Idiopathic Chronic Enteropathy in Older Cats

David A. Williams, MA, VetMB, PhD, DACVIM, DECVIM

University of Illinois at Urbana-Champaign School of Veterinary Medicine Small Animal Internal Medicine Urbana, IL daw@illinois.edu

Abstract

Up to approximately 40% of cats over 10 years of age are affected by an enteropathy that causes malabsorption of a variety of nutrients and protein-losing enteropathy. These changes are commonly asso-

Glossary of Abbreviations

fPL: Feline Pancreatic Lipase
fTLI: Feline Trypsin-Like Immunoreactivity
GI: Gastrointestinal
IBD: Inflammatory Bowel Disease
ICE: Idiopathic Chronic Enteropathy

ciated with increased serum pancreatic marker enzymes (feline trypsin-like immunoreactivity [fTLI] and feline pancreatic lipase [fPL]) reflecting probable pancreatitis. Studies of the fecal microbiome and serum metabolome have demonstrated significant relationships between the fecal microbiome and cobalamin status but not with the increased pancreatic marker enzymes. However, concentrations of serum fTLI, and especially fPL, are associated with changes in the serum metabolome, but the associations are dissimilar for these two pancreatic marker enzymes.

Decline in body weight is common in cats older than 11 years of age.¹ Sometimes this loss is readily attributable to apparent disease, but in many cases cats exhibit no obvious signs of illness and routine diagnostic approaches fail to reveal evidence of an underlying problem.^{2,3} Energy requirements of older cats apparently do not decline as markedly as they do in dogs and humans, perhaps because physical activity does not decrease as much with age in cats. Indeed, the maintenance energy requirement of older cats may increase rather than decrease.^{3,4} Although cats may be expected to regulate their energy intake to compensate for these changes to maintain body weight, this clearly is not always the case.^{4,5}

It has been observed that both protein and fat digestibility decrease in many apparently normal cats after 10 years of age. While the cause of the decreases remains unclear, the changes are quite marked in some individuals and can be particularly dramatic with regard to fat digestibility.^{4,5} Often these changes are not readily apparent from casual observation of feces and may only be verified if fecal fat content is quantified by appropriate analytic testing. Methods for such testing are rarely available for evaluation of veterinary patients, even at referral centers.

Whatever the explanation for weight loss and decline in nutrient digestibility in older cats, progressive decline in body weight has been reported in the two years prior to death. As cats live increasingly longer lives and receive attentive

health care, this weight loss is more frequently recognized. It is often associated with a variety of seemingly unrelated diseases or laboratory abnormalities and an obvious explanation remains elusive. This article reviews what is known about common age-related changes and what may be done to halt or reverse the decline in body weight that is apparently a predictable prelude to death.^{3:4,6}

Attributable Weight Loss

Well-recognized causes of weight loss in old cats include chronic renal disease, diabetes mellitus, hyperthyroidism, inflammatory bowel disease (IBD), exocrine pancreatic insufficiency, and dental problems, to name a few. Most are readily suspected and confirmed based on physical examination and routine laboratory testing. At times, selected additional testing of parameters such as serum thyroxine, trypsin-like immunoreactivity, pancreatic lipase, cobalamin, and folate, as well as orthopedic and dental radiography or gastrointestinal (GI) endoscopy and biopsy may be necessary. Despite thorough investigation, however, the underlying cause of even severe weight loss can sometimes be remarkably difficult to establish conclusively.

Unattributed Weight Loss

Subtle weight loss may not even be noted unless careful records of body weight and body condition scores are recorded over repeated veterinary examinations. Similarly, moderate increases or decreases in food or water intake will go unnoticed by many owners. Even when the most attentive owners provide the best veterinary care for their cats, a substantial proportion of senior cats will experience weight loss, despite apparently otherwise good health and no detectable change in food intake. Evidence indicates that in these older cats with no apparent classic diseases to explain the weight loss, food digestibility declines with increased age.³ There is a significant negative correlation between age and fat digestibility (Figure 1). Approximately 10 to 15% of mature cats (8 to 12 years of age) and 30% of geriatric cats (>12 years of age) have low fat digestibility. In some geriatric cats, fat digestibility was found to be as low as 30%, with large stools (not frank diarrhea) and low body weight as the only clinical signs.

There is a significant negative correlation between age and protein digestibility as well (Figure 2). Low protein digestibility also seems to affect mature and geriatric cats. Although the incidence of low protein digestibility is not as high as that of low fat digestibility, approximately 20% of cats older than 14 years of age show protein digestibility lower than 77%. The incidence of low fat and protein digestibility tends to occur in the same cats. A marked decline becomes particularly prevalent after around age 10 (Figures 1 and 2).

It is perhaps not surprising that these changes were correlated with several other measures of health or well-being, including serum tocopherol (vitamin E), cobalamin (vitamin B12), folate, skin thickness, body fat, and body condition score. Overall,





Figure 3. After 12 years of age there is a marked decline in body weight among cats. This change supplants obesity as a common life-threatening condition.³



| Table 1 Inci | idence of Feline | Obesity and | Inderweigh | nt hv Δσe ³ |
|----------------|------------------|--------------|-------------|------------------------|
| I able I. IIIC | | cobesity and | Under weigi | IL DY AGE |

| Age Group | Body Weight (kg) | Obesity Incidence | Percent Underweight Incidence |
|-----------------------|---------------------|----------------------|-------------------------------------|
| Adult (1–7 years) | 3.7 ffl 0.8 | <1% | <1% |
| Mature (7–12 years) | 4.4 ffl 1.7 | 28% | <1% |
| Geriatric (>12 years) | 2.9 ffl 1.0 | <1% | 23% |

while obesity tends to be the predominant body-mass concern in cats between 7 and 12 years of age, in those older than 12 years of age, obesity is rare, and being underweight is a far greater life-threatening risk factor (Figure 3 and Table 1).³

Nutrient Digestibility

The cause or causes of this decline in nutrient digestibility are unknown but presumably reflect an enteropathy of some type since exocrine pancreatic function is not impaired. In some cases, this intestinal dysfunction may overlap with what is commonly loosely classified as (idiopathic) IBD. However, the term idiopathic chronic enteropathy (ICE) is preferred since this is certainly a functional disorder, while morphologic changes are notoriously difficult to quantify and standardize, and may or may not be present. Some cats may compensate for the loss in digestive function by eating more and therefore exhibit no weight loss. It is important to recognize that many cats show only subtle changes in stool characteristics (slightly larger volumes of stool with a more clay-like consistency), but not frank diarrhea, even when steatorrhea is marked.

Regardless of the precise cause(s), weight loss in otherwise healthy older cats, as well as changes in fecal characteristics, should be investigated, as should potential malabsorption. Appropriate investigation methods may include thorough physical examination, routine CBC, serum biochemistry profile, urinalysis, fecal examination, and radiographic and ultrasonographic evaluations. If **Figure 4.** Compared to unaffected geriatric cats of equal age, those with poor fat digestibility due to idiopathic chronic enteropathy may exhibit a poor, unkempt-looking hair coat in addition to progressive weight loss.





nothing specific is found to explain the weight loss, then levels of serum thyroxine, feline pancreatic lipase (fPL), feline trypsin-like immunoreactivity (fTLI), and cobalamin/ folate should all be determined. It is this author's recommendation that these be determined concurrently, as studies have indicated that approximately 50% of hyperthyroid cats have evidence of concurrent intestinal and/or pancreatic abnormalities, including sometimes severe hypocobalaminemia, at the time of initial diagnosis of the endocrinopathy.^{7,8}

Furthermore, all abnormalities detected should be treated concurrently to optimize clinical response to treatment. Many hyperthyroid cats are appropriately diagnosed and treated, but GI signs — especially weight loss — persist despite return to the euthyroid state. Subsequent evaluation of GI function as outlined above then reveals evidence of enteric disease and cobalamin deficiency. Only when these abnormalities are appropriately treated do the cats return to optimal health.

The Diagnostic Process

Unless weight loss is extreme, many affected cats appear normal on physical examination apart from a poor hair coat and unkempt appearance in some cases (Figure 4). Determination of fecal fat (by percentage) would be desirable and may be the only way to confirm an intestinal problem in some patients. Fecal fat greater than 20% would be indicative of fat malabsorption. Unfortunately, such a test is not commercially available for pet cats. It has been reported that 100% of cats older than 7 years of age with serum tocopherol less than 5 mg/L also have low fat digestibility and that more than 90% of cats with serum cobalamin less than 100 ng/L have low fat digestibility.³ Finding such low serum concentrations of either cobalamin or tocopherol can be the basis of inferring that a cat has low fat (and probably protein) digestibility.³

An immunoassay for fecal feline α_1 -proteinase inhibitor (which was available from the GI Laboratory at Texas A&M University until recently) showed increased results in 73% (11 of 15) of relatively mildly affected cats with early disease, indicating the presence of a component of protein-losing enteropathy in addition to malabsorption (Figure 5).^{9,10} Interestingly, only two of these cats had decreased serum albumin, and the reductions were minimal; none had hypoalbuminemia and hypoglobulinemia. However, this enteric protein loss will certainly exacerbate the effects of decreased protein digestibility over time and contribute to gradual depletion of lean body mass.

Recent studies have also revealed the importance of the intestinal microflora in the cobalamin malabsorption that is so common in older cats. In 46 cats examined, serum cobalamin concentration was significantly correlated with the fecal microflora, with 12 species being positively correlated with serum cobalamin and seven species being negatively correlated.^{11,12} An additional study evaluated the effective-ness of high dose oral cobalamin supplementation of 13 cats with idiopathic chronic enteropathy, as well as the

Figure 5. Fecal alpha1-proteinase inhibitor ($f\alpha$ 1-PI) concentration was increased in 11 of 15 geriatric cats with idiopathic chronic enteropathy, indicating active protein-losing enteropathy in addition to the previously-recognized nutrient malabsorption. The shaded area indicates the reference range of $f\alpha$ 1-PI concentration in healthy cats.





longevity of normal serum cobalamin concentration after withdrawal of oral supplementation. There were clear and significant differences between the fecal microflora of cats with "good" cobalamin status that responded well to oral supplementation and cats with "poor" cobalamin status that did not.^{11,12} One of the latter cats developed undetectable serum cobalamin concentrations within one month of cessation of oral supplementation, while five cats had subnormal serum cobalamin within three months of cessation of supplementation (Figure 6).¹²

Finally, it should be noted that almost 90% of cats with ICE have some pancreatic involvement as reflected in increased serum fTLI and/or pancreatic lipase (Spec fPL®). These increases can be substantial in some patients (Figure 7). Given the superior sensitivity and specificity of these markers for pancreatic abnormalities compared to that of cobalamin and folate for small intestinal dysfunction, it is likely that some older cats with chronic elevations of pancreatic marker enzymes have a concurrent enteropathy that is not yet sufficiently severe or chronic to have caused changes in serum cobalamin or folate.

Figure 7. Pancreatic pathology is also present in a high proportion of geriatric cats with idiopathic chronic enteropathy, as reflected in increased serum concentrations of trypsin-like immunoreactivity (fTL1) and pancreatic lipase (Spec fPL[®]). The shaded areas indicate the reference ranges for each enzyme in healthy cats. Only 2 of 15 affected cats had normal values for both enzymes.



The genesis of the increases in serum pancreatic marker enzymes in these cats is not clear, but unlike the case with cobalamin our investigations have revealed little evidence of direct associations with the fecal microbiome. Utilization of metabolomic technology has indicated that several metabolites are associated with either fTLI or fPL, but of 89 associated metabolites only three were common to both marker enzymes. Most notably there were highly significant associations between increases in some serum bile acids, decreases in some serum amino acids and serum fPL.¹³

In any case, although it is not possible to differentiate the relative clinical importance of the concurrent pancreatic and intestinal abnormalities in affected cats, it is important to avoid overestimating the significance of sometimes dramatically increased pancreatic marker concentrations compared to sometimes mild-to-moderate decreased concentrations of serum cobalamin or folate; the latter abnormalities only develop secondary to severe and chronic malabsorption, whereas it is now well-established that pancreatitis, especially when chronic, can be clinically silent.

In the future, assay of enteric inflammatory markers such as fecal calprotectin might prove useful in confirming the presence of enteric disease, but the relationship of inflammation to this enteropathy currently is uncertain. Even histologic examination of intestinal biopsy specimens may not provide evidence of a conclusive diagnosis; lesions may be patchy and interpretation of biopsy findings is inherently subjective. It also is increasingly clear that in cats, as in dogs, functional problems in the intestine may not be associated with either inflammation or villous atrophy, but rather with intraluminal microbial changes and biochemical derangements in the enterocytes lining the small intestine that are not revealed by classic histologic evaluation.

Treatment

While evidence for the presence of ICE can often be obtained by the approach outlined above, in some cats despite the most thorough investigation a conclusive diagnosis is not possible, and a presumptive diagnosis of idiopathic enteropathy is the best that can be achieved. Currently, the approach to management of cats with a presumptive diagnosis is the same as those with either histolocially or functionally confirmed ICE, that is dietary change (low-carbohydrate, alternative fiber source, hydrolzyed, or novel antigen diet)), prebiotic or probiotic supplementation, correction of low serum cobalamin/ folate concentrations, supplementation with vitamin E and perhaps other antioxidants, antibiotic treatment with metronidazole or tylosin (both often impractical in cats), and perhaps glucocorticoid therapy or immunomodulation with chlorambucil or cyclosporine (Table 2).¹⁴ However, in the absence of specific laboratory abnormalities or overt clinical signs to monitor other than perhaps very slowly

| Table 2. Treatment Options for Cats with Idiopathic Interopathy | | | | |
|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|--|--|--|
| Management Approach | Suggestions | | | |
| Dietary change | Low carbohydrate Hydrolyzed diet Alternative fiber source Novel antigen | | | |
| Supplementation (May be accomplished by dietary change) | Prebiotic Probiotic Vitamin E and other antioxidants | | | |
| Correction of low serum cobalamin/folate/ tocopherol concentrations | Specific parenteral or oral supplementation as appropriate | | | |
| Antibiotic treatment | Metronidazole Tylosin (Both often impractical in cats and not recommended) | | | |
| Enhance enterocyte function | Glucocorticoid (prednisolone) | | | |
| Immunosuppression | Chlorambucil, cyclosporine, other | | | |
| Treat Pancreatitis | Analgesics (buprenorphine), antiemetics (maropitant) and appetite stimulants (mirtazapine) | | | |

progressive weight loss, it is probably premature to recommend particularly aggressive treatment for these patients and a cautious, conservative approach is warranted.

As many of the observations about digestive disturbances in elderly cats are relatively new, appropriate clinical studies evaluating treatment interventions have not been performed. Dietary changes and supplements would certainly be the safest and most easily administered interventions. When specific nutrient abnormalities such as hypocobalaminemia are identified, they should be rectified. It is now clear that abnormalities in cobalamin metabolism can vary substantially between cats and that supplementation may need to be more aggressive in some individuals to maintain normal serum concentrations. Following cessation of cobalamin supplementation in five cats with idiopathic chronic enteropathy, serum cobalamin concentration fell below normal within three months and was undetectable in one cat within one month.^{11,12} Lifelong supplementation is therefore required and periodic monitoring is recommended so that supplementation can be modified as needed. Daily oral supplementation is likely to be effective and can be utilized as an alternative to parenteral (subcutaneous) administration when tolerated.15

The effect of dietary changes has to be evaluated on an individual trial-and-error basis, which can be difficult if gradual weight loss is the only clinical sign to evaluate. Observing improvements in the newer GI disease markers such as fecal α 1-proteinase inhibitor, should they become readily available, may provide objective evidence of a positive response, but the value of this approach remains to be evaluated.

Careful observation of stool characteristics may provide some evidence of improved digestibility, especially if grossly apparent abnormalities are present at the outset. If there is no apparent response to dietary change after two to four weeks, an alternative diet should be tried. This author prefers to select diet changes based on reduced carbohydrate content (generally associated with increased protein content) and/or different amounts or types of fermentable fiber. Adjusting the fat content of the diet does not appear to be particularly useful in treating feline enteropathies. Unfortunately, definitive studies in geriatric cats with malabsorption have not been done. Treatment needs to be individualized and evaluated on a trial-and-error basis.

With regard to older cats in general, evidence suggests that diet can play a role in maintaining body weight and fat mass — and prolonging life. A control diet (nutritionally complete and balanced adult cat food) supplemented with antioxidants (vitamin E and β -carotene), a blend of n-3 and n-6 fatty acids, and a prebiotic (dried chicory root) was associated with reduced decline in body weight and increased longevity (by more than one year) compared with feeding the control diet alone or the control diet supplemented with antioxidants alone.^{6,16} These striking observations illustrate the potential benefit to be gained from dietary and other interventions to address the gastrointestinal changes that appear to be so common in aging cats.

References

1. Pittari J, Rodan I, Beekman G, et al. American Association of Feline Practitioners. Senior Care Guidelines. *J Feline Med Surg.* 2009;11:763-778.

2. Caney S. Weight Loss in the Elderly Cat. Appetite Is Fine, and Everything Looks Normal ... *J Feline Med Surg*. 2009;11:738-746.

3. Patil AR, Cupp CJ. Addressing Age-Related Changes in Feline Digestion. *Proc Companion Anim Nutr Summit*. Focus Gastroenterology. Nestlé Purina PetCare. 2010;55-61. 4. Taylor EJ, Adams C, Neville R. Some Nutritional Aspects of Aging Cats and Dogs. *Proc Nutr Soc*. 1995;54:645-656.

5. Fahey GC, Barry KA, Swanson KS. Age-Related Changes in Nutrient Utilization by Companion Animals. *Annu Rev Nutr*. 2008;28:425-445.

6. Cupp CJ, Kerr WW. Effect of Diet and Body Composition on Life Span in Aging Cats. *Proc Companion Anim Nutr Summit*. Focus Gastroenterology. Nestlé Purina PetCare. 2010;36-42.

7. Steiner JM, Peterson MA, Ruaux CG, et al. Serum Cobalamin and Folate Concentrations in Cats with Hyperthyroidism. *J Vet Intern Med.* 2005;19:474-475.

8. Cook AK, Suchodolski JS, Steiner JM, Robertson JE. The Prevalence of Hypocobalaminaemia in Cats with Spontaneous Hyperthyroidism. *J Small Anim Pract*. 2011;52:101-106.

9. Burke KF, Broussard JD, Craig G, et al. Evaluation of Fecal α 1-Proteinase Inhibitor Concentrations in Cats with Idiopathic Inflammatory Bowel Disease and Cats with Gastrointestinal Neoplasia. *Vet J.* 2013;196:189-196

10. Williams DA, Czarnecki-Maulden G. Protein-Losing Enteropathy Commonly Co-Exists with High Fecal Fat Output in Geriatric Cats with Idiopathic Malabsorption and Persists Following Correction of Subnormal Serum Cobalamin Concentration. *J Vet Intern Med.* 2014;28:740. 11. Williams DA, Czarnecki-Maulden G. Oral Cobalamin Supplementation Effectively Raises Serum Cobalamin Concentration in Geriatric Cats with Idiopathic Malabsorption, but Concentrations Decrease Rapidly Following Cessation of Supplementation. *J Vet Intern Med.* 2015;29:436.

12. Williams DA, Mazunon M, Ramadan Z, Czarnecki-Maulden G. Serum Cobalamin Concentration in Geriatric Cats and Response to Oral Cobalamin Supplementation Is Associated with Differences in the Composition of the Fecal Microbiome. *J Vet Intern Med.* 2016;32:359.

13. Williams DA, Manuzon M, Ramadan Z, Czarnecki-Maulden G. Microbiomic and Metabolomic Associations with Increased Serum Pancreaticlipase (fPL) and Trypsin-Like Immunoreactivity (fTLI) in Geriatric Cats with Idiopathic Chronic Enteropathy (ICE). *J Vet Intern Med*. 2017;31:225.

14. Webb CB. Feline Inflammatory Bowel Disease. *Clinician's Brief*. 2012;10:11-14.

15. Toresson L, Steiner JM, Olmedal G, et al. Oral Cobalamin Supplementation in Cats with Hypocobalaminemia: A Retrospective Study. *J Feline Med Surg.* 2017;19:1302-1306.

16. Cupp CJ, Clementine J-P, Kerr WW, et al. Effect of Nutritional Interventions on Longevity of Senior Cats. *Int J Appl Res Vet M*. 2006;4(11)34-50.