Gruel, guts and gonads

2023 Small Animal Conference

Joined by the Reproduction Group

KNOWLEDGE

AUSTRALIAN **SMALL ANIMAL VETERINARIANS**

AUSTRALIAN **REPRODUCTIVE VETERINARIANS**

LET'S END PET OBESITY TOGETHER

With Hill's Metabolic Weight Management Foods

Hill's is making it our mission to End Pet Obesity once and for all, with tools to help you have the weight loss conversation with your clients:

New Quick Reco tool

BFI tool

Educational content

Downloadable pet parent resources

Animated films

Ask your Hill's Territory Manager about weight nutrition

IMMIJ52142

A simple and seamless preventive care solution.

IDEXX Preventive Care Simple Start

IDEXX Preventive Care profiles

Detect disease early with the most advanced menu of tests

Tools to get clients to yes

Resources to gain compliance before, during, and after the visit

Tools for protocol implementation

Integrate practice-wide guidelines into your daily workflow

Dedicated IDEXX support

Guidance and expertise to help you every step of the way

> TO LEARN MORE, VISIT US AT THE IDEXX STAND OR SCAN THE QR CODE

IDEXX

Visit the IDEXX stand for your chance to win an instant prize!

Immerse yourself in an unforgettable wellness journey at the IDEXX ASAV stand and you'll be rewarded.

At IDEXX we're all about improving the lives of pets and people. Part of this is ensuring that Preventive Care protocols are easily implemented into practices all over Australia.

With our comprehensive diagnostics, you can get deeper insights into your patients' health, helping them live their best lives.

To learn more about how IDEXX can help you seamlessly integrate Preventive Care into your practice, visit our stand or scan the QR code.

> IDEXX.COM.AU/SIMPLESTART

IDEXX

Table of Contents
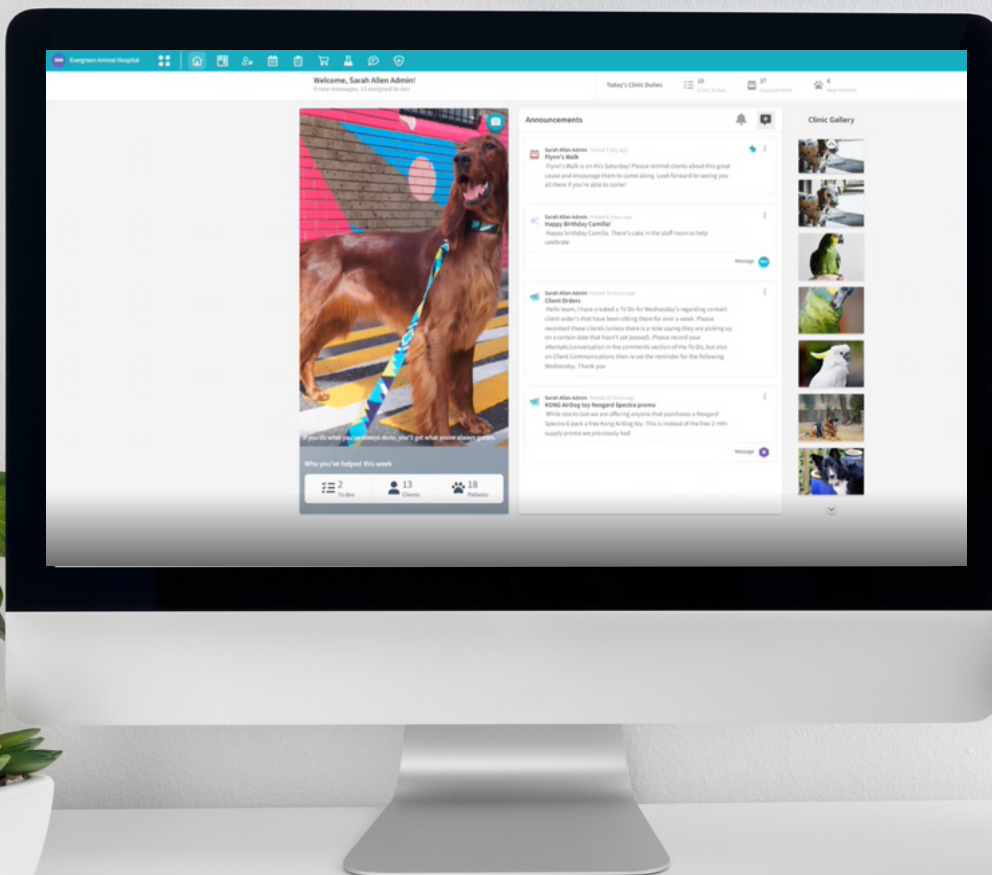
Small Animal

Reproduction

Webinar: Introduction to Covetrus Ascend

INCLUDING

- How Ascend helps save clinics up to 20% more time weekly
- Top features and benefits
- 30-min cloud-based demo walkthrough
- BONUS spotlight on 2023 feature updates

→ Watch Now

Dietary carbohydrate in health and disease

Nick Cave BVSc MVSc PhD DipACVIM (Nutrition)
School of Veterinary Sciences
Massey University, Palmerston North, New Zealand

Carbohydrates are the most abundant compounds found in plants, and are present as either simple sugars, or as sugars joined into chains or more complex forms called polysaccharides. Polysaccharides can be classified as either digestible carbohydrates, or undigestible carbohydrates. Most digestible carbohydrate in foods is in the form of starches, which are large chains of simple sugars and when cooked, are highly digestible. All of the common simple sugars are digestible, and do not require cooking. The most common simple sugar, glucose, is an essential energy source for cells, and some cells, such as red blood cells, cannot use any other fuel such as lipids or ketones. However, both dogs and cats can synthesise all the glucose they require from amino acids, and thus digestible carbohydrates are not essential in their diet.[1]

Domestic dogs evolved alongside humans, changing from wolves that rarely ate much plant material, to domesticated dogs that would have consumed the same sorts of foods that their human cohabitants ate. As the result of thousands of years of genetic changes, dogs are now more able to digest, absorb, and utilise carbohydrates than their wolfish ancestors.[2] Indeed, some dogs will prefer to consume diets that are high in carbohydrate rather than diets very high in protein.[3]

In contrast, the domestication of cats appears to have done little to alter their carbohydrate metabolism, and their wild counterparts consume a diet that is almost completely free of digestible carbohydrate. Cats lack the sweet taste receptor, and it is rare to find a cat that will select digestible carbohydrate over fat and protein. Their expression of pancreatic amylase and brush boarder disacharridases is significantly less than dogs, and they do not physiologically adapt when switched from low to high carbohydrate diets.[4] Glucose phosphorylation is less than dogs, and they have a lower tolerance of dietary glucose, whereby glucosuria will result when fed a highly digestible diet that contains 25% glucose. Yet despite these features, glucose is still an essential fuel for feline erythrocytes, and normoglycaemia is essential for neuronal function. Whether the glucose is obtained by dietary intake or hepatic gluconeogenesis does not influence the utilisation of the fuel once taken up by cells.

Including carbohydrate in the diet of dogs and cats as a source of fuel reduces the requirement for protein and fat as fuel sources. This decreases the need for gluconeogenesis from amino acids, and reduces the amount of urea that is filtered by the kidneys. In addition, it reduces the amount of the most expensive ingredients, and in a world where dietary protein is becoming increasingly difficult to produce without damaging the environment, it has wider benefits.

Indigestible carbohydrates
Dietary fiber has been defined as the edible portion of plants or analogous carbohydrates that are resistant to digestion and absorption in the small intestine, which are then

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

8

available to be completely or partially fermented by resident microflora in the distal small intestine, and large intestine.[5] Most fibers are polysaccharides, although others, such as the polyphenolic compound lignin are not. Restriction of the definition to plant-derived compounds, omits indigestible carbohydrates derived from animal sources (e.g. chitin) or synthetic sources (e.g. fructooligosaccharides). Lastly, such a definition fails to include digestible carbohydrates that are in a form that is inaccessible to digestive enzymes (e.g. resistant starch). These compounds share many of the characteristics of fiber present in plant foods. Thus a unifying definition of dietary fiber must be species-specific, and incorporate all compounds that share the biological characteristics of fiber in the intestine. Dietary fiber can be classified according to physical or chemical characteristics, according to its effects on bowel microflora, or its effects on specific variables in the whole animal. In regard to its effects on gastrointestinal physiology and pathophysiology, the most important characteristics are direct physical stimulation, viscosity, luminal absorption, and fermentability.

Fiber viscosity

Some types of soluble dietary fiber increase the viscosity of water when in solution, and have the capacity to retain water within the viscous gel ("water-holding capacity"). This effect increases fecal water content and mass. Psyllium hydrocolloid (e.g. Metamucil®) has a greater water-holding effect than pea, oat, or sugar beet fiber.[6] The formation of viscous gels slows gastric emptying, increases small intestinal transit times, and slows the absorption and reduces the digestibility of some nutrients.[7,8] Viscosity of ileal contents increases greatly with certain soluble dietary fibers.[9] This effect of fiber can be thought of as an anti-nutritive effect, and excessive dietary fiber may be counter-productive.

Although fibers that are soluble and capable of forming viscous gels are more likely to be fermentable, that is not always the case because the chemical requirements for both properties are different. The gel-forming component of psyllium seed husk for instance, is not readily fermented by human colonic microflora and contributes significantly to its effect on increasing fecal bulk.[10]

The ability to form viscous gels in the stomach may be the mechanism by which dietary fiber facilitates the gastrointestinal transit of ingested hair. Dietary fiber (e.g. psyllium) has been shown to increase hair transit time and to decrease retching and vomiting associated with hairballs in chronically affected cats.[11,12]

Non-fermentable dietary fiber reduces bile acid solubility in fecal water and reduces the potential for interactions with the colonic epithelium [13,14]. Bile acids can have a direct effect on the epithelium through their detergent effect. However, bacterial metabolites of bile acids ("secondary bile acids") can have other biological effects. Luminal fiber directly protects the colonic epithelium though preventing direct interactions, reducing concentrations, and indirectly through the production of butyrate.[15] Wheat bran fiber (13.5–25 g/day for up to 12 months) can significantly lower both total and secondary (*e.g.* DCA) bile acid concentrations in the solid-phase of human feces [16,17]

Fiber fermentability

Dietary fibers undergoing bacterial degradation include polysaccharides such as resistant starch, pectin, inulin, guar gum and oligosaccharides (e.g. fructooligosaccharides (FOS)).[18]

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

9

The extent to which fiber is utilised by microflora and the fermentative by-products produced is influenced by the structure of the carbohydrate, and also the composition of the microflora within the individual. The effect of providing such substrate in the bowel lumen is to create a selection advantage to those species best adapted to its use. When the shift in microbiota has a positive effect on the host, the fiber is defined as a probiotic. Proposed positive effects include reduction in mucosal adherence of pathogenic species, reduction in the numbers of pathogenic species, and immune-modulation of the host.[18-21]

Effects of short chain volatile fatty acids on the colon

In most domestic species studied, including dogs, butyrate is oxidised by colonocytes, and in dogs is also oxidised by enterocytes.[22,23] It has been observed that when colonocytes are provided with butyrate, glutamine, glucose, and proprionate, the most used substrate is butyrate.[23] In response to butyrate from fiber fermentation, colonocyte proliferation increases, intestinal mucosal weight increases, water and electrolyte absorption increases, and brush boarder enzyme activities increase.[24-27] Short chain fatty acids (SCFA), butyrate in particular, stimulate longitudinal but not circular colonic smooth muscle contractions, via a direct effect on smooth muscle, and improve the arboreal passage of feces in the colon.[28] Luminal butyrate also increases mucin secretion, which reduces microbial adhesion and translocation and improves secretory IgA function.[29] Some effects may be concentration dependant, since at high concentrations, butyrate can also inhibit colonocyte proliferation.[22,30-32]

Effects of butyrate on intestinal immunity

At reasonable physiological concentrations, colonic luminal butyrate suppresses the immune response by inhibiting the formation of the nuclear transcription factor NF-κB in colonocytes, endothelial cells, and resident leukocytes.[33,34] NF-κB regulates several cellular processes that vary according to the individual cell type and activation state, but includes adaptive and innate immune responses in the intestinal tract, with several inflammatory cytokines and cell adhesion molecules under direct transcriptional control.[35] The ability of butyrate to inhibit NF-κB activation and signalling appears to be the mechanism for the anti-inflammatory effect of butyrate in colitis.[33,36] The non-toxic inhibition of lymphocyte proliferation may be a significant component of the immunological tolerance to large numbers of micro-organisms in the colonic lumen.

However, not all the beneficial effects of fermentable fiber can be reduced to the luminal production of butyrate. In a model of acute colitis in rats, feeding dietary inulin (a highly fermentable fiber) prior to the insult reduced signs and histological evidence of colitis, neutrophil recruitment, and eicosanoid production (PGE_2, LTB_4, and TXB_2).[37] The administration of fecal water from inulin-fed rats via an enema had a similar effect. However, when administered by enema, neither butyrate nor inulin had a significant effect on the colitis in that model. Again, that suggests a more complex effect of dietary fiber on the mucosa than that explained simply by the production of volatile fatty acids.

The effect of fermentable fiber on immunity is not limited to cells resident within the intestinal mucosa. Feeding the highly fermentable fiber pectin to rats, affects lymphocytes isolated from mesenteric lymph nodes. Isolated lymphocytes secrete a cytokine profile more Th_1-biased than those from cellulose fed rats, which suggests that activation within the mucosa when there are luminal fermentative by-products of fiber, affects the

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

10

immunophenotype of activated lymphocytes that subsequently leave the intestine and recirculate to other mucosal sites.[38] Thus dietary fiber may affect mucosal immunity throughout the intestinal tract, and probably at other mucosae as well.

Effect of fiber on intestinal flora - Prebiosis

Certain fibres, such as the β-2 fructans (e.g. inulin, fructooligosaccharides), stimulate the growth and/or activity of intestinal bacteria such as *Lactobacillius* and *Bifidobacterium* species.[39,40] It has been proposed that increasing the numbers of these non-pathogenic species may have several direct effects including, competition with pathogens for substrate, interference with pathogen binding with and competition for epithelial binding sites, and direct interaction with the mucosal immune system. Elimination of *Clostridium difficile* from the colonic flora within 6 days has been documented in mice by feeding a diet containing 20% fermentable fiber.[41] Similar effects on the fecal microflora have been seen in dogs given highly fermentable fiber.[42] However, colonic microflora populations in dogs and cats may be relatively resistant to changes resulting from changes in dietary fiber intake.[43]

Choice of fiber

The combined effects of fiber fermentation with the absorptive effects of non-fermentable fiber make mixed fiber sources (e.g. psyllium) theoretically ideal for the management of colitis, over more completely fermentable fiber sources (e.g. hydrolysed guar gum). In addition, the most highly fermentable fibers may also increase the production of methane which has the capacity to disturb motility and exacerbate signs. In other cases, more highly fermentable sources that produce higher concentrations of butyrate in the more proximal colon may be more effective that less fermentable sources of fiber. In a model of induced colitis in rats, both short-chain fructo-oligosaccharides and a resistant starch were evaluated for their ability to improve clinical and histological signs of colitis.[44] Only the resistant starch in that model improved the histological colitis score, and there was a trend towards more rapid resolution of the diarrhoea, and less hematochezia. Clearly, the choice of fiber is important in certain disease states, however insufficient information is available in feline and canine medicine to make any informed therapeutic recommendations beyond initially introducing mixed fermentable sources, then proceeding with trial and error if required.

Carbohydrate restriction

Whilst there is no evidence that feeding a moderate amount of digestible carbohydrate causes harm, there are disease states where it is beneficial to reduce the intake.

Diabetes

Simply put, the dose of insulin required to maintain a given serum glucose concentration will be proportional to the mass of digestible carbohydrate fed.[45] Diabetic remission in cats is more likely in those fed a low carbohydrate diet.[46] There is a common misconception that hypoglycemia is more likely in diabetics and that feeding *some* digestible carbohydrate is safer. However, aside from during the post-prandial period, serum glucose is the result of hepatic output, and failure of insulin to suppress that results in the fasting hyperglycemia. In type 2 diabetes, a low carbohydrate diet improves hepatic insulin sensitivity, but does not produce hypoglycemia unless excessive exogenous insulin is administered.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

11

Seizures

Normally, c.20% of glucose oxidised in the body is oxidised by the brain, despite only being 2% of total bodyweight. However, during prolonged fasting, up to 75% of ATP produced in the brain can be derived from ketones, rather than glucose. Switching utilisation from glucose to ketones has effects on seizure thresholds, [The ketogenic diet: metabolic influences on brain excitability and epilepsy, Lutas], and neuronal recovery following injury.[47] Restricting dietary carbohydrate may be helpful in managing both seizure disorders, and following neuronal injury.

Cancer

It is almost 100 years since Otto Warburg first described the observation that tumours oxidise glucose anaerobically, even when ample oxygen is available.[48] This "Warburg effect" is found in the majority of tumours in humans and rodents, and there is no fundamental reason to believe it is different in dogs and cats.[49,50] Reducing glucose availability slows tumour growth, reduces the rate of metastasis, and can increase the sensitivity of tumours to radiotherapy and chemotherapy. Restricting dietary carbohydrate leads to consistently lower interstitial glucose concentrations in dogs.[51] Whether the elimination of digestible carbohydrate from the diet of dogs and cats with cancer will have any therapeutic effect is yet to be properly tested, and it will be a long time before we know which tumours at which stage will benefit the most.

Conclusion

Dietary carbohydrate can be categorised broadly into digestible, and non-digestible forms. Digestible carbohydrate is not required by either species, however it is a source of calories, and reduces the amount of protein included in diets. Non-digestible carbohydrate is usually defined as dietary fibre, which has several important benefits for both dogs and cats, and should be considered an important, if not essential nutrient. However, the lack of essentiality of digestible carbohydrate raises the question of when avoidance might be beneficial. There is a strong case for avoiding digestible carbohydrate in diabetes and cancer, and it might be helpful managing patients with seizure disorders, and following neuronal trauma. For those conditions, it remains to be seen how effective simple carbohydrate restriction is, compared with specific ketogenic diets.

References

1. Beitz DC, Bauer JE, Behnke KC, et al. Nutrient requirements of dogs and cats, Revised Edition ed. Washington: National Academies Press; 2006.
2. Axelsson E, Ratnakumar A, Arendt ML, et al. The genomic signature of dog domestication reveals adaptation to a starch-rich diet. Nature 2013;495:360-364.
3. Roberts MT, Bermingham EN, Cave NJ, et al. Macronutrient intake of dogs, self-selecting diets varying in composition offered ad libitum. J Anim Physiol Anim Nutr (Berl) 2018;102:568-575.
4. Kienzle E. Carbohydrate Metabolism of the Cat. 3. Digestion of Sugars 1. Journal of Animal Physiology and Animal Nutrition 1993;69:203-210.
5. DeVries JW. On defining dietary fibre. Proc Nutr Soc 2003;62:37-43.
6. McBurney MI. Potential water-holding capacity and short-chain fatty acid production from purified fiber sources in a fecal incubation system. Nutrition 1991;7:421-424.
7. Ashraf W, Lof J, Jin G, et al. Comparative effects of intraduodenal psyllium and senna on canine small bowel motility. Aliment Pharmacol Ther 1994;8:329-336.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

12

8. Bednar GE, Patil AR, Murray SM, et al. Starch and fiber fractions in selected food and feed ingredients affect their small intestinal digestibility and fermentability and their large bowel fermentability in vitro in a canine model. J Nutr 2001;131:276-286.

9. Dikeman CL, Murphy MR, Fahey GC, Jr. Diet type affects viscosity of ileal digesta of dogs and simulated gastric and small intestinal digesta. J Anim Physiol Anim Nutr (Berl) 2007;91:139-147.

10. Marlett JA, Fischer MH. The active fraction of psyllium seed husk. Proc Nutr Soc 2003;62:207-209.

11. Hoffman LA, Tetrick MA. Added Dietary Fiber Reduces Feline Hairball Frequency. J Vet Intern Med 2003;17.

12. Dann JR, Adler MA, Duffy KL, et al. A potential nutritional prophylactic for the reduction of feline hairball symptoms. J Nutr 2004;134:2124S-2125S.

13. Ebihara K, Schneeman BO. Interaction of bile acids, phospholipids, cholesterol and triglyceride with dietary fibers in the small intestine of rats. J Nutr 1989;119:1100-1106.

14. Gallaher D, Schneeman BO. Intestinal interaction of bile acids, phospholipids, dietary fibers, and cholestyramine. Am J Physiol 1986;250:G420-426.

15. Bartram HP, Scheppach W, Englert S, et al. Effects of deoxycholic acid and butyrate on mucosal prostaglandin E2 release and cell proliferation in the human sigmoid colon. JPEN J Parenter Enteral Nutr 1995;19:182-186.

16. Alberts DS, Ritenbaugh C, Story JA, et al. Randomized, double-blinded, placebo-controlled study of effect of wheat bran fiber and calcium on fecal bile acids in patients with resected adenomatous colon polyps. J Natl Cancer Inst 1996;88:81-92.

17. Reddy BS, Engle A, Simi B, et al. Effect of dietary fiber on colonic bacterial enzymes and bile acids in relation to colon cancer. Gastroenterology 1992;102:1475-1482.

18. Blaut M. Relationship of prebiotics and food to intestinal microflora. Eur J Nutr 2002;41 Suppl 1:I11-16.

19. Bamba T, Kanauchi O, Andoh A, et al. A new prebiotic from germinated barley for nutraceutical treatment of ulcerative colitis. J Gastroenterol Hepatol 2002;17:818-824.

20. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics--approaching a definition. AmJClinNutr 2001;73:361S-364S.

21. Guarner F, Casellas F, Borruel N, et al. Role of microecology in chronic inflammatory bowel diseases. Eur J Clin Nutr 2002;56 Supplement 4:S34-S38.

22. Marsman KE, McBurney MI. Dietary fiber increases oxidative metabolism in colonocytes but not in distal small intestinal enterocytes isolated from rats. J Nutr 1995;125:273-282.

23. Beaulieu AD, Drackley JK, Overton TR, et al. Isolated canine and murine intestinal cells exhibit a different pattern of fuel utilization for oxidative metabolism. J Anim Sci 2002;80:1223-1232.

24. Farness PL, Schneeman BO. Effects of dietary cellulose, pectin and oat bran on the small intestine in the rat. J Nutr 1982;112:1315-1319.

25. Poksay KS, Schneeman BO. Pancreatic and intestinal response to dietary guar gum in rats. J Nutr 1983;113:1544-1549.

26. Marsman KE, McBurney MI. Dietary fiber and short-chain fatty acids affect cell proliferation and protein synthesis in isolated rat colonocytes. J Nutr 1996;126:1429-1437.

27. Forman LP, Schneeman BO. Dietary Pectin's effect on starch utilization in rats. J Nutr 1982;112:528-533.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

13

28. McManus CM, Michel KE, Simon DM, et al. Effect of short-chain fatty acids on contraction of smooth muscle in the canine colon. Am J Vet Res 2002;63:295-300.
29. Barcelo A, Claustre J, Moro F, et al. Mucin secretion is modulated by luminal factors in the isolated vascularly perfused rat colon. Gut 2000;46:218-224.
30. Lupton JR. Butyrate and colonic cytokinetics: differences between in vitro and in vivo studies. Eur J Cancer Prev 1995;4:373-378.
31. Chapkin RS, Fan Y, Lupton JR. Effect of diet on colonic-programmed cell death: molecular mechanism of action. Toxicol Lett 2000;112-113:411-414.
32. Lupton JR. Microbial degradation products influence colon cancer risk: the butyrate controversy. J Nutr 2004;134:479-482.
33. Luhrs H, Gerke T, Muller JG, et al. Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 2002;37:458-466.
34. Yin L, Laevsky G, Giardina C. Butyrate suppression of colonocyte NF-kappa B activation and cellular proteasome activity. J Biol Chem 2001;276:44641-44646.
35. Perkins ND. Integrating cell-signalling pathways with NF-kappaB and IKK function. Nat Rev Mol Cell Biol 2007;8:49-62.
36. Venkatraman A, Ramakrishna BS, Shaji RV, et al. Amelioration of dextran sulfate colitis by butyrate: role of heat shock protein 70 and NF-kappaB. Am J Physiol Gastrointest Liver Physiol 2003;285:G177-184.
37. Videla S, Vilaseca J, Antolin M, et al. Dietary inulin improves distal colitis induced by dextran sodium sulfate in the rat. Am J Gastroenterol 2001;96:1486-1493.
38. Lim BO, Lee SH, Park DK, et al. Effect of dietary pectin on the production of immunoglobulins and cytokines by mesenteric lymph node lymphocytes in mouse colitis induced with dextran sulfate sodium. Biosci Biotechnol Biochem 2003;67:1706-1712.
39. Gibson GR, Beatty ER, Wang X, et al. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. Gastroenterology 1995;108:975-982.
40. Kaplan H, Hutkins RW. Fermentation of fructooligosaccharides by lactic acid bacteria and bifidobacteria. Appl Environ Microbiol 2000;66:2682-2684.
41. Ward PB, Young GP. Dynamics of Clostridium difficile infection. Control using diet. Adv Exp Med Biol 1997;412:63-75.
42. Grieshop CM, Flickinger EA, Fahey GC, Jr. Oral administration of arabinogalactan affects immune status and fecal microbial populations in dogs. J Nutr 2002;132:478-482.
43. Simpson JM, Martineau B, Jones WE, et al. Characterization of fecal bacterial populations in canines: effects of age, breed and dietary fiber. Microb Ecol 2002;44:186-197.
44. Moreau NM, Martin LJ, Toquet CS, et al. Restoration of the integrity of rat caeco-colonic mucosa by resistant starch, but not by fructo-oligosaccharides, in dextran sulfate sodium-induced experimental colitis. Br J Nutr 2003;90:75-85.
45. Frank G, Anderson W, Pazak H, et al. Use of a high-protein diet in the management of feline diabetes mellitus. Veterinary therapeutics: research in applied veterinary medicine 2001;2:238-246.
46. Bennett N, Greco DS, Peterson ME, et al. Comparison of a low carbohydrate–low fiber diet and a moderate carbohydrate–high fiber diet in the management of feline diabetes mellitus. Journal of feline medicine and surgery 2006;8:73-84.
47. Prins ML, Matsumoto JH. The collective therapeutic potential of cerebral ketone metabolism in traumatic brain injury. J Lipid Res 2014;55:2450-2457.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

14

48. Warburg O, Wind F, Negelein E. The metabolism of tumours in the body. The Journal of general physiology 1927;8:519-530.

49. Liu C, Jin Y, Fan Z. The Mechanism of Warburg Effect-Induced Chemoresistance in Cancer. Front Oncol 2021;11:698023.

50. Vaupel P, Multhoff G. Revisiting the Warburg effect: historical dogma versus current understanding. J Physiol 2021;599:1745-1757.

51. Gal A, Cuttance W, Cave N, et al. Less is more? Ultra-low carbohydrate diet and working dogs' performance. PloS one 2021;16:e0261506-e0261506.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary carbohydrate in health and disease

15

Dietary management for gastrointestinal surgery

Nick Cave
BVSc MVSc PhD DipACVIM (Nutrition)
School of Veterinary Sciences
Massey University, Palmerston North, New Zealand

To feed or not to feed?

Perhaps no other organ system is so directly and immediately affected by nutrition than the gastrointestinal tract. Timing and frequency of feeding, route of feeding, macronutrient and micronutrient compositions of the diet have profound influences on oral and intestinal health. In addition to the direct effect of diet on the body, there is a considerable indirect effect through dietary influences on the intestinal microflora. However, there are few controlled clinical trials that have evaluated specific dietary manipulation in either prevention or management of canine and feline gastroenteric diseases.

Malnutrition is a significant risk factor for poor surgical outcomes in human patients.[1-3] Several outcome measures have been shown to be affected including

- Higher surgical complication rates
- Delayed wound healing, fistula, dehiscence
- Decreased immunity
- Systemic sepsis
- Longer hospital stays
- Resources
- Increased hospital readmission rate
- Greater risk of mortality

There are no studies in the veterinary literature where nutritional status has been properly assessed and linked to surgical outcome, and several have used surrogate measures such as serum albumin. However, there is little reason to believe that we cannot infer from human studies to dogs and cats, and in the absence of evidence to the contrary, we should continue to do so. Dehiscence of anastomoses and biopsy sites is still common enough to be concerning, and can be a catastrophic event in even relatively healthy animals. The incidence of dehiscence in patients managed in primary practice is uncertain, and may be different from reports in referral or teaching hospitals. However, whatever the rate, it is essential that all steps be taken to minimise the risks where those steps are relatively easy to take. Adequate nutrition is one such step.

Benefits of luminal nutrition post-operatively

Even in the absence of enteritis, fasting for even as short a period as one day in rats causes a significant decrease in villous height and/or crypt depth in jejunum, ileum, and, to a lesser extent, colon.[4,5] In addition, fasting is associated with gut mucosal cell impairment marked by decreased levels of reduced glutathione (GSH), the major intracellular antioxidant, enhanced permeability to macromolecules, increased bacterial translocation from the lumen, and increased rates of enterocyte apoptosis.[6] Even with total parenteral nutrition, after 14 days of oral fasting in cats, small intestinal villous atrophy, fusion, and infiltration of the lamina propria with lymphocytes, plasma cells, and neutrophils occurs.[7]

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

16

Thus oral fasting alone, and in the absence of nutritional deficiency, induces an intestinal insult.

Fasting also significantly reduces the specific activity and expression of certain digestive enzymes in the small bowel mucosa such as disaccharidases, which can lead to impaired digestion following the re-introduction of food.[8] Transient lactase deficiency is common, particularly after rotavirus gastroenteritis.[9] Occasionally it persists, and lactose intolerance may be a cause of post-gastroenteritis diarrhoea. Gastric and pancreatic secretions are markedly reduced following a period of under-nutrition.[10] Generalized malnutrition, protein depletion, or deficiencies of specific nutrients, including essential fatty acids, folate, zinc, vitamin A, and vitamin B12 inhibit the growth and turnover of the intestinal mucosa. It has long been recognized that small intestinal enterocytes utilize luminally-derived glutamine as their main oxidative fuel (see above). In addition, glutamine provides the carbon skeleton and amino nitrogen required for purine synthesis and hence is critical for normal DNA synthesis involved in enterocyte turnover. Oral supplementation with zinc improves histological recovery, normalizes absorption, decreases permeability, and decreases NF-κB nuclear binding in experimental models of diarrhoea.[11,12] Additional mechanisms for the effect of zinc treatment on the duration of diarrhoea include improved absorption of water and electrolytes, increased levels of brush border enzymes, and faster regeneration of the intestinal epithelium.

Multiple factors, including luminal nutrients, pancreaticobiliary secretions, and humoral agents have been implicated in controlling the intestinal adaptive response after an intestinal insult. Despite the multifactorial regulation of intestinal adaptation, luminal nutrients are fundamental to the adaptive response such that recovery is minimized or prevented in the absence of luminal nutrients. This conclusion is largely based on studies that show significant adaptive intestinal re-growth in rats and dogs fed orally compared with those fed parenterally following an intestinal resection. Indeed even in the absence of an intestinal insult, total parenteral nutrition (TPN) causes dramatic intestinal atrophy in dogs, cats, rats and humans.[7,13, 14] This fasting-induced atrophy is accompanied by inflammatory cell infiltrates in the lamina propria, increased intestinal permeability, and increased bacterial translocation.

It has long been known that the immunological derangements that accompany malnutrition cannot all be prevented when nutrients are delivered parenterally.[15] A lack of luminal nutrients results in an increased expression of proinflammatory adhesion molecules, especially ICAM-1.[16] This results in an increased number of primed neutrophils adhered to the microvasculature throughout the intestinal tract where they are able to contribute to oxidative and enzymatic tissue damage following activation. Fasting or TPN results in decreases in IL-4 and IL-10 that correlate with decreases in IgA and increases in ICAM-1.[17] Lack of enteral feeding impairs the coordinated system of sensitization, distribution, and interaction of T and B cells important in the production of IgA, in the maintenance of normal gut cytokines, and in the regulation of endothelial inflammation.[5,13,18,19] Thus the lack of luminal nutrients has been described as a "first hit", and increases the inflammatory response to a secondary insult in the GIT, but also the lungs, liver, and potentially other organs as well.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

17

The amino acid glutamine reverses many of these defects and favourably influences the proinflammatory effects of gut starvation.[20] The source of supplemental glutamine can influence gut mucosal glutamine concentrations, suggesting differences in its availability or utilization. Glutamine-rich intact proteins appear to be more effective in increasing mucosal glutamine content than glutamine-enriched solutions.[21] Arginine is an essential amino acid for cats because of their inability to synthesize sufficient quantities in the fasting state. However, beyond its role as an essential intermediate in the ornithine cycle, dietary arginine has long been known to enhance certain aspects of immunity.

Even short periods of enteral fasting result in an increase in intestinal permeability in humans.[22] Early refeeding of dogs and cats with acute gastroenteritis has been shown to reduce the increase in intestinal permeability that occurs in response to the inflammation and apoptosis.[21,23] Some of the effect of luminal feeding may come from the luminal provision of glutamine alone, which can restore enterocyte glutathione concentrations, proteins synthesis, and normalise intestinal permeability. Even in single layer cell cultures of enterocytes, the application of glutamine to the apical (luminal) membrane normalises permeability to a large molecular weight molecule, whereas applying glutamine to the basal membrane (simulating parenteral nutrition) does not.[24]

There appears to be a linear association between the size of the caloric deficit and the subsequent atrophy that occurs in the intestine, which is notable within 48 hours.[25] Any effect of hypocaloric feeding will be magnified when a diet is fed that is deficient. In those cases, protein synthesis – including collagen- can be profoundly impaired.[26]

Pre-operative feeding

For some cases we see, there is no alternative to immediate surgical intervention. Those cases would include surgical emergencies such as gastric dilation-volvulus, intestinal foreign bodies, and intestinal perforation. However, for other cases, such as chronic diarrhoea or intestinal mass excision, procurement of biopsy specimens or resection of a mass, are not urgent procedures. A proportion of those cases are malnourished at the time of presentation, and may be in a state of catabolism. Added to that, poor intake post-operatively may well further hinder recovery. These concerns have led to increased interest in whether improved nutrition prior to surgery might significantly affect outcome.

Human patients with intestinal cancer who have a poor nutritional status have a higher risk of an adverse outcome including higher mortality rate.[27] It is often unsure if such observations are indicative of the effect of nutrition on surgical outcome, or simply that sicker patients are more likely to have a poorer nutritional status. The best evidence for the former, comes from studies that show that increasing intake – especially of protein – during the immediate pre-operative period, significantly improves outcome in cancer patients undergoing intestinal resection.[28] Thus, consideration should always be given to whether a delay in surgery is warranted, during which time attention can be given to improving the nutritional status. However, there is little veterinary experience, and no evidence to guide decisions as to what to feed, how long to delay, or even which patients would benefit the most.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

18

Post-operative feeding

The key surgical determinants of anastomosis healing are:

- Excessive resection
- Excessive tension on the anastomotic site
- Disrupted blood supply
- Peritonitis

Those factors are almost solely within the domain of the surgeon. Outside of those, pre- and post-operative feeding are paramount.

The effect of early enteral nutrition has been evaluated in dogs with severe parvoviral enteritis and in cats with severe mucosal damage from methotrexate toxicity. Early enteral nutrition in canine parvovirus reduced the time for normalization of demeanour, appetite, vomiting, and diarrhoea, increased bodyweight, and may have improved mucosal permeability compared with the traditional approach of fasting until resolution of vomiting.[23] In methotrexate-induced enteritis, feeding a complex diet abrogated the proximal small intestinal atrophy and bacterial translocation associated with feeding an amino acid-based purified diet, and was associated with a marked attenuation of the clinical signs associated with the toxicity.[21,29] In contrast, when dogs that presented with severe haemorrhagic gastroenteritis were fed a commercial dry hydrolyzed protein diet soon after presentation, there was an initial increase in the frequency of vomiting, despite being fed at below maintenance rates.[30] Thus early reintroduction of feeding does not seem to exacerbate disease even in severely affected animals, and complex diets appear to be superior to purified diets in some models. Clinicians must make individual decisions about the risks and benefits of feeding in patients with persistent vomiting.

Immediate post-operative feeding significantly increases the strength of anastomosis sites.[31] Although the presence of luminal nutrients is clearly important, the simple presence of intestinal contents, and the effect of peristalsis is sufficient to increase healing, fibroplasia, and surgical site strength. Mechanical loading stimulates fibroplasia, even without luminal nutrients, as there is a difference between healing rates in animals fasted, and those force fed water.[32]

It can be seen then that not only can the traditional concerns of feeding immediately post-operatively be allayed, but there are considerable arguments for not delaying feeding at all. However, it is unlikely that attempting to feed the daily maintenance energy requirements (MER) is a sensible approach in the short-term management of dogs and cats immediately post-operatively, especially if they are severely ill. Therefore, if only 25% of the animals resting energy requirements (RER) is fed as a highly digestible, low fat diet, mucosal recovery may be optimized, and exacerbation of any diarrhoea or vomiting minimized. This has led to the concept of "minimal luminal nutrition". At the current point of understanding, the ideal dietary characteristics would be:

- High digestibility. This is easier to recommend than it is to specifically practice. Most commercial premium dry diets would qualify, as would many home-prepared ingredients. For protein sources, cooked fresh chicken or fish, cottage cheese, or egg would qualify. Cooked white rice or potato are suitable carbohydrate sources, although rice may be superior (see below). Commercially canned diets generally have a lower

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

19

digestibility than dry diets, often have a high fat or viscous fibre content, and thus cannot be recommended over a similar dry product. However, there is no evidence that the difference in digestibility has any clinically measurable consequences.

- Low fat. No fat-titration studies have been performed to guide firm recommendations. However, a pragmatic recommendation would be to choose the lowest fat content available. An almost arbitrary cut off of 20% of ME could be made.
- Novel antigen content. For cases with existing enteritis, strict adherence to protein novelty is not prioritized over other considerations, and simple avoidance of the staple dietary protein sources of the particular patient is prudent, without being excessive. Some hydrolyzed protein diets are also excellent choices.[33] However, extensively hydrolysed formulae may not produce the mucosal stimulation required, have lower protein contents, and may be less effective than intact protein diets.[34]
- Dietary fibre content. Some fermentable fibre is almost always beneficial, especially following colonic surgery, whilst excessive contents can exacerbate delayed gastric emptying, diarrhoea, flatulence, and abdominal pain. An empirical recommendation is to select diets that contain less than 8% dietary fibre, or less than 5% crude fibre.
- Initial feeding should not exceed 25% of the calculated RER, divided into 3 feeds per day. This amount can be rapidly increased with clinical improvement.

Few commercial diets are currently available that could be considered ideal in all respects, and commercial formulations change such that firm recommendations cannot be made. Most commercial diets both provide significantly more fat (> 25% of ME) but are complete and balanced. In addition, when feeding as little as 25% of RER, it is unlikely that the fat content will be sufficient to exacerbate post-operative vomiting or diarrhoea, if less than 30% of ME is composed of fat.

The evaluation of diets formulated around protein hydrolysates such as Hill's z/d, Nestle-Purina HA, and Royal Canin Anallergenic, warrants further study. Despite the greater than ideal fat content, the combination of high digestibility and reduced antigenicity make them attractive options for the management of acute gastroenteritis. It may be that the degree of hydrolysis is influential, and not all hydrolysed diets may be equally effective. None-the-less, it is likely that the difference in efficacy between individual diets is considerably less than the difference between early feeding, and the traditional approach of fasting.

Concerns and problems with early enteral feeding

Vomiting: The most commonly voiced objection is with patients with vomiting.[30] As mentioned above, vomiting in dogs with CPV is reduced when they are force fed, even when fed rather aggressively.[23] The sensation of nausea is greatest on an empty stomach, as is evidenced by intractable nausea and vomiting in early pregnancy, which can be effectively managed by nasogastric tube feeding.[35] Vomiting can be exacerbated by over-feeding, especially early in the disease, or by using a poorly digestible or perhaps - high fat formula. However, with judicious introduction (e.g. 25% RER day one), and the use of highly digestible diets, vomiting will not be increased. If vomiting results in little retention of food then outflow obstruction or complete gastric ileus should be suspected.

Pancreatitis: Oral feeding is often withheld when acute pancreatitis is a differential diagnosis. In a recent small study of canine acute pancreatits, early enteral nutrition was compared with parenteral nutrition.[36] Placement of an oesophagostomy tube and

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

20

instigation of feeding on the day of admission was not associated with signs of abdominal pain or clinical complications, and vomiting and regurgitation was significantly less in the enterally fed group. Although a much larger study is required to determine the magnitude of the benefit, it is clear that early enteral is not associated with a poorer outcome than parenteral, and it is superior to fasting.

Diarrhoea: Diarrhoea is the most common complication of tube feeding in patients in the MUVTH. Diarrhoea is a common complication of tube feeding, and there are several potential mechanisms that should be considered in any patient. Firstly, quantity and rate of feeding should be evaluated. If diarrhoea develops, reduce feeding back to 25% of RER, and if the faeces do not improve in 24 hours, consider another mechanism. If the diarrhoea improves, gradually increase the feeding again until 75% of the previous volume is fed. The presence of fermentable fibre is very important for optimal intestinal function, and some patients may require an increased fibre content than is being fed. In long term patients, a soluble, fermentable fibre source (e.g. hydrolysed guar gum, Benefibre®) can be added. This should be titrated to effect. It is unlikely that a higher fibre content than 10% dry matter will be helpful, so if this is reached without effect, the fibre should be discontinued. If a high fat diet (>30% ME) is being fed, transition to a lower fat diet.

References

1. Spychalska-Zwolinska M, Zwolinski T, Anaszewicz M, et al. The influence of patients' nutritional status on the prevalence, course and treatment outcomes of lower limb ischemia: an overview of current evidence. Int Angiol 2018;37:100-111.
2. Zangenberg MS, Horesh N, Kopylov U, et al. Preoperative optimization of patients with inflammatory bowel disease undergoing gastrointestinal surgery: a systematic review. Int J Colorectal Dis 2017;32:1663-1676.
3. Tobert CM, Hamilton-Reeves JM, Norian LA, et al. Emerging Impact of Malnutrition on Surgical Patients: Literature Review and Potential Implications for Cystectomy in Bladder Cancer. J Urol 2017;198:511-519.
4. Ziegler TR, Evans ME, Fernandez-Estivariz C, et al. Trophic and cytoprotective nutrition for intestinal adaptation, mucosal repair, and barrier function. Annu Rev Nutr 2003;23:229-261.
5. Kudsk KA. Effect of route and type of nutrition on intestine-derived inflammatory responses. Am J Surg 2003;185:16-21.
6. Jonas CR, Estivariz CF, Jones DP, et al. Keratinocyte growth factor enhances glutathione redox state in rat intestinal mucosa during nutritional repletion. J Nutr 1999;129:1278-1284.
7. Lippert AC, Faulkner JE, Evans AT, et al. Total parenteral nutrition in clinically normal cats. J Am Vet Med Assoc 1989;194:669-676.
8. Holt PR, Yeh KY. Effects of starvation and refeeding on jejunal disaccharidase activity. Dig Dis Sci 1992;37:827-832.
9. Zijlstra RT, Donovan SM, Odle J, et al. Protein-energy malnutrition delays small-intestinal recovery in neonatal pigs infected with rotavirus. J Nutr 1997;127:1118-1127.
10. Winter TA. The effects of undernutrition and refeeding on metabolism and digestive function. Curr Opin Clin Nutr Metab Care 2006;9:596-602.
11. Altaf W, Perveen S, Rehman KU, et al. Zinc supplementation in oral rehydration solutions: experimental assessment and mechanisms of action. J Am Coll Nutr 2002;21:26-32.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

21

12. Sturniolo GC, Di LV, Ferronato A, et al. Zinc supplementation tightens "leaky gut" in Crohn's disease. Inflamm Bowel Dis 2001;7:94-98.

13. Renegar KB, Johnson CD, Dewitt RC, et al. Impairment of mucosal immunity by total parenteral nutrition: requirement for IgA in murine nasotracheal anti-influenza immunity. J Immunol 2001;166:819-825.

14. Thor PJ, Copeland EM, Dudrick SJ, et al. Effect of long-term parenteral feeding on gastric secretion in dogs. Am J Physiol 1977;232:E39-43.

15. Dionigi R, Ariszonta, Dominioni L, et al. The effects of total parenteral nutrition on immunodepression due to malnutrition. Ann Surg 1977;185:467-474.

16. Fukatsu K, Lundberg AH, Hanna MK, et al. Route of nutrition influences intercellular adhesion molecule-1 expression and neutrophil accumulation in intestine. Arch Surg 1999;134:1055-1060.

17. Fukatsu K, Kudsk KA, Zarzaur BL, et al. TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression. Shock 2001;15:318-322.

18. Ikeda S, Kudsk KA, Fukatsu K, et al. Enteral feeding preserves mucosal immunity despite in vivo MAdCAM-1 blockade of lymphocyte homing. Ann Surg 2003;237:677-685; discussion 685.

19. Johnson CD, Kudsk KA, Fukatsu K, et al. Route of nutrition influences generation of antibody-forming cells and initial defense to an active viral infection in the upper respiratory tract. Ann Surg 2003;237:565-573.

20. Kudsk KA, Wu Y, Fukatsu K, et al. Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels. JPEN J Parenter Enteral Nutr 2000;24:270-274; discussion 274-275.

21. Marks SL, Cook AK, Reader R, et al. Effects of glutamine supplementation of an amino acid-based purified diet on intestinal mucosal integrity in cats with methotrexate-induced enteritis. AmJVet Res 1999;60:755-763.

22. Hernandez G, Velasco N, Wainstein C, et al. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care 1999;14:73-77.

23. Mohr AJ, Leisewitz AL, Jacobson LS, et al. Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. J Vet Intern Med 2003;17:791-798.

24. Le Bacquer O, Laboisse C, Darmaun D. Glutamine preserves protein synthesis and paracellular permeability in Caco-2 cells submitted to "luminal fasting". Am J Physiol Gastrointest Liver Physiol 2003;285:G128-136.

25. Chappell VL, Thompson MD, Jeschke MG, et al. Effects of incremental starvation on gut mucosa. Dig Dis Sci 2003;48:765-769.

26. Leite SN, Jordao Junior AA, Andrade TA, et al. Experimental models of malnutrition and its effect on skin trophism. An Bras Dermatol 2011;86:681-688.

27. Schwegler I, Von Holzen A, Gutzwiller JP, et al. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. Br J Surg 2010;97:92-97.

28. Manasek V, Bezdek K, Foltys A, et al. The impact of high protein nutritional support on clinical outcomes and treatment costs of patients with colorectal cancer. Klin Onkol 2016;29:351-357.

29. Marks SL, Cook AK, Griffey S, et al. Dietary modulation of methotrexate-induced enteritis in cats. Am J Vet Res 1997;58:989-996.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

22

30. Will K, Nolte I, Zentek J. Early enteral nutrition in young dogs suffering from haemorrhagic gastroenteritis. J Vet Med A Physiol Pathol Clin Med 2005;52:371-376.

31. Khalili TM, Navarro RA, Middleton Y, et al. Early postoperative enteral feeding increases anastomotic strength in a peritonitis model. The American Journal of Surgery 2001;182:621-624.

32. Tadano S, Terashima H, Fukuzawa J, et al. Early postoperative oral intake accelerates upper gastrointestinal anastomotic healing in the rat model. J Surg Res 2011;169:202-208.

33. Cave NJ. Hydrolyzed protein diets for dogs and cats. Veterinary Clinics of North America-Small Animal Practice 2006;36:1251-+.

34. Zarrabian S, Buts JP, Fromont G, et al. Effects of alimentary intact proteins and their oligopeptide hydrolysate on growth, nitrogen retention, and small bowel adaptation in inflammatory turpentine rat. Nutrition 1999;15:474-480.

35. Hsu JJ, Rene C-G, Nelson DK, et al. Nasogastric enteral feeding in the management of hyperemesis gravidarum. Obstet Gynecol 1996;88:343-346.

36. Mansfield CS, James FE, Steiner JM, et al. A pilot study to assess tolerability of early enteral nutrition via esophagostomy tube feeding in dogs with severe acute pancreatitis. J Vet Intern Med 2011;25:419-425.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management for gastrointestinal surgery

23

Dietary management of chronic inflammatory enteropathies

Nick Cave BVSc, MVSc, PhD, DipACVIM (Nutrition)
School of Veterinary Sciences
Massey University, Palmerston North, New Zealand

In the canon of clinical nutrition, the inflammatory bowel diseases are amongst those where dietary manipulation is considered an essential part of the management. The dietary considerations for management include:

- Protein antigens
- Digestibility
- Nutrient deficiency
- Fat absorption
- Anti-inflammatory effects
- Manipulation of the microflora

Protein and amino acids

Dietary protein interacts with the gastrointestinal tract in several ways. It is a source of essential amino acids for the gastrointestinal tract, is a source of dispensable amino acids for oxidation by the gastrointestinal tract, is a source of energy and amino acids for the luminal flora, and is also the largest source of foreign antigens.[1-3] The digestibility of protein affects all these interactions. Protein digestibility is an inherent characteristic of the protein, but it also varies between animals in health, and notably in disease (e.g. exocrine pancreatic insufficiency), and is modified by food processing to either increase or decrease digestibility.

Regardless of the underlying etiology for any given patient, abnormal immune responses to dietary antigens are often suspected, and the clinical response to novel protein diets supports that hypothesis [4,5]. Exaggerated humoral and cellular responses, and clinical food intolerance have been recorded in human IBD patients.[6-8]   Serum IgG concentrations specific to dietary antigens are consistently greater in dogs with chronic gastrointestinal disease than normal dogs, and faecal IgE specific to dietary antigens is consistently found in Soft Coated Wheaten terriers with IBD.[9,10] However, the frequency with which these might occur and the significance that immune responses play in the pathogenesis of canine and feline IBD are unknown.

Also unknown in any given patient is whether any abnormal immune response to the diet is the cause or result of a mucosal infiltrate. If the cause, it is expected that removal of the inciting antigen would lead to improvement. If the effect, it still may be that removing the largest single source of antigen during an elimination-diet trial is sufficient to reduce the inflammatory stimulus, allowing restoration of normal intestinal immunity.

Because of the consistent partial or complete response, restriction or manipulation of individual dietary components is perhaps the single most important factor in the treatment of IBD, and may be sufficient in mild cases. Despite this fact, there is a paucity of information pertaining to the nutritional requirements of dogs and cats with IBD.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

24

The theoretical basis for the use of protein hydrolysate diets in IBD is that a reduction in immunogenic epitopes being presented to the mucosal immune system whilst dysregulation is present, will increase the potential for resolution. Thus the argument for the use of a hydrolysate diet is independent of whether a dietary specific immunological response is suspected to be present or not. Experience with protein hydrolysate diets is increasing, and anecdotally they appear to be very effective adjuncts to pharmacological therapy, even as sole therapy.

Digestibility

The inflammatory milieu in the intestine causes vilus blunting and a reduced surface area, which when coupled with reduced brush boarder enzyme activity leads to significantly reduced diet digestibility. Feeding a highly digestible diet is important for improving the nutritional status, reduces the antigenic load, and reduces signs of maldigestion/malabsorption. It is common for IBD patients to show some degree of improvement when transitioned to a higher digestibility diet, independent of any other factor. However, "feeding a highly digestible diet" is easier to recommend than it is to specifically practice. Most commercial premium dry diets would qualify, as would many home-prepared ingredients. Of particular note, the commercially available hydrolyzed protein diets are extremely highly digestible.

Nutrient deficiency

The basic deficiencies of IBD such as caloric and protein deficiency, are managed through feeding a highly digestible, novel or hydrolysed protein diet.

Low serum B12 and/or folate have been described in cats in association with a wide variety of gastrointestinal disease including IBD [11,12]. In one study, cats affected with IBD apparently had a greatly decreased serum half-life of B12, which may have contributed to the deficiency [12]. However, not all authors have reported common B12 deficiency in cats with IBD. In one study in the United Kingdom, B12 deficiency was extremely rare, although only 5 cats with IBD were included [13]. In a further study of serum B12 and folate concentrations in cats with a variety of diseases in the United Kingdom, there was no association between the presence of gastrointestinal disease and serum B12 or folate concentrations.[11]

Cats with low serum B12, and with low B12/folate have been reported to have a lower body condition score than non-deficient cats [11]. It is likely that mucosal repair is impeded in the initial management of IBD when B12 is deficient and its absorption impaired, and there is anecdotal evidence that correction of deficiency may reduce the requirement for immunosuppression, or that response to therapy may be limited until it is corrected. In a study of cats severely deficient in B12 with chronic intestinal disease, vitamin B12 supplementation resulted in increased weight gain, reduced vomiting, and reduced diarrhoea in most cats.[14] Unfortunately, the numbers of cats studied was small, the specific diseases were not defined, and there was no control group. However, in the absence of clear evidence, and in light of their safety, consideration should be given to B12 assays in the initial evaluation of dogs and cats with chronic intestinal disease, and parenteral administration during the initial management of IBD if low serum cobalamin is identified. Dogs and cats are typically supplemented with B12 at a dose of 250 µg (cats) or 500 µg (dogs) per dose, subcutaneously or intramuscularly, weekly for 4 to 5 weeks [12]. No

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

25

study has yet evaluated the clinical response to folate supplementation in dogs or cats with chronic intestinal disease.

Vitamin D deficiency is increasingly recognised as a component of the disease in perhaps the majority of patients with IBD, with the risk of deficiency being higher with higher disease grades.[15-17] Vitamin D, along with the other fat soluble vitamins, may be malabsorbed as the result of lymphatic obstruction leading to the loss of chylomiocrons into the lumen. Some animals with a severe protein-losing enteropathy may have a hypocalcaemia that is disproportional to the hypoalbuminaemia, or does not resolve with improving serum albumin. Hypovitaminosis D should be suspected. However, beyond its role in modulating intestinal   calcium absorption, vitamin D has effects on a wide variety of cells. Suboptimal vitamin D status impairs intestinal microbial defense, exaggerates Th2-lymphocyte responses, and contributes to the pathogenesis of IBD. Assaying 25-OHD$_3$ is not commonplace in the diagnostic evaluation of IBD, but probably should be, as supplementation of deficient patients is likely to speed recovery and may significantly improve the prognosis.

Vitamin K deficiency leading to coagulopathy and clinically recognisable haemorrhage has been reported to occur commonly in cats in association with IBD and may also occur in dogs [18]. Coagulation tests normalised in all the cats reported that were treated with parenteral vitamin K1 (2.5–5 mg per cat, repeated 2 or 3 times at 12-hour intervals). All affected cats had severe IBD, and some had concurrent cholangiohepatitis.

Fat
Dietary fat is an important source of energy and animals with chronic intestinal disease are frequently malnourished and thus may benefit greatly from higher fat diets. In addition, the absorption of dietary fat is required for the concurrent optimal absorption of the fat soluble vitamins A, D, E, and K. The absorption of fat through intestinal lymphatics increases lymphatic flow rates and pressure, and luminal bile-acid fat micelles increase capillary permeability resulting in a postprandial increase in intestinal lymph production.[19] Triacylglycerides (TAG) are hydrolysed in the intestinal lumen prior to uptake by the enterocytes, which absorb non-esterified fatty acids (NEFA) and mono-acylglycerides (MAG) with the remaining fatty acid at the sn-2 position of the glycerol backbone. A large proportion of medium-chain TAGs (6-12 carbon) are absorbed directly into the blood stream rather than the lymphatics, and they increase lymphatic pressures less than conventional long-chain TAGs.[20] This effect can be important when there is leakage of high protein fluid from congested lymphatics.

Fibre, and prebiosis
Dietary fibre can be practically, if not precisely defined as carbohydrates that are resistant to digestion and absorption in the small intestine, which are then available to be completely or partially fermented by resident microflora in the distal small intestine, and large intestine.[21] Most fibres are polysaccharides, although others, such as lignin are not. Dietary fibre can be classified according to physical or chemical characteristics, according to its effects on bowel microflora, or its effects on specific variables in the whole animal. In regards to its effects on gastrointestinal physiology and pathophysiology, the most important characteristics are viscosity, and fermentability. Some types of soluble dietary fibre increase the viscosity of water when in solution, and have the capacity to retain water

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

26

within the viscous gel ("water-holding capacity"). This effect increases faecal water content and mass. Psyllium hydrocolloid (e.g. Metamucil®) has a greater water-holding effect than pea, oat, or sugar beet fibre.[22] The formation of viscous gels slows gastric emptying, increases small intestinal transit times, slows the absorption and reduces the digestibility of some nutrients.[23,24] Viscosity of ileal contents increases greatly with certain soluble dietary fibres.[25] This effect of fibre can be thought of as an anti-nutritive effect, and excessive dietary fibre may be counter-productive. The gel-forming component of psyllium seed husk is not readily fermented by human colonic microflora and contributes significantly to its effect on increasing faecal bulk.

Some dietary fibres can be degraded by colonic bacteria (fermented) including, pectin, inulin, guar gum and oligosaccharides (e.g. fructooligosaccharides (FOS)).[26] Fermentation will produce H_2, CO_2, H_2O, and methane, whilst volatile fatty acids (acetone, proprionate, and butyrate) will be produced during less complete utilisation.[24] The effect of providing such substrate in the bowel lumen is to create a selection advantage to those species best adapted to its use. When the shift in microbiota has a positive effect on the host, the fibre is defined as a prebiotic. Proposed positive effects include reduction in mucosal adherence of pathogenic species, reduction in the numbers of pathogenic species, and immune-modulation of the host.[26-29] Fructooligosaccharides, inulin, and resistant starch lead to significant increases in the fermentative production of butyrate in dogs, whilst in both dogs and cats, SCFA production from other sources ranked from most to least is: citrus pectin > citrus pulp > beet pulp > cellulose.[30,31]

In most domestic species studied, including dogs, butyrate is oxidised by colonocytes, and in dogs is also oxidised by enterocytes.[32,33] It has been observed that when colonocytes are provided with butyrate, glutamine, glucose, and proprionate, the most used substrate is butyrate.[33] In response to butyrate from fibre fermentation, colonocyte proliferation increases, intestinal mucosal weight increases, water and electrolyte absorption increases, and brush boarder enzyme activities increase.[34-37] SCFA, butyrate in particular, stimulate longitudinal but not circular colonic smooth muscle contractions via a direct effect on smooth muscle and improve the arboreal passage of faeces in the colon.[38] Luminal butyrate also increases mucin secretion, which reduces microbial adhesion and translocation and improves secretory IgA function.[39]

At reasonable physiological concentrations, colonic luminal butyrate suppresses the immune response by inhibiting the formation of the nuclear transcription factor NF-κB in colonocytes, endothelial cells, and resident leukocytes.[40,41] NF-κB regulates several cellular processes that vary according to the individual cell type and activation state, but includes adaptive and innate immune responses in the intestinal tract with several inflammatory cytokines and cell adhesion molecules under direct transcriptional control.[42] The ability of butyrate to inhibit NF-κB activation and signalling appears to be the mechanism for the anti-inflammatory effect of butyrate in colitis.[40,43]

The combined effects of fibre fermentation with the absorptive effects of non-fermentable fibre make mixed fibre sources (e.g. soybean hulls, beet pulp, psyllium) theoretically ideal for the management of colitis, over more completely fermentable fibre sources (e.g. hydrolysed guar gum). In addition, the most highly fermentable fibres may also increase the production of methane which has the capacity to disturb motility and exacerbate signs.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

27

In other cases, more highly fermentable sources that produce higher concentrations of butyrate in the more proximal colon may be more effective that less fermentable sources of fibre. Clearly, the choice of fibre is important in certain disease states, however insufficient information is available in feline and canine medicine to make any informed therapeutic recommendations beyond initially introducing mixed fermentable sources, then proceeding with trial and error if required.   The addition of powdered products to diets can be easily achieved with moist diets, but often make dry diets unpalatable, even when mixed with water or stock

Conclusion

The optimal nutritional approach for dogs and cats with IBD remains to be determined, and certainly varies from animal to animal. Although there are several mechanisms by which diet can affect the progression, maintenance, or resolution of chronic mucosal inflammation, it is undetermined how important any individual component is. None-the-less, proper dietary management can result in decreased utilization or dosage of pharmacologic therapy, and in some cases can lead to clinical resolution as a sole therapy. The current recommended management following diagnosis is as follows:

- Assess the nutritional status of the patient. This will include physical parameters such as body condition, lean body mass, history of recent weight loss, current appetite, hydration, presence of oedema, and coat condition.
- Address specific concerns regarding malnutrition. This may include vitamin B12, D, or vitamin K1 supplementation
- Address anorexia through pharmacological means (i.e. specific therapy for IBD) and consider supplemental or supportive nutrition in severely malnourished individuals. Indicators for the need for supportive nutrition would include persistent anorexia, weight loss of > 10% bodyweight, anaemia, hypoalbuminaemia, and a body condition score of 3 or less with poor appetite.
- Select a highly digestible, novel protein or hydrolyzed protein diet and feed exclusively until immunosuppressive therapy can be discontinued.
- Consider fat restriction in severe cases, or where there is histological evidence of lymphangiectasia.
- If dietary fat is not limiting, then consider enrichment of the diet with n-3 PUFA using fish oil, to achieve a crude ratio of < 2:1, n-6:n-3.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

28

References

1. Ames JM, Wynne A, Hofmann A, et al. The effect of a model melanoidin mixture on faecal bacterial populations in vitro. BrJNutr 1999;82:489-495.
2. Brandtzaeg P. Current Understanding of Gastrointestinal Immunoregulation and Its Relation to Food Allergy. AnnNYAcadSci 2002;964:13-45.
3. Bounous G, Kongshavn PA. Differential effect of dietary protein type on the B-cell and T-cell immune responses in mice. JNutr 1985;115:1403-1408.
4. Nelson RW, Dimperio ME, Long GG. Lymphocytic-plasmacytic colitis in the cat. J Am Vet Med Assoc 1984;184:1133-1135.
5. Nelson RW, Stookey LJ, Kazacos E. Nutritional management of idiopathic chronic colitis in the dog. J Vet Intern Med 1988;2:133-137.
6. Pearson M, Teahon K, Levi AJ, et al. Food intolerance and Crohn's disease. Gut 1993;34:783-787.
7. Van Den BJ, Cahill J, Emmanuel AV, et al. Gut mucosal response to food antigens in Crohn's disease. Aliment Pharmacol Ther 2002;16:1903-1915.
8. Van Den BJ, Kamm MA, Knight SC. Immune sensitization to food, yeast and bacteria in Crohn's disease. Aliment Pharmacol Ther 2001;15:1647-1653.
9. Foster AP, Knowles TG, Moore AH, et al. Serum IgE and IgG responses to food antigens in normal and atopic dogs, and dogs with gastrointestinal disease. Vet ImmunolImmunopathol 2003;92:113-124.
10. Vaden SL, Hammerberg B, Davenport DJ, et al. Food hypersensitivity reactions in Soft Coated Wheaten Terriers with protein-losing enteropathy or protein-losing nephropathy or both: gastroscopic food sensitivity testing, dietary provocation, and fecal immunoglobulin E. J VetInternMed2000Jan-Feb;14(1):60-7 2000;14:60-67.
11. Reed N, Gunn-Moore D, Simpson K. Cobalamin, folate and inorganic phosphate abnormalities in ill cats. Journal of Feline Medicine & Surgery 2007;9:278-288.
12. Simpson KW, Fyfe J, Cornetta A, et al. Subnormal concentrations of serum cobalamin (vitamin B12) in cats with gastrointestinal disease. J Vet Intern Med 2001;15:26-32.
13. Ibarrola P, Blackwood L, Graham PA, et al. Hypocobalaminaemia is uncommon in cats in the United Kingdom. Journal of Feline Medicine & Surgery 2005;7:341-348.
14. Ruaux CG, Steiner JM, Williams DA. Early biochemical and clinical responses to cobalamin supplementation in cats with signs of gastrointestinal disease and severe hypocobalaminemia. J Vet Intern Med 2005;19:155-160.
15. Gow AG, Else R, Evans H, et al. Hypovitaminosis D in dogs with inflammatory bowel disease and hypoalbuminaemia. J Small Anim Pract 2011;52:410-417.
16. Mellanby RJ, Mellor PJ, Roulois A, et al. Hypocalcaemia associated with low serum vitamin D metabolite concentrations in two dogs with protein-losing enteropathies. J Small Anim Pract 2005;46:345-351.
17. Titmarsh H, Gow AG, Kilpatrick S, et al. Association of Vitamin D Status and Clinical Outcome in Dogs with a Chronic Enteropathy. J Vet Intern Med 2015;29:1473-1478.
18. Center SA, Warner K, Corbett J, et al. Proteins invoked by vitamin K absence and clotting times in clinically ill cats. J Vet Intern Med 2000;14:292-297.
19. Granger DN, Perry MA, Kvietys PR, et al. Permeability of intestinal capillaries: effects of fat absorption and gastrointestinal hormones. Am J Physiol 1982;242:G194-201.
20. Jensen GL, McGarvey N, Taraszewski R, et al. Lymphatic absorption of enterally fed structured triacylglycerol vs physical mix in a canine model. Am J Clin Nutr 1994;60:518-524.
21. DeVries JW. On defining dietary fibre. Proc Nutr Soc 2003;62:37-43.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

29

22. McBurney MI. Potential water-holding capacity and short-chain fatty acid production from purified fiber sources in a fecal incubation system. Nutrition 1991;7:421-424.

23. Ashraf W, Lof J, Jin G, et al. Comparative effects of intraduodenal psyllium and senna on canine small bowel motility. Aliment Pharmacol Ther 1994;8:329-336.

24. Bednar GE, Patil AR, Murray SM, et al. Starch and fiber fractions in selected food and feed ingredients affect their small intestinal digestibility and fermentability and their large bowel fermentability in vitro in a canine model. J Nutr 2001;131:276-286.

25. Dikeman CL, Murphy MR, Fahey GC, Jr. Diet type affects viscosity of ileal digesta of dogs and simulated gastric and small intestinal digesta. J Anim Physiol Anim Nutr (Berl) 2007;91:139-147.

26. Blaut M. Relationship of prebiotics and food to intestinal microflora. Eur J Nutr 2002;41 Suppl 1:I11-16.

27. Bamba T, Kanauchi O, Andoh A, et al. A new prebiotic from germinated barley for nutraceutical treatment of ulcerative colitis. J Gastroenterol Hepatol 2002;17:818-824.

28. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics--approaching a definition. AmJClinNutr 2001;73:361S-364S.

29. Guarner F, Casellas F, Borruel N, et al. Role of microecology in chronic inflammatory bowel diseases. Eur J Clin Nutr 2002;56 Supplement 4:S34-S38.

30. Sunvold GD, Hussein HS, Fahey GC, Jr., et al. In vitro fermentation of cellulose, beet pulp, citrus pulp, and citrus pectin using fecal inoculum from cats, dogs, horses, humans, and pigs and ruminal fluid from cattle. J Anim Sci 1995;73:3639-3648.

31. Vickers RJ, Sunvold GD, Kelley RL, et al. Comparison of fermentation of selected fructooligosaccharides and other fiber substrates by canine colonic microflora. Am J Vet Res 2001;62:609-615.

32. Marsman KE, McBurney MI. Dietary fiber increases oxidative metabolism in colonocytes but not in distal small intestinal enterocytes isolated from rats. J Nutr 1995;125:273-282.

33. Beaulieu AD, Drackley JK, Overton TR, et al. Isolated canine and murine intestinal cells exhibit a different pattern of fuel utilization for oxidative metabolism. J Anim Sci 2002;80:1223-1232.

34. Farness PL, Schneeman BO. Effects of dietary cellulose, pectin and oat bran on the small intestine in the rat. J Nutr 1982;112:1315-1319.

35. Poksay KS, Schneeman BO. Pancreatic and intestinal response to dietary guar gum in rats. J Nutr 1983;113:1544-1549.

36. Marsman KE, McBurney MI. Dietary fiber and short-chain fatty acids affect cell proliferation and protein synthesis in isolated rat colonocytes. J Nutr 1996;126:1429-1437.

37. Forman LP, Schneeman BO. Dietary Pectin's effect on starch utilization in rats. J Nutr 1982;112:528-533.

38. McManus CM, Michel KE, Simon DM, et al. Effect of short-chain fatty acids on contraction of smooth muscle in the canine colon. Am J Vet Res 2002;63:295-300.

39. Barcelo A, Claustre J, Moro F, et al. Mucin secretion is modulated by luminal factors in the isolated vascularly perfused rat colon. Gut 2000;46:218-224.

40. Luhrs H, Gerke T, Muller JG, et al. Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 2002;37:458-466.

41. Yin L, Laevsky G, Giardina C. Butyrate suppression of colonocyte NF-kappa B activation and cellular proteasome activity. J Biol Chem 2001;276:44641-44646.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

30

42. Perkins ND. Integrating cell-signalling pathways with NF-kappaB and IKK function. Nat Rev Mol Cell Biol 2007;8:49-62.

43. Venkatraman A, Ramakrishna BS, Shaji RV, et al. Amelioration of dextran sulfate colitis by butyrate: role of heat shock protein 70 and NF-kappaB. Am J Physiol Gastrointest Liver Physiol 2003;285:G177-184.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of chronic inflammatory enteropathies

31

Dietary management of patients with acute vomiting or diarrhoea

Nick Cave BVSc, MVSc, PhD, DipACVIM (Nutrition)
School of Veterinary Sciences
Massey University, Palmerston North, New Zealand

Perhaps no other organ system is so directly and immediately affected by nutrition than the gastrointestinal tract. Timing and frequency of feeding, route of feeding, macronutrient and micronutrient compositions of the diet have profound influences on oral and intestinal health. In addition to the direct effect of diet on the body, there is a considerable indirect effect through dietary influences on the intestinal microflora. However, there are few controlled clinical trials that have evaluated specific dietary manipulation in either prevention or management of canine and feline gastroenteric diseases. Acute gastroenteritis is a common reason for presentation of cats and dogs to veterinarians. Common causes include bacterial toxin ingestion (e.g. staphylococcal enteritis), bacterial endotoxin production (e.g. Clostridium perfringens enteritis), viral enteritis (e.g. rotavirus, coronavirus, parvovirus), self-limiting infections (e.g. Cryptosporidium felis and parvum, Coccidia spp), and adverse reactions to food. Because of the transient and non-life threatening nature of many cases, the cause of the majority remains undetermined. Despite ignorance of the exact cause, standard therapy is instigated, of which, dietary management remains the cornerstone. Standard dietary recommendations for dogs and cats with acute gastroenteritis have been to withhold food for 24-48 hours, followed by the introduction of small quantities of a "bland" diet fed 4-6 times per day for 3-7 days. These dietary recommendations have stood the test of time but are based on common assumptions rather than any specific research. Arguments offered in support are that withholding food provides bowel rest, reduces the risk of vomiting, increases bacterial proliferation and fermentation, and produces osmotic diarrhoea.   However, such arguments can be rebutted, or satisfied by optimal feeding. Thus the long-held belief in the value of bowel rest for the treatment of diarrhoea has been challenged by the benefits of "feeding-through" diarrhoea. Recent studies of acute diarrhoea in several species have shown that feeding through diarrhoea maintains greater mucosal barrier integrity.

Benefits of luminal nutrition in acute enteritis

Even in the absence of enteritis, fasting for even as short a period as one day in rats causes a significant decrease in villous height and/or crypt depth in jejunum, ileum, and, to a lesser extent, colon.[1, 2] In addition, fasting is associated with gut mucosal cell impairment marked by decreased levels of reduced glutathione (GSH), the major intracellular antioxidant, enhanced permeability to macromolecules, increased bacterial translocation from the lumen, and increased rates of enterocyte apoptosis.[3] Even with total parenteral nutrition, after 14 days of oral fasting in cats, small intestinal villous atrophy, fusion, and infiltration of the lamina propria with lymphocytes, plasma cells, and neutrophils occurs.[4] Thus oral fasting alone, and in the absence of nutritional deficiency, induces an intestinal insult.

Fasting also significantly reduces the specific activity and expression of certain digestive enzymes in the small bowel mucosa such as disaccharidases, which can lead to impaired digestion following the re-introduction of food.[5] Transient lactase deficiency is common,

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of patients with acute vomiting or diarrhoea

32

particularly after rotavirus gastroenteritis.[6] Occasionally it persists, and lactose intolerance may be a cause of post-gastroenteritis diarrhoea. Gastric and pancreatic secretions are markedly reduced following a period of under-nutrition.[7] Generalized malnutrition, protein depletion, or deficiencies of specific nutrients, including essential fatty acids, folate, zinc, vitamin A, and vitamin B12 inhibit the growth and turnover of the intestinal mucosa. It has long been recognized that small intestinal enterocytes utilize luminally-derived glutamine as their main oxidative fuel (see above). In addition, glutamine provides the carbon skeleton and amino nitrogen required for purine synthesis and hence is critical for normal DNA synthesis involved in enterocyte turnover. Oral supplementation with zinc improves histological recovery, normalizes absorption, decreases permeability, and decreases NF-κB nuclear binding in experimental models of diarrhoea.[8, 9] Additional mechanisms for the effect of zinc treatment on the duration of diarrhoea include improved absorption of water and electrolytes, increased levels of brush border enzymes, and faster regeneration of the intestinal epithelium. Multiple factors, including luminal nutrients, pancreaticobiliary secretions, and humoral agents have been implicated in controlling the intestinal adaptive response after an intestinal insult. Despite the multifactorial regulation of intestinal adaptation, luminal nutrients are fundamental to the adaptive response such that recovery is minimized or prevented in the absence of luminal nutrients. This conclusion is largely based on studies that show significant adaptive intestinal re-growth in rats and dogs fed orally compared with those fed parenterally following an intestinal resection. Indeed even in the absence of an intestinal insult, total parenteral nutrition (TPN) causes dramatic intestinal atrophy in dogs, cats, rats and humans [4, 10, 11]. This fasting-induced atrophy is accompanied by inflammatory cell infiltrates in the lamina propria, increased intestinal permeability, and increased bacterial translocation.

It has long been known that the immunological derangements that accompany malnutrition cannot all be prevented when nutrients are delivered parenterally.[12] A lack of luminal nutrients results in an increased expression of proinflammatory adhesion molecules, especially ICAM-1.[13] This results in an increased number of primed neutrophils adhered to the microvasculature throughout the intestinal tract where they are able to contribute to oxidative and enzymatic tissue damage following activation. Fasting or TPN results in decreases in IL-4 and IL-10 that correlate with decreases in IgA and increases in ICAM-1.[14] Lack of enteral feeding impairs the coordinated system of sensitization, distribution, and interaction of T and B cells important in the production of IgA, in the maintenance of normal gut cytokines, and in the regulation of endothelial inflammation[2, 10, 15, 16]. Thus the lack of luminal nutrients has been described as a "first hit", and increases the inflammatory response to a secondary insult in the GIT, but also the lungs, liver, and potentially other organs as well.

The amino acid glutamine reverses many of these defects and favourably influences the proinflammatory effects of gut starvation.[17] The source of supplemental glutamine can influence gut mucosal glutamine concentrations, suggesting differences in its availability or utilization. Glutamine-rich intact proteins appear to be more effective in increasing mucosal glutamine content than glutamine-enriched solutions.[18] Arginine is an essential amino acid for cats because of their inability to synthesize sufficient quantities in the fasting state. However, beyond its role as an essential intermediate in the ornithine cycle, dietary arginine has long been known to enhance certain aspects of immunity.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of patients with acute vomiting or diarrhoea

33

Even short periods of enteral fasting result in an increase in intestinal permeability in humans. [19] Early refeeding of dogs and cats with acute gastroenteritis has been shown to reduce the increase in intestinal permeability that occurs in response to the inflammation and apoptosis.[18, 20] Some of the effect of luminal feeding may come from the luminal provision of glutamine alone, which can restore enterocyte glutathione concentrations, proteins synthesis, and normalise intestinal permeability. Even in single layer cell cultures of enterocytes, the application of glutamine to the apical (luminal) membrane normalises permeability to a large molecular weight molecule, whereas applying glutamine to the basal membrane (simulating parenteral nutrition) does not. [21]

Veterinary evidence and recommendations

The effect of early enteral nutrition has been evaluated in dogs with severe parvoviral enteritis and in cats with severe mucosal damage from methotrexate toxicity. Early enteral nutrition in canine parvovirus reduced the time for normalization of demeanour, appetite, vomiting, and diarrhoea, increased bodyweight, and may have improved mucosal permeability compared with the traditional approach of fasting until resolution of vomiting.[20] In methotrexate-induced enteritis, feeding a complex diet abrogated the proximal small intestinal atrophy and bacterial translocation associated with feeding an amino acid-based purified diet, and was associated with a marked attenuation of the clinical signs associated with the toxicity.[18] In contrast, when dogs that presented with severe haemorrhagic gastroenteritis were fed a commercial dry hydrolyzed protein diet soon after presentation, there was an initial increase in the frequency of vomiting, despite being fed at below maintenance rates.[22] Thus early reintroduction of feeding does not seem to exacerbate disease even in severely affected animals, and complex diets appear to be superior to purified diets in some models. Clinicians must make individual decisions about the risks and benefits of feeding in patients with persistent vomiting.

It can be seen then that not only can the traditional concerns of feeding in acute gastroenteritis be allayed, but there are considerable arguments for not delaying feeding at all. However, it is unlikely that attempting to feed the daily maintenance energy requirements (MER) is a sensible approach in the short-term management of dogs and cats suffering from acute diarrhoea, and certainly not in cases of frequent vomiting. Therefore, if only 25% of the animals resting energy requirements (RER) is fed as a highly digestible, low fat diet, mucosal recovery may be optimized, and exacerbation of diarrhoea or vomiting minimized. This has led to the concept of "minimal luminal nutrition". At the current point of understanding, the ideal dietary characteristics would be:

- High digestibility. This is easier to recommend than it is to specifically practice. Most commercial premium dry diets would qualify, as would many home-prepared ingredients. For protein sources, cooked fresh chicken or fish, cottage cheese, or egg would qualify. Cooked white rice or potato are suitable carbohydrate sources, although rice may be superior (see below). Commercially canned diets generally have a lower digestibility than dry diets, often have a high fat or viscous fibre content, and thus cannot be recommended over a similar dry product. However, there is no evidence that the difference in digestibility has any clinically measurable consequences.
- Low fat. No fat-titration studies have been performed to guide firm recommendations. However, a pragmatic recommendation would be to choose the lowest fat content available. An almost arbitrary cut off of 20% of ME could be made.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of patients with acute vomiting or diarrhoea

34

- Novel antigen content. For acute gastroenteritis, strict adherence to protein novelty is not prioritized over other considerations, and simple avoidance of the staple dietary protein sources of the particular patient is prudent, without being excessive. Some hydrolyzed protein diets are also excellent choices.[23] However, extensively hydrolysed formulae may not produce the mucosal stimulation required, and may be less effective than intact protein diets.[24]
- Dietary fibre content. Some fermentable fibre is almost always beneficial, whilst excessive contents can exacerbate delayed gastric emptying, diarrhoea, flatulence, and abdominal pain. An empirical recommendation is to select diets that contain less than 8% dietary fibre, or less than 5% crude fibre.
- Initial feeding should not exceed 25% of the calculated RER, divided into 3 feeds per day. This amount can be rapidly increased with clinical improvement.

Few commercial diets are currently available that could be considered ideal in all respects for acute non-specific gastroenteritis and commercial formulations change such that firm recommendations cannot be made. Most commercial diets both provide significantly more fat (> 25% of ME) but are complete and balanced. In addition, when feeding as little as 25% of RER, it is unlikely that the fat content will be sufficient to exacerbate vomiting or diarrhoea, even if more than 30% of ME is composed of fat. When feeding tubes are utilised, clinicians must choose between high fat, high protein formulae, or formulae that are very high in simple carbohydrate. The evaluation of diets formulated around protein hydrolysates such as Hill's z/d, Nestle-Purina HA, and Royal Canin Anallergenic, warrants further study. The combination of high digestibility and reduced antigenicity make them attractive options for the management of acute gastroenteritis. It may be that the degree of hydrolysis is influential, and not all hydrolysed diets may be equally effective. None-the-less, it is likely that the difference in efficacy between individual diets is considerably less than the difference between early feeding, and the traditional approach of fasting.

References

1. Ziegler TR, Evans ME, Fernandez-Estivariz C, Jones DP. Trophic and cytoprotective nutrition for intestinal adaptation, mucosal repair, and barrier function. Annu Rev Nutr 2003;23:229-261.
2. Kudsk KA. Effect of route and type of nutrition on intestine-derived inflammatory responses. Am J Surg 2003;185:16-21.
3. Jonas CR, Estivariz CF, Jones DP et al. Keratinocyte growth factor enhances glutathione redox state in rat intestinal mucosa during nutritional repletion. J Nutr 1999;129:1278-1284.
4. Lippert AC, Faulkner JE, Evans AT, Mullaney TP. Total parenteral nutrition in clinically normal cats. J Am Vet Med Assoc 1989;194:669-676.
5. Holt PR, Yeh KY. Effects of starvation and refeeding on jejunal disaccharidase activity. Dig Dis Sci 1992;37:827-832.
6. Zijlstra RT, Donovan SM, Odle J et al. Protein-energy malnutrition delays small-intestinal recovery in neonatal pigs infected with rotavirus. J Nutr 1997;127:1118-1127.
7. Winter TA. The effects of undernutrition and refeeding on metabolism and digestive function. Curr Opin Clin Nutr Metab Care 2006;9:596-602.
8. Altaf W, Perveen S, Rehman KU et al. Zinc supplementation in oral rehydration solutions: experimental assessment and mechanisms of action. J Am Coll Nutr 2002;21:26-32.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of patients with acute vomiting or diarrhoea

35

9. Sturniolo GC, Di LV, Ferronato A, D'Odorico A, D'Inca R. Zinc supplementation tightens "leaky gut" in Crohn's disease. Inflamm Bowel Dis 2001;7:94-98.

10. Renegar KB, Johnson CD, Dewitt RC et al. Impairment of mucosal immunity by total parenteral nutrition: requirement for IgA in murine nasotracheal anti-influenza immunity. J Immunol 2001;166:819-825.

11. Thor PJ, Copeland EM, Dudrick SJ, Johnson LR. Effect of long-term parenteral feeding on gastric secretion in dogs. Am J Physiol 1977;232:E39-43.

12. Dionigi R, Ariszonta, Dominioni L, Gnes F, Ballabio A. The effects of total parenteral nutrition on immunodepression due to malnutrition. Ann Surg 1977;185:467-474.

13. Fukatsu K, Lundberg AH, Hanna MK et al. Route of nutrition influences intercellular adhesion molecule-1 expression and neutrophil accumulation in intestine. Arch Surg 1999;134:1055-1060.

14. Fukatsu K, Kudsk KA, Zarzaur BL et al. TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression. Shock 2001;15:318-322.

15. Ikeda S, Kudsk KA, Fukatsu K et al. Enteral feeding preserves mucosal immunity despite in vivo MAdCAM-1 blockade of lymphocyte homing. Ann Surg 2003;237:677-685; discussion 685.

16. Johnson CD, Kudsk KA, Fukatsu K, Renegar KB, Zarzaur BL. Route of nutrition influences generation of antibody-forming cells and initial defense to an active viral infection in the upper respiratory tract. Ann Surg 2003;237:565-573.

17. Kudsk KA, Wu Y, Fukatsu K et al. Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels. JPEN J Parenter Enteral Nutr 2000;24:270-274; discussion 274-275.

18. Marks SL, Cook AK, Reader R et al. Effects of glutamine supplementation of an amino acid-based purified diet on intestinal mucosal integrity in cats with methotrexate-induced enteritis. AmJVet Res 1999;60:755-763.

19. Hernandez G, Velasco N, Wainstein C et al. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care 1999;14:73-77.

20. Mohr AJ, Leisewitz AL, Jacobson LS et al. Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. J Vet Intern Med 2003;17:791-798.

21. Le Bacquer O, Laboisse C, Darmaun D. Glutamine preserves protein synthesis and paracellular permeability in Caco-2 cells submitted to "luminal fasting". Am J Physiol Gastrointest Liver Physiol 2003;285:G128-136.

22. Will K, Nolte I, Zentek J. Early enteral nutrition in young dogs suffering from haemorrhagic gastroenteritis. J Vet Med A Physiol Pathol Clin Med 2005;52:371-376.

23. Cave NJ. Hydrolyzed protein diets for dogs and cats. Vet Clin North Am Small Anim Pract 2006;36:1251-1268, vi.

24. Zarrabian S, Buts JP, Fromont G et al. Effects of alimentary intact proteins and their oligopeptide hydrolysate on growth, nitrogen retention, and small bowel adaptation in inflammatory turpentine rat. Nutrition 1999;15:474-480.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Dietary management of patients with acute vomiting or diarrhoea

36

Grain free diets for dogs: What every veterinarian should know

Nick Cave BVSc MVSc PhD DipACVIM (Nutrition)
School of Veterinary Science
Massey University, Palmerston North, New Zealand

In New Zealand, where we remain blissfully free of heartworm, and throughout most of Australia, dilated cardiomyopathy (DCM) is probably the second most common cardiac disease affecting dogs, after myxomatous valvular degeneration. DCM should strictly be defined as a primary myocardial disorder characterized by reduced contractility, and ventricular dilation involving the left or both ventricles, and is idiopathic or genetic in cause.[1] Most cardiologists insist that when a cause other than genetics is known, the disease is not called DCM, but rather as "cardiomyopathy" of that cause. The example *du jour*, is "taurine deficiency cardiomyopathy", though that has not been widely accepted. For simplicity, and in keeping with the literature on the subject at the moment, I will adopt the plebeian approach, and refer to taurine as a cause of DCM.

Taurine and DCM

Taurine is an amino acid that is not incorporated into proteins, but has a very high intracellular concentration, notably in neurons, myocytes, and some leucocytes, and has the highest intracellular-to-plasma concentration gradient of all the normal amino acids. The functions of taurine are many, but osmoregulation and calcium regulation are perhaps the two most important. As an osmoregulator, it is very important in neurons, which accumulate high concentrations during sustained dehydration to preserve cellular integrity without disturbing the membrane potential. In muscle, taurine facilitates the binding of Ca^{2+} to actin, although when asked to explain what that means, the cognoscenti usually engage in a lot of hand waving, and resort to terms such as "not completely elucidated". Nonetheless, in deficient states, there is a reduction in actively contracting elements, and a reduction of the shortening fraction of the ventricle. The reduced cardiac output results in activation of the renin-angiotensin system, and initiation of remodelling pathways to cause eccentric hypertrophy. The resulting increase in wall stress exacerbates the contractile failure, leading to more remodelling, and subsequently, clinical DCM.

Taurine deficiency was identified as a cause of DCM in cats in 1987.[2] Not long after, the same phenomenon was identified in the US in farmed foxes that were fed diets that contained only a small amount of taurine.[3] At that time, it was apparent that domestic dogs differed from foxes, because it had been shown that dogs can synthesise taurine from the dietary sulphur amino acids, methionine and cysteine. However, cats have a very high rate of amino acid oxidation, and have lost any appreciable synthetic capacity, meaning they have a dietary requirement. Similarly, foxes probably have a very low synthetic capacity, meaning that they may have an absolute dietary requirement. Taurine deficiency can also cause DCM in humans, rats, and giant anteaters, and probably many other species.

Dogs and cats differ from mice and men in, amongst other things, the bile salts they synthesise. Bile salts are synthesised from metabolites of cholesterol, of which there are many, but the most common are cholic acid, and chenodeoxycholic acid. To make these functional bile salts, they are conjugated to a water soluble compound. Humans and

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Grain free diets for dogs: What every veterinarian should know

37

rodents conjugate most bile acids to glycine, and a small amount to taurine. In contrast, dogs and cats both exclusively use taurine as the conjugate, and cannot switch to glycine conjugation in taurine deficiency.

Once secreted into the intestine, a proportion of bile salts are hydrolysed by the bacterial enzyme bile salt hydrolase (BSH), yielding a bile acid, and its free conjugate. The conjugate is then available for fermentation by bacteria and is lost to the host. To date, more than 100 different genera of bacteria are known to express BSH, although the amount expressed by the whole intestinal bacteriome varies massively between individuals.[4] Thus, different individuals can have very different taurine turnover, or in the case of dogs and cats different requirements, simply because of the bacteria present in their intestines.

Initial studies into taurine requirements in cats revealed that a cat requires more dietary taurine if it is being fed a canned diet, than when being fed a kibbled diet.[5] The difference can be completely abolished if the cats consuming the canned diet are treated with oral antibiotics, which highlights the role of the intestinal bacteria in causing taurine depletion.[6] The difference in diets was related to the creation of maillard compounds (browning products) during the heating process.[6] These compounds decrease the digestibility of the protein, and provide substrate that promotes the proliferation of BSH-expressing bacteria. Surprisingly, at least to me, was that we did not detect a significant expression of that, or similar enzymes, in the fecal bacteriome of cats fed canned or dry diets in our colony.[7] That remains an inconvenient and mysterious side note for the time being. Nonetheless, modification of the intestinal bacteriome can lead to increased loss of intestinal taurine, and over time, depletion of body stores, and clinical deficiency.

As noted above, dogs are capable of synthesising taurine, and it is not considered an essential nutrient. However, in the early part of the century, dogs with DCM and taurine deficiency were being seen.[8] The mechanism in those cases turned out to be identical to that defined in cats. Certain diets modified the bacteriome and led to bile salt degradation and depletion of taurine. If those diets had a low content of methionine and cysteine, and no taurine, then the dogs were unable to synthesise enough, and deficiency developed. Features that were common to the diets originally incriminated were: no added taurine, low protein content, low methionine/cysteine content, low protein digestibility, and the presence of rice bran. A cruel twist of fate occurred when Nutro, who produced of one of the incriminated diets, sponsored and provided food for the Newfoundland breeders association in the US.[9] A perfect storm. Rice bran appeared to be particularly potent at bacterial modification, and was shown to be capable of accelerating taurine deficiency in cats fed a diet not supplemented with taurine.[10] Manufacturers had several options for dietary correction: increase the protein content, add supplemental methionine/cysteine, change the fibre content, or simply add taurine. Problem solved. Or at least, that is what was thought.

Grain-free diets and DCM
In July 2018, the US Food and Drug Administration (FDA) announced it was investigating a possible link between cases of canine DCM and certain diets.[11] At time of writing, they have produced data on 515 cases reported to the FDA from January 1st 2014, to April 30th 2019.[11] They have released the list of brands "incriminated", but it would be very hard to conclude a causal relationship, since there is uncertainty of the temporal association, most

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Grain free diets for dogs: What every veterinarian should know

38

dogs were exposed to multiple foods, and there is a growing potential for recall bias amongst owners and veterinarians. Nonetheless, more than 90% of products were marketed under the moniker "grain-free", and 93% of reported products included peas and/or lentils as significant ingredients.

Of the diets most strongly associated, there are some familiar common themes. Small or new manufacturers are prominent. A complete absence of testing via feeding trials. The use of unconventional ingredients with unknown digestibilities. The use of protein sources with low contents of sulphur amino acids (legumes). And probably all are rich in plant fibres that have similar or identical effects to the rice bran. And of course none have adequate taurine to offset those features.

The list of breeds is almost completely concordant with the relative risk of DCM in those breeds, coupled with the breed popularity. In fact, of the breeds identified, only Shi Tzu and Pitbulls are not reported breeds of predisposition - if you count arrhythmogenic right ventricular cardiomyopathy as a cause of DCM. And even for those two outlier breeds, severe mitral valvular disease can lead eventually to myocardial failure that can be difficult to distinguish from primary DCM. Given that the cases were not necessarily diagnosed by a cardiologist with exclusion of other causes, we cannot be confident. Yet had the list been dominated by atypical breeds, it would have been greater cause for concern as to a novel mechanism. Nonetheless, of those cases specifically investigated, taurine deficiency is prominent. In a case series of 24 Labrador Retrievers investigated between 2016 and 2018 at UC Davis (not all included in the FDA series), 23 were taurine deficient.[12] Several different diets had been fed, but none of the diets had been tested using Association of American Feed Control Officials (AAFCO) procedures.

With the exception of the study by Kaplan et al (2018), the quality of information available at present is low.[12] The FDA data set does not have any case controls, and only a subset were tested for taurine deficiency. In addition, the almost complete concordance between affected breeds and breeds of predisposition, and the inconsistency of diagnosis, means that many of the cases were almost certainly breed-associated DCM that were not caused by any dietary effect. Perhaps the most pressing need is to determine if there are cases of DCM in atypical breeds that are not taurine deficient. To emphasise the point, only 1 of the 5 Shi Tzu's in the FDA case series was tested for taurine deficiency, and it was not deficient. However, it had an antibiotic-responsive cough, and there was no information on an echocardiographic diagnosis beyond "heart enlargement on radiographs".

Some studies have taken a broad, "metabolomics" approach, to identify different serum metabolites in dogs eating grain-free, and grain-inclusive diets.[13] Although such studies can form the basis for hypotheses, they are unlikely to elucidate any mechanistic basis for an association, if it exists. Other studies have followed the echocardiographic parameters of dogs consuming diets that have been categorised as "non-traditional", and compared them with dogs eating "traditional" diets. Although two studies have demonstrated changes, interpreted as "improvements" in echocardiographic parameters, they are not known to be clinically relevant, and the studies were not controlled enough to identify what dietary factors might be involved.[14]

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Grain free diets for dogs: What every veterinarian should know

39

More recently, attempts have been made to identify if there is a direct effect of ingredients typically included in grain-free products, most notably legumes. A generous interpretation of the data available so far would be that it is inconclusive. One group identified a biologically irrelevant reduction in the red cell mass in dogs fed one grain-free diet, and an increase in phosphate, compared with dogs fed a grain-inclusive diet.[15] It is not possible to conclude what the significance is, what the relevance to any cardiac disease is, let alone which of the myriad of differences between the diets might have been responsible. Other authors have fed dogs diets with very high concentrations of legumes, and not found any effect on echocardiographic parameters, or cardiac biomarkers, after 20 weeks of feeding.[16] Thus, it remains uncertain if there is any effect, what might cause that effect, and certainly if there is any effect *other than* taurine depletion, when dogs are fed diets that are "grain-free".

Since 2010, there has been a startling increase in the number and sales of "grain-free" pet foods globally. Their popularity in the US forced even conventional heavyweights such as Hill's Pet Care to hop on the bandwagon ("Ideal Balance Grain Free" range). Sales of "grain-free" diets increased in the US from US$900 million, to US$3 billion between 2011 and 2016, and was the market segment responsible for growth during that period.[17] In short, if you are a new manufacturer, you will want to enter the market with a "grain-free" product.

New and small pet food manufacturers very rarely test products with feeding trials, few have veterinary nutritionists even consulting for them, and many have no animal nutritionist at all. Quality control, consistency of ingredients, careful monitoring of animals fed their diets, and a clear understanding of the problems, are frequently lacking in small and new companies. In contrast, better manufacturers use established ingredients, perform appropriate testing, prove dietary adequacy through feeding trials, have excellent quality control procedures, batch test their products, and have a deep understanding of the complexities that actually lie behind the deceptively simple appearing task of manufacturing dog food.

Conclusion and recommendations

So what should our approach to this subject be? Clearly the "absence of grains" is irrelevant to whether a diet is good or bad, though that hasn't stopped many commentators from suggesting that dogs "should be fed diets that contain grains". Since dogs don't have a requirement for "grain", the absence of "grain" cannot be causal, after all, the diets are also free of rhino horn, tuatara, and the penises of capybara, and they aren't suggested as causes. In addition, diets that are free of grains have been fed for eons in various forms, notably in this country, where the basic ingredients are not as readily available. Lastly, several excellent companies manufacture diets marketed as "grain free" that clearly do not cause DCM.

So, perhaps I can suggest a few precepts to help the daily grind, and fend off the difficult conversations:
1. Only encourage owners to feed diets that have been formulated to meet the requirements established by AAFCO or FEDIAF.
2. If asked for a specific recommendation, I think we should recommend diets that have been proven in AAFCO / FEDIAF feeding trials.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Grain free diets for dogs: What every veterinarian should know

40

3. Make sure you understand the added value that manufacturers give when they produce diets using high quality ingredients that they understand, have rigorous quality control regimes, test diets appropriately both in the laboratory and in the animal, and truly know what they are doing. We are not hiding behind corporate muscle like scared sycophants in so doing, we are standing behind our recommendations because of the confidence in the products. I want to have confidence that the diets I feed my animals are complete, balanced, and appropriately tested.

4. Recognise that "grains" are no more responsible for adverse food reactions than any other major conventional ingredients, and whilst they are neither essentially good nor bad, they can be a source of highly digestible and essential nutrients, and there is no nutritional value to avoiding them in the diet of dogs.

5. The success of "grain free" diets is a triumph of marketing over evidence, and the label is neither a mark of quality, nor deficiency. I would happily feed a diet from Hill's Ideal Balance Grain Free range, not because it is grain free, but because it is good. I would *unhappily* feed my dog a diet from a small manufacturer that has not demonstrated they have formulated the diet properly, has not tested the diet in a feeding trial, and about which I know nothing, irrespective of whether it is grain free or not.

6. At this point in time, a dog presenting with DCM that is on a diet about which you are not confident, should be treated with taurine until you have reason not to, and the owner offered the option of a taurine assay. Taurine is cheap, readily available, non-toxic, and taurine deficiency cardiomyopathy is reversible.

7. Dog breeds of predisposition for DCM eating "grain free" diets, can develop DCM independent of the diet.

8. If you have a suspicion of any adverse reaction to any diet, please report it.

9. If you wish to directly quiz a manufacturer, consider asking the following:
   - How do they ensure their diets are complete and balanced?
   - Have they tested whole blood taurine in dogs fed their diets for long periods?
   - What is the taurine content of the diets?
   - What is the protein and sulphur amino acid content?
   - What is the protein digestibility?

10. It remains to be seen if there is any mechanism other than taurine deficiency by which the current diets are causing DCM in dogs.

Taurine supplementation

Give 500 mg per 10kg, up to a maximum of 2000mg orally per day. It does not have to be given twice daily, and can be given with, or without food.

References

1. O'Grady MR, O'Sullivan ML. Dilated cardiomyopathy: an update. Veterinary Clinics of North America: Small Animal Practice 2004;34:1187-1207.
2. Pion PD, Kittleson MD, Rogers QR, et al. Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. Science 1987;237:764-768.
3. Moise NS, Pacioretty LM, Kallfelz FA, et al. Dietary taurine deficiency and dilated cardiomyopathy in the fox. Am Heart J 1991;121:541-547.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Grain free diets for dogs: What every veterinarian should know

41

4. Song Z, Cai Y, Lao X, et al. Taxonomic profiling and populational patterns of bacterial bile salt hydrolase (BSH) genes based on worldwide human gut microbiome. Microbiome 2019;7:9.

5. Morris JG, Rogers QR, Kim SW, et al. Dietary taurine requirement of cats is determined by microbial degradation of taurine in the gut. AdvExpMed Biol 1994;359:59-70.:59-70.

6. Kim SW, Rogers QR, Morris JG. Maillard reaction products in purified diets induce taurine depletion in cats which is reversed by antibiotics. J Nutr 1996;126:195-201.

7. Young WN, Moon CD, Thomas DG, et al. Pre- and post-weaning diet alters the faecal metagenome in the cat with differences vitamin and carbohydrate metabolism gene abundances. Scientific Reports 2016;6.

8. Fascetti AJ, Reed JR, Rogers QR, et al. Taurine deficiency in dogs with dilated cardiomyopathy: 12 cases (1997-2001). J AmVet Med Assoc 2003;223:1137-1141.

9. Backus RC, Cohen G, Pion PD, et al. Taurine deficiency in Newfoundlands fed commercially available complete and balanced diets. J AmVet Med Assoc 2003;223:1130-1136.

10. Stratton-Phelps M, Backus RC, Rogers QR, et al. Dietary rice bran decreases plasma and whole-blood taurine in cats. J Nutr 2002;132:1745S-1747S.

11. FDA. FDA Investigation into Potential Link between Certain Diets and Canine Dilated Cardiomyopathy. In: FDA; 2019.

12. Kaplan JL, Stern JA, Fascetti AJ, et al. Taurine deficiency and dilated cardiomyopathy in golden retrievers fed commercial diets. PLoS One 2018;13:e0209112.

13. Adin DB, Haimovitz D, Freeman LM, et al. Untargeted global metabolomic profiling of healthy dogs grouped on the basis of grain inclusivity of their diet and of dogs with subclinical cardiac abnormalities that underwent a diet change. Am J Vet Res 2022;83.

14. Freeman L, Rush J, Adin D, et al. Prospective study of dilated cardiomyopathy in dogs eating nontraditional or traditional diets and in dogs with subclinical cardiac abnormalities. J Vet Intern Med 2022;36:451-463.

15. Bakke AM, Wood J, Salt C, et al. Responses in randomised groups of healthy, adult Labrador retrievers fed grain-free diets with high legume inclusion for 30 days display commonalities with dogs with suspected dilated cardiomyopathy. BMC Vet Res 2022;18:157.

16. Singh P, Banton S, Raheb S, et al. The Pulse of It: Dietary Inclusion of Up to 45% Whole Pulse Ingredients with Chicken Meal and Pea Starch in a Complete and Balanced Diet Does Not Affect Cardiac Function, Fasted Sulfur Amino Acid Status, or Other Gross Measures of Health in Adult Dogs. J Nutr 2023;153:1461-1475.

17. Department SR. Grain-free pet food sales in the United States from 2011 to 2016 (in million U.S. dollars)*. In: 2019.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ – Grain free diets for dogs: What every veterinarian should know

42

Raw food diets: Facts, philosophy, and fallacy

Nick Cave, BVSc, MVSc, PhD, DipACVIM (Nutrition)
School of Veterinary Science
Massey University, Palmerston North, New Zealand

It would be historically inaccurate to suggest, as some have done, that raw-food diets are a recent phenomenon. Raw animal products and cooked scraps have probably been the dominant diet of domesticated cats and dogs throughout the millennia that we have cohabitated, and although commercial pet foods were probably first developed in the 1880's, they have only been widely available for a few decades. Nonetheless, the popularity of feeding raw food diets has increased considerably recently.

10 to 20 years ago, >98% of pet owners in Australia and New Zealand consistently fed predominantly conventional commercial diets, and almost no owners exclusively fed raw food diets (RFDs).[1-4] However, in the 10 years between 2008 and 2018, the popularity of feeding raw food diets has increased dramatically across the world, and it may be that more than 50% of owners choose raw food to be at least a component of their pet's diet.[5] Although not specifically studied, when prescribed by veterinarians, it is likely that the most common reasons are for the short term management of non-specific gastroenteritis, or for the diagnosis or therapy of food hypersensitivity. Indeed, in cases of food hypersensitivity in the USA, HPDs were more commonly prescribed than commercial diets (prior to the availability of commercial selected protein or hydrolysed protein diets).[6] However, there has been a groundswell of interest specifically in raw food feeding over the past 20 years, which has been fuelled by negative opinions of commercial pet foods and manufacturers.

Australia holds special prominence in this area, largely as the result of the evangelical approaches of Ian Billinghurst and Tom Lonsdale, and the success of popular literature on the subject. The unappealing acronym "BARF" was originally coined to define a "bones and raw food diet", but, for whatever reason, has morphed into the more apparently palatable "biologically appropriate raw food diet". Although for some time, raw food feeding was the domain of the home enthusiast, several companies around the world have followed the call to battle and produce varieties of raw food diets (RFDs). These commercial varieties range from raw meat only, where no attempt is made to formulate a complete and balanced diet, to diets that are formulated to meet the nutrient requirements established by the NRC.[7]

There has perhaps been no topic in veterinary nutrition that has been more emotionally charged over the ensuing 20 years or so. Typical of human dilemmas, interested individuals are characterised as being on one of two sides: you are either a BARF fanatic, fuelled with all the zealous and irrational passions of a religious fundamentalist, or you are a corporate lap dog, having surrendered your willingness to question, and to the detriment of your patients you are slavish soulless sycophants. Caricatures these may be, but unheard they are not. If we are true to our profession and to the "Sc" on the end of our degree letters, we will remain aloof of hysterics, and play the role of the objective and rational philosopher. Truth will out.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

43

Definitions

One of the features of the topic is the confusion of terms. "Raw food" simply means "uncooked", yet the term is rarely limited to that definition. Definitions of RFDs include:

- Uncooked ingredients that are included to emulates whole prey.
- Uncooked meat, with or without some plant ingredients
- Uncooked meat, with various ingredients and a vitamin and mineral supplement

Owners motives for feeding raw foods are as varied as the diets.[5,8-10] However, by far the most common reasons can be placed into two categories: 1) the perception that RFDs are healthier, or offer some benefit in specific diseases, or 2) the belief that conventional diets are specifically unhealthy. Unsurprisingly, veterinarians are not the major source of these perceptions and beliefs.

The characteristics of the ideal diet have been determined

It is sobering to realise that even the basic nutrient requirements are not completely defined, and we are a very long way from determining what is "ideal", for any life-stage. When we do not know what is ideal for any member of a species, we cannot suggest that one diet is ideal for all. There is no better indicator of the daunting scope of our ignorance than the money that large pet food manufacturers are prepared to spend on nutritional research. So any claim that a dietary composition is ideal, even one regarding a single nutrient concentration, should be treated with a pinch of salt. And then a good dollop of mustard as well. It is simply not true that anyone has identified the ideal diet.

Potential benefits

Dental disease is the most common disease affecting dogs and cats throughout their lives, and it is in this regard that diets containing bones have their greatest measurable benefit. Periodontitis will develop in almost all animals fed commercial diets if they do not have other regular measures to prevent the disease. Even more so, softer diets appear convincingly to be worse. Cats fed dry food develop less calculus and gingivitis than cats fed exclusively canned food.[11] In a large survey of domestic cats in Japan, calculus was more common in cats fed canned or home-cooked (boneless) meals than cats fed dry foods (41% vs. 25%).[12] Similarly, it was shown many years ago that soaking dry food prior to feeding is a reliable method of inducing the rapid formation of plaque, calculus, gingivitis, and eventually periodontitis in dogs.[13] In a study of dogs in Brazil, those that were fed diets of home-prepared foods and scraps (presumably without bones) had significantly more dental disease than those fed commercial dry diets.[14]

Additionally, when commercial diets are supplemented with more abrasive, "natural" ingredients, the development of periodontitis is retarded, or even prevented. Feeding raw oxtails as a supplement to a dry food has been shown to be effective in minimising the development of gingivitis and periodontitis in long term (> 6 years) studies in beagles.[15] Once weekly feeding of oxtails was shown to remove existing calculus to 5% of previous amounts within 2 weeks and to maintain them at that level for years. Further, a diet consisting of raw bovine trachea and attached tissues was much more effective in reducing plaque, calculus and gingivitis than the same diet when fed minced.[16]

Thus, commercial diets are associated with periodontal disease, and softer diets are worse than dry diets, though perhaps there is less difference between the two types of

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

44

commercial diet than one might expect. In addition, the supplementation of commercial diets with "natural" chews, such as oxtails, dramatically improves oral health.

It should be noted however, that periodontitis still occurs, and is surprisingly common in wild felids and canids. It was present in 41% of African Wild Dogs surveyed, 61% of feral cats on a seabird diet, and in a study in Australia, there was no difference in the prevalence of periodontitis between feral trapped cats and age matched owned cats.[17-19] Thus the "wild diet" does *not* prevent periodontitis, even though appropriate chewing behaviour significantly helps.

The palatability of RFDs is often claimed to be higher. Much of this claim stems from the neophilic feeding behaviours of dogs, and to a lesser degree cats. Moist diets are almost universally more palatable than dry diets. However, in our nutrition colony, cats reared and fed for years on high moisture canned diets prefer dry premium diets when they are offered. In addition, both dogs and cats generally (though not always) select for the flavour of cooked meat, rather than raw meat.[20-23] Thus the observations of RFD enthusiasts that the palatability is higher, are correct, but only in the respect of novelty and moisture.

The protein digestibility of raw meat can be higher or lower than cooked meat depending on the amount of collagen and the type of cooking. As a general rule however, cooked meat has a lower digestibility than raw meat for both dogs and cats, and especially when compared with meat by-products commonly used in commercial pet foods.[24,25] However, even between types of meat (e.g. horse and beef) there can be significant differences in digestibility and faecal quality when fed raw.[26] In a study that compared home-kill mutton with Tux biscuits, it was found that the protein digestibility of Tux was 83%, whilst that of the raw mutton was 95%.[27] It may be that some animals with severe intestinal dysfunction and maldigestion will show clinical improvement if fed a cooked HPD rather than a commercial diet, but whether feeding the same diet raw will yield any further benefit remains untested. For all other animals, the digestibility of premium commercial diets is still very high, and there is no experimental nor logical reason to abandon commercial diets in favour of RFDs based on digestibility.

Food processing, especially cooking, induces changes in all of the macronutrients, especially proteins. Proteins denature, and can become glycosylated to form Maillard compounds (browning reaction). The effect of heating during the canning process on the immunogenicity of dietary proteins has been evaluated in cats.[28] Using soy and casein proteins, the canning process resulted in the creation of new antigens not present in the uncooked product. In addition, a product of heated casein induced a salivary IgA response that was not induced by the raw product. Thus, commercial food processing can qualitatively and quantitatively alter the immunogenicity of food proteins. Although the significance of this finding is uncertain at present, it emphasises that food processing can have effects that are not always benign.

Other claims regarding health benefits, faecal consistency, and increased activity have not been tested, are unable to be critiqued, and are probably unfounded.

Risks to pet
Microbial contamination of meat varies according to the source. Meat products not intended or suitable for human consumption are commonly used as pet foods. The nature

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

45

of these tissues and the less stringent handling requirements compared with products approved for human consumption, increases the risk of bacterial contamination.

There are numerous reports in the literature that describe the prevalence of contamination of fresh meat with *Salmonella spp, Campylobacter spp, Yersinia spp*, and enterotoxigenic *E.coli*.[29-33] Equally numerous are the reports of high rates of intestinal carriage in dogs and cats fed such diets.[31,34-37] Studies originating in Canada and the USA dominate the literature, and poultry based diets are the most frequently incriminated. Regional differences in farming, slaughtering, and meat storage and handling procedures could lead to very different results elsewhere in the world, and such data may not apply to Australia and New Zealand where raw poultry is much less commonly fed than beef, lamb, and other red meats. However, in a recent survey of 50 different commercial RFDs in New Zealand, most of which were red-meat based, *Campylobacter jejuni* or *coli* were isolated from 22%.[38]

One study that clearly demonstrated the potential for disease was conducted at a greyhound breeding unit in which there had been several cases of acute enteritis and death associated with *Salmonella spp* infection in puppies.[36] *Salmonella* was isolated from many locations and insect vectors. *Salmonella spp* were isolated from 57 of 61 (93%) faecal samples and the majority were genetically identical, and that organism was recovered from raw meat fed at the facility.

It can be concluded then that feeding RFDs to dogs and cats commonly results in intestinal colonisation with important human pathogens. Intestinal and even systemic disease can occur as the result of this colonisation. However, intestinal disease is not commonly reported in dogs or cats fed RFDs, and intestinal carriage of these organisms is not normally associated with clinical signs, and only sporadic reports of intestinal disease associated with RFD feeding exist.[39,40] Thus, although the risk to the pet of colonisation is great, the risk of disease has not been established, will be difficult to quantify, and is likely to be small.

In contrast to bacterial contamination, parasitic contamination leading to infection and disease of dogs and cats is well established. Toxoplasma, Neospora spp, and Sarcocystis have all been reported as causes of disease in pets fed RFDs in North America, and Australia.[32,41-43] The high rates of meat contamination and successful infection of pets consuming the diets makes protozoal disease of greater concern than bacterial when considering the risk of RFD feeding.[32,44]

The ingestion of bone fragments is associated with tooth fracture, intestinal irritation, obstruction and perforation, diarrhoea, and constipation.[45] An interesting suggestion is that puppies and kittens that are introduced to bones early in life may be less likely to experience adverse effects because they learn through observation of their mothers, and presumably through experience. In contrast, adult dogs that are fed bones for the first time may be more likely to swallow large fragments or whole bones. This theory is intriguing, but untested.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

46

Nutritional adequacy

RFDs can, and should, be formulated to be the equal of commercial diets. However, a combination of inadequate recipes, owner (and veterinarian) ignorance, and the natural tendency for "recipe drift" combine to produce a large proportion of inadequate diets.

In Europe, a survey of HPDs (mostly cooked diets) found that energy, fat and protein were above AAFCO recommendations, whereas calcium, Ca:P ratio and vitamins A and E, and potassium, copper and zinc concentrations were below recommendations.[46] Relative fatty acid contents of serum phospholipid fractions of HPD-fed dogs were significantly lower in 18:2(n-6) and 20:4(n-6) than those from a population of 37 normal dogs consuming commercial dry, US-manufactured diets. In the USA, previous studies have found that the great majority (>90%) of HPD recipes are nutritionally inadequate.[6] I have evaluated 43 HPD recipes, mostly RFDs, fed to dogs (predominantly) and cats in New Zealand, and not one recipe was complete and balanced. The most common nutritional inadequacy would be a deficiency of calcium and too low Ca:P ratio, which is an inevitable consequence of an unsupplemented meat-based diet. Other common deficiencies include vitamins B_{12}, E, D, and A; copper, manganese, and iodine. Common excesses include total fat, 18:2(n-6), and B-vitamins (>1000x NRC maximum for B12 in racing greyhounds is common).

Most properly formulated HPDs contain a minimum of 6, and up to 9 separate ingredients. Although not studied, client compliance probably decreases, the larger the ingredient list is. Formulating complete diets without using "supplements" is perfectly possible, but requires many more ingredients. An unpublished phone-survey of clients of the Nutrition Consulting Service of the University of California, Davis, found that within weeks of starting a prescribed HPD, the great majority of clients either modify, add commercial food, or abandon the diet completely.

That dogs and cats do not apparently become ill with short-term feeding of such diets, or that owners that feed RFDs on an ongoing basis with no apparent ill effects, is credit to several factors including:
1. Our inability to measure the effects of short-term nutritional inadequacy
2. The uncertainty of the absolute physiology requirements
3. The difference between long term requirements averaged out as a daily requirement, vs a true short-term requirement
4. Non-compliance, and the pragmatic tendency for a varied diet to be more likely to be complete than a restricted one
5. The robust nature of our patients!

Risks to owner and society

Although carriage of the "classic" enteric pathogens by dogs and cats rarely seems to cause overt disease, there is growing realisation of the potential for dogs and cats to infect household members. Campylobacteriosis is the most frequently reported notifiable human enteric infection in the USA, and household contact with dogs is a significant risk factor for development of campylobacteriosis in humans.[47] Transmission of Yersinia enterocolitica from a pet dog to a family resulting in clinical disease has also been reported.[48] Surveys of public understanding suggest that most owners are unaware of the potential for transmission of enteropathogens between their pets and themselves, and we are obliged to

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

47

fill that knowledge gap since it is unlikely to be discussed by other health care professionals.[49]

As stated above, dogs routinely fed RFDs are commonly infected with *Sarcocystis* spp, and may contaminate the environment by shedding sporocysts in their faeces, posing a risk for livestock grazing in the same environment.[50] Taenia ovis and hydatigena shedding by dogs and subsequent infection of livestock results in condemnation of tissues at slaughter and related economic losses. Not surprisingly, working farm dogs remain the overwhelming source of infection for livestock, although it has been observed that properties bordering highways are at an increased risk, suggesting roadside contamination from passing dogs, enjoying some rural roadside relief. We should remember that the feeding of uncooked offal to dogs in New Zealand remains illegal, under the Biosecurity act. Although the risk of infection from tripe is probably small, it is still illegal and uncooked tripe should not be fed.

For countries with significant agricultural industries, veterinarians should be in the vanguard of holistic public and livestock health, and reducing needless parasitic infections is one avenue for intervention.

Arguments against feeding commercial diets

Much of the rhetoric directed against commercial diet feeding is fuelled by an intrinsic dislike of large corporations, xenophobia, and a feeling that companies that profit from selling food, are unlikely to work with the animals' best interests at heart. Although we should disregard such sentiments as unfounded, we should continue to question the ethics of our feeding practices. Many veterinarians object to the conditions that intensively reared pigs and poultry are kept in, and reasonably choose to eat only free range, or even vegetarian diets. We should apply the same moral reasoning to pet food manufacturing, since the suffering of the production animal is the same regardless of its end use. Products manufactured from farming practices that we find more acceptable - perhaps those of pasture reared beef and sheep - could be argued to be more ethical than those made from intensively reared chickens or pigs. Likewise, for those that are concerned with the energy cost, and carbon output from shipping food across the globe may wish to favour pet foods of equal quality that are manufactured on our own shores. And the recent recognition of the imbalance in polyunsaturated fatty acids (PUFA) that has resulted from the most commonly used ingredients, has lead to the increased incorporation of fish by-products to increase the content of n-3 PUFA. The section of humanity that truly believes our modern fishing practices are sustainable is dwindling.

Perhaps the future of ethically produced pet foods will depend on the production of diets that are even less "natural", than the currently available ones. Complete and balanced nutrition can be provided using vegetable ingredients, when careful formulation and supplementation is applied. If we *can* do it, perhaps we should.

Conclusion

There are arguments for and against the feeding of RFDs, but there is an unfortunate dearth of any research that documents the objective benefits of such feeding practices. Several concerns about the diets could be allayed simply by cooking, with little, if any, loss of the presumed benefits. Arguments for RFDs based on the premise of what is "natural" are flawed, and should not be promoted. In nature, the life expectancy African Wild Dogs is

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

48

about 5 years, and very few feral cats live longer than 4 years. The life expectancy of domestic dogs and cats, including animals kept in colonies and maintained on commercial diets, is 2-4 times that "naturally" seen. That difference between wild and domestic life expectancy is sobering. The establishment of nutritional requirements of dogs and cats through the research efforts of many individuals over the past 50 years has lead to the development of diets that, although imperfect, have transformed pet ownership. Modern commercial diets are not perfect, and there is no feeding practice that has zero risk. Many reasonable people may object to some commercial diets, and we have a long way to go before they are ideal, let alone ideally made. None-the-less, those companies with rigorous quality control measures, that subject their diets to properly conducted feeding trials, produce diets of extremely high quality on which we can rely.

Our role

Owners that feed RFDs are not stupid, and they have the same concerns for the health of their pets that any owner does, and that we should. We should start from a position of commonality – we want what is best for their pets. If an owner wishes to feed a raw diet, I suggest that our approach should be as follows:

- Be supportive of the intention to feed a healthy diet
- Ask how they ensure that the diet is complete and balanced. Feeding a pet a deficient diet is no more acceptable than any other form of mistreatment.
- Explain that it is possible, but difficult to do so without the use of vitamin or mineral supplements.
- Suggest the means to feed a complete and balanced diet
  a) Feed a commercially prepared diet that has been formulated to meet the requirements established by AAFCO
  b) Create a recipe that is supplemented with a balanced vitamin and mineral product. E.g. www.balanceit.com
  c) Feed a recipe that has been formulated by a veterinary nutritionist
- Ensure that the owner is aware of the small bacterial and parasitic risks, and that freeze-thawing of ingredients would reduce, and cooking would resolve the risks.

References

1. Toribio JA, Norris JM, White JD, et al. Demographics and husbandry of pet cats living in Sydney, Australia: results of cross-sectional survey of pet ownership. *J Feline Med Surg* 2008.
2. Robertson ID. The influence of diet and other factors on owner-perceived obesity in privately owned cats from metropolitan Perth, Western Australia. *Prev Vet Med* 1999;40:75-85.
3. Cave NJ, Allan FJ, Schokkenbroek SL, et al. A cross-sectional study to compare changes in the prevalence and risk factors for feline obesity between 1993 and 2007 in New Zealand. *Prev Vet Med* 2012;107:121-133.
4. Laflamme DP, Abood SK, Fascetti AJ, et al. Pet feeding practices of dog and cat owners in the United States and Australia. *J Am Vet Med Assoc* 2008;232:687-694.
5. Dodd S, Cave N, Abood S, et al. An observational study of pet feeding practices and how these have changed between 2008 and 2018. *Vet Rec* 2020;186:643-643.
6. Roudebush P, Cowell CS. Results of a hypoallergenic diet survey of veterinarians in North America with a nutritional evaluation of homemade diet prescriptions. *Veterinary Dermatology* 1992;3:23-28.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

49

7. Beitz DC, Bauer JE, Behnke KC, et al. *Nutrient requirements of dogs and cats*. Revised Edition ed. Washington: National Academies Press, 2006.

8. Dodd SAS, Cave NJ, Adolphe JL, et al. Plant-based (vegan) diets for pets: A survey of pet owner attitudes and feeding practices. *PLoS One* 2019;14:e0210806.

9. Wall M, Cave NJ, Vallee E. Owner and Cat-Related Risk Factors for Feline Overweight or Obesity. *Frontiers in veterinary science* 2019;6:266.

10. Morgan SK, Willis S, Shepherd ML. Survey of owner motivations and veterinary input of owners feeding diets containing raw animal products. *PeerJ* 2017;5:e3031.

11. Studer E, Stapley RB. The role of dry foods in maintaining healthy teeth and gums in the cat. *Vet Med Small Anim Clin* 1973;68:1124-1126.

12. Anon. Survey on the Health of Pet Animals, 2nd Report. *Japan Small Animal Association* 1985:25.

13. Burwasser P, Hill TJ. The effect of hard and soft diets on the gingival tissues of dogs. *J Dent Res* 1939;18:389-393.

14. Domingues LM, Alessi AC, Canola JC, et al. Type and frequency of dental diseases and disorders in dogs in the region of Jaboticabal, SP. *Arquivo Brasileiro De Medicina Veterinaria E Zootecnia* 1999;51:323-328.

15. Brown MG, Park JF. Control of dental calculus in experimental beagles. *Lab Anim Care* 1968;18:527-535.

16. Egelberg J. Local Effect of Diet on Plaque Formation and Development of Gingivitis in Dogs. I. Effect of Hard and Soft Diets. *Odontol Revy* 1965;16:31-41.

17. Steenkamp G, Gorrel C. Oral and dental conditions in adult African wild dog skulls: a preliminary report. *J Vet Dent* 1999;16:65-68.

18. Verstraete FJ, van Aarde RJ, Nieuwoudt BA, et al. The dental pathology of feral cats on Marion Island, part II: periodontitis, external odontoclastic resorption lesions and mandibular thickening. *J Comp Pathol* 1996;115:283-297.

19. Clarke DE, Cameron A. Relationship between diet, dental calculus and periodontal disease in domestic and feral cats in Australia. *Aust Vet J* 1998;76:690-693.

20. Dust JM, Grieshop CM, Parsons CM, et al. Chemical composition, protein quality, palatability, and digestibility of alternative protein sources for dogs. *J Anim Sci* 2005;83:2414-2422.

21. Stasiak M. The development of food preferences in cats: the new direction. *Nutr Neurosci* 2002;5:221-228.

22. Thombre AG. Oral delivery of medications to companion animals: palatability considerations. *Adv Drug Deliv Rev* 2004;56:1399-1413.

23. Van den Bos R, Meijer MK, Spruijt BM. Taste reactivity patterns in domestic cats (Felis silvestris catus). *Appl Anim Behav Sci* 2000;69:149-168.

24. Murray SM, Patil AR, Fahey GC, Jr., et al. Raw and rendered animal by-products as ingredients in dog diets. *J Anim Sci* 1997;75:2497-2505.

25. Vester BM, Burke SL, Liu KJ, et al. Influence of feeding raw or extruded feline diets on nutrient digestibility and nitrogen metabolism of African wildcats (Felis lybica). *Zoo Biol*;29:676-686.

26. Vester BM, Beloshapka AN, Middelbos IS, et al. Evaluation of nutrient digestibility and fecal characteristics of exotic felids fed horse- or beef-based diets: use of the domestic cat as a model for exotic felids. *Zoo Biol*;29:432-448.

27. Singh I. Digestibility of homekill (mutton carcass) and TUX Energy dog biscuits. *Institute of Food, Nutrition, and Human Health*. Palmerston North: Massey University, Submitted for a PhD.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

50

28. Cave NJ, Marks SL. Evaluation of the immunogenicity of dietary proteins in cats and the influence of the canning process. *Am J Vet Res* 2004;65:1427-1433.

29. Finley R, Reid-Smith R, Ribble C, et al. The occurrence and antimicrobial susceptibility of salmonellae isolated from commercially available canine raw food diets in three Canadian cities. *Zoonoses Public Health* 2008;55:462-469.

30. Chengappa MM, Staats J, Oberst RD, et al. Prevalence of Salmonella in raw meat used in diets of racing greyhounds. *J Vet Diagn Invest* 1993;5:372-377.

31. Joffe DJ, Schlesinger DP. Preliminary assessment of the risk of Salmonella infection in dogs fed raw chicken diets. *Can Vet J* 2002;43:441-442.

32. Strohmeyer RA, Morley PS, Hyatt DR, et al. Evaluation of bacterial and protozoal contamination of commercially available raw meat diets for dogs. *J Am Vet Med Assoc* 2006;228:537-542.

33. Weese JS, Rousseau J, Arroyo L. Bacteriological evaluation of commercial canine and feline raw diets. *Can Vet J* 2005;46:513-516.

34. Finley R, Ribble C, Aramini J, et al. The risk of salmonellae shedding by dogs fed Salmonella-contaminated commercial raw food diets. *Can Vet J* 2007;48:69-75.

35. Lefebvre SL, Reid-Smith R, Boerlin P, et al. Evaluation of the risks of shedding Salmonellae and other potential pathogens by therapy dogs fed raw diets in Ontario and Alberta. *Zoonoses Public Health* 2008;55:470-480.

36. Morley PS, Strohmeyer RA, Tankson JD, et al. Evaluation of the association between feeding raw meat and Salmonella enterica infections at a Greyhound breeding facility. *J Am Vet Med Assoc* 2006;228:1524-1532.

37. Leonard EK, Pearl DL, Finley RL, et al. Evaluation of Pet-Related Management Factors and the Risk of Salmonella spp. Carriage in Pet Dogs from Volunteer Households in Ontario (2005-2006). *Zoonoses Public Health*;58:140-149.

38. Acke E, Midwinter A, Collins-Emerson J, et al. *Campylobacter* species and multilocus sequence types from commercial raw meat diets for pets *European College of Veterinary Internal Medicine, Abstract*, 2011.

39. Fukushima H, Nakamura R, Iitsuka S, et al. Presence of zoonotic pathogens (Yersinia spp., Campylobacter jejuni, Salmonella spp., and Leptospira spp.) simultaneously in dogs and cats. *Zentralblatt fur Bakteriologie Mikrobiologie und Hygiene, B*;181:430-440.

40. Cave NJ, Marks SL, Kass PH, et al. Evaluation of a routine diagnostic fecal panel for dogs with diarrhea. *J Am Vet Med Assoc* 2002;221:52-59.

41. de Brito AF, de Souza LC, da Silva AV, et al. Epidemiological and serological aspects in canine toxoplasmosis in animals with nervous symptoms. *Mem Inst Oswaldo Cruz* 2002;97:31-35.

42. Dubey JP, Ross AD, Fritz D. Clinical Toxoplasma gondii, Hammondia heydorni, and Sarcocystis spp. infections in dogs. *Parassitologia* 2003;45:141-146.

43. Reichel MP, Ellis JT, Dubey JP. Neosporosis and hammondiosis in dogs. *J Small Anim Pract* 2007;48:308-312.

44. Smielewska-Los E, Rypula K, Pacon J. The influence of feeding and maintenance system on occurrence of Toxoplasma gondii infections in dogs. *Pol J Vet Sci* 2002;5:231-235.

45. Cave NJ, Bridges JP, Cogger N, et al. A survey of diseases of working farm dogs in New Zealand. *N Z Vet J* 2009;57:305-312.

46. Streiff EL, Zwischenberger B, Butterwick RF, et al. A comparison of the nutritional adequacy of home-prepared and commercial diets for dogs. *J Nutr* 2002;132:1698S-1700S.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

51

47. Brieseman MA. A further study of the epidemiology of Campylobacter jejuni infections.

48. Gutman L, Ottessen E, Quan T. An inter-familial outbreak of *Yersinia enterocolitica* enteritis. . *N Engl J Med* 1973;288:1372-1377.

49. Lenz J, Joffe D, Kauffman M, et al. Perceptions, practices, and consequences associated with foodborne pathogens and the feeding of raw meat to dogs. *Can Vet J* 2009;50:637-643.

50. Savani G, Dunsmore J, Robertson ID. A survey of Western Australian dogs for *Sarcocysti*s spp and other intestinal parasites. *Aust Vet J* 1993;70:275-276.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Cave, NJ - Raw food diets: Facts, philosophy, and fallacy

52

How to approach a cat with a gastrointestinal mass

Dr. Catherine Chan BVSc (Hons I) FANZCVS (Veterinary Oncology) DACVIM (Oncology)
The Pet Oncologist
1A Norman Street, Fig Tree Pocket,
Brisbane QLD 4069

Introduction

As a veterinarian, you will be presented with a cat with a gastrointestinal mass. These notes will discuss the cancer biology, prognosis, diagnostics, and treatment options for the three most common gastrointestinal cancers in cats (lymphoma, adenocarcinoma and mast cell tumours). Other diseases (such as adenomatous polyps), and less common gastrointestinal cancers (such as carcinoids, sarcomas and plasma cell tumours), can also occur in cats. It is important to recognise these types of cancers. However, discussion of these diseases and less common gastrointestinal cancers is beyond the scope of these notes.

Lymphoma

Lymphoma is the most common haematopoietic cancer in cats. Lymphoma usually arises in lymphoid tissues such as the lymph nodes, spleen, and bone marrow. However, lymphoma may arise in any tissue of the body.

Lymphoma is the most common primary gastrointestinal cancer in cats. Gastrointestinal lymphoma can be confined to the intestinal or gastric location, or a combination of intestinal, mesenteric lymph node, and hepatosplenic involvement. These tumours may be solitary, but more commonly are diffuse throughout the intestines.

Cats with gastrointestinal lymphoma typically present with a palpable abdominal mass and non-specific clinical signs of vomiting, diarrhoea, inappetence or weight loss.

The median age of affected cats is approximately 10 to 13 years of age. However, lymphoma may occur in cats of any age. Oriental breeds (such as Siamese breed) are predisposed. However, most cases occur in domestic shorthair (DSH) cats. Males appear slightly more frequently affected than females (1.1-1.5:1 male-to-female ratio).

The prognosis for lymphoma in cats is highly variable and depends on several factors. Unfavourable prognostic factors include not achieving complete remission with therapy,[1-3] high histologic grade, large-cell morphology,[4] positive FeLV status,[1] clinical substage b[1,5,6] (particularly weight loss and anaemia at presentation), transmural gastrointestinal lymphoma,[4] not receiving doxorubicin in a treatment protocol,[1,7] possibly pre-treatment steroids,[2] and probably T-cell immunophenotype for cats with high-grade or large-cell lymphoma.

Overall there are many prognostic factors associated with lymphoma in cats. However, the single most important independent prognostic factor is achieving complete remission with therapy. The response to therapy will not be known until therapy is trialled.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Chan, C – How to approach a cat with a gastrointestinal mass

53

Diagnosis is usually confirmed by cytology or histopathology of the gastrointestinal mass. B- and T-cell immunophenotyping, flow cytometry, and PARR (PCR for Antigen Receptor Rearrangement) are special tests sometimes required to confirm lymphoma. Three-view thoracic radiographs and abdominal ultrasonogram are recommended to determine if there are other sites of lymphoma and to help monitor responses to therapy. Haematology (including blood film review), serum biochemistry and routine urinalysis are a minimum database, recommended in all cats with lymphoma, particularly before starting chemotherapy, to assess the cat's general health and determine if there are any co-morbidities. Renal and hepatic function is crucial to assess before chemotherapy because if there are any abnormalities, chemotherapy may be contraindicated. The results of these tests will allow veterinarians to develop individualised treatment recommendations for each cat. Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) retroviral testing are also recommended. FeLV-positive cats are associated with a worse prognosis and are more likely to have systemic involvement. FIV-positive cats anecdotally have been associated with a higher risk of myelosuppression (particularly neutropenia) with chemotherapy.

The prognosis for untreated high-grade lymphoma in cats is guarded, with a median survival time of approximately two months or less. Most cats are humanely euthanised due to poor quality of life.

The treatment of choice is multiple-agent chemotherapy. The reported complete remission rate and median survival times with multiple-agent chemotherapy are approximately 50-70%, for approximately 4 to 12 months, respectively. Some cats are cured, living up to 2.5 years or longer. However, this is less likely (although not impossible) with gastrointestinal lymphoma. Also, cats that achieve a complete remission with chemotherapy have reported median survival times between 8 months and 1.5 years, compared to 2 to 3 months in cats that do not achieve a complete remission (i.e. cats that achieved partial remission, stable disease or progressive disease). Single-agent lomustine (CCNU) is also a reasonable option. A recent retrospective study evaluated 32 cats with treatment naïve intermediate to large-cell gastrointestinal lymphoma treated with single-agent CCNU.[8] Some cats received a single dose of l-asparaginase with the first CCNU treatment. The response rate (i.e. complete and partial remission) to CCNU was approximately 50%. Most cats had a clinical benefit from treatment. However, 30% of cats did not respond to therapy. The median survival time for all cats in this study was 3.5 months. However, if cats achieved complete remission with CCNU, the median survival time increased to 10 months.

What if the gastrointestinal mass is solitary? In these cases, surgery followed by chemotherapy or chemotherapy alone is recommended. Surgery alone is not recommended. Which cats do I take to surgery? I recommend surgery in cats with discrete/solitary gastrointestinal mass, when gastrointestinal perforation is suspected/confirmed, or there is a high risk of gastrointestinal perforation. However, before considering surgery, I strongly recommend thorough staging to ensure there is no evidence of lymphoma present elsewhere.

Is there a survival advantage with surgery and chemotherapy, over chemotherapy alone? This is a challenging question. In one study of 20 cats with high-grade discrete gastrointestinal lymphoma undergoing surgery followed by CHOP chemotherapy, the

Proceedings of 48th ASAV Annual Conference together with Reproduction
Chan, C – How to approach a cat with a gastrointestinal mass

54

median survival time was 14 months.[9] In another study evaluating 40 cats with discrete intermediate- or large-cell gastrointestinal lymphoma undergoing surgery ± chemotherapy, the overall median survival time was three months.[10] The median survival time of cats with small intestinal lymphoma was two months. Whilst the latter study showed no survival benefit with the addition of chemotherapy after surgery, only 25% of cats that underwent surgery received chemotherapy. The median survival time in cats with complete histologic margins was seven months, compared to 2.5 months in cats with incomplete histologic margins. Based on these two studies, the median survival times with surgery followed by chemotherapy was three months and 14 months. Chemotherapy alone is associated with a median survival time of between 4 and 12 months. Therefore, at this stage, it is uncertain whether the addition of surgery provides cats with a survival advantage over chemotherapy alone.

In one study of 23 cats with discrete intermediate- or large-cell gastrointestinal lymphoma, the risk of gastrointestinal perforation appears to be low at 17%, between 23 and 87 days after the induction of chemotherapy.[11] The magnitude of weight loss within 2 to 4 weeks of chemotherapy was greater in cats with perforation.

For cats with small-cell or low-grade alimentary lymphoma (LGAL), the gold standard treatment involves oral administration of chlorambucil and prednisolone indefinitely, which cat owners can administer from home. The prognosis is excellent, with an overall response rate of 85-95% and reported median survival times of around 1.5-3 years. Occasionally, cats will not respond to therapy or transform into large-cell or high-grade lymphoma or develop a second malignancy. These cats have a worse prognosis.[12-14]

It can be challenging to distinguish LGAL from inflammatory bowel disease (IBD). Cats with both LGAL and IBD can both present with diffusely thickened small intestines, a segmental/focal gastrointestinal mass, with or without lymphadenopathy. The most common sonographic feature of LGAL is diffuse thickening of the muscularis propria of the small intestines. In general, LGAL has more pronounced thickening of the muscularis propria, when compared to the submucosa.[15,16] Full thickness intestinal biopsies are recommended. PARR can sometimes be helpful in distinguishing between LGAL and IBD. However, PARR only has an accuracy of 77% in determining if cats have LGAL.[17]

Gastrointestinal adenocarcinoma
Carcinoma is the second most common gastrointestinal tumour in cats. The small intestines (particularly ileum) are the most common site. Older cats (mean age of 10 to 12 years) are primarily affected. Males appear slightly more frequently affected than females. Siamese cats and domestic short-haired cats may be overrepresented.

Cats usually present with a palpable abdominal mass and non-specific clinical signs such as anorexia, vomiting, weight loss, lethargy, diarrhoea, melaena, and abdominal pain. Generally, the clinical signs are not distinguishable from other benign or malignant conditions, and consequently, the disease is often insidious in onset. Most cats present with clinical signs for one to three months before a diagnosis of small intestinal carcinoma is made. Some cats present with partial or complete obstruction.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Chan, C – How to approach a cat with a gastrointestinal mass

55

Intestinal carcinomas are locally invasive and highly metastatic, with around 76% having distant metastasis at the time of presentation. Around half of cats have metastasis to regional lymph nodes, 30-81% to the peritoneal cavity (carcinomatosis), and 9-20% to the lungs. Intestinal carcinomas are often advanced at the time of diagnosis.

The prognosis for untreated cats is poor, with most cats humanely euthanised within two weeks from poor quality of life. Positive prognostic factors include cats that present with a solitary mass and surgery to achieve complete histologic margins. Negative prognostic factors include the presence of metastasis or carcinomatosis and unresectable tumours. Cats with evidence of nodal or distant metastasis usually have a survival time of less than a few months, compared to more than one year in cats without evidence of metastasis.[18] However, long-term survival can be seen in cats with the presence of metastasis or carcinomatosis after surgical excision of the primary tumour.

Diagnosis is similar to all cats with a gastrointestinal mass, with sampling of the primary tumour and staging to check for evidence of metastasis. Of particular importance is histopathology to remove the locoregional lymph nodes at the time of surgery. The presence of nodal metastasis is associated with a worse prognosis.

In one study of 18 cats with small intestinal carcinoma, the median survival time after intestinal resection anastomosis was one year. The median survival time in cats without metastasis was 2.3 years, compared to one year in cats with gross nodal or distant metastasis.[18] In the most recent study of 58 cats with intestinal carcinoma that were treated with surgical resection and chemotherapy in half of the cats, the median survival time was just over nine months.[19] In that study, approximately half of cats had nodal metastasis, and 81% had carcinomatosis. Therefore, surgery is still recommended in cats with evidence of metastasis. In one study of 32 cats with small intestinal carcinoma, carcinomatosis was associated with a median survival time of 4.5 months. However, if surgery was performed, the median survival time was improved to 2.3 years.

Surgery with intestinal resection and anastomosis with wide surgical margins of 5.0-cm on either side of the tumour is recommended to achieve adequate resection of small intestinal tumours. If this is not possible, then at least 3.0-cm surgical margins are recommended. Removal of a mesenteric lymph node and biopsies of any abnormal structures is recommended for prognostic purposes.

Currently, there is no standard of chemotherapy treatment for cats with small intestinal carcinoma. In the adjuvant setting, I recommend carboplatin and/or doxorubicin.

Mast cell tumour

Feline intestinal mast cell tumour (MCT) is the third most common gastrointestinal cancer in cats. There are three distinct syndromes in cats with MCTs that may overlap, including cutaneous, splenic/visceral, and intestinal MCT. Older cats are primarily affected (mean age of 13 years). Most cats present with non-specific signs of illness, such as vomiting, diarrhoea, hyperoxia and a solitary palpable abdominal mass. Signs are often chronic and progressive over weeks to months. Clinical signs associated with the release of mast cell mediators, such as gastrointestinal ulceration, haemorrhage and hypotensive shock, may be seen. Occasionally, cats present with no clinical signs of illness.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Chan, C – How to approach a cat with a gastrointestinal mass

56

The most common site is the small intestines, and lesions may be solitary or multiple. Most cats (>65%) present with metastasis to the regional lymph nodes, liver and spleen.

There is also a unique histologic variant of sclerosing intestinal MCTs. However, the biologic behaviour is similar to cats with intestinal MCTs.

Diagnosis is similar to all cats that present with a gastrointestinal mass with sampling of the primary tumour and staging to check for evidence of metastasis. However, it is important to check for involvement of MCT in the locoregional lymph nodes, skin, spleen and liver. It is also important to sample any peritoneal effusions, and perform a buffy coat smear to look for peripheral mastocytosis. The most common sonographic feature of feline intestinal MCTs is focal, hypoechoic jejunal wall thickening, noncircumferential and eccentric location.[20] However, they can look like anything!

The prognosis for feline intestinal MCT is usually poor because most cats are diagnosed with metastasis and usually die or are humanely euthanised due to poor quality of life within two months of diagnosis. For cats with solitary intestinal MCTs, I usually recommend surgery followed by adjuvant chemotherapy. Surgery alone is unlikely to be successful, with most cats still dying within three months of surgery. Because most cats present with metastasis (or will go on to develop metastasis within a short period following surgery), I recommend adjuvant chemotherapy or Palladia®, alongside prednisolone following surgery.

However, in two recent studies on 48 cats with intestinal MCT, treatment with surgery and/or medical management (e.g. Palladia®, lomustine, chlorambucil, and/or prednisolone) is associated with a more favourable prognosis, with a median survival time of 1.5 years.[21] Surgery is recommended for palliation of clinical signs (e.g. gastrointestinal obstruction) or in cats that have gastrointestinal perforation (e.g. septic peritonitis).

For owners with financial constraints or do not wish for chemotherapy treatment, prednisolone concurrently with antihistamines, gastroprotectants, and serotonin antagonists is recommended. In one study of feline intestinal MCTs, six cats treated with prednisolone had a median survival time of 1.5 years.[21] However, these numbers were small. I still think surgery or Palladia® (concurrently with prednisolone) has a higher chance of working.

Vets, I hope this information helps you understand a bit more about how to approach a cat with a gastrointestinal mass. If you have a question about this topic, please do not hesitate to get in touch. Email: info@thepetoncologist.com.

References
1. Vail DM, Moore AS, Ogilvie GK, et al. Feline lymphoma (145 cases): proliferation indices, cluster of differentiation 3 immunoreactivity, and their association with prognosis in 90 cats. J Vet Intern Med 1998;12:349-354.
2. Taylor SS, Goodfellow MR, Browne WJ, et al. Feline extranodal lymphoma: response to chemotherapy and survival in 110 cats. J Small Anim Pract 2009;50:584-592.
3. Limmer S, Eberle N, Nerschbach V, et al. Treatment of feline lymphoma using a 12-week, maintenance-free combination chemotherapy protocol in 26 cats. Vet Comp Oncol 2016;14:21-31.

4. Moore PF, Rodriguez-Bertos A, Kass PH. Feline gastrointestinal lymphoma: mucosal architecture, immunophenotype, and molecular clonality. Vet Pathol 2012;49:658-668.

5. Krick EL, Moore RH, Cohen RB, et al. Prognostic significance of weight changes during treatment of feline lymphoma. J Feline Med Surg 2011;13:976-983.

6. Krick EL, Cohen RB, Gregor TP, et al. Prospective clinical trial to compare vincristine and vinblastine in a COP-based protocol for lymphoma in cats. J Vet Intern Med 2013;27:134-140.

7. Moore AS, Cotter SM, Frimberger AE, et al. A comparison of doxorubicin and COP for maintenance of remission in cats with lymphoma. J Vet Intern Med 1996;10:372-375.

8. Rau SE, Burgess KE. A retrospective evaluation of lomustine (CeeNU) in 32 treatment naïve cats with intermediate to large cell gastrointestinal lymphoma (2006-2013). Vet Comp Oncol 2017;15:1019-1028.

9. Gouldin ED, Mullin C, Morges M, et al. Feline discrete high-grade gastrointestinal lymphoma treated with surgical resection and adjuvant CHOP-based chemotherapy: retrospective study of 20 cases. Vet Comp Oncol 2017;15:328-335.

10. Tidd KS, Durham AC, Brown DC, et al. Outcomes in 40 cats with discrete intermediate- or large-cell gastrointestinal lymphoma masses treated with surgical mass resection (2005-2015). Vet Surg 2019;48:1218-1228.

11. Crouse Z, Phillips B, Flory A, et al. Post-chemotherapy perforation in cats with discrete intermediate- or large-cell gastrointestinal lymphoma. J Feline Med Surg 2018;20:696-703.

12. Kiselow MA, Rassnick KM, McDonough SP, et al. Outcome of cats with low-grade lymphocytic lymphoma: 41 cases (1995-2005). J Am Vet Med Assoc 2008;232:405-410.

13. Stein TJ, Pellin M, Steinberg H, et al. Treatment of feline gastrointestinal small-cell lymphoma with chlorambucil and glucocorticoids. J Am Anim Hosp Assoc 2010;46:413-417.

14. Lingard AE, Briscoe K, Beatty JA, et al. Low-grade alimentary lymphoma: clinicopathological findings and response to treatment in 17 cases. J Feline Med Surg 2009;11:692-700.

15. Daniaux LA, Laurenson MP, Marks SL, et al. Ultrasonographic thickening of the muscularis propria in feline small intestinal small cell T-cell lymphoma and inflammatory bowel disease. J Feline Med Surg 2014;16:89-98.

16. Zwingenberger AL, Marks SL, Baker TW, et al. Ultrasonographic evaluation of the muscularis propria in cats with diffuse small intestinal lymphoma or inflammatory bowel disease. J Vet Intern Med 2010;24:289-292.

17. Hammer SE, Groiss S, Fuchs-Baumgartinger A, et al. Characterisation of a PCR-based lymphocyte clonality assay as a complementary tool for the diagnosis of feline lymphoma. Vet Comp Oncol 2017;15:1354-1369.

18. Green ML, Smith JD, Kass PH. Surgical versus non-surgical treatment of feline small intestinal adenocarcinoma and the influence of metastasis on long-term survival in 18 cats (2000-2007). Can Vet J 2011;52:1101-1105.

19. Czajkowski PS, Parry NM, Wood CA, et al. Outcome and Prognostic Factors in Cats Undergoing Resection of Intestinal Adenocarcinomas: 58 Cases (2008-2020). Front Vet Sci 2022;9:911666.

20. Laurenson MP, Skorupski KA, Moore PF, et al. Ultrasonography of intestinal mast cell tumors in the cat. Vet Radiol Ultrasound 2011;52:330-334.

21. Barrett LE, Skorupski K, Brown DC, et al. Outcome following treatment of feline gastrointestinal mast cell tumours. Vet Comp Oncol 2018;16:188-193.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Chan, C – How to approach a cat with a gastrointestinal mass

58

Hill's

Transforming Lives

PRESCRIPTION DIET

Hill's

URINARY CARE

SANTÉ URINAIRE / CUIDADO URINARIO

c/d Multicare Stress

VETERINARIAN RECOMMENDED
RECOMMANDÉE PAR LES VÉTÉRINAIRES /
RECOMENDADO POR VETERINARIOS

CLINICAL NUTRITION

S+OX SHIELD

WITH CHICKEN

THERAPEUTIC CAT NUTRITION
NOURRITURE THÉRAPEUTIQUE POUR CHATS
NUTRICIÓN TERAPÉUTICA PARA GATOS

SOME SEE BARRIERS
WE SEE BREAKTHROUGHS

Prescription Diet c/d Urinary Stress is formulated to reduce rate of recurrent FIC signs — so your patient can rejoin the family.

1 Nutrition shown in a controlled study to reduce the rate of recurring feline idiopathic cystitis (FIC) signs by 89%[1]

2 Dissolves struvite stones in as little as 7 days (average 27 days)[2]

3 Formulated to reduce stress, a risk factor for common urinary signs

Ask your Hill's Territory Manager about Prescription Diet Urinary Care foods for your patients.

FSC
MIX
Paper | Supporting responsible forestry
FSC® C007421
www.fsc.org

[1]Kruger JM, Lulich JP, MacLeay J, *et al.* Comparison of foods with differing nutritional profiles for long-term management of acute nonobstructive idiopathic cystitis in cats. *J Am Vet Med Assoc.* 2015;247(5):508-517. [2]Lulich JP, Kruger JM, MacLeay JM, *et al.* Efficacy of two commercially available, low-magnesium, urine acidifying dry foods for the dissolution of struvite uroliths in cats. *J Am Vet Med Assoc.* 2013;243(8):1147-1153. Average 27 days *in vivo* study in urolith forming cats.

(C) 2023 Hill's Pet Nutrition Inc. HIMA-DK-2314FFC0

IMM1J53083/0423

Canine protein-losing enteropathy

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences
Iowa State University, Ames, Iowa, USA

Definition
A spectrum of GI disorders characterized by intestinal loss of plasma proteins. Major differential diagnoses for PLE include intestinal lymphangiectasia and severe mucosal inflammation.

History and physical exam
Diarrhea, weight loss, and lethargy are most frequently reported. However, a significant number of dogs with PLE have normal stools. Ascites, dependent edema, and dyspnea from pleural effusion may be detected with marked hypoproteinemia. Abdominal palpation may reveal thickened bowel loops indicative of infiltrative mucosal disease.

CBC/biochemistry
Hypoalbuminemia and hypoglobulinemia (panhypoproteinemia) are common, hypocalcemia, hypocholesterolemia and lymphopenia can also be seen.

Imaging
Abdominal ultrasound may show mucosal specks/striations (dilated lymphatics) suggestive of lymphangiectasia and/or thickened intestinal mucosa (infiltrative disease).

Diagnostic procedures
Broad-spectrum anthelminthics for potential parasitism with a variety of gastrointestinal endoparasites; dietary trial using an elimination diet to rule out adverse reactions to food; GI endoscopy-to visualize the gastrointestinal mucosa and to collect endoscopic biopsies for histopathologic evaluation. Laparotomy for intestinal biopsies and histopathology.

Histopathology
Lymphangiectasia is characterized by ballooning dilation of the villi caused by markedly dilated lacteals; the villi can be edematous, and some have a blunted appearance; mucosal edema is usually present and diffuse or multifocal accumulations of lymphocytes and plasma cells can be identified in the lamina propria (aka, lymphoplasmacytic enteritis [IBD]).

Treatment
For severe hypoalbuminemia, administering plasma transfusions or colloids (such as hetastarch) should be considered to increase plasma oncotic pressure. Abdominocentesis for fluid analysis.

Diet
Low-fat and/or hydrolyzed rations are preferred. If lymphangiectasia is diagnosed, there is strong EBD for the use of low-fat rations. Generally a 2–3-week trial is initiated.

Medications

Animals with inflammatory enteric disease (IBD) may be treated with glucocorticoids such as prednisone. As PLE dogs often lose antithrombin, administer clopidogrel (1-3 mg/kg PO q 24h) +/- rivaroxaban for thromboembolism prophylaxis.

Patient monitoring

Check body weight, serum albumin, and recurrence of clinical signs. Prognosis is guarded-to-poor in PLE dogs that fail to respond to diet and immunosuppressive therapy.

References

1. Dossin O, Lavoué R. Protein-losing enteropathies in dogs. Vet Clin North Am Small Anim Pract. 2011 Mar;41(2):399-418.

Chronic inflammatory enteropathies: Update on disease pathogenesis and diagnosis

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences,
Iowa State University, Ames, Iowa, USA

Presentation overview

Over the last decade, chronic inflammatory enteropathies (CIE) in dogs and cats have received great attention in the basic and clinical research arena. The 2010 ACVIM Consensus Statement, including guidelines for the diagnostic criteria for canine and feline CIE, was an important milestone to a more standardized approach to patients suspected of a CIE diagnosis. Great strides have been made since understanding the pathogenesis and classification of CIE, and novel diagnostic and treatment options have evolved. New concepts in the microbiome-host-interaction, metabolic pathways, crosstalk within the mucosal immune system, and extension to the gut-brain axis have emerged. Novel diagnostics have been developed, the clinical utility of which remains to be critically evaluated in the next coming years. New directions are also expected to lead to a larger spectrum of treatment options tailored to the individual patient.

CIE characterizes an exaggerated immune response and has a multifactorial pathophysiology. The immunopathology of CIE results from a complex interplay between elements of innate and adaptive immunity. The innate immune system as the first line of host defense is characterized by a system of circulating cells and molecules, sentinel cells, and cellular molecules that orchestrate a complex immune reaction. These signaling pathways including the inflammasome modulate the adaptive immune response, which in turn is subject to adaptive control. Advances in the fields of genomics, microbiome, and metabolomics over the last decade have revealed further important aspects of CIE pathogenesis, but evaluation of the canine CIE exposome (i.e., the life-course of environmental effects or modulators of disease risk) is still in its infancy.
The specific areas to be covered will include:

Disease prevalence and subclassification

Chronic inflammatory enteropathies are generally classified based on therapeutic trials as FRE, ARE, SRE/IRE, and NRE.

Role of genetics

There are several canine breeds that exhibit increased susceptibility to CIE that have a genetic basis. Genetic studies have not been performed in the cat.

Immunopathogenesis of chronic intestinal inflammation

The pathogenesis of canine and feline CIE is multifactorial and involves a loss of tolerance to diet and microbial components that cause an aberrant immune response in genetically susceptible hosts.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Chronic inflammatory enteropathies: Update on disease pathogenesis and diagnosis

62

Microbiome and metabolome

Intestinal dysbiosis is associated with mucosal inflammation and GI dysfunction in dogs with CIE. Dysmetabolism is prevalent in diseased animals and key disturbances in bile acids, SCFAs, and essential amino acids (tryptophan) contribute to disease pathogenesis.

GI endoscopy and mucosal healing

The decision to perform GI endoscopy in dogs with CIE is best determined on a case-by-case basis. Treatment trials are the best tools to differentiate the varied forms of CIE but GI endoscopy is required for definitive diagnosis in some instances.

Histologic assessment of mucosal inflammation

Diagnosis of intestinal inflammation in dogs and cats with CIE has historically posed great challenges for clinicians and pathologists. Modification of the WSAVA guidelines have resulted in the generation of a new histologic score.

References

1. Jergens and Heilmann. Front Vet Sci. 2022 Sep 21;9:923013

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Chronic inflammatory enteropathies: Update on disease pathogenesis and diagnosis

63

Chronic inflammatory enteropathies: Update on treatment strategies

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences,
Iowa State University, Ames, Iowa, USA

For some CIE subgroups, research over the last decade led to a change in the role of diet and recommended dietary strategies. Demonstrating the existence of food-responsive PLE (FR-PLE) and several effects of diet on the intestinal microbiome and metabolome (e.g., influence on fecal concentrations of secondary bile acids and abundances of *Peptaceobacter* [*Clostridium*] *hiranonis*) emphasizes the importance of selecting an optimal dietary strategy for dogs (and likely cats) with CIE.

Strategies for PLE

The cornerstone of PLE treatment is lifelong dietary management with a high-protein, low-fat diet (≤20% fat on a caloric basis or ≤20 g fat per 1000 kcal), which can break the cycle of intestinal protein leakage and catabolism. No clinical, clinicopathologic, histologic, or other markers can currently predict food-responsiveness in dogs with PLE (FR-PLE). Dogs failing diet trials may require immunosuppressive drug administration for remission induction.

Elimination diets for FRE

In general, a highly digestible antigen-restricted diet is fed to reduce antigenic stimulation and decrease intestinal inflammation. Ideally, use a diet that has low fat levels, moderate protein levels, and moderate to decreased carbohydrate levels. An elimination diet using a novel intact protein or hydrolyzed protein (lower molecular weight) will reduce antigenic stimulation and are particularly useful in animals with dietary sensitivity. Studies indicate that 50-60% of dogs and most cats will respond favorably to dietary trials.

Antibiotics

Antimicrobial treatment is premised on the belief that it may reduce gut bacterial loads and aid in clinical remission. Caution is advised for using antimicrobials since they exacerbate antimicrobial resistance and aggravate intestinal dysbiosis. The incidence of ARE is low (~10%) and dogs treated with antibiotics are prone to frequent relapses once they are discontinued.

Immunosuppressant drugs

Different clinical trials and case series describing IBD therapy will attest to the efficacy of immunosuppressives in inducing short-term (weeks to months) clinical remission in dogs and cats. Commonly used medications include prednisone/prednisolone, azathioprine, cyclosporine, and budesonide.

Cobalamin supplementation

Cobalamin is supplemented in dogs and cats, as needed, with severe enteropathy. Failure to diagnose and treat hypocobalaminemia may delay clinical recovery despite appropriate dietary and pharmacologic therapies.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Chronic inflammatory enteropathies: Update on treatment strategies

64

Probiotics, prebiotics, and synbiotics

Probiotics are live bacterial cultures that confer health benefits to the host. Multiple mechanisms of action have been suggested to explain the protective effects of probiotics in intestinal inflammation, including (1) inhibition of pathogenic enteric bacteria, (2) improved epithelial/mucosal barrier function, and (3) altered immunoregulation. These products must be administered continuously for their effects to be realized.

Prebiotics are complex carbohydrates, such as fructo-oligosaccharides (FOS), that promote the growth of beneficial bacterial species. Prebiotics promote the establishment of beneficial bacteria (probiotics). Probiotic + prebiotic = synbiotic. Pro/synbiotic trials for treatment of canine or feline CIE are sparse.

Fecal microbiota transplant

Few studies are published; multiple treatments are required.

References

1. Jergens and Heilmann. Front Vet Sci. 2022 Sep 21;9:923013

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Chronic inflammatory enteropathies: Update on treatment strategies

65

Evidence-based therapy of GI disease: Case studies

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences,
Iowa State University, Ames, Iowa, USA

This presentation will deliver actual cases seen by Jergens at the ISU teaching hospital. They represent routine referral cases where cases have been seen by local practitioners.

Evidence-based medicine (EBM) is a systematic approach in which doctors use the best available scientific evidence from clinical research to help make decisions about the care of individual patients. The use of EBM optimizes treatment to improve quality of care and patient outcomes. Let's review these cases looking at the available evidence.

Case 1
- 34 kg, CM, Italian Spumoni; dog is aggressive
- Presents to ISU emergency service
- 2–3-week history of progressive regurgitation
- Physical exam – NSF
- Diagnostic work up?

Case 2
- 8kg, FS, Dachshund
- ISU referral: recheck of IMHA with dog in remission following prednisone therapy
- New abnormalities have surfaced on repeat lab work
- Physical exam – NSF
- Diagnostic work up?

Case 3
- 23 kg, Pitbull adopted from 'ditch'; GREAT DOG
- ISU referral: severe diarrhea, vomiting, weight loss
- Owner wants the dog 'fixed'
- Primary vs. secondar enteropathy vs other disease?
- Physical exam – what is your assessment?
- Diagnostic work up?

Case 4
- 10-year-old, CM, DSH
- Presents to ISU emergency service
- Presenting for 3-week history of vomiting, hyporexia, and weight loss (1 kg)
- Physical examination – icteric; past history of neutrophilic cholangitis Diagnostic work up?
- Diagnostic work up?

Case 5
- 1.5-year-old, MC, Great Pyrenes; Two-week history of vomiting and hyporexia
- Physical examination – NSL, possibly mild dehydration
- Diagnostic work up?

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Evidence-based therapy of GI disease: Case studies

66

Exocrine pancreatic diseases in the dog and cat

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences,
Iowa State University, Ames, Iowa, USA

Pathgogenesis of pancreatitis

The etiology for acute and chronic pancreatitis in most instances remains unknown. An episode of pancreatitis first begins with a triggering event followed by the activation of pancreatic enzymes within the pancreas and the release of cytokines and other inflammatory mediators causing cell injury and resulting in both local and systemic effects. Acute pancreatitis can progress to chronic pancreatitis characterized by lymphocytic inflammation, variable fibrosis, and acinar atrophy. The latter potentially results in exocrine pancreatic insufficiency (EPI).

History/Physical exam

Affected animals are generally middle-aged or older. Dogs and cats with a acute pancreatitis often present with signs of lethargy, anorexia, and vomiting, Abdominal palpation may elicit pain, presence of a cranial abdominal mass, or mild ascites. Severity of disease varies widely, and subclinical disease may be present in some animals. Physical examination often reveals jaundice and dehydration in cats while abdominal discomfort and dehydration predominate in dogs.

Diagnostic testing

A diagnosis of pancreatitis may be suspected by the following observations:

- Suspicious history and physical examination
- Diagnostic imaging – ultrasound is very sensitive for diagnosis of pancreatitis in dogs (70%) vs. cats (30%). Enlargement of the pancreas, hypoechoic echogenicity, pain on pressure with the probe, and localized effusion may be seen on abdominal ultrasound. Hyperechogenicity of pancreatic parenchyma indicates fibrosis and is seen with chronic pancreatitis.
- Laboratory tests – results of a CBC, biochemistry, and urinalysis are highly variable and reflect severity and duration of the underlying disease process. Anemia, leukocytosis, elevated liver enzymes, azotemia, and electrolyte disturbances have all been reported. Hypocalcemia is often seen with hypoalbuminemia and is a poor prognostic sign in cats. Pancreatic lipase testing using a species-specific quantitative assay (i.e., Spec PL) is the biomarker of choice.

Treatment

Treatment of pancreatitis is mainly symptomatic and supportive. **Intravenous fluid therapy, analgesics, antiemetics and enteral nutrition are the cornerstones of therap**y. Antimicrobial therapy is reserved for severe cases, such as those presenting with shock, fever, marked leukocytosis or pancreatic abscessation. There is some evidence that prednisolone administration to dogs with acute pancreatitis may improve survival post-hospitalization. The presence of comorbidities (i.e., triaditis) in cats is common but only confirmed if biopsy of affected organs is performed (uncommon).

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Exocrine pancreatic diseases in the dog and cat

67

Prognosis

The prognosis in most cases of acute pancreatitis is favorable with appropriate medical therapy.

References

1. Nivy R, Kaplanov A, Kuzi S, et al. A retrospective study of 157 hospitalized cats with pancreatitis in a tertiary care center: Clinical, imaging and laboratory findings, potential prognostic markers and outcome. *J Vet Intern Med* 2018;32:1874-1885.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Exocrine pancreatic diseases in the dog and cat

68

Indications, pitfalls, and practical tips for lower GI endoscopy

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences,
Iowa State University, Ames, Iowa, USA

Enteroscopy

Indications
Patients with small intestinal disease including chronic small bowel diarrhea, weight loss, alterations in appetite (often anorexia), vomiting, and melena.

Patient preparation
Withhold food for 12-18 hours for upper small bowel examination. Retrograde ileoscopy will require more extensive patient preparation (see colonoscopy).

Instrumentation
Flexible endoscopy is required to traverse the pylorus and to visualize the descending duodenum. Serrated cup forceps (without bayonet) are often useful for small bowel biopsy procedures, but personal preference will influence forceps selection.

Abnormal findings
Alterations in mucosal texture (increased granularity), friability, and hyperemia are commonly observed. Increased granularity, friability, and erosions are often associated with mucosal inflammation seen with IBD and intestinal neoplasia. White specks or striations from distended villi may be seen in dogs with intestinal lymphangiectasia.

Biopsy recommendations and technique
Duodenal tissue is normally quite friable and good technique is essential. Serrated cup (non-bayonet) biopsy forceps should be used to obtain 10-15 quality specimens.

Colonoscopy

Indications
Clinical signs of chronic colonic disease including large bowel diarrhea (tenesmus, dyschezia, hematochezia, or mucoid feces).

Patient preparation
Withhold food for 18-24 hours. Perform PEG prep, 20 ml/kg/dose orally given twice.

Instrumentation
Flexible endoscopy allows for visualization of all colonic regions as well as retrograde ileoscopy. Biopsy instruments should include serrated cup forceps. Always obtain ileal biopsies if possible.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Indications, pitfalls, and practical tips for lower GI endoscopy

69

Abnormal findings

Similar as for enteroscopy including increased mucosal granularity, increased friability, and the presence of ulcer/erosions.

Biopsy recommendations and technique

Colonic biopsies are always obtained regardless of mucosal appearance. Flexible endoscopy is preferable since examination and biopsy of the transverse and ascending colons may also be performed. Focal mass lesions or mucosal lesions of increased granularity and/or erosions are biopsied directly. In the absence of gross mucosal abnormalities, obtain 3-4 biopsy specimens from each colonic region (e.g., ascending, transverse, and descending colon) using serrated cup biopsy forceps.

Ileoscopy

Retrograde ileoscopy should be performed as part of routine upper and lower GI endoscopic examination in animals, if possible. Furthermore, this procedure is useful to perform in patients in which insufficient quantity or poor-quality duodenal biopsies have been obtained. This procedure will necessitate thorough colonic cleansing and advancement of the endoscope tip through the ileocecal sphincter in dogs. Note that the ileal mucosa has an identical appearance to that of the proximal duodenum. Alternatively, 'blind' biopsies may be procured by passing the biopsies forceps through the ileocecal orifice. Ileal biopsies may be particularly useful for diagnosis of occult lymphosarcoma in cats.

References

1. Jergens et al. Vet J 2016 Aug; 214:50-60.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Indications, pitfalls, and practical tips for lower GI endoscopy

70

Indications, pitfalls, and practical tips for upper GI endoscopy

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences
Iowa State University, Ames, Iowa, USA

Esophagoscopy

Indications
Clinical signs of dysphagia, regurgitation, excessive salivation, vomiting, hematemesis, suspicion of stricture, diverticulum, or foreign body.

Patient preparation
Withhold food for 12-18 hours. Animals with retention of ingesta or barium contrast may require additional time.

Instrumentation
Flexible endoscopy is preferred. Biopsy accessories should include serrated jaw pinch forceps (most useful), foreign body graspers, and a balloon catheter for dilatation of strictures. Mucosal biopsy of the esophagus is uncommonly required except for intraluminal mass lesions.

Abnormal findings
Mass lesions (neoplastic most commonly), esophagitis (mucosal erythema, hemorrhage, erosions), stricture, foreign body, focal or generalized dilatation, and perforation.

Biopsy recommendations and technique
It is difficult to obtain esophageal biopsy specimens since the mucosa is tough and the biopsy instrument cannot be easily positioned perpendicular to the mucosal surface. Mass lesions should be biopsied deeply to avoid necrotic surface debris and superficial cells which may obscure a correct diagnosis. Exfoliative cytology of mass lesions is more useful than histopathology.

Gastroscopy

Indications
Clinical signs referable to gastric diseases, including anorexia, weight loss, chronic vomiting, hematemesis, and melena. Specific diseases diagnosed via gastroscopy include chronic gastritis, gastric ulcer/erosions, foreign bodies, gastric nematodes, gastric neoplasia, and pyloric hypertrophy.

Patient preparation
Withhold food for 12-18 hours. Animals having gastric retention of ingesta or barium contrast will require that food be withheld for 24-36 hours.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Indications, pitfalls, and practical tips for upper GI endoscopy

71

Instrumentation
Flexible endoscopy to visualize the cardia, fundus, body, antrum, and pyloric regions of the stomach. Instrumentation should include serrated jaw pinch forceps for mucosal biopsy and retrieval forceps (three-pronged and basket types) for removal of foreign bodies.

Abnormal findings
Mucosal granularity, increased tissue friability, excessive erythema, mass lesions, rugal distortion, ulcer/erosions, incomplete gastric distention, retained gastric contents, foreign body, and intraluminal parasites.

Biopsy recommendations and technique
Gastric biopsies are always obtained regardless of mucosal appearance. Serrated jaw pinch forceps produce the greatest tissue purchases. Six to eight good quality biopsy specimens should be procured. Focal lesions such as masses, erosions, and ulcers should be biopsied directly. Masses are repeatedly biopsied deeply, and at the junction of normal from abnormal appearing mucosa. Ulcerative lesions are best biopsied by obtaining specimens from the ulcer rim as it interfaces with adjacent tissue. Brush cytology may allow for rapid tentative diagnosis of mucosal disease. In the absence of gross mucosal abnormalities, obtain multiple random biopsies from the rugal folds of the gastric body. The antrum is not routinely sampled unless gross lesions are present.

References
1. Jergens et al. Vet J 2016 Aug; 214:50-60.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – Indications, pitfalls, and practical tips for upper GI endoscopy

72

What's new in GI from 2020 - 2023?

Albert E. Jergens, DVM, PhD, DACVIM
Veterinary Clinical Sciences
Iowa State University, Ames, Iowa, USA

This presentation will be eclectic in its coverage of several different topics of practical relevance to practitioners and specialists alike:

Bile acid dysmetabolsim in dogs and cats: who cares?

Bile acids (BAs) are now recognized as crucial cell signalling molecules mediating GI health and disease. As microbial imbalances are common in dogs and cats with chronic intestinal inflammation, BAs are dysregulated which contributes to abnormal microbial structure and sustained intestinal inflammation.

Dysbiosis index in dogs and cats

The dysbiosis index (DI) is a qPCR assay-based algorithm that quantitates the magnitude of fecal dysbiosis. The DI measures the abundance of 7 key bacterial taxa and the total bacterial abundance in canine and feline feces. The DI calculates a single number that expresses the extent of intestinal dysbiosis present: a DI <0 indicates a normal microbiota while a DI >2 indicates dysbiosis in dogs. The DI can be used to assess normal versus abnormal microbiota at a single time point or longitudinally in response to disease progression or therapeutic intervention.

Fecal microbiota transplantation (FMT)

The efforts to restore eubiosis in dogs and cats with GI disease by administration of FMT has been investigated only to a limited extent. Guidelines regarding optimal donor screening and clinical indications, as well as the method of delivery (oral vs. rectal catheter vs. endoscopy) and frequency of administration of FMT, are currently lacking. Much of the EBD is generated from dogs with acute diarrhea. Recently, a single large trial (41 dogs) investigated FMT as adjunct therapy for CE. We will discuss methods and long-term outcome in this cohort.

Non-antibiotic treatment for acute diarrhea

What and when are antibiotics used for treatment of acute diarrhea? What are the consequences of indiscriminate antibiotic use in patients?

Diet-responsive enteropathy and *clostridium hiranonis*

A recent clinical trial has shed new light on the possible mechanism of a hydrolysed protein diet on remission in dogs with FRE. *C. hiranosis* plays an important role in host-microbiome interactions mediating GI health and disease.

Feline triaditis: the essential facts (as time permits)

A definitive diagnosis of triaditis requires histologic confirmation of inflammation in each organ, but this may not be possible because of financial or patient-related constraints. Evidence-based data indicate that histologic lesions of triaditis are present in 30% to 50% of cats diagnosed with pancreatitis and cholangitis/inflammatory liver disease. Treatment

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – What's new in GI from 2020 - 2023?

73

of triaditis is based on the overall health status of the patient and the type and severity of disease in component organs.

References

1. Wang *et al.* Diet-induced remission in chronic enteropathy is associated with altered microbial community structure and synthesis of secondary bile acids. *Microbiome* **7**, 126 (2019).

Proceedings of 48th ASAV Annual Conference together with Reproduction
Jergens, AE – What's new in GI from 2020 - 2023?

74

Abdominal multi-detector computed tomography
(emphasis on gastrointestinal tract)

Kristina Miles, DVM, MS, DACVR
Iowa State University
Ames, Iowa, USA

Multi-detector computed tomography (MDCT)

Multi-detector computed tomography (MDCT) is now more readily available in veterinary specialty practice settings. The rapid isotropic data acquisition available from a 32-slice (detector array) MDCT scanner, or greater, results in a markedly shortened scan acquisition time. Abbreviated scan times allow for selection of sedation protocols for small animal and exotic veterinary patients, rather than general anesthesia. Sedation alone results in shortened patient recovery time and decreasing client cost.[1-4]

MDCT also provides a larger scan range (length of area covered) and may be used as a rapid screening tool for a wide variety of abdominal, thoracic and large animal evaluations. Companion animal studies may range from senior wellness exams to dogs presented with acute abdominal signs for the purpose of differentiating surgical from non-surgical conditions.[5] Small animal patients are placed in sternal recumbency for abdominal scans whenever possible at Iowa State University's Lloyd Veterinary Medical Center, for standardization.

Standard data acquisition obtained with MDCT scanners is volumetric, resulting in evaluations that consist of hundreds of images per study. Commonly, each patient evaluation includes dedicated computer workstation post-processing of two, or more, volumetric datasets, such as pre and post-intravenous contrast administration or both soft tissue and bone algorithms. Initial transverse (axial) scans are routinely evaluated with 2D multiplanar reformation (MPR) to add dorsal (coronal) and sagittal planes for anatomic correlation of normal structures, as well as pathology. Additional 3D volume rendering (VR) software may be selected to enhance conspicuity a wide variety of features based on the specific clinical questions in each patient.

The vast majority of abdominal MDCT studies require administration of an intravenous positive contrast agent (nonionic, iodinated) to enhance differentiation of vascular structures. MDCT angiography (CTA) is particularly useful for evaluation of portosystemic shunts and other vascular abnormalities.[6-12] Use of a power injector for intravenous contrast delivery delivers a consistent flow rate and volume from scan to scan and allows for a more precise delivery time of the positive contrast agent to targeted anatomy. However, patient related factors, including those influenced by sedation or anesthesia protocols (heart rate), will also affect timing of contrast delivery to targeted structures. General anesthesia will allow for application of breath hold techniques to minimize patient respiratory motion artifacts in cases where visualization of abdominal vasculature is critical.

MDCT evaluation of small animal patients to confirm suspected neoplastic lesions involving the abdomen[13-14] or to identify organ of origin for known abdominal masses provides rapid, non-invasive diagnostic information that may be used for clinical staging[15], to prioritize

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Abdominal multi-detector computed tomography (emphasis on gastrointestinal tract)

75

ultrasound-guided fine needle aspirates and/or for pre-surgical planning. Sedated small animals are positioned in sternal recumbency for abdominal MDCT at Iowa State's Lloyd Veterinary Medical Center diagnostic imaging service. MDCT studies are performed using a Canon, Aquilion 32 slice, large aperture unit. General anesthesia is encouraged for animals with suspected portosystemic shunts or pancreatic disease, such as an insulioma, to decrease cranial abdominal respiratory artifacts. Dorsal and sagittal scout images are initially obtained for planning and collimation purposes followed by a minimum two phase (arterial and venous) study with option for a third delayed phase at approx. 3 minutes post-intravenous contrast administration, to include the full lower urinary tract.

Gastrointestinal abnormalities

MDCT provides visualization of all portions of the gastrointestinal tract, without the gas interface artifacts produced by abdominal ultrasound. Total gastrointestinal wall thickness, total small intestinal diameter[14] and adjacent mesenteric fat or regional lymph node changes may all be evaluated. Nonspecific fat stranding is observed as web-like increase of soft tissue/fluid attenuation of the mesenteric fat adjacent to underlying neoplasia or inflammatory lesions.[16]

MDCT is also effective in identifying mechanical obstruction in dogs and cats, due to either the presence of intraluminal foreign material or mural abnormalities.[17] When identified with MDCT, only 12.5% of dogs with mechanical obstructions improved with medical management alone (aggressive intravenous fluid therapy, pain management). None of the cats in this study improved with medical management alone when a mechanical obstruction was present on the MDCT scan.[17] MDCT has also demonstrated accuracy for differentiating surgical from non-surgical causes of disease in dogs with acute abdominal signs.[18] MDCT showed increased detection of size and number of specific lesions when compared with ultrasound, as well as improved identification of free gas in the peritoneal space.

Urogenital abnormalities

MDCT is also well suited for rapid, noninvasive assessment of urogenital anomalies and other renal and ureteral abnormalities with the increased resolution afforded by isotropic volumetric scanning.[19-22] MDCT has been particularly effective when combined with sedation alone for evaluation of fragile exotic animal patients.[23-24]

References
1. Fields EL, Robertson ID, Brown JC. Optimization of contrast-enhanced multidetector abdominal computed tomography in sedated canine patients. VRUS 2012; 53:507-512.
2. Shanaman MM, Hartman SK, O'Brien RT. Feasibility for using dualphase contrast-enhanced multi- detector helical computed tomography to evaluate awake and sedated dogs with acute abdominal signs VRUS 2012; 53:605-612.
3. Oliveria CR, Mitchell MA, O'Brien RT. Thoracic computed tomography in feline patients without use of chemical restraint. VRUS 2011; 52:368-376.
4. Bertolini G, Prokop M. Multidetector-row computed tomography: Technical basics and preliminary clinical applications in small animals. Vet Journal 2011; 189;15-26.
 5. Shanaman MM, Schwarz T, Gal, A, et al. Comparison between survey radiography, B-mode ultrasonography, contrast-enhanced ultrasonography and contrast-enhanced multi-

detector computed tomography findings in dogs with acute abdominal signs. VRUS 2013; 54(6);591-604.

6. Bertolini G, Rolla EC, Zotti A, et al. Three-dimensional multislice helical computer tomography techniques for canine extra-hepatic portosystemic shunt assessment. VRUS 2006; 47;439-443.

7. Schwarz T, Rossi F, Wray JD, et al. Computed tomographic and magnetic resonance imaging features of canine segmental caudal vena cava aplasia. JSAP 2009; 50;341-349.

8. Leeman JJ, Kim SE, Reese DJ, et al. Multiple congenital PSS in a dog: case report and literature review. JAAHA 2013; 49;281-285.

9. Nelson NC, Nelson LL. Anatomy of extrahepatic portosystemic shunts in dogs as determined by computed tomography angiography. VRUS 2011; 52(5);498-506.

10. Bertolini G. Portal collateral circulation in dog and cat. VRUS 2010; 51;25-33.

11. Chandrashekhara SH, Sharma R, Arora R. Periportal hypodensity on CT: Significance and differential diagnosis of an overlooked sign. Clinics and Research in Hepatology and Gastroenterology 2011; 35;247-253.

12. Kim SE, Giglio RF, Reese DJ, et al. Comparison of Computed tomographic angiography and ultrasonography for the detection and characterization of portosystemic shunts in dogs. VRUS 2013; 54(6);569-574.

13. von Babo V, Eberle N, Mischke R, et al. Canine hon-hematopoietic gastric neoplasia. Epidemiologic and diagnostic characteristicsin 38 dogs with post-surgical outcome of five cases. Tierarztl Prax Ausg K Kleintiere Heimtiere 2012; 40(4);243-249.

14. Hoey S, Drees R, Hetzel S. Evaluation of the gastrointestinal tract in dogs using computed tomography. Vet Radiol & Ultrasound 2012;54 (1);25-30.

15. Vignoli M, Terragni R, Rossi F, et al. Whole body computed tomographic characteristics of skeletal and cardiac muscular metastatic neoplasia in dog and cats. VRUS 2013; 54(3);223-30.

16. Jang S, Lee S, Choi J. CT imaging features of fat stranding in cat and dogs with abdominal disorders. J Vet Ci 2022; 23(6);e70. Doi: 10.4142/jvs.22059. PMID: 3603819.

17. Miniter BM, Goncalves Arruda A, Zuckerman J, et al. Use of computed tomography (CT) for the diagnosis of mechanical gastrointestinal obstruction in canines and felines. PLOS ONE 2019; https://doi.org/10.1371/journal.pone.0219748

18. Shanaman MM, Schwarz T, Gal A, et al. Comparison between survey radiography, b-mode ultrasonography, contrast-enhanced ultrasonography and contrast-enhanced multi-detector computed tomography findings in dogs with acute abdominal signs. Vet Radiol & Ultrasound 2013; 54(6);591-604.

19. Lee S, Jung J, Chang J, et al. Evaluation of triphasic helical computed tomography of the kidneys in clinically normal dogs. Am J Vet Res 2011; 72(3);345-349.

20. Secrest S, Essman S, Nagy J, et al. Effects of furosemide on ureteral diameter and attenuation using computed tomographic excretory urography in normal dogs. VRUS 2013: 54(1);17-24.

21. Specchi S, Lacava G, d'Anjou MA, et al. Ultrasound-guided percutaneous antegrade pyelography with computed tomography for the diagnosis of spontaneous partial ureteral rupture in a dog. Can Vet J 2012; 53(11);1187-1190.

22. zur Linden AR, Riedesel EA, Alexander K. Multi-detector CT urography protocol design and optimization. Abstract Proceedings ACVR 2012;67.

23. Lee KJ, Sasaki M, Miyauchi A, et al. Virtopsy in a red kangaroo with oral osteomyelitis. J Zoo Wildl Med 2011; 42(1):128-130.

24. Olds JE, Miles KG, Hofer S. Health screening of red-necked wallabies (macropus rufogriseus) using computed tomography (CT) in addition to conventional diagnostic methods. Abstract Proceedings AAZV 2013;47

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Abdominal multi-detector computed tomography (emphasis on gastrointestinal tract)

78

Gastrointestinal ultrasonography of the dog and cat

Kristina Miles, DVM, MS, DACVR
Iowa State University
Ames, Iowa, USA

Gastrointestinal anatomy

Survey abdominal radiographs are commonly obtained for non-invasive screening of dogs and cats presented with clinical signs of gastrointestinal disease (vomiting, diarrhea, inappetence, constipation). However, discrimination of abnormalities involving the gastrointestinal wall cannot be differentiated with survey radiographs alone. As a result, abdominal ultrasound plays an integral role in evaluation of gastrointestinal disease of small animal patients, working synergistically with survey abdominal radiographs to provide diagnostic information.[1-2]

Examination of gastrointestinal layers is best performed in dogs and cats held off food for a minimum of 12 hours whenever possible. Animal aerophagia will produce increasing gas-interface artifacts. Appropriate animal sedation is encouraged to minimize panting, discomfort or vocalizations and results in improved image quality and scanning efficiency.

Use of a scanning protocol is strongly encouraged to ensure that all structures are included in the ultrasound evaluation. The gastrointestinal component of the ISU LVMC protocol includes evaluation of the gastric wall in both sagittal and transverse planes, notation of gastric contents, visualization of the pyloroduodenal junction, the proximal duodenum in both sagittal and transverse planes, the duodenal papilla, the mid to distal duodenum, multiple jejunal segments, the descending colon adjacent to the urinary bladder, transverse and ascending colon, the ileocecocolic junction and the ileum in both sagittal and transverse planes. Mesenteric lymph nodes adjacent to the ileocecocolic junction provide a good anatomic landmark for this intestinal structure.

Normal sonographic gastrointestinal wall layering in dogs and cats is well documented.[3-8] A mucosal surface to surface hyperechoic interface is present in the empty intestine, surrounded by a distinct hypoechoic mucosal layer. The thin hyperechoic submucosa, with connective tissue stroma, is present and is more prominent in the ileum than the jejunum. The peripheral hypoechoic muscularis is normally less prominent than the mucosal layer. Finally, the thin, hyperecohic serosa is best seen when oriented as a specular reflector at a 90 degree angle to the transducer.

The anatomic location of the duodenum in the right lateral abdomen and its connection to the pylorus provide good landmarks for identification. Visualization of the junction of the pylorus and duodenum may be more difficult to obtain in deep-chested dogs without the use of a right intercostal window. The major duodenal papilla is included in the ISU LVMC protocol and is an additional anatomic landmark frequently observed. The presence or absence of normal peristaltic contractions throughout the gastrointestinal tract should be noted, but may be affected by animal anxiety or sedation.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Gastrointestinal ultrasonography of the dog and cat

79

Abnormalities of the intestinal wall may be focal, segmental or diffuse and may obliterate or maintain wall layering. Total thickness of the various portions of the gastrointestinal tract, as well as thickness of individual layers, can be measured.[3-4,9] The mucosa and submucosa typically contribute a greater percentage of the total wall thickness than the muscularis layer. Commonly used normal total thickness measurements of the canine stomach, duodenum, jejunum, ileum and colon are: 3-5 mm, up to 5 mm, 2-5 mm, 2-4 mm and 2-3 mm, respectively. Commonly used normal total thickness measurements of the feline stomach, duodenum, jejunum, ileum and colon are: 2-4 mm, 2-2.5 mm, 2.2-5 mm, 2.5-3.2 mm and 1.4-2.5 mm, respectively.[10] Measurement of mesenteric lymph nodes adjacent to the gastrointestinal tract in dogs, based on body weight and age, may also be performed.[11]

Considerable overlap between the sonographic appearance of neoplastic disease and non-specific inflammation of the intestine exists. However, focal loss of wall layering is much more commonly observed with neoplastic conditions or fungal infections.[7-20] Evaluation of surrounding tissues to assess for abnormally hyperechoic mesenteric fat, pockets of free peritoneal fluid or enlarged, rounded and/or hypoechoic regional lymph nodes is critical for prioritizing differentials and next diagnostic steps.

Chronic inflammatory disease may result in mild to moderate increases in total wall thickness or may alter individual layers. Hyperechoic striations and speckles within the mucosal layer are nonspecific findings. Parallel hyperechoic linear striations oriented perpendicular to the long axis of the intestinal wall layers may be more consistent with crypt abscessation or dilated lacteals associated with lymphangectiasia. Contrast enhanced sonography of dogs with acute abdominal signs and of the normal feline intestine has been described and may highlight additional differences in abnormal tissues with future study.[19-22]

Sonographic evaluation of the gastrointestinal tract is also commonly performed to confirm the presence of suspected gi foreign bodies, including linear foreign bodies, prior to surgical removal.[21-29] Evaluation of associated structures, such as the pancreas and biliary tree, should not be overlooked during a complete ultrasound examination of the gastrointestinal tract.[30-33]

References
1. Penninck DG, Nyland TG, Kerr LY, Fisher PE. Ultrasonographic evaluation of gastrointestinal diseases in small animals. VRUS 1990; 31;134–141.
2. Gaschen L, Kircher P, Stussi A, et al. Comparison of ultrasonographic findings with clinical activity index (CIBDAI) and diagnosis in dogs with chronic enteropathies. VRUS 2008; 49(1);56-64.
3. Di Donato P, Penninck D, Pietra M, et al. Ultrasonographic measurement of the relative thickness of intestinal wall layers in clinically healthy cats. J Feline Med & Surg 2013; 0(0); 1-7. DOI: 10.1177/1098612X13509080
4. Winter MD, Londono L, Berry CR, et al. Ultrasonographic evaluation of relative gastrointestinal layer thickness in cats without clinical evidence of gastrointestinal tract disease. J Feline Med & Surg 2014; 16(2);118-124.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Gastrointestinal ultrasonography of the dog and cat

80

5. Rudorf H, van Schaik G, O'Brien RT, et al. Ultrasonographic evaluation of the thickness of the small intestinal wall in dogs with inflammatory bowel disease. JSAP 2005: 46(7);322-326.

6. Daniaux LA, Laurenson MP, Marks SL, et al. Ultrasonographic thickening of the muscularis propria in feline small intestinal small cell T-cell lymphoma and inflammatory bowel disease. J Feline Med & Surg 2014; 16(2);89-98.

7. Norsworthy GD, Estep JS, Kiupel M, et al. Diagnosis of chronic small bowel disease in cats: 100 cases (2008-2012) JAVMA 2013; 243(10);1455-1461.

8. Sutherland-Smith J, Penninck DG, Keating JH, et al. Ultrasounographic intestinal hyperechoic mucosal striations in dogs are associated with lacteal dilation. VRUS 2007; 48(1);51-57

9. Gladwin NE, Penninck DG, Webster CR. Ultrasonographic evaluation of the thickness of the wall layers in the intestinal tract of dogs. *Am J Vet Res* 2014;75(4):349-353.

10. Huynh E, Berry CR. Ultrasonography of the gastrointestinal tract: Ileum, cecum, colon. Today's Veterinary Practice 2018. https://todaysveterinarypractice.com/radiology-imaging/ultrasonography-of-the-gastrointestinal-tract-ileum-cecum-colon/

11. Teodori S, Aste G, Tamburro R, et al. Computed Tomography Evaluation of Normal Canine Abdominal Lymph Nodes: Retrospective Study of Size and Morphology According to Body Weight and Age in 45 Dogs. Vet Sci. 2021 Mar 7;8(3):44. doi: 10.3390/vetsci8030044. PMID: 33800083 PMCID: PMC7999630

12. Kaser-Hotz B, Hauser B, Arnold P. Ultrasonographic findings in canine gastric neoplasia in 13 patients. VRUS 1996; 37:51–56.

13. Lamb CR, Grierson J. Ultrasonographic appearance of primary gastric neoplasia in 21 dogs. JSAP 1999; 40;211–215.

14. Penninck DG, Matz M, Tidwell A. Ultrasonography of gastric ulceration in the dog. VRUS 1997; 38;308–312.

15. Penninck DG, Moore AS, Gliatto J. Ultrasonography of canine gastric epithelial neoplasia. VRUS 1998; 39;342–348.

16. Rivers BJ, Walter PA, Johnston GR, et al. Canine gastric neoplasia:utility of ultrasonography in diagnosis. JAAHA 1997; 33;144-155.

17. Taeymans O, Holt N, Penninck DG, et al. Ultrasonographic characterization of feline ileocecolic abnormalities. VRUS 2011; 52(3);335-339.

18. Diana, A, Specchi S, Baron Toaldo M, et al. Contrast-enhanced ultrasonography of the small bowel in healthy cats. VRUS 2011; 52(5);555-559.

19. Garcia DAA, Froes TR, Vilani RGDOC, et al. Ultrasonography of small intestinal obstructions; a contemporary approach. JSAP 2011; 52;484-490.

20. Hoffman KL. Sonographic signs of gastroduodenal linear foreign body in 3 dogs. VRUS 2003; 44;466–469.

21. Tidwell AS, Penninck DG. Ultrasonography of gastrointestinal foreign bodies. VRUS 1992; 33;160–169.

22. Sharma A, Thompson MS, Scrivani PV, et al. Comparison of radiography and ultrasonography for diagnosing small-intestinal mechanical obstruction in vomiting dogs. VRUS 2011; 52:248–255.

23. Tyrrell D, Beck C. Survey of the use of radiography vs. ultrasonography in the investigation of gastrointestinal foreign bodies in small animals. VRUS 2006; 47:404–408.

24. Boysen SR, Tidwell AS, Penninck DG. Ultrasonographic findings in dogs and cats with gastrointestinal perforation. VRUS 2003; 44;556–564.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Gastrointestinal ultrasonography of the dog and cat

81

25. Grassi R, Romano S, Pinto A, Romano L. Gastro-duodenal perforations: conventional plain film, ultrasonography and CT findings in 166 consecutive patients. Eur J Radiol 2004; 50:30–36.

26. Ferrell EA, Graham JP. Ultrasound corner diagnosis of pneumoperitoneum. VRUS 2003; 44;307–308.

27. Penninck DG, Mitchell SL. Ultrasonographic detection of ingested and perforating wooden foreign bodies in four dogs. JAVMA 2003; 223;206–209.

28. Penninck DG, O'Sullivan Brisson J, Webster CRL. Sonographic assessment of gallbladder volume in normal cats. VRUS 2010; 51(6);665-666.

29. Gaillot HA, Penninck DG, Webster CRL, et al. Ultrasonographic features of extrahepatic biliary obstruction in 30 cats. VRUS 2007; 48(5);439-447.

30. Hecht S, Penninck DG, Keating JH. Imaging findings in pancreatic neoplasia and nodular hyperplasia in 19 cats. VRUS 2007; 48(1):45-50.

31. Hecht S, Penninck DG, Mahony OM, et al. Relationship of pancreatic duct dilation to age and clinical findings in cats. VRUS 2006; 47(3);287-294.

32. Williams JM, Panciera DL, Larson MM, et al. Ultrasonographic findings of the pancreas in cats with elevated serum pancreatic lipase immunoreactivity. JVIM 2013; 27(4);913-918.

33. Penninck DG, Zeyen U, Taeymans ON, et al. Ultrasonographic measurement of the pancreas and pancreatic duct in clinically normal dogs. Am J Vet Res 2013; 74(3);433-437.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Gastrointestinal ultrasonography of the dog and cat

82

Highlights of the ACVR/ECVDI consensus statement on standardisation of the abdominal ultrasound examination

Kristina Miles, DVM, MS, DACVR
Iowa State University
Ames, Iowa, USA

Consensus basics

Small animal abdominal ultrasound examinations may vary greatly between individual veterinary sonographers making interpretation of exam findings more challenging. An ACVR and ECVDI consensus statement concerning standardization of abdominal ultrasound exams was published in 2022 [1] The information discussed includes animal preparation, image acquisition protocols and recommended image documentation.

The purpose of the veterinary consensus statement is to provide a set of guidelines toward establishing a standard of care. However, this consensus is statement is not a legally binding document. The consensus process included survey and discussion of each line item until consensus was achieved. This consensus statement does not address Point-of-Care ultrasound studies (POCUS).

A full, comprehensive ultrasound examination is considered the basic standard of care. The gold standard identified in the consensus is interpretation of ultrasound information at the time that the examination is performed by a board certified veterinary radiologist, incorporating information about the animal signalment and clinical data.

Equipment requirements

Minimal transducer requirements for evaluations of dogs and cats should include transduces with a frequency range between 5 and 18 MHz. In physics of ultrasonography, the highest frequency transducer available for adequate depth of penetration should be used to obtain improved axial image resolution. Continuous adjustment of the focal zone to the area of interest is needed to obtain improved lateral resolution and reduce imaging artifacts.

Color Doppler and Power (low flow) Doppler are useful tools in evaluation of abdominal lesions and should be available for a full, comprehensive abdominal examination of the dog or cat.   High quality video clips of areas of interest are an important tool, but should be no more than 5-10 seconds in length. Ultimately, optimal use of the equipment to obtain a diagnostic study is the responsibility of the sonographer.

Preparing for the exam

Information provided to the sonographer should include a complete animal signalment, a concise history with summary of clinical and physical exam findings, indications for the ultrasound study and concerns that include preliminary differential diagnoses. Ideally, the animal should be held off food for at least 8 hours prior to the study. Animal urination and defecation prior to the exam may also be helpful. The abdominal hair coat must be clipped. Importantly, as animal compliance may be a limiting factor during the exam, animal sedation will yield a higher quality ultrasound study that is obtained more efficiently.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Highlights of the ACVR/ECVDI consensus statement on standardisation
of the abdominal ultrasound examination

83

Specifically at Iowa State University's Lloyd Veterinary Medical Center, dogs 30 kgs or greater are imaged with computed tomography (CT) to increase diagnostic visualization of abdominal structures. Abdominal CT may be followed by ultrasound guided fine needle aspirates of abnormalities identified during the CT

Sonographic images
Images should be archived for retrieval in DICOM format. Both static images and video clips must be labelled. As with digital radiography orientation, the cranial aspect of the animal is placed on the left for sagittal images. The right side of the animal is placed on the left for transverse images. Static images should be obtained both with, and without, digital measurement calipers. Video clips should include recognizable anatomic landmarks whenever possible.

Sonographic report
Use of an ultrasound report template may be of benefit to enhance ease of review. Sonographic reports should include a description of organ size, shape and echogenicity. Factors affecting image quality, such as lack of animal compliance or animal obesity should be noted in the final report, along with documentation of any interventional procedures performed, such as cystocentesis. Report conclusions for each abnormality identified should include ranked differential diagnoses. Next step suggestions may, or may not be added to the report.

Examination of anatomic structures
Use of intercostal windows may be required for visualization of cranial abdominal anatomy. Split screen images may be needed to compare the echogenicity of the spleen and liver, spleen and renal cortices or renal cortex with hepatic parenchyma. Do not change imaging parameters between organs during acquisition of comparative images. Minimum evaluation of the hepatic parenchyma includes left, middle and right regions, as well as comparison of hepatic echogenicity with adjacent falciform fat. Notation of echogenic gall bladder debris, either gravity dependent, suspended or both, should be included in the study. A portal vein/Aorta diameter ratio obtained near the porta hepatis should be included in animals with a suspected portosystemic shunt.[2] Measurement of the spleen at the splenic hilus in the sagittal/long axis/longitudinal plane is recommended for both dogs and cats.

Measurement of the largest parenchymal lesion in a minimum of two, preferably three, planes is recommended if multiple similar abnormalities are present. Total wall thickness of intestinal segments should be obtained in a sagittal orientation to assist in placement of the transducer at the center of the selected bowel loop.

Both right and left pancreatic lobes, as well as the pancreatic body region images should include adjacent anatomic landmarks, such as the duodenum, pylorus, portal and pancreaticoduodenal vein, stomach, transverse colon, splenic vein/spleen and left kidney. Evaluation of peripancreatic fat, perinodal fat and periureteral fat are important features of a complete abdominal examination.

Phrenicoabdominal vessels are useful landmarks for adrenal glands, sometimes described as an "equal –sign" appearance in the dog. The aorta, caudal vena cava, celiac and cranial

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Highlights of the ACVR/ECVDI consensus statement on standardisation of the abdominal ultrasound examination

84

mesenteric and left renal artery and vein provide additional anatomic landmarks for localization of adrenal glands.

Renal length to aortic diameter ratios are obtained with measurement of the abdominal aorta immediately caudal to the left renal artery. Orientation of the renal hilus at the six o'clock position is recommended for transverse images of each kidney, including evaluation of the renal pelvis. Reproductive tract structure assessment is included in a complete abdominal ultrasound. Structures not present or not visualized should be noted in the final report.

A complete abdominal ultrasound study will also include evaluation of the peritoneal and retroperitoneal spaces, as well as mesenteric lymph nodes. Medial iliac and jejunal lymph node thickness should be documented.[3] Additional mesenteric lymph nodes may be included, particularly those associated with any other identified abnormalities.

References
1. Seiler GS, Cohen EB, d'Anjou MA, et al. ACVR and ECVDI consensus statement for the standardization of the abdominal ultrasound examination. Vet Radiol Ultrasound 2022;63:661-674. DOI:10.1111/vru.13151
2. D'Anjou MA,Penninck D,Cornejo L, et al. Ultrasonographic diagnosis of portosystemic shunting in dogs and cats. Vet Radiol Ultrasound.2004;45(5):424–437.
3. Teodori S, Aste G, Tamburro R, et al. Computed Tomography Evaluation of Normal Canine Abdominal Lymph Nodes: Retrospective Study of Size and Morphology According to Body Weight and Age in 45 Dogs. Vet Sci. 2021 Mar 7;8(3):44. doi: 10.3390/vetsci8030044. PMID: 33800083 PMCID: PMC7999630

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Highlights of the ACVR/ECVDI consensus statement on standardisation
of the abdominal ultrasound examination

85

Radiographic interpretation of the gastrointestinal tract

Kristina Miles, DVM, MS, DACVR
Iowa State University
Ames, Iowa, USA

Esophagus

The normal esophagus is a collapsed tubular structure that is not visualized on survey radiographs because it lies within the mediastinum where it's borders are effaced by the surrounding soft tissues. However, at the thoracic inlet the esophagus lies to the left of the trachea and slightly ventral. This positioning may create a soft tissue opacity along the dorsal margin of the trachea that could mimic tracheal collapse.[1] Alternatively, this dorsal tracheal membrane "sign" may be associated with asymptomatic muscle laxity and should be correlated with clinical signs.[2] A left lateral view of the thorax may provide more separation between these two tubular structures to help differentiate between a radiographic entrapment and patient pathology.

Small amounts of air may be seen in the normal esophagus due to aerophagia associated with patient excitement. Common sites for this transient gas accumulation are: 1) immediately caudal to the cranial esophageal sphincter, 2) at the thoracic inlet, and 3) dorsal to the heart base. Air surrounding the soft tissue opacity of the upper esophageal sphincter should not be mistaken for a mass or foreign body. Transient localized enlargement of the esophagus may be caused by a bolus of air or ingesta. A repeat survey radiograph may be used to differentiate a swallowed bolus from a focal gas or fluid accumulation within a dilated segment cranial to an esophageal lesion. Air will highlight the serosal margins of the esophagus when a pneumomediastinum is present.

The diameter of the normal esophagus should not exceed the smallest diameter of the thoracic aorta seen on the same radiograph. A generalized, gas and/or fluid dilated esophagus (megaesophagus) may be visualized on survey radiographs. A large megaesophagus will displace the trachea and heart base ventrally on the lateral view. Gas accumulation within the lumen of the dilated esophagus may result in visualization of the esophageal walls as thin, radiopaque lines that converge in a "V" shape at the lower esophageal sphincter.[3] However, the radiolucent lung field observed between the descending aorta and the caudal vena cava on lateral thoracic radiographs should not be mistaken for an air-filled esophagus. Radiographic changes consistent with secondary aspiration pneumonia are often seen as a sequela to megaesophagus.

Many suspected abnormalities involving the location, function, or morphology of the esophagus must be confirmed with esophagography. Survey radiographs should be obtained prior to the esophagram to establish optimal radiographic technique and serve as reference films. Barium sulfate is the contrast medium of choice.

Suspected esophageal lesions may first be evaluated with a liquid barium preparation, to determine if the esophagus is patent. Unfortunately, liquid barium does not adhere well to the esophageal mucosa. Following the liquid barium, oral administration of a thicker barium sulfate paste will coat the esophageal folds and provide better visualization of the mucosa.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Radiographic interpretation of the gastrointestinal tract

86

Barium sulfate dosages range between 1.5 and 3 mls/lb. Lastly, a barium meal may be given to demonstrate a partial esophageal obstruction or a difference in ability to swallow solids versus liquids. Use of chemical restraint will alter esophageal motility and is not generally required. Orthogonal radiographs, +/- oblique VD projections, should be obtained post- contrast. The patient may be held erect for 5-10 mins. following barium administration to evaluate passage of the contrast material through the lower esophageal sphincter with the aid of gravity. If an esophageal perforation is suspected, a water-soluble, ionic contrast material can be used in lieu of barium sulfate. A bronchoesophageal fistula should not be mistaken for inadvertent aspiration of the contrast agent.

A normal canine esophagram appears as a series of parallel longitudinal folds along the entire length of the esophagus. A slight irregularity of the mucosal pattern of the skeletal muscle at the level of the thoracic inlet may be seen in young dogs as the esophagus deviates ventrally. A small amount of contrast may also be retained in the cervical portion of the esophagus, immediately caudal to the cranial esophageal sphincter. In cats, only the cranial two-thirds of the esophagus exhibits these characteristic longitudinal folds. Oblique striations of the caudal one-third of the esophagus corresponds to the smooth muscle segment of the esophagus and creates a characteristic "herring bone" pattern. This species variation should not be misdiagnosed as a foreign body or esophageal inflammation.

A regional esophageal dilation is most commonly seen cranial to an intraluminal or an extrinsic obstruction. Esophageal foreign bodies most commonly lodge in one of three locations: 1) at the thoracic inlet, 2) at the base of the heart, or 3) at the esophageal hiatus, near the diaphragm. Esophageal neoplasia and diverticuli are uncommon.

Stomach

The stomach can be divided into four sections: 1) the cardia, 2) fundus, 3) body, and 4) pylorus. The pylorus may be further sub-divided into a pyloric antrum and pyloric canal. Rugal folds are especially prominent in the fundus, which is located in the left cranial abdominal quadrant. The normal gastric axis should lie between a line drawn parallel to the ribs and a line drawn perpendicular to the spine, on the lateral view. The body of the stomach is located at midline on the ventrodorsal view of the dog, with the pyloric antrum and canal positioned to the right of the spinal column. In the cat, the majority of the stomach remains to the left of midline, with the pyloric region more centrally located.

Distribution of gas and fluid (or contrast) within the gastric lumen is highly dependent on animal positioning in the dog. The gastric gas bubble will classically "float up" into the fundus when the patient is in right lateral recumbency. The pyloric region will be fluid-filled and should not be misdiagnosed as a soft tissue mass. In left lateral recumbency, gastric gas will locate in the pyloric region of the stomach. The round, air-filled pylorus should not be mistaken for a radiolucent foreign body. The fundus and body of the stomach will be filled with dependent fluid. On the dorsoventral projection, the gastric gas bubble will be seen in the fundic region, while fluid settles into the body and pylorus. Fluid fills the fundus and body of the stomach on the ventrodorsal view; Gas is located in the pyloric antrum.[3] Three view abdominal radiographs may be less effective in altering gastric gas position in the cat.[4] Gastric wall thickness cannot be reliably assessed on survey films due to variations in gastric distention and border effacement of the serosal margin with adjacent soft tissue structures.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Radiographic interpretation of the gastrointestinal tract

87

Small intestine

Careful evaluation of the small intestines should be performed on all survey abdominal radiographs. Important factors to consider in this evaluation include: 1) location, 2) amount of intestine visualized/affected, 3) gas pattern, 4) intraluminal contents, 5) diameter of intestinal loops, and 5) contour of the bowel walls. The small intestinal loops should be uniformly spread throughout the midventral region of the abdomen. On the VD projection, the majority of small intestinal loops may be located to the right of midline. Gastric distention may cause transient caudal displacement of the intestines, while a distended urinary bladder will result in cranial intestinal displacement. If a large amount of intra-abdominal fat is present, the small intestinal loops may be more dorsally located and confined to a smaller area around the mesenteric root.

Normal small bowel diameter in the dog and cat will typically not exceed 1.6 X the central height of L2 on the lateral view.[6] An alternate evaluation method for cats uses a small intestinal total diameter ratio > 2 (when compared with the height of the cranial end-plate of the L2 vertebral body on a lateral projection) as an indicator more likely to be seen with obstructive intestinal disease.[8] Abnormalities affecting > 50 % of the small intestinal loops are considered generalized. Regional or localized changes affect < 50 % of the intestinal loops, but involve more bowel segments than focal lesions. Focal disease indicates that only 1-3 intestinal loops are abnormal. Gas within normal small intestines tends to have an ovoid or curvilinear pattern as it follows along the smoothly contoured walls of intestine. Comma-shaped gas foci or numerous tiny bubbles are atypical. The amount of intestinal gas is usually less than that present in the stomach and colon. However, recent administration of an enema will increase the volume of small intestinal gas. Overall, the opacity of the intestines will vary depending on the mixture of fluid, gas, and more radiopaque ingesta within the lumen.

Failure of distended small intestinal loops to propel luminal contents aborally is described as ileus. Ileus may be functional or mechanical. Mechanical obstructions occlude the intestinal lumen. In cases of functional ileus, when the motor function of the intestine is impaired, peristaltic contractions cease, but the lumen remains patent. Mild gaseous distention of a single intestinal loop that persists between radiographic studies may be described as a "sentinel loop". This form of localized, functional ileus indicates that a focal area of disease lies adjacent to, or involves, the affected intestinal segment.

In occasional cases of mechanical obstruction, dilated intestinal loops may lie parallel with one another resulting in a "layered" or "stacked" pattern. As these loops change direction, the appearance of a "hairpin turn" is created. Severity of the intestinal distention will correspond to duration and completeness of the obstruction. Ultimately, the bowel wall will become weak and atonic, combining mechanical with functional ileus. Intestinal loops distal to the lesion will retain normal size.

Intestinal lumen size, wall thickness, and mucosal lesions cannot be reliably evaluated on survey films alone. However, an upper g.i. series is not required prior to exploratory celiotomy if survey films are highly suggestive of a mechanical obstruction. Stable animals should be properly prepared before contrast administration. Remember to avoid anticholinergic drugs and use an adequate volume of contrast material. Five ml/lb of a 30-50 % barium sulfate suspension is considered a standard dose.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Radiographic interpretation of the gastrointestinal tract

88

The normal small intestinal mucosal pattern is smooth or finely fimbriated. Pseudoulcers may be seen in the descending duodenum of dogs along the antimesenteric margin. These "mesa-like" depressions in the wall are located over lymphoid follicles. In the cat, normal increased segmentation of the duodenum may create a "string-of-pearls" or beaded appearance. The small intestinal loops are generally cleared of contrast material within 5 hours in the dog and 3 hours in the cat. Lesions causing functional or mechanical ileus, administration of anticholinergics, and inadequate contrast volume may all result in a delayed intestinal transit time. Hypermotility is most often seen in association with enteritis or peritonitis.

Obstructive lesions generally result in dilated intestines with smooth mucosal margins. An irregular or spiculated mucosal pattern is often seen with ulceration originating from fungal enteritis, inflammatory bowel disease, or neoplasia. The lumen may be dilated or narrowed. The mucosal surface is generally smooth when hypersegmentation of intestinal loops is associated with spasm, enteritis, or peritonitis. Focal narrowing of a bowel lumen may be due to a stricture of neoplasm. A mucosal irregularity combined with focal narrowing of the lumen is often associated with intestinal neoplasia, and may be described as having an "apple core" appearance.

The number of small intraluminal gas bubbles are often increased and may form a "dot-dash" pattern, or comma shapes, when a linear foreign body is present. The classic, eccentric accordion-like pleating of the small bowel is best visualized on a positive contrast study. "Climbing" of the intestines along the linear foreign body will ultimately result in small perforations and localized peritonitis.

The cecum is located in the dorsal half of the abdomen on the lateral view. On the VD projection, it is seen at the level of the 2-4 lumbar vertebra and to the right of midline. The canine cecum has a semicircular "C" shape. The short, cone-like feline cecum is less frequently visualized on survey films because it contains little gas. The ileocolic junction is the narrowest part of the gastrointestinal tract caudal to the pylorus. If an intestinal foreign body passes beyond this level, it is usually capable of passage through the rest of the intestinal tract.

Colon

The entire abdomen and pelvic region should be included on both (right lateral, VD) radiographic views if colonic disease is suspected. The urinary bladder should be empty to minimize colon displacement. The normal diameter of the colon should not exceed the length of the seventh lumbar vertebral body (1.5 X length of L7 *if transient*). Increased size of the large bowel may be seen with constipation, colonic or rectal obstruction, and neurological dysfunction. Megacolon describes enlargement of the colon to greater than 1.5 times the length of L7in dogs. Megacolon may be generalized or focal.

More recently, the total diameter of the feline colon has been compared with the length of the L5 vertebral body.[9] A normal colon diameter ratio of <1.28 has been identified, while a ratio of >1.48 suggests megacolon.[9] The cecum and colon are usually identified on survey radiographs by the presence of intraluminal gas and/or fecal material. If free of feces, the normal colon has a smooth mucosal surface and uniform diameter. The rectum is frequently empty.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Radiographic interpretation of the gastrointestinal tract

89

The ascending colon is located to the right of midline, with the transverse colon passing from right to left, cranial to the mesenteric root and caudal to the greater curvature of the stomach. The descending colon courses to the left of midline before entering the pelvic canal as the rectum. Positional variations of the descending colon are normal due to a variable volume of fecal material and urinary bladder distention.

A partial contrast study of the large bowel can be performed by introducing air (pneumocolon) into the rectum via a large syringe. Partial studies are rapid and used to evaluate the anatomic position of the colon in cases caudal abdominal masses or when differentiating small and large bowel segments.[7]

Oral administration of barium will not result in a diagnostic study of the colon. For example, barium adhering to fecal material and mucus may produce radiographic entrapments that must be differentiated from colonic lesions. A complete positive contrast evaluation of the large bowel is achieved by performing a barium enema. Because of the exacting technical requirements for this two-stage procedure, the barium enema has been replaced in veterinary practice by colonoscopy.

References
1. Miles K. Consultations in Feline Internal Medicine 4 2001;73
2. Schwarz TA. BSAVA Manual of Canine and Feline Thoracic Imaging 2008: BSAVA
3. Burk R, et al. Small Animal Radiology and Ultrasonography 1996:23.
4. Paradise H, Gaschen L, Wanderer M, et al. Vet Radiol Ultrasound 2019; 60:633.
5. Mahaffey M, et al. Textbook of Veterinary Diagnostic Radiology 2002:615.
6. Jergens AE, Moore FM, Haynes JS, Miles KG. JAVMA 1992; 201:1603
7. Hudson J, Brawner W, Holland M, et al. Abdominal Radiology or the Small Animal Practioner. 2002:61
8. Adams WM, Sisterman LA, Klauaer JM, et al. JAVMA 2010; 236:880
9. Trevail T, Gunn-Moore D, Carrera I,et al. Vet Radiolol Ultrasoud 2011; 52:516.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Miles, K – Radiographic interpretation of the gastrointestinal tract

90

Pre-pubertal desexing of cats

Dr. Xavier Schneider BIT BLM (Hons) BVSc (Hons) MANZCVS (Anim. Reprod.) DipACT
Animal Reproduction Specialists
telemed@reprovet.com.au

Surgical sterilisation is the irreversible intervention causing permanent cessation of reproductive function. Approaches include:

- Surgical methods including ovariectomy/ovariohysterectomy, orchidectomy, vasectomy and salpingectomy
- Chemical methods include GnRH agonists/antagonists and melatonin
- Traumatic methods (usually reserved for wild/feral population)

Removal of the gonads at the time of desexing cause a disruption to the feedback loop of the hypothalamic-pituitary-gonadal axis, creating a supraphysiologic release of FSH and LH. Removal of the gonads also causes a cessation of sex-steroid hormones produced by the gonads including oestrogen, progesterone and testosterone, among others. There is, however some involvement of the adrenal glands, with levels of sex steroids measured by Monroe et al 2012 for dogs, but not cats after ACTH stimulation for both entire and neutered males and females[1].

Several conditions in dogs and cats can be impacted by elective gonadectomy, including neoplasia and orthopaedic diseases[2]. Gonadal hormone influences reproductive, skeletal, physical and behavioural development in immature animals[1] and there is a trend to allow bitches and queens to experience an oestrus cycle before surgical sterilisation. Knowledge of the benefits and detriments associated with this procedure enables veterinarians to provide appropriate science to clients to make informed decisions and promote animal health[2].

The effects of gonadectomy on specific diseases reported in dogs and cats include:

- Non-Neoplastic Disorders
  - Obesity
  - Urinary Incontinence
  - Urinary Calculi
  - Diabetes Mellitus
  - Hypothyroidism
  - Hip Dysplasia
  - CCL Rupture
  - IVD
  - Behaviour
  - Cognitive Dysfunction Syndrome
  - Urogenital Tract Disorders
- Neoplastic Disorders
  - Prostatic Disease
  - TCC
  - Osteosarcoma
  - Haemangiosarcoma
  - Mastocytoma
  - Lymphoma

The effect of gonadectomy and the supraphysiologic release of LH on specific organs and/or diseases discussed include:

- canine lower urinary tract
- normal and adenomatous thyroid tissue
- anterior cruciate ligament
- structural support tissue of the canine hip and femoral tibial joints
- neoplastic endothelial cells of splenic, cardiac, cutaneous and dermal haemangiosarcoma
- lymphocytes and lymphoid tissue

Specific effects of desexing in cats include:

- a 91% risk reduction of mammary tumour development if desexed prior to 6 months of age
- a 86% risk reduction of mammary tumour development if desexed prior to 1 year of age
- desexing reduces the risk of mammary hyperplasia, with removal of the gonads, reported as a treatment of choice
- cats are 3.4 times more likely to become obese with gonadectomy
- cats are at an increased risk of capital physeal fractures if gonadectomised if desexed pre-pubertal (however is multi-factorial)

References

1. Roberts, M. L., Beatty, J. A., Dhand, N. K. & Barrs, V. R. (2015) Effect of age and surgical approach on perioperative wound complication following ovariohysterectomy in shelter-housed cats in Australia. *J. Feline Med. Surg.*
2. Kustritz M. Determining the optimal age for gonadectomy of dogs and cats. Journal of the American Veterinary Medical Association 2007;231:1665-1675.
3. Reichler I. Gonadectomy in Cats and Dogs: A Review of Risks and Benefits. Reproduction in Domestic Animals 2009;44:29–35.
4. Zwida K, Kutzler M. Non-Reproductive Long-Term Health Complications of Gonad Removal in Dogs as Well as Possible Causal Relationships with Post-Gonadectomy Elevated Luteinizing Hormone (LH) Concentrations. Journal of Etiology and Animal Health 2016;1:1-11.
5. Schneider R, Dorn C, Taylor D. Factors influencing canine mammary cancer development and postsurgical survival. Journal of the National Cancer Institute 1969;43:1249–1261.
6. Overley B, Shofer FS, Goldschmidt MH, et al. Association between ovarihysterectomy and feline mammary carcinoma. Journal of veterinary internal medicine / American College of Veterinary Internal Medicine 2005;19:560–563.
7. Melo, E. H. de et al. Effectiveness of ovariohysterectomy on feline mammary fibroepithelial hyperplasia treatment. J. Feline Med. Surg. 23, 351–356 (2021).
8. Schäfer-Somi, S. Effect of melatonin on the reproductive cycle in female cats: a review of clinical experiences and previous studies. Journal of Feline Medicine and Surgery 19, 5–12 (2017).

Desexing: Making sense of the literature and conversations with clients

Dr Abbie Tipler ATCL BVSc MANZCVS, FANZCVS (Surgery)
Veterinary Specialist Services

The decision whether to desex a dog and the ethics surrounding the decision are complex. There is a lack of evidence that desexing reduces the population of shelter dogs, and in some countries where desexing is not performed, there are lower rates of shelter surrender. This likely means that vets and owners need to make decisions based on the individual dog and the owner circumstances (e.g. do they have a fenced yard etc), versus a simple calculation of 'desexing is the responsible pet ownership decision'.

In one owner survey, 61% of male dog owners and 47% of female dog owners reported that they would not make the same decision, if given the choice again to desex. This highlights the importance of giving pet owners all the available information to make the decision. This may also provide a huge opportunity to build a more loyal client base with pet owners.

This pros and cons list should be interpreted in light of the disease prevalence, which can vary based on breed and region. For example, although desexing females reduces the risk of ovarian tumours, these tumours are uncommon. Some breeds are more prone to orthopaedic disease or various cancers, and it may be more important to delay desexing or find an alternative, in these breeds.

Therefore, although this information gives an overview, more detailed information may be required. The information should also be combined with the recommendation from a dog's own veterinarian, who will have knowledge of the region and pet owner base.

A **printable handout**, that may help assist to give some of the information to pet owners, can be found at this link. Warn owners that this information may change over time. https://www.vss.net.au/desexing-your-dog.html

In regards to desexing, there are some generally accepted trends based on the literature. The literature is a constantly changing entity, however there are some useful summary papers that have been published in the last two years and these references can be found within these notes. Three useful references are;
"Assisting Decision-Making on Age of Neutering for 35 Breeds of Dogs: Associated Joint Disorders, Cancers, and Urinary Incontinence"
https://www.frontiersin.org/articles/10.3389/fvets.2020.00388/full

"Assisting Decision-Making on Age of Neutering for Mixed Breed Dogs of Five Weight Categories: Associated Joint Disorders and Cancers"
https://www.frontiersin.org/articles/10.3389/fvets.2020.00472/full

"An Ancient Practice but a New Paradigm: Personal Choice for the Age to Spay or Neuter a Dog"
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8017224/
The generally accepted trends are as follows;

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

93

1. Desexing at greater than 12-18 months will result in less influence on developmental diseases e.g. orthopaedic disease
2. Desexing at a later age, can still have effects on degenerative disease. Preserving the hormones for longer, may reduce these diseases – e.g. neoplasia
3. Hormones have an effect on growth plate closure, ligament and muscle formation, relaxin and Luteinizing Hormone (LH).
4. There is literature bias. Literature bias is often the result of studies being retrospective in nature. When interpreting the literature, we need to look at why a patient is desexed or kept entire. For example, desexing in many countries is often coupled with better general husbandry and more compliant owners. Therefore any paper that shows a lifespan advantage with desexing is likely to be affected by bias. Some dogs are screened for orthopaedic disease because they are breeding dogs. These dogs will be intact. In some regions where a study is performed, there are greater numbers of various breeds, which can effect results. These are just three sources of bias, but there are many.

One other factor involved in decision making, is you have your pros and cons list - but also consider relative risk. An example, is that there is an increased risk of prostate cancer, however this is a low cause of overall dog mortality.

Below, is an overall summary of the Pros and Cons of desexing, with a few comments.

Pros of desexing in females

Mammary Cancer potential reduction
There is likely a reduction in risk of mammary neoplasia. The evidence is conflicting and a meta-analysis found overall the evidence showed only a weak association. Prevalence of mammary cancer varies by breed, so taking a look at the breed related studies is advised.
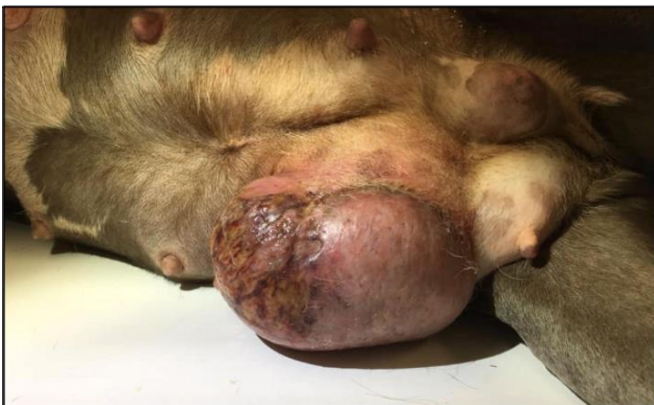
You can monitor a dog for mammary neoplasia via palpation, so mammary cancer can be diagnosed early by dedicated owners (versus for example hemangiosarcoma).
Age, hormonal control and breed are the main influencing factors when it comes to mammary cancer.

A recent 2021 summary paper by Hart, expressed that the dangers of not desexing, in regards to mammary neoplasia, *may* be overrated. Mammary cancer in dog is generally treatable. (note - mammary cancer in cats is generally much more malignant).

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

94

"An Ancient Practice but a New Paradigm: Personal Choice for the Age to Spay or Neuter a Dog"
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8017224/

"Epidemiology of canine mammary tumours on the Canary Archipelago in Spain"
https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-022-03363-9
supports the trend towards neutering being protective, and identified at risk breeds. These breeds seem to be consistent across multiple papers.
The breeds most at risk – Samoyed, Schnauzer, Poodle, German Pinscher, Cocker Spaniel, Dobermann, West Highland White Terrier, Dalmatian, Dachshund, Yorkshire Terrier and Boxer.
Lower risk – Chihuahua, English Pointer, Labrador Retriever.

Ovarian tumours, uterine neoplasia, vaginal and vulval tumours.

These tumours are rare with a low mortality.
Uterine neoplasia is often benign so ovariohysterectomy is curative.
Ovarian tumours are rare and ovariectomy and ovariohysterectomy are protective. Mortality rate for these is low.
Desexing may be protective against vaginal and vulval tumours, which are commonly leiomyomas. In dogs with confirmed leiomyoma, desexing is often part of the treatment.

Pyometra, metritis and ovarian cysts

Ovariohysterectomy, ovariectomy and ovary-sparing hysterectomy prevent and treat pyometra and metritis. Ovariohysterectomy and ovariectomy prevent ovarian cysts. They all prevent problems associated with pregnancy and parturition.

Incidence in intact dogs has been reported to be between 2 and 25% by 10 years. The incidence also seems to vary based on breed, so referral to breed related studies as above is recommended. Pyometra can result in septic shock and renal failure and mortality rates between 4 and 17% have been reported. It is important to note, that in regards to ovary sparing hysterectomy, it is important to remove the entire uterus.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

95

Pros of desexing in males

Testicular tumour reduction

Testicular tumours are common, but they have a low rate of metastasis. Castration is preventative and generally curative. Cryptorchid testicles may be more prone to testicular tumours. This condition is also heritable so it is recommended that cryptorchid dogs are castrated for both these reasons.

Reduction in benign prostatic hyperplasia, chronic prostatitis, perianal adenomas and perianal hernias

Benign prostatic hyperplasia (BPH) affects around 50% of intact dogs by 5 years of age and 95-100% by 9 years. Dogs with BPH are prone to prostatic cysts, prostatitis and prostatic abscesses.

Pros of desexing in males and females

Reduction in transmissible venereal tumours

Transmissible venereal tumours are fairly common in regions where there are lots of intact dogs. Maybe if we start advocating against desexing we may see a greater prevalence of these. They are sexually transmitted and metastasis occurs in 5-17%.

Overall lifespan advantage?

One study found that lifespan was increased in dogs that were desexed. They found that although the risk of death by neoplasia increased, the risk of death by trauma and infectious disease increased. There are biases in this type of research, in that in some regions desexing is often associated with better husbandry and compliant owners. It does highlight however, that it is important for dogs that are kept entire, to be kept in a secure yard to avoid escape episodes that can result in vehicular trauma.

Lifespan studies also do not take age at desex into account, so some dogs may have been exposed to hormones for longer than others. Also, the finding of increased lifespan seems more consistent in desexed females and the association is less for desexed males.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

96

Lifespan studies also do not take into account quality of life. Is it better to live for a shorter period of time in less pain? This is an ethical dilemma.

Cons females

Urinary incontinence
This problem affects around 6-9% of neutered females and larger breeds are more prone to this. There is some evidence to suggest that those dogs spey prior to 3 months of age have the highest risk. Desexed females in general, have a much higher prevalence compared to intact females. Prevalence also varies by breed, so checking breed specific studies is recommended (see examples above). Dogs greater than 10kg, as especially dogs greater than 30kg, are at the greatest risk.

It can be medically managed, however this can be an expense to owners.

Female vulval development
Development of the female vulvar is dependent on sex steroids. There is an increased risk of recessed vulva when females are desexed before development.

Cons of desexing in the male

Increased risk of prostatic carcinoma
Prostatic carcinoma is potentially more prevalent in desexed dogs. Prostatic carcinoma is an aggressive neoplasia with a high metastatic rate.
There is a low prevalence of this disease. Risk varies by breed.

Cons of desexing in males and females

Cancer
The prevalence of various cancers, and whether or not the risk is increased or not with desexing, varies by breed. It may also vary depending on the age the patient is desexed i.e. period of time they were exposed to hormones.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

97

Briefly, these are the cancers that evidence suggests are increased with desexing. All of these cancers have multiple factors affecting their development, prevalence and prognosis and cancer is a complex disease. For further information on these neoplasias an excellent resource is vsso.org, specifically the webpage, https://vsso.org/home/#homecancercatsdogs

I also highly recommend The Pet Oncologist. https://www.thepetoncologist.com/

This below reference looks at 35 common dog breeds and the prevalence of joint disorders, cancers and urinary incontinence. https://www.frontiersin.org/articles/10.3389/fvets.2020.00388/full

It is important to note, that this article does not take into consideration the potential decreased risk of trauma and infectious disease in the desexed population.

In a similar article examining mixed breed dogs, no increased risk of cancer was found in any weight group with desexing. They examined lymphoma, mast cell tumour, hemangiosarcoma and osteosarcoma.

Transitional cell carcinomas
Transitional cell carcinomas account for around 2% of cancer. Desexing increases the risk. It is also an aggressive cancer with a high metastatic rate. Risk also varies by breed.

Lymphoma
Lymphoma is a fairly common tumour. There is an increased prevalence in desexed dogs. It has fairly high remission rates with chemotherapy (60-90%). Risk varies by breed.

Mast cell tumours
These are common tumours and account for around 20% of cutaneous tumours. The prognosis is variable depending on the grade and stage of mast cell tumour. Risk varies with breed.

Hemangiosarcoma
Hemangiosarcoma accounts for around 5-7% of non-cutaneous neoplasia. It has a poor prognosis and only 10% of dogs survive greater than 12 months even with surgery and chemotherapy. Risk of splenic and cardiac hemangiosarcoma is increased in desexed dogs. Risk varies by breed.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

98

Osteosarcoma

Osteosarcoma is a malignant bone tumour. It is malignant in nature with local aggressiveness and a high rate of metastasis often to the lungs. Around 90% of patients die of metastatic disease within a year if amputation is the only treatment. There is an increased risk in desexed dogs. Risk varies by breed, and larger breeds are more prone. Of important note, is the Rottweiler, 25% of which will develop an osteosarcoma. The earlier the Rottweiler is desexed, the higher the risk of osteosarcoma. This trend is seen in some other breeds, and desexing after a year of age may reduce the risk, some studies have shown.

Orthopaedic disease

There have been a number of breed specific studies and the finding is generally that some breeds, when desexed prior to skeletal maturity, have an increased risk of joint diseases. The finding is not always consistent among males and females.

A few examples of breeds at increased risk of orthopaedic disease are Golden Retrievers, Labrador Retrievers, German Shepherds, Rottweilers, male Beagles and female Australian cattle dogs. This is evidence that for these patients, we should consider desexing at skeletal maturity.

This below reference looks at 35 common dog breeds and the prevalence of joint disorders, cancers and urinary incontinence.
https://www.frontiersin.org/articles/10.3389/fvets.2020.00388/full

A similar article examined mixed breeds of various weight ranges.
"Assisting Decision-Making on Age of Neutering for Mixed Breed Dogs of Five Weight Categories: Associated Joint Disorders and Cancers"
https://www.frontiersin.org/articles/10.3389/fvets.2020.00472/full

It is important to note, that these articles do not take into consideration the potential decreased risk of trauma and infectious disease in the desexed population.

Orthopaedic disease is also complex, with many different proposed etiological contributors. Further information beyond the scope of this post, should be obtained as there are other factors that can reduce the incidence of orthopaedic disease (namely, weight control and core strengthening activities).

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

99

Briefly, specific orthopaedic diseases, that may have an increased prevalence in the desexed population are;

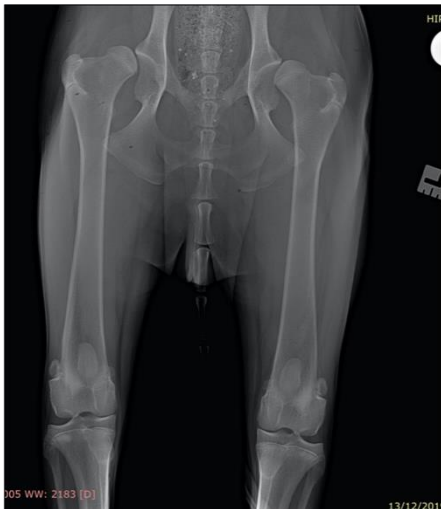- *Cruciate ligament disease*

2-4% of dogs get cruciate disease
Desexing is a risk factor for some breeds and larger mixed breeds.
One study found dogs desexed prior to skeletal maturity had a 3 fold increase in tibial plateau angle

- *Hip dysplasia*

Some breeds and mixed breeds >20kg desexed prior to skeletal maturity, have an increased risk of hip dysplasia.
Golden Retrievers have an increased risk in males desexed prior to 1 year of age.
Boxers de-sexed at least 6 months prior to diagnosis were 1.5x more likely to develop hip dysplasia.

- *Elbow dysplasia*

The link between elbow dysplasia and desexing is less well defined. Desexed mixed breed dogs over 20kg had a higher risk of elbow dysplasia if desexed <12 months.

Other cons of desexing (not related to cancer or orthopaedic disease)

Obesity
Desexing results in increased appetite and slowed metabolism. It results in a 30% less energy requirement.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients
100

Diabetes

There is an increased risk in the desexed population

Autoimmune disease

There is a possible increase in risk of immune-mediated disease, addisons, hypothyroidism, IBD, cushings and epilepsy – the effect tends to be stronger in females.

Intervertebral disc disease

There is an increased risk in desexed females and an increased risk in males and females desexed prior to 12 months of age. Consider desexing dachshunds >12 months of age.

Other

There is a possibly an increased risk of GDV and cardiomyopathy but the literature is inconclusive and one study doesn't always reproduce another.

Surgery and anaesthetic risk

The anaesthetic mortality rate in cats is around 0.11% cats and in dogs around 0.05%.

Other anaesthetic complications include hypotension, hypoventilation, bradycardia, arrhythmias and hypothermia.

Surgical complications occur in roughly 10% of patients. These include haemorrhage, wound infection, stump pyometra, ovarian remnant syndrome, seroma, iatrogenic ureteral ligation, pain, splenic laceration, iatrogenic urethral trauma.

Older, larger dogs may have an increased risk and this may need to be considered if we are recommending a delay in desexing.

Behaviour - Mixed results - Pros and cons

The effects on behaviour are less straightforward than it was once believed. This is especially true for aggressive and nuisance behaviours, where there are multiple factors involved.

A summary of the pros of desexing are;

- It decreases urine marking, mounting and roaming in some studies of dogs (one study reported around a 40% reduction in these behaviours). One study revealed that the effect of reducing urine marking was lost as the age of desexing increased. This seemed specific to males. A recent paper (link below) found an increase in problem behaviours however in the desexed population.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

101

- It can reduce hormonally based inter-dog aggression (one study reported around a 20% reduction only however)
- The most serious human bite injuries involve intact dogs. This could be related to the desexed population being tied to better husbandry and owner compliance however. There are many factors involved in dog bite behaviour. Overall, a recent human systematic review was in favour of desexing to reduce dog bites. It did however note many limitations to the observational studies included in the review.
- Intact dogs were significantly more likely to be referred for aggression and reactivity in one study (the same bias as above may apply)

A summary of the cons of desexing are;
- Intact German shepherds were found to be more trainable in one study - it is unknown if this applies to other breeds
- In one recent paper, there was an increased number of dogs that were fearful of unfamiliar dogs/humans and had increased sound phobia in the desexed population
- Potential negative effect on aggressive behaviours - see below.
- A recent 2023 paper, found that the longer the dog was exposed to hormones, the less nuisance and problematic behaviours were exhibited. This paper defined problematic behaviour as aggression, anxiety-based behaviours, and extreme fears, and nuisance behaviours as urine marking and mounting behaviour.

Aggression
The effect on aggression is conflicting. Aggressive behaviours in ENTIRE dogs may decrease as dogs age.

There is potentially an increased dominance aggression towards family members. Females and puppies that had already shown signs of aggression had the highest risk. The risk reduced the older they were de-sexed. This finding of increased aggression towards family members is not replicated in all studies and one study found a 30% reduced risk.

Age to desex, in regards to behaviour
In terms of the age to desex. In one study they compared groups desexed prior to around 6 months versus post 6 months of age. Those desexed early were more likely to display noise phobias and sexual behaviours and males were more likely to show aggression towards family members and bark at visitors, but the post 6 month group were more likely to develop separation anxiety, urination due to fear and escape behaviour.
In a further study however, there was no difference before and after the 6 month mark in these behaviours.

A 2022 paper, based on owner questionnaire, found that desexing reduced aggressive behaviours towards other dogs, roaming, mounting, urine marking and decreased dogs overall activity.

In 2023, a paper found a decrease in nuisance and problematic behaviours, in dogs with longer exposure to hormones.
https://avmajournals.avma.org/view/journals/javma/261/3/javma.22.08.0382.xml

Summary - there are very conflicting results on the evidence of desexing on behaviour.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

102

Procedure options

Females:
Ovariohysterectomy – traditional approach.
Ovariectomy – spares the uterus. This is the traditional method for laparoscopic spey. Because you remove the hormonal effect on the uterus this procedure will not result in pyometra etc. It is essentially the same procedure as above in most respects.

Ovary-sparing hysterectomy – this procedure renders a dog sterile, however the hormones are maintained. You can leave one or both ovaries and it should be outlined in the records which ovary is left. The dog has a heat cycle and there may be a small amount of bloody discharge and they will be attractive to male dogs. They may have the behavioural side effects of being on heat such as yowling etc. Theoretically they cannot get a pyometra, however if you leave any uterine stump then this can result in a stump pyometra. You need to aim to remove the uterus beyond the cervix.
There is a new paper reporting on the outcomes and complications of this procedure, that was published in 2023.
https://avmajournals.avma.org/view/journals/javma/261/3/javma.22.08.0382.xml

Salpingectomy - Tubal ligation – in every way this dog is intact, but just can't become pregnant. There are no major advantages to this procedure, the exact technique has not been reported in the literature, it can be technically challenging and one complication is iatrogenic uterine ligation instead, which leads to fluid building up in the uterus and problems. It is not my preferred technique for hormone-sparing sterilisation for these reasons.

Males:
Traditional castration - removes the hormones

Vasectomy - preserves the hormones.
The outcomes of vasectomy were also looked at in the 2023 paper
https://avmajournals.avma.org/view/journals/javma/261/3/javma.22.08.0382.xml

In summary, the new paradigm, is for the vet and pet owner to use the available data-based information to decide on the best age and procedure for the dog dependent on owner situation and dog breed. If there is no data available on a certain breed, extrapolation from similar breeds may be possible.

Description of vasectomy and OSS can be found by following the link to this paper
https://www.frontiersin.org/articles/10.3389/fvets.2020.00342/full

AVA statement
https://www.ava.com.au/policy-advocacy/policies/companion-animals-health/desexing-surgical-sterilisation-of-companion-animals

American College of Theriogenology Statement
https://cdn.ymaws.com/www.theriogenology.org/resource/resmgr/Docs/spay-neuter_basis.pdf

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

References

1. Hart B, Hart L, Thigpen A, Willits N. Assisting Decision-Making on Age of Neutering for 35 Breeds of Dogs: Associated Joint Disorders, Cancers and Urinary Incontinence. *Front. Vet. Sci 2020, 07 July.*

2. Schneider R, Dorn CR, Taylor DO. Factors influencing canine mammary cancer development and postsurgical survival. *J Natl Cancer Inst*. 1969;43:1249–1261.

3. Rutteman GR, Misdorp W. Hormonal background of canine and feline mammary tumors. *J Reprod Fertil Suppl*. 1993;47:483–487.

4. Henry CJ. Mammary cancer. In: Bonagura JD, Twedt DC, editors. *Kirk's Current Veterinary Therapy*. 14th ed. St Louis: Saunders Elsevier; 2009:363–368.

5. Dow C. The cystic hyperplasia-pyometra complex in the bitch. *Vet Rec*. 1958;70:1102–1108.

6. Smith FO. Pyometra. In: Bonagura JD, Twedt DC, editors. *Kirk's Current Veterinary Therapy*. 14th ed. St Louis: Saunders Elsevier; 2009:1008–1009.

7. Berry SJ, Strandberg JD, Saunders WJ, Coffey DS. Development of canine benign prostatic hyperplasia with age. *Prostate*. 1986;9:363–373.

8. Berry SJ, Coffey DS, Strandberg JD, Ewing LL. Effect of age, castration, and testosterone replacement on the development and restoration of canine benign prostatic hyperplasia. *Prostate*. 1986;9:295–302.

9. Sirinarumitr K. Medical treatment of benign prostatic hypertrophy and prostatitis in dogs. In: Bonagura JD, Twedt DC, editors. *Kirk's Current Veterinary Therapy*. 4th ed. St Louis: Saunders Elsevier; 2009:

10. Stubbs WP, Bloomberg MS. Implications of early neutering in the dog and cat. *Semin Vet Med Surg (Small Anim)*. 1995;10:8–12.

11. Kustritz MV. Early spay-neuter in the dog and cat. *Vet Clin North Am Small Anim Pract*. 1999;29:935–943.

12. Kustritz MV. Early spay-neuter: clinical considerations. *Clin Tech Small Anim Pract*. 2002;17:124–128.

13. Howe LM. Short-term results and complications of prepubertal gonadectomy in cats and dogs. *J Am Vet Med Assoc*. 1997;211: 57–62.

14. Misdorp W. Canine mammary tumors: protective effect of late ovariectomy and stimulating effect of progestins. *Vet Q*. 1988;10:26–33.

15. Chang SC, Chang CC, Chang TJ, Wong ML. Prognostic factors associated with survival two years after surgery in dogs with malignant mammary tumors: 79 cases (1998–2002). *J Am Vet Med Assoc*. 2005;227:1625–1629.

16. Itoh T, Uchida K, Ishaikawa K, et al. Clinicopathological survey of 101 canine mammary gland tumors: differences between small-breed dogs and others. *J Vet Med Sci*. 2005;67:345–347.

17. Moe L. Population-based incidence of mammary tumors in some dog breeds. *J Reprod Fertil Suppl*. 2001;57:439–443.

18. Moulton JE, Rosenblatt LS, Goldman M. Mammary tumors in a colony of beagle dogs. *Vet Pathol*. 1986;23:741–749.

19. Gilbertson SR, Kurzman ID, Zachrau RE, Hurvitz AI, Black MM. Canine mammary epithelial neoplasms: biological implications of morphologic characteristics assessed in 232 dogs. *Vet Pathol*. 1983;20: 127–142.

20. Sorenmo KU, Shofer FS, Goldschmidt MH. Effect of spaying and timing of spaying on survival of dogs with mammary carcinoma. *J Vet Intern Med*. 2000;14:266–270.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

104

21. Beauvais W, Cardwell JM, Brodbelt DC. The effect of neutering on the risk of mammary tumours in dogs – a systematic review. *J Small Anim Pract*. 2012;53:314–322.
22. Overley B, Shofer FS, Goldschmidt MH, Sherer D, Sorenmo KU. Association between ovariohysterectomy and feline mammary carcinoma. *J Vet Intern Med*. 2005;19:560–563.
23. Johnston SD, Root Kustritz MV, Olson PN. Disorders of the canine testes and epididymes. In: Johnston SD, Root Kustritz MV, Olson PN, editors. *Canine and Feline Theriogenology*. Philadelphia: WB Saunders; 2001:312–332.
24. Cohen D, Reif JS, Brodey RS, Keiser H. Epidemiological analysis of the most prevalent sites and types of canine neoplasia observed in a veterinary hospital. *Cancer Res*. 1997;34:2859–2868.
25. Towle HA. Testes and scrotum. In: Tobias KM, Johnston SA, editors. *Veterinary Surgery: Small Animal*. St Louis: Elsevier Saunders; 2012:1907.
26. Heuter KJ. Diseases of the prostate. In: Morgan RV, editor. *Handbook of Small Animal Practice*. 5th ed. St Louis: Saunders Elsevier; 2008: 559–568.
27. Howe LM. Diseases of the uterus. In: Morgan RV, editor. *Handbook of Small Animal Practice*. 5th ed. St Louis: Saunders Elsevier; 2008: 578–581.
28. Biddle D, Macintire DK. Obstetrical emergencies. *Clin Tech Small Anim Pract*. 2000;15:88–93.
29. Johnston SD, Root Kustritz MV, Olsen PN. Disorders of the canine uterus and uterine tubes (oviducts). In: Johnston SD, Root Kustritz MV, Olson PN, editors. *Canine and Feline Theriogenology*. Philadelphia: WB Saunders; 2001:206–220.
30. Hagman R. *New Aspects of Canine Pyometra: Studies on Epidemiology and Pathogenesis* [doctoral thesis]. Uppsala, Sweden: Swedish University of Agricultural Sciences; 2004. Available from: http://pub.epsilon.slu.se/736/1/Avhandlingsramen_f%C3%B6r_n%C3%A4rpublikation_R.Hagman.pdf. Accessed June 30, 2014.
31. Hagman R, Lagerstedt AS, Hedhammar Å, Egenvall A. A breed-matched case-control study of potential risk-factors for canine pyometra. *Theriogenology*. 2001;17:1251–1257.
32. Barsanti JA, Finco DR. Canine prostatic diseases. *Vet Clin North Am Small Anim Pract*._
33. Olson PN, Wrigley RH, Thrall MA, Husted PW. Disorders of the canine prostate gland: pathogenesis, diagnosis, and medical therapy. *Compend Contin Educ Pract Vet*. 1987;9:613–623.
34. Johnson SD, Kamolpatana K, Root-Kustritz MV, et al. Prostatic disorders in the dog. *Anim Reprod Sci*. 2000;60:405–415.
35. Sirinarumitr K. Benigh prostatic hypertrophy and prostatitis in dogs. In: Bonagura JD, Twedt DC, editors. *Current Veterinary Therapy*. 15th ed. St. Louis: Saunders Elsevier; 2014:1012–1015.
36. White RAS. Prostate. In: Tobias KM, Johnston SA, editors. *Veterinary Surgery Small Animal*. St. Louis: Saunders Elsevier; 2012:1934–1937.
37. Kutzler MA, Yeager A. Prostatic diseases. In Ettinger SJ, Feldman EC, editors. *Textbook of Veterinary Internal Medicine*. 6th ed. St Louis: Elsevier Saunders; 2005:1809–1819.
38. Bray JP, White RAS, Williams JM. Partial resection and omentalization: A new technique for management of prostatic retention cysts in dogs. *Vet Surg*. 1997:76:202–209.
39. Black GM, Ling GV, Nyland TG, Baker T. Prevalence of prostatic cysts in adult, large-breed dogs. *J Am Anim Hosp Assoc*. 1998;34:177–180.
40. White RA, Williams JM. Intracapsular prostatic omentalization: a new technique for management of prostatic abscesses in dogs. *Vet Surg*. 1995;24:390–395.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

105

41.	Hardie EM, Barsanti JA, Rawlings CA. Complications of prostatic surgery. *J Am Anim Hosp Assoc*. 1984;20:50–56.

42.	White RA. Prostate. In: Tobia KM, Johnston SA, editors. *Veterinary Surgery: Small Animal*. St Louis: Elsevier Saunders; 2012:1907.

43.	Thrusfield MV, Holt PE, Muirhead RH. Acquired urinary incontinence in bitches: its risk and relationship to neutering practices. *J Small Anim Med*. 1998;39:559–566.

44.	Arnold S, Arnold P, Hubler M, Casal M, Rüsch P. Urinary incontinence in spayed female dogs: prevalence and breed predisposition. *Schweiz Arch Tierheilkd*. 1989;131:259–263.

45.	Coates JR, Kerl ME. Micturition disorders. In: Morgan RV, editor. *Handbook of Small Animal Practice*. St Louis: Saunders Elsevier; 2008:540–550.

46.	Gregory SP. Developments in the understanding of the pathophysiology of urethral sphincter mechanism incompetence in the bitch. *Br Vet J*. 1994;150:135–150.

47.	Beauvais W, Cardwell JM, Brodbelt DC. The effect of neutering on the risk of urinary incontinence in bitches – a systematic review. *J Small Anim Pract*. 2012;53:198–204.

48.	Stöcklin-Gautschi NM, Hässig M, Reichler IM, Hubler M, Arnold S. The relationship of urinary incontinence to early spaying in bitches. *J Reprod Fertil Suppl*. 2001;57:233–263.

49.	Spain VC, Scarlett JM, Houpt KA. Long-term risks and benefits of early-age gonadectomy in dogs. *J Am Vet Med Assoc*. 2004;224:380–387.

50.	Forsee KM, Davis GJ, Mouat EE, Salmeri KR, Bastian RP. Evaluation of the prevalence of urinary incontinence in spayed female dogs: 566 cases (2003–2008). *J Am Vet Med Assoc*. 2013;242:959–962.

51.	Vail DM, MacEwan EG. Spontaneously occurring tumors of companion animals as models for human cancer. *Cancer Invest*. 1985;18: 781–792.

52.	Teske E, van Heerde P, Rutteman GR, Kurzman ID, Moore PF, MacEwen EG. Prognostic factors for treatment of malignant lymphoma in dogs. *J Am Vet Med Assoc*. 1994;205:1722–1728.

53.	National Canine Cancer Foundation. Lymphoma. Available from: http://www.wearethecure.org/lymphoma. Accessed June 30, 2014.

54.	Villamil JA, Henry CJ, Hahn AW, Bryan JN, Tyler JW, Caldwell CW. Hormonal and sex impact on the epidemiology of canine lymphoma. *J Cancer Epidemiol*. 2009;2009:591753.

55.	Zink MC, Farhoody P, Elser SE, Ruffini LD, Gibbons TA, Rieger RH. Evaluation of the risk and age of onset of cancer and behavioral disorders in gonadectomized vizslas. *J Am Vet Med Assoc*. 2014;244:309319.

56.	Torres de la Riva G, Hart BL, Farver TB, et al. Neutering dogs: effects on joint disorders and cancers in golden retrievers. *PLoS One*.

57.	Hart BL, Hart LA, Thigpen AP, Willits NH. Long-term health effects of neutering dogs: comparison of Labrador retrievers with golden retrievers. *PLoS One*. 2014;9:1–10.

58.	Spangler WL, Kass PH. Pathologic factors affecting postsplenectomy survival in dogs. *J Vet Intern Med*. 1997;11:166–171.

59.	Wood CA, Moore AS, Gliatto JM, Ablin LA, Berg RJ, Rand WM. Prognosis for dogs with stage I or II splenic hemangiosarcoma treated by splenectomy alone: 32 cases (1991–1993). *J Am Anim Hosp Assoc*. 1998;34:417–421.

60.	Spangler WL. Disorders of the spleen. In: Morgan RV, editor. *Handbook of Small Animal Practice*. 5th ed. St Louis: Saunders Elsevier; 2008: 701–706.

61.	Clifford CA, de Lorimier LP. Canine hemangiosarcoma. In: Bonagura JD, Twedt DC, editors. *Current Veterinary Therapy*. 14th ed. St Louis: Saunders Elsevier; 2009:328–331.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

106

62. Prymak C, McKee LJ, Goldschmidt MH, Glickman LT. Epidemiologic, clinical, pathologic, and prognostic characteristics of splenic hemangiosarcoma and splenic hematoma in dogs: 217 cases (1985). *J Am Vet Med Assoc*. 1988;193:706–712.

63. Ru G, Terracini B, Glickman LT. Host risk factors for canine osteosarcoma. *Vet J*. 1998;156:31–39.

64. Cooley DM, Beranek BC, Schlittler DL, Glickman NW, Glickman LT, Waters DJ. Endogenous gonadal hormone exposure and bone sarcoma risk. *Cancer Epidemiol Biomark Prev*. 2002;11:1434–1440.

65. Ehrhart NP, Fan TM. Osteosarcoma. In: Bonagura JD, Twedt DC, editors. *Current Veterinary Therapy*. St Louis: Saunders Elsevier; 2009: 358–362.

66. Rostami M, Tateyama S, Uchida K, Naitou H, Yamaguchi R, Otsuka H. Tumors in domestic animals examined during a ten-year period (1980 to 1989) at Miyazaki University. *J Vet Med Sci*. 1994;56:403–405.

67. Mukaratirwa S, Chipunza J, Chitanga S, Chimonyo M, Bhebhe E. Canine cutaneous neoplasms: prevalence and influence of age, sex and site on the presence and potential malignancy of cutaneous neoplasms in dogs from Zimbabwe. *J S Afr Vet Assoc*. 2005;76:59–62.

68. Welle MM, Bley CR, Howard J, Rüfenacht S. Canine mast cell tumours: a review of the pathogenesis, clinical features, pathology and treatment. *Vet Dermatol*. 2008;19:321–339.

69. Tham DH, Vail DM. Mast cell tumors. In: Withrow SJ, Vail DM, editors. *Small Animal Clinical Oncology*. 4th ed. St Louis: Saunders; 2007:402.

70. Villamil JA, Henry CJ, Bryan JN, et al. Identification of the most common cutaneous neoplasms in dogs and evaluation of breed and age distributions for selected neoplasms. *J Am Vet Med Assoc*. 2011;239: 960–965.

71. Dobson JM, Samuel S, Milstein H, Rogers K, Wood JL. Canine neoplasia in the UK: estimates of risk rates from a population of insured dogs. *J Small Anim Pract*. 2002;43:240–246.

72. Kowaleski MP. Diseases of joints and ligaments. In: Morgan RV, editor. *Handbook of Small Animal Practice*. St Louis: Saunders Elsevier; 2008:767–769.

73. Smith GK, Biery DN, Gregor TP. New concepts of coxofemoral joint stability and development of a clinical stress radiographic method for quantitating hip joint laxity in the dog. *J Am Vet Med Assoc*. 1990;196: 59–70.

74. Todhunter RJ, Lust G. Hip dysplasia: pathogenesis. In: Slatter DH, editor. *Textbook of Small Animal Surgery*. 3rd ed. Philadelphia: WB Saunders; 2003:2009–2019.

75. Smith GK, Paster ER, Powers MY, et al. Lifelong diet restriction and radiographic evidence of osteoarthritis of the hip joint in dogs. *J Am Vet Med Assoc*. 2006;229:690–693.

76. Lust G. An overview of the pathogenesis of canine hip dysplasia. *J Am Vet Med Assoc*. 1997;210:1443–1445.

77. Smith GK, Mayhew PD, Kapatkin AS, McKelvie PJ, Shofer FS, Gregor TP. Evaluation of risk factors for degenerative joint disease associated with hip dysplasia in German shepherd dogs, golden retrievers, Labrador retrievers, and rottweilers. *J Am Vet Med Assoc*. 2001;219:

78. van Hagen MA1, Ducro BJ, van den Broek J, Knol BW. Risk, risk factors, and heritability estimates of hind limb lameness caused by hip dysplasia in a birth cohort of boxers. *Am J Vet Res*. 2005;66:307–312.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

107

79. Lefebvre SL, Yang M, Wang M, Elliott DA, Buff PR, Lund EM. Effect of age at gonadectomy on the probability of dogs becoming overweight. *J Am Vet Med Assoc*. 2013;243:236–243.

80. Whitehair JG, Vasseur PB, Willits NH. Epidemiology of cranial cruciate ligament rupture in dogs. *J Am Vet Med Assoc*. 1993;203:1016–1019.

81. Slauterbeck JR, Pankratz K, Xu KT, Bozeman SC, Hardy DM. Canine ovariohysterectomy and orchiectomy increases the prevalence of ACL injury. *Clin Orthop Relat Res*. 2004:301–305.

82. Stubbs WP, Bloomberg MS, Scruggs SL, Schille VM, Senior DF. Prepubertal gonadectomy in the domestic feline: effects on skeletal, physical, and behavioral development. *Vet Surg*. 1993;22:401.

83. Kustritz MV. Early spay-neuter in the dog and cat. *Vet Clin North Am Small Anim Pract*. 1999;29:935–943.

84. McNicholas WT, Wilkens BE, Blevins WE, et al. Spontaneous femoral capital physeal fractures in adult cats: 26 cases (1996–2001). *J Am Vet Med Assoc*. 2002;221:1731–1736.

85. Perry KL, Fordham A, Arthurs GI. Effect of neutering and breed on femoral and tibial physeal closure times in male and female domestic cats. *J Feline Med Surg*. 2014;16:149–156.

86. Hart BL, Eckstein RA. The role of gonadal hormones in the occurrence of objectionable behavior in dogs and cats. *Appl Anim Behav Sci*. 1997;52:331–344.

87. Hart BL. Problems with objectionable sociosexual behavior of dogs and cats: therapeutic use of castration and progestins. *Compend Contin*

88. Measuring behavior and temperament. Poster presented at: American Kennel Club Canine Health Foundation Biennial National Parent Club Canine Health Conference; October 21–23, 2005; St Louis, MO.

89. Roll A, Unshelm J. Aggressive conflicts among dogs and factors affecting them. Appl Anim Behav Sci. 1997;52:229–242.

90. Spain CV, Scarlett JM, Houpt KA. Long-term risks and benefits of early-age gonadectomy in cats. J Am Vet Med Assoc. 2004;224:372–379.

91. Porters N, de Rooster H, Verschueren K, Polis I, Moons CP. Development of behavior in adopted shelter kittens after gonadectomy performed at an early age or at a traditional age. J Vet Behav. 2014;9: 196–206.

92. Viña J, Sastre J, Pallardó FV, Gambini J, Borrás C. Role of mitochondrial oxidative stress to explain the different longevity between genders. Protective effect of estrogens. Free Radic Res. 2006;40:1359–1365.

93. Horstman AM, Dillon EL, Urban RJ, Sheffield-Moore M. The role of androgens and estrogens on healthy aging and longevity. J Gerontol A Biol Sci Med Sci. 2012;67:1140–1152.

94. Viña F, Borrás C, Gambini J, Sastre J, Pallardó FV. Why females live longer than males? Importance of the upregulation of longevity-associated genes by oestrogenic compounds. FEBS Lett. 2005;579:2541–2545.

95. Maggio M, Laurentani F, Ceda GP, et al. Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti area (InCHIANTI) study. Arch Intern Med. 2007;167: 2249–2254.

96. Hoffman JM, Creevy KE, Promislow DE. Reproductive capability is associated with lifespan and cause of death in companion dogs. PLoS One. 2013;8:e61082.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

108

97. Waters DJ, Kengeri SS, Clever B, et al. Exploring mechanism of sex differences in longevity: lifetime ovary exposure and exceptional longevity in dogs. Aging Cell. 2009;8:752–755.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Tipler, A – Desexing: Making sense of the literature and conversations with clients

109

Vets, pets and people are at the heart of Covetrus

Visit us at **stand 20-23** to find out why our goal is to become the go-to partner and advocate for veterinarians.

Self-compassion for veterinarians

Kat Williams BVSc (Hons), BPsySc
KW Veterinary Wellbeing
Brisbane, QLD

Self-criticism and perfectionism

As veterinarians and high achievers, we can often be our own worst critics. Most of us can probably relate to the experience of beating ourselves up over a clinical error such as a missed diagnosis. Anecdotally, many of us identify as perfectionists. Akin to wider populations, perfectionism in veterinarians has been associated with higher levels of stress, anxiety, and lower levels of resilience (Crane et al., 2015). Perfectionism was also found to increase the vulnerability of veterinarians to moral distress (Crane et al., 2015). If harsh self-judgment and being overly self-critical is not serving us well – could we benefit from being kind to ourselves?

Self-compassion: treating yourself as you would a close friend

Informally, self-compassion can be thought of as turning compassion inwards. When we are facing our own perceived inadequacy, failure, or other difficult life circumstances, self-compassion is treating ourselves with the same kindness, understanding and support that we would a close friend. Self-compassion researcher Dr. Kristin Neff (2003) defines self-compassion as composed of three distinct but interrelated elements: a) mindfulness b) common humanity, and c) self-kindness. Mindfulness refers being present with our suffering as it is. It involves turning towards our painful experience with non-reactive, non-judgemental awareness, neither overidentify with our pain (e.g., ruminating, catastrophising) or avoiding it. Common humanity refers to acknowledging that we all suffer. It's seeing our shortcomings and suffering as part of the shared human condition. It's recognising that our failures and pain are not reason to consider ourselves abnormal or alienated from others, but rather seeing our suffering as something that in fact connects us to the rest of humanity. Self-kindness is providing ourselves the same intuitive tenderness, warmth, and care that we would offer to someone else who was suffering. It involves asking oneself, "What do I need right now?" and making healthy efforts to take care of ourselves. Self-compassion is a personal resource we can draw on in the face of our failures but also in response to any difficult circumstance. In the Australian Veterinary Association Veterinary Wellness Strategy Report, five key stressors identified by veterinarians were difficult interactions with clients, interpersonal conflict with colleagues, working long hours, financial strain, and high workload and pressure (Superfriend, 2021). Being our own inner ally and supporting ourselves with self-kindness and self-advocacy can help bolster our resilience through these challenges.

The benefits of self-compassion

Being compassionate to ourselves has been repeatedly linked with several positive outcomes. A meta-analysis found self-compassion was positively correlated with wellbeing ($r = .47$, $k = 79$, $N = 16,416$) including psychological wellbeing ($r = .62$, $k = 12$, $n = 1586$), cognitive wellbeing ($r = .47$, $k = 48$, $n = 11,181$) and positive affect wellbeing ($r = .39$, $k = 32$, $n = 5779$) (Zessin et al., 2015). In veterinary students, mindfulness and self-compassion were positively correlated with resilience, suggesting their role as protective

resources and strategies (McArthur et al., 2017). In a small sample of medical trainees, self-compassion was positively associated with mental health, resilience, and confidence providing calm, compassionate care (Olson et al., 2014). In paediatric residents, self-compassion was positively associated with resilience and inversely associated with burnout (Olson et al., 2015). Self-compassion was also found to be negatively correlated with symptoms of depression, anxiety, and stress (r = -.54, k = 20, N = 4007) (MacBeth & Gumley, 2012), although the strength of these relationships may be overestimated (Muris & Petrocchi, 2017).   It has also been linked with higher levels of health-promoting behaviours (r = .25, k = 15, N = 3252) (Sirios et al., 2014), and greater self-improvement motivation (Brienes & Chen, 2012).

Cultivating self-compassion

Self-compassion is a learnable skill and mindset that we can develop through both formal (sitting meditation) and informal (during daily life) practices (Neff & Germer, 2013). Although the evidence base for compassion-based interventions relies mostly on small sample sizes, the results indicate that these interventions hold promise for cultivating self-compassion, reducing psychological distress, and increasing wellbeing (Kirby et al., 2017). Intervention studies, including randomised controlled trials, are being conducted to evidence the causal role of self-compassion in the associated positive psychological outcomes. A pilot study in nurses found preliminary evidence that Mindfulness Self-Compassion training reduced secondary trauma and burnout and increase resilience and compassion satisfaction in nurses (Delaney, 2018). An online compassion-focused imagery intervention tailored for veterinarians showed feasibility and preliminary efficacy in reducing perfectionism, self-criticism, and work-related rumination (Wakelin et al., 2022). Resources to increase self-compassion, including free worksheet exercises, guided audio practices are available at Dr. Kristin Neff's website (https://self-compassion.org/) and the Centre for Mindful Self-Compassion (https://centerformsc.org/).

References

1. Brienes, J. G., & Chen, S. (2012). Self-compassion increases self-improvement motivation. *Personality and Social Psychology Bulletin*, *39*(9), 1133-1143. https://doi.org/10.1177/0146167212445599
2. Crane, M. F., Phillips, J. K., & Karin, E. (2015). Trait perfectionism strengthens the negative effects of moral stressors occurring in veterinary practice. *Australian Veterinary Journal*, *93*(10), 354-360. https://doi.org/10.1111/avj.12366
3. Delaney, M.C. (2018). Caring for the caregivers: Evaluation of the effect of an eight-week pilot mindful self-compassion (MSC) training program on nurses' compassion fatigue and resilience. *PLoS One*, *13*(11), 1-20. https://doi.org/10.1371/journal.pone.0207261
4. Kirby, J.N., Tellegen, C.L., & Steindl, S.R. (2017). A meta-analysis of compassion-based interventions: Current state of knowledge and future directions. *Behaviour Therapy*, *48*, 778-792. https://doi.org/10.1016/j.beth.2017.06.003
5. MacBeth, A., & Gumley, A. (2012). Exploring compassion: A meta-analysis of the association between self-compassion and psychopathology. *Clinical Psychology Review*, *32*, 545-552. https://doi.org/10.1016/j.cpr.2012.06.003
6. McArthur, M., Mansfield, C., Matthew, S., Zaki, S., Brand, C., Andrews, J., & Hazel, S. (2017). Resilience in veterinary students and the predictive role of mindfulness and self-compassion. *Resilience, Mindfulness, and Mindset*, *44*(1), 106-115. https://doi.org/10.3138/jvme.0116-027R1

7. Muris, P., & Petrocchi, N. (2017). Protection or vulnerability? A meta-analysis of the relations between the positive and negative components of self-compassion and psychopathology. Clinical Psychology and Psychotherapy, 24, 373-383. https://doi.org/10.1002/cpp.2005

8. Neff, K. (2003). Self-compassion: An alternative conceptualisation of a healthy attitude toward oneself. *Self and Identity*, *2*(2), 85-101. https://doi.org/10.1080/15298860309032

9. Neff, K. D., & Germer, C. K. (2013). A pilot study and randomised controlled trial of the Mindful Self-Compassion Program. *Journal of Clinical Psychology*, *69*(1), 28-44. https://doi.org/10.1002/jclp.21923

10. Olson, K., & Kemper, K. J. (2014). Factors associated with well-being and confidence in providing compassionate care. *Journal of Evidence-Based Complementary & Alternative Medicine*, *19*(4), 292–296. https://doi.org/10.1177/2156587214539977

11. Olson, K., Kemper, K. J., & Mahan, J. D. (2015). What factors promote resilience and protect against burnout in first-year pediatric and medicine-pediatric residents? *Journal of Evidence-Based Complementary & Alternative Medicine*, *20*(3), 192–198. https://doi.org/10.1177/2156587214568894

12. Sirios, F. M, Kitner, R., & Hirsch, J. (2014). Self-compassion, affect, and health-promoting behaviors. *Health Psychology*, *34*(6), 661-669. https://doi.org/10.1037/hea0000158

13. SuperFriend. (2021). *Australian Veterinary Association Veterinary Wellness Strategy – Final Report*. https://www.ava.com.au/siteassets/resources/thrive/documents/ava-sf-veterinary-wellness-report-oct2021.pdf

14. Wakelin, K. E., Perman, G., & Simmonds, L. M. (2022). Feasibility and efficacy of an online compassion-focused imagery intervention for veterinarian self-reassurance, self-criticism and perfectionism. *VetRecord*, *192*(2), 1-17. https://doi.org/10.1002/vetr.2177

15. Zessin, U., Dickhauser, O., Garbade., S. (2015). The relationship between self-compassion and wellbeing: A meta-analysis. *Applied Psychology: Health and Well-being*, 7(3), 340-364. https://doi.org/10.1111/aphw.12051

Digestive diseases in Brachycephalics

Dr Clinton Yudelman
Insight Mobile Veterinary Diagnostics
Jan Juc, Victoria

Brachycephalic dog breeds are increasing in popularity and digestive diseases are very common amongst them. Typically, these breeds are renowned for their upper respiratory tract issues. However, digestive diseases are all too common as well, and it is important to be familiar with them. Their URT disease is also thought to potentiate their digestive disease. Investigation and treatment can be challenging, and often multiple concurrent abnormalities are present in the one patient, resulting in a clinical conundrum.

The most commonly encountered digestive disease in Brachycephalic dogs are related to the oesophagus and gastro-oesophageal sphincter (Hiatal hernia [HH], Gastro-Oesophageal Reflux Disease [GORD]), the stomach (Pyloric Stenosis), general GIT (Inflammatory Bowel Disease) and colon (Histiocytic Ulcerative Colitis [HUC]).

For diseases involving the oesophagus and gastro-oesophageal sphincter, regurgitation is the most common presenting complaint. Ptyalism, retching and prayer posture stance can also occur. There is a well-accepted theory that disease involving this region of the upper digestive tract is caused or exacerbated by Brachycephalic Obstructive Airway Syndrome (BOAS) and that the severity of BOAS is directly linked to severity of upper GI signs[1]. Increased negative intrathoracic pressure associated with BOAS during inspiration may promote HH and GORD. Also, aerophagia from URT disease can lead to increased intragastric pressure and increased risk of herniation.

As part of the investigation and treatment of regurgitation, examination for and correction of BOAS is recommended. This may resolve or reduce the severity of upper GI signs. Studies show that up to 77%[2] of dogs with BOAS have GIT signs and that GIT pathology may be present despite no report of clinical disease by the owner. As the disease may be intermittent, fluoroscopy and oesophagoscopy may both be required. If there is oesophagitis and/or GORD, treatment with omeprazole, sucralfate and cisapride should be trialled. If medical therapy fails to significantly improve or resolve clinical signs, then surgical correction may be required.

Recent studies have demonstrated that a true HH need not be present to cause clinical disease, but instead gastroesophageal incompetence is present. Pre-operative diagnostic investigation may not readily identify this. French Bulldogs are the most commonly affected Brachycephalic breed[3]. Subsequent surgical correction involving circumferential hiatal reconstruction and oesophagopexy has shown to resolve the issue completely in 84% of dogs with surgery alone, and dramatically improve clinical signs in the remaining 16% with the addition of medications.[4]

Muscular PS and Pyloric Mucosal Hypertrophy (PMH) can occur on their own, together, and in addition to oesophageal disease. In a study of 73 brachycephalic dogs, 30% were found to have PS[1]. It has been hypothesised that excessive autonomic nervous system activity

Proceedings of 48th ASAV Annual Conference together with Reproduction
Yudelman, C – Digestive diseases in Brachycephalics

114

from BOAS reduces gastric motility leading to a dilated antrum, causing increased gastrin production leading to PS/PMH. PS and PMH are best diagnosed through a combination of ultrasound and gastroscopy. Mild cases may be amenable to management with a liquid consistency food and small meal size along with prokientics. Failing response to this, or for more severe cases, surgical correction is necessary. Y-U pyloroplasty is preferred for mild to moderate cases and cases involving mucosal hypertrophy, as it permits removal of some hypertrophic tissue. It is associated with a lower complication rate compared to a gastro-duodenostomy (Billroth I) procedure, generally reserved for more severe cases or those isolated to the muscular component.

Another common disease of Brachycephalic dogs, and in particular, Boxers and French Bulldogs, is HUC. In Boxer dogs and French Bulldogs with GC, both breeds who share common ancestry, genetic susceptibility is linked to a region encoding the CD48/SLAM family of genes on chromosome 38, which has been associated with human inflammatory bowel disease[5]. Prior to 2004, HUC was thought to be an immune mediated disease despite poor response to immunosuppressive medication regimes. In 2004, a case series demonstrated clinical resolution in response to enrofloxacin[6]. In 2006, Adherent-Invasive strains of Escherichia Coli (AIEC) was confirmed via culture as the aetiological agent[7]. The diagnosis of HUC typically relies on characteristic histopathologic findings of PAS-positive macrophages in colonic biopsies, and FISH, to date, is considered the gold-standard method to demonstrate invasive *E. coli* within the mucosa. Whilst most cases will respond to enrofloxacin, not all do, and collecting samples for enrichment culture, MALDI-TOF and sensitivity patterns for refractory cases is recommended. Routine first-line treatment consists of 10mg/kg enrofloxacin once daily for 10 weeks.

References
1. Poncet CM, Dupre GP, Freiche VG, et al. Long-term results of upper respiratory syndrome surgery and gastrointestinal tract medical treatment in 51 brachycephalic dogs. J Small Anim Pract 2006;47:137–42
2. Poncet CM, Dupre GP, Freiche VG, et al. Prevalence of gastrointestinal tract lesions in 73 brachycephalic dogs with upper respiratory syndrome. J Small Anim Pract 2005;46:273–9
3. Reeve EJ, Sutton D, Friend EJ, et al. Documenting the prevalence of hiatal hernia and oesophageal abnormalities in brachycephalic dogs using fluoroscopy. J Small Anim Pract 2017;58:703–8
4. Hosgood G, Appelgrein C, Gelmi C. Circumferential esophageal hiatal rim reconstruction for treatment of persistent regurgitation in brachycephalic dogs: 29 cases (2016-2019). J Am Vet Med Assoc. 2021:15;258(10):1091-1097.
5. Hayward JJ, Castelhano MG, Oliveira KC, et al. Complex disease and phenotype mapping in the domestic dog. *Nat Commun*. 2016;7:10460.
6. Roger A. Hostutler, Brian J. Luria, Susan E. Johnson, Steven E. Weisbrode, Robert G. Sherding, Jordan Q. Jaeger, and W. Grant Guilford. Antibiotic-Responsive Histiocytic Ulcerative Colitis in 9 Dogs. J Vet Intern Med 2004;18:499–504
7. Simpson KW, et al. Adherent and invasive *Escherichia coli* is associated with granulomatous colitis in boxer dogs. Infect Immun 2006;74:4778–4792.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Yudelman, C – Digestive diseases in Brachycephalics

115

How to become a shit stirrer: Faecal Microbiota Transplants and their role in small animal gastroenterology

Dr Clinton Yudelman
Insight Mobile Veterinary Diagnostics
Jan Juc, Victoria

Faecal Microbiota Transplants (FMTs) are a relatively new mainstream treatment in veterinary gastroenterology despite being performed for centuries in humans, tracing back to the 1600s.

An estimated 100 trillion microbial cells are present within the intestine, up to 10 times the number of mammalian cells in the whole body. These are essential for GIT health, including providing substrates for the enterocytes, inhibiting diseases caused by opportunistic pathogens, the development of immunity, and the maintenance of the intact epithelial barrier.

The disruption of these functions can be linked to various medical conditions, not merely localised to the gut, but systemic conditions such as metabolic, autoimmune, allergic, neuropsychiatric disorders, and even some tumours. Specifically for small animal GIT disorders, FMTs are becoming increasingly popular and an effective treatment method for various common small animal diseases such as Parvovirus enteritis, AHDS/HGE and IBD.

FMTs may be administered orally in an enteric coated capsule, via nasogastric tube, gastroduodenoscopy, retention enema or colonoscopic administration. Enteric coating for gastric administration is necessary for survival of the microorganisms through the stomach.

Rectal administration may be indicated for severe cases and for cases with clinical signs of distal small intestinal or colonic involvement. Human studies comparing deposition location suggest colonic administration preferable over the upper GI route[1]. Deposition location will depend on the location of the patient's disease, the size of the patient, the equipment available etc.

There are commercially available freeze dried enteric coated FMT capsules for dogs and cats produced by AnimalBiome. Additionally, there are also commercially available faecal test kits which can be used in the FMT setting to analyse the donor faecal population and allow selection of optimal donors. Two companies producing these kits are AnimalBiome and RevelaBiome. This may eventually lead to the formation of a frozen stool bank, akin to how there is already a blood bank.

FMTs are also growing in popularity as a first line treatment for humans with Crohn's disease. Preliminary studies suggest that FMT may be an effective therapy in Crohn's disease; however, large, controlled trials are needed. No serious safety concerns have been identified[2]. Frozen FMT samples have been studied in humans and found to be equipotent to fresh FMT samples[3].

Proceedings of 48th ASAV Annual Conference together with Reproduction
Yudelman, C – How to become a shit stirrer: Faecal Microbiota Transplants and their role in small animal gastroenterology

116

There are only few published studies evaluating the benefits of FMTs in dogs and cats. The literature is scare in cats. In one case report, an FMT enema was successful in a 10-year-old cat with ulcerative colitis that had not responded to other therapies. Faecal consistency improved immediately. The cat's stools became normal after a second procedure and remained so for the 11 month follow up[4].

There are numerous reports of the success of FMTs in dogs. FMTs have been demonstrated to work very well for acute infectious enteropathies. Faster resolution of diarrhoea in puppies with canine parvovirus enteritis, compared with puppies that received only IV fluids and antimicrobials[5]. An additional study demonstrated clinical resolution in all cases of *Clostridium perfringens* diarrhoea that had failed to respond to antibiotics[6].

There is mixed evidence for the efficacy of FMTs in IBD. One study found no significant differences in Canine Chronic Enteropathy Clinical Activity Index (CCECAI)[7] when administered FMTs compared to those who weren't. In another controversial and possibly biased study produced by the company selling commercially available FMT capsules, 80 and 83% of dogs and cats respectively had improvements in clinical signs when given a 25 day course of capsules[8].

References

1. Furuya-Kanamori L, Doi SA, Paterson DL, et al. Upper versus lower gastrointestinal delivery for transplantation of fecal microbiota in recurrence or refractory Clostridium difficile infection: a collaborative analysis of individual patient data from 14 studies. J Clin Gastroenterol. 2017; 51(2):145-150.
2. Fehily SR, Basnayake C, Wright EK, Kamm MA. Fecal microbiota transplantation therapy in Crohn's disease: Systematic review. J Gastroenterol Hepatol. 2021 Oct;36(10):2672-2686.
3. Lee CH, Steiner T, Petrof EO. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection. A Randomized Clinical Trial. JAMA. 2016;315(2):142-149.
4. Furmanski S, Mor T. First case report of fecal microbiota transplantation in a cat in Israel. Israel Journal of Veterinary Medicine; 2017;72(3): 35-41.
5. Pereira GQ, Gomes LA, Santos IS, Alfieri AF, Weese JS and Costa MC. Fecal microbiota transplantation in puppies with canine parvovirus infection. Journal of Veterinary Internal Medicine; 32(2): 707-711.
6. Murphy, T, J. Chaitman, and E. Han. "Use of fecal transplant in eight dogs with refractory Clostridium perfringens-associated diarrhea." GI-31 Proceedings of 2014 ACVIM Forum Journal of Veterinary Internal Medicine 28.3 (2014):1047.
7. Collier AJ, Gomez DE, Montleigh G, Plattner BL, Verbrugghe A, et al. Investigation fecal microbial transplant as a novel therapy in dogs with IBD: A preliminary study. Plos One. 2022 Oct 18;17(10):e0276295.
8. AnimalBiome Pilot Study.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Yudelman, C – How to become a shit stirrer: Faecal Microbiota Transplants and their role in small animal gastroenterology

117

To scope or cut? Delving deep into which method is best to procure GI biopsies and when?

Dr. Clinton Yudelman
Insight Mobile Veterinary Diagnostics
Jan Juc, Victoria

A conundrum commonly encountered in small animal practice when performing a diagnostic evaluation of a dog or cat presenting with a Chronic Enteropathy (CE) is when to and what method is best to procure GI biopsies.

The healthier the patient (i.e. minimal weight loss, good body condition score, normal serum albumin concentration, no ultrasonographic evidence of infiltrative disease), the more consideration should be given to therapeutic dietary, antihelmintic and probiotic trials prior to collecting biopsies. Conversely, the more critically ill the patient (i.e. severe weight loss, poor body condition score, hypoalbuminemia, anorexia, ultrasonographic evidence of infiltrative disease), the more reasonable it is to perform biopsies before a therapeutic trial. Almost two thirds of dogs and cats with a CE will respond to a dietary trial and considered to have a food responsive enteropathy.

Prior to performing biopsies, a comprehensive minimum database is required including haematology, biochemistry, urinalysis, total T4 (cats) and FIV/FeLV (outdoor or multihousehold cats), UCCR or resting cortisol (dogs), PLI, TLI, Folate and B12. Measurement of albumin is necessary, as wound healing is impaired with hypoalbuminaemia and may limit the choice of which procurement method is selected. Studies have demonstrated an 8-fold increased risk of dehiscence when albumin is below 25g/L[1]. Furthermore, the lower the albumin, the greater the concern for neoplastic disease. In such cases, endoscopy is the only safe biopsy method.

Measurement of cobalamin and folate is important for a variety of reasons. It helps localise the disease to a particular segment of small intestine (i.e. low folate from duodenal disease and low cobalamin from ileal disease), provides a target for therapy and can correlate with severity, since more severe cases tend to have greater deficiencies.

Abdominal ultrasound plays a critical role in helping decide on which biopsy method is best. Abdominal ultrasound can localise disease to a particular segment and also to a particular section within that segment (i.e. the mucosal layer within the jejunum). If the segment is out of reach of the endoscope (such as the distal jejunum), a surgical approach is required. Abdominal ultrasonography also enables assessment of the remainder of the abdominal viscera and can be used to collect additional samples via aspiration. Importantly, 15% of cats with low grade intestinal T-cell lymphoma (LGITL), 54% of cats with inflammatory bowel disease (IBD)[2] and 63% of dogs[3] with IBD present with no sonographic abnormalities. The more pronounced the sonographic enlargement of the mesenteric lymph node or thickness of the jejunal mucosa, the more likely the cat will have LGITL[2].

The two options for biopsy procurement are surgical full thickness or endoscopic mucosal partial thickness. The decision on which method is best is an interplay of many factors

Proceedings of 48th ASAV Annual Conference together with Reproduction
Yudelman, C – To scope or cut? Delving deep into which method is best to procure GI biopsies and when?

118

including cost, disease localisation (which segment of the small intestinal tract), equipment availability, urgency in needing to start treatment etc. Knowing that the mucosa (and lamina propria within the mucosa) is the most critical section to sample and that the most common site of lymphoma involvement for cats is the jejunum and dogs is the duodenum, can also help decide on which method is preferred.

Gastroduodenoscopy and ileocolonoscopy present technical challenges and require an experienced endoscopist with the correct equipment. This combination has limited availability in small animal practice. Equipment selection is particularly important in smaller dogs and cats, where a small outer diameter is required to intubate through the pylorus or ileo-caecal valve without compromising on working length or working channel diameter. If the length is too short, access to the jejunum, the most common site of disease involvement in cats, will not be achievable. And if the working channel is small (i.e. 2mm vs 2.8mm), this results in smaller, shallower intestinal biopsies, resulting in sub-optimal tissue biopsies. Endoscopy is less invasive, less stressful, less expensive, less morbid, quicker, associated with fewer complications, allows excellent mucosal visualisation and targeted samples, collection of a greater number of samples and permits immediate treatment. Sampling depth is limited to mucosa and possibly some sub-mucosa.

On the other hand, a surgical approach, most often via laparotomy, enables full thickness biopsies and sampling of extra-intestinal sites (i.e. lymph nodes) but has other shortcomings. Laparotomy is generally considered more expensive and takes longer than endoscopy. There is both the abdominal wound and intestinal wound that can breakdown. The risk of complications is higher. For example, the risk of dehiscence of the intestinal wound alone is 3%[4] compared to the risk of perforation with endoscopy is 0.1% in cats and 1.6% in dogs[5]. Patient stress and morbidity is higher with surgery. Whilst surgery permits a full thickness biopsy, the disease focus for a CE lies in the mucosa. Endoscopy yields a greater amount of mucosa compared to surgery. Targeted sampling may be more challenging with a surgical approach as mucosa is not visualised and reliance of palpation and serosal appearance is required. A surgical approach often necessitates a delay in starting treatment until wound healing is complete. Sufficient mucosal retrieval is necessary and a wedge-shaped incision with a larger serosal and smaller mucosal size is discouraged. A round punch biopsy method is preferred.

Even once diagnostic quality biopsies are procured, delicate sample handling and manipulation is required. Placement of samples on a foam cassette is recommended, as, if they are placed directly into formalin, curling and retraction can distort architecture. Endoscopic samples should be gently extracted using a 25g hypodermic needle and placed on a cassette with the villi up. Avoiding desiccation is necessary.

Pathologic interpretation can be challenging due to a variety of reasons. Lymphoplasmacytic Enteritis (LPE) and LGITL are thought to lie on a spectrum with disease overlap and often with both occurring adjacent to each other. Interobserver variability can also affect interpretation, despite WSAVA guidelines to minimise this[5]. Additional testing using immunohistochemistry (IHC) and PCR for Antigen Receptor Rearrangement (PARR) can be added to aid in differentiation of LPE and LGITL. All routine histopathological assessment indicative of LGITL should have IHC added as a minimum.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Yudelman, C – To scope or cut? Delving deep into which method is best to procure GI biopsies and when?

119

PARR assesses clonality, but it is important to note that clonality does not equate to neoplasia. All neoplastic lesions are clonal but not all clonal lesions are neoplastic. Furthermore, PARR can sometimes be misleading, as demonstrated in 9% of cases where cross-lineage rearrangement can misdiagnose a LGITL as a B-cell lymphoma due to cross lineage rearrangement[8]. Furthermore, studies in cats have shown specificity of 33% when comparing PARR to aid in differentiation of LGITL from LPE[9]. PARR should always complement but not replace IHC. Despite every best effort and test performed, some ambiguous cases will remain.

In the past, some have argued that a comprehensive diagnostic evaluation of cats with CE to differentiate LPE from LGITL may be unnecessary because it does not appear to change prognosis or treatment. However, recent studies indicate that prognosis and treatment strategies do differ substantially between the two entities[8]. An evaluation including intestinal biopsies does not only exclude other differential diagnoses including large cell lymphomas, infectious, eosinophilic, or mast cell disease but also could allow for a more accurate prognosis and treatment plan in the future.

References
1. Ralphs SC. Risk factors for leakage following intestinal anastomosis in dogs and cats: 115 cases (1991–2000). JAVMA. 2003; 223 (1): 73-77
2. Jugan MC, August JR. Serum cobalamin concentrations and small intestinal ultrasound changes in 75 cats with clinical signs of gastro- intestinal disease: a retrospective study. J Feline Med Surg. 2017;19:48-56
3. Ivasovic F. Prevalence of inflammatory versus neoplastic lesions in dogs with chronic gastrointestinal signs undergoing gastroduodenoscopy: 195
cases (2007–2015). Res Vet Sci 2022;146:28-33
4. Irom S, Sherding R. Gastrointestinal Perforation Associated with Endoscopy in Cats and Dogs. J Am Anim Hosp Assoc. 2014;50(5):322-9
5. Day M, Bilzer T, Mansell J, et al. Histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat: a report from the World Small Animal Veterinary Association Gastrointestinal Standardization Group. J Comp Pathol. 2008;138(suppl 1): S1–S43.
6. Swinbourne F, Jeffery N. The incidence of surgical site dehiscence following full-thickness gastrointestinal biopsy in dogs and cats and associated risk factors. J Small Anim Pract 2017;58(9):495-503
7. Andrews C, Operacz M, Maes R, Kiupel M. Cross lineage rearrangement in feline enteropathy-associated T-cell lymphoma. Vet Pathol. 2016;53:559-562.
8. Freiche V, Paulin MV, Cordonnier N, et al. Histopathologic, phenotypic, and molecular criteria to discriminate low-grade intestinal T- cell lymphoma in cats from lymphoplasmacytic enteritis. J Vet Intern Med. 2021;35(6):2673-2684.
9. Freiche V, Paulin MV, Cordonnier N, et al. Histopathologic, phenotypic, and molecular criteria to discriminate low-grade intestinal T- cell lymphoma in cats from lymphoplasmacytic enteritis. J Vet Intern Med. 2021;35(6):2673-2684.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Yudelman, C – To scope or cut? Delving deep into which method is best to procure GI biopsies and when?

120

Triaditis: Truth and treatment

Dr. Clinton Yudelman
Insight Mobile Veterinary Diagnostics
Jan Juc, Victoria

Triaditis is an inflammatory condition used to describe concurrent inflammation in the bile ducts and or liver, pancreas, and small intestine. The condition was first recognised and described in 1975 in a jaundiced cat with pancreatitis[1]. The term differs from the human version triaditis, which refers to inflammation of the portal triads. The feline condition gained traction as an emerging condition in the 1990s with numerous case reports being published and since then has become universally recognised. The incidence of true feline triaditis remains unclear due to difficulties in confirming diagnosis in all three organs (see below) but one paper reported it to be as high as 39% of sick cats in a referral population[2].

Although only 39% of cats investigated demonstrated triaditis, studies also show that cats are often affected by two of the three diseases concurrently, with 50%-60% of cases having cholangitis and pancreatitis, 30%-83% cholangitis and IBD, and 12% having pancreatitis and IBD[3]. These studies therefore suggest that the presence of two concurrent conditions is actually more common than triaditis.

Aetiology

There is no clear consensus that is widely accepted amongst internists as to the underlying pathophysiological cause for triaditis. Numerous postulated causes have been proposed.

The unique feline anatomy involving the merging of the common bile duct and pancreatic duct before emptying into the duodenum at the major duodenal papilla, plus the relatively high duodenal bacterial load are believed to predispose cats to triaditis[4].

There are two commonly proposed mechanisms for how triaditis develops. The first hypothesis suggests that the act of vomiting (i.e from enteritis) causes an increase in proximal duodenal pressure resulting in reflux of duodenal contents up into the major duodenal papilla, bile and pancreatic ducts, triggering inflammation and/or infection. The other more widely accepted hypothesis centres around intestinal inflammation as a trigger, and due to enteritis and compromised intestinal health, bacterial translocation occurs whereby it gains access to the portal vasculature and haematogenous spread into the liver. Evidence to support this arises from a study which identified bacteria associated with the portal vessels, venous sinusoids and parenchyma more so than in the bile ducts[5]. This inflammatory/infectious disease of the bile ducts can cause secondary functional obstruction of the pancreatic duct, triggering pancreatic inflammation.

Diagnosis

The gold standard diagnostic testing required for confirmation of triaditis requires tissue biopsies from the liver, pancreas and small intestinal tract with histopathological inflammation being demonstrated across all 3 organs. Whilst in theory this is fine, in practice, it is rarely performed for various reasons including expense, invasiveness and lack of suitability for acutely unwell cats presenting with possible triaditis.

A minimum data base including haematology and biochemistry is necessary, which often demonstrates evidence of liver damage and cholestasis. Liver function testing through bile acid tolerance testing or ammonia analysis can be performed. Quantitative feline specific pancreatic lipase immunoreactivity is also encouraged, although it can lead to false negatives if pancreatitis is mild or false positives when adjacent organs are involved. TLI testing, along with cobalamin and folate assays are also encouraged to look for evidence of exocrine pancreatic insufficiency and further localise small intestinal disease.

Abdominal ultrasound imaging is recommended to further visualise the three organs affected by triaditis. It is important to consider that a normal sonographic appearance to any or all three organs fails to exclude disease but can be used to assess for changes in these organs, guide sampling, assess lymph nodes and presence of free abdominal fluid etc.

Middle ground options for less invasive ways to confirm triaditis could involve fine needle aspirates of the liver including for culture (and bile for culture), quantitative fPLI and gastroduodenoscopy with biopsies. Exclusion of bacterial involvement is recommended prior to commencing corticosteroid therapy, often necessary in the treatment of triaditis (see below).

Treatment

There is no specific treatment for the condition on a whole, but rather, treatment is directed towards each entity. If acutely unwell, intensive supportive care such intravenous fluid therapy is often necessary. If cholestasis is present, vitamin K_1 parenteral treatment is necessary as coagulopathies are common with severe liver disease from reduced clotting factor production and or from EHBDO impairing intestinal absorption of the fat soluble Vitamin K_1. Pre-treatment with Vitamin K_1 is imperative before performing needle aspirates, oesophageal feeding tube placement or laparotomy/laparoscopy.

Commencing early enteral nutrition is important to prevent hepatic lipidosis and to promote restoration of gastrointestinal health. If liver failure is demonstrated or suspected, an appropriate hepatic diet is recommended. Otherwise, a diet compatible for all 3 conditions would be a hydrolysed or novel highly digestible protein and moderate fat level.

Outpatient treatment for the cholangitis/cholangiohepatitis component requires SAMe and possibly ursodeoxycholic acid (if no EHBDO) supplementation. For acute cholangitis, where a bacterial aetiology is common, fluoroquinolone or potentiated penicillin antibiotics are often necessary with E. Coli, Enterococcus and Clostridium commonly isolated. For chronic disease, corticosteroids and possible further chlorambucil therapy is necessary. Corticosteroids are often beneficial for the pancreatitis and enteritis components as well. For the pancreatitis component, analgesia and antiemetics are often required. For the enteritis component, a novel or hydrolysed protein diet, cobalamin and folate supplementation and synbiotics are required.

Prognosis

This depends on the extent of disease involving each of the three affected organs. Negative prognostic indicators include hypoalbuminaemia, hypoglycaemia leukopaenia and hypotension[6].

References

1. Kelly DF, Baggott DG, Gaskell CJ. Jaundice in the cat associated with inflammation of the biliary tract and pancreas. J Small Anim Pract 1975;16:163–72.

2. Fragkou FC, Adamama-Moraitou KK, Poutahidis T, et al. Prevalence and clinicopathological features of triaditis in a prospective case series of symptomatic and asymptomatic cats. *J Vet Intern Med* 2016; 30: 1031–1045.

3. Simpson, K. E. (2016). Feline triaditis: Does it exist and what are the implications in a cat diagnosed with triaditis? Proceedings of the European Veterinary Conference Voorjaarsdagen, The Hague, The Netherlands.

4. Johnston KL, Swift NC, Forster-van Hijfte M, et al. Comparison of the bacterial flora of the duodenum in healthy cats and cats with signs of gastrointestinal tract disease. *J Am Vet Med Assoc* 2001; 218: 48–51

5. Twedt DC, Cullen J, McCord K, et al. Evaluation of fluorescence in situ hybridization for the detection of bacteria in feline inflammatory liver disease. J Feline Med Surg 2014;16:109–17

6. Cerna P, Kilpatrick S, Gun-Moore Danielle. Feline comorbidities. What do we really know about feline triaditis. J Feline Med Surg 2020;22:1047-1067

Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

Karen Copley RNC BSN
Veterinary Perinatal Specialties
9111 w 38th Ave Wheat Ridge, CO 80033

Parturition management has been the gold standard for achieving optimal maternal and foetal outcomes in the human world for over 100 years. Technology to support management of canine and feline patients was first introduced in the mid 1990's by Karen Copley RNC BSN, whose monitoring service "WhelpWise" demonstrated significantly better outcomes for canine and feline patients by placing a tocodynamometer and hand-held ultrasound doppler in breeders' homes. This equipment is capable of transferring data through a WiFi connection to a 24 hour staffed monitoring centre. This ability for remote parturition management allows expert veterinary guidance while facilitating a comfortable whelping experience for the bitch and her care-giver, allowing them to whelp in a familiar location and only sending animals in for a veterinary evaluation that have demonstrated abnormalities in the veterinarians prescribed plan of care.

WhelpWise is only offered in conjunction with the clients' veterinarian. How we approach care of the animal on service is guided by specific veterinary orders provided to us by the veterinarian [1]. The WhelpWise service monitors both uterine contractions, and foetal heart rates using obstetrical equipment specifically designed for remote data collection. This data is transferred to the monitoring centre for evaluation and discussion with the client or veterinarian about what the current data shows and what the next step in whelping management should be. Prior to having the ability to objectively monitor uterine contractions and foetal heart rates parturition management was based on a "best guess" plan of care; using interventions from subjective symptoms or unreliable parameters such as temperature change. By using objective data as the base for interventions, assessments and interventions can now be made with a higher degree of safety and reliability for both the dam and foetuses. Clients that have utilized our services are interested in improving maternal and foetal outcomes by being proactive in the detection and management of whelping issues. A significant benefit offered by the service is to be able to safely manage inertia through labour augmentation protocols developed specifically for canines, and designed for safe use in the home setting.

Currently we have monitored over 45,000 whelpings; maintaining a data base that has included parity, prior dystocias, diet history, progesterone/LH timing for breeding, X-ray counts, and specific parturition events. The most scrutinized part of our data analysis is maternal/foetal outcomes (live vs. deceased births) and parturition management; evaluating medication doses and their tocometric response.

What have we learned in our 45,000 litters?
The balance of my paper will explain what we see with our uterine monitoring and foetal doppler equipment and how we use this information to manage whelpings through our monitoring service. I also will address some of the more common perceptions of how the

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in
home-based obstetrical management

125

whelping process takes place by using what we see with our monitoring equipment both to educate but also to dispel many common myths about canine parturition.
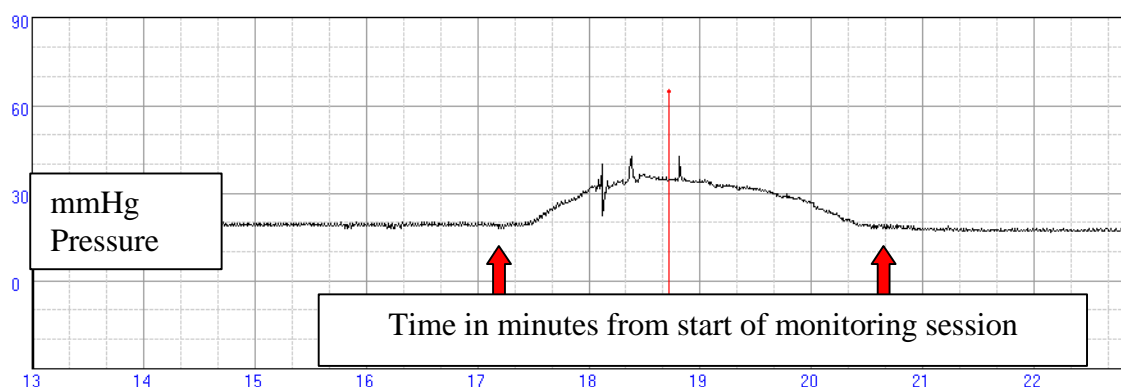
Temperature drop prior to parturition

As described in a prior WhelpWise study, maternal core temperature change occurs in only 33% of bitches in a predictable manner, contrary to what is described in a multitude of veterinary resources [2,3]. These time-honoured veterinary studies, conducted in a controlled kennel situation, describe a change in basilar temperature, with parturition occurring 8 hours after the nadir of the decline. A more recent study of one hundred multiple breed bitches on the WhelpWise service, utilised data that was collected in the home setting. This data was compared to data from the uterine monitor, documenting the onset of labour. When comparing temperature changes to uterine activity it showed that 35% of the time there was no temperature change of more than 1 degree Fahrenheit. If a detectable temperature change of more than one degree was noted, delivery of the foetuses averaged 37-48 hours after the change rather than 12-24 hours as veterinary resources describe. [4] Additionally, multiple fluctuations in temperature were common and overall temperature changes had no impact on maternal/foetal outcomes.

Length of labour

Labour, as defined for this document, is the presence of an organised pattern of uterine contractions that is detected by our external monitoring equipment. Our definition of labour is not related to behavioural symptoms of parturition, temperature changes or the presence of vaginal discharge. A detectable uterine contraction pattern, i.e. "labour" is sustained until the completed delivery of the foetuses, and throughout early uterine involution. We have found that labour patterns will vary with breed, litter size, and abdominal mass of the bitch, and that every bitch tends to have her own variety of a labour pattern.

Uterine contractions are detected by applying an external uterine pressure sensor. This sensor detects changes in intrauterine pressure using a tocodynamometer specifically designed for use in animals. "Contractions" are traced on a linear axis, graphing changes in intrauterine pressure. As the myometrium contracts, the pressure inside the uterus will increase, as the contraction relaxes, the pressure decreases. Uterine activity graphs are documented as time in minutes on the X-axis, and strength of the contraction shown as an increase in pressure in millimetres of mercury on the Y-axis (figure 1). To obtain optimal data it is important that the bitches are monitored in a lateral recumbent position. This position will eliminate uterine contractions caused by physical activity.

Uterine contraction (figure 1)

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

During normal gestation it is expected that uterine contractions are present in a frequency of 1-3 per hour beginning about 56 days post LH surge.

Labour (figure 2)
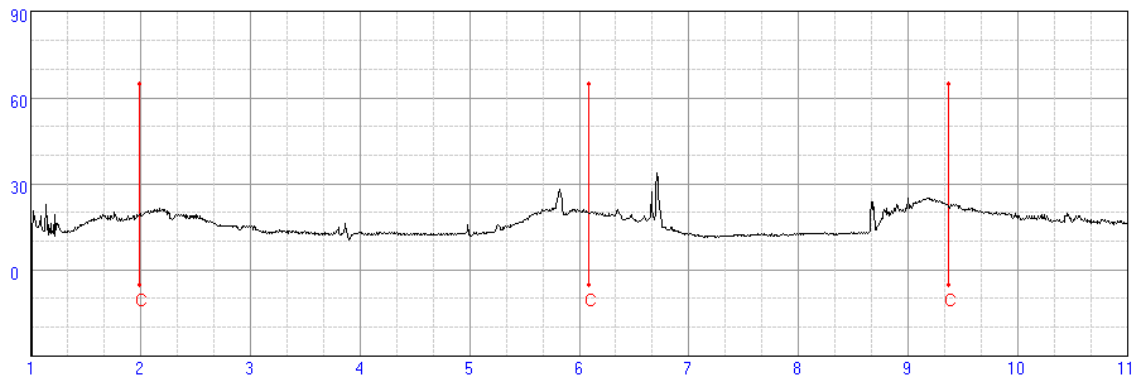
Presence of an organised pattern of uterine contractions. (figure 2)
Contractions are marked with a "C" and red line.
Note the consistency in spacing and strength.

Once first stage labour is established, our data strongly supports that deliveries will begin on an average of 9 hours from the presence of an organised pattern of labour. The range for delivery times averaged 9 to 14 hours, with a significant increase in foetal mortality and cesarean section rates when labour is extended beyond 14-16 hours of an organised labour pattern. During our early research the difference in foetal outcomes related to prolonged labour were so clear that labour augmentation protocols were established early in the development of the service. These protocols were based on the human model of parturition management. (5) Human labour management strongly documents that parturition should follow a specific progression once active labour has been established. [6, 7]. This predictable passing through parturition in human medicine has been called "Friedman's curve" after the physician who documented that poor foetal outcomes were the result of an ineffective labour; pioneering the concept of human labour management to improve foetal outcomes (8)
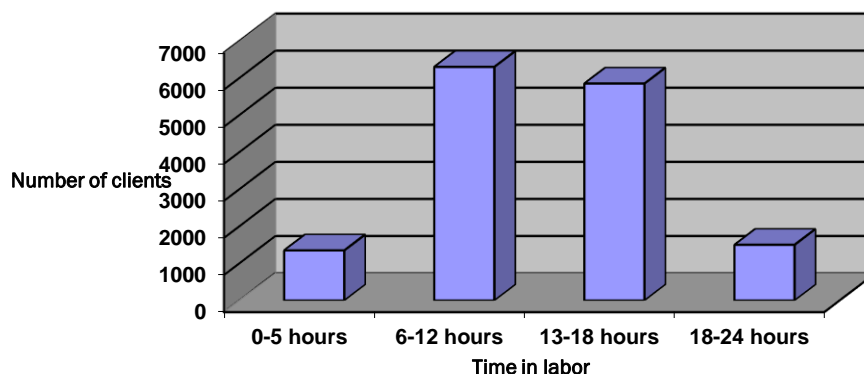
Inertia

Inertia describes the failure to maintain an adequate contraction pattern during active labour. Inertia may be the inability to move from first to second stage labour, or once second stage has occurred, the lack of contractility to continue to deliver pups.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

127

The incidence of primary uterine inertia has been an extremely rare occurrence (less than .1%). In almost every client with acceptable timing, we have noted an attempt by the bitch to establish first stage labour. This attempt is frequently asymptomatic and will not be associated with a change in temperature change. It is not uncommon for maiden bitches to establish a short episode (3-5 hours) of mild contractions that are in a disorganised pattern that will subside and return within 12-24 hours; moving into an organised active labour pattern. If this attempt to establish labour re-occurs more than twice without progression to active labour, we have found that there is a strong correlation with dystocias. These dystocias are frequently from an over distended uterus from polyhydramnios, foetal malposition, or exceptionally large pups.

Medical management of labour

Using the human model for medical management of labour, foetal outcome data consistently shows that lack of progression of labour per Friedmans Curve with an active labour pattern requires medical intervention, as low Apgar scores are strongly associated with prolonged labour. (6,7,8)

Early studies for our service evaluated whelping outcomes associated with prolonged labour. These studies also documented a strong increase in foetal loss correlating with lengthy labour, and early intervention with medical management when inertia is identified drastically reduced foetal demises from 33% to around 6%. In the whelping study a prolonged first stage also was associated with increased foetal deaths. Also noted was an increased incidence of fading puppy syndrome; 19% compared to the labour managed group 1%. (5)

Secondary inertia, or the inability to progress from either stage one labour to stage two, or stage two to stage three appears to be the primary cause for foetal mortality and morbidity in our client population. Early detection and proactive medical management of inertia is a priority for our clients. Whelping management protocols have been modified over the last 26 years of data collection, fine-tuning the "art" of whelping management. This fine-tuning has further decreased our foetal mortality rate to around 4% for home breeder management, and less than 1.5% for educated whelping kennels such as the service dog organisations. Our average C-section rate is 16%, broken down; 6% for abnormal uterine contraction patterns, 10% for foetal distress. When inertia is detected early we expect that 80% of our clients will respond favourably to medical management protocols, titrating small doses of either oxytocin, injectable calcium, or both, with our only goal being to return the bitch to her "normal" labour pattern without causing uterine hyper-stimulation, uterine tetany or foetal distress.

Evaluating a bitch to determine if she has inertia (subjectively) is very difficult. As demonstrated with the uterine monitor session below, there is no inherent contraction strength in the labour pattern, but the veterinarian evaluating the case felt that the "observed contractions were strong". What the veterinarian was evaluating was the abdominal expulsive efforts of the bitch, as she was indeed pushing very hard. However, if the contraction strength was improved by labour augmentation the bitch would require less physical effort to deliver the pups.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

128

Pushing with severe inertia (figure 3). Spikes are caused by increased abdominal pressure as bitch bears down.
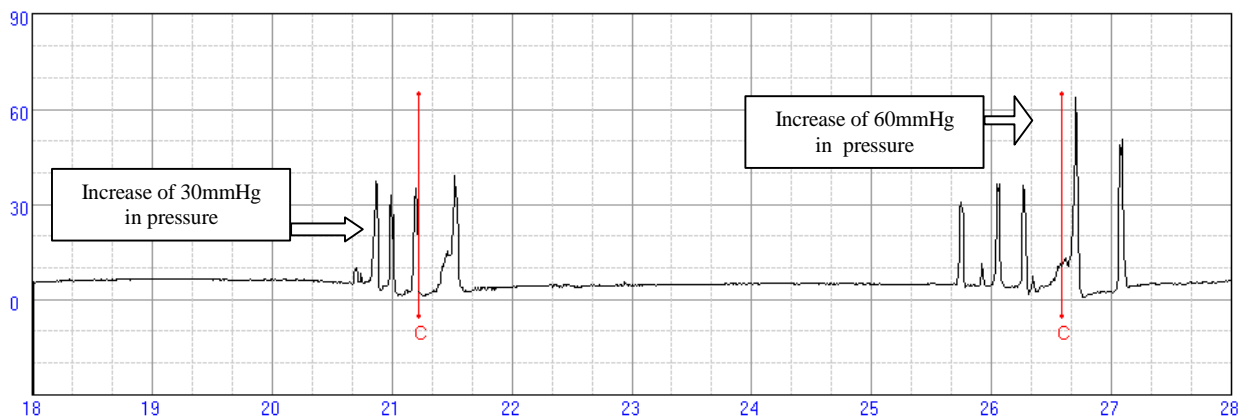
(Figure 3)

Injectable calcium

The use of injectable calcium to assist parturition has been documented as an uterotonic since 1947 (9) Uterine myometrium is dependent on adequate calcium levels to contract effectively and creates its own calcium consumptive state. (3,10) It is this author's opinion that frequently calcium levels can be within an acceptable range based on traditional laboratory values, but the bitch may be experiencing a calcium-based inertia, as her calcium levels may have decreased but are still within a normal range. This decrease has impacted the contractility of the uterus. We believe this to be the case, as we have administered injectable calcium (sub-cutaneous) and seen a marked improvement in the contraction pattern even though calcium levels were "normal". Inadequate calcium levels are also suspect in bitches that will establish a pattern of labour and then stop contracting. I question the ability of the parathyroid gland to rapidly respond to a declining calcium level because of foetal consumption or active labour. We have seen that calcium supplementation both oral and injectable have frequently supplied the needed base for an effective contraction pattern. We have objectively noted that administration of calcium will increase the strength of the contraction rather than the frequency of the contractions. A study of serum calcium levels conducted at the Guiding Eyes, also has documented that low ionized calcium had direct impact on stillbirths. (11)

Miniature Schnauzer, labour pattern X 10 hours, beginning of inertia (figure 4)
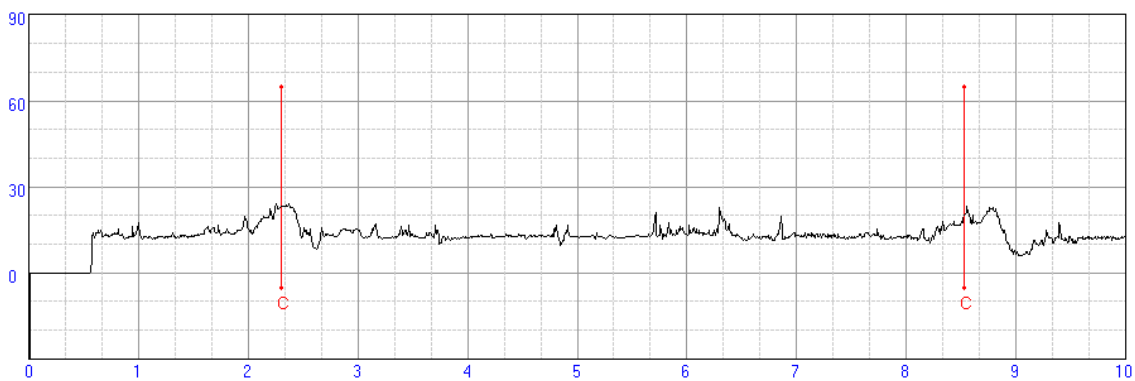

Figure 4

Session beginning 20 minutes after administration of Calcium Gluconate 10% SQ (figure 5)
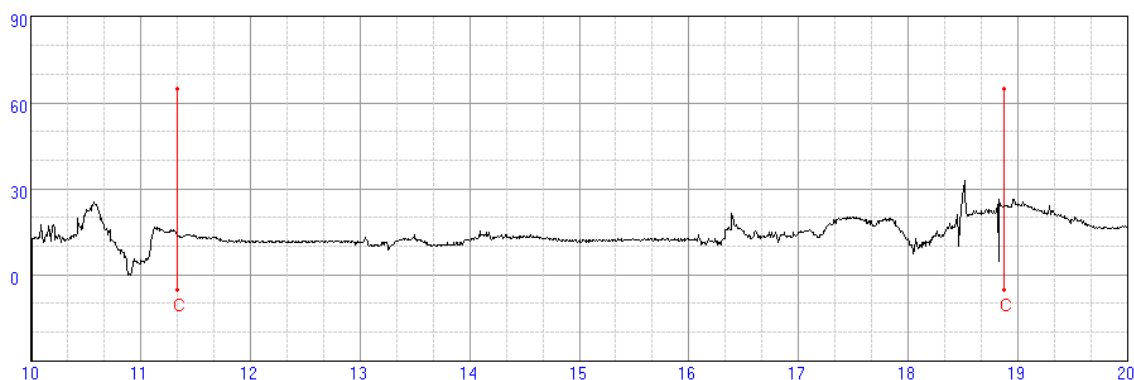

Figure 5
Note not only the increase in strength, but also the improvement of overall shape and duration of the contraction.

Dosage range for injectable calcium has been successful at ½ to 1 ml of 10% calcium gluconate, per 4.5kg current gravid maternal body weight, administered subcutaneously. Adverse effects have not been noted unless a stronger concentration of calcium has been used (23%). Injection sites using 23% calcium have been very painful for the animal and a corresponding tissue slough have been reported, but rarely. No cardiac problems have been experienced with the subcutaneous administration of the 10% solution because of the gradual absorption of the medication. We have had no reported incidence of accidental IV infusion when administering the medication subcutaneously.

In our client population, oral calcium supplements have been successful for proactive prevention of calcium-based inertias especially for bitches that are inappetent or for exceptionally large litters, which appear to be somewhat predisposed to calcium imbalances. Beginning oral supplementation based on meeting minimal dietary needs 2-3 days prior to parturition or as early first stage labour is established does seem to be beneficial, without noted complications of antepartum eclampsia.   The presence of adequate Vitamin D levels in the diet has also been significant to the prevention of calcium-based inertia. Vitamin D is frequently markedly decreased to completely absent for owners feeding the raw diet, and whelping complications related to this imbalance are frequently not medically manageable, and surgical intervention is required for deliveries. We have not seen a corresponding improvement in contraction patterns from the oral calcium gel products and have had several dogs using these products experience G.I. bleeding after their use.

Oxytocin

Oxytocin historically has been the most frequently used drug for labour augmentation. Dosing prior to the use of the uterine monitor was arbitrary, usually based on animal weight, not uterine contraction patterns. (13) Administering oxytocin in excessive amounts can be a detriment to both labour progression and foetal well-being, as a hyper stimulated uterus does not contract effectively, and the constriction of the myometrium will impede blood flow to the foetus. The relaxation phase between each contraction is important to allow blood to circulate to the foetus. Excessive doses of oxytocin can cause uterine rupture. According to our database, effectiveness of oxytocin is related to length of labour,

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in
home-based obstetrical management

130

with best response noted after first stage labour has been present for at least 8 hours, but not over 16 hours. Administering oxytocin before 8 hours of active labour or after 16 hours of labour frequently has minimal effect on the contraction pattern.

From our perspective oxytocin dosing should always be titrated to the existing uterine contraction pattern, without regard for body weight of the bitch. Our general protocol begins with ½ unit of oxytocin; administered either subcutaneous or intramuscular, depending on the desired rate of response and duration of action. Our protocol describes that Oxytocin is only administered after 8 hours of first stage labour and documented inertia. Expected results with oxytocin would be an increased frequency of the uterine contractions. Because of the short half-life of oxytocin, dosing is usually every 45-60 minutes. If the desired response of increased uterine contractility is not achieved with the first dose, doses are increased in ½ to 1 unit increments until an adequate pattern of contractions is achieved. After administering 3 subsequent doses of oxytocin, incrementally increasing each dose, critical evaluation is made of the success of the augmentation. Failure to improve the inertia after 3 doses of oxytocin and one dose of calcium generally shows that medical management of the dystocia will not be successful and surgical intervention is a frequent necessity.

When medical management is contraindicated

A marked change in the contraction pattern is usually noted as the foetus enters the uterine body that presents on our monitoring sessions as fairly strong, close coupled contractions. With the presence of close-coupled contractions a delivery should occur within 1 hour. Frequently when this type of contraction pattern is noted the presenting foetal part may be palpated on vaginal exam. *Note of interest,* the bitch was sleeping during this session, showing once again that subjective symptoms are not adequate markers of labour progression. Medication would be contraindicated with this uterine contraction pattern, as there is no inertia. The first pup was delivered 15 minutes after the end of the session.
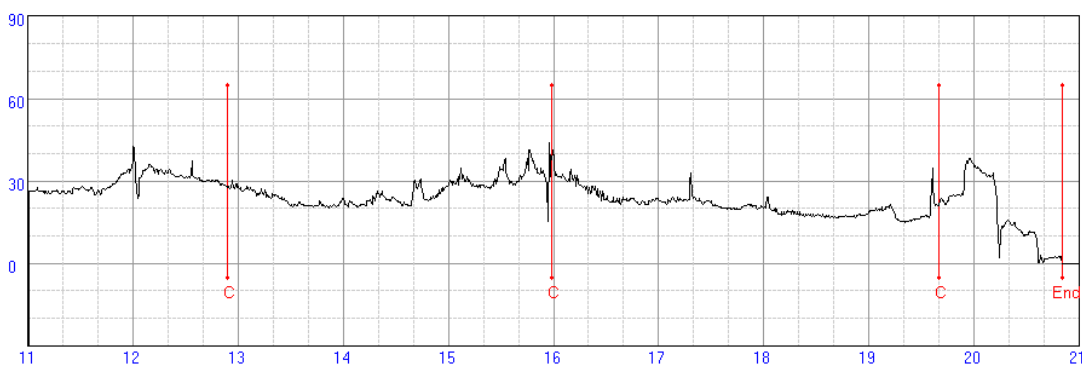
Contraction pattern with foetal/pelvic engagement (figure 6)

High risk pregnancy management

Premature labour

The presence of uterine contractions in an organised fashion in the canine was first documented in 1989 by G.C van der Weyden et al, by surgically implanting electrodes in the canine myometrium. (9) van der Weyden's observation of the presence of 1-3 contractions an hour 7 days before the onset of an active labour pattern has been strongly duplicated in

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

131

our client population. We consider the occurrence of 1-3 contractions an hour a <u>normal</u> "baseline" uterine contraction pattern <u>after</u> 53 days post LH surge. Uterine contractions occurring <u>BEFORE</u> day 53, especially with the presence of irritability (contractions that are less than a minute in length) have a high incidence of premature delivery and/or premature placental separation.

Our overall client base consists of about 15% "high-risk" premature labour clients, either being monitored because of a problematic history or acute premature labour. Documented conditions associated with the increased premature contractions from our client population have included uterine infections; both acute pyometra and low-grade metritis, hypolutealism, and uterine contractions associated with no known cause. Regardless of the cause, premature labour has been controllable in 99% of our clients. Keys to successful management have been the early documentation of uterine contraction patterns, early intervention, and medication titration to maintain uterine quiescence.
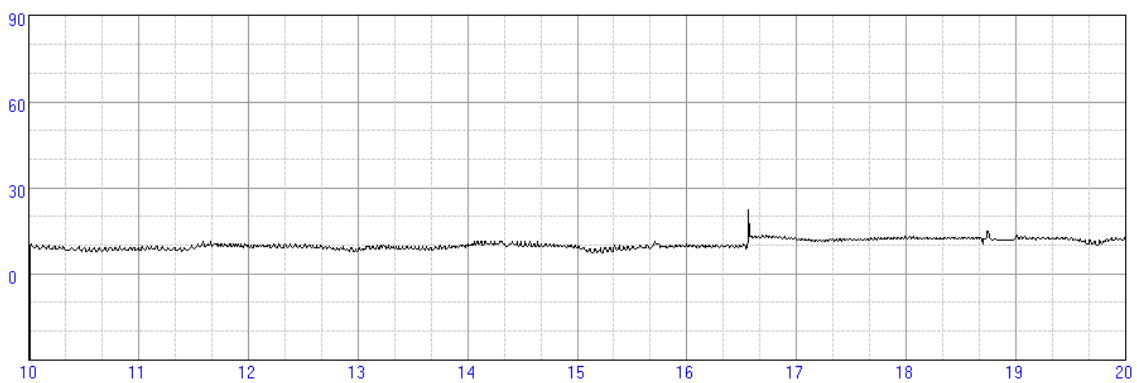
Uterine irritability at **27 days** post LH surge, prior history of losing litter around 40-45 days of gestation. Irritability is defined as uterine contractions that are less than 1 minute in duration.
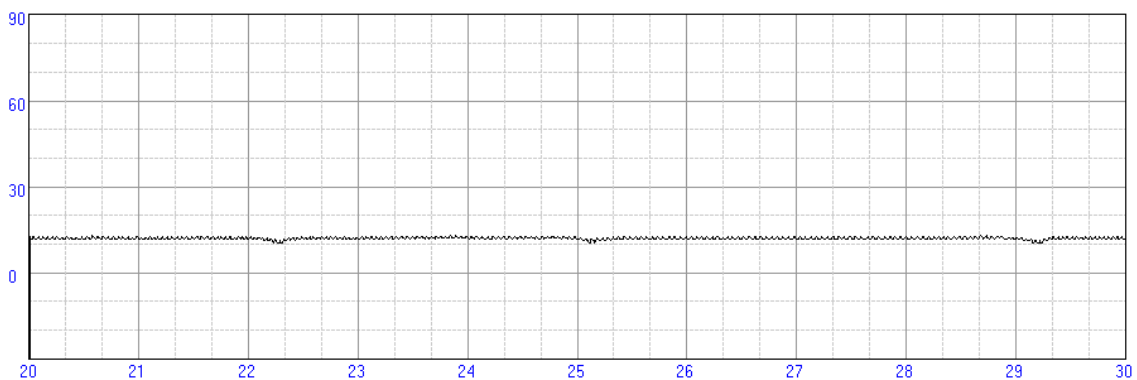
Uterine irritability **20 days** post LH surge. History of complete litter loss at ultrasound in two litters

Of particular concern for premature labour management is the presence of a pattern within the uterine contractions or irritability. Once a pattern of contractility is established the pattern frequently will escalate into active labour within 48 hours if not treated. Clients using the WhelpWise service have a high motivation for success; in most cases they have already lost litters. Our "failure" rate, or "what happens if you don't treat the contractions" has occurred from clients that are non-compliant with treatment protocols. Clients that have not been treated aggressively have gone on to lose a significant amount of pups in the

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

132

litter, or lose the entire litter. Foetuses that have been compromised by preterm labour but have managed to make it to the end of gestation frequently are intrauterine growth retarded and have severely compromised placentas. It is also very important to note that rarely are there symptoms associated with premature labour, nor is premature labour associated with a decline in maternal temperature. Frequently the presence of uteroverdin is the first symptom of a problem with the pregnancy.

In the era of dog "over population", one must ask the question of, why do you want to breed this bitch with all her whelping problems? The answer in many cases is because this is the last animal from a specific lineage, or frequently bred as an older bitch because of obtaining multiple working titles. Also, painstakingly selective breeding has eliminated many adult health issues in a line but has not been selective for good whelpers.

Medications for premature labour management

Antibiotics
As documented in both human and veterinary medicine infection plays a significant role in preterm labour because of the prostaglandin F2 alpha release with resulting leutolysis. (12) The presence of infection can be difficult to ascertain and frequently high-risk bitches, especially those with a prior history of infective loss, are prophylactically placed on antibiotic therapy.

Tocolyitcs
Terbutaline, (Brethine) was one of the most frequently used drugs in the treatment of human preterm labour. Unfortunately, thanks to a spate of corporate espionage, Terbutaline has received a "black-box" warning from the United States FDA. Removing this medication from preterm labour management in humans has resulted in a static level of preterm birth rates from the 1990's to 2021. (18) Currently, in human medicine, patients are managed with long-term maternal hospitalization and intravenous Magnesium Sulfate to control the preterm contractions. This therapy continues until the foetus reaches a date where the administration of cortical steroids will promote enough surfactant that the foetus can be allowed to deliver and will usually survive in the NICU. Unfortunately, these babies are left with life-long health issues that could have been prevented if the preterm labour was managed more effectively. For the canine population we have found Terbutaline Sulfate (Brethine) to be the most effective medication to manage preterm labour in dogs. We have managed around 6,750 clients using Terbutaline with no untoward effects.

Terbutaline is in the class of drugs called beta-mimetics. These Beta $_2$-adrenergic receptor agonists are sympathomimetic, causing smooth muscle relaxation by decreasing free intracellular calcium ions. (14) Controversy exists in human medicine about the long-term effectiveness of Terbutaline; some of this controversy is related to the b-site saturation causing the drug to become ineffective. Titrating doses: beginning with the smallest effective dose to control the uterine activity, proactively monitoring uterine activity, and increasing the doses in very small amounts to maintain control has proven effective in human medicine. (15, 16) We use this model for preterm labour management, and I believe that a primary reason for our success with Terbutaline is that we do not begin with an arbitrary dose, but rather titrate dosing to control concerning uterine contraction patterns, increasing doses as needed. I do see an increased C-section rate for high-risk

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

133

clients primarily because most high-risk clients do not want to take the chance of any foetal loss. Of those that do choose to free whelp, the incidence of foetal distress or severe inertia is high, (70%) so clients are informed before the parturition date of the potential risks of a free-whelp so they may plan with their veterinarian the best choice for the whelp.

Hypolutealism

Progesterone decline during gestation leading to active labour has been well accepted in veterinary research. (3, 11, 17) What is unclear in the current general management of hypolutealism is the correlation of an "acceptable" level of progesterone for a specific point in gestation, without factoring in the litter size, prior history of litter loss and breed pre-disposition for hypolutealism. Data from our high-risk clients strongly suggests that the perception of a progesterone level that is "greater than 2ng/ml will maintain a pregnancy" appears valid only in the last 2-3 days of gestation. One can only know if the progesterone level is adequate by assessing uterine activity. Documented progesterone levels within our client population range greatly and are strongly influenced by the breed of dog and the number of whelps in the litter.

In our high-risk client population proactive uterine and progesterone monitoring have given early evidence that the existing progesterone level, regardless of laboratory value, is or is not adequate to promote a healthy uterine environment. For clients experiencing preterm labour that is hypoluteal based, using information from the uterine monitor can document the need to obtain further progesterone levels or modifying current supplemental progesterone. This need to modify treatment plan is alerted by changes in the uterine activity rather than lab values alone. Extremely difficult preterm labour cases have occasionally been managed by adding in progesterone even with a "normal" progesterone level. Cooperative management with the clients' veterinarian; evaluating uterine contractility, actual progesterone levels and foetal well-being have provided an effective team approach.

In clients experiencing hypolutealism, we have seen the best response and long-term stability when using injectable progesterone (50mg/ml) in an oil-based carrier, usually sesame, apricot, or cottonseed oil. The oil-based medication is absorbed slower and maintains a more constant progesterone level. Additionally, the efficacy of oil-based therapy can also be documented through laboratory testing. Injectable progesterone doses have ranged from 1-3mg/kg, given QD to every 4th day, with dosing schedules determined by both laboratory values and uterine monitor results. While the uterine monitor provides early notification for an unstable uterus monitoring can also be helpful in weaning progesterone at term gestation. If concerning uterine activity presents while weaning the progesterone, other short acting medications such as Terbutaline can be added or adjusted to promote uterine quiescence while the progesterone is allowed to dissipate from the system. Weaning the progesterone also allows for a normal transition into lactation and maternal skills.

Oral progesterone (Regumate/Prometrium) has not shown a significant impact in the control of uterine contractions in our client population. While it appears somewhat effective in some clients, the majority have not demonstrated a stable uterine environment. These medications may prohibit actual delivery of the foetuses, but rarely does it promote a healthy placenta and good foetal weights.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

134

In extremely difficult cases of premature labour the use of combinations of progesterone, terbutaline and antibiotics have been employed. Management of these exceptionally high-risk clients is a day-to-day, monitor session-monitor session plan of care. Unfortunately, because of the multiple dynamics and the multifaceted nature of high-risk pregnancy management, no specific "cook-book" technique exists.

How can the WhelpWise service help you take care of your clients?

How often is your day interrupted by a phone call from one of your breeding clients who is concerned about their bitch? They are concerned but can't really articulate exactly what they are concerned about. "She was panting all night", "she doesn't want to eat", "I think she was in labour and stopped".

Wouldn't it be helpful to have objective information about what is occurring with the whelp? Instead of "she is panting", we can say she is panting, has a very nice labour pattern established and we would expect to see puppies start to deliver in three to four hours, or she is having symptoms, but she is not having contractions. All the heart rates on the puppies are doing well so nothing to worry about!

Would it help you to receive communication from us that lets you know that "we believe that we are beginning to see an issue with the whelping". She could be beginning to demonstrate a contraction pattern that would be consistent with an obstructive dystocia. Having the information that her labour pattern is abnormal and the concern is an obstruction would help prevent uterotonics from being administered incorrectly.

Consider the owner that has a bitch that is an amazing example of excellent standards and health for their breed, except for a prior history of pyometra not associated with pregnancy. The owner would really like to get a litter of puppies but on her first breeding she experienced a litter failure for no known reason. Bitches with a history of a prior uterine or vaginal infection tend to have an issue with preterm contractions or actual preterm delivery. Uterine monitoring can be initiated at pregnancy confirmation and proactive management of preterm labour can be initiated and she can have a successful pregnancy outcome!

Whelping success

Successful management of all aspects of medicine is dependent upon objective information on which to base decisions. Management of diabetic patients requires the measurement of objective blood glucose parameters to determine how to dose insulin, Orthopedic problems require x-rays or MRI to assist the veterinarian with their diagnosis and treatment. Maternal and foetal management is no different.

The best whelping outcomes will be achieved when decisions are based on objective data; detecting whelping issues early and interventions based on objective rather than subjective data.

References

1. Davidson, Autumn. Obstetrical monitoring in dogs. Veterinary Medicine; June 2003 508-516
2. Concannon, Patrick W. Canine Pregnancy and Parturition. Veterinary Clinics of North America: Small Animal Practice 1986 Vol 16, (3) May

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management
135

3.   Johnston Shirley D., Root Kustritz, Margaret V., Olson Patricia N. S., Canine and Feline Theriogenology 1st ed. W.B. Saunders 2001 p 105-108, p 121, 125, p 105

4.   Copley, Karen., Comparison of Traditional Methods for Evaluating Parturition in the Bitch versus Using External Uterine and Fetal Monitors. Society for Theriogenology Conference Proceedings. August 2002 p 375-382

5.   Pernicka, Carol. A closer look at labor. AKC Gazette August 1996. p 47-49

6.   Friedman, Emanuel A., Sachtleben, Marlene R., Bresky Patricia A. Obstetrics and Gynecology – Dysfunctional Labor. American Journal of Obstetrics and Gynecology. April 1, 1977 p 779-783

7.   Wilson, Robert J., Beecham, Clayton T., Carrington, Elise Reed Obstetrics and Gynecology 3rd edition C.V. Mosby Company 1966

8.   Friedman, Emanuel A., Labor: Clinical Evaluation and Management. Appleton, New York, 1967

9.   van der Weyden, G.C et al., Physiological aspects of pregnancy and parturition in dogs. J. Reproductive Fertility., Suppl 39 (1989) 211-224

10.   Noble K, Matthew A, Burdyga T, Wray S., A review of recent insights into the role of the sarcoplasmic reticulum and Ca entry in uterine smooth muscle. Eur J Obstetrics Gynecology Reproductive Biology May 2009 144 Suppl p 11-19

11.   Hollinshead, F.K. et al. Serum Calcium and Parathyroid Concentrations in the Whelping Bitch. Proceeding from the 32nd WSVA Congress, Sidney Australia 2007

12.   Johnson, C.A., High-risk pregnancy and hypoluteoidism in the bitch. Theriogenology 2008 (70) 1424-1430

13.   Feldman, Edward., Nelson, Richard., Canine and Feline Endocrinology and Reproduction 3rd edition p. 823

14.   Calixto, Joao Batista., Simas, Cidalia Maria. Mechanish of Action of Isoprenaline, Isoxuprine, Terbutaline and Orciprenaline on Gravid Human Isolated Myometirum. Biology of Reproduction; 1984 (30) p.1117-1123

15.   Norwitz, E.R., Robinson, J.N. A systematic approach to the management of preterm labor. Seminars in Perinatology 2001 Aug 25 (4) 223-235

16.   Souney P.F, Kaul A.F, Osathanondh, R., Pharmacotherapy of preterm labor. Clin Pharmacology 1983 Jan-Feb 2 (1): 29-44

17.   Concannon, P.W., Hansel W., Visek W.J., The Ovarian Cycle of the Bitch: Plasma Estrogen, LH and Progesterone. Biology of Reproduction 1975 (13) 112-121

18.   https://www.statista.com/statistics/276075/us-preterm-birth-percentage/

Proceedings of 48th ASAV Annual Conference together with Reproduction
Copley, K - Remote tocodynamometry monitoring using WiFi to support veterinarians in home-based obstetrical management

136

Phage therapy: Basics and use in reproductive therapies

Dr. Lisa Elliott
AusPhage
Townsville

Introduction

The World Health Organization (2014) states, "Increasingly, governments around the world are beginning to pay attention to a problem so serious that it threatens the achievements of modern medicine. A post-antibiotic era — in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century." Almost 10 years down the track, this statement still rings true!

It is estimated that at least 2.8 million people die annually (in the US), due to multi-drug resistant (MDR) bacteria. The total health care cost related to just 6 of the major MDR bacteria in the US is as much as US$4.6 billion annually [1]. In addition to this, production losses and suffering due to emergent MDR bacteria in livestock has a devastating effect on the economy of developing countries and animal health and welfare.

With the rise in antimicrobial resistance and chemical residues in food, and the tightening of regulations surrounding the use of chemotherapeutics, bacteriophages provide a natural, sustainable solution to successfully address this need.

Bacteriophage

Since their discovery almost 100 years ago, bacteriophages have been investigated extensively and a plethora of literature reviewing these studies exists. Bacteriophages (commonly called phages) are a group of naturally occurring antibacterial agents (viral in nature) that infect only bacterial cells. It is estimated that more than 10^{30} phages exist, making them the most abundant entities on earth. In all known environments, phages exist as part of a complex microbial ecosystem. They can be part of a free-living environment such as soils, vegetation and oceans, or as part of a microbial environment within a macro-organism such as a human or animal system. To date, phages have been used in several areas of biotechnology and medical science including rapid bacterial detection and diagnosis of disease (phage typing), prevention of bacterial disease (phage vaccine), treatment (phage therapy) and biocontrol [2].

Bacteriophages are highly specific and can only infect bacterial cells that present cell surface receptors matching those of the phage (like a lock and key mechanism) [3,4]. Without the matching receptors, phages are unable to multiply and are quickly degraded in the environment.

Phage therapy

Phage therapy can be described as the use of bacteriophages to control specific pathogenic or problematic bacteria. Due to the specificity of phages, virulent phage can be considered a natural and effective way to target difficult or problem bacteria, without affecting normal beneficial bacteria and without negatively affecting the host or

Proceedings of 48th ASAV Annual Conference together with Reproduction
Elliott, L – Phage therapy: Basics and use in reproductive therapies

137

environment. Importantly, phages can infect bacteria regardless of their susceptibility to antibiotics and are capable of penetrating biofilms.

In human and animal health sectors, phage therapy has been practiced in regions of Eastern Europe with proven success for more than 60 years. (The Phage Therapy Centre http://www.phagetherapycenter.com).

Phage therapy in veterinary practice

Antibiotic resistance and difficult to treat bacterial infections are on the rise in domesticated and farmed animals. Phage therapy has been successfully used to treat MDR and difficult to resolve infections in a multitude of animals including the following examples [5, 6]:

- bovine (e.g. mastitis),
- equine (e.g. uterine infection),
- canine (e.g. otitis externa, JRI, wound),
- feline (e.g. UTI, wound)
- poultry (e.g. enterititis, respiratory),
- porcine (diarrhea, respiratory).

It must be noted that bacteriophages do not discriminate between host species. The same bacterium causing a uterine infection in a horse (e.g., *Pseudomonas spp)* may in fact be the same as that infecting the ear of a dog. Thus the same phage therapy has the potential to be used for both. This characteristic of phages provides a plethora of treatment possibilities across multiple species.

Conclusion

Bacteriophages have been investigated, tested and extensively used in human and animal medicine for more than 60 years. Although early studies were often inconclusive, modern technology, methods and a greater understanding of phages and pathogen biology have provided an excellent basis for the development of improved preparations, overcoming many of the perceived disadvantages of phage therapy. Virulent phages are natural, sustainable antimicrobials that are nontoxic and, when correctly selected and prepared, do not pose any risk to plants, animals or the environment. Future research and development of bacteriophage preparations as therapies will contribute to environmental, social and economic sustainability in global health and welfare and should be fully embraced and supported by government, researchers, medical professionals and farmers.

References

1. Nelson, R., Hatfield, K., Wolford, H., Samore, M., Scott, R., Reddy, S., Olubajor, B., Paul, Prabasaj., Jernigan, J., and Baggs, J., 2021. National Estimates of Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Hospitalized Patients in the United States, *Clinical Infectious Diseases*, 72 (1), S17–S26, https://doi.org/10.1093/cid/ciaa1581
2. Haq, I.U., Chaudhry, W.N., Akhtar, M.N., Andleeb, S., Qadri, I., 2012. Bacteriophages and Their Implications on Future Biotechnology: A Review. *Virology* J 9, 9.
3. Lindberg, A.A., 1973. Bacteriophage Receptors. *Annual Review of Microbiology* 27, 205-241.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Elliott, L – Phage therapy: Basics and use in reproductive therapies
138

4. Kutter, E., Sulakvelidze, A., 2005. Bacteriophages: *Biology and Applications*. CRCn Press, Florida, 528 p.

5. Ferriol-González, C., and Domingo-Calap, P. 2021. Phage therapy in livestock and companion animals. *Antibiotics* (10) 559 https://doi.org/10.3390/antibiotics10050559

6. Loponte, R., Pagnini, U., Lovane, G., Pisanelli, G. 2021. Phage therapy in Veterinary Medicine. *Antibiotics (*10*)* 421 https://www.mdpi.com/2079-6382/10/4/421

Proceedings of 48th ASAV Annual Conference together with Reproduction
Elliott, L – Phage therapy: Basics and use in reproductive therapies
139

Seroprevalence of canine alphaherpesvirus-1 in a district in North Queensland

Carolynne Joone
James Cook University
1 Solander Drive, James Cook University
Paul Horwood, Holly Dever and Bruce Gummow

Introduction
Canine alphaherpesvirus-1 (CaHV-1) generally causes mild or inapparent disease in adult dogs but can have serious consequences on unborn litters and very young pups. Few studies have reported on the presence of CaHV-1 in Australia to date. In some countries, but not Australia, a vaccine is available for use in pregnant bitches.

Materials and methods
Serum samples were collected from randomly selected household dogs living in a Townsville district, through door-to-door requests for study participation. In addition, serum samples were collected from dogs volunteered by their owners, at two dog shows, in Woodstock and Proserpine, QLD. Only dogs over the age of one year, with no significant current health concerns, were eligible for inclusion in this study. All serum samples underwent testing for CaHV-1 antibodies using a commercially available enzyme-linked immunosorbent assay (ELISA). A sample/positive ratio $\geq$ 0.23 was considered a positive titre.

Results
Of 182 randomly selected household dogs, 21 showed evidence of previous exposure to CaHV-1 (11.5%). For dogs volunteered at dog shows, 13 of 75 (17.3%) demonstrated antibodies to CaHV-1.

Discussion
The results of this study demonstrate that CaHV-1 is present in the north Queensland dog population. The seroprevalence of CaHV-1 reported here is lower than that reported in dogs in Belgium (Ronsse *et al.* 2002), Italy (Rota *et al.* 2020), Turkey (Yeşilbağ *et al.* 2012), England (Reading and Field 1998) and South Africa (Nöthling *et al.* 2008), but similar to that reported in household dogs in Lithuania (11%; Musayeva *et al.* (2013)), bearing in mind that sampling frames and testing methods may differ widely between studies.

Conclusion
Canine alphaherpesvirus-1 is circulating in north Queensland and is likely to be ubiquitous across Australia. This virus may pose a significant threat to pregnant dams and newborn puppies.

References
1. Musayeva, K., Šengaut, J., Petkevičius, S., Malakauskas, A., Gerulis, G. and Šalomskas, A. (2013) 'Seroprevalence of canine herpes virus in Lithuanian dog population', *Veterinarija ir Zootechnika*, 61(83), 48-52.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Joone, C – Seroprevalence of canine alphaherpesvirus-1 in a district in North Queensland

140

2. Nöthling, J., Hüssy, D., Steckler, D. and Ackermann, M. (2008) 'Seroprevalence of canine herpesvirus in breeding kennels in the Gauteng Province of South Africa', *Theriogenology*, 69(3), 276-282.

3. Reading, M. and Field, H. (1998) 'A serological study of canine herpes virus-1 infection in the English dog population', *Archives of virology*, 143(8), 1477-1488.

4. Ronsse, V., Verstegen, J., Onclin, K., Guiot, A., Aeberlé, C., Nauwynck, H. and Poulet, H. (2002) 'Seroprevalence of canine herpesvirus-1 in the Belgian dog population in 2000', *Reproduction in Domestic Animals*, 37(5), 299-304.

5. Rota, A., Dogliero, A., Biosa, T., Messina, M., Pregel, P. and Masoero, L. (2020) 'Seroprevalence of canine herpesvirus-1 in breeding dogs with or without vaccination in Northwest Italy', *Animals*, 10(7), 1116.

6. Yeşilbağ, K., Yalçın, E., Tuncer, P. and Yılmaz, Z. (2012) 'Seroprevalence of canine herpesvirus-1 in Turkish dog population', *Research in veterinary science*, 92(1), 36-39.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Joone, C – Seroprevalence of canine alphaherpesvirus-1 in a district in North Queensland

141

Non-antibiotic therapies in a post-antibiotic world

J.A. Rodger
Jerry's Plains Veterinary Hospital
10 Pagan Street, Jerrys Plains NSW 2330

1. Introduction

The rapidly increasing antibiotic resistance among pathogenic bacteria is a global concern of which we are all aware. Possibly some are not as aware as they might be. The World Health Organization predicts human deaths due to antibiotic resistance will escalate from 700,000 per year to around 10 million per year by 2050.

The most concerning aspect is that the bacteria have the ability to pass this resistance to other bacteria. We are therefore not just chasing a resistant bacterium but a transferable resistant gene or genes that can be passed around.

This was illustrated recently when identifying a multiple resistant *Staphylococcus aureus* (MRSA) in a stallion. The samples were repeated in three laboratories for confirmation. The third laboratory was a commercial laboratory that cultured not only the MRSA but also the non-pathogenic contaminants that were also present on the stallions' penis. Remarkably these non-pathogens exhibited the same pattern of resistance as the MRSA. In other words, the resistance had been passed around so there was now a cohort of "sleeper" bacteria with the potential to become effective resistant pathogens.

The reasons for the rapid rise of antibiotic resistance have been well recognised, overuse or inappropriate use of antibiotics, inappropriate dosing regimes, movement of world population, antibiotic feed additives as growth promoters, etc. The method of transfer is becoming more understood and that it is a genetic trait that the organisms acquire.

A return to treatments used before antibiotics along with the development of new techniques is the necessary way forward to supplement current therapies as our antibiotics become ineffective or unavailable.

The object of this paper is to indicate some of the developing technologies and to have a lengthier introduction to bacteriophage therapy in particular.

2. Future technologies

2.1 Traditional medicines

Both in the human field and in Veterinary medicine there has been a resurgence in traditional medicines particularly medicinal herbs. Some of these traditional medicines have a modern application often as a result of research. These include immunomodulators and herbal analgesics.

The group of phytomedicines can be taken to include tea tree oil for skin infections, cranberry juice for urinary tract infections and honey for wound infections.

Probiotics are well into the fore with current medications and are a familiar treatment and prophylactic in both human and veterinary medicine.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Rodger, JA - Non-antibiotic therapies in a post-antibiotic world

142

Possibly the most promising is the development of bacteriophage therapy, relatively new in veterinary medicine but well established in human medicine and will be discussed more fully further in this paper.

Photodynamic therapy involves the activation of a topical agent using light. Some agents act by releasing nascent oxygen, which is also the active principal in hydrogen peroxide treatment.

The use of mesenchymal stem cells is a promising approach. Being part of the basal structure of the body they can become a source of antimicrobial peptides used to control inflammation and infection.
Stem cell produced antimicrobial peptides include human B-defensin-1 and RNase-7. They can also be used to attack cancer cells.

Quorum sensing inhibitors attack the communication system between bacteria. Surprisingly bacteria communicate and coordinate their efforts. This is illustrated in their ability to form biofilms for example. QSI's breakdown the communication system and leave the bacteria exposed or with reduced function.
Quorum sensing inhibitors work by different mechanisms and can be produced naturally or synthetically. They include substances like garlic, cranberry, curcumin and quinolones and sulphonamides.

2.2 CRISPR – Cas is used to cleave specific strands of DNA.

There are different types of CRISPR – Cas and can be used for procedures such as gene editing, gene regulation and gene therapy. The Nobel prize in chemistry was awarded in 2020 to Emmanuelle Charpentier and Jennifer Doudna for development of the technique.

The science of nanotechnology has provided an additional tool in that it can enable small particles of antibiotic to penetrate tissues and reach areas that otherwise would be inaccessible by conventional therapy.

Vaccination has sometimes been controversial, usually seen as an additional cost, and in the relative disease-free environment of Australia is often seen as unnecessary. The lack of uptake of the highly effective tetanus toxoid against the fatal disease of tetanus is astonishing.
Recent exposure to Covid-19 and influenza has encouraged people to think about vaccinations but even in the human population the uptake is disappointingly low.
In the USA which the horse owners usually see as a gold standard, vaccinations for 9-10 diseases are available and often mandatory.

3. How do we apply this to practice?

Preventive medicine and good hygiene, isolation and early recognition and notification of disease are our main armaments. Australia remains backward in disease notification in the horse industry. The World-wide notification of disease initiated by Lloyds of London has persistently failed in Australia. For example, no cases of strangles are ever recorded. Officially strangles remains a notifiable disease with no action to be taken. Certain diseases such as Equine herpes-1 abortion and arbovirus infections such as Japanese encephalitis

Proceedings of 48th ASAV Annual Conference together with Reproduction
Rodger, JA - Non-antibiotic therapies in a post-antibiotic world

143

are now being pursued effectively by the Department of Primary Industry which is a great step forward.

Early diagnosis of disease helps early treatment and reduced spread. New techniques such as in-house PCR machines will speed up diagnosis or identification. Identification by gene sequencing is now the norm in human hospital medicine.

4. Bacteriophage therapy in equine practice
Bacteriophage therapy is not a routine procedure in Veterinary practice.

4.1 How did we come to use it?
A few years ago, we were coming up against the problem of resistant bacteria in particular the problem of Pseudomonas. Pseudomonas is a ubiquitous organism and there are many strains. It is often a contaminant of water supplies.

The first real contact for the practice was one of the wound contaminations from coiled-up hosepipes- left in the sun the warm water left in the coiled tube became an ideal incubator especially in non-chlorinated water from river, bore or water tanks. Wounds that were hosed off with this water became contaminated with serious consequences.

Pseudomonas produces amongst other things hyaluronidase which rapidly causes wound and tissue breakdown.

In human medicine it is often a feature of lung infections along with its friend Staphylococcus aureus. Both these organisms are well known for developing multi resistance to antibiotics.

In stud practice we found it was an occasional contaminant of the clitoral sinus and pathogenic strains could be transmitted to stallions. The increase importance over recent years may well be related to the frequent [often unnecessary] use of antibiotics. We were therefore faced with increasing difficult infection which were coming more and more resistant, and we hence turned to the possibility of phage therapy. To our delight the treatment as supplied by special phage services was effective.

After a few cases we then had a stallion with a multi resistant Pseudomonas in his semen and a resulting infertility. Again, treatment by topical and oral medications resulted in elimination of the bacterium.

4.2 What are bacteriophages?
Bacteriophages are viruses that live on bacteria. They were first discovered by a Frenchman although much of the credit for their development is left with the Georgians. In the early 20th century while the West chose to pursue the development of antibiotics the bacteriophages were left to those behind the Iron Curtain.

Our dilemma now is because of our continued use and often misuse of antibiotics, bacteria have developed a resistance to them which is increasing rapidly. Not only do bacteria develop resistance but they are able – particularly is the case of gram negatives such as Pseudomonas and E Coli they are able by gene transfer to transfer that resistance to other

Proceedings of 48th ASAV Annual Conference together with Reproduction
Rodger, JA - Non-antibiotic therapies in a post-antibiotic world

144

bacteria. The so called "superbugs" can therefore pass on their antibody resistance to other bacterial species.

This was brought home to us recently when dealing with a multi resistant Staphyloccus aureus.

This bacterium showed resistance to all the antibiotics tested in vitro. Fortunately, one of the antibiotics tested gave a positive effect in vivo and after prolonged treatment at high doses the infection was cleared.

What was worrying was that when the sample was collected – in this case from a stallion's penis, other non-pathogenic "contaminants" were also cultured. The frightening thing was that they all showed exactly the same resistance as the MRSA. In other words, they had "learnt" this property and in effect the MRSA now had a cohort of apprentice's potential pathogens. Also, we don't know if they in turn were able to transfer that resistance to other bacteria.

This leaves one with the uncomfortable awareness that the glorious safety of the last 50 – 70 years with antibiotics use can easily come to an end. The answer cannot be just producing new antibiotic for reasons of convenance, cost etc. A new approach is required.

We get used to depiction of bacteria that look like sausages and viruses have various depictions although since Covid-19 we have become used to seeing representation of viruses with horns and protuberances. Anybody familiar with the bizarre or extraordinary shapes of plankton and microorganisms will know the variation in form is infinite and fascinating. No less the bacteriophages look like something from science fiction. They have an extraordinary shape with a tower containing chromatin standing on legs which they attach to the bacterium, and a probe which lowers down to inject the phage's DNA into the bacterium. Once in there it will replicate thousands of times until the bacterium bursts and releases many, many phages.

To attach the bacterium the feet, which are host specific, attach to the sugar coating of the bacterial wall causing it to dissolve. These "legs" then contract, lowering the probe down and into the bacterium.

Phages are extremely host specific and will only attach to the specific bacterium and will not affect anything else.

4.3 How can bacteriophages be used?
The first use is obviously as a form of therapy. The problem is that they have to be produced which takes time.

Traditional identification of an infection by isolation and culture [and sensitivity testing for possible antibiotic use] take time. This can be shortened using new techniques such as PCR testing and genetic identification of pathogens. The idea of phage banks with a sort of "phage soup" has been suggested but there is much work to be done.

A week taken to prepare a phage treatment can be too long for an acute infection.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Rodger, JA - Non-antibiotic therapies in a post-antibiotic world

145

Another use that has been suggested is the use of phage vaccination.

Use of the specificity of the legs or footplates of the phage has been suggested. It involves producing a pure culture of the foot plates to study how they dissolve the coating of the bacteria. This in itself may open doors as a new technique in attacking bacteria.

5. What is the future?
Unlike antibiotics, phages cannot at present be bulk produced and stored on the shelf the way antibiotics are although a phage bank is being developed. This makes them less attractive to the multinational producer and there is therefore less interest in development. It is harder to get investment which can finance research. Without that finance and hence research the science cannot progress to a stage where is can be mass produced.

Progress in this essential field is, therefore, very slow.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Rodger, JA - Non-antibiotic therapies in a post-antibiotic world

146

The **MOST** complete parasite protection, all in one tasty chew

Gonadectomy and effects on physiological function

Dr. Xavier Schneider BIT BLM (Hons) BVSc (Hons) MANZCVS (Anim. Reprod.) DipACT
Animal Reproduction Specialists
telemed@reprovet.com.au

Surgical sterilisation of dogs and cats is one of the most frequently employed methods of preventing pet overpopulation[1]. In the United States, gonadectomy is one of the most common veterinary procedures performed[2]. Its timing is controversial, mainly because it presents a mixture of benefits and adverse effects that depend upon the age at neutering, sex, species and breed[3].

At present, most veterinarians in the United States recommend that elective gonadectomy be performed in dogs and cats at 6 to 9 months of age, however there does not appear to be any scientific evidence to document that this is the optimal age[2]. It is argued that to optimise the effectiveness, gonadectomy should be performed prior to the onset of puberty[1].

Several conditions in dogs and cats can be impacted by elective gonadectomy, including neoplasia and orthopaedic diseases[2]. Gonadal hormone influences reproductive, skeletal, physical and behavioural development in immature animals[1] and there is a trend to allow bitches and queens to experience an oestrus cycle before surgical sterilisation. Knowledge of the benefits and detriments associated with this procedure enables veterinarians to provide appropriate science to clients to make informed decisions and promote animal health[2].

The effects of gonadectomy on specific diseases discussed include:

- Non-Neoplastic Disorder
  - Obesity
  - Urinary Incontinence
  - Urinary Calculi
  - Diabetes Mellitus
  - Hypothyroidism
  - Hip Dysplasia
  - CCL Rupture
  - IVD
  - Behavior
  - Cognitive Dysfunction Syndrome
  - Urogenital Tract Disorders
- Neoplastic Disorders
  - Prostatic Disease
  - TCC
  - Osteosarcoma
  - Hemangiosarcoma
  - Mastocytoma
  - Lymphoma

The effect of gonadectomy and the supraphysiologic release of LH on specific diseases discussed include:

- canine lower urinary tract
- normal and adenomatous thyroid tissue
- anterior cruciate ligament
- structural support tissue of the canine hip and femoral tibial joints

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Gonadectomy and effects on physiological function

148

- neoplastic endothelial cells of splenic, cardiac, cutaneous and dermal hemangiosarcoma
- lymphocytes and lymphoid tissue

More recently Hart et al published research assisting decision making on age of neutering for mixed breed dogs of five weight categories and for 35 breeds of dogs associated with joint disorders, cancers and urinary incontinence. At present this research serves as a guide for discussion with clients when deciding when to perform gonadectomy.

References

1. Salmeri K, Bloomberg, Scruggs S, et al. Gonadectomy in immature dogs: effects on skeletal, physical, and behavioral development. Journal of the American Veterinary Medical Association 1991;198:1193–1203.
2. Kustritz M. Determining the optimal age for gonadectomy of dogs and cats. Journal of the American Veterinary Medical Association 2007;231:1665-1675.
3. Reichler I. Gonadectomy in Cats and Dogs: A Review of Risks and Benefits. Reproduction in Domestic Animals 2009;44:29–35.
4. Zwida K, Kutzler M. Non-Reproductive Long-Term Health Complications of Gonad Removal in Dogs as Well as Possible Causal Relationships with Post-Gonadectomy Elevated Luteinizing Hormone (LH) Concentrations. Journal of Etiology and Animal Health 2016;1:1-11.
5. O'Farrell V, Peachey E. Behavioural effects of ovariohysterectomy on bitches. J Small Anim Pract 1990;31:595–598.
6. Jeusette I, Detilleux J, Cuvelier C, et al. Ad libitum feeding following ovariectomy in female Beagle dogs: effect on maintenance energy requirement and on blood metabolites. J Anim Physiol An N 2004;88:117–121.
7. Schneider R, Dorn C, Taylor D. Factors influencing canine mammary cancer development and postsurgical survival. Journal of the National Cancer Institute 1969;43:1249–1261.
8. Overley B, Shofer FS, Goldschmidt MH, et al. Association between ovarihysterectomy and feline mammary carcinoma. Journal of veterinary internal medicine / American College of Veterinary Internal Medicine 2005;19:560–563.
9. Salmeri K, Bloomberg, Scruggs S, et al. Gonadectomy in immature dogs: effects on skeletal, physical, and behavioral development. J Am Vet Med Assoc 1991;198:1193–203.
10. Reichler I, Hubler M. Urinary Incontinence in the Bitch: An Update. Reprod Domest Anim 2014;49:75–80.
11. Spain VC, arlett J, Houpt KA. Long-term risks and benefits of early-age gonadectomy in dogs. Journal of the American Veterinary Medical Association 2004;224:380–387.
12. Bryan JN, Keeler MR, Henry CJ, et al. A population study of neutering status as a risk factor for canine prostate cancer. The Prostate 2007;67:1174–1181.
13. Belanger JM, Bellumori TP, Bannasch DL, et al. Correlation of neuter status and expression of heritable disorders. 2017;4:6.
14. Slauterbeck J, Pankratz K, Xu K, et al. Canine Ovariohysterectomy and Orchiectomy Increases the Prevalence of ACL Injury. Clinical orthopaedics and related research 2004;429:301–305.
15. Ru G, Terracini B, Glickman L. Host related risk factors for canine osteosarcoma. The Veterinary Journal 1998;156:31–39.
16. Cooley DM, Beranek BC, Schlittler DL, et al. Endogenous gonadal hormone exposure

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Gonadectomy and effects on physiological function

149

and bone sarcoma risk. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2002;11:1434–1440.

17. Hart, B. L., Hart, L. A., Thigpen, A. P. & Willits, N. H. Assisting Decision-Making on Age of Neutering for Mixed Breed Dogs of Five Weight Categories: Associated Joint Disorders and Cancers. *Frontiers Vet Sci* **7**, 472 (2020).
18. Hart, B. L., Hart, L. A., Thigpen, A. P. & Willits, N. H. Assisting Decision-Making on Age of Neutering for 35 Breeds of Dogs: Associated Joint Disorders, Cancers, and Urinary Incontinence. *Frontiers Vet Sci* **7**, 388 (2020).

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Gonadectomy and effects on physiological function

150

Monitoring canine pregnancies and managing elective caesarean sections

Dr. Xavier Schneider BIT BLM (Hons) BVSc (Hons) MANZCVS (Anim. Reprod.) DipACT
Animal Reproduction Specialists
telemed@reprovet.com.au

With the increase in value of canine litters, there has been added attention to the diagnosis and monitoring of pregnancy as well as managing elective caesareans. Increasingly clinicians are presented with an animal that is pregnant, with an unknown or incomplete history of breeding and an owner wanting an elective caesarean performed with the value of the litter in mind. Understanding the physiology of gestation and delivery and knowing what tools are available will help guide the decision of when pregnancy is over and when it is safe to perform an elective caesarean.

The gestation length in the bitch varies due to an extended period of receptivity[1], the prolonged viability of spermatozoa[2] and the identification of ovulation from LH or ovulation[1]. Gestation can be estimated from 65 ± 1 days when timed from LH surge, 63 ± 2 days when based on ovulation but can vary between 57 – 72 days from any mating date without identification of the LH surge or ovulation. To complicate gestation length Mir et al reported that litter size and weight had an effect on gestation[3].

There are multiple methods available for pregnancy diagnosis and monitoring in the bitch including sonography[4], radiology[4] and serum proteins including acute phase proteins, relaxin and progesterone.

Sonography can be used to calculate an estimated gestation length[5] however accuracy varies depending on advancement of gestation[6]. More recently Gil et al described the morphology of fetal maturation via sonography and has been used as an indicator of fetal advancement. Heart rates can also be monitored indicating fetal distress[8,9].

Progesterone assay is an important indicator of gestation, however, can be mis-interpreted with pseudopregnancy (a normal phenomenon of the bitch)[10,11]. Progesterone is thermoregulatory, and can sometimes correlate to a temperature drop[10]. An important point to remember is that progesterone can be reported in different units (nmol/L or ng/ml). Progesterone is affected by a diurnal variation[13,14], and sampling technique can also have an effect on the result. A rapid decline in progesterone from ~30nmol/L to <6nmol/L over a 12-24 hour interval usually precedes parturition.

Parturition in the bitch occurs in 3 stages:
- Stage 1: 6-12 h (possibly up to 36 h)
  - Relaxation and dilation of the cervix
  - Restless and nervous, anorexia, shivers and pants
  - Temperature falls and progesterone levels are very low (basal)
- Stage 2: 6-24 h (possibly up to 30 h)
  - Cervix is fully open, strong uterine contractions, pups are born
  - Licking vulva, rupture of allontochorion (clear fluid), amnion appears (dark green discharge)

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Monitoring canine pregnancies and managing elective caesarean sections

151

- o Expulsion of pups: 1-2 min (longer in smaller breeds), average 30-60 min interval between pups
- Stage 3: 5-15 min
  - o Expulsion of placenta often following each pup or after 2 pups
  - o The bitch cleans the pups and eat the placentas

Parameters for intervention include:
- if the bitch is systemically ill
- fetal heart rates <180bpm
- no birth at due date
- more than 2 hours from the beginning of Stage II labour to pup birth
- more than 2 hours between pups
  - o 30% increase in mortality[15]
- more than 20 minutes of active abdominal straining with no pup
- more than 20 minutes from the appearance of a pup part at the vulva and no complete birth of that pup

A dose of 1IU oxytocin i/v (per bitch) will induce intrauterine pressure of over 100mm HG in a proestrus bitch and 58mmHg in an anoestrus bitch so it is still active in the absence of oestrogen, and is not recommended as a treatment for dystocia[16].

If a caesarean is performed, the uterotomy incision is closed with a Utrecht (inverting) pattern.

References

1. Concannon PW, Whaley S, Lein D, Wisler R, (1983) Canine gestation length: variation related to time of mating and fertile life of sperm. Am J Vet Res 44, 1819– 1821.
2. Doak, R., Hall, A. and Dale, H. (1967) Longevity of Spermatozoa in the reproductive tract of the bitch. J. Reprod. Fert. 13, 51-58.
3. Mir, F., Billault, C., Fontaine, E., Sendra, J. and Fontbonne, A. (2011) Estimated pregnancy length from ovulation to parturition in the bitch and its influencing factors: a retrospective study in 162 pregnancies. Reprod. Domest. Anim. 46, 994–998.
4. Lopate, C. (2008) Estimation of gestational age and assessment of canine fetal maturation using radiology and ultrasonography: a review. Theriogenology 70, 397–402.
5. Luvoni, G.C. and Beccaglia, M. (2006) The Prediction of Parturition Date in Canine Pregnancy. Reprod. Domest. Anim. 41, 27–32.
6. Beccaglia, M. & Luvoni, G. C. Prediction of Parturition in Dogs and Cats: Accuracy at Different Gestational Ages. *Reproduction in domestic animals* **47**, 194–196 (2012).
7. Gil, E.M.U., Garcia, D.A.A. and Froes, T.R. (2015) In utero development of the fetal intestine: Sonographic evaluation and correlation with gestational age and fetal maturity in dogs. Theriogenology 84, 681–686.
8. Zone, M., Wanke, M. (2001) Diagnosis of canine fetal health by ultrasonography. J Reprod Fertil Suppl 57, 215–219.
9. Kutzler, M., Yeager, A. et al. (2003) Accuracy of canine parturition date prediction using fetal measurements obtained by ultrasonography. Theriogenology 60, 1309–1317.
10. Concannon, P., Powers, M, and Hansel, W. (1977) Pregnancy and Parturition in the Bitch. Biology of Reproduction 16, 517-526.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Monitoring canine pregnancies and managing elective caesarean sections

152

11. Verstegen-Onclin, K. and Verstegen, J. (2008) Endocrinology of pregnancy in the dog: A review. Theriogenology 70, 291–299.

12. STEINETZ, B. G., GOLDSMITH, L. T. & HASAN, S. H. Diurnal variation of serum progesterone, but not relaxin, prolactin, or estradiol-17β in the pregnant bitch.

13. *J Reprod Fertil Suppl* (1990).

14. Thuroczy, J. et al. Effect of Anticoagulants and Sampling Time on Results of Progesterone Determination in Canine Blood Samples. Reprod Domest Anim 38, 386–389 (2003).

15. Cornelius, A. J., Moxon, R., Russenberger, J., Havlena, B. & Cheong, S. H. Identifying risk factors for canine dystocia and stillbirths. *Theriogenology* **128**, 201–206 (2019).

16. Wheaton, L. G., Benson, G. J., Tranquilli, W. J. & Thurmon, J. C. The oxytocic effect of xylazine on the canine uterus. *Theriogenology* **31**, 911–915 (1989).

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Monitoring canine pregnancies and managing elective caesarean sections

153

Partnering for success: Navigating initial repro consults for better breeding outcomes

Dr Xavier Schneider BIT BLM (Hons) BVSc (Hons) MANZCVS (Anim. Reprod) DipACT
Animal Reproduction Specialists
telemed@reprovet.com.au

The initial breeding consult can be a daunting process. Gathering a detailed breeding history can aid in identifying causes of suboptimal breeding outcomes. Initial consult questions include:

- Was the bitch bred by the owner or was she acquired from another breeder?
- Does the bitch live at home with the breeder or is she living with a guardian?
- Has she had any diseases or illness recently?
- Is she on any medications at present?
- Has she been exposed to exogenous sex steroids?
- Has she had a litter previously?
- Has she had any failed attempts at mating/pregnancy?
- Has she had any previous surgeries?
- Is she on any supplements or additives to promote fertility?
- What diet is the bitch being fed?
- What day in her cycle is she now or what day did she begin to cycle?

Other tests that can be performed (not at the time of oestrous) but in the planning phase can include screening tests such as Hip/Elbow imaging (and spine/trachea for brachycephalic breeds) and Genetic Disease Panel Testing. These tests are breed specific and are generally governed by breed societies.

Vaginal exam

The digital vaginal exam is extremely important in a pre-breeding exam, allowing for the identification of vaginal hyperplasia, vaginal septum anomalies, and vaginal strictures.

Vaginal hyperplasia is poorly defined in the literature however is an over-exaggeration of the natural proliferation of the vaginal floor cranial to the urethral meatus[2]. Vaginal hyperplasia is classified as[2]:

a) Stage I – perineal swelling
b) Stage II – vaginal floor mucosa eversion
c) Stage III – prolapse of the entire circumference of the vaginal mucosa

Very little is known about the hereditary aspect, but there is evidence of breed and familial incidence[3-5].

Digital examination of the vestibule/vagina can also reveal failure of fusion of the paired mullerian ducts leading to a vaginal septum or stricture (narrowing).

Vaginal cytology

Oestrogen has a mitogenic effect on vaginal epithelium, causing cells in the wall to multiply and thicken[1]. Capillary blood supply to these cells is on the basement membrane, where nutrient exchange occurs. As the cycle progresses, the vaginal epithelium thickens and

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Partnering for success: Navigating initial repro consults for better breeding outcomes

154

cells move further away from blood supply[1].

Cells change shape as they cannot exchange waste, so the cell cytoplasm swells[1].
- parabasal -> intermediate -> superficial cells

Eventually, with no exchange in waste, cells keratinise and die[1].
- anuclear superficial (cornified or keratinised)

Serum hormonal assay

Progesterone in the bitch comes primarily from luteal tissue in the ovaries. During anoestrus, baseline serum progesterone concentrations are typically <1 ng/mL or <3.18 nmol/L. During pro-oestrus, preovulatory luteinisation occurs in granulosa cells, causing them to switch from oestrogen to progesterone production days prior to ovulation. Concentrations will begin to rise again and will reach around 5 ng/mL or 16 nmol/L before the bitch ovulates[1]. Once this rise in progesterone starts, the rate at which the progesterone concentrations rise is relatively consistent among most individuals and thus the clinician can correlate the physiological events of the LH surge, ovulation, and the start of the fertile period with subsequent concentrations of serum progesterone[1].

Ovulation and maturation of oocytes

In all other domestic species the oocyte is fertile immediately after ovulation. This is not the case in the bitch[1]. In the bitch, the oocyte is not fertile until usually one to two days after ovulation (i.e. the fertile period starts around day four where LH surge = day 0) [1]. The bitch is unique among domestic species in that she ovulates a primary oocyte, which still must complete meiosis before it is a secondary oocyte ready for fusion with the sperm cell. This process takes about two days to complete and therefore there is a need to wait an additional two days after ovulation before the canine oocytes are fertile[1]. and timing for breeding is optimal.

References

1. Christensen, B.W. (2011) The physiology of ovulation timing in the bitch. Clinical Theriogenology 3, 1–15.
2. Post, K., Haaften, B. V. & Okkens, A. C. Vaginal hyperplasia in the bitch: Literature review and commentary. *The Canadian veterinary journal. La revue vétérinaire canadienne* **32**, 35–37 (1991).
3. Wykes PM, Olson PN. The vulva. In: Slatter DH, ed. Textbook of Small Animal Surgery. Vol. 2. Philadelphia: WB Saunders, 1985: 1678-1684.
4. Jones DE, Joshua JO. Reproductive Clinical Problems in the Dog. Bristol: Wright PSG, 1982: 22-28. 10.
5. Wykes PM. Diseases of the vagina and vulva in the bitch. In: Morrow DA, ed. Current Therapy in Theriogenology. Vol. 2. Philadelphia: WB Saunders, 1986: 476-481.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Schneider, XJ – Partnering for success: Navigating initial repro consults for better breeding outcomes

155

Estimated breeding values for dog breeding: Pros and cons

Claire M Wade
School of Life and Environmental Sciences
The University of Sydney NSW 2006

Abstract

Estimated breeding values (EBVs) have been widely used in animal breeding to improve complex traits since the 1970s. They have been particularly successfully applied in the dairy and swine production industries where good quality phenotypic and pedigree information is available. In the past decade, the promotion of EBVs to improve complex trait scores in dog breeding has been proposed. In particular, the use of EBVs to improve traits relating to orthopaedic health, working performance and cardiovascular disease have been promoted. To date, the availability of EBVs for dog breeding has been limited. The reasons for this are partly historical and partly practical. In Australia, the establishment of EBVs for orthopaedic traits is likely achievable in the medium term. EBVs for other traits are unlikely to be available for the foreseeable future.

Introduction

Traditional estimated breeding values (EBVs) were developed for the breeding of cattle in the 1970s for the purpose of improving the rate of response to selection. Phenotypic EBVs employ phenotypic information in a method known as Best Linear Unbiased Predictor to allow for environmental factors that might influence trait outcomes, as well as the relevant family (pedigree) information and correctly account for all of these to predict the genetic "worth" of the animal as a parent.

In more recent times, the use of phenotypic and pedigree records in calculating EBVs in livestock has been partly superseded by DNA-based methods such as genome-wide genetic marker data. Rather than being known as phenotypic EBVs these then become known as Genomic EBVs or GEBVs. GEBVs are particularly useful when the parentage information for animals is lacking (such as in the breeding of livestock that use multiple sire mating systems) because the DNA markers reveal pedigree relationships as well as providing clues to the genetic "worth" of an animal as a parent.

Estimated Breeding Values are accepted as the most effective strategy for undertaking selection based on phenotype and/or on DNA markers associated with phenotypes. They work well to improve all traits, including those that have low heritability such as traits related to reproductive success that are already subjected to strong natural selection.

Estimated breeding value basics

In traditional genetics, "breeding value" is the "heritable" aspect of the trait that we can see or measure (the phenotype). The phenotype though is also impacted by other genetic

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

156

Figure 1. Estimated Breeding Values simultaneously account for genetics and environment to predict the heritable aspect of an animal's measurement. N.B. If these were Willis hip scores then Sire 1 would be better!
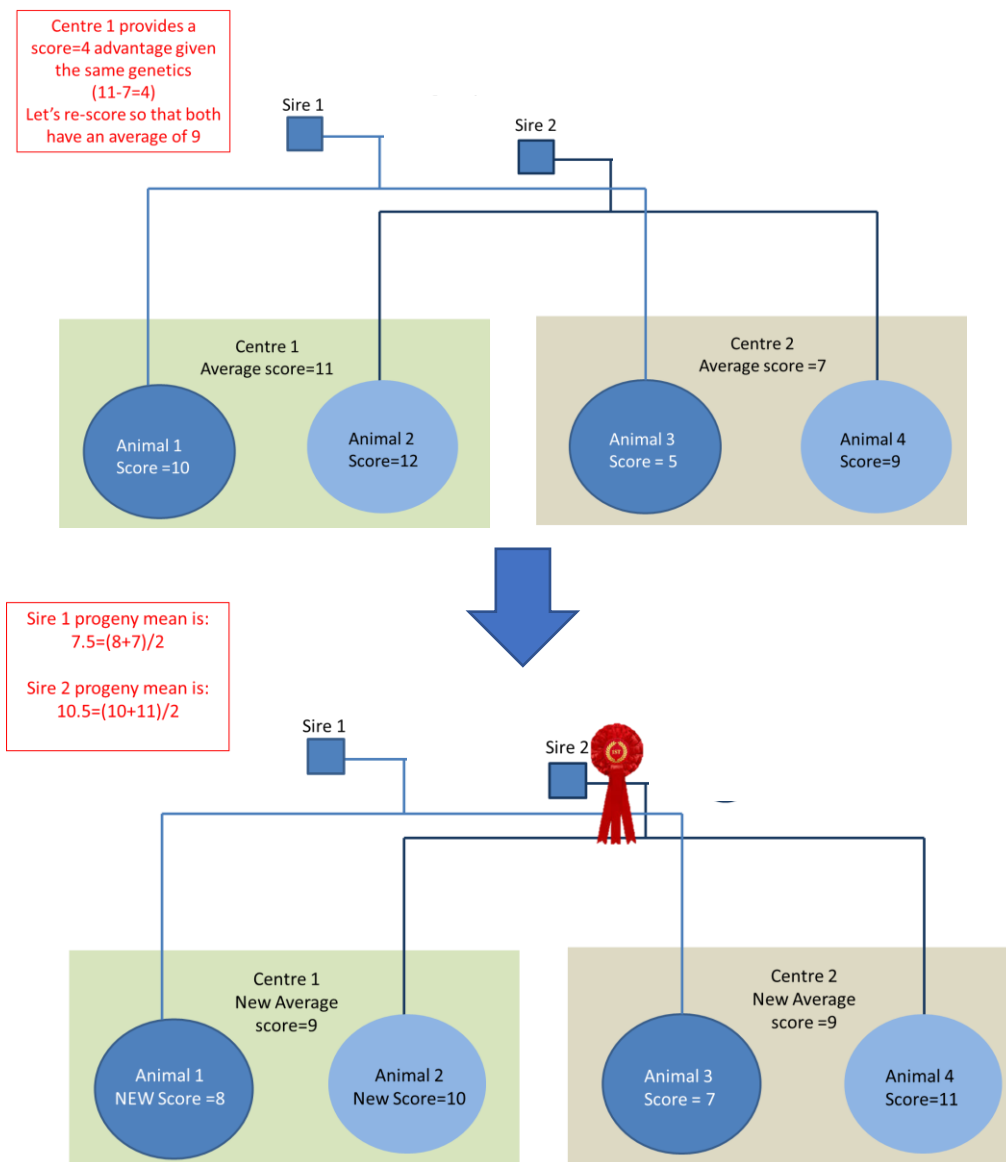
phenomena (such as inbreeding depression or hybrid vigour) and also by non-genetic factors, including those contributed by the housing, feeding, neuter status, and training of the animal.

The statistical methods employed have certain requirements before they can work well. Traditionally, the estimation of breeding value of sires was made by comparing their progeny when they were raised and measured in a similar environment (in cattle: herd-year-season). Ranking progeny from different sires when they are otherwise treated similarly enables us to see the effects of each sire's genetic contribution. Next, to observe the environmental contributions, we need the animals from the same sires to be used in different herd-year-seasons (Figure 1).

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

157

The ranking of breeding animals via EBVs has several requirements:
1. The same breeding animals must be used over multiple years or in multiple locations.
2. Different breeding animals must be used in the same location.
3. The same measurements must be applied to all animals (apples to apples comparison).
4. The trait being measured must be heritable to some extent.
5. There must be trustworthy participation.
6. There must be organisation so that the measurements are paid for, properly collected, analysed, and reported.
7. There must be an education program that enables the end users of the data to understand its strengths, limitations and best practice uses.

In dog breeding, there are some traits that are well suited for the generation of estimated breeding values and there is some movement towards the provision of estimated breeding values for these. Already, internationally, some canine organisations have started to make Estimated Breeding Values available for hip and elbow scoring at a national level. International breeding organisations for assistance dogs have also started calculating Estimated Breeding Values for orthopaedic traits and they are in development for traits such as successful graduation from training programs. More recently there are moves to institute a scheme for Respiratory Function Grading in breeds that are prone to Brachycephalic Obstructive Airway Syndrome.

Barriers to successful establishment of EBVs for dog breeding
Other traits are harder to evaluate in the breeding context available for dogs. Over several years, we attempted to establish a facility for generating phenotypic EBVs for livestock-herding dogs. This effort revealed several practical difficulties and some of these are discussed later. In the following pages, we will consider the application of EBVs mainly for measurement of orthopaedic traits – since these are likely to be the first for which EBVs will become available.

Economic value
In livestock breeding, individual trait EBVs are combined into a selection index that enables breeders to consider several characteristics simultaneously. Typically, the weightings applied to the different traits in the selection index are based on their respective economic values. Even in species that have a distinct product, economic values rely on the availability of information on discounted cash flows – a region of expertise far beyond me! For production livestock, the outputs are discrete and readily measured – kilograms of liveweight, litres of milk, piglets per sow, mm of back fat. Market forces bend the relative values of these units, so that back fat might be penalised and lean muscle mass valued. Breeding programs utilising estimated breeding values are run in pure breeding populations (typically by breed societies) to avoid the confounding effects of heterosis from cross breeding.

In dog breeding, the economic value of an orthopaedic trait is only indirectly tied to the trait under selection. The majority of product consumers (puppy buyers) are unaware of the relative trait values or their importance, even when direct trait measurements are available. Currently the main drivers for trait improvement for orthopaedic traits are breeder desire to improve animal welfare and organisational desire for improved repute. This means that

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

158

combining the use of EBVs into a wider breeding program is not a simple task and breeders with access to EBVs are not likely to use them optimally.

Breeding objectives
Unlike production animal enterprises that have clear economic goals, many dogs bred in Australia are bred to an intangible optimum of several characteristics that include personality, performance in the desired venue of activity, external appearance, and health. The relative weightings placed on these characteristics by breeders vary widely and unpredictably. Even within a health-focused breeding program, selection for complex traits must take a seat behind DNA-based selection against recessive genetic disease. Most breeding for traits other than radiographic measurements aim for a central value rather than an increase in any one product. Many breeders employ corrective matings to achieve animals within the frame of acceptability for their puppy buyers. Differences in breeding objectives among breeders mean that EBVs cannot be readily combined into an effective selection index that is broadly applicable.

Population structure
In Australia, 40% of Australian households have a dog and the average dogs per household is 1.3 for an estimated 5 million dogs (https://www.aph.gov.au). In this country the main avenues for breeding dogs include:
1. Livestock herding
2. Racing Greyhounds
3. Assistance/Guide
4. Police/Military
5. Commercial
6. Dogs bred with registering bodies (e.g. Dogs Australia affiliated organisations and the Master Dog Breeders Association)
7. Randomly bred by unaffiliated breeders
8. Imported from internationally bred dogs
9. Breeding in rescue (retail rescue)

Of these avenues for breeding, thus far only the Dogs Australia affiliated breeders and Assistance dog organisational breeders have commenced serious data collection for the calculation of phenotypic and genomic EBVs.

In livestock breeding, animals are typically kept as herds/flocks comprising tens to thousands of animals. Animals of the same age can be run together and subjected to the same seasonal and environment conditions. For pasture-raised livestock, dams have few progeny and sires have many progeny. By comparison, legislative requirements in dog breeding force most breeders to have very few breeding animals in their household. This reduces the opportunities for the kinds of comparisons and replication of family and environmental factors that are required to generate high quality EBVs.

Dogs bred are theoretically controlled by animal welfare legislation in each state or territory. Most of the state codes of practice place restrictions on the numbers of entire animals that can be kept on any one premise. Further restrictions can be enforced by local council laws and zonings. These factors place downward pressure on the numbers of animals that can be housed and bred in any one location and limit the abilities of breeders to generate high

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

159

quality genetic comparisons within locations. Conducting comparisons across locations is possible (and this is how the evaluations are currently conducted) but the lack of correction for environment is likely to reduce the trait heritability and increase the measurement error in comparisons.

Unlike sheep and cattle but like pigs, dogs produce puppies in litters. Whilst this seems a good method for generating replications of genetics within a site, it can create a statistical effect whereby litter environment effects are confounded with genetic effects from the dam.

Finally, and importantly, dog breeders typically select their replacement breeding stock at 8 weeks of age before any measurement relevant to the estimated breeding value for an orthopaedic trait is available for animals being selected. Because there is no individual measurement available, all puppies in a litter will have the same EBV.

Measurement difficulties

Hip scoring can cost breeders several hundred dollars. For this reason, it is unusual for all offspring in a litter to be scored for orthopaedic traits. Instead, only the potential breeding animals are scored unless there is a clinical problem that emerges. Thus, sampling across the pedigree is scant.

Several different strategies for measuring orthopaedic traits are commercially available. The most well known in Australia are the Willis scoring system and the PennHIP scoring system. Internationally, several other scoring systems exist, and it is difficult to make use of international data in the national system.

The use of the PennHIP scoring system can be problematic for the generation of phenotypic EBVs because the data are proprietary to the PennHIP organisation and the dog owner. Consequently, only the PennHIP organisation is in a position to calculate PennHIP phenotypic EBVs. It is for this reason that Dogs Australia has chosen to stay with the Willis orthopaedic scoring system. In Australia, there has been heavy marketing of the PennHIP evaluation system to veterinarians and dog owners as being superior to other scoring strategies. Whether or not this is true, the use of the PennHIP evaluation system for the national comparison of animals in a genetic evaluation system is not possible at this time for data access reasons. As stated earlier, EBVs allow selective advances with even low heritability traits and a decision has been taken that it is better to use something than nothing.

During her doctoral studies investigating the application of EBVs for the improvement of hip scores in pedigreed dogs, Dr Bethany Wilson identified that there was a strongly significant effect of radiographic scorer on the scores submitted for use in genetic evaluation. Further, it was common practice for animal owners to request re-scoring if an unfavourable result was returned. In response to these identified problems, the Australian National Kennel Council (ANKC – now Dogs Australia) instituted an accredited scoring program for radiographic images using the Willis scoring method. While Dogs Australia took over the Canine Hip and Elbow Dysplasia scheme since 2016, it is only in the past few years that the scorer accreditation scheme has been in place. With the newer scheme, radiographers submit results directly to the Dogs Australia ORCHID (Officially Registered Canine Health Information Database). All scorers use the same radiographic software to generate the

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

160

primary data for analysis and all dogs are anaesthetised to ensure image quality. To this point in time, phenotypic EBVs have not yet been calculated. Individual owners have the opportunity to publicly share results and all results are used to generate breed-level statistics.

Guide Dogs Australia is participating in the International Working Dog Registry (IWDR) which is an international group generating phenotypic EBVs and GEBVs for orthopaedic and working success traits. This involvement was started in 2018 with an in-kind contribution of genotyping array data to Guide Dogs NSW and Guide Dogs Vic. Both organisations are enrolled with the IWDR.

Reputational risk

As stated earlier, the connection between health traits being assessed using EBVs and the economic value of a pup is tenuous. The same is true when assessing working traits for livestock herding dogs. Many livestock herding dog breeders have developed a repute for producing a particular style of working dog over often generations of breeding. There is a great reluctance for established breeders with strong returning customer bases to have their dogs directly compared using a scoring strategy that is obscure to them. The combination of high likelihood of sampling error due to low genotype by environment replication, paired with the potential risk of abuse by breeders loading the data through coercion of their loyal customer base means that the desirability of participation is low and the trust for the rankings produced is also low. With strong downward pressure on breeding animal numbers - these problems seem unlikely to be surmounted in the short-medium term.

Purebred-Crossbred

In the past 10-20 years, the desire to own crossbred dogs has rapidly increased. The statistics that are applied to generate Estimated Breeding Values work poorly in crossbreeding enterprises because it is not possible to dissociate the genetic effects that are heritable from the genetic effects that are not heritable. In combination with other factors that depress the accuracies of the breeding values produced (largely the effects of depressed sample sizes and replication) it is difficult to foresee value for the generation of EBVs outside of the contributing parental purebred populations.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

161

Other strategies are showing success

While the application of phenotypic EBVs represents the highest standard of phenotypic selection, other selection strategies do work. Without the benefit of EBVs and using only phenotypic selection, humans have altered the shape of dogs to the many forms and sizes that we see today. Having puppies in litters means that breeders have the opportunity to apply effective selection on aspects of dogs that can be observed before pups are dispersed to new homes.

In the area of orthopaedic traits for which selection using phenotypic EBVs is feasible, the literature demonstrates that considerable genetic improvement is occurring in hip dysplasia scoring as a result of the current selective practices, i.e. phenotypic selection alone (see Figure 2) (Hedhammer et al 2020, Hou et al 2010, Wilson et al 2012, Lewis et al 2013).

Figure 2. From Hedhammer (2020) shows the decline in the percentage of dogs diagnosed with grades 2–4/D–E of HD over the last 50 years for seven breeds in Sweden. These results are typical of those seen in all countries applying hip screening without the use of EBVs
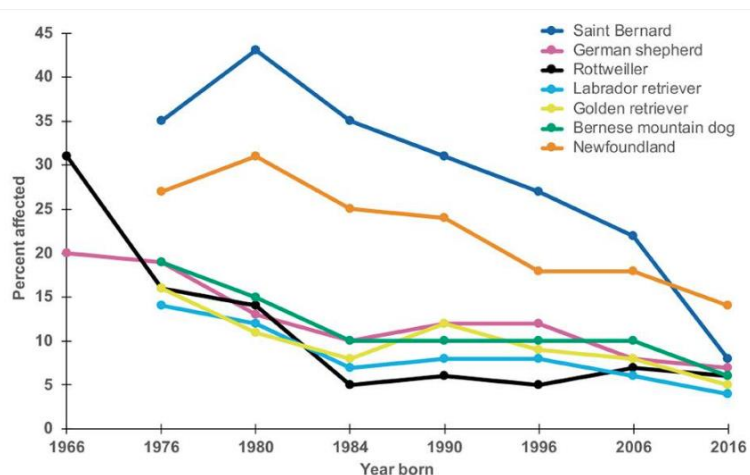
In the pedigreed dog world, breeders that are registered with a Dogs Australia affiliated state organisation may have Litter Registration Limits (LRL) that require both parents of a litter to have radiographic hip scores. Even without these regulations, many ethical breeders will conduct hip radiographic assessment of their potential breeding animals before they are used (typically when they are more than one year of age). Breeders typically aim for a mean parental hip score that is at or below the breed average as reported by the scoring scheme. This means that an animal with an above-average hip score may still be used but is more likely to be bred with a mate that has a low hip score (corrective mating).

What will work?

There is considerable willingness within the registration organisations for tools to facilitate the improvement of animal welfare to be available to breeders. Yet, most openly commercial dog breeders produce crossbred animals and have few purebred animals. The purebred animals contributing to the crossbred commercial offspring are unlikely to be participants in organised orthopaedic scoring programs due to the ethical or political constraints of the organisations controlling the schemes.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

162

Dogs Australia has a commitment to the availability of a scheme to improve scores for orthopaedic traits. While at this time phenotypic EBVs are not available via this scheme, there is a glacial pace being made to bring a system that could generate phenotypic EBVs to fruition. In contrast, the UK Kennel Club has been calculating phenotypic EBVs since around 2010. Phenotype scoring is also underway in the UK and Australia for other traits that might benefit from this kind of scheme, such as respiratory function grading for brachycephalic dogs.

The various guide dog and assistance dog organisations are motivated to generate EBVs for orthopaedic traits and other working traits, and it is likely that these will be generated as GEBVs rather than phenotypic EBVs. The guide and assistance dog organisations are in a better position to accomplish this as they have greater control over the breeding objectives of their organisational members.

Selection for complex traits based on EBVs is expected to outperform selection based just on phenotypes or just on genetic markers for complex traits. GEBVs typically show advantages in populations that have limited pedigree information, as the relatedness among animals can be assessed using the genetic markers; and do a far better job at utilising DNA marker information.

Conclusions

Selection for health is a high priority for most dog breeders, regardless of the sector of operations. However, selection for health is typically only one aspect of a breeding program and most breeders have aims competing with selection for complex traits including controlling recessive genetic disease with genetic testing. Many dogs that are bred are not just pets. Many dogs have important working roles, or may be used in high level competitions that add selection criteria to the breeding program. Given these barriers against genetic improvement, it is heartening to observe that improvement in metrics for complex traits undergoing phenotypic selection has been observed in many different populations, and to realise that selection based on EBVs will do an even better job.

To date in Australia, phenotypic EBVs have been calculated for orthopaedic traits and for working traits. All have been conducted as elements of research projects. As such, they occur on an unpredictable schedule that is subject to the availability of funding to support the salaries and computing environment required for the analysis of existing data. There is a strong attempt to improve the quality of data collection for various complex health traits for dogs in Australia. To date, the capacity to analyse the data on a regular basis has not been achieved. The predominant barrier to the availability of EBVs is financial. Most organisations that would seek to make EBVs available are charity based or are run by volunteers. The connection between the trait under selection and economic value of the pups produced is difficult to quantify meaning that the financial incentive to pay additional fees and charges is not there.

Take home messages:
- Dog population structure is different than livestock population structure.
- Trait measurements must be standardised between individuals and populations.
- Education is required on how to use EBVs in dog breeding programs.
- EBVs are not suited to crossbred animals.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Estimated breeding values for dog breeding: Pros and cons

163

References

1. Hedhammer, A. (2020) Swedish Experiences From 60 Years of Screening and Breeding Programs for Hip Dysplasia—Research, Success, and Challenges Front Vet Sci. 2020; 7: 228.

2. Hou Y, Wang Y, Lust G, Zhu L, Zhang Z, Todhunter RJ. Retrospective analysis for genetic improvement of hip joints of cohort Labrador Retrievers in the United States 1970-2007. PLoS ONE. (2010) 5:e9410. doi: 10.1371/journal.pone.0009410

3. Wilson BJ, Nicholas FW, James JW, Wade CM, Tammen I, Raadsma HW, et al. Heritability and phenotypic variation of canine hip dysplasia radiographic traits in a cohort of Australian German Shepherd Dogs. PLoS ONE. (2012) 7:e39620. doi: 10.1371/journal.pone.0039620

4. Lewis TW, Blott SC, Woolliams JA. Comparative analyses of genetic trends and prospects for selection against hip and elbow dysplasia in 15 UK dog breeds. BMC Genet. (2013) 14:16. doi: 10.1186/1471-2156-14-16

Proceedings of 48th ASAV Annual Conference together with Reproduction
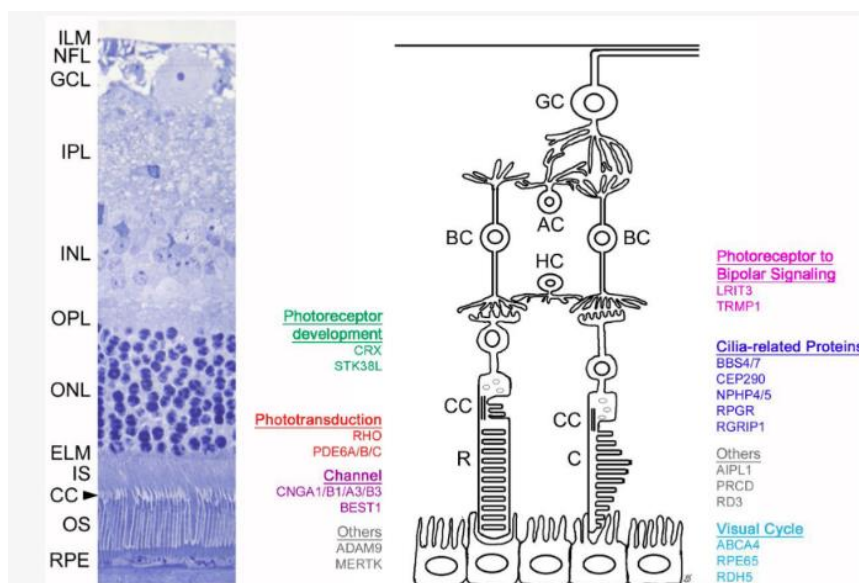Wade, CM - Estimated breeding values for dog breeding: Pros and cons

164

Using genetic tests and reporting inherited disorders in dog breeding: How veterinarians can help (parts 1 and 2)

Claire Wade BSc (Hons) PhD UNSW GCertEd UQ
University of Sydney
School of Life and Environmental Sciences

Introduction

Veterinarians work at the coalface of inherited disorders in animals. The disorders seen may range from novel congenital syndromic disorders to Mendelian inherited disorders to complex traits. Many, though not all Mendelian inherited disorders have DNA-based tests available. Historically, the earlier genetic tests that were made commercially available were relevant across many dog breeds (e.g., the tests for Drug sensitivity caused by the gene ABCB1 (formerly known as MDR1) and Progressive Retinal Atrophy caused by Progressive rod-cone dysplasia). However, across breed relevance for DNA-based tests is not always the case. Many tests are valid only for the single breed for which they were developed. Sometimes inherited disorders are labelled by their symptomatic effects and these symptoms might be caused by different genetic factors. For example, progressive retinal atrophy is a degenerative disorder of the retina and at the time of writing there are tens of variants that are known to cause retinal degeneration in animals (Figure 1) and at least 28 genes affecting the condition in dogs (Kaukonen et al 2020).

Figure 1. From Winkler et al (2020) Schematic of retinal layers and associated genes discussed within their review. The left image shows a histologic section of a feline retina (with comparable anatomy to the human retina). The right panel depicts a schematic showing the genes detailed in Winkler (2020) and their site of expression, grouped per biological process. Inner limiting membrane (ILM), nerve fiber layer (NFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexifom layer (OPL), outer nuclear layer (ONL), external limiting membrane (ELM), photoreceptor inner segment (IS), connecting cilium (CC), photoreceptor outer segment (OS), retinal pigmentary epithelium (RPE). Ganglion cell (GC), amacrine cell (AC), bipolar cell (BC), horizontal cell (HC), rod (R), cone (C)

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Using genetic tests and reporting inherited disorders in dog breeding: How veterinarians can help (parts 1 and 2)

165

The diaspora of tests available is challenging for any person (even the most knowledgeable) to navigate and new tests are published regularly. Knowing the places to go to find breed-relevant tests and understanding the relative merits of different testing systems is imperative.

Clinical disorder reporting

Scientists from The University of Sydney have initiated a disorder reporting portal for use by owners, breeders, managers, and veterinarians. The portal is expected to go live late in 2023 and is known as the *Anstee Hub for Inherited Diseases in Animals (AHIDA* https://ahida.sydney.edu.au*)*.

With its development funded by a generous bequest from the late Ronald Anstee to the University of Sydney, the portal was initially developed for the purpose of providing an anonymous reporting structure for livestock but will accept reports across all species including companion animals and wildlife. The AHIDA portal will complement the Online Mendelian Inheritance In Animals (OMIA omia.org). When active, the portal will have the capacity to collate clinical information relating to submissions and uses Artificial Intelligence to identify clusters of common disorders without the need for a lay person to know clinical Latin terminology. Species based reports will be generated and breed-level reporting is possible upon request to the AHIDA team. The portal is expected to work in reciprocal collaboration with VetCompass Australia (https://www.vetcompass.com.au/).

It is envisaged that the AHIDA reporting hub will not only provide evidence for disorder prevalence but might also enable the better connection between breeders and researchers working to develop breed-relevant tests. It is hoped that the capacity for anonymous reporting will enable the capture of emerging neonatal disorders that are currently invisible. The portal might also assist breed clubs that wish to conduct breed health surveys. While no sample collection is undertaken directly via the portal, the participating submitters are invited to connect with researchers active in research for their breed or species.

Veterinarians can help by either reporting disorders themselves or encouraging their breeder clients to report.

Identifying breed-relevant genetic tests

The websites of commercial genetic test providers (GTPs) will often list tests offered according to breed. Unfortunately, these offerings are not universally accurate or complete. Not all genetic tests offered for dogs are published or available through all providers. Two high quality resources for understanding the testing that is available more widely and actively used by breeders are available. Another less developed resource is being made available in Australia, but it is currently less complete than the two listed first.

1. *The International Partnership for Dogs (dogwellnet.com/ctp/)* is a resource provided by a multi-national non-profit organisation that aims to collect in one location the tests available for dog breeds according to the breed and test provider. Owners, breeders, or veterinarians can search the database by breed, by test provider, or by disorder. Each test is given a "paw rating" using a traffic light system. The site includes tests that are unpublished and not widely available but relies on these to be notified by breed clubs. No individual animal results are reported on this portal.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Using genetic tests and reporting inherited disorders in dog breeding: How veterinarians can help (parts 1 and 2)

166

2. The USA-based *Orthopedic Foundation for Animals (OFA) (ofa.org)* provides a resource for breeders to publicly report their phenotypic and DNA-based testing results. The results are sent directly to the OFA by the genetic test provider with the permission of the owner and a transfer fee. The strength of this site is the ability to provide both DNA-based and phenotype-based results in a common portal. The portal includes both published and unpublished DNA test results for individual animals from around the world.

The newer resource that is relevant for Australian phenotypic result sharing is:

3. The Dogs Australia *Officially Registered Canine Health Information Database (ORCHID https://orchid.ankc.org.au/).* This resource enables owners to publicly share health screening results. This database uses information submitted directly from the accredited phenotypic screening agent (typically a radiographer, ophthalmologist, or cardiologist). Dogs must have been positively identified by microchip. The resource is available only to Dogs Australia registered breeders and owners and will form the basis for the generation of respiratory function, hip and elbow estimated breeding values in coming years.

Veterinarians can assist by encouraging the sharing of phenotypic information on these resources, by understanding that not every test is relevant to every breed, and by directing owners/breeders to the correct tests. The best advice is always that if you do not understand what to do then please reach out to a knowledgeable person (canine geneticist) that does not have a conflict of interest. The AHIDA portal will provide an avenue to connect with the right people.

Using genetic tests

The availability of a genetic test for an inherited disorder is very beneficial for breeders. When a disorder is known to occur but has no test, breeders will actively avoid using family bloodlines that have been known to exhibit the disorder. This may mean that large sectors of the breeding population are not used. The availability of a test enables breeders to safely use the breed lines exhibiting the disorder in addition to others that are not known to carry the disorder. It is not uncommon for the recessive disorders to be identified in lines previously believed to be clear.

Breeding carriers is ok

Historically, veterinarians have advised breeders against breeding with carriers. This is potentially harmful for breed diversity and is not good genetic practice. The purpose of genetic testing is to prevent the clinical manifestation of the genetic disorder. For recessive conditions, the carrier individuals are clinically normal and if bred with a DNA clear animal (for the same relevant genetic test) then no affected puppies can result.

As the number of genetic tests available increases, breeders (particularly from breeds that actively participate in research to improve the welfare of their breed) are faced with the need to incorporate more and more genetic tests in their breeding program. After considering the tested disorders, the breeders must then consider the other important aspects of their breed, including complex-trait health, working performance, breed type and behaviour. Breeding programs are definitely a complex puzzle and advice for one component of the program in isolation is usually not useful.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Using genetic tests and reporting inherited disorders in dog breeding: How veterinarians can help (parts 1 and 2)

167

Panel testing

There are a number of commercial companies that offer panel testing of multiple gene variants in one sample submission. The testing panels are by necessity limited to the variants already known and published at the time of the panel design. Therefore, not all breed-relevant genetic tests may be included in the panel. Because the same panel is typically used for every breed. It is possible that occasionally irrelevant DNA test results for the breed under inquiry will be reported in error. Testing companies should report the breeds for which the tested variant has been validated but this is not always done.

One clear mate for every test, every time

Veterinarians can assist breeders by guiding the breeder to the correct breed tests using the resources mentioned above. Where breeders are using animals tested for well-defined recessive disorders, veterinarians should not dissuade breeders from using carriers in their breeding programs but should encourage their clients to include at least one DNA-test clear parent for every relevant test in every breeding. The DNA clear result can come from either parent (one animal need not be clear for everything tested).

DNA clear

Increasingly animals are advertised for stud or for sale as "DNA clear". This statement is potentially misleading. New mutations occur in every meiosis and the chance of a new mutation affecting a protein coding gene is small but not absent. Animals that are widely used in breeding programs for whatever reason have the potential to disperse new recessive genetic disorders through the population. Breeders should be encouraged to always list the specific test results and the source of the result.

Clear by parentage

Clear by parentage is sometimes offered as a DNA test result. It means that either both parents or all four grandparents have been tested using a trusted DNA test and all have returned a result of two normal alleles (no carriers). For Mendelian recessive disorders this is possibly acceptable, but the parentage of the animals must be known with absolute certainty. Acceptance of clear by parentage beyond a single generation has risk unless DNA-based parentage is properly confirmed.

Veterinarians can help by encouraging their clients to list the specific DNA test results for their animals and encourage them to request the direct test results rather than relying on verbal reports of test results. A direct test on an animal is always better than a result inferred by pedigree. Animals with no test result should be treated as carriers.

Diversity and coefficient of inbreeding

Some companies are offering assessments of diversity or coefficient of inbreeding (COI). It is important to understand that COI is not heritable. This means that it is possible to breed together two high COI dogs and achieve a low COI progeny. Some breeds have historically higher homozygosity than other breeds. If there has been active selection for health in the breeds, then excess homozygosity does not necessarily correlate with genetic load of disease predisposing genes. The availability of COI information on dogs does not negate the importance of breeders following good breeding practices. That is, they should not breed closely related animals together.

Overly stringent attention to breeding for "all clear" DNA test results can be very dangerous for breed diversity by severely restricting the numbers of potential breeding animals. History has shown that attempting to clear a genetic mutation from a breed can elevate the gene frequencies for new inherited conditions that have no genetic test available.

I often hear it suggested that too few individuals from litters are bred. This is a mathematically ridiculous comment. If every puppy born was bred, then the population would exponentially grow, overwhelming the availability of homes and shelter spaces. Breed diversity is promoted by the perpetuation of animals from many different families in the breeding population, rather than through a larger number of animals being bred in total.

Are some breeds too sick to be bred?

Gene mapping has revealed that some breeds have high frequencies of possibly damaging mutations. In some countries, this has been used to restrict the breeding of the breeds affected. Is banning breeds the answer?

There are two assumptions at play here:
1. That it is proven that the mutation of concern is the functional cause of the clinical outcome.
2. That the breeds in question are entirely "fixed" for the harmful mutant.

Both of these assumptions are likely untrue. It is very difficult to prove causality for a mutation. Very likely even with mutations that are broadly accepted as being harmful, there may be individuals with compensatory mutations in different genes that prevent clinical disease from occurring. Two traits that are under the microscope with respect to breed health are heart disease and brachycephaly. Both of these traits are likely multigenic and can be improved by selective breeding.

Research has shown that in the global population of dogs, there are very likely some that have the healthy version of a gene even in breeds with high frequency of a deleterious mutation. Where they are truly fixed – the only example to date is the Dalmatian being fixed for SLC2A9 causing hyperuricosuria, then careful crossing programs can introduce the normal gene version without the breed being banned. Our research, for example, has shown that the normal versions of mutants predicted to increase risk for cardiovascular disease are present in pedigree registered Cavalier King Charles Spaniels. Providing breeders with the information to assist the identification of the healthy animals will help them to rapidly increase the frequencies of good genes in the breed.

Banning of breeding is an ineffective response to problems that are caused by identifiable mutations. Banning historically only increases the invisibility of the breeding programs (rather than stopping them), it increases the value of the increasingly rare animals and fosters illicit trading and importation.

Veterinarians can help by supporting breeders and breed organisations to undertake health-focused breeding. Encourage breeders to screen breeding animals for health traits e.g. echocardiogram for heart disease, hip radiographs for hip dysplasia, and respiratory function grading for brachycephaly. Encourage clients to seek out breeders that are actively

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Using genetic tests and reporting inherited disorders in dog breeding: How veterinarians can help (parts 1 and 2)

169

engaging in health-focused breeding and who provide evidence of the use of verifiable health information to potential puppy purchasers.

Acknowledgements

References

1. Kaukonen M, Quintero IB, Mukarram AK, Hytönen MK, Holopainen S, Wickström K, et al. (2020) A putative silencer variant in a spontaneous canine model of retinitis pigmentosa. PLoS Genet 16(3): e1008659. https://doi.org/10.1371/journal.pgen.1008659
2. Winkler, P.A., Occelli, L.M., and Petersen-Jones, S.M (2020) Large Animal Models of Inherited Retinal Degenerations: A Review Cells 2020, 9(4), 882; https://doi.org/10.3390/cells9040882

Proceedings of 48th ASAV Annual Conference together with Reproduction
Wade, CM - Using genetic tests and reporting inherited disorders in dog breeding: How veterinarians can help (parts 1 and 2)

170

Diagnosis and management of uterine conditions using transcervical catheterisation in bitches

Dr John Watts BVSc (Hons) PhD Diplomate ECAR MANZCVS FRCVS
Animal Reproduction Australia Pty Ltd
133 Market Road
Werribee VIC 3030

Introduction

Transcervical uterine catheterisation is a useful technique which facilitates the diagnosis and treatment of uterine disease, intra-uterine artificial insemination (Romagnoli & Lopate, 2014) and embryo transfer in many species. The technique can be used in bitches using an endoscope to overcome the physical barriers of the elongated vagina, which has a narrowed cranial portion and a ventrally pointing cervix with no dorsal fornix (Pineda, Kainer, & Faulkner, 1973).

The cervix is visualised with a rigid endoscope and a catheter passed through the cervix into the uterus. For diagnosis, samples of endometrial cells and micro-organisms can be collected. In addition, transcervical catheterisation permits contrast hysterography with radiographs and CT. The endoscope can also be passed into the uterus postpartum to examine the endometrium. When treating pyometra, indwelling catheters can be placed for drainage and used for uterine lavage.

The purpose of this paper is to outline the use of transcervical uterine catheterisation to obtain samples for microbiology and cytology from normal bitches, describe hysteroscopy and to discuss the application of transcervical uterine catheterisation in the and treatment of uterine disease.

Technique

The method of transcervical uterine catheterisation for the collection of samples for microbiology and cytology using an endoscope has been described in detail (Watts & Wright, 1995). A rigid endoscope is used. Initially rod lens telescopes were used and now fibreoptic rigid endoscopes are used which are commonly ureteroscopes. The fibreoptic endoscopes have a poorer picture quality than the rod lens ones, however, they are narrower and therefore more comfortable for the bitches when performing the procedure. Air is introduced through a channel in the operating sheath of the endoscope to dilate the reproductive tract (insufflation). The endoscope is passed up the vagina until the cervix is visualised, and a cannula passed into the uterus. Samples for cytology are then obtained by the injection and aspiration of sterile normal saline (2 to 5 ml).

Success of uterine catheterisation is dependent upon the experience of the operator and on the stage of the reproductive cycle. Complications associated infrequently with the procedure were endometritis, vaginitis, vaginal tears and vaginal adhesions (Watts & Wright, 1995; J. Watts, unpublished). Endometritis was associated with the use of cytobrushes, frequent sampling and inadequate asepsis. Vaginitis was associated with repeated vaginoscopies when the vaginal wall was thin during anoestrus, postpartum and dioestrus. Vaginal tears also occurred when the vaginal wall was thin during anoestrus and in dioestrus. It must be emphasised that the endoscope should never be forced and

Proceedings of 48th ASAV Annual Conference together with Reproduction
Watts, J – Diagnosis and management of uterine conditions using transcervical catheterisation in bitches

171

vaginoscopy should be concluded if the endoscope does not pass easily through the narrowed cranial vagina. Another attempt can be made later when the bitch is in pro-oestrus or oestrus, when the vaginal wall is thick and the lumen wider than at other stages of the reproductive cycle.

Catheters, guide wires and cytology brushes may be introduced into the uterus through the cervix. Catheters with a stylet to maintain rigidity are the most suitable, ranging in size from 4 French to 6 French. These catheters are commercially available. Guide wires can be difficult to manoeuvre through the cervix but may be of value if passing a catheter through the cervix is difficult. Cytobrushes have also been used to collect samples for cytology but permit the collection of cells only from a localised area of the endometrium and may lead to the development of endometritis.

Uterine microbiology

The diagnosis of endometritis during pro-oestrus and oestrus requires a positive uterine microbial culture and other clear evidence of disease such as an increase in leukocytes in uterine cytology, a purulent cervical discharge or a peripheral leukocytosis. Micro-organisms are frequently recovered from the uterus during pro-oestrus and oestrus and are most likely of vaginal origin (Watts, Wright, & Whithear, 1996). This access of vaginal microbes probably reflects the patency of the cervix at this time (Allen & France, 1985; Verstegen & Silva, 1995).

The isolation of micro-organisms from the uterus during dioestrus, anoestrus and postpartum often indicates uterine microbial disease. Micro-organisms are rarely isolated from uterine microbial cultures from normal bitches at these stages (Watts et al., 1996). The diagnosis of uterine infection should be always supported with other evidence of disease in case of vaginal microbial contamination of the sample.

The identification of isolates which are likely to lead to reproductive tract disease from the uterus is difficult during pro-oestrus and oestrus. The uterus is exposed to a wide range of bacteria which may include potential opportunistic pathogens such as *Escherichia coli*, *Streptococcus canis* and *Staphylococcus intermedius* during pro-oestrus and oestrus. *Escherichia coli* is the most common pathogen isolated from the uterus in cases of pyometra.

It is unlikely that the *Haemophilus sp* most closely resembling *H. haemoglobulinophilus* is a cause of infertility in bitches. This micro-organism has been isolated from the vagina of bitches with histories of infertility and vaginitis (Farstad, 1982; Osbaldiston, 1971). The frequency of isolation of this bacterium from normal bitches indicates that it is most likely part of the vaginal micro-flora and is of low pathogenic potential (Watts et al., 1996).

Endometrial cytology

Endometrial cytology is very useful in the diagnosis of endometritis, misalliance, sub-involution of placental sites and the detection of endometrial repair following endometrial exfoliation (Watts, Wright, & Lee, 1998) The cells found in endometrial cytology samples from normal bitches included endometrial epithelial cells, erythrocytes, leukocytes, cervical cells, spermatozoa and bacteria. The types, proportions, morphology and numbers of these cells vary throughout the reproductive cycle. Their pattern is also altered dramatically in

Proceedings of 48th ASAV Annual Conference together with Reproduction
Watts, J – Diagnosis and management of uterine conditions using transcervical catheterisation in bitches

172

reproductive diseases. In cases of endometritis there is a marked elevation in the number of leukocytes in relation to number of endometrial epithelial cells in the endometrial cytology samples. In bitches that have mated, spermatozoa are seen in endometrial cytology samples during oestrus. Motile spermatozoa have been recovered post mortem from the uterus for up to 11 days after mating (Doak, Hall, & Dale, 1967). The disappearance of the spermatozoa from the uterus has been linked to the start of dioestrus (Doak et al., 1967). This contrasts with vaginal cytology which is of little value for the diagnosis of misalliance unless taken soon after mating (Feldman & Nelson, 1987). The repair of the endometrium following endometrial exfoliation during anoestrus can be detected from endometrial cytology samples. Endometrial exfoliation is characterised by endometrial epithelial cells with signs of nuclear degeneration and cytoplasmic vacuolation. The endometrial epithelial cells lack these features when the endometrium is repaired. In bitches with sub-involution of placental sites, where this repair is delayed, degenerate cells are found in endometrial cytology samples for a longer period than normal. Endometrial cytology may also be of value in the diagnosis of uterine neoplasia.

Hysteroscopy

The endometrium can be readily examined with an endoscope postpartum (Watts & Wright, 1995) and during oestrus when the cervical os is more open than other times. The cervix often appears closed postpartum but can easily be dilated with insufflation to allow passage of the endoscope. Hysteroscopy on the third day postpartum reveals brown, lochial fluid covering the endometrium. By the seventeenth day postpartum, the endometrium of non-implantation sites is white in colour and relatively free of debris while the implantation sites may be identified where the endometrium is a dark green colour. Folds are visible in the thickened endometrium. The hysteroscope may be passed to the end of the uterine horn in small bitches and the papilla where the oviduct enters the uterus visualised. This technique may be used to diagnose and treat retained placenta (Dreier & Dreier, 1993) and to diagnose a ruptured uterus (Watts & Wright, 1995). This technique has also assisted the diagnosis of abortion when a dilated cervix was visualised and the uterus inspected in a bitch with a vaginal discharge. During oestrus, when performing artificial insemination, the endoscope can sometimes be passed through the cervix and into the uterus. Care should be taken not to traumatise the uterus prior to insemination.

Hysterography

Plain hysterography is an inadequate method of detecting uterine disease due to the possibility of not detecting the enlarged uteri in bitches with pyometra (van Bree, de Schepper, & Capiau, 1988). In addition, any enlargement of the uterus detected can be due to many causes which cannot be distinguished (Rivers & Johnston, 1991). The normal uterus is not usually visible on plain radiographs except during mid to late pregnancy and for around 10 days postpartum.

On the other hand, contrast hysterography is a useful method for evaluating uterine disease. Contrast hysterography has been used to diagnose cystic endometrial hyperplasia, pyometra, retained placenta and uterine cysts (Cobb & Archibald, 1959; Funkquist, Lagerstedt, Linde, & Obel, 1985; Reid & Frank, 1973) and may be of value in the diagnosis of uterine neoplasia, torsions and rupture. Contrast hysterography requires the introduction of contrast medium into the uterus. This can be achieved by transcervical uterine catheterisation at all stages of the reproductive cycle. During pro-oestrus, oestrus and

Proceedings of 48th ASAV Annual Conference together with Reproduction
Watts, J – Diagnosis and management of uterine conditions using transcervical catheterisation in bitches
173

postpartum filling the vagina with contrast medium will also enable contrast hysterography to be carried out (Allen & France, 1985).

CT provides a 3D view of the uterus and can be performed with a similar technique to standard radiographs.

Hysterosalphinography is not a reliable method of detecting patency of the oviducts in bitches (Cobb, 1959; Funkquist et al., 1985). The radiopaque medium used to outline the uterus does not always enter the oviducts in normal bitches, in contrast to women. When the dye does enter the oviducts, it may enter the ovarian bursa and outline the ovaries. This has enabled the detection of cystic ovaries (Cobb & Archibald, 1959).

Treatment of pyometra

The treatment of uterine infections, particularly pyometra, is greatly facilitated by the technique of transcervical uterine canulation. Firstly, the type and in vitro antimicrobial sensitivity of significant isolates may be used to select the appropriate antibiotic to treat the infection after uterine microbial culture. The antibiotics could also be administered locally as well as systemically. Contrast hysterography could be performed which aids in the diagnosis of uterine disease (Funkquist et al., 1985). There are many reports of bitches with uterine disease having secondary pyometra hence it is important to evaluate the uterus for existing pathology before commencing medical treatment. The uterus can be drained of exudate and indwelling catheters can be left in place to allow further drainage (Lagerstedt, Obel, & Stavenborn, 1987). Serial samples for endometrial cytology and microbiology can be taken during treatment to monitor treatment efficacy and confirm recovery.

The use of these techniques may reduce the often-high recurrence rate of pyometra when bitches are treated. This high recurrence rate may have been due to unsuccessful treatment or the continuation of the factors which enabled the pyometra to develop. This treatment should always be used in combination with prostaglandin F2a therapy to induce uterine contractions and complete luteolysis in bitches with infections during dioestrus. Progesterone facilitates the CEH reaction and has immunosuppressive effects on the uterus. The plasma progesterone concentration should be confirmed to be at basal levels with serial assays to ensure luteolysis.

Conclusion

The increased use of transcervical uterine catheterisation for collecting uterine samples, contrast hysterography and uterine treatment will promote understanding of the pathogenesis, and the diagnosis and therapy of uterine disease. When this technique is used in conjunction with existing methods, veterinarians will have very powerful tools for the investigation, diagnosis and treatment of infertility in bitches.

References

1. Allen, W. E., & France, C. (1985). A contrast radiographic study of the vagina and uterus of the normal bitch. *Journal of Small Animal Practice, 26*, 153-166.
2. Cobb, L. M. (1959). The radiographic outline of the genital system of the bitch. *Veterinary Record, 71*(4), 66-68.

Proceedings of 48th ASAV Annual Conference together with Reproduction
Watts, J – Diagnosis and management of uterine conditions using transcervical catheterisation in bitches

174

3. Cobb, L. M., & Archibald, J. (1959). The radiographic appearance of certain pathological conditions of the canine uterus. *Journal of the American Veterinary Medical Association, 134*, 393-397.

4. Doak, R. L., Hall, A., & Dale, H. E. (1967). Longevity of spermatozoa in the reproductive tract of the bitch. *Journal of Reproduction and Fertility, 13*, 51-58.

5. Dreier, H. K., & Dreier, C. (1993). Endoscopic examination of the reproductive tract of the bitch. *Journal of Reproduction and Fertility, 47*(Supplement), 525.

6. Farstad, W. (1982). Bakteriologiske funn i kjønnsveiene hos tisper med reproduksjonsforstyrrelser. *Nordisk Veterinaermedicin, 34*, 451-456.

7. Feldman, E. C., & Nelson, R. W. (1987). Canine female reproduction: Induced abortion; pregnancy termination; mismating. In E. C. Feldman (Ed.), *Canine and Feline Endocrinology and Reproduction* (pp. 436). Philadelphia: WB Saunders Company.

8. Funkquist, B., Lagerstedt, A.-S., Linde, C., & Obel, N. (1985). Hysterography in the bitch. *Veterinary Radiology, 26*(1), 12-18.

9. Lagerstedt, A.-S., Obel, N., & Stavenborn, M. (1987). Uterine drainage in the bitch for treatment of pyometra refractory to prostaglandin F2a. *Journal of Small Animal Practice, 28*, 215-222.

10. Osbaldiston, G. W. (1971). Vaginitis in a bitch associated with *Haemophilus* sp. *American Journal of Veterinary Research, 32*(12), 2067-2069.

11. Pineda, M. H., Kainer, R. A., & Faulkner, L. C. (1973). Dorsal median postcervical fold in the canine vagina. *American Journal of Veterinary Research, 34*(12), 1487-1491.

12. Reid, J. S., & Frank, R. J. (1973). Double contrast hysterogram in the diagnosis of retained placenta in the bitch: A case report. *Journal of the American Animal Hospital Association, 9*, 367-368.

13. Rivers, B., & Johnston, G. R. (1991). Imaging of the reproductive organs of the bitch. Methods and limitations. *Veterinary Clinics of North America Small Animal Practice, 21*(3), 437-466.

14. Romagnoli, S., & Lopate, C. (2014). Transcervical artificial insemination in dogs and cats: review of the technique and practical aspects. *Reprod Domest Anim, 49 Suppl 4*, 56-63. doi:10.1111/rda.12395

15. van Bree, H., de Schepper, J., & Capiau, E. (1988). The significance of radiology in the diagnosis of pyometra (endometritis post oestrum) in dogs: an evaluation of the correlation between radiographic and laboratory findings in 131 cases. *Journal of Veterinary Medicine, A Animal Physiology, Pathology and Clinical Veterinary Medicine, 35*(3), 200-206.

16. Verstegen, J. P. L., & Silva, L. D. M. (1995). *Cervical opening in relation to progesterone and estradiol during heat is the limiting factor for oocytes fertilisation in the Beagle bitch.* Paper presented at the 28th Annual Meeting of the Society for the Study of Reproduction, Davis, California.

17. Watts, J. R., & Wright, P. J. (1995). Investigating uterine disease in the bitch: Uterine cannulation for cytology, microbiology and hysteroscopy. *Journal of Small Animal Practice, 36*, 201-206.

18. Watts, J. R., Wright, P. J., & Lee, C.-S. (1998). Endometrial cytology of the normal bitch throughout the reproductive cycle. *Journal of Small Animal Practice, 39*, 2-9.

19. Watts, J. R., Wright, P. J., & Whithear, K. C. (1996). Uterine, cervical and vaginal microflora of the normal bitch throughout the reproductive cycle. *Journal of Small Animal Practice, 37*(2), 54-60. doi:10.1111/j.1748-5827.1996.tb01936.x

Proceedings of 48th ASAV Annual Conference together with Reproduction
Watts, J – Diagnosis and management of uterine conditions using transcervical catheterisation in bitches

175

ROYAL CANIN®
INCREDIBLE IN EVERY DETAIL

GUT HEALTH IS SUPPORTED
WITH EVERY BITE

The ROYAL CANIN® Gastrointestinal Puppy & Gastrointestinal Kitten wet diets are precisely formulated for the nutritional management of diarrhoea in puppies and kittens.

New

At the time of weaning, puppy and kitten digestive capacities are not yet fully developed. Digestive maturity progressively takes place during growth.
ROYAL CANIN® Gastrointestinal Puppy and Gastrointestinal Kitten diets were developed with an opitmal growth formula while supporting immature digestive systems.

Visit the Royal Canin stand at the ASAV Conference to learn more.

Thank you to our 2023 conference sponsors

Platinum Sponsor

AVA Platinum Supporter

Gold Sponsors

Silver Sponsor

AVA Platinum Education Supporter

AVA Platinum Education Supporter

PROVET
A covetrus Company

covetrus

IDEXX

ROYAL CANIN

vetoquinol
ACHIEVE MORE TOGETHER

Boehringer
Ingelheim

ASAV Practitioner of the Year Award

ASAV Recent Graduate Dinner

ASAV Recent Graduate Pre-dinner Drinks

S8

AVA Platinum Supporter

Hill's
Transforming Lives

AVA Gold Finance Partner

BOQ
SPECIALIST
Distinctive banking

Ultrasound Workshop

Breakfast Sponsors

RADINCON
SPECIALIST MEDICAL IMAGING

AVA Platinum Supporter

Hill's
Transforming Lives

ROYAL CANIN

vetoquinol
ACHIEVE MORE TOGETHER

Virbac