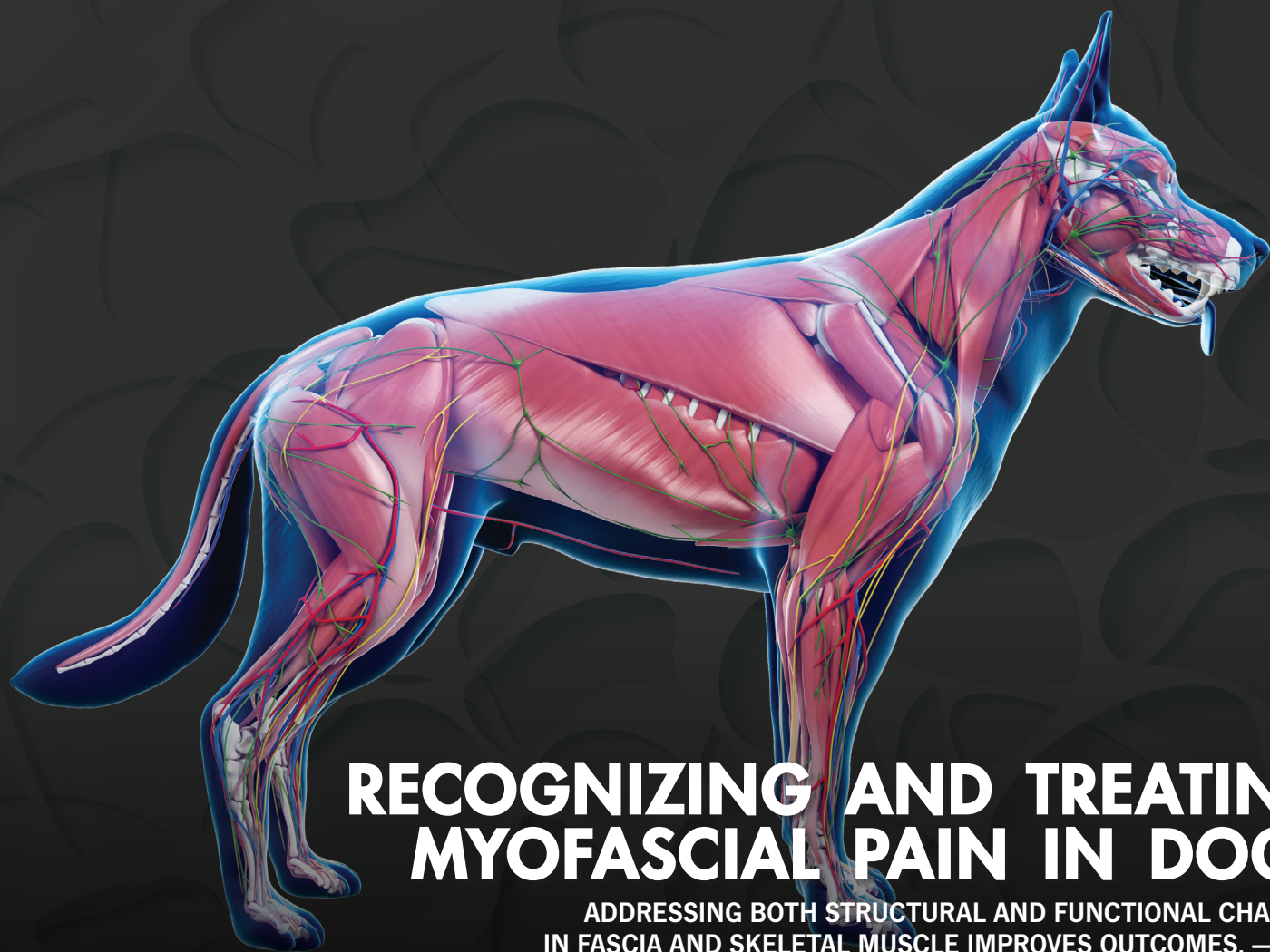




RECOGNIZING AND TREATING MYOFASCIAL PAIN IN DOGS

ADDRESSING BOTH STRUCTURAL AND FUNCTIONAL CHANGES IN FASCIA AND SKELETAL MUSCLE IMPROVES OUTCOMES. — P. 37

HOW OZONE THERAPY TREATS INFECTIONS

Ozone therapy can be an effective and cost-effective weapon in the fight against viral, bacterial, and fungal infections in animals. — P. 29

DIAGNOSING GASTROINTESTINAL AND PANCREATIC DISEASES IN DOGS

A look at some of the currently available or pending tests that help get to the root of these common canine problems. — P. 10

KEEP FELINE PATIENTS HEALTHY AS THEY AGE

Engaging clients in their cats' care early on can help keep feline patients healthy when they enter their senior years. — P. 45



METRONIDAZOLE — IT'S NOT ALWAYS THE ANSWER

Why you shouldn't automatically reach for this common medication when your patients have diarrhea. — P. 51

INAPPROPRIATE SUPPLEMENTATION IN A PUPPY

Over-supplementation was the suspected cause of imbalance and illness in a German Shepherd pup. — P. 58

SIX WAYS TO PUT YOUR WEBSITE TO WORK

How to use your website to grow and engage your client base, and increase your bottom line. — P. 62



RETHINKING THE ROLE OF **METRONIDAZOLE** IN VETERINARY MEDICINE

This article discusses the appropriate and inappropriate uses of metronidazole, highlights current research that contradicts our older assumptions, and prompts some questioning to determine if this drug is an ideal choice.

BY DAWN KINGSBURY, DVM, PHD, DIP. ACVIM (SAIM),*
ELLEN BARBER,[°] AND HOLLY GANZ, PHD*

When your patients have diarrhea, a course of metronidazole (Flagyl) might be the appropriate treatment. However, this antibiotic has become a knee-jerk response to cases of diarrhea based on good theory and historical practice, rather than scientific evidence. A growing body of evidence-based research suggests that metronidazole is much less effective for some gastrointestinal conditions than previously thought. In addition to potential adverse side effects, we now know that metronidazole can cause unhealthy long-term changes in a pet's gut microbiome.^{1,2}

Because metronidazole has activity against several diarrhetic agents, it has become the most frequently-used antibiotic for nonspecific diarrhea.³ But in some cases, it may be the wrong choice. Several studies have found that metronidazole doesn't help inflammatory bowel disease (IBD)⁴ or acute diarrhea in dogs.⁵

So is metronidazole the right treatment for your patients? Or could we be doing more harm than good by prescribing it?

WHEN IS METRONIDAZOLE THE RIGHT CHOICE?

Metronidazole is an extremely useful antibiotic and antiprotozoal agent that's been around since the 1950s. In both human and veterinary medicine, it has cured life-threatening anaerobic infections. Being bactericidal, metronidazole has the potential to work faster and more efficiently than other antibiotics (e.g. clindamycin).

- Metronidazole is effective against *Bacteroides fragilis*, a normal gut and mouth commensal that can be isolated from wound infections, abscesses, pyothorax, and cholangiohepatitis. Metronidazole has historically been used for suspected anaerobic osteomyelitis, especially involving the jaw and mouth.⁶ However, more recent reviews suggest suboptimal bone penetration.⁷
- Metronidazole works well against *Clostridioides* — a genus of bacteria that includes *C. difficile*, a well-known cause of antibiotic-associated diarrhea in humans and an implicated

cause in animals.⁸⁻¹⁰ With regards to acute, nonspecific, canine diarrhea cases given metronidazole, a one-to-two-day shorter recovery has been reported.¹¹

- In pets, metronidazole has been used to treat *Helicobacter* gastritis. However, resistance is problematic.¹²⁻¹⁴ When polymicrobial sepsis is suspected, it's a valuable and inexpensive addition to the arsenal to broaden anaerobic coverage. Whether used for *Helicobacter* or sepsis, metronidazole is combined with other medications, which can complicate interpretation of in vitro culture and sensitivities.
- Historically, metronidazole was effective against *Giardia*.¹⁵ However, resistance has developed, so again, combination therapy is often recommended for refractory infections.¹⁶

A NEW STUDY URGES CAUTION IN CHOOSING METRONIDAZOLE

Along with the pathogens, most antibiotics also alter the commensal populations needed for health. As a result, important gut microbiome populations can be decimated, leading to

TEST YOUR PATIENT'S MICROBIOME COMPOSITION AFTER A COURSE OF ANTIBIOTICS

After finishing a course of metronidazole or any other antibiotic, it's important to find out what changes the medication might have made to your patient's unique microbiome, especially dysbiosis. Testing your patient's microbiome composition will give you valuable information about the bacterial populations present, along with any missing beneficial taxa, and help you assess how to best support your patient's health.

For example, if your patient's fecal sample shows a deficiency in the important *Fusobacteria* phylum (which metronidazole can reduce), increasing the amount of protein in the pet's diet may help, since *Fusobacteria* flourish in protein-rich environments.^{1,45}

If antibiotic therapy has resulted in missing beneficial bacteria that your patient needs for gut health, FMT material can be administered with a fresh feces enema in-clinic, or via freeze-dried feces made into oral capsules to replenish the missing microbial diversity.

dysbiosis. A new study published this year in the *Journal of Veterinary Internal Medicine* calls attention to metronidazole's dramatic effects on the canine gut microbiome.¹

Healthy dogs were medicated with a 14-day course of metronidazole; more than 50% developed diarrhea during treatment. The gut microbiome composition changed significantly, and included decreases in important beneficial bacteria, such as *Fusobacteria* — one of the dominant phyla of bacteria in the gut microbiomes of dogs and cats — and reductions in overall richness (the number of different bacterial species present). Effects were not temporary: four weeks post metronidazole, microbiome changes had not fully resolved, compromising healthy gut function.

The authors recommend that veterinarians adopt a more cautious approach when using metronidazole, particularly in dysbiotic patients.

QUESTIONS TO ASK WHEN CONSIDERING METRONIDAZOLE FOR A PATIENT

While metronidazole is shown to be an appropriate choice for some conditions, in other cases, it may not be as effective as we have assumed. Consider whether metronidazole will be beneficial for your patient. Here are some questions to ask:

1. Does my patient need antibiotics?

In many cases of canine diarrhea, the answer may be no. Though some health issues, such as life-threatening bacterial infections, do require antibiotics, other conditions may resolve with supportive care alone.

For example, dogs with hemorrhagic gastroenteritis are often given antibiotics, but according to veterinary consensus guidelines, antibiotics are appropriate for this condition only when sepsis is present.^{17,18} Researchers have found that as long as sepsis is not involved, even hemorrhagic gastroenteritis responds just as well to supportive care as to antibiotics.¹⁹

In fact, several studies have shown that metronidazole can actually make diarrhea worse, not only by reducing populations of "good" anaerobic bacteria, but also by altering the intestinal mucus.^{20,21}

2. What are the possible side effects of metronidazole?

Most medications have potential adverse side effects. Metronidazole has a very bitter taste and often causes excessive salivation, drooling, gagging, or frothing at the mouth, especially in cats. In both cats and dogs, the drug may also cause nausea and hyporexia. Pets taking metronidazole may eat less than

usual or refuse meals altogether. Vomiting and diarrhea are also relatively common. More serious, though less common, adverse effects include lethargy, weakness, hepatopathy, central nervous system signs such as nystagmus, head tilt, loss of balance and coordination, stumbling, knuckling, or even seizures. Teratogenicity has been recorded in rodents, though not humans.²² Rare idiosyncratic reactions in dogs have included pancytopenia.²³ In cats, metronidazole has been found to cause reversible DNA damage to lymphocytes.²⁴ Given long term and at a high dose in female mice, tumor-promoting effects are documented, and its carcinogenic potential has been questioned in people.^{25,26}

3. Does my patient have any conditions that would make a bad reaction more likely?

Metronidazole should not be used when a patient has had an adverse reaction to it in the past. While some medications have been shown to increase the metabolism of metronidazole (e.g. prednisone and phenobarbital), no medications have been shown to clearly decrease metabolism.²⁷ Don't use metronidazole if your patient might be pregnant.²⁸ If your patient has liver disease, metronidazole should be used very cautiously and at a lowered dose. It should also be used cautiously in any animal with a compromised nervous system or suspected neoplasia.

4. Are there any supplements that can be combined with metronidazole to improve the outcome for my patient?

- Certain probiotics may help support better outcomes and reduce side effects. In a study of shelter dogs with diarrhea, a combination of the probiotic *Enterococcus faecium* SF68 and metronidazole led to better overall results than metronidazole alone.²⁹
- When silymarin (an anti-inflammatory flavonoid derived from milk thistle seed) was combined with metronidazole to treat *Giardia* in another study, dogs had better appetite, less intermittent vomiting, and less weight loss than when receiving metronidazole alone.³⁰
- Adding the yeast *Saccharomyces boulardii* to a pet's food may reduce the risk of antibiotic-associated diarrhea.³¹ *S. boulardii* is a probiotic that works by supporting beneficial gut bacteria and inhibiting the growth of pathogenic bacteria.

5. What are the alternatives to metronidazole?

Are there alternatives to metronidazole for treating aspects of your patient's gastrointestinal (GI) signs? Hippocrates is often credited with the maxim, "Let thy food be thy medicine and medicine be thy food." Veterinarians have long used dietary modification in disease management. Given the plethora of amassing scientific evidence, diet is



INTERNATIONALLY AWARDED FOR EXCELLENCE & SCIENTIFIC ACHIEVEMENT.
(All awards authenticated by state of MN)

EVOLUTION DIET
PET FOODS & ANIMAL CARE

Use Evolution Ultra Life Organic - Non GMO
Cat - Dog Foods for Best Health & Longest Life!
A 2018-2019 University Of Guelph, Ontario Veterinary College Study Proves EVOLUTION DIET types of Cat - Dog Foods provide Better Health than ALL Flesh Based Foods Respondents used in the Study.

Free Assessment-Consultation By Phone

Available at:
Evolution Animal Care
St. Paul, Hwy 36 at Hwy 61
Vecado.com
1-800-256-1518

Get a Free Copy of our COVID - 19
Human Avoidance & Healing Protocol
651-228-0632
www.petfoodshop.com

A qualified supplement compound technology practice working in thousands of previous cases that incorporates vitamin, botanical, seed extracts, mineral compounds applications for disease. Not a medically qualified veterinary practice that uses chemicals, drugs or surgery. A practice authorized by the State of MN.



LESS LAUNDRY, CALMER PATIENTS

- ✓ Available in a variety of sizes
- ✓ Great for use during exams, treatment and recovery
- ✓ Reduces laundry by up to three loads per day!

Designed to reduce laundry in practices, the Bella Bed is made of scratch- and puncture-resistant material that can hold up to the regular use of disinfectants.

Each of these durable hospital mats are welded shut so nothing can penetrate the inner cavity.

BELLA
Veterinary Medical Solutions

BELLAVMS.COM

A PERSPECTIVE ON ANTIBIOTIC USE IN VETERINARY MEDICINE

Antimicrobial therapies, including antibiotics, have had a profound impact on both human and animal health. Prior to Alexander Fleming's discovery in 1928 that penicillin inhibited the growth of bacteria, no treatments existed for infections such as pneumonia, gonorrhea, and rheumatic fever. Many surgical procedures and chemotherapies that are common today would not be possible without the availability of antimicrobial therapies.

ANTIMICROBIAL STEWARDSHIP

However, as Fleming himself warned, the overuse of antimicrobials can lead to the development of antimicrobial resistance, not only in the bacterial pathogens being targeted but also in other related microorganisms. The modern world continues to see valuable, lifesaving antibiotics lose their effectiveness as pathobionts become resistant to them.

In order to prevent antibiotic resistance, doctors and veterinarians must use these medications judiciously — which includes identifying the actual cause of a given infection through diagnostics and making sure the antibiotic being prescribed has been proven effective against that cause. This approach, known as antimicrobial stewardship, can produce better patient outcomes, reduce resistance to antimicrobial drugs, and decrease the spread of deadly infections caused by multidrug-resistant microorganisms.

MICROBIOME DISRUPTION

Another danger is the tendency of antimicrobials to disrupt the gut microbiome, causing dysbiosis. Furthermore, concerns grow regarding the use of antimicrobials in animals whose gut microbiomes are already imbalanced, such as pets with IBD or other chronic gastrointestinal disorders.

Given these risks, it's important to explore the viable alternatives to antibiotic usage. For example, both probiotics and fecal microbiota transplantation (FMT) have been investigated as alternative approaches to IBD and other causes of diarrhea in dogs.^{49,50} A 2020 study concluded that FMT works better than metronidazole in dogs with acute diarrhea because FMT helps restore gut health, whereas metronidazole "has a negative impact" on the microbiome.⁵

cemented as the foundation of health. For example, diarrhea often equates with dysbiosis. Prebiotic fibers such as inulin and psyllium may help by feeding beneficial bacterial populations while also firming up the stool. As mentioned previously, probiotic blends can help resolve diarrhea and support gut function. Empirical evidence for the use of phytonutrients like carvacrol (extracted from oregano, thyme and several other plants) is accumulating.^{32–38}

Other symptomatic treatments include anti-nausea medications, proton pump inhibitors (to reduce acid production), motility inhibitors (to reduce cramping and the sense of urgency), bile acid sequestrants (to control bile acid malabsorption in chronic diarrhea cases), and vitamin B12 (cobalamin, which is often deficient in chronic diarrhea cases).^{39–42} While some of these approaches may also cause changes to the gut microbiome, those changes will generally be less profound than the effects associated with metronidazole.

Lastly, if your patient's microbiome is significantly dysbiotic, the introduction of beneficial microbes via fecal microbiota transplantation (FMT) — i.e. Microbiome Restoration Therapy (MBRT) — can help by seeding the gut with a whole healthy community of dog- or cat-specific bacteria. Recent studies have found that FMT improves restoration of the gut microbiome from antibiotic exposure; one of these studies also found that probiotics may impair its recovery.^{43,44}

INAPPROPRIATE USES OF METRONIDAZOLE

Because past research has found metronidazole to be effective against certain causes of diarrhea in dogs, it has become many veterinarians' go-to treatment for diarrhea in general. The problem is that there isn't much scientific evidence that metronidazole actually helps some of the conditions it's being used for. And yet, even without strong scientific evidence of its effectiveness, metronidazole has become the most commonly prescribed antimicrobial agent for acute diarrhea in dogs.³ Here are three common situations in which research has found metronidazole to be the wrong choice.

• *Giardia* infection

In the past, metronidazole was commonly used to treat infections caused by the protozoan parasites *Giardia* and *Tritrichomonas*, which are known to cause diarrhea in cats and dogs. Over time, however, both these organisms have developed metronidazole resistance, so this medication by itself is no longer a curative treatment for these protozoal infections.⁴⁶

• **Inflammatory bowel disease (IBD)**

Because metronidazole has a positive effect on Crohn's disease in humans, it is often used for diarrhea in dogs with IBD and other chronic diseases of the intestines, usually in combination with the steroid prednisone.⁴⁷ However, researchers established in 2010 that metronidazole doesn't actually add any benefit in this scenario: prednisone plus metronidazole is no more effective for IBD than prednisone by itself.⁴

• **Acute diarrhea**

Because of its historical effectiveness against such diarrhea-inducing agents as *Giardia* and *C. diff*, metronidazole has been increasingly used by veterinarians to manage diarrhea due to other causes. But there is little evidence that it actually helps acute, nonspecific diarrhea (diarrhea with an undetermined cause) — a category that represents the majority of diarrhea cases in both cats and dogs.

In the veterinary sphere, there is some evidence that metronidazole reduces the time it takes for acute diarrhea to resolve. However, a study in dogs found that this reduction amounted to only a couple of days. And as the authors pointed out, most cases of diarrhea in dogs resolve in a few days “regardless of treatment.”¹¹

Another study that looked at treating acute diarrhea in dogs found no significant difference between metronidazole and a placebo. The authors concluded that the use of metronidazole for such cases “should be discouraged until evidence-based data demonstrate a difference in treatment outcome.”⁴⁸

SUMMARY RECOMMENDATIONS

We encourage veterinarians to discuss these issues with their clients. Metronidazole and other antibiotics can be valuable tools in treating a sick pet, but it's important to make sure the chosen drug's effectiveness in a given situation is supported by scientific evidence. And if your patient already suffers from an imbalanced gut microbiome, due to chronic GI issues or other health problems, antibiotics should be used only if absolutely necessary.

Additionally, testing your patient's microbiome after a course of antibiotics (see sidebar on page 52) is recommended, especially if GI signs linger. Identifying and correcting any dysbiosis can make an enormous difference in your patient's long-term health and happiness.

*Affiliated with AnimalBiome

°Affiliated with Condensed Light

MINIMIZING METRONIDAZOLE'S BITTER TASTE

If you prescribe metronidazole, consider putting the medication in an empty food-grade capsule (either gelatin or plant-based) or have a compounding pharmacy formulate a palatable liquid to minimize the drug's bitter taste.

¹Pilla R, Gaschen FP, Barr JW, et al. Effects of metronidazole on the fecal microbiome and metabolome in healthy dogs. *J Vet Intern Med*. Published online August 28, 2020. doi:10.1111/jvim.15871

²Igarashi H, Maeda S, Ohno K, Horigome A, Odamaki T, Tsujimoto H. Effect of oral administration of metronidazole or prednisolone on fecal microbiota in dogs. *PLoS One*. 2014;9(9):e107909.

³Singleton DA, Noble PJM, Sánchez-Vizcaíno F, et al. Pharmaceutical Prescription in Canine Acute Diarrhoea: A Longitudinal Electronic Health Record Analysis of First Opinion Veterinary Practices. *Front Vet Sci*. 2019;6:218.

⁴Jergens AE, Crandell J, Morrison JA, et al. Comparison of oral prednisone and prednisone combined with metronidazole for induction therapy of canine inflammatory bowel disease: a randomized-controlled trial. *J Vet Intern Med*. 2010;24(2):269-277.

⁵Chaitman J, Ziese A-L, Pilla R, et al. Fecal Microbial and Metabolic Profiles in Dogs With Acute Diarrhea Receiving Either Fecal Microbiota Transplantation or Oral Metronidazole. *Front Vet Sci*. 2020;7:192.

⁶Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54(3):393-407.

⁷Thabit AK, Fatani DF, Barnakhrama MS, Barnawi OA, Basudan LO, Alhejaili SF. Antibiotic penetration into bone and joints: An updated review. *Int J Infect Dis*. 2019;81:128-136.

⁸Marks SL, Kather EJ. Antimicrobial susceptibilities of canine *Clostridium difficile* and *Clostridium perfringens* isolates to commonly utilized antimicrobial drugs. *Vet Microbiol*. 2003;94(1):39-45.

⁹Wetterwik K-J, Trowald-Wigh G, Fernström L-L, Krovacek K. *Clostridium difficile* in faeces from healthy dogs and dogs with diarrhea. *Acta Vet Scand*. 2013;55:23.

¹⁰Chon J-W, Seo K-H, Bae D, Park J-H, Khan S, Sung K. Prevalence, toxin gene profile, antibiotic resistance, and molecular characterization of *Clostridium perfringens* from diarrheic and non-diarrheic dogs in Korea. *J Vet Sci*. 2018;19(3):368-374.

¹¹Langlois DK, Koenigshof AM, Mani R. Metronidazole treatment of acute diarrhea in dogs: A randomized double blinded placebo-controlled clinical trial. *J Vet Intern Med*. 2020;34(1):98-104.

¹²Baele M, Decostere A, Vandamme P, et al. *Helicobacter baculiformis* sp. nov., isolated from feline stomach mucosa. *Int J Syst Evol Microbiol*. 2008;58(Pt 2):357-364.

¹³Veyrier FJ, Ecobichon C, Boneca IG. Draft Genome Sequence of Strain X47-2AL, a Feline *Helicobacter pylori* Isolate. *Genome Announc*. 2013;1(6). doi:10.1128/genomeA.01095-13

¹⁴Kondadi PK, Pacini C, Revez J, Hänninen M-L, Rossi M. Contingency nature of *Helicobacter bizzozeronii* oxygen-insensitive NAD(P)H-nitroreductase (HBZC1_00960) and its role in metronidazole resistance. *Vet Res*. 2013;44:56.

¹⁵Scorza AV, Lappin MR. Metronidazole for the treatment of feline giardiasis. *J Feline Med Surg*. 2004;6(3):157-160.

¹⁶Argüello-García R, Leitsch D, Skinner-Adams T, Ortega-Pierres MG. Drug resistance in *Giardia*: Mechanisms and alternative treatments for Giardiasis. *Adv Parasitol*. 2020;107:201-282.

¹⁷Lutz B, Lehner C, Schmitt K, et al. Antimicrobial prescriptions and adherence to prudent use guidelines for selected canine diseases in Switzerland in 2016. *Vet Rec Open*. 2020;7(1):e000370.

¹⁸Weese JS, Giguère S, Guardabassi L, et al. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance. *J Vet Intern Med*. 2015;29(2):487-498.

¹⁹Unterter S, Strohmeyer K, Kruse BD, Sauter-Louis C, Hartmann K. Treatment of aseptic dogs with hemorrhagic gastroenteritis with amoxicillin/clavulanic acid: a prospective blinded study. *J Vet Intern Med*. 2011;25(5):973-979.

²⁰Wells CL, Maddaus MA, Reynolds CM, Jechorek RP, Simmons RL. Role of anaerobic flora in the translocation of aerobic and facultatively anaerobic intestinal bacteria. *Infect Immun*. 1987;55(11):2689-2694.

²¹Włodarska M, Willing B, Keeney KM, et al. Antibiotic treatment alters the colonic mucus layer and predisposes the host to exacerbated *Citrobacter rodentium*-induced colitis. *Infect Immun*. 2011;79(4):1536-1545.

References continued on page 56.

From the AVH



The **Academy of Veterinary Homeopathy** is comprised of veterinarians who share a common desire to restore true health to their patients through the use of homeopathic treatment. Members of the Academy are dedicated to understanding and preserving the principles of Classical Homeopathy.

NERVOUS DOGS, NERVOUS OWNERS?

Nervous dog owners tend to have nervous dogs. One trainer has said: “The tension flows down the leash.” I like this, as it relates to the energetic nature of the problem. This truth has become obvious to me during my 30+ years of veterinary practice, and is finally being recognized in scientific literature. The conclusion seems to be that neurotic owners behave differently, and dogs read this emotion and react to it. The result is that long-term stress levels become synchronized in dogs and their owners.

Although mental symptoms are tricky to gauge in animals, homeopathy offers some options for anxiety. *The New World Veterinary Repertory* lists 208 remedies under the rubric “MIND; anxiety”, and then breaks this down into subcategories. Here are a few highlights, covering some of the more common presentations in our animal friends, with the number of remedies in parentheses:

- During thunderstorm (6); *Phosphorus* main remedy
- In a vehicle (2); *Borax*, *Lachesis*
- From noise (11); *Aurum*, *Causticum*, *Pulsatilla*, *Silicea* main remedies
- Restless, rapid walking (5); *Arsenicum album*, *Tarentula* main remedies
- Startled easily (4); *Aloe*, *Apis*, *Lycopodium*, *Sulphur*
- Restlessness (74); *Arsenicum album*, *Kali-c*, *Tarentula* main remedies

Treating early signs of anxiety with homeopathy, while considering the symptom totality, offers a powerful option, and can hopefully spare an animal from the damaging effects of chronic stress/anxiety and a lifetime of pharmacological symptom manipulation that doesn't stimulate deeper improvement or healing.

Find a homeopathic vet at the AVH.org.

Submitted by Todd Cooney, DVM, CVH

References continued from page 55.

- ²² Sheehy O, Santos F, Ferreira E, Berard A. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf.* 2015;10(2):170-179.
- ²³ Weiss DJ. Bone marrow necrosis in dogs: 34 cases (1996-2004). *J Am Vet Med Assoc.* 2005;227(2):263-267.
- ²⁴ Sekis I, Ramstead K, Rishniw M, et al. Single-dose pharmacokinetics and genotoxicity of metronidazole in cats. *J Feline Med Surg.* 2009;11(2):60-68.
- ²⁵ Bendesky A, Menéndez D, Ostrosky-Wegman P. Is metronidazole carcinogenic? *Mutat Res.* 2002;511(2):133-144.
- ²⁶ Adil M, Iqbal W, Adnan F, et al. Association of Metronidazole with Cancer: A Potential Risk Factor or Inconsistent Deductions? *Curr Drug Metab.* 2018;19(11):902-909.
- ²⁷ Eradiri O, Jamali F, Thomson AB. Interaction of metronidazole with phenobarbital, cimetidine, prednisone, and sulfasalazine in Crohn's disease. *Biopharm Drug Dispos.* 1988;9(2):219-227.
- ²⁸ Pichler L. Teratogenicity in dogs and cats-a review for practitioners and toxicologists. *Wien Tierarztl Monatsschr.* 2007;94(9/10):214.
- ²⁹ Fenimore A, Martin L, Lappin MR. Evaluation of Metronidazole With and Without Enterococcus Faecium SF68 in Shelter Dogs With Diarrhea. *Top Companion Anim Med.* 2017;32(3):100-103.
- ³⁰ Chon S-K, Kim N-S. Evaluation of silymarin in the treatment on asymptomatic Giardia infections in dogs. *Parasitol Res.* 2005;97(6):445-451.
- ³¹ McFarland LV, Sarawicz CM, Greenberg RN, et al. Prevention of beta-lactam-associated diarrhea by *Saccharomyces boulardii* compared with placebo. *Am J Gastroenterol.* 1995;90(3):439-448.
- ³² Mousavi S, Schmidt A-M, Escher U, et al. Carvacrol ameliorates acute campylobacteriosis in a clinical murine infection model. *Gut Pathog.* 2020;12:2.
- ³³ Yuan W, Seng ZJ, Kohli GS, Yang L, Yuk H-G. Stress Resistance Development and Genome-Wide Transcriptional Response of *Escherichia coli* O157:H7 Adapted to Sublethal Thymol, Carvacrol, and trans-Cinnamaldehyde. *Appl Environ Microbiol.* 2018;84(22). doi:10.1128/AEM.01616-18
- ³⁴ Gaur S, Kuhlenschmidt TB, Kuhlenschmidt MS, Andrade JE. Effect of oregano essential oil and carvacrol on *Cryptosporidium parvum* infectivity in HCT-8 cells. *Parasitol Int.* 2018;67(2):170-175.
- ³⁵ Giovannoni G, Rossi B, Tugnoli B, et al. Thymol and Carvacrol Downregulate the Expression of Salmonella typhimurium Virulence Genes during an In Vitro Infection on Caco-2 Cells. *Microorganisms.* 2020;8(6). doi:10.3390/microorganisms8060862
- ³⁶ Sánchez C, Aznar R, Sánchez G. The effect of carvacrol on enteric viruses. *Int J Food Microbiol.* 2015;192:72-76.
- ³⁷ Katsoulos PD, Karatzia MA, Dovas CI, et al. Evaluation of the in-field efficacy of oregano essential oil administration on the control of neonatal diarrhea syndrome in calves. *Res Vet Sci.* 2017;115:478-483.
- ³⁸ Mooyottu S, Flock G, Upadhyay A, Upadhyaya I, Maas K, Venkitanarayanan K. Protective Effect of Carvacrol against Gut Dysbiosis and Clostridium difficile Associated Disease in a Mouse Model. *Front Microbiol.* 2017;8:625.
- ³⁹ Senderovich H, Ghassem Khani E. The Role of Bile Acid Sequestrant in Diarrhea Management: Too Good to Be True? *Clin Gastroenterol Hepatol.* 2018;02(03). doi:10.21767/2575-7733.1000048
- ⁴⁰ Enright EF, Griffin BT, Gahan CGM, Joyce SA. Microbiome-mediated bile acid modification: Role in intestinal drug absorption and metabolism. *Pharmacol Res.* 2018;133:170-186.
- ⁴¹ Toresson L, Steiner JM, Olmedal G, Larsen M, Suchodolski JS, Spillmann T. Oral cobalamin supplementation in cats with hypocobalaminemia: a retrospective study. *J Feline Med Surg.* 2017;19(12):1302-1306.
- ⁴² Toresson L, Steiner JM, Spodsberg E, et al. Effects of oral versus parenteral cobalamin supplementation on methylmalonic acid and homocysteine concentrations in dogs with chronic enteropathies and low cobalamin concentrations. *Vet J.* 2019;243:8-14.
- ⁴³ Taur Y, Coyte K, Schluter J, et al. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. *Sci Transl Med.* 2018;10(460). doi:10.1126/scitranslmed.aap9489
- ⁴⁴ Suez J, Zmora N, Zilberman-Schapira G, et al. Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT. *Cell.* 2018;174(6):1406-1423.e16.
- ⁴⁵ Martínez-López LM, Pepper A, Pilla R, Woodward A, Suchodolski J, Mansfield C. Effect of Sequentially Fed High Protein, Hydrolysed Protein, and High Fibre Diets on The Faecal Microbiota of Healthy Dogs: A Cross-Over Study. Published online 2020.
- ⁴⁶ Upcroft P, Upcroft JA. Drug targets and mechanisms of resistance in the anaerobic protozoa. *Clin Microbiol Rev.* 2001;14(1):150-164.
- ⁴⁷ Sprockett D, Fischer N, Boneh RS, et al. Treatment-Specific Composition of the Gut Microbiota Is Associated With Disease Remission in a Pediatric Crohn's Disease Cohort. *Inflammatory Bowel Diseases.* 2019;25(12):1927-1938. doi:10.1093/ibd/izz130
- ⁴⁸ Shmalberg J, Montalbano C, Morelli G, Buckley GJ. A Randomized Double Blinded Placebo-Controlled Clinical Trial of a Probiotic or Metronidazole for Acute Canine Diarrhea. *Front Vet Sci.* 2019;6:163.
- ⁴⁹ 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(4):e94699.
- ⁵⁰ Niina A, Kibe R, Suzuki R, et al. Improvement in Clinical Symptoms and Fecal Microbiome After Fecal Microbiota Transplantation in a Dog with Inflammatory Bowel Disease. *Vet Med (Auckl).* 2019;10:197-201.