Received: 7 May 2019 | Accepted: 7 May 2019

DOI: 10.1111/jvim.15523

LETTER TO THE EDITOR

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Response to letter to editor regarding Results of histopathology, immunohistochemistry, and molecular clonality testing of small intestinal biopsy specimens from clinically healthy client-owned cats

Dear Dr DiBartola and Dr Hinchcliff,

Thank you for the opportunity to respond to the letter from Dr Norsworthy regarding our recent publication "Results of histopathology, immunohistochemistry, and molecular clonality testing of small intestinal biopsy specimens from clinically healthy client-owned cats." We are grateful for Dr Norsworthy's comments and insights on this article.

We fully support Dr Norsworthy's opinion that chronic enteropathy in cats is very common and should receive more attention. Feline medicine, especially feline chronic enteropathy (FCE), has long been consigned to the shadow of canine medicine. Therefore, discussions on this disorder are imperative to trigger more research efforts and increase our understanding of FCE, and we are thankful for Dr Norsworthy's numerous contributions to the initiation of this overdue discourse.

Dr Norsworthy commented on our inclusion of cats with vomiting up to twice a month. We agree that chronic gastrointestinal disease could not be entirely excluded in some of our patients, as pointed out in our discussion. We also concur with Dr Norsworthy's argument that an abdominal ultrasound would have been an asset to this study. However, in our opinion, occasional vomiting in cats or the incidental finding of increased intestinal wall thickness on abdominal ultrasound do not necessarily require rigorous diagnosis, treatment, and follow-up.

Overdiagnosis and overmedicalization ("too much" health care) is becoming a significant concern in human medicine, especially in the field of cancer screening.[1,2] The US Preventive Services Task Force recently released multiple statements and reviews on the topics of overdiagnosis, overdefinition, overuse of diagnostic procedures, and overtreatment.

Overdiagnosis is defined as the identification of an abnormality where detection will not benefit the patient.[3] Overdefinition refers to the lowering of a threshold for a risk factor without evidence that doing so helps patients feel better or live longer or to the expansion of disease definitions to include patients with ambiguous or very mild clinical signs.[4] Overdiagnosis results in overuse of diagnostic procedures and overtreatment.[3] Overdiagnosis is present when an increased disease incidence coincides with an unchanged morbidity and mortality (ie, outcome).

The authors concur that some owners and even veterinarians are unaware of the clinical signs of FCE, especially if these are subtle or slowly progressive over a long period of time. Therefore, we followed our patients over a substantial period of time to document the outcome of the cats in our study with findings considered abnormal based on histopathology, immunohistochemistry, clonality testing, or some combination of these.

In our study, data on the outcome was available on all 20 of the cats. At enrollment, only 4/20 cats showed occasional vomiting (supplemental table 1); 2 of these were diagnosed with small cell lymphoma based on histopathology and were eventually euthanized because of progressive signs of FCE at 654 and 295 days post endoscopy, respectively. We agree with Dr Norsworthy that in some cases occasional vomiting can be an early sign of FCE and should be monitored very closely. However, the other 2 cats with occasional vomiting at the time of inclusion were diagnosed with moderate lymphoplasmacytic enteritis (LPE) or minimal to mild LPE, respectively, and remained clinically unchanged for follow-up periods of 869 and 837 days. Thus, in our opinion, classifying cats such as these 2 as "ill" would fulfill the criteria for overdefinition and overdiagnosis, potentially leading to unnecessary and potentially harmful procedures and treatments, as well as unnecessary expense and emotional distress to the owners. In addition, 16 cats with no clinical signs of FCE at enrollment were found to have histopathologic changes (3 cats had minimal to mild LPE, 4 cats had mild LPE, 6 cats had mild to moderate LPE, and 3 cats had moderate LPE). Of those, only 1 developed signs of FCE 544 days post endoscopy and was previously diagnosed with mild LPE. Thus, our study demonstrates that the finding of histopathologic changes does not allow inference about clinical illness. Educating owners about clinical signs of FCE and sensitizing veterinarians for the differences in the phenotype of canine and FCE will clearly benefit our feline patients. However, in the author's opinion, overmedicalization will not.

Dr Norsworthy also commented on the limitations of endoscopic biopsies for the diagnosis of small intestinal diseases in cats. The authors agree that every diagnostic test has advantages and disadvantages. One disadvantage of endoscopic biopsies is that they are limited to the mucosa and occasionally submucosa, that there is a limited

range for the endoscope (ie, jejunal lesions or localized lesions), and that extramural lesions cannot be biopsied. However, we would disagree with the statement that endoscopic access is usually limited to just 2.5 cm of the duodenum or ileum. With appropriate endoscopic equipment and expertise, an endoscope can commonly be advanced well into the duodenum, sometimes reaching the proximal jejunum.[5] Current guidelines recommend to collect a minimum of 6 adequate mucosal biopsies from the feline duodenum and 3-5 from the ileum for a reliable histopathological assessment.[6] Therefore, adequate endoscopic biopsies can provide a minimally invasive method to acquire substantial data representative of a large portion of the small intestinal mucosa. In contrast, surgical biopsies, even if taken from every section of the small intestines (ie, the duodenum, jejunum, and ileum), represent only a single site within each section. A recent, yet unpublished, study at the Gastrointestinal Laboratory at Texas A&M University revealed that the diagnostically available mucosal surface can be substantially decreased in full-thickness compared to endoscopic biopsies because of the number of specimens available. The overwhelming majority of diffuse small intestinal lesions starts in or involves the mucosa, and thus can be detected on adequate endoscopic biopsies. Thus, full-thickness biopsies are, in our opinion, unnecessary in most patients with diffuse disease involving the duodenum and ileum.

In summary, we agree with Dr Norsworthy that FCE is an important disorder with increasing prevalence and a substantial need for further research efforts. However, results of histopathology and clonality assays should be interpreted carefully and only in conjunction with other patient data. Our study shows that, similarly to humans, even high-quality laboratories, such as the one used in our study, experience difficulties with the specificity of clonality assays as a laboratory-independent issue. A recent study in human patients with lymphoproliferative disease found a specificity of T-cell receptor clonality assay of 54.3% using the highly standardized BIOMED-2 clonality assay.[7] Thus, reclassification of patients based on clonality tests alone is not recommended in humans. Being aware of limitations and pitfalls of currently available diagnostic methods or disease definitions is essential. In both veterinary and human medicine, overmedicalization and the overuse or misinterpretation of diagnostic tests must be avoided if we are to provide the best possible outcomes for patients.

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