotic-responsive enteropathy (ARE) has been recognized as one form of CE.<sup>72</sup> However, it is also to be noticed that the association among suspected bacterial imbalance, diarrhea, and AMs was suggested earlier than the complexity of the intestinal microbiome and of its implications in maintaining intestinal homeostasis was began to be understood.<sup>69</sup> ARE is reported clinically indistinguishable from other types of CE and it is associated with intestinal microbiota dysbiosis. It should respond well to the administration of AMs, most often tylosin, metronidazole, or oxytetracyclines, but most dogs relapse within few weeks when the antibiotic is discontinued.<sup>68,69,73,74</sup> Also interesting is that it has been reported that some AMs (in particular metronidazole) may have anti-inflammatory or immunomodulatory effects.<sup>75</sup> Moreover, it was observed an increase of potentially probiotic bacteria following the administration of tylosin to some dogs with ARE.<sup>67</sup>

However, since AMs have been suggested for years as empirical therapy in dogs with chronic diarrhea, this practice has led to their unnecessary administration or over-

**Since the administration of antimicrobials cause severe long-lasting dysbiosis, bacterial resistance and promotion of the inflammatory processes, their use should be discouraged in dogs and cats with chronic enteropathy.**

use, also considering the variable number of dogs that are actually diagnosed with ARE<sup>68,70,76,77</sup> and their possible overestimation. In addition, in a randomized-controlled trial of dogs with CE, oral prednisone alone has been demonstrated to be clinically as effective as prednisone plus metronidazole, suggesting that the use of AMs might not always be necessary.<sup>78</sup> Results of another small pilot study indicate that metronidazole and tylosin were not successful in arresting mitogen-stimulated proliferation of lymphocytes, in contrast to conjugated linoleic acid.<sup>79</sup> It is known that not only acute and chronic gastrointestinal inflammatory diseases but also the administration of AMs cause severe changes in the intestinal microbiome in dogs and cats.<sup>20,31,33,80-83</sup>

The resulting dysbiosis has measurable repercussions on the metabolome that may negatively affect the host's health, leading to higher susceptibility for translocation

of pathogens, toxins, or dietary antigens. Moreover, the immune system can be affected, which in turn promotes proinflammatory processes.<sup>84,85</sup> Recent research has shown the beneficial effects of secondary bile acids (BA) on the host, and how *Clostridium bifermentans* is the main BA-converting bacterial species in dogs.<sup>65,86,87</sup>

AMs such as tylosin or metronidazole led to reduction of *C. bifermentans* and secondary BA conversion. This, in turn, causes long-lasting subclinical dysbiosis.<sup>65</sup>

Very recently, it was shown that the administration of tylosin induced dysbiosis in healthy dogs and eubiosis was not uniformly restored following tylosin discontinuation.<sup>33</sup>

Also, metronidazole and amoxicillin administered orally to healthy dogs reduced fecal bacterial diversity, and increased the number of multiple resistance fecal *E. coli* during and after treatment.<sup>88,89</sup> Antibiotic resistance represents a serious problem worldwide and could be passed from commensal bacteria or probiotics to potential pathogens sharing the same intestinal environment.<sup>90</sup> More specifically, dogs are considered a possible reservoir of antibiotic resistant strains, potentially dangerous for humans.<sup>91</sup> Because of these negative effects (even though some studies refer to healthy patients), the use of AMs for non-antimicrobial effects should be discouraged in dogs and cats with CE, unless effectively needed for their primary action,<sup>9,18,92</sup> while new multimodal therapeutic approaches to restore eubiosis should be used first.

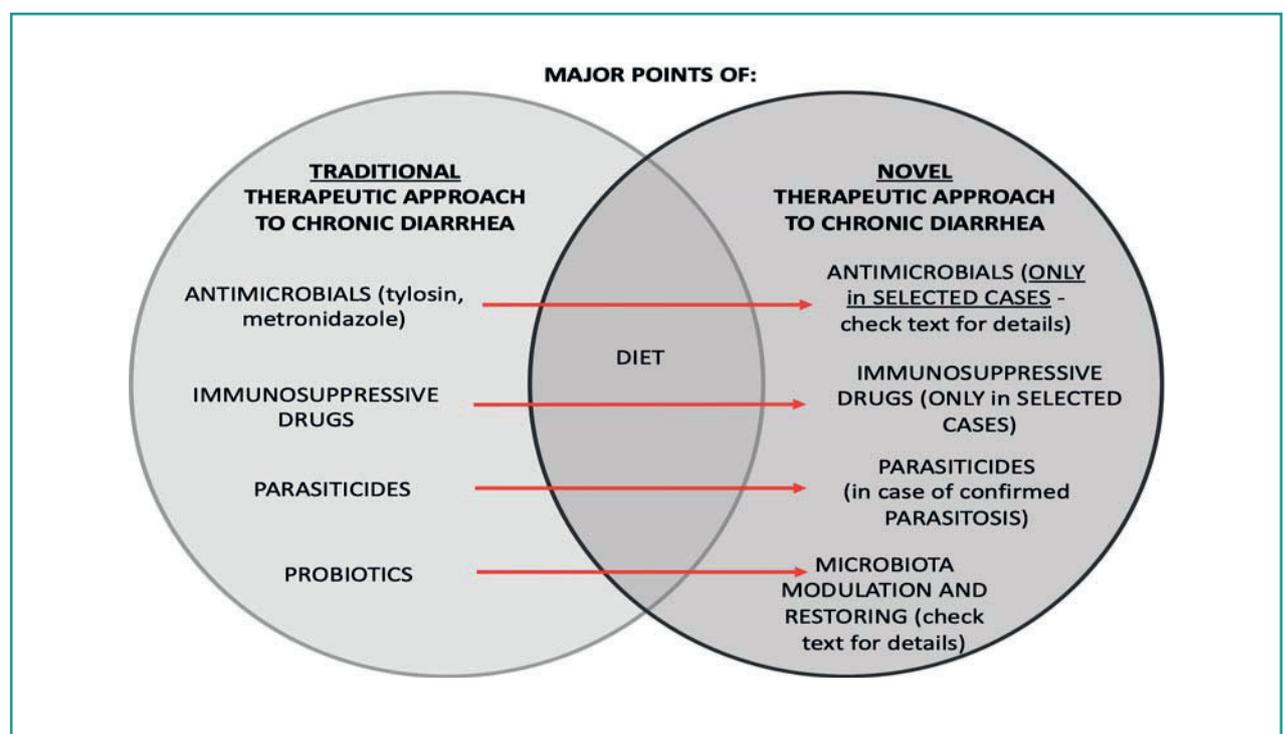


Figure 4 - Changes in the management of chronic diarrhea<sup>18</sup>.

## INTESTINAL ENVIRONMENT RESTORATION IN CANINE CHRONIC DIARRHEIC DOGS

There is growing interest and clinical evidence supporting new multimodal therapeutic approaches to modulate bacterial populations, which could include the administration of prebiotics, probiotics, synbiotics, and fecal microbiota transplantation. However, it is currently unclear if these treatments can be used as an adjunctive or a replacement for current therapies. In most studies, there is no treatment response up to 40% of dogs with CE, and the long-term response seems to be adequate only in food-responsive dogs.<sup>93,99,100</sup> This raises questions regarding the adequacy of current treatments and the need for a better understanding of the different pathogeneses leading to CE and for new treatments. Indeed, the most commonly prescribed treatments for dogs and cats with CE are directed toward suppressing the overactive immune responses causing chronic gastrointestinal signs. However, there is an important role for non-immunosuppressive therapies that may decrease mucosal inflammation, counter microbial dysbiosis, and promote a more favorable risk-benefit profile in patients.<sup>101</sup>

To date, there is some evidence that probiotics or synbiotics add little benefit when treating food- or antibiotic-responsive canine CE,<sup>73,81,102-104</sup> but could be promising adjunctive treatments in canine inflammatory bowel disease. Indeed, in immunosuppressive-responsive enteropathy, specific probiotic strains or mixtures can decrease clinical severity as well as induce a more tolerogenic microenvironment in the intestinal mucosa,<sup>105-106</sup> and, also, improve the integrity of the intestinal barrier.<sup>107</sup> However, molecular effects

**To date, probiotic or synbiotics add little benefit to food-responsive canine chronic enteropathy, and could be promising in immunosuppressive-responsive enteropathies. Further studies are needed.**

of probiotics are not only specific to the genus of the bacteria used, but even species or strain specific.<sup>108</sup> This, in addition to several limitations of the studies available in chronic gastrointestinal conditions, such as nonspecific inclusion criteria, lack of control group, or insufficient statistical power, emphasizes the need for more well-designed studies evaluating the potential benefit of probiotics in CE.

As previously reported, another therapy attracting a lot of attention currently is fecal microbiota transplantation (FMT).<sup>109</sup> However, the effects of FMT in chronic gastrointestinal disorders are much less well documented, although the existing data consisting of case reports and small case series seem to document that the technique may be beneficial in some instances.<sup>110-113</sup>

Notwithstanding, dogs with chronic diarrhea may improve for a few days to a week after FMT, but generally relapse thereafter, requiring multiple FMTs over time. Unfortunately, donor selection, exact indications, and dosage of FMT in dogs is currently unknown, and more data are needed to define which canine patients could be helped by FMT.<sup>18,60</sup>

**The proper use of antimicrobials is of primary importance in both human and veterinary medicine.**

## CONCLUSIONS

In the light of the risks associated with the isolation of antimicrobial resistant bacteria, the importance of AMs, and patient-related risks (i.e. antibiotic-associated gastrointestinal signs),<sup>114</sup> the proper use of AMs is of primary importance in both human and veterinary medicine. It is the opinion of the authors, as also reported in the literature,<sup>8,12,18,35,43</sup> that in case of acute or chronic diarrhea AMs should be used with great caution and should not be administered in the absence of systemic signs of disease/inflammation/sepsis or true infections (i.e. depressed mental status, tachycardia, tachypnea, hypotension, hyperthermia, hypothermia), and of immunocompromising underlying disease (i.e. immunosuppressive treatments, neutropenia). Regarding intestinal infections, as traditionally diagnosed by culture, it should be properly considered that fecal standard microbial tests recently showed to be unable to differentiate between healthy dogs and dogs with chronic diarrhea.<sup>115</sup> The presence of fresh blood in feces should not be a reason itself for AMs administration, and AMs should not be used empirically as a tool in the diagnostic work-up, neither in acute nor in chronic diarrhea. Supportive cares and dietary management represent a first line successful approach, possibly including the use of pre-probiotics although supplementary studies are deemed necessary in this direction.

PUNTI CHIAVE

- Supportive care, dietary management, and possibly pre-probiotics, should represent the first line approach for acute and chronic canine diarrhea
- The presence of fresh blood in feces should not be a reason itself for antimicrobials administration
- Antimicrobials should not be used empirically as a tool in the diagnostic work-up, neither in acute nor in chronic diarrhea
- Antimicrobials should be administered to dogs with acute and chronic diarrhea only in the presence of systemic signs of disease/inflammation/sepsis, true infections or immunocompromising underlying disease

Review critica sull'utilizzo degli antimicrobici e sul ripristino dell'ambiente intestinale nelle diarree acute e croniche del cane

Riassunto

*Gli antimicrobici vengono spesso utilizzati per la gestione terapeutica delle diaree acute e croniche del cane. L'obiettivo del presente lavoro è quello di fornire una revisione critica della letteratura attuale sull'argomento, individuando in quali casi i batteri possono effettivamente causare diarree acute e croniche, e descrivendo da un punto di vista clinico i più frequenti effetti collaterali dell'impiego degli antimicrobici. Inoltre, viene fornita una breve panoramica sui principali approcci terapeutici volti alla "riabilitazione" dell'ambiente intestinale.*

*Gli antimicrobici non sempre migliorano il quadro clinico, a meno che i batteri non siano una causa accertata dei sintomi clinici osservati (p.es. diarrea), come raramente accade, o delle eventuali complicazioni correlate (p.es. sepsi). L'approccio alle diarree acute e croniche non dovrebbe prevedere sistematicamente il ricorso ad una terapia empirica antimicrobica, né la presenza di sangue fresco nelle feci dovrebbe implicare necessariamente il ricorso a tale terapia.*

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