Feline Infectious Peritonitis: Is There Hope?

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Objectives

- Overview of feline infectious peritonitis (FIP)
  - Epidemiology
  - Clinical presentation
  - Diagnostics
- Historic therapies
- Newer therapies
- Case examples
- Questions

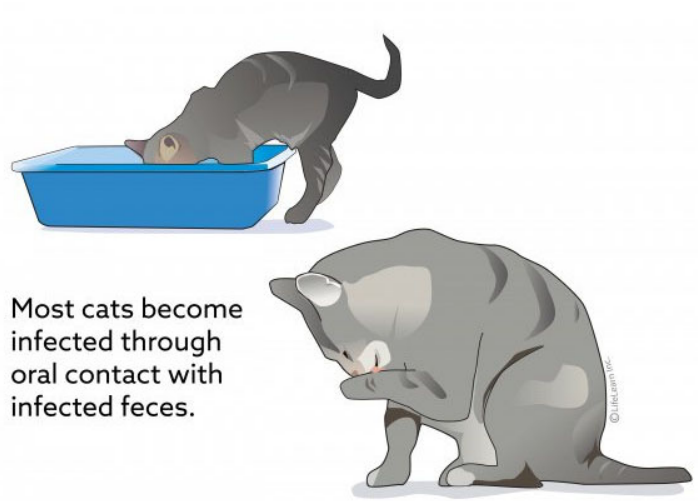
Overview

- History of FIP
  - 1963 - syndrome of immune-mediated vasculitis and pyogranulomatous inflammatory reaction.
  - 1978 - virus was identified (ssRNA virus, pleomorphic, enveloped)
  - Present - #1 cause of infectious-related death (previously FeLV)
    - Avirulent feline coronavirus (FCoV) replicating in enterocytes. Mutation occurs leading to virus replication in macrophages, which is the key pathogenic event to FIP development
    - 0.55% of new feline and 0.36% total feline cases were FIP presented for North American Veterinary teaching hospitals (Rohrbach et al 2001.)

Epidemiology

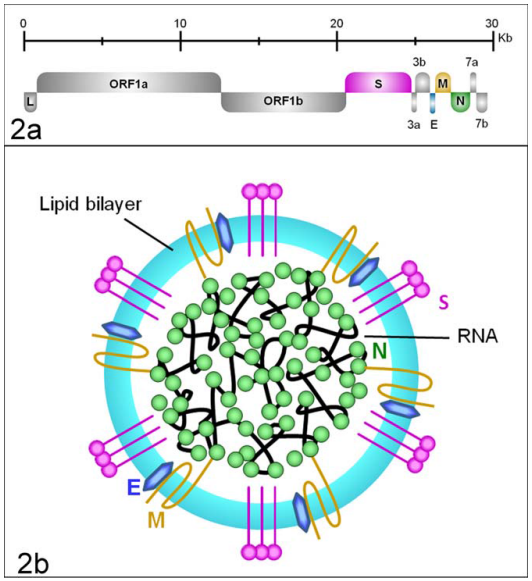
- Prevalence
  - Antibodies against FCoVs found in:
    - 50% cats in USA overall
    - 80–90% of the animals living in catteries or multiple-cat households
    - Up to 50% of solitary cats
      - only 1–5% develop FIP
  - Shelters, catteries, or any multicat household has highest risk namely due to feces as the main route of transmission
  - Example: feral cats tested upon intake to shelter and at 1-2 week intervals. 15% positive at admission. Rapid increase after.
- Risk
  - Age – young and immunocompromised cats have less controlled mutation or older
  - > 50% cats with FIP are under 1yo
  - Cheetah has deficiency in their cellular immunity that predisposes them to FIP
  - Young, male, purebred, sexually intact (Pesteanu-Somogyi et al 2006)
    - 1.3% in purebreds vs 0.35% in mixed breed cats presented to NCState

Epidemiology



- Transmission
  - Oronasal
    - Mainly shed in feces. In early infection, found in saliva, respiratory secretions or urine
    - Intermittent shedding for 10mths, some years to lifelong
    - Higher the antibody titer → more likely to shed and more consistently
    - FIP-infected cats still shed nonmutated CoV in feces, but usually less once FIP has developed
  - Secondary: grooming, shared bowls, close contact, transplacental
    - Most kittens removed from virus-shedding adult at 5-6 weeks of age do not become infected. Usually infected at 6-8wks as maternal antibodies wane.
    - CoV can survive a week outside of cat if dry → fomites
  - No FIP-causing FCoV found in feces or other excretions
  - Unless iatrogenic, only FCoV is cat-to-cat, not FIP

FCoV vs. FIP



- Feline Coronavirus (FCoV)
  - Asymptomatic
  - Replication in enterocytes via enzyme aminopeptidase-N of brush border → diarrhea
- FIP
  - Spontaneous mutation at genes 3C or 7B, but at varied locations
  - 99.5% homology of parent virus to mutated
  - Mutation allow phagocytosis by macrophages to bind to ribosomes in the macrophages → replication in macrophages
  - Higher viral load makes odds of mutation higher
  - Mutation favored by: Young age, breed, immune status, stress, glucocorticoid therapy, surgery, amount of virus, reinfection rate in multiple-cat households

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Disease Progression

- Within 14 days after mutation, it's body-wide (including CNS)
- Theories:
  - 1) FCoV-infected macrophages leave the blood and allow virus to enter tissues. Virus attract antibodies leading to complement fixation and more macrophages are drawn in. Granulomatous lesions are made.
  - 2) Circulating immune complexes exiting circulation into vessel walls leading to development of granulomatous lesions.
  - Ultimately, both bring in more inflammatory mediators leading to vascular permeability and retraction of capillary endothelial cells allows plasma proteins to escape (protein-rich exudate)
  - Immune-mediated vasculitis leads to DIC

Antibody-dependent Enhancement

- Controversial
- Theory that antibodies (vaccination) already being present leads to higher uptake of FCoV into macrophages
- Antibody positive cats showed earlier development of disease, as well as higher mortality
- Complicated, as some studies show cat naturally reinfected by FCoV had no evidence of ADE. Has driven vaccination concern.

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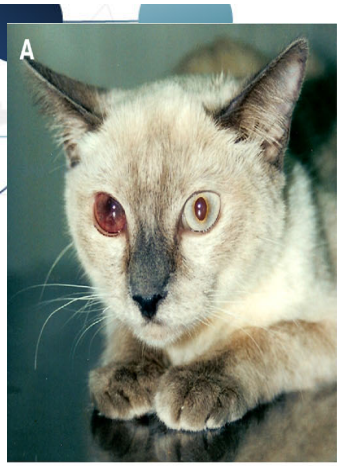
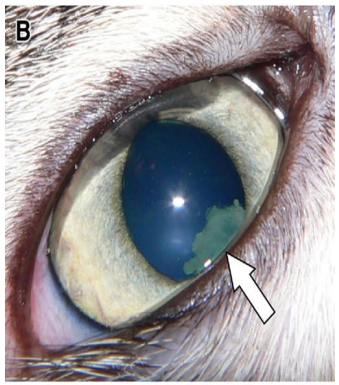
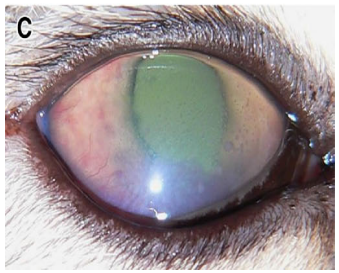
Clinical Signs

- Feline coronavirus
  - None
  - Upper respiratory signs
  - Diarrhea, vomiting
  - Rare stunted growth or chronic v/d/weight loss

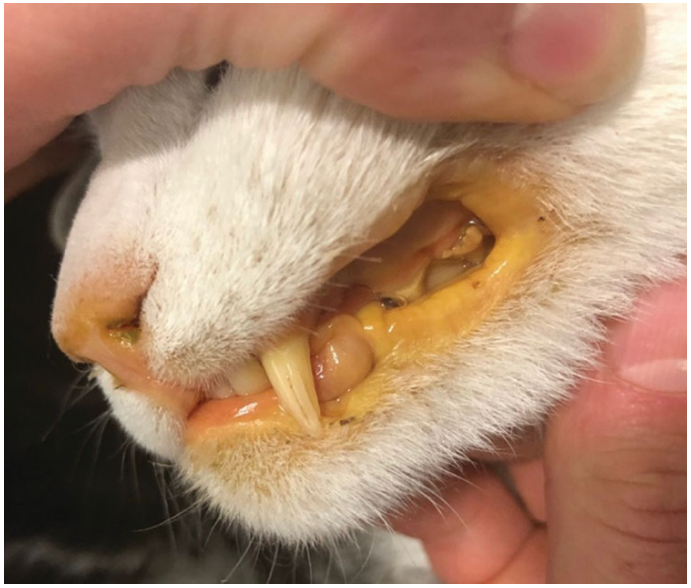
- FIP
  - Multiorgan involvement → vasculitis and organ failure due to damaged vessels that supply organs





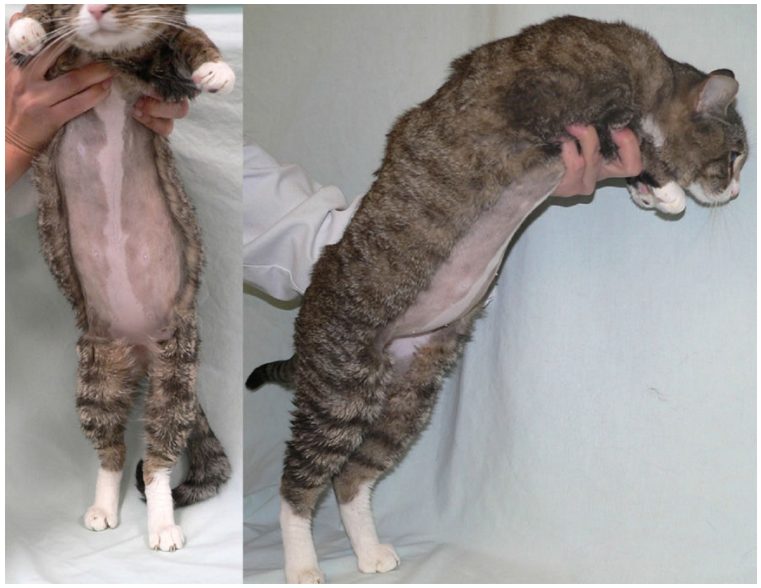


Clinical signs of FIP



- Fever
- Weight loss
- Hyporexia
- Jaundice
- Abdominal mass on palpation – ileocecocolic junction
- Ocular – retinal lesions, uveitis
- Neurologic
  - 13% of FIP cats have neuro signs
  - Ataxia, nystagmus, seizures followed by incoordination, intention tremors, hyperesthesia, behavior change, or cranial nerve defects
  - 75% hydrocephalus (lacking with crypto, toxo, lymphoma)

FIP Forms



- 1) Effusive (“wet”)
  - Immune-mediated, fibrinous-granulomatous serositis (Addie et al. 2009)
  - Fibrinous peritonitis
  - Pleuritis
  - Pericarditis
  - Effusions in abdomen, thorax, pericardium
- 2) Non-effusive (“dry”)
  - No effusion
  - Pyogranulomatous lesions in various organs and around vessels: eye, CNS (Addie et al. 2009, Pedersen 2009, 2014)
- 3) Mixed

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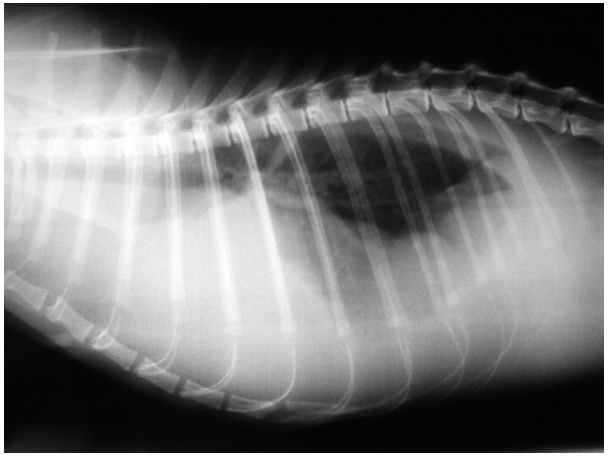
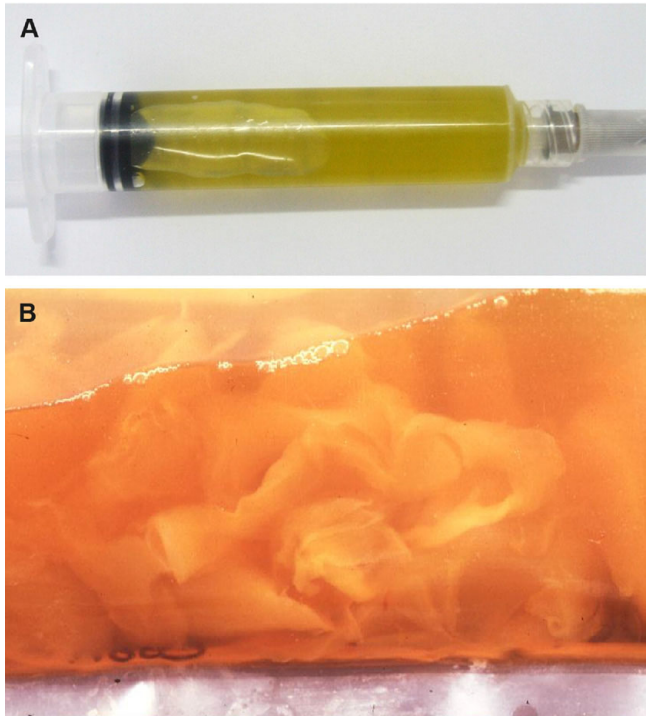
Effusion

- 62% ascites, 17% thoracic, 21% other
- Less than 50% of cats presenting with effusion are due to FIP
  - 30% of thoracic
  - 30% thoracoabdominal
  - 60% ascites





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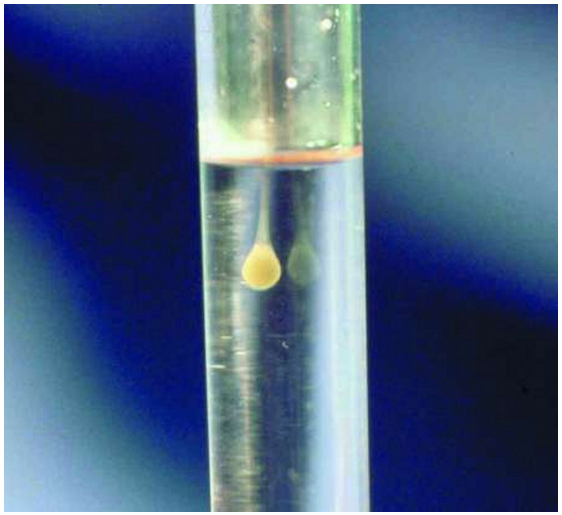
Bloodwork Changes

- CBC
  - WBC – variable
  - Thrombocytopenia due to DIC
    - Elevated D-Dimer, elevated fibrinogen degradation products
  - Anemia (65%)
    - Secondary IMHA or heinz bodies
    - 50% FIP cats have nonspecific bone marrow changes at necropsy
- Chemistry
  - Elevated TP (50% with effusion, 70% without effusion)
    - Hyperglobulinemia (y-globulins)
    - Reduced albumin: globulin is better than albumin or globulin level alone
    - Can be monoclonal or polyclonal making electrophoresis less helpful
  - Hyperbilirubinemia – hepatic necrosis (despite unremarkable ALP/ALT)
    - Compromised metabolism and excretion with FIP.
    - Not typical hemolysis, liver, or cholestasis.

Diagnostics



- Effusion testing
  - Variable grossly.
  - Modified transudate or exudate
    - TP > 35g/L, low cellularity (<1000 nucleated cells/ml)
  - LDH >300 IU/L (released by inflammatory cells)
  - Elevated alpha-amylase (pancreas releases)
  - Alpha-1 acid glycoprotein in effusion > 1500ug/ml with FIP
  - Cytology: pyogranulomatous
  - Rivalta's Test to differentiate transudate vs. exudate
    - Positive if high protein content, fibrin, and inflammatory mediators
    - Add one drop to distilled water/acetic acid tube
    - Drop retains its shape, stays at surface, or slowly floats = positive
    - PPV 86%, NPV 97%. Can have false positive with bacterial peritonitis but cytology/culture differentiates

Diagnostics

- Histopathology
  - Perivascular mixed inflammation with macrophages, neutrophils, lymphs, and plasma cells
  - Pyogranulomatous inflammation
  - Lymphoid tissues show depletion from apoptosis

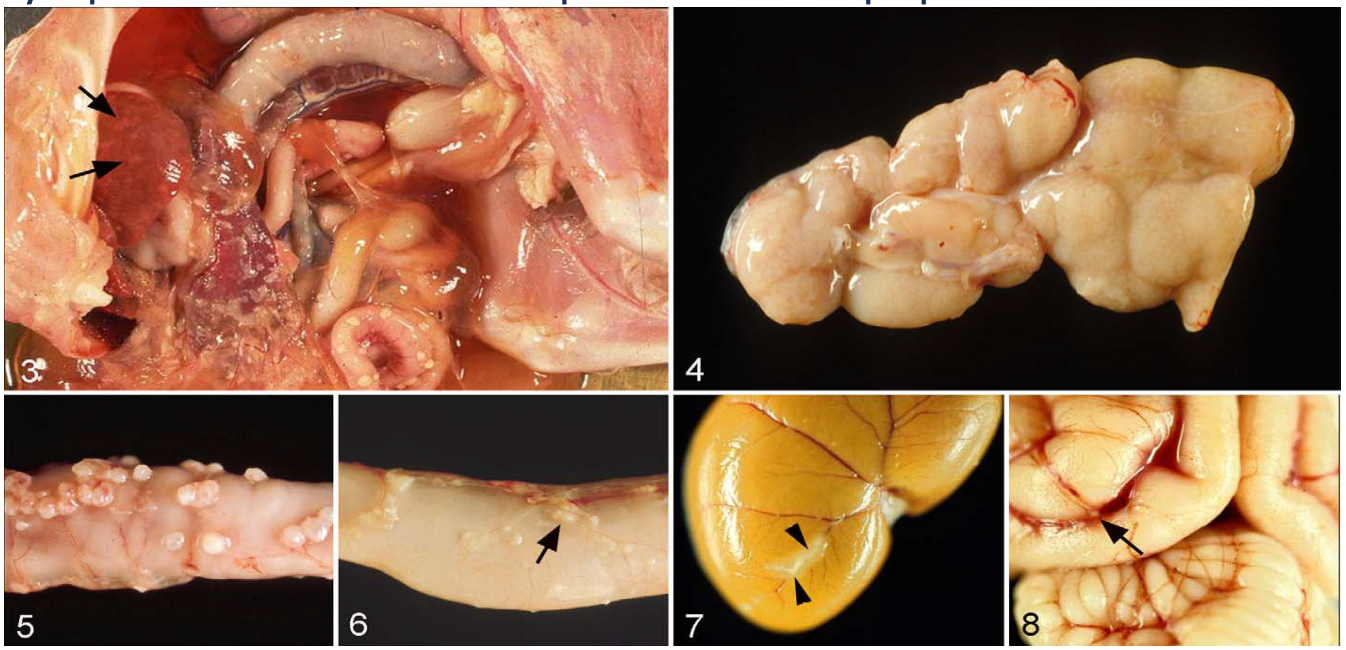


Figure 3 – effusive
Figures 4-8 - dry

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Diagnostics

- CSF
  - Normal or non-specific inflammatory
- Antibody (titer)
  - Presence does not confirm FIP.
  - Absence does not exclude FIP.
  - Only use if:
    - Diagnosis of FCoV-induced enteritis or narrow FIP
    - Healthy cat that has had contact with FCoV-cat
    - Breeding facilities
    - Screening cattery
    - Screening a cat to enter a FCoV-free population

Antigen

- Antibody antigen complex detection
  - ELISA – PPV 67% with many false positives
- Antigen in tissue
  - Immunohistochemistry
    - Positive staining of macrophages in effusion predicts FIP 100%
    - Cannot differentiate between harmless nonmutated FCoV and mutated FIP-causing FCoV
      - Only FIP-causing virus can replicate in macrophages → positive staining
      - Therefore, use intracellular FCoV antigen by immunoflourescene or immunohistochemistry with histopathology whenever possible for most definitive.
  - Immunofluorescence staining of antigen in effusion
    - PPV 100%
    - NPV 57% - can't rule it out if negative staining

mRNA PCR

- Sample: EDTA blood, biopsy/aspirate, ascites, pleural effusion
  - Feces only to exclude acute enteric FCoV
- Methodology (Simons et al, 2005):
  - Detects mRNA of the M gene of all known FCoV strains. Therefore, for detection of FIP, only the detection of mRNA outside of the gi tract is indicative
  - Highly specific
  - If multi-test, NPV and PPV are nearly 100% for confirmation or ruling out

<u>Interpretation</u>

- High Positive (> 50 copies/specimen) FIP (interpretation must be correlated to clinical symptoms)
- Low positive (<50 copies/specimen) FIP (interpretation must be correlated to clinical symptoms)
- Negative FIP viral mRNA not detectable

Therapy

- FCoV positive, asymptomatic
  - Lower stress only

- FCoV positive with enteritis
  - Most are self-limiting
  - Support
  - Steroid may aid diarrhea, but this is contraindicated with harmless FCoV

FIP Therapy - Historical

- Steroid
- Antibiotics
- Antivirals
  - Ribavirin – not effective with FIP, high side effects (hemolysis, bone marrow toxicity, liver toxicity)
  - Feline interferon-w
    - No antibody creation even with long-term therapy
    - In vitro, inhibits FCoV replication
  - Human interferon-alpha – SQ (high-dose) or oral (low-dose)
    - Common neutralizing antibodies form after 3-7 weeks with high-dose SQ form; not with PO
    - Synergism with ribavirin
    - High-dose SQ may prolong survival a few days
    - Broken down by gastric acid and undetectable when given PO. May have some immunomodulatory properties due to oral lymphoid stimulation → ultimately leads to FIP progression

Prevention

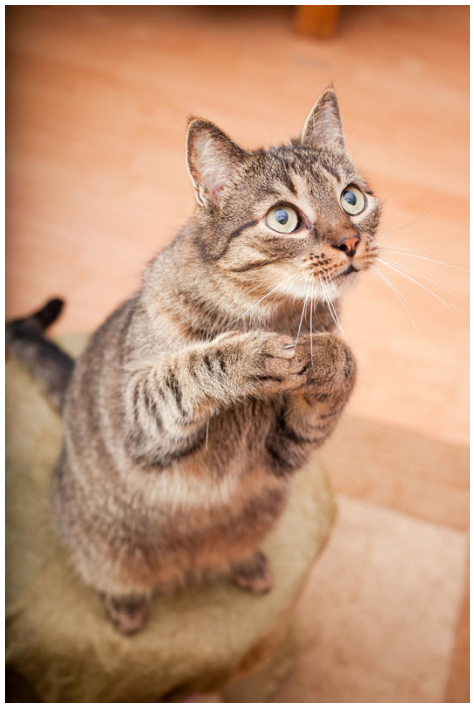
- Only via avoidance of infection with FCoV
- Vaccination
  - Does not prevent FIP or FCoV. Concern of antibody dependent enhancement. Titers can be hard to interpret later.
  - Unclear if no effect vs. small effect
  - Not currently recommended
- Kittens
  - Early weaning at 4-6wks, strict quarantine of queens and kittens, and isolation of queen 2-3 weeks prior to parturition

Household Response

- Contact with FIP suspect or confirmed FIP cat
  - Exposed cat is likely antibody positive, but unlikely to develop FIP.
  - Can monitor antibodies every 6months if desired.

- After a FIP+ feline dies
  - New feline introduction - wait 3 months because FCoV remains in environment at least 7 weeks
    - Ideally wait until all cats are antibody negative (may be years)
  - Other felines in household are already exposed. No prevention for those already exposed.
  - Eliminating FCoV from household – less younger (<1yo) and feces management +/- antibody titer/PCR monitoring

Newer Therapies



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Therapy

- Goals: Clinical resolution of illness with normal HCT, TP, Globulin, Albumin, and A: G ratio

- 3 approaches:
  1) Modulate patient's immune system
  2) Immunosuppress to reduce inflammatory response
  3) Antivirals to inhibit viral replication

Immunostimulants

- *Staphylococcal* A protein (Pedersen 2014)
- *Propionibacterium acnes* (Weiss et al. 1990)
- Lymphocyte T-cell immunomodulators such as omega interferon (Pedersen 2014)
- Plant extracts such as polyprenyl immunostimulant (PI) (Legendre and Bartges 2009)

- All failed.

Immunosuppression

- To help control signs
- Glucocorticoids (GC)
- Cytokine inhibitors (pentoxifylline, propentofylline)
- Alkylating agents (cyclophosphamide, chlorambucil)

- GC reduce clinical signs, but not curative (Ritz et al 2007, Fischer et al 2011)

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Antivirals

- GS-441524
  - Active metabolite of Remdesivir
  - RNA-chain terminator of viral RNA dependent RNA polymerase (Murphy et al 2018, Pedersen et al 2019)
  - Strongly inhibits FIP both in tissue culture and infection
  - Murphy et al 2018:
    - GS-441524 was highly effective at dose of 4mg/kg SQ SID for 12 weeks in 10 cats

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GS-441524

- Pederson et al 2019: In vivo effects in both wet and dry form.
  - 31 cats (26 wet, 5 dry) 2mg/kg SQ for 12 weeks.
  - Increased by 4mg/kg if clinical signs worsened.
  - 26 cats successfully completed 12-week course.
    - 18 after one year were healthy.
    - 8 had relapses within 3-84 days.
    - 3 were treated again at same dose and 5 had increased retreatment dose (by 2-4mg/kg).
      - 5 retreated at higher dose remained healthy. Two of the three retreated at lower dose relapsed again and needed third treatment at higher dose. One relapsed again.
    - 25 overall long-term survivors.
  - Adverse effects
    - Injection site reactions #1
  - Conclusions:
    - Safe and effective to give 4mg/kg SQ daily for 12 weeks
    - Higher dose of 5-10mg/kg SQ SID for neuro cases (Dickinson et al 2020)

GS-441524 Therapy

- Commonly used dosage:
  - 4-6mg/kg SQ daily for 12 weeks
  - Wet form, younger cases can respond to lower end of dosage
  - Dry form often requires higher end of dose range
  - Ocular signs (no neuro): 8mg/kg SID for 12 weeks
  - Neuro signs: 10mg/kg SID for 12 weeks
  - Adjust dose weekly with weight
  - PO form (Aura, Mutian) shows lower absorption at high dosages

GS-441524 Therapy

- Complications:
  - Injection site sores
  - Pain upon injection (pH, scarring, wounds)
- Protocol:
  - Response within 24-72hr with normalcy in 2-4 weeks (average 3.85)
  - Estimated success of 80%
  - Failure due to:
    - Misdiagnosis
    - Inadequate dosage
    - Complicating disease
    - Resistance
    - Non-neurologic patients are easier to cure
    - Younger are easier to treat with higher cure rate than >7yo cats

Supplemental Therapy to GS-441524?

- Cap off treatment with higher dosage – no benefit
- Concurrent interferon omega or other immunostimulants
- Antiviral (GC376) – needs research
- B12, steroid – unknown benefit

When to stop GS-441524?

- 12 weeks is standard
- If dose increase is needed, this should be given for at least 4 weeks. Course may exceed 84 days.
- Based on clinical picture namely

- Relapses to brain, spine, or eyes
  - Retreat for at least 8 weeks at a dosage at least 5mg/kg higher than initial. Use injectable if dose > 10mg/kg
  - If 15mg/kg dosage and still no impact, likely resistance
  - Most resistance in neurologic cases

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Monitoring of GS-441524?

- No documented protocol
- Based on individual concerns
- Monitoring weight, clinical progress, effusion, and labwork
- Commonly CBC/Chem 1-2 weeks after starting therapy, 1 month into therapy, end of therapy, and 1 month after conclusion of therapy

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Concerns about safety

- No regulation
- Lack of FDA approval
  - Hopeful in next 2 years
- Questions about purity, pH, dosing, monitoring, and safety
- Unknown complications
- Some sources require CBC/chem, fluid analysis to receive assistance; others are 100% owner driven
- 65.6% owners followed up with veterinarian for monitoring (Jones et al 2021)

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GS-441524

- Jones et al 2021
  - Unlicensed, crowd-sourced GS-441524 for FIP suspects
  - 411 surveys via FIP Warriors
    - All had completed at least 84 days of therapy (n = 393)
  - Only 8.7% owners reported significant aid from their vet in treating their cat
    - 30% found GS therapy via a website (23% Facebook); 25% from veterinary guidance
    - 25% had no veterinary help at all to discover therapy
  - 88.2% reported improvement within one week (appetite, movement, fever)
  - Mean cost $4920 (USD)
  - Complications namely related to owner SQ injection (vocal, pain, wounds at site, etc)

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Jones et al. 2021

- Therapies used:
  - 71.7% injectable, 8.2% oral, 20.1% combination
  - Mutian, multiple, Shire, Capella, Hero – white or blue cap, other
- Supplemental:
  - Vitamin B1 or B12 – 41%
  - Steroids – 37%
  - Fluids (SQ or IV) – 27%
  - Antibiotics – 22%
  - Light therapy (photobiomodulation) – 11%
  - Anti-nausea – 11%
  - Appetite stimulant – 1-%
  - Gabapentin – 8%

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Jones et al -Results

- Results:
  - 96.7% lived (n = 380/393)
  - 54% considered cured
  - 3.3% died despite therapy
    - Wet form (n = 224): 3.6% died
    - Dry form (n = 169): 2.96% died
    - No significant difference in mortality between groups
    - Neurologic signs: 4.7% died

- Relapse (recurrence of signs following the end of 12 wk therapy)
  - 12.7% overall
  - not statistically different with or without neuro/ocular signs at time of diagnosis

Remdesivir

- GS-5734
- Prodrug of GS-441524
- Currently FDA approved for COVID-19 under controlled conditions
- Gets broken down to GS immediately in humans, mice, cats, and primates.
- Compared to GS-441524, Remdesivir has higher molecular weight with a varying dilutant.
- Signs of mild liver and kidney toxicity in humans

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Other Antivirals

- GC376
  - 3C-like protease inhibitors
  - Pederson et al 2018
    - 20 cats with various forms of FIP
    - 15mg/kg SQ BID for 12 weeks
    - 19/20 regained outward health within 2 weeks
      - Many relapsed
    - 7 cats did well with MST 11.2 mths
    - Excluded neurologic patients
    - Wet or dry form
  - Side effects: pain on injection, sq fibrosis, alopecia, abnormal permanent tooth development if treated before 16-18 weeks of age

Other Antivirals

- Ribavirin
  - Marginal antiviral activity against FIP and toxicity to cats in vivo (Weiss et al 1993)
- Cyclosporin A
  - Cyclophilin inhibitor
  - Inhibits replication of FCoV in vitro (Pfefferle et al 2011, Tanaka et al 2012-13)
- Galanthus nivalis agglutinin (GNA) & nelfinavir (protease inhibitor)
  - In combination, inhibit FCoV replication in vitro (Hshieh et al 2010), but not effective with FIP

Other Therapies

- Itraconazole
  - Increased lymphocyte count and decrease in alpha-1-acid glycoprotein was noted after treatment started
  - Combination with anti-human TNF-alpha monoclonal antibody for those with FIP (Doki et al 2020)
  - 2/3 cats improved, 1/3 failed to respond
  - Itraconazole with prednisolone reduced pleural effusion (Kameshima et al 2020), but status epilepticus developed

Other Available Therapies

- Mefloquine
  - Reduced viral load of FIP without cytotoxic effects (McDonagh et al 2014)
  - Pharmacokinetic studies in cats now available (Izes 2019)
  - Trials against FCoV, FIP, and calicivirus are occurring (Yu et al 2020)
- Hydroxychloroquine
  - Used with interferon, increased antiviral activity against FIP in vitro (Takano et al, 2020)
- Chloroquine
  - Human antimalarial
  - Inhibits FIP virus replication in vitro (Takano et al 2013, McDonagh et al 2014); poor in vivo
  - Anti-inflammatory and antiviral properties
  - Improved clinical scores but no statistically significant survival improvement
  - Increased ALT noted on 10mg/kg twice weekly SQ

Case Examples

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Case #1

- 5 month FS DSH
- Previously diagnosed
  - Capella therapy for effusive FIP
- Presented for fever, lethargy, vomit
- PE: ascites, fever, lethargy
- BW: TP > 12, ALT 161, HCT 19%
- Therapy impact:
  - Marked improvement in ascites within one week
  - Weight gain
  - Resolution of fever, improved Alb:Glob
  - Complications: regenerative anemia, thrombocytopenia, neutropenia, ringworm, skin at injection site
    - Multiple transfusions given
  - Successful therapy with last recheck 7mth post-treatment
    - Lymphocytosis, rest wnl

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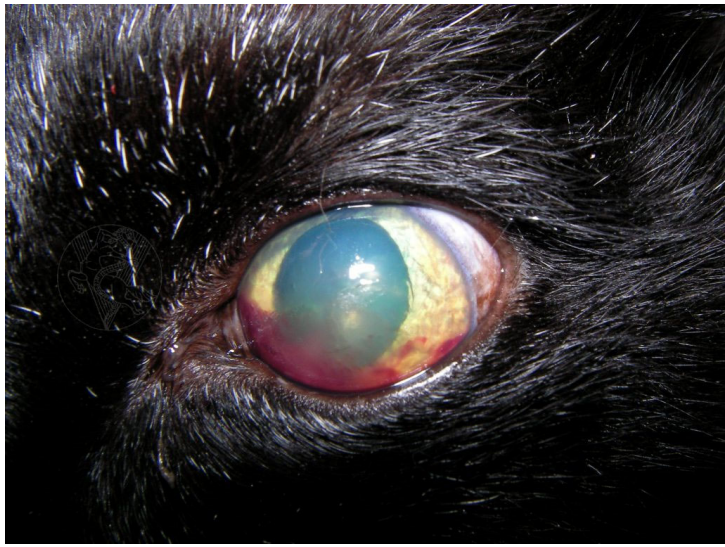
Case #2



- 6-year-old FS DSH
- Presented for hyphema, hyporexia, and lethargy
- BW: non-regenerative anemia, hyperglobulinemia, lymphocytosis
- Diagnostics:
  - FeLV/FIV/HW: negative
  - Toxoplasma IgG/IgM: negative
  - Feline vector panel: negative
  - AUS: splenic change, bilateral suspect renal degenerative changes (although cannot rule out lyphosarcoma/FIP)
  - Splenic aspirate: reactive lymphoid hyperplasia
  - Protein electorphoresis: polyclonal gammopathy
- Tx: steroid, support.
  - Signs improved initially, but then hyperglobulinemia and anemia recurred → further testing declined in favor of empiric GS-441524 therapy (other testing declined)
  - Monitoring with monthly cbc/chemistry
- Successful therapy and now released
- Doing great!

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Case #3

- 7-month-old M Scottish Fold
- Presented 11/23/2019 - straining to urinate and lethargy
  - PE: fever (103.6F), rest unremarkable
  - BW 11/23 – Glob 6.7, A:G 0.5, Tbili 0.5, HCT 39%, WBC 24.57
  - U/A: pyuria. Culture negative.
  - DDx: FLUTD vs. UTI vs. other
  - Tx: Gabapentin, Buprenorphine, Clavamox
- Re-presented 11/29/2019 - diarrhea and tenesmus
  - PE: fever (103.5F), soft tubular structure in abdomen, rest unremarkable
  - BW: Glob 5.6, Alb 3.0, A:G 0.5, Tbili 0.4, WBC 22.55, Neutro 20.8, HCT 34%
  - AUS – colonic wall thickening with loss of layering and colonic lymphadenopathy
  - FNA (LN and colon) – Granulomatous to pyogranulomatous with evidence of hemorrhage
  - Histoplasma – negative
  - Pythium – negative
  - Fecal PCR - negative
  - Coronavirus titer – positive @ >/= 1:12800
- Tx: Mutian (200mg PO SID. Ultimately on 400-450mg PO SID. Average 100mg/1kg BW)
  - Approximately 10days after starting, POCUS showed no ascites or pleural effusion. Subjective improvement in colonic wall thickening.
  - Within about 1 month, globulins and bilirubin normalized. Lymphocytosis occurred.
  - 2/2020 – resolution of colonic change on ultrasound with normal labwork
- Now in clinical remission

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References

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