Feline Enteropathies: Advances in Diagnostic Testing and Treatment

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Outline
- Clinical signs associated with feline enteropathies
- Differential diagnoses for feline enteropathies
- Diagnostic evaluation of feline enteropathies
- Infectious enteropathies
- Inflammatory enteropathies
- Neoplastic enteropathies

Clinical History
- Common clinical signs of gastrointestinal disease in cats:
  - Vomiting
  - Diarrhea
  - Inappetence or anorexia
  - Weight loss
  - Lethargy
- Are clinical signs acute or chronic?
- If the patient has diarrhea, is it large bowel or small bowel?
  - Large bowel diarrhea: tenesmus, increased frequency of defecation, smaller volume of fecal output, hematochezia, increased urgency to defecate
  - Weight loss is not common
  - Vomiting is not common
  - Loss of appetite is not common
  - Weight loss is common
  - Vomiting is common
  - Loss of appetite or increased appetite are both possible
- Weight loss is often the ONLY clinical sign of small intestinal disease in cats!!

Acute Small Intestinal Disorders
- Differential diagnoses:
  - Dietary indiscretion
  - Intestinal parasites
  - Toxin ingestion
  - Viral infection
  - Bacterial infection
  - Intestinal obstruction
### Chronic Small Intestinal Disorders
- Differential diagnoses:
  - Intestinal parasites
  - Food responsive enteropathy
  - Inflammatory bowel disease
  - Intestinal neoplasia
  - Chronic obstruction (usually partial obstruction)
  - Bacterial infection
  - Gastrointestinal Phythiosis
  - Gastrointestinal Histoplasmosis
  - Feline infectious peritonitis (dry form)

### Acute Large Intestinal Disorders
- Differential diagnoses:
  - Dietary indiscretion
  - Intestinal parasites
  - Toxin ingestion
  - Viral infection
  - Bacterial infection

### Chronic Large Intestinal Disorders
- Differential Diagnoses
  - Intestinal parasites
  - Bacterial infection
  - Food responsive enteropathy
  - Inflammatory bowel disease
  - Colonic neoplasia
  - Feline infectious peritonitis (dry form)
  - Gastrointestinal Phythiosis
  - Gastrointestinal Histoplasmosis

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### Diagnostic Evaluation of Acute Intestinal Signs
- Diagnostic evaluation is often dependent on the severity of signs and the specific gastrointestinal signs that are present
- Rule out extra-intestinal disease
  - Complete blood count
  - Serum biochemical profile
  - Urinalysis
  - Total T4
  - Spec IPL
  - FELV/FIV
- Rule out foreign body obstruction
  - Abdominal radiographs
  - Abdominal ultrasound
- Rule out infectious disease
  - Fecal flotation
  - Fecal testing for bacterial organisms
  - Fecal testing for Trichomonas

### Diagnostic Evaluation of Chronic Intestinal Signs
- Rule out extra-intestinal diseases
  - Complete blood count
  - Serum biochemical profile
  - Urinalysis
  - Total T4
  - Spec IPL
  - FELV/FIV
FELINE ENTEROPATHIES

Diagnostic Evaluation of Chronic Intestinal Signs

- Evaluate for infectious intestinal diseases
  - Fecal flotation with centrifugation on at least 2 fecal samples
  - Fecal Giardia ELISA on at least 2 fecal samples
  - Fecal *Trichomonas* PCR
  - *Clostridium* spp., *Campylobacter* spp. testing
  - *Pythium* testing
    - Perform based on clinical suspicion
  - *Histoplasma* testing
    - Perform based on clinical suspicion

- Non-Invasive abdominal imaging
  - +/- Abdominal radiography
  - Abdominal ultrasound

- Intestinal biopsies
  - Full thickness surgical biopsies if focal disease is seen on abdominal ultrasound in a segment that cannot be accessed endoscopically, or if a mass lesion is obstructive or appears likely to become obstructive.
  - Endoscopic evaluation with biopsy if disease is considered diffuse (ie. no ultrasonographic changes or diffuse ultrasonographic changes)

- Cobalamin testing

Abdominal Ultrasound

- Normal small intestine has alternating hyperechoic and hyperechoic layers as follows (from lumen outwards): mucosa (hypo), submucosa (hyper), muscularis (hypo), serosa (hyper)
- Normal gastric and small intestinal wall thickness in cats is approximately 3.6-3.8mm.
- The mucosal layer should be the thickest layer in the small intestine
  - When the muscularis layer is as thick as, or thicker than, the mucosal layer, this is abnormal
  - The muscularis and mucosal layers are normally equal in thickness in the stomach

- Foreign body obstruction—causes moderate to marked distension of bowel loops and gastric lumen oral to the obstruction
  - Any areas of distension should be followed to assess for the presence of an obstructive lesion
  - The composition of a foreign object determines its ultrasonographic appearance
  - The majority of foreign bodies result a bright echogenic interface with marked acoustic shadowing
  - Ultrasound has been shown to be both highly sensitive and highly specific for the detection of foreign bodies, suggesting that contrast studies are not necessary in the majority of cases

- Linear foreign bodies
  - Cause severe plication of the bowel in the affected segment.
  - Echogenic linear structure is seen within the plicated segment of intestine
  - Bowel orad to the obstructed segment is dilated
  - Occasionally linear foreign bodies can result in intussusception
  - Do not confuse corrugation with plication of the bowel!

- Intussusceptions
  - When visualized in cross section, result in a "bull's eye" appearance.
  - In a longitudinal plane, an intussusception appears to be multiple bowel loop layers aligned in a parallel fashion
  - Mesenteric fat is carried with the intussusceptum, leading to the appearance of hyperechoic tissue around the intussuscepted segment of intestine
  - The bowel orad to the intussusception is typically dilated.
Abdominal Ultrasound

- Infiltrative disease
  - Differentiate focal infiltrative disease (mass) vs. diffuse infiltrative disease
  - Intestinal masses
    - A focal area of significant thickening and loss of wall layering is consistent with an intestinal mass
    - The majority of intestinal masses are neoplastic
      - Top differentials: High grade lymphosarcoma, mast cell tumor, intestinal leiomyosarcoma, leiomyoma
      - Intestinal mast cell tumor was shown to cause a non-circumferential, eccentric wall thickening in 100% of cases in one study
      - Lymphosarcoma/leiomyoma typically causes non-circumferential thickening
      - High grade lymphosarcoma and carcinoma typically cause circumferential thickening
  - Some inflammatory or infectious processes can cause intestinal mass formation
    - Feline gastrointestinal eosinophilic granulomatosis
    - Aspergillosis

- Mesenteric lymph nodes
  - May become thickened or have an alteration in their echogenicity/echotexture in response to intestinal disease
  - Nearly impossible to differentiate between reactive lymphoid hyperplasia and neoplastic infiltration on ultrasound
  - Thickening of the mesenteric lymph nodes in addition to muscularis layer thickening was associated with significantly higher odds of small cell lymphosarcoma

- Abdominal effusion
  - May occur with severe hypoalbuminemia (rare in cats with diffuse intestinal disease), intestinal perforation, or neoplastic spread to the mesentery (e.g., carcinomatosis)

Endoscopy

- Upper GI endoscopy vs. colonoscopy vs. both
  - Upper and lower GI endoscopy are recommended in any patient with mixed bowel signs or large bowel signs
  - Upper and lower GI endoscopy are recommended in patients with low cobalamint levels
  - Recent literature suggests that biopsies obtained via upper and lower GI endoscopy may provide a higher likelihood of correctly diagnosing cats with small cell lymphosarcoma than biopsies obtained via upper GI endoscopy alone
  - One study showed that endoscopic abnormalities correlate with both clinical activity and histopathologic lesions at diagnosis in cats

Intestinal Biopsies

- No correlation between clinical disease index and histologic grading of inflammatory bowel disease
- Microarchitectural changes may be more important than cellular infiltrates in assessing disease severity
- Large amount of variability between pathologists, even when new WSAVA grading scheme is used
- Use the same pathologist
Intestinal Biopsies

- Difficulties in differentiating between inflammatory bowel disease and small cell alimentary lymphosarcoma (SCLSA)
  - Overlap in histological features of inflammatory bowel disease versus small cell alimentary lymphosarcoma leads to underdiagnosis of small cell lymphosarcoma
  - Invasive or lymphocytes into the submucosa and muscularis is suggestive of SCLSA
  - However, SCLSA may be present only in the distal ileum, particularly if diagnosed early in the disease
  - This problem is the reason to use PARR and immunophenotyping

- Endoscopic vs. full thickness biopsies
  - One advantage for endoscopic biopsies obtained via upper GI endoscopy
  - The problem was noted because of IBD cats, and endoscopic examination of the duodenum was not available.
  - One study showed that endoscopic biopsies in both submucosa and muscularis (the performing-user Campylobacter and enteropathogenic) will increase diagnosis of SCLSA

Suggested diagnostic algorithm for evaluation of intestinal biopsies:

1. Hemorhorhagic: assessment
2. Immunophenotyping
3. PCR to identify clonality of infiltrating T- and B-cell populations

Cobalamin

- Cobalamin is abundantly present in commercial pet diets and is bound to protein
- After partial digestion in the stomach, cobalamin binds the R-binder protein in the stomach
- In the duodenum, the R-binder protein is digested by pancreatic derived proteases
- Cobalamin then binds intrinsic factor (produced by the pancreas) for intestinal transport
- Receptor mediated absorption in the ileum
- Causes of hypocobalaminemia:
  - Exocrine pancreatic insufficiency
  - Severe, long-standing disease of the distal small intestine
- Low cobalamin levels suggest a need to obtain samples if intestinal biopsies are abnormal
- Negative prognostic indicator
- Supplementation may improve clinical signs regardless of the underlying diagnosis

Campylobacteriosis

- Most species of Campylobacter are non-pathogenic.
- Most common species isolated in cats are C. helveticus and C. upsaliensis
- Campylobacter jejuni is the most common cause of Campylobacteriosis
  - May also be found in normal cats
  - True rate of Campylobacter in cats is difficult to determine because healthy animals have a high prevalence of Campylobacter as well
- Campylobacter cell wall, but is considered likely to be a cause of Campylobacteriosis as well
- Fecal cytology is useful because Campylobacter is not the only spiral bacteria that occurs in the GI track
- Fecal culture is considered the standard for diagnosis
- PCR is available and may have increased sensitivity compared to fecal culture
- Treatment: Benig (e.g., chloramphenicol, erythromycin, tetracycline, chloramphenicol, or second generation cephalosporins for severely clinically affected patients (diarrhea > 10 days, fever, 20,000 white cells/mm²)
- Zoonotic potential—Campylobacter is an important enteropathogen in humans, and living with a pet that has diarrhea is a known risk factor for Campylobacteriosis in humans

Clostridium difficile

- Much more commonly reported in dogs than in cats
- Infection is commonly a community associated disease rather than hospital or antimicrobial associated (as is the case in humans)
- Toxin A and Toxin B are the cause of clinical disease
  - Some strains do not have the genes to produce any toxins and are therefore non-pathogenic
  - Clinical signs are variable, ranging from mild self-limiting diarrhea to severe acute hemorrhagic gastroenteritis
  - May be present as large bowel diarrhea, small bowel diarrhea, or mixed
  - Sometimes presents as chronic diarrhea
  - Diagnosis: fecal culture (does not determine whether the strain is actually producing a toxin), ELISA for common antigen (same problem as culture), cell culture (cytotoxic assay, CTA, current gold standard), fecal toxin detection via ELISA (less sensitive in cats than in humans), PCR for toxin B genes (best used in combination with culture or ELISA for common antigen)
- Treatment: metronidazole (10 mg/kg PO BID x 5 days)
- Zoonotic potential is unclear at this time

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Polymerase Chain Reaction for Antigen Receptor Rearrangements (PARR)

- Significantly increases the diagnostic utility of small intestinal biopsies with regards to differentiating inflammatory bowel disease vs. small cell alimentary lymphosarcoma
- In one study, 29%, of cats that were diagnosed with IBD on histopathology were diagnosed with lymphosarcoma based on PARR
  - It may be that studies performed prior to PARR availability misclassified cats with small cell lymphosarcoma as having IBD
**FELINE ENTEROPATHIES**

**Clostridium perfringens**
- 5 major isolates (A-E) based on toxin production
  - Clostridium perfringens enterotoxin (CPE) and beta 2 (B2) toxin can be found in all strains
- Found in similar percentages of healthy cats vs. cats with diarrhea
- Clinical signs are most commonly large bowel diarrhea
  - Small or mixed bowel diarrhea are also possible
- Diagnosis: CPE detection in addition to fecal toxicogenic culture or PCR
- Treatment: Metronidazole, tylosin
- Zoonotic potential: Likely minimal

**Giardiasis**
- Seven different molecular subtypes have been identified, designated A-G
  - F is the subgroup seen in cats
- A and B are the subgroups seen in people
- Giardia is therefore not considered a zoonotic infection
- Direct life cycle
  - Both trophozoite and encysted form are passed in the feces
- Transmission: fecal-oral route
  - Cysts are environmentally resistant and highly infectious
- Clinical signs
  - Not all infected cats show clinical signs
  - Diarrhea may be small or large intestinal
- Diagnosis
  - Zinc sulfate flotation recommended (three specimens)
  - ELISA is not shown to be more sensitive than flotation with an adequate number of specimens
- Treatment
  - Fenbendazole 50 mg/kg PO x 3-7 days
  - Metronidazole 50 mg/kg/day x 5 days

**Salmonellosis**
- >2400 serotypes
- Prevalence in healthy dogs ad cats is similar to that observed in pets with diarrhea
- Significantly higher rates of detection in pets fed raw meat
- Exposure to Salmonella can result in colonization or infection
- Clinical signs range from mild self limiting diarrhea to severe hemorrhagic gastroenteritis with fever.
- Clinical signs may be acute (more common) or chronic
- Detection of Salmonella in the stools does not necessarily indicate disease because some patients have colonization without infection
- Detection: culture on multiple specimens. PCR (not validated, preferably performed following incubation in enrichment broth)
- Treatment: Supportive therapy, antibiotics (e.g. gentamicin, chloramphenicol), should be based on in vitro susceptibility testing (empirically use combination ampicillin and metronidazole)
- Zoonotic potential: Transmission from cats to humans has been documented

**Gastrointestinal Pythiosis**
- Chronic, invasive, life-threatening infection caused by oomycete
- Rare in cats, usually causes cutaneous lesions
- Two cases of GI pythiosis reported in cats
- Both cats had palpable abdominal masses
- Extraluminal mass involving ileum and mesentery
- Abscessed duodenal mass
- Phytophthora spp. are present worldwide in soil and aquatic habitats, most commonly in tropical and subtropical habitats
- Histology—eosinophilic and granulomatous inflammation with fibrosis
- Organisms do not typically stain with HE but appear hyphae with an eosinophilic rim
- Serology, immunohistochemistry, and PCR are available for Phytophthora
- Serology is also helpful for monitoring treatment
- Treatment: Surgical resection if possible, itraconazole and terbinafine if incompletely resected
- Differential diagnosis: coccidiosis, lagenidiosis

**Tritrichomonas foetus**
- Important cause of large bowel diarrhea in cats
- Diarrhea is often chronic
- Should not be ruled out in cats that live in single cat environments
- Should not be ruled out in older cats
  - Infection may have been acquired early in life prior to adoption
- Other clinical signs: anorexia, depression, vomiting, weight loss
- Co-infection with Giardia is common
- Transmission: Fecal-oral
- Diagnosis: Most sensitive test is Tritrichomonas foetus PCR
- Treatment: Ronidazole (50 mg/kg PO BID x 14 days)
  - 64% good response
  - 36% inadequate response or relapse shortly after completion of treatment
- Lower Ronidazole dosages are associated with relapse
- Neurotoxicity is the most commonly reported side effect of Ronidazole
- 6% of cases in one retrospective report

**Gastrointestinal Histoplasmosis**
- Caused by Histoplasma capsulatum
- Gastrointestinal Histoplasmosis is a relatively rare form of the disease
- Disseminated and respiratory forms are more common
- Most commonly diagnosed via histopathology or cytology of samples obtained from the GI tract (usually gastric or duodenal histopathology or cytology of rectal scrapings)
- Ultrasonographic findings are non-specific in the majority of cases
- Histoplasma antigen testing (serum, urine) is sensitive for the detection of Histoplasma in humans with the disseminated form of the disease
- Not well studied in cats
- Histoplasma PCR is also available, also not well validated in cats
- Many cats diagnosed with Histoplasma were FELV positive in one retrospective study of feline histoplasmosis
- Treatment: Itraconazole
- Prognosis: Guarded (55% survival to discharge in one retrospective study)
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Inflammatory Bowel Disease

- Definition: A group of poorly understood intestinal disorders that are associated with vomiting, diarrhea, and weight loss in cats
- Diagnosis is achieved via intestinal biopsies
  - Subjective analysis of numbers and types of inflammatory cells, as well as abnormalities in mucosal architecture such as crypt distortion, villous blunting/fusion, and fibrosis
  - Increased expression of MHC class II antigen by leukocytes in the lamina propria and enterocytes
  - Upregulation of pro-inflammatory and immunoregulatory cytokines

Inflammatory Bowel Disease

- Pathogenesis
  - Humans: Interplay of innate immunity receptors with intestinal microbiome commensals (Allenspach 2013)
  - Cats: imbalances detected in bacterial microbiome via molecular methods
    - The number of mucosa associated Enterobacteriaceae was significantly higher in cats with intestinal inflammation than in healthy cats
    - Enterobacteriaceae, E.coli, and Clostridium were strongly associated with changes in mucosal architecture and density of cellular infiltrates, as well as proinflammatory cytokine upregulation and clinical disease index
    - Marked difference in mucosal flora of healthy cats versus cats with intestinal disease: probes to Enterobacteriaceae, E.coli, Streptococcus, Clostridiales, and Bacteroides account for 6% of mucosal bacteria in healthy cats versus 91% in cats with intestinal disease

Inflammatory Bowel Disease

- Types of inflammatory bowel disease:
  - Lymphoplasmacytic IBD
  - Eosinophilic IBD
  - Consider parasitic and allergic causes of inflammation
  - Neutrophilic IBD
  - Consider bacterial causes of inflammation (e.g. Campylobacter, Clostridium)

Inflammatory Bowel Disease

- Treatment
  - Diet trial
    - Novel protein or hydrolyzed protein diet for 2 weeks
  - Antibiotic trial
    - Metronidazole vs. Tylosin
  - Immunosuppressive drugs in patients that are non-responsive to diet change/antibiotics or in patients that are severely affected
    - Prednisolone
    - Chlorambucil
    - Cyclosporine
  - Adjunctive therapy
    - Cobalamin supplementation—based on serum cobalamin testing
    - Probiotics

Food Responsive Enteropathy

- Clinical signs are identical to other causes of chronic enteropathy
- Patients respond to an elimination diet alone, without the addition of immunomodulatory/immunosuppressive medications
- Histopathology typically reveals mild changes
- Uncommon to have concurrent biochemical abnormalities
- May present with concurrent dermatological signs
**Feline Chronic Enteropathy Activity Index (FCEAI)**

- Used to assess clinical response to treatment in patients with chronic enteropathy (most commonly IBD or food responsive enteropathy), and to objectively assess severity of disease at the time of diagnosis
- Components of FCEAI
  - Gastrointestinal signs
    - Appetite
    - Vomiting
    - Diarrhea
    - Weight loss
  - Endoscopic lesions
  - Total protein (normal versus increased)
  - ALT/ALP enzyme activity (normal versus increased)
  - Phosphorus level (normal versus decreased)

**Feline Gastrointestinal Eosinophilic Sclerosing Fibroplasia (FGESF)**

- Nodular, non-neoplastic, fibroproliferative, eosinophil and mast cell replete inflammatory response
- Can affect any portion of the gastrointestinal tract
- Clinical signs are similar to other chronic enteropathies
- Abdominal ultrasound/surgery detect a gastrointestinal mass/masses, often leading to a presumptive diagnosis of neoplasm
- Unknown pathogenesis, one study showed the presence of intralesional bacterial (most commonly *Staphylococcus aureus*) in 56% of cases
- Treatment: Surgical resection of masses, antibiotic therapy, prednisolone
  - Treatment with prednisolone prolonged survival times in comparison to surgery and antibiotic therapy alone in one retrospective study.

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**Neoplastic enteropathies - Outline**

- Incidence, risk factors,
- History and clinical signs
- Diagnostic testing
- Review of most common neoplastic enteropathies
  - Lymphoma
  - Adenocarcinoma
  - Mast cell tumor
- **NOTE**: see last slide for abbreviations

**Neoplastic Enteropathies**

- Incidence of feline intestinal cancer = 0.4%¹
  - 20-35% of all feline alimentary tumors
  - 5-12% of all feline cancers
  - Small intestinal tumors most common
- Risk factors (increased risk)
  - >7 years old
  - Siamese breed
  - Castrated males and spayed females

**Neoplastic Enteropathies**

- Most common tumors¹
  - Lymphoma (50% of all intestinal tumors)
    - 80% small intestine
    - 20% large intestine
  - Adenocarcinoma (30% of all intestinal tumors)
    - 30% small intestines
    - 70% large intestine
    - **MOST COMMON TUMOR IN THE LARGE INTESTINES**
  - Mast cell tumor (5% of all intestinal tumors)²
    - 64% small intestine
    - 29% ileocecal junction
    - 3% colon
  - Sarcomas and others (GIST, histiocytic, carcinoid)

¹Rissetto et al. JAAHA, 2011; ²Laurenson et al. VRU, 2011.
**FELINE ENTEROPATHIES**

### Neoplastic Enteropathies

![Graph showing the duration of disease processes](image)

Rissetto et al. JAAHA, 2011.

### History and Clinical signs

- **Duration depends on disease process**
  - **Lymphoma**
    - LGAL – slow, indolent disease processes
    - IGAL/HGAL – acute onset, rapidly progressive
  - **Solid tumors**
    - Slow vs. fast growing \(\rightarrow\) obstruction
    - Metastatic disease present

- **Type of symptoms may depend on location**
  - **Proximal (small intestinal) lesions**
    - Vomiting
    - Weight loss
    - Small bowel diarrhea
    - Anorexia
    - Malaise
    - Lethargy
  - **Distal (large intestinal) lesions**
    - Large bowel diarrhea
    - Tenesmus
    - Can see vomiting (with obstruction)
    - Weight loss, anorexia, lethargy can also be seen but much less common

- **Physical Exam**
  - Dehydration
  - Unkempt hair coat
  - Palpable abdominal mass
    - 50% of cats with nonlymphomatous tumors
    - 85% of cats with LSA
  - Thickened intestines
  - Pale mucous membranes
  - Mass and/or bleeding on rectal exam

- **Clinical pathology**
  - **CBC**
    - Anemia: Bleeding mass, Anemia of inflammatory disease
    - Neutrophilic leukocytosis
    - Eosinophilia (lymphoma or MCT)
    - Lymphocytosis
      - most common with LGLL
    - Thrombocytopenia
      - Consumption if bleeding
      - Primary bone marrow involvement (lymphoma)
  - **Chemistry panel**
    - Hypoproteinemia
    - Azotemia
      - Dehydration or CKD
      - Elevated liver enzymes
    - Elevated BUN with intestinal bleeding
    - Hyper or hypoglycemia
  - **Urinalysis**
    - Non-specific findings
  - **Cobalamin (Vitamin B12) level**
    - Binds intrinsic factor (pancreas) \(\rightarrow\) absorption in the ileum
    - Any issue with this process can cause low cobalamin levels
    - If suspect intestinal disease, sampling the ileum may be warranted
    - Marker of GI disease but does not differentiate between disease processes
      - Low - detected in up to 80% of cats with LGAL and is negative prognostic indicator
      - High - reported in some patients (not supplemented) with LSA or liver disease
  - **Folate**
    - Marker of proximal intestinal disease
    - Low in 4% and high in 37% of cats with LGAL

**Imaging - Radiography**

- Abdominal radiographs
  - GI mass(es)
  - Obstructive pattern
  - Loss of serosal detail
  - Enlargement of other organs
  - MAY indicate metastasis, ASPIRATE FOR CONFIRMATION!!!
- Thoracic radiographs
  - 3-view - assess for intrathoracic involvement
  - Mediastinal mass/enlarged lymph nodes
  - Pulmonary nodules
  - Diffuse pulmonary infiltrates
  - Pleural effusion

**Imaging - Abdominal Ultrasound**

- Ultrasound more sensitive than radiography
- Non-invasive method of tumor localization
  - Diffusely thickened intestines
  - Loss of normal wall layering
  - Intestinal mass(es) or focal thickening
  - Is this a surgical candidate?
- Metastatic disease
  - Enlarged lymph nodes
  - Peritoneal effusion (ie carcinomatosis, lymphoma, MCT)
  - Nodules/change in echotexture of other organs
  - Guidance for fine needle aspiration or tru-cut biopsy

**Imaging - Abdominal Ultrasound Specific findings**

- **Lymphoma**
  - IGAL/HGAL
    - Hypoechoic mass
    - Transmural thickening with loss of wall layering
    - Usually affects small to medium-sized intestines
    - MCT and AML usually symmetrical or eccentric
    - Often extra-intestinal involvement
    - May see abdominal effusion
  - LGAL
    - Thickening of muscularis layer, less commonly mass effect
    - Usually preservation of wall thickening
    - May be eccentric
    - Mesenteric lymph node enlargement common
  - LSA vs. IBD
    - Cats with LSA more likely to have thickening of muscularis propria compared to cats with IBD
    - Cats with LSA were NOT more likely to have lymphadenopathy as compared to IBD

- **Adenocarcinoma**
  - Usually mixed echogenicity and asymmetrical
  - May see abdominal effusion (carcinomatosis)
  - Enlarged mesenteric lymph nodes
  - Bright mesentery
  - Mast cell tumor
    - > 21% more than one tumor
    - 7% diffuse thickening of SI (no mass)
  - Of the focal tumors
    - 56% noncircumferential and eccentric
    - 38% circumferential and eccentric
    - 6% nodular/multifocal and luminal
    - Muscularis propria most commonly affected
    - Most focal lesions were hypoechoic

**Cytology**

- Cytology
  - Obtained via ultrasound guided fine needle aspiration
  - Very low risk of complications (no clinically significant complications in one study)
  - 89% agreement between diagnosis of inflammation vs. neoplasia when compared to histopathology
  - 89% sensitivity, 100% specificity
  - 100% PPV, 56% NPV
Histopathology
- Evaluation of cells in context of tissue architecture
  - Aids in obtaining definitive diagnosis = GOLD STANDARD
  - Can distinguish between:
    • Inflammatory vs. neoplastic
    • Benign vs. malignant
  - Important for grading various tumor types
    • Cannot get this information from cytology
  - May help determine diagnosis in ambiguous cases

Histopathology
- Tru-cut biopsies
  - Risky due to possibility of perforation!
- Endoscopic biopsies
  - May not be useful for solid tumors
  - May misdiagnose LSA as IBD (see Dr. Morgan’s slides)
- Exploratory laparotomy
  - Allows full thickness biopsies of multiple sites
  - Best when only one mass is detected → can acquire diagnosis and treat with one procedure

Advanced Diagnostics
- Immunohistochemistry
- PARR
- Others
  - Flow cytometry
  - Immunocytochemistry

Immunohistochemistry
- Detection of cell markers in tissue sections by utilization of specific antibodies
  - Aids in diagnosis with ambiguous cases
    • IBD vs. LSA → uniform cell population with LSA
    • Determine tissue of origin
      - Cytokeratin → epithelial cell (carcinoma)
      - Vimentin → mesenchymal cell (sarcoma)
    • “Round cell tumor” or “discrete cell neoplasia”
      - CD3 → T-cell lymphoma
      - CD79a, CD20 → B-cell lymphoma
      - CD1, CD18 → histiocytic disease
      - CD117 (c-kit), toluidine blue → mast cell tumor
  - Determination of immunophenotype for lymphoma

PARR
- Molecular diagnostic test used to diagnose LSA
- Detects clonally expanded population of lymphocytes
- Immunophenotyping (B- vs. T-cell)
  • Cross rearrangements (clonal rearrangement of IGH gene) reported in up to 9% of cases of low grade T-cell lymphoma
- Sensitivity and specificity
  - T-cell
    • Sensitivity = 78-90% (90% if oligoclonal cases included)
    • Specificity = 100%
  - B-cell
    • Sensitivity = 68-70%
    • Specificity = 100%

Alimentary Lymphoma
- Most common anatomical form (>50% of all LSAs)
- Not commonly associated with FIV/FelV
- Immunophenotype alone not prognostic indicator
- Classification of intestinal lymphoma
  - Based on mitotic index
    • Small cell/low grade (LGAL)
    • Intermediate cell grade (IGAL)
    • Large cell/high grade (HGAL)
  - Large granular lymphocyte lymphoma (LGLL)
    • Important differences
      • Clinical signs, techniques required for diagnosis, treatment, and prognosis
**Alimentary Lymphoma**

- **LGAL** – behavior and diagnostic considerations
  - Relatively indolent with slow progression of disease
  - Tends to be diffuse or multifocal\(^1,2\)
    - Jejunal and ileal involvement in >90% of cases
    - Duodenal involvement in >70% of cases
  - >90% T-cell with 60% showing epitheliotropism\(^3\)
  - More difficult to diagnose with cytology
  - Lymphocytic infiltration (cells are small and well-differentiated)
  - Best diagnosed with a combination of histopathology, IHC and PARR to distinguish from IBD
    - Tissue evaluated for specific patterns of epitheliotropism, lymphocytic infiltrate into deep mucosa, severe disruption of villous and crypt architectures, and intraepithelial invasion.

- **I/HGAL** – behavior and diagnostic considerations
  - Acute onset, rapid clinical course
  - Tends to be mass-lesions present (multifocal) with extra-intestinal involvement
  - Can be T- or B-cell (30-50% T-cell)\(^1,2\)
  - Not prognostic for outcome (different than canines)
  - Generally easy to diagnose with cytology

**Alimentary Lymphoma**

- **LGAL – Treatment and prognosis**
  - Prednisone PO 5-10mg/cat
  - Chlorambucil (+ pred) PO
    - 15mg/m\(^2\) q4hr x 4d q3 weeks → 70-75% complete remission, MST 15-17 months\(^2\)
    - 2mg/cat q4hr → 36% complete remission, MST 25 months\(^3\)
    - 20mg/m\(^2\) q2 weeks → 96% complete remission, MST 26 months\(^4\)
  - Very well tolerated with minimal side effects
  - Cytopenias uncommon with prolonged use
  - Acquired Fanconi’s syndrome in 4 cats (resolved after discontinuation)\(^5\)
  - Rescue therapy
    - Cyclophosphamide/prednisone → 100% response for median duration of 6 months\(^6\)
    - CCNU → Median response duration 6 months\(^6\)

- **I/HGAL – treatment and prognosis**
  - Whether or not patients achieve a complete remission is strongest prognostic indicator
  - COP (cyclophosphamide in patients with GI toxicity from vincristine)\(^1,2,4\)
    - MST 7.3 months
      - For cats in complete remission (25%) MST 7-19 months
    - CHOP (± mitoxantrone with renal disease)\(^1,2,3,4\)
      - 46.7% achieve complete remission
      - Older studies → MST 7.1 months (most included nasal and LGAL)
      - Cats with HGAL less likely to achieve a CR (30% vs. 52% in all other locations)
    - Newer studies:
      - 24 week CHOP → MST 3 months; for CR patients MST 11 months
      - 24 cats that achieved a CR → 85% progression free at 3 yr, 52% progression free at 5 yr
      - 12 week CHOP → MST 2.5 months; for CR patients MST 15.3 months

**Alimentary Lymphoma**

- **LGAL – behavior and diagnostic considerations**
  - Varies between extranodal sites of involvement in >90% of cases
  - Duodenal involvement in >70% of cases
  - >90% T-cell with 60% showing epitheliotropism\(^3\)
  - More difficult to diagnose with cytology
  - Lymphocytic infiltration (cells are small and well-differentiated)
  - Best diagnosed with a combination of histopathology, IHC and PARR to distinguish from IBD
  - Tissue evaluated for specific patterns of epitheliotropism, lymphocytic infiltrate into deep mucosa, severe disruption of villous and crypt architectures, and intraepithelial invasion.

- **I/HGAL – behavior and diagnostic considerations**
  - Acute onset, rapid clinical course
  - Tends to be mass-lesions present (multifocal) with extra-intestinal involvement
  - Can be T- or B-cell (30-50% T-cell)\(^1,2\)
  - Not prognostic for outcome (different than canines)
  - Generally easy to diagnose with cytology

**Alimentary Lymphoma**

- **I/HGAL – treatment and prognosis**
  - Chemotherapy
    - Whether or not patients achieve a complete remission is strongest prognostic indicator
  - COP (cyclophosphamide in patients with GI toxicity from vincristine)\(^1,2,4\)
    - MST 7.3 months
      - For cats in complete remission (25%) MST 7-19 months
    - CHOP (± mitoxantrone with renal disease)\(^1,2,3,4\)
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**Alimentary Lymphoma**

- **LGALL**
  - Cytotoxic T-cell or NK-cell origin (characterized by cytoplasmic azurophilic granules)
  - Most aggressive form of alimentary lymphoma
  - MST 1-2 months with CHOP/COP chemotherapy\(^4\)

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\(^3\) Evans et al. Vet Path, 2012.

Intestinal Adenocarcinoma

- Small intestinal ACA
  - 30% of all intestinal ACA in cats
  - ≥60% metastasis at diagnosis to mesenteric lymph nodes, omentum/mesentery, abdominal wall, liver, lungs
- Surgery +/- chemotherapy
  - Older studies suggest significant perioperative risk with many patients dying within 2 weeks
  - Patients surviving perioperative period have mean survival 15 months
- Evaluation of surgery vs. no surgery (no chemotherapy)
  - MST 12 months with surgical removal of mass vs. <1 month without surgery
  - MST 28 months for patients with no metastasis vs. 12 months with metastatic disease
- Patients can still do well with metastatic disease
  - Cats with confirmed carcinomatosis have survived 4.5 and 28 months following surgery
  - Potentially chemotherapy would prolong survival in these cases

Other visceral lesions may regress, although unsure if this includes intestinal lesions

Although significant controversy surrounding this lesion in cats

Significant perioperative risk with many patients dying within 2 weeks

Poor prognosis with MST <2 months

Evaluation of surgery vs. no surgery (no chemotherapy)

- Kit = receptor tyrosine kinase (RTK)
- Role of RTKs in treatment of feline intestinal MCT is unknown

Masitinib

MST 28 months for patients with no metastasis vs. 12 months with chemotherapy

- Subtotal colectomy with Adriamycin → MST 9 months (vs. 2 months without chemotherapy)
- Subtotal colectomy with Carboplatin → MST 9 months

- Nodal and distant metastasis: poor prognostic indicators
  - MST 11 months without mets (vs 6 months with mets)

Feline intestinal MCT is relatively uncommon compared to other forms

- Relatively poor prognosis due to high rate of metastatic disease
  - Although studies lacking regarding outcome with therapy for intestinal MCT specifically
  - Surgery
    - MCT of large intestine: survival 6.5 months with surgery alone
    - Splenectomy with concurrent splenic involvement
      - Other second lesions may do worse, although unsure if this includes intestinal lesions
  - Chemotherapy
    - CCNU → 50% response 3–6 weeks
    - Vincristine/etoposide
    - Others → cyclophosphamide, mustargen, chlorambucil
  - Targeted therapy (receptor tyrosine kinases)
    - Tyrosine phosphatase (Palifermin)
    - Mastindifosamide (Knaveat)
    - Imatinib mesylate (Gleevec)

Intestinal Mast Cell Tumor

- Three main forms of MCT in cats
  - Cutaneous
  - Visceral (spleen, liver, lymph nodes bone marrow)
  - Intestinal

**NOTE:** there is overlap between forms (especially visceral and intestinal)

- Feline intestinal MCT is relatively uncommon compared to other forms
- Can be seen with visceral MCT (17% of cases at the time of necropsy)
- Has a high rate of metastasis (71%) in some cases difficult to know if started as visceral or intestinal form
  - Abdominal lymph nodes (50%), liver (29%), spleen (21%), pancreas (7%)
  - Positive bony involvement in 3/2 cats evaluated in one study (historically reported to be less common than visceral forms)
  - Long has been reported
  - Mast cell granules contain vasoactive substances such as histamine and heparin
    - Coagulation disorders
    - GI ulceration
    - Anaphylactoid reactions
    - May have phagocytic activity
    - May see concurrent LGAL detected in 39% of cats in one study
  - Unique sclerosing variant of feline intestinal mast cell tumor
  - Poor prognosis with MST <2 months
  - Although significant controversy surrounding this lesion in cats

Stem cell factor (ligand) binds KIT

• Exons 8 and 9
• Majority in exons 8 and 9
• Evaluated in cutaneous lesions, liver, spleen, and patients with widespread involvement, but not intestinal lesions specifically
• Role of RTKs in treatment of feline intestinal MCT is unknown, although anecdotical responses have been reported

Intestinal Mast Cell Tumor

- KIT = receptor tyrosine kinase (RTK)
  - Expressed on mast cells (and others) → hematopoetic stem cells, melanocytes, etc
  - Stem cell factor (Kitlg) binds KIT → intracellular signaling that ultimately leads to cellular proliferation
  - Activating mutations in c-kit documented in up to 67% of feline MCT
  - Majority in exons 8 and 9
  - Evaluated in cutaneous lesions, liver, spleen, and patients with widespread involvement, but not intestinal lesions specifically
  - Role of RTKs in treatment of feline intestinal MCT is unknown, although anecdotical responses have been reported

- CCNU (lomustine, Lanustine) → MST 28 months for patients with no metastasis vs. 12 months with chemotherapy
- Vincristine/prednisone
- Toceranib
- Imatinib mesylate (Gleevec)
QUESTIONS?

**Abbreviations**

- Lymphoma = LSA
  - Low grade alimentary lymphoma – LGAL (same as small cell lymphoma or SCLSA)
  - Intermediate grade alimentary lymphoma – IGAL
  - High grade alimentary lymphoma – HGAL
- Large granular lymphocyte lymphoma - LGLL
- Mast cell tumor = MCT
- Adenocarcinoma = ACA
- Inflammatory bowel disease = IBD
- Gastrointestinal = GI
- Small intestine = SI
- PCR for antigen receptor rearrangement = PARR