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Diagnostic Dilemmas and Failed Therapies

Learning Objectives

1. None of us are perfect.

2. All of us face challenges and make mistakes.

3. All of us can learn from those challenges and those mistakes.

Introduction

If our patients read textbooks our job would be much easier. If our patients came to us with Presenting Complaints such as “lymphangiectasia”, or “low-grade alimentary lymphoma” our job would be much easier. If our patients restricted themselves to one disease at a time, our job would be much easier. If our patients segregated themselves such that the positive predictive value of our diagnostic tests were through the roof, our job would be much easier. And if our prescribed therapy never failed, our job would be much easier. Our job is not very easy. I have learned (or been forced) to embrace the importance of diagnostic dilemmas and developing some form of organized approach to evaluating my therapeutic failures. If nothing else, I have gained a deep appreciation for the connection between diagnostic dilemmas and failed therapy.

The Appointment

When a client pays for an appointment they are paying for the clinical expertise of the veterinarian (well, that and the electricity, the receptionist’s salary, the mortgage on the building, etc.). The clinical expertise of the veterinarian has a profound impact on how much more the client will pay on diagnostic testing, how effectively and efficiently a diagnosis is identified, and the likelihood the patient leaves the appointment with the correct diagnosis and the appropriate treatment. But even the best clinicians encounter diagnostic dilemmas where the presenting complaint or the clinical signs scream for one diagnosis while much softer signs suggest an alternative interpretation. The gastrointestinal tract offers a number of interesting examples to consider. The gastrointestinal tract also highlights the concept that failed therapy does not mean failure. Instead, failed therapy often represents an important diagnostic clue and if considered thoughtfully, will likely have a significant and beneficial impact on case management.

Basic Principles

- Verify the Problem: Define the Problem
- Signalment, Presenting Complaint, History, Physical Examination
- Diagnostic tests are only as good as you are
- Treatment: Know your drugs before you use them
- Cats are not Small Dogs
- Cats and Concurrent Diseases go together

Understanding Cognitive Medical Errors

A cognitive error is defined as an error in clinical reasoning due to lack of or erroneous knowledge, data gathering, or synthesis (Canfield et al. JFMS, 18:240-247, 2016).

Bias, in its many forms, is the factor that most often contributes to cognitive errors. The following table of common biases and their relationship to cognitive error is adapted from Canfield et al. JFMS, 2016, Table 1 (with permission).

Confirmation bias: tendency to search for, interpret, focus on and remember information in a way that confirms one's preconceptions about a case

Anchoring bias: tendency to rely too heavily on one trait or piece of information

Gambler's fallacy: tendency to think that the probability of a cat having a particular diagnosis or prognosis is influenced by preceding but independent cases.

Availability bias: tendency to overestimate the likelihood of events that have a greater 'availability' in memory.

Feedback bias: tendency to interpret no feedback on a case as positive feedback.

Overconfidence bias: Confident diagnosis based on a belief of infallibility.

Omission bias: tendency towards diagnostic "inaction" because of lack of confidence or fear for owner consequences if diagnosis is serious or terminal illness.

Hindsight bias: false confidence in future diagnostic ability based on retrospective confirmation of correct diagnosis, i.e. ignoring the previous diagnostic challenges faced in "real time"

Visceral bias: tendency to harbor negative (or positive) feelings towards owner (or breed), which may result in a diagnosis being missed or ignored

Shared information bias: tendency for group members to spend more time discussing familiar or shared information than is spent working through information that is not shared by all group members.

It is important to take time for "metacognition": to think about how you think (Canfield & Malik, JFMS 18: 2016). This will help you to avoid, or at least better understand those times when you make cognitive errors. Canfield et al. offer the following metacognitive strategies for managing cognitive errors.

Develop an understanding of common cognitive errors (above).

Reflection, review problematic cases, personal bias, and decision-making process

Assess the Big Picture and accept uncertainty

Take time or make time for review, and objectively review results that agree, and disagree, with a presumed diagnosis.

Consider alternative diagnoses.

Acknowledge the emotional component to clinical performance.

Be openly accountable and seek constructive feedback as well as advice

Develop checklists based on difficult cases for future direction.

Case Examples

Feline Hypereosinophilic Syndrome

A syndrome that appears to be unique to the Feline, eosinophilic infiltrates are found in the intestinal tract, and the diagnosis may stop there, being deemed Eosinophilic Gastroenteritis. But in this syndrome the GI tract is just part of the pathologic picture, and eosinophils are found to be invading a number of other parencymal organs, particularly the spleen. Cats with this syndrome are usually > 7 years old and most frequently present with diarrhea (often bloody) and weight-loss. Physical examination reveals thickened small intestines, again leading the clinician to conclude that this is only a disease of the tube itself, not the rest of the animal. Peripheral eosinophilia can be seen, sometimes to a minor degree (2,000 cells/µl) and sometimes to an astonishing degree (60,000 cells/µl). The biggest dilemma is the difference in prognosis: garden-variety eosinophilic gastroenteritis should usually respond quite favorably to standard IBD treatment, while Hypereosinophilic Syndrome responds poorly to a similar protocol, and in fact, to most any protocols attempted, ie. the prognosis is quite poor for these patients.

Tritrichomonas

Dr. Jody Gookin wrote the book (or I should say published the articles) that introduced feline practitioners to Tritrichomonas, a flagellated protozoan causing large bowel diarrhea (video available online at www.jodygookin.com). It is seen most frequently in cats < 2 years of age, often coming from shelters, catteries, or multi-cat households. Clinical signs include chronic waxing & waning malodorous large bowel diarrhea, or the kittens (and older cats) may be asymptomatic. The stool is semi-formed to liquid or cow patty, containing mucus and fresh blood, accompanied by flatulence. The kitten often strains to defecate (tenesmus) frequently enough to develop perianal inflammation, but is otherwise in good body condition with a normal appetite. The only dewormer demonstrating efficacy is Ronidazole (30 mg/kg PO q24hr 14d, potential neurotoxicity), although Dr. Gookin now reports strains that are resistant to this attempt!

Food Responsive Diarrhea

The terminology in veterinary medicine is evolving and it is now common place for clinicians to refer to “Food Responsive Diarrhea.” This term is able to encompass the classic food allergy and food intolerance while taking into account the observation that some cats will respond well to diets that are not actually designed to target a disease! A number of research efforts and publications over the last 10 years or so have highlighted the importance of early dietary intervention in cases of feline chronic diarrhea and vomiting. One of the most clinically significant findings of that research is that unlike a dermatologist, a gastroenterologist only needs about 2 weeks to determine if a diet trial has had an effect (8-12 for the dermatologist). So we can (and probably should) get the owner on board for attempting several food trials before we give up on seeing a beneficial effect, because it also appears that individual cats can respond to very specific diets; what diet works for one may not work for another, and visa-versa. The list of potentially beneficial diets is also expanding just about as fast as the pet food companies can produce them; hypoallergenic, hydrolyzed, no-grain, highly digestible, canned or dry, high protein-low carbohydrate, gluten free, lactose free, preservative free, etc. Dietary intervention can also include dietary supplementation, another list that is fast outpacing the research available to

support its use – but including cobalamin, liquid “toppings” of vitamins and micronutrients, fiber, omega-3 fatty acids, antioxidants, prebiotics, probiotics, etc.

Inflammatory Bowel Disease

Signalment, History, Physical Examination An Effective Diagnostic Pathway is Dictated by a Sound Clinical Diagnosis The Use and Timing of Therapeutic Trials is Guided by the Severity of the Condition (dose recommendations can be highly variable; check current formulary)
Fecal centrifugation flotation and wet mount
Giardia/Cryptosporidium IFA or *Giardia* ELISA
Tritrichomonas foetus PCR or InPouch culture
Tritrichomonas: Ronidazole 30mg/kg q24hr 2 wks
Empirical Deworming, Broad-spectrum anthelmintic (Fenbendazole 50mg/kg/day, 5 d)
Food Responsive Diarrhea: Diet Trial 2-3 weeks per dietary intervention Hypoallergenic/hydrolyzed, Easily Digestible, Low Fat, Hi Fiber
Biochemical profile (fasted), CBC, Urinalysis, FeLV/FIV, TT4 if appropriate
2^{o} GI Causes of Diarrhea/Vomiting: Examples
TX A&M GI Panel (fasted and species specific): TLI, PLI, Folate, Cobalamin
Imaging: Abdominal radiography (+/- air or contrast), Ultrasound
Ultrasound-guided Fine Needle Aspirate: low morbidity, low yield
Ultrasound Guidance: Infiltrative disease – Inflammatory vs. Neoplastic
Histopathology: Endoscopy (mucosal) vs. Surgical/Laparoscopy (full-thickness)
H&E stain, Giemsa, Gram, acid-fast, GMS, PAS, Warthin-Starry stains
IHC, FISH, PCR, PARR
Idiopathic Inflammatory Bowel Disease
Dietary Intervention: Hypoallergenic or Hydrolyzed
Cobalamin Inj & Oral available
+/-Antibiotics: Tylosin# 10 mg/kg q24hr (bitter, may cause Dysbiosis) Metronidazole* 10 mg/kg q12hr (bitter, may cause Dysbiosis)
Prednisolone 1-2mg/kg BID, taper per clinical signs & side-effects
OR Budesonide 1 mg/cat/day, then taper
Poorly Responsive IBD OR GI Lymphoma
Chlorambucil 2mg total/cat q4d If cat < 2kg, 2mg total/cat q1wk

Additional Therapies to Consider as Warranted
E-tube placement, Probiotics, unflavored Psylliuim, canned Pumpkin
Mirtazapine 15mg tab, 1/8 tab q24hr (q48hr in CKD)
Cerenia 1.0 mg/kg/day (reduce with liver failure) May be given for > 5 consecutive days

Motility Disorders

Motility disorders may be famous enough to warrant their own name, as in Feline Megacolon, but otherwise are often a secondary complication of the more standard enteropathies, or even non-GI systemic disease. Barium and BIPS are messy and variable, leaving us with few diagnostic options when trying to identify motility disorders. Our therapeutic options are also limited, often non-specific, and all too frequently, quite non-satisfactory. It is important to remember that likely the ideal way to induce normal gastric motility in an abnormal animal (diseased or recovering) is eating!

Drug	Dose	Comment
Metoclopramide	0.2-0.2 mg/kg TID-QID	Efficacy in Question
Cisapride	1.25 – 5.0 mg/cat TID	Compounding Pharmacy
Ranitidine	1-2 mg/kg PO BID-TID	Stim feline colonic activity
Lactulose	2-3 ml PO TID	Go-To standard
Psyllium	1-4 tsp q12-24hr	Great source of fiber
Canned Pumpkin	1 tbsp BID	Not Pumpkin Pie filling
Kristalose	¼ to 1 tsp BID	Powdered lactulose
Miralax granules	¼ tsp BID	GoLytely minus electrolytes
Misoprostol	25-50 µg/day	PGE1 intestinal motility

Summary

- Recognizing cognitive errors is the first step towards correcting them.
- Exceptions, incongruities, subtle signs, and things that do not make sense are important
- Therapeutic failure may be a diagnostic opportunity

Suggested Reading (same as those featured in Diagnosing Feline GI Disease)

Margolis C, Jotkowitz A, Sitter H. A problem solving and decision making toolbox for approaching clinical problems and decisions. Inflamm Res Suppl 2:S179-183, 2004.

Cockcroft PD. Clinical reasoning and decision analysis. Vet Clin Small Anim 37:499-520, 2007.

Canfield PJ, Whitehead ML, Johnson R, et al. Case-based clinical reasoning in feline medicine: 1: Intuitive and analytical systems. J Feline Med Surg 18:35-45, 2016.

Canfield PJ, Whitehead ML, Johnson R, et al. Case-based clinical reasoning in feline medicine: 2: Managing cognitive error. J Feline Med Surg 18:240-7, 2016.

Whitehead ML, Canfield PJ, Johnson R, et al. Case-based clinical reasoning in feline medicine: 3: Use of heuristics and illness scripts. J Feline Med Surg 18:418-26, 2016.

Diagnostic Dilemma, Failed Therapy?

- Cats are not Small Dogs
- Read up on medication side-effects BEFORE you administer them
- Owner Compliance
- Partial Diagnosis
- Wrong Treatment
- Natural History of the Disease
- Concurrent Disorders