24th Annual Fred Scott Feline Symposium

July 27–29, 2012

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General Information and Logistics

24th Annual Fred Scott Feline Symposium
July 27 - 29, 2012

Course Overview

This year's 24th Annual Fred Scott Feline Symposium will educate and update veterinarians in feline infectious diseases, ophthalmology, neurology, nutrition, anesthesia, and dentistry as these disciplines pertain to infectious diseases and to the most common and important applications in clinical practice.

RACE Accreditation and Continuing Education Credit

This symposium has been submitted and approved for 17 hours of continuing education credit in jurisdiction which recognize AAVSB RACE approval; however participants should be aware that some boards have limitations on the number of hours accepted in certain categories and/or restrictions on certain methods of delivery of continuing education. Call Amanda Mott at 607.253.3200 for further information.

The College of Veterinary Medicine at Cornell University has been recognized as a sponsor of continuing education by the State Education Department and will offer 17 hours of continuing education for the 24th Annual Fred Scott Feline Symposium.
You are asked to sign-in at the registration desk on the first day so that there is evidence of your attendance.

For questions about accreditation and continuing education credit please contact:

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Evaluation

It is important for the Cornell Office of Continuing Education, faculty, corporate sponsors, and exhibitors to receive your feedback. We ask that you complete the evaluation form and return it to the registration desk before you leave the symposium. The information you provide us is essential in the development of future educational programs. We welcome and encourage your comments on all aspects of this symposium.

Meals

Meal tickets are in the back of your nametag for:

- Lunch on Friday and Saturday. These lunch meal tickets are to be turned into the cafeteria cashier after you select your lunch on Friday and at the cafeteria entrance on Saturday.
- Lunch with Dr. Bruce Kornreich on Friday and Saturday. If you signed up to have lunch with Dr. Kornreich on Friday or Saturday please turn in your ticket to the staff member at the room entrance.
- Dinner on Friday evening at the Animal Health Diagnostic Center

Tours

If you registered to participate in a tour of the college during lunch on Friday you will find an admittance ticket in the back of your nametag. Please meet in the Atrium at the beginning of your lunch break.

Course Materials

The course materials that are distributed during this symposium are under the auspices of the Office of Continuing Education at the College of Veterinary Medicine at Cornell University. Duplication of these materials is prohibited.

Disclaimer

The lectures offered during this symposium will include some discussion of off-label use and commercial products and/or services. The opinion and recommendations expressed by the faculty are their own.

Agenda

Agenda

24th Annual Fred Scott Feline Symposium
July 27-29, 2012

Friday, July 27, 2012

8:15-8:45 a.m.	Registration and Continental Breakfast
8:45-9:00 a.m.	Welcome
9:00-9:50 a.m.	FIP, the Ultimate Hypersensitivity *-Dr. Melissa Kennedy*
9:50-10:05 a.m.	Break
10:05-10:55 a.m.	Update on Feline Viral Diseases *-Dr. Melissa Kennedy*
10:55-11:10 a.m.	Break
11:10-12:00 p.m.	**James R. Richards, Jr. Memorial Feline Lecture** Feline Coronaviruses: Dissecting out the internal mutations in the viral spike protein that allow macrophage tropism and lead to FIP. *-Dr. Gary Whittaker*
12:00-1:10 p.m.	Lunch - **Sponsored by Merial** Lunch with Dr. Bruce Kornreich
1:10-2:00 p.m.	The Role of Infectious Agents in Feline Dental and Oral Disease-Part I *-Dr. Santiago Peralta*
2:00-2:15 p.m.	Break
2:15-3:05 p.m.	The Role of Infectious Agents in Feline Dental and Oral Disease-Part II *-Dr. Santiago Peralta*
3:05-3:20 p.m.	Break
3:20-4:10 p.m.	Neurologic Manifestations of Feline Infectious *-Dr. Starr Cameron*
4:10-5:00 p.m.	Feline Encephalitides *-Dr. Starr Cameron*
6:30-9:00 p.m.	Annual Picnic

Saturday, July 28, 2012

8:30-9:00 a.m.	Continental Breakfast
9:00-9:50 a.m.	Those Wonderful Cat Eyes! What are they telling us? Part I: Anterior Ocular translations. *-Dr. Ronald Riis*
9:50-10:05 a.m.	Break
10:05-10:55 a.m.	Those Wonderful Cat Eyes! What are they telling us? Part II: Posterior Ocular Segment *-Dr. Ronald Riis*
10:55-11:10 a.m.	Break
11:10-12:00 p.m.	Beyond the Carnivore Connection: Enterohepatic Diseases and Feline Nutrition. - *-Dr. Jason Gagne*
12:00-1:10 p.m.	Lunch - **Sponsored by Merck Animal Health** Lunch with Dr. Bruce Kornreich
1:10-2:00 p.m.	Updates in General Anesthesia for the Feline Patient *-Dr. Manuel Martin-Flores*
2:00-2:15 p.m.	Break
2:15-3:05 p.m.	Controversies with Pain Management in Cats *-Dr. Manuel Martin-Flores*
3:05-3:20 p.m.	Break
3:20-5:00 p.m.	Non-domestic Felids Conservation and Medicine *-Dr. Noah Abou-Madi*
5:00-6:00 p.m.	Wine and cheese cocktail hour

Sunday, July 29, 2012

8:30-9:0 a.m.	Continental breakfast
9:00-11:50 a.m.	Lab - A cornucopia of critters: Having a (microscope) field day with infectious agents. *-Dr. Tracy Stokol, Dr. Erica Behling-Kelly, Dr. Erika Gruber*
9:00-9:50 a.m.	Feline Cardiology Update *-Dr. Bruce Kornreich*
9:50-10:10 a.m.	Break
10:10-11:50 a.m.	Clinical Cardiology *-Dr. Bruce Kornreich*

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24th Annual Fred Scott Feline Symposium
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James R. Richards, Jr. Memorial Feline Lecture

The James R. Richards Jr. Memorial Feline Lectures were established to honor the outstanding contributions that the late Dr. James R. Richards Jr., made to the field of feline medicine to improve the health and well being of cats everywhere. A series of state-of the-art lectures on various areas of feline medicine will be held (1) periodically at the College of Veterinary Medicine, (2) at the annual New York State Veterinary Conference, and (3) at the annual Fred Scott Feline Symposium.

Dr. Richards was Director of the Cornell Feline Health Center (1997-2007), and Past President of the American Association of Feline Practitioners. Funds contributed to the James R. Richards, Jr. Memorial Fund for Feline Health at Cornell University by his many friends and colleagues are being placed in an endowment fund, and the income from this fund will support these memorial lectures in perpetuity.

Annual Picnic

This year's annual picnic will be catered by Blue Stone of Ithaca. Enjoy dinner and music at the New York State Animal Health Diagnostic Center at Cornell University.

Exhibitors

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24th Annual Fred Scott Feline Symposium
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Noha Abou-Madi, DVM, Msc, DACZM

Noha Abou-Madi received her Doctor in Veterinary Medicine in 1984 and Master of Sciences degree in 1986 from the University of Montréal, Québec, Canada. She completed a residency in anesthesiology and in zoological medicine at the University of Florida and worked at Silver Springs Inc. in Ocala, Florida in a joint position as staff veterinarian and general curator. Prior to coming to Cornell University in 1996, she was an associate veterinarian at Busch Gardens for nearly 5 years. In her current position at the College of Veterinary Medicine, Dr. Abou-Madi is a Senior Lecturer in the Department of Clinical Sciences in the Zoological Medicine Section. Her clinical work is centered on conservation medicine, integrating the practice of zoological and wildlife medicine to the training of students and residents in this field. Her research interests are mainly clinical and aimed at improving the health of species of wild and captive animals as well as studying the elephant endotheliotropic herpesvirus.

Erica Behling-Kelly, DVM, PhD, DACVP

Dr. Erica Behling-Kelly received her DVM from the University of Georgia. She completed her graduate studies in Comparative Biomedical Sciences at the University of Wisconsin-Madison; studying the cellular mechanisms used by gram negative bacteria to break down the blood brain barrier, using Histophilus somnus as a model. She then went on to a post-doctoral fellowship at the University of Texas Southwestern Medical Center in Dallas in the study of atherosclerosis, followed by a residency in veterinary clinical pathology at the University of Wisconsin-Madison. She passed the veterinary pathology boards in September of 2011 and joined the faculty at Cornell in November of 2011. Her research interests are thrombosis and vascular biology, specifically the contribution of red blood cell pathologies and disturbances in lipid metabolism.

Starr Cameron, BVetMed

Starr Cameron is originally from Wisconsin where she received her bachelor's degree at Carroll College, a small liberal arts college just outside Milwaukee. She then ventured off to London, England where she gained her veterinary degree at the Royal Veterinary College. Upon returning to the US, Starr completed a rotating small animal internship in Pittsburgh at the Pittsburgh Veterinary Specialty & Emergency Center. Starr is now a 3rd year resident at Cornell specializing in Neurology and Neurosurgery. Her research interests include: head trauma, feline meningiomas, and seizure management. Starr is known for being a bit of "cat lady" and claims any cat that comes to visit Cornell for a neurology appointment. She lives here in Ithaca with her husband, James, her dog, Josie, and her two cats, Sapphire and Chloe. Starr loves being outdoors, playing saxophone for the Ithaca Concert Band, and playing kickball on Sunday afternoons!

Manuel Martin Flores, MV, DACVA

Dr. Manuel Martin-Flores graduated from the Veterinary College at the Catholic University of Cordoba, Argentina in 2002. He worked for 2 years as a small animal general practitioner, as well as an Instructor of Veterinary Pharmacology and Toxilocology at his home school. Dr. Martin-Flores came to Ithaca in 2004 to enroll in a residency in Anesthesiology at Cornell University. After successfully completing the residency and achieving Diplomate status from the

American College of Veterinary Anesthesiologists, he joined the Faculty at Cornell University as Lecturer in Anesthesiology. Dr. Martin-Flores is now an Assistant Professor of Anesthesiology at the College of Veterinary Medicine. His research interests are focused on the safe use and monitoring of neuromuscular blockers during general anesthesia and the monitoring of cardiac output. He is also currently investigating alternatives for improving airway management in cats, and possible causes for anesthesia associated blindness in cats.

Jason W. Gagne, DVM

Jason Gange is currently finishing his residency in Clinical Nutrition at Cornell University. He has a particular interest in the cluster of chronic enteropathies known as inflammatory bowel disease (IBD). He is also pursuing a PhD in Comparative Biomedical Sciences focusing on gastroenterology. He graduated from Cornell Veterinary College in 2009 and spent a year in private practice in Syracuse, NY prior to starting his residency.

Erika Gruber, DVM

Dr. Erika Gruber graduated from the New York State College of Veterinary Medicine at Cornell in 2006. She completed a rotating small internship at Colorado State University, and then practiced for three years as a relief veterinarian in Tennessee. She is currently a third year resident in Clinical Pathology at Cornell University.

Melissa Kennedy, DVM, PhD

Dr. Melissa Kennedy attended undergraduate and veterinary school at the University of Tennessee graduating in 1983. For five years she practiced in small animal at various locales. She returned to the University of Tennessee in 1988, completing a PhD in Comparative and Experimental Medicine in 1991. Dr. Kennedy completed a residency in microbiology in 1993. She was employed by University of Tennessee as Associate Professor. She is certified by American College of Veterinary Microbiologists in Virology, Bacteriology, and Immunology. She currently directs the Clinical Virology laboratory at UTCVM; instructs veterinary students in virology, immunology, and infectious diseases; and researches on feline viruses, including calicivirus and coronavirus. Dr. Kennedy also has an interest in veterinary diagnostics, and diseases of wildlife.

Bruce G. Kornreich, DVM, PhD, DACVIM

Bruce Kornreich received his DVM from Cornell University in 1992. Following one year of small animal private practice experience in central New Jersey, he returned to the College of Veterinary Medicine as the first Cardiology resident. He became board certified in cardiology by the American College of Veterinary Internal Medicine in 1997. After one year as a postdoctoral associate in the Department of Pharmacology, he began graduate studies in the Department of Molecular Medicine and received his PhD in Pharmacology from Cornell University in 2005. Following completion of his thesis, he was appointed as a Research Associate in the Department of Biomedical Sciences, and then as a Senior Research Associate in the Department of Clinical Sciences in 2007. In March of 2012, Dr. Kornreich was appointed Associate Director for Education and Outreach of the Cornell Feline Health Center, and continues to provide clinical cardiology service in the Cornell University Hospital for Animals and to teach veterinary students in the curriculum in Cornell's College of Veterinary Medicine. Dr. Kornreich has published numerous papers in peer-reviewed journals, has mentored five cardiology residents, and recently received the Pfizer Distinguished Teaching Award for Veterinary Medicine at the College of Veterinary Medicine.

Santiago Peralta, DVM, DAVDC

Dr. Santiago Peralta obtained his DVM degree from Universidad de la Salle in Bogota, Colombia in 1999. After 6 years of general practice, he joined the Dentistry and Oral Surgery Service at University of California - Davis where he successfully completed a 3-year residency in 2009. Since 2011, Dr. Peralta is a lecturer in Dentistry and Oral Surgery at the College of Veterinary Medicine at Cornell University. Dr. Peralta is a Diplomate of the American Veterinary Dental College.

Ronald Riis, MT, DVM, MS, DACVO

Ronald Riis is originally from South Dakota where he received his bachelor's degree of Arts and Science at South Dakota State University. A year later, he moved to Minneapolis, Minnesota where he began his postgraduate in Medical Technology at Swedish Hospital. In 1971, he received his DVM from the University of Minnesota Veterinary College in Minneapolis. After an internship at the College of Veterinary Medicine at Cornell University, Ronald Riis completed his Residency in Comparative Ophthalmology and a Master of Veterinary Science. In the second year of his five year position as an Assistant Professor of Ophthalmology, he achieved Diplomate status from the American College of Veterinary Ophthalmologists. Dr. Riis has worked for the College of Veterinary Medicine at Cornell University for 36 years and is currently an Emeritus Professor of Ophthalmology. His research interests include equine motor neuron disease, neuronal ceroid-lipofuscinosis and dyslipoproteinemias and their effect upon ocular tissues.

Tracy Stokol, BVSc, PhD, DACVP

Dr. Tracy Stokol received her veterinary degree from the University of Melbourne, Australia, in 1987. After 2 years in veterinary practice in the Melbourne Metropolitan area, she returned to the University of Melbourne to complete a PhD in von Willebrand Disease in dogs. In 1993 she left Australia for the shores of Cayuga Lake for an instructor position in Clinical Pathology at Cornell University. Under the guidance of Drs. Julia Blue and Tracy French, she achieved board certification in veterinary clinical pathology through the American College of Veterinary Pathologists in 1995. Dr. Stokol essentially remained at Cornell University, with a brief sojourn to Harvard University in Boston, and is now tenured faculty in the College of Veterinary Medicine. Her clinical pathology interests are varied and include hemostasis, hematopoietic neoplasia (particularly leukemia), hematopoietic disorders (e.g. immune-mediated hemolytic anemia) and validation of clinical pathology tests.

Gary Whittaker, PhD

Dr. Gary Whittaker received his Bachelor's degree in Biochemistry from the University of Leeds in the UK, along with a PhD in Microbiology from the same institution. During the course of his PhD studies on the envelope glycoproteins of equine herpesviruses, Dr. Whittaker realized the importance of studying the functional interactions of viruses with their host cells, with a view to understanding disease processes, and embarked on further postdoctoral training in the Department of Cell Biology at Yale University in the laboratory of Ari Helenius – one of the world-leaders in virus entry mechanisms. Dr. Whittaker joined the Cornell College Veterinary Medicine faculty in 1996 and in his lab has studied virus entry for influenza viruses, rhabdoviruses and arenaviruses, as well as more recently coronaviruses. A study of FIP and how feline coronaviruses cause disease has been a particular focus in recent years.

There were no pages

in this section

FIP, The Ultimate Hypersensitivity

Melissa Kennedy, DVM, PhD, DACVM
Associate Professor, Department of Biomedical and Diagnostic Sciences
University of Tennessee
College of Veterinary Medicine

Learning objectives:

1. To provide a clear understanding of the pathogenesis of FIP
2. To instruct on the limitations and usefulness of various diagnostic assays for FIP
3. To discuss new work being done on FIP therapeutics.

FIP – nothing's ever simple....It is a multifactoral disease involving virus factors, host factors, and environmental factors. The virus of FIP is feline coronavirus (FCoV) – interestingly, it is required but not sufficient for FIP. Coronaviruses have a large RNA genome. They are enveloped with helical capsid. The spike protein in the envelope is used for cellular attachment – determines in part cellular tropism. The virus is transmitted via the fecal oral route. It initially infects the intestines, where it infects mature epithelia of villus tips. It may cause mild to severe enteritis. In many infections, viremia and systemic spread may occur. The virus targets monocytes, and may be found in most parenchymal organs. The majority of infected cats remain healthy despite the systemic spread. Efficient replication of FCoV in monocytes and macrophages is a requirement for FIP development.

Coronaviruses mutate frequently – an infected cat may have a "cloud" of variants - viruses that differ genetically and/or antigenically have been identified within a single host. These changes may lead to change in virulence of the virus. However, no specific mutation has been identified that *consistently* correlates with disease production.

Host factors are important as well, specifically, the character and magnitude of the immune response to the virus. There appears to be a genetic predisposition, with heritability along familial lines. Concurrent disease can also predispose, especially immunosuppressive disease such as FeLV or FIV infection (affects CMI). FIP is often precipitated by 'stressful' episode (affects CMI).Cats that develop FIP have an exaggerated humoral response. The inflammation induced by virus and virus-infected cells produces the lesions of FIP.

Lymphocytes, specifically T lymphocytes undergo apoptosis in cats with FIP. This is not due to virus infection of these cells – so what's the mechanism? Cytokine production/imbalance? At

least one study (Regan, A. D., et al., Virology, Nov 2008) has shown that virus infection leads to alteration of intra-cellular signaling pathways in infected monocytes. This in turn leads to production of pro-inflammatory cytokines.

Tests for FCoV *cannot distinguish infection with avirulent vs. virulent FCoV thus no test specific for FIP exists.* Serology is often used as a diagnostic aid, but caution is required in interpretation of FCoV serologic results - magnitude does NOT always correlate, i.e. a cat with FIP may have a low or even negative titer, and healthy cats exposed to or infected with FCoV may have very high titers. Serology assessing the response to a specific viral protein, the 7b protein was speculated to be specific for FIP. However, the presence of 7b-specific antibodies cannot confirm the FIP diagnosis, as cats with other conditions, as well as healthy cats, may be 7b seropositive. Virus-specific assays have also not shown specificity for the diagnosis of FIP. Is there a consistent difference between the "evil twin" and the "good twin" that can be exploited in a specific assay? There may be no single virus factor that consistently correlates with virulence that could be exploited in an FIP-specific assay; host factors are important. Diagnosis remains a combination of parameters.

Various therapies have been tried for FIP. Immunosuppressive drugs to reduce the inflammation and control the immune response may ameliorate some of the signs. Nonspecific immune Interferon has not shown success in treatment of FIP. A new treatment using a T lymphocyte stimulator has shown some promise. Also under investigation is a new type of antiviral called small interfering RNA (siRNA). This technique has the potential to inhibit coronavirus replication.

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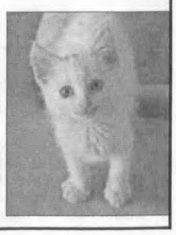
Feline Infectious Peritonitis – the ultimate hypersensitivity

Melissa Kennedy, DVM, PhD, DACVM
University of Tennessee College of Veterinary Medicine
Knoxville, Tennessee

Update on Feline Infectious Peritonitis

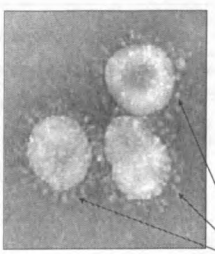
- Pathogenesis – do we know what causes the disease?
- Diagnostics – what's new?
- Is there any effective treatment?

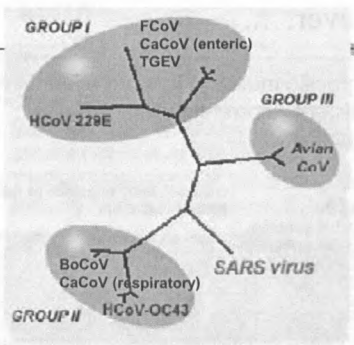
FIP – nothing's ever simple….

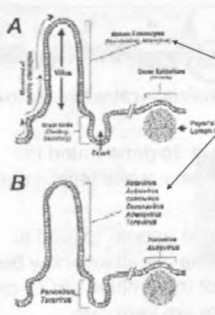
- Multifactoral disease
- Virus factors
- Host factors
  - Immune response
  - Genetics
  - Age
  - Concurrent disease
- Environmental factors
  - Stressors
  - Multicat household

The virus: Feline coronavirus – required but not sufficient for FIP.



- Group I coronavirus
  - All group I coronaviruses are antigenically related.
  - Within this group are two serotypes of FCoV – I and II; FCoV II antigenically similar to CaCoV.
- Biotype (FIPV vs FECV) of virus varies independently from serotype.
- Large RNA genome.
- Enveloped with helical capsid.
- Spike protein used for cellular attachment – determines in part cellular tropism.





- Fecal-oral transmission.
- Transit through GI tract to intestines, where it infects mature epithelia of villus tips.
- May cause mild to severe enteritis.
- Viremia and systemic spread may occur.
  - Monocyte infection.
  - Virus found in most parenchymal organs.
  - Majority of infected cats remain healthy despite the systemic spread.

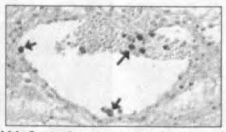
Efficient replication of FCoV in monocytes and macrophages is a requirement for FIP development.

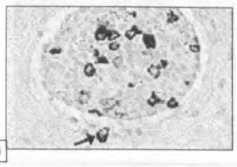
SHORT COMMUNICATION

Natural FCoV infection: cats with FIP exhibit significantly higher viral loads than healthy infected cats

Journal of Feline Medicine and Surgery (2006) 8, 69–72

Anja Kipar, Keith Baptiste, Andreas Barth, Manfred Reinacher





FCoV-infected monocytes in vascular lumen and adhered to endothelia;
Kipar et al. Vet Pathol 42:321–330 (2005)

What do we know about the virus?

- Mutation rate:
  - Mutates frequently – an infected cat may have a "cloud" of variants.
    - Viruses that differ genetically and/or antigenically have been identified within a single host.
  - May lead to change in virulence of the virus.
  - Is a mutation responsible for FIP production?
- Candidate genes for disease production:
  - Spike
  - Nonstructural proteins (3c, 7a, 7b).
  - Others? Multiple? Is it the same mutation in all?

7b gene

3c gene

The Molecular Genetics of Feline Coronaviruses: Comparative Sequence Analysis of the ORF7a/7b Transcription Unit of Different Biotypes

ARNOLD A. P. M. HERREWEGH, HARRY VENNEMA, MARIAN C. HORZINEK, PETER J. M. ROTTIER, and RAOUL J. de GROOT

Feline Infectious Peritonitis Viruses Arise by Mutation from Endemic Feline Enteric Coronaviruses

7a gene

Spike gene

Deletions in the 7a ORF of feline coronavirus associated with an epidemic of feline infectious peritonitis

Melissa Kennedy, Nancy Boedeker, Pam Gibbs, Stephen Kania

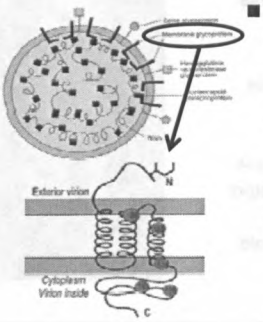
Acquisition of Macrophage Tropism during the Pathogenesis of Feline Infectious Peritonitis Is Determined by Mutations in the Feline Coronavirus Spike Protein

Peter J. M. Rottier, Kazuya Nakamura, Pepijn Schellen, Haukeline Volders, and Bert Jan Haijema

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 9, September 2009

Genetics and Pathogenesis of Feline Infectious Peritonitis Virus

Meredith A. Brown, Jennifer L. Troyer, Jill Pecon-Slattery, Melody E. Roelke, and Stephen J. O'Brien



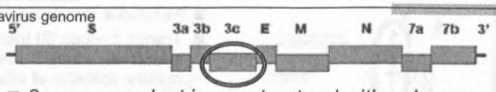
- Is the membrane protein the key?
  - Abundant structural protein.
  - Functions in virus budding and is important in host cell immunity.
  - 5 amino acids at various locales in the membrane protein associated with FIP.

Viruses 2009, *1*, 166-184

Significance of Coronavirus Mutants in Feces and Diseased Tissues of Cats Suffering from Feline Infectious Peritonitis

Niels C. Pedersen, Hongwei Liu, Kimberly A. Dodd and Patricia A. Pesavento

Coronavirus genome



- 3c gene product is nonstructural with unknown function.
- Viruses with deletions in 3c gene found in diseased tissue of FIP cats, while fecal isolates all had intact 3c genes.
- Deletions within the gene appear to lead to inability to replicate in the intestines; may be why FIPV is not shed, is not transmitted cat-to-cat, and why FIP outbreaks are very rare.

However…..

- No specific mutation has been identified that *consistently* correlates with disease production.

And, in fact….

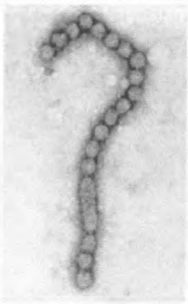
Comparing virus genome from intestine vs FIP lesion in liver from a single cat with FIP:

Genomic RNA sequence of feline coronavirus strain FCoV C1Je

Charlotte Dye, Stuart G Siddell

the virus, [redacted]. Comparisons of the enteric (jejunum) and non-enteric (liver) derived viral RNA sequences revealed 100% nucleotide identity, a finding that questions the well accepted 'internal mutation theory' of FIPV pathogenicity.

So if it's not just the virus….??



Host factors are important…..

- Character and magnitude of the immune response to the virus:
- Genetic predisposition.
  - Heritability along familial lines.
  - Breed predilection.
- Concurrent disease, esp immunosuppressive disease such as FeLV or FIV infection (affects CMI).
- Precipitated by 'stressful' episode (affects CMI).
  - May be obvious, e.g. spay.
  - May be subtle, e.g. change in social hierarchy.

Journal of Feline Medicine and Surgery (2006) 8, 1–5
doi:10.1016/j.jfms.2005.06.005

Prevalence of feline infectious peritonitis in specific cat breeds ☆

Loretta D Pesteanu-Somogyi DVM[1], Christina Radzai DVM[1], Barrak M Pressler DVM, DACVIM[2*]

Abyssinians, Bengals, Birmans, Himalayans, Ragdolls and Rexes had a significantly higher risk, whereas Burmese, Exotic Shorthairs, Manxes, Persians, Russian Blues and Siamese cats were not at increased risk for FIP

The inheritance of susceptibility to feline infectious peritonitis in purebred catteries
Foley JE, Pedersen NC
FELINE PRACTICE 24 (1): 14-22 JAN-FEB 1996

All are likely related to the effectiveness of the cat's immune response to FCoV infection….

- Humoral vs CMI
- Cytokine production
- MHC diversity
- Lymphocyte apoptosis
- Viral clearance

…..all appear to play a role

We know…..

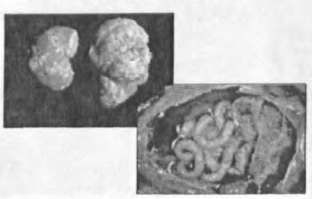
- Cats that develop FIP have an exaggerated humoral response.
  - Manifests as increased total protein, increased gamma globulins, and decreased A:G.
  - T helper lymphocytes in cats that develop FIP are primarily Th2 – push antibody response.

SUPERCHEM PROFILE 2

AST (SGOT)	75		10-100
ALT (SGPT)	53		10-100
T. BILIRUBIN	0.3		0.1-0.4
ALK PHOS	12		6-102
GGT	6		1-10
TOTAL PROTEIN	8.1		5.2-8.2
ALBUMIN	2.1	(L)	2.6-3.8
GLOBULIN	6.0	(H)	2.3-5.3
A/G RATIO	0.4		0.35-1.5
CHOLESTEROL	145		75-220
BUN	14		14-36
CREATININE	1.2		0.6-2.4
BUN/CREAT RATIO	12		4-33

We know…..

- The inflammation induced by virus and virus-infected cells produces the lesions of FIP.
  - Macrophages, monocytes major players; neutrophils; B cells.
  - Associated with vasculature.
    - Infected macrophages are activated.
    - Adhere to endothelia and emigrate from vessels.
- Complement activation contributes to tissue destruction.
- This inflammatory response leads to tissue destruction.
  - Vasculitis.
  - Perivascular necrosis.

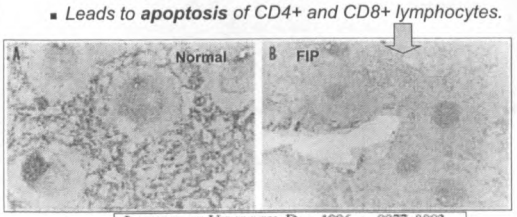


We know….

- Lymphocytes, specifically T lymphocytes undergo apoptosis in cats with FIP.
  - Depletion in lymph nodes found.
  - Cytotoxic T cells, T helper cells.
  - Manifests as lymphopenia.
  - Decrease in lymphocyte subsets, esp CD4+ and CD8+ detected by flow cytometry.
- Not due to virus infection of these cells – so what's the mechanism?
- And what's the mechanism for the exaggerated humoral response?

Cytokine production/imbalance?

- **TNF α** production **increased** in cats with FIP (Takano et al., Veterinary Microbiology 119:121-131, 2007).
  - Produced by FCoV-infected macrophages.
  - Up-regulation of TNFR found on T cells (esp CD8+).
  - *Leads to **apoptosis** of CD4+ and CD8+ lymphocytes.*



JOURNAL OF VIROLOGY, Dec. 1996, p. 8977–8983

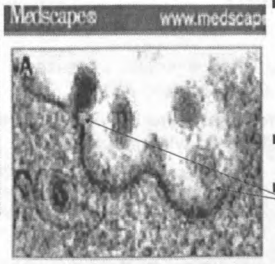
- Several studies have found **IFN γ decreased peripherally** (impairs CMI as result), but **increased locally** in lesions (enhances macrophage activation, viral uptake, and virus replication) in cats with **FIP**.
- A recent study (Takano et al., Arch Virol 154:27–35, 2009) found that **FIP-infected macrophages** over-produce B lymphocyte differentiation and survival factors.
- **Promote B cell differentiation** into plasma cells in FIP cats.
- Is this the reason for the exaggerated humoral response?

Other cytokine changes….

- **Higher IL-10** levels in **healthy** cats with FCoV vs cats with FIP.
  - Insures an effective and specific immune response, but avoids inflammatory-induced lesions.
- **IL-12** production appear to be **decreased** in cats with **FIP**.
  - Impairs Th1 response and viral clearance as a result.
  - Allows monocyte/macrophage activation.
- **IL-1β** production **increased** in cats with **FIP**.
  - Fever.
  - Endothelial cell activation.
- **CK levels can vary in serum vs lesions - It's not simple!**
  - Confounds use of cytokines for treatment.

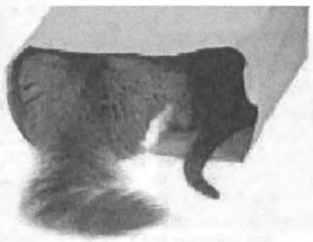
In a nutshell….though the precise mechanism remains unclear:

- Humoral response is not effective at viral clearance, and may enhance disease (ADE).
- Control of virus infection is T cell mediated – response determines outcome.
- ***If T cell response is weak…FIP.***
  - Reduced viral clearance and increased viral load.
  - Exaggerated humoral response.
  - Immune-mediated disease production.
  - This may be determined in part by the haplotype of the animal.
  - What is the mechanism for these cytokine changes – virus, host, environmental, or a combination?



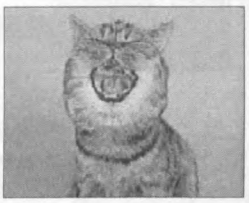
- At least one study (Regan, A. D., et al., Virology, Nov 2008) has shown that virus infection leads to *alteration of intra-cellular signaling pathways in infected monocytes*.
- This in turn leads to production of pro-inflammatory cytokines.
- The **trigger** may be interaction of the **viral spike protein** with the cellular receptor on the monocyte/macrophage.
- May offer hope for treatment in terms of inhibitors of this pathway.

What's new in diagnostics for FIP?



Why is FIP difficult to diagnose?

- Signs may be vague, esp with dry form – "ADR"
- Lab results do not always "fit" the case definition, and other diseases can cause the same abnormalities as FIP.
- Histopathology, the gold standard, may not be feasible for ante mortem testing.
- Tests for FCoV:
  - *Cannot distinguish infection with avirulent vs. virulent FCoV thus no test specific for virus of FIP!!*



- This one….. not so tough….

- This one….tougher.

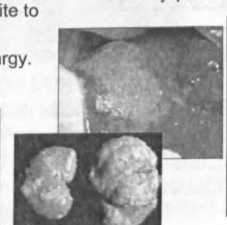
- Diagnosis of FIP requires building the "diagnostic wall"
  - **No single test**, except histopathology/IHC, can confirm a diagnosis of FIP.
  - Various parameters consistent with FIP provide strong evidence for the diagnosis.

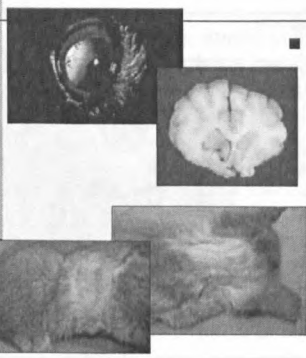
History and Signalment

- From multicat household.
  - Cattery
  - Shelter
  - Rescue group
- History of FIP in breeding line.
- May have history of concurrent stressor or dz.
- Young cat, <2-3 years, most common at 6-12 mos.; elderly >~13 years.
- Purebred>mixed breed.

Clinical Signs

- General
  - Fever; may wax and wane.
  - Decreased appetite to anorexia.
  - Depression, lethargy.
  - Weight loss.
- Effusive
  - Distended abdomen
  - Dyspnea.

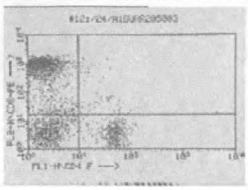




- Noneffusive
  - Signs may be vague and variable.
  - Referable to tissue affected.
  - Eyes, CNS, abdominal organs most common.
  - May be a combination of organs.
  - Papular lesions have been associated with FIP (Declercq et al., Vet Derm 19(5):255-258, Oct 2008)

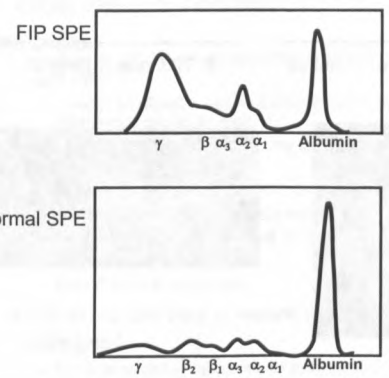
Clinical Laboratory Testing

- CBC
  - Normocytic normochromic anemia.
  - Leukocytosis
    - Neutrophilia
    - Lymphopenia
    - Flow cytometry may show decrease in all subsets of T cell levels.
      - Normal results on flow cytometry has a high negative predictive value for FIP diagnosis.



- Chemistry
  - Elevated serum total protein.
  - Elevated globulins.
  - Decreased A:G
  - Other changes referable to tissue affected.

- Serum protein analysis
  - Protein electrophoresis
    - Polyclonal gammopathy
    - Elevated alpha/beta proteins



J Vet Intern Med 2003;17:781–790

Comparison of Different Tests to Diagnose Feline Infectious Peritonitis

Katrin Hartmann, Christina Binder, Johannes Hirschberger, Dana Cole, Manfred Reinacher, Simone Schroo, Jens Frost, Herman Egberink, Hans Lutz, and Walter Hermanns

Table 1. Specificity, sensitivity, and optimum cutoff value of different total protein concentrations (n = 314), γ-globulin concentrations (n = 133), and albumin to globulin ratios (n = 118) in serum.

Total Protein			γ-Globulin			Albumin to Globulin Ratio		
Total Protein (g/dL)	SP	SE	γ-globulin (g/dL)	SP	SE	Albumin to Globulin Ratio	SP	SE
5.0	0.05	0.96	0.5	0.28	0.98	0.5	0.92	0.50
6.0	0.15	0.88	0.8	0.57	0.89	0.6	0.87	0.75
7.0	0.33	0.76	1.5	0.72	0.72	0.7	0.65	0.77
8.0*	0.60	0.62	2.0	0.82	0.71	0.8*	0.82	0.90
9.0	0.83	0.38	2.5*	0.88	0.70	0.9	0.78	0.85
10.0	0.91	0.24	3.0	0.93	0.45	1.0	0.95	0.90
11.0	0.96	0.12	3.5	0.95	0.40			
12.0	0.97	0.10	4.0	0.97	0.25			
			4.5	0.99	0.15			

SP, specificity; SE, sensitivity.
*Optimum cutoff value as determined by differential positive rate analysis.

A:G had highest diagnostic utility with 0.8 as the optimal cutoff (highest number of correct predictions)

Table 2. Positive predictive values of different total protein concentrations, γ-globulin concentrations, and albumin to globulin ratios in serum in populations with different FIP prevalences.

	Total Protein			γ-Globulin			Albumin to Globulin Ratio		
Total Protein (g/dL)	PPV (0.25)	PPV (0.50)	PPV (0.75)	γ-Globulin (g/dL)	PPV (0.25)	PPV (0.50)	PPV (0.75)	Albumin to Globulin Ratio	PPV (0.25)	PPV (0.50)	PPV (0.75)
5.0	0.25	0.50	0.75	0.5	0.31	0.58	0.80	0.5	0.68	0.88	0.96
6.0	0.26	0.51	0.76	0.8	0.36	0.65	0.85	0.6	0.66	0.85	0.95
7.0	0.27	0.53	0.77	1.5	0.46	0.72	0.89	0.7	0.63	0.84	0.94
8.0	0.34	0.61	0.82	2.0	0.57	0.80	0.92	0.8	0.60	0.82	0.93
9.0	0.43	0.69	0.87	2.5	0.63	0.83	0.94	0.9	0.56	0.79	0.92
10.0	0.47	0.73	0.91	3.0	0.68	0.87	0.95	1.0	0.48	0.74	0.89
11.0	0.50	0.75	0.92	3.5	0.73	0.89	0.96				
12.0	0.53	0.77	0.93	4.0	0.80	0.92	0.97				
				4.5	0.83	0.94	0.98				

SERUM

FIP, feline infectious peritonitis; PPV, calculated positive predictive value in a population with a FIP prevalence of 0.25, 0.50, or 0.75.

Table 3. Specificity, sensitivity, positive predictive value, negative predictive value, and optimum cutoff value of different total protein concentrations, γ-globulin concentrations, and albumin to globulin ratios in effusion (n = 64; prevalence 0.53).

EFFUSION

Total Protein					γ-Globulin					Albumin to Globulin Ratio				
Total Protein (g/dL)	SP	SE	PPV	NPV	γ-Globulin (g/dL)	SP	SE	PPV	NPV	Albumin to Globulin Ratio	SP	SE	PPV	NPV
5.0	0.10	1.00	0.56	1.00	0.5	0.47	0.94	0.67	0.87	0.5	0.89	0.62	0.85	0.76
6.0	0.33	0.88	0.60	0.71	0.8*	0.83	0.82	0.84	0.80	0.6	0.85	0.67	0.81	0.70
7.0	0.53	0.82	0.66	0.72	1.5	0.93	0.65	0.89	0.70	0.7	0.82	0.69	0.81	0.71
8.0*	0.90	0.55	0.78	0.62	2.0	0.97	0.44	0.94	0.61	0.8	0.79	0.78	0.85	0.68
9.0	0.93	0.32	0.84	0.55	2.5	0.99	0.15	0.98	0.57	0.9*	0.74	0.86	0.79	0.82
10.0	0.95	0.23	0.85	0.52	3.0	1.00	0.06	1.00	0.55	1.0	0.65	0.94	0.75	0.91
11.0	0.98	0.12	0.87	0.50										
12.0	0.99	0.07	0.89	0.49										

SP, specificity; SE, sensitivity; PPV, positive predictive value; NPV, negative predictive value.
*Optimum cutoff value as determined by differential positive rate analysis.

- Acute phase proteins may be elevated.
  - Alpha 1-acid glycoprotein
  - Serum amyloid A
  - Haptoglobin

- According to researchers at the University of Milan, Italy, AGP level was the most sensitive and specific assay for FIP (incl histopathology) as compared to IHC (gold std).

- Small study – only 12 cats.
- **Magnitude** of elevation was important - >1.5 mg/ml

that, although AGP can increase in any inflammatory condition, the increase is more pronounced in FIP than in other diseases.

Table 2. Concordance between test results and IHC results and sensitivity and specificity of the different tests

	Coefficient k (95% CI)	Sens (%)	Spec (%)
History and symptoms	−0.04 (−0.41/0.50)	62.5	0
Effusion	−0.52 (−0.99/−0.04)	50	0
RPP	0.54 (−0.07/0.95)	87.5	93
AGP	1.00 (1.00/1.00)	100	100
Serology or PCR	−0.08 (−0.71/0.72)	50	86
Postmortem examination or histology	0.65 (−0.11/0.29)	87.5	100

When the pretest probability of FIP is high (when most of the in vivo or postmortem tests are consistent with but not absolutely conclusive of FIP), a "positive test" (a high AGP value) can increase the posttest probability of disease. In other words, although AGP alone cannot be used to confirm a clinical suspicion of FIP, it could be confirmatory when FIP is probable but not definitely diagnosed based on other clinicopathological findings or on postmortem examination results.

Journal of Small Animal Practice • Vol 52 • March 2011 • © 2011 British Small Animal Veterinary Association

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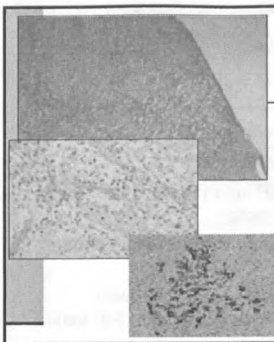

Histopathology and Immunohistochemistry

- Gold standard for diagnosis of FIP
- Perivascular pyogranulomatous lesions, vasculitis
- Difficult to obtain ante mortem as patient is often debilitated.

MORPHOLOGIC DIAGNOSES: PYOGRANULOMATOUS AND NECROTIZING LYMPHADENITIS, HEPATITIS, AND PERITONITIS WITH VASCULITIS

COMMENTS:
The character and distribution of lesions is typical for disease secondary to infection with feline infectious peritonitis virus (coronavirus). The characteristic vasculitis was most evident in samples obtained from the omentum. Thank you for the photographs

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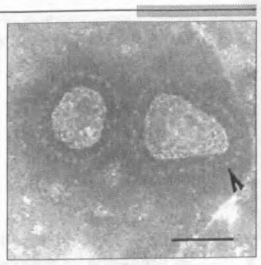
FCoV-Specific Testing

- Virus-specific antibody detection
  - IFA
  - ELISA
  - 7b antibody
- Virus detection
  - Virus propagation
  - Electronmicroscopy
  - Antigen detection
  - Genetic detection



Detection of Virus-specific Antibody

- Use virus protein (whole or subunit; FCoV I or II, or TGEV) to "capture" antibody in patient's serum.
- IFA, ELISA most common methodology.
- Magnitude of titer used to aid diagnosis; specific level varies with the laboratory.

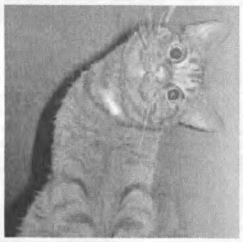
	Presence of Antibodies	Antibody Titer 1:1,600
Number of cats	342	342
Prevalence	0.28	0.28
Portion of correct test results	0.65	0.89
Specificity	0.57	0.98
Sensitivity	0.65	0.67
Positive predictive value	0.44	0.94
Negative predictive value	0.90	0.88
PPV (0.28)	0.44	0.94
NPV (0.28)	0.90	0.88

Caution is required in interpretation of FCoV serologic results!

- Detects antibody to Group I coronavirus.
- Does not distinguish infection with "FIPV" from avirulent FCoV, regardless of claims.
- Magnitude does NOT always correlate, i.e. a cat with FIP may have a low or even negative titer, and healthy cats exposed to or infected with FCoV may have very high titers.

Serology can fool you…..

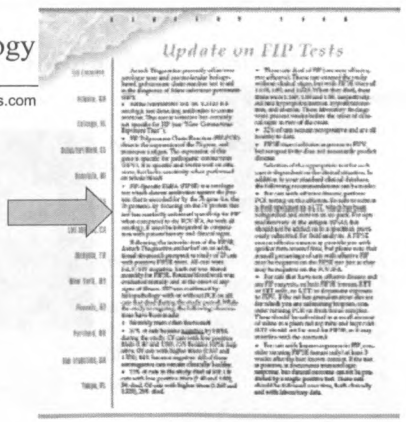
18	FIP	<1:40	+	+	ND	-	ND	ND
19	FIP	1:160	ND	+	+	-	+	ND
20	FIP	<1:40	ND	+	-	-	-	ND
21	FIP	>1:5120	ND	+	+	-	+	ND
22	FIP	1:640	ND	ND	+	ND	ND	ND
23	FIP	1:320	ND	ND	ND	-	ND	ND



- Negative titer doesn't rule it out…..
- High positive doesn't confirm FIP.
- If serology conflicts with other data, ignore the serology.

7b serology

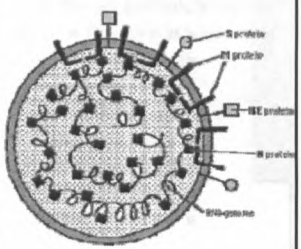
www.antechdiagnostics.com



Update on FIP Tests

The 7b protein

- Nonstructural protein of unknown function.
- Postulated to have a role in virulence of FCoV.
- Hypothesis: if 7b is expressed, virus is virulent; thus, cat infected with FIPV ⇒ 7b is being expressed ⇒ presence of antibody in serum specific for 7b protein.



- We investigated the usefulness of 7b antibody detection for diagnosis of FIP:
  - 7b gene from virus of FIP kitten (from ascitic fluid) cloned into expression vector.
  - 7b protein produced and purified, used as capture antigen in western blot.
  - Serum samples from healthy cats, cats with conditions other than FIP, and cats with FIP tested for antibody to 7b protein.

Evaluation of antibodies against feline coronavirus 7b protein for diagnosis of feline infectious peritonitis in cats

Melissa A. Kennedy, DVM, PhD; Mohamed Abd-Eldaim, DVM, PhD; Sarah E. Zika, DVM; Joseph M. Matkin, DVM; Stephen A. Krawa, PhD

Table. Western blot results using FCoV 7b protein.

	Strong Positive	Weak Positive	Negative
FIP	19	0	0
Other conditions	2	4	3
Healthy:			
SPF cats	0	0	20
FIP housemate	4	0	0
Other	5	0	2
Cheetahs:			
FIP	1	0	0
Known FI	2	0	0
Healthy	0	0	8
Animals of unknown status	18	18	0
TOTAL	51	22	33

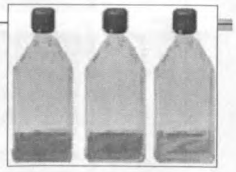
Conclusions and Clinical Relevance—Expression of the 7b protein, as indicated by detection of antibodies against the protein, was found in most FCoV-infected cats. Seropositivity for this protein was not specific for the FCoV virulent biotype or a diagnosis of FIP. (Am J Vet Res 2008;69:xxx–xxx)

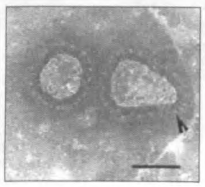
Therefore….

- This assay may be a useful tool to aid the diagnosis of FIP, as all animals with FIP were strongly 7b seropositive.
- Presence of 7b-specific antibodies cannot confirm the FIP diagnosis, however, as cats with other conditions, as well as healthy cats, may be 7b seropositive.
- The presence of antibodies to the 7b protein is not specific for FIP disease production.
  - Could 7b expression be specific for the virulent biotype, but most cats clear it successfully (thus no disease)?
  - Another study (C. N. Lin et al., J Fel Med Surg, Sept 2008) found deletions in the 7b gene of FCoV from several cats with FIP; thus, these mutations did not lead to loss of virulence.

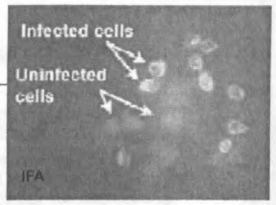
Virus Detection

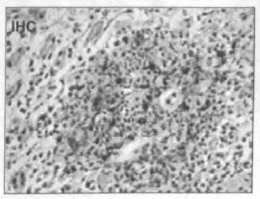
- Virus isolation
  - Gold standard for many virus infections
  - Agent of FIP difficult to propagate in cell culture
  - Many false negatives
- Electronmicroscopy on feces to detect FCoV shedding.
  - Relatively insensitive
  - Cats with FIP may not be shedding virus in feces; conversely, infected cats without FIP may shed virus.





- Antigen detection
  - IFA - Tissue impressions, cells from fluid; 3rd eyelid swab.
  - Immunohistochemistry on fixed tissue -requires biopsy, or post.
- Antigen detection assays detect FCoV only – do not distinguish virulent from avirulent FCoV.
- IFA has relatively low sensitivity; IHC has good sensitivity.
- Detection of FCoV in association with lesions (IHC) considered diagnostic for FIP.





J Fel Intern Med 2003;17:781–790

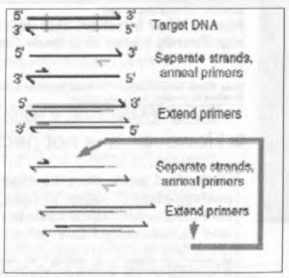
Comparison of Different Tests to Diagnose Feline Infectious Peritonitis

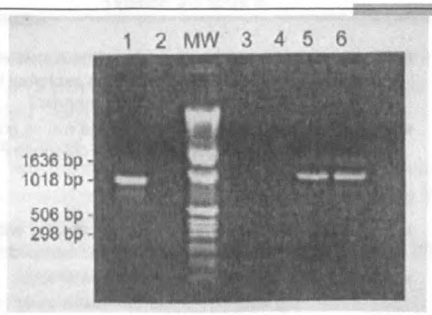
Katrin Hartmann, Christina Binder, Johannes Hirschberger, Dana Cole, Manfred Reinacher, Simone Schroo, Jens Frost, Herman Egberink, Hans Lutz, and Walter Hermanns

From effusion...	Antigen Staining in Macrophages
Number of cats	171
Prevalence	0.64
Portion of correct test results	0.73
Specificity	1.00
Sensitivity	0.57
Positive predictive value	1.00
Negative predictive value	0.57
PPV (0.51)	1.00
NPV (0.51)	0.69

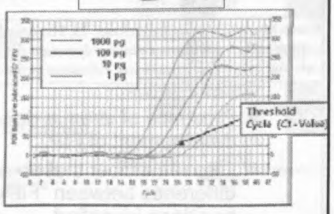
Genetic detection

- Blood, effusion, tissue; feces for shedding.
- Requires strict quality control.
- Conventional PCR
  - Single or two (nested) rounds of amplification.
  - Generally target conserved regions.
  - Product visualized on agarose gel; identity confirmed by sequencing, enzyme digestion or probes.





- Real Time PCR
  - Variation on conventional PCR
  - Reaction may be done in one tube.
  - Products detected and identified by labeled probe.
  - Allows for quantitation of virus in sample.

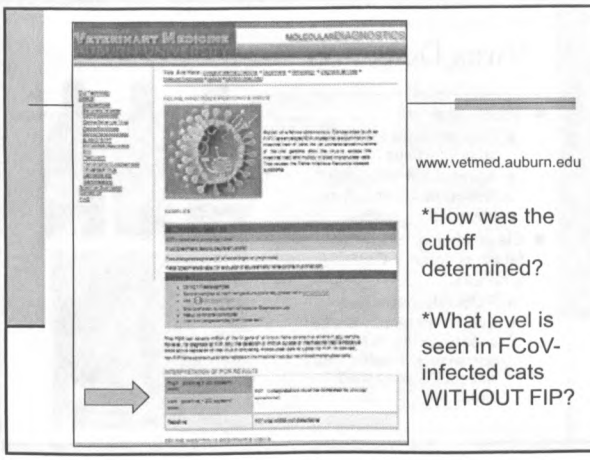


Quantitation of viral RNA by RT-PCR

- Replication in macrophages as evidenced by presence of viral **mRNA** in monocytes isolated from whole blood was found to correlate with FIP.
- This was the basis for a test offered by the Diagnostic Lab at Auburn University that quantitates the level of viral mRNA.

A mRNA PCR for the diagnosis of feline infectious peritonitis

Fermin A. Simons[a,*], Harry Vennema[b], Jolanda E. Rofina[b], Jan M. Post[b], Marian C. Horzinek[a], Peter J.M. Rottier[a], Herman F. Egberink[a]



www.vetmed.auburn.edu

*How was the cutoff determined?

*What level is seen in FCoV-infected cats WITHOUT FIP?

- High level viremia is characteristic of end-stage FIP, thus this test may be helpful.

SHORT COMMUNICATION

Natural FCoV infection: cats with FIP exhibit significantly higher viral loads than healthy infected cats

Anja Kipar, Keith Baptiste, Andreas Barth, Manfred Reinacher

Journal of Feline Medicine and Surgery (2006) 8, 69–72

- However, it is not necessarily specific….

High viral loads despite absence of clinical and pathological findings in cats experimentally infected with feline coronavirus (FCoV) type I and in naturally FCoV-infected cats

M. Meli, A. Kipar, C. Müller, K. Jenal, E. Gönczi, N. Borel, D. Gunn-Moore, S. Chalmers, F. Lin, M. Reinacher, H. Lutz

Journal of Feline Medicine and Surgery (2004) 6, 69–81

- Additionally, viral mRNA has been detected in the blood of healthy cats.

The detection of feline coronaviruses in samples from cats by mRNA RT-PCR

Kezban Can-Şahna, Veysel Soydal Ataseven, Dilek Pınar, Tuba Çiğdem Oğuzoğlu

the cat with clinical disease, but the high rate of positivity among healthy cats suggested a poor specificity for the clinical diagnosis of FIP among these cats. It was observed that the positivity rate was highest in cats aged between 6 months–1 year old. Our findings suggest that FCoVs may be present in the blood samples from healthy cats as well as cats with clinical FIP.

Journal of Feline Medicine and Surgery (2007) doi:10.1016/j.jfms.2007.03.002

- To make matters worse, unpublished data indicates mRNA may NOT be detected in dry (focal) form of FIP (A. Legendre, personal communication).

- In a study by Gunn-Moore et al., it was found that up to **80%** of cats in households where FCoV is endemic are **viremic** irrespective of health status.

Gunn-Moore DA, Gruffydd-Jones TJ, Harbour DA. Detection of feline coronaviruses by culture and reverse transcriptase-polymerase chain reaction of blood samples from healthy cats and cats with clinical feline infectious peritonitis. Vet Microbiol 1998;62:193–205.

- Presence of viremia **does not** predispose to development of FIP.
- Also remember that no consistent genetic difference between "FIPV" and avirulent FCoV has been identified.

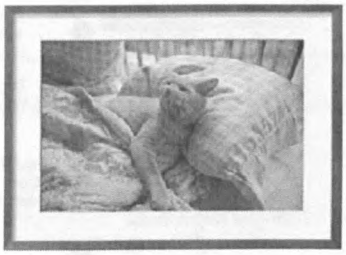
- Is there a consistent difference between the "evil twin" and the "good twin" that can be exploited in a specific assay?
  - There may be no single virus factor that consistently correlates with virulence that could be exploited in an FIP-specific assay; host factors are important.
  - If there is a consistent difference in the evil vs good twin of FCoV, is finding it sufficient to diagnose FIP?

.....I'm not so sure…..

- **It is critical that any new assay developed with claims to this ability be carefully scrutinized.**
- Diagnosis likely to remain combination of tests.

Diagnosis remains a combination of parameters….

How about treating FIP?



Various therapies have been tried.

- Immunosuppressive drugs to reduce the inflammation and control the immune response.
  - May slow disease progression, but no cure.
- Nonspecific immune stimulators not recommended.
  - FIP is an immune-mediated disease.
- Antiviral drugs.
  - Ribavarin – serious side effects in cats.
  - Others?

Immunomodulation.

- Cytokines
  - Recombinant **Human IFNα**.
    - Has not been shown to reduce mortality in vivo.
    - Neutralized by antibody w/I 3-7 weeks of treatment.
  - Recombinant **Feline IFNω** - Not available in US.
    - Inhibits FCoV replication in vitro.
    - One study (not controlled, FIP not confirmed) showed increased survival;

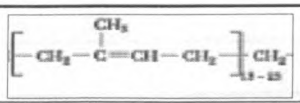
Ishida, T., Shibanai, A., Tanaka, S., Uchida, K., Mochizuki, M., 2004. Use of recombinant feline interferon and glucocorticoid in the treatment of feline infectious peritonitis. J. Feline Med. Surg. 6, 107–109.

    - However, another study with placebo controls and double blinded showed no increase in survival in IFN-treated cats.

J Vet Intern Med 2007;21:1169–1187

Effect of Feline Interferon-Omega on the Survival Time and Quality of Life of Cats with Feline Infectious Peritonitis

Susanne Rätz, Herman Egberink, and Katrin Hartmann



Polyprenyl

- A new report in press has promise in treating the dry form (Legendre and Bartges, J Fel Med Surg, 2009).
  - Treated three cats with the dry form of FIP (confirmed) with an immunostimulant (polyprenyl).
  - Investigatory veterinary biologic; up-regulates Th1 cytokines; unknown mechanism of action.
  - Two of the three cats are still alive two years after diagnosis; one survived 14 months.
  - More study is needed (ongoing).

New technology may hold the key.

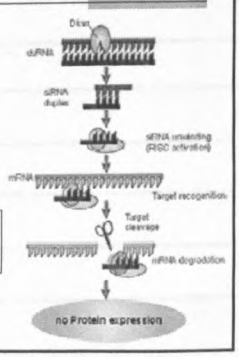
- Small interfering RNA (siRNA).
  - Exploits normal cellular processing.
  - Sequence of the siRNA determines the target.
  - Targets viral RNA for destruction.

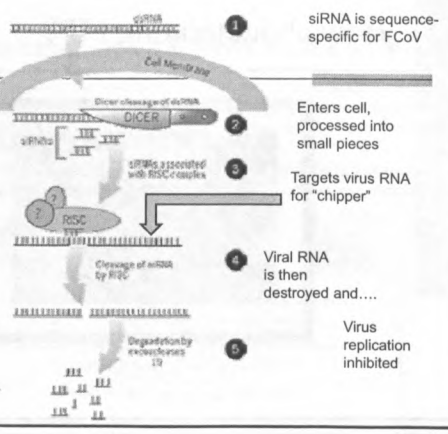
In vitro inhibition of feline coronavirus replication by small interfering RNAs

Phillip McDonagh, Paul A. Sheehy, Jacqueline M. Norris*

Veterinary Microbiology 150 (2011) 220–229

- Inhibit virus replication, decrease tissue damage.





siRNA is sequence-specific for FCoV

Enters cell, processed into small pieces

Targets virus RNA for "chipper"

Viral RNA is then destroyed and....

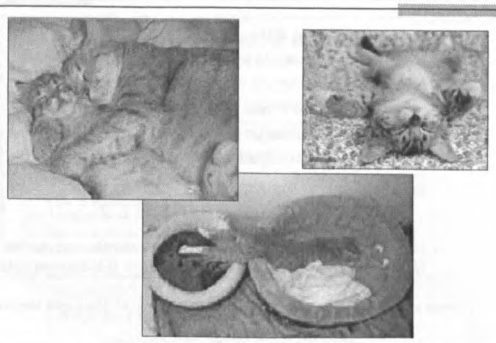
Virus replication inhibited

▪Currently, no effective treatment for FIP but hope springs eternal!

- What about vaccination?
  - Some (small amount?) efficacy in seronegative cats.
  - In high-risk situations (households/catteries where FCoV is endemic), kittens become infected by 4 weeks of age, while the vaccine regimen is initiated at 16 weeks of age.
  - Concern over ADE – non-neutralizing antibodies could enhance disease.
  - Not widely recommended.

Any questions?

mkenned2@utk.edu



Feline Viral Pathogens

Melissa Kennedy DVM, PhD, DACVM
University of Tennessee
Knoxville, Tennessee

Learning objectives

1. To provide the latest information on classical feline pathogens
2. To provide information on newly recognized pathogens
3. To promote a clear understanding of the role of viruses in feline disease.

Feline Herpesvirus

Feline herpesvirus (FHV) is a common pathogen of domestic cats. The virus is a ds DNA virus with a lipid envelope. The virus primarily targets epithelia of the upper respiratory tract and conjunctiva, and only rarely spreads beyond these regions to cause disease. As with all herpesviruses, after acute infection it enters a latent state in innervating sensory nerves. In cats, this most commonly occurs in the trigeminal ganglion. From this latent state, the virus can be reactivated leading to replication in the epithelia, virus shedding, and in a minority of cats, disease. Termed recrudescence, it can be stimulated by any stressor, including trauma, concurrent disease, parturition, boarding, or changes in social hierarchy.

The typical presentation of FHV infection is that of upper respiratory tract disease: sneezing, nasal and/or ocular discharge, depression, and decreased appetite. Conjunctivitis is not uncommon, and can progress to severe hyperemia and chemosis, with mucopurulent ocular discharge. Infection may lead to corneal ulceration. Less common manifestations of FHV are ulcerative dermatitis and stomatitis.

Diagnostics for FHV infection primarily involves virus detection, as most cats are seropositive from either natural exposure or vaccination. Antigen detection using immunofluorescence is fast and inexpensive; however, sensitivity is relatively low, especially in chronic infections. Virus isolation remains the gold standard. However, in chronic infections, notably chronic conjunctivitis or other ocular disease, the virus may be neutralized by locally-produced antibody leading to false negative results. Genetic detection using polymerase chain reaction (PCR) has high sensitivity, such that subclinical, and even latent infections may be detected. Thus, positive results must be interpreted in light of other clinical information.

Advancements have been made in the treatment of FHV infection in cats. Nucleoside analogs developed for human herpesvirus infections have shown some efficacy against feline herpesvirus, at least in vitro. Toxic side effects have been reported with some, such as acyclovir, but others, such as ganciclovir may prove to be useful clinically. Topical administration of antiviral medications has been used with some success, and include trifluridine and idoxuridine. Interferon (IFN) has been used with some success, and has been shown to be efficacious in vitro (human alpha IFN – US; and feline omega IFN – Europe). L-lysine given orally inhibits viral protein synthesis and restricts virus replication. It is optimal when used early in infection, or as a means to prevent recrudescence during stress. Experimentally, lactoferrin has been shown to inhibit virus attachment and entry, and may be eventually be available as an antiviral treatment for FHV.

Protection following recovery is not long-lived, and reinfections may occur. Antigenic variation is not a significant problem with feline herpesvirus, thus, the antigenic coverage of vaccines is adequate. Non-adjuvanted modified live vaccines are recommended. Vaccines do not prevent infection, nor production of the carrier state. They do offer protection from disease, however.

Feline calicivirus

Feline calicivirus (FCV) continues to be an important respiratory pathogen of cats. It is a nonenveloped virus making it very hardy in the environment, and easily spread by fomites. It is a

ss RNA virus with a significant mutation rate. This may lead to changes in antigenicity (many strains that vary antigenically exist) as well as virulence.

Clinical presentations with FCV infection can vary from mild upper respiratory tract disease to viral pneumonia to lethal systemic disease. The typical presentation is similar to FHV infection, though the ocular discharge generally remains serous, corneal ulcers do not occur, and oral ulcers are common. The majority of infections are mild and self-limiting. However, following recovery, infection with shedding in oropharyngeal secretions may persist for periods of week to months, even in the face of vaccination. Lameness, ulcerative dermatitis, and gingivitis have also been associated with FCV, though the pathogenesis is unclear.

Currently, no specific antiviral medication for FCV exists. A recent study showed efficacy of virus-specific compounds in blocking FCV replication in vivo. It was safe, reduced disease development, virus shedding, and mortality.

Persistent infections following recovery from acute disease are not uncommon. Infected cats may continue to shed the virus throughout their lifetime, but most shed for periods of weeks to a few months. Vaccination is the main means of control, and as with FHV, prevents disease, but not infection nor the carrier state. Most vaccines contain a single strain. Manufacturers are investigating the utility of and including additional strains in vaccines to increase the spectrum of protection. Newer vaccinal strains appear to induce neutralizing antibodies against a higher proportion of caliciviral field strains. However, because of the strain variability, it will be difficult to achieve a vaccine that provides protection to all strains in circulation. In addition, it is important to bear in mind that inclusion of two or more strains isolated from different disease manifestations does not necessarily insure broad protection against the varied pathogenic phenotypes.

Environmental decontamination is also important for control in multi-cat situations. During outbreaks of VSD due to FCV, strict quarantine measures and barrier nursing is required to prevent the spread.

Virulent Systemic Calicivirus

In 2000, an isolated epizootic of a virulent systemic disease (VSD) attributed to feline calicivirus (FCV) was described by Pedersen and others. Since then, additional outbreaks in the US and UK have been described. The symptoms have included a high fever, oral ulcers, subcutaneous edema, and ulcerative dermatitis. Interstitial pneumonia, as well as hepatic, splenic and pancreatic necrosis have also been described. The disease has a significant mortality, even in vaccinated cats.

Mutations in the viral genome are believed to be responsible for the change in phenotype of the virus, but each variant from the different outbreaks have been distinct. In fact, no consistent genetic motif has been associated with this disease manifestation. Most have arisen from a shelter or rescue facility, and have “burned out” almost as quickly as they started. This last fact is likely due to the lack of subclinical infection, and the strict quarantine and other control measures implemented in these outbreaks. Host and immune factors are also speculated to play a role in this disease syndrome. Alterations in certain cytokines have been found in affected tissues, suggesting an immunopathogenicity.

Diagnosis of VSD associated with calicivirus involves clinical signs, history, identification of calicivirus in lesions (e.g. swabs of oral ulcers, blood, epidermal biopsies), and elimination of other potential causes. As stated above, no specific viral assay for the FCV of VSD currently exists. At least one commercial vaccine has been released that contains two FCV strains, including one associated with VSD. Since antigenicity does not correlate with disease syndrome, inclusion of two or more strains isolated from different disease manifestations does not necessarily insure broad protection against the varied pathogenic phenotypes. Synergy with the combination of isolates must be demonstrated to substantiate claims of broad antigenic protection.

Feline Parvovirus

The virus, a single-stranded DNA virus, has a significant mutation rate that more closely approaches that of RNA viruses. This has led to amino acid changes in the capsid protein that alter antigenicity, though current variants are closely related. Interestingly, the canine parvovirus emergent strains 2a, 2b, and the recently identified 2c all have the ability to infect and cause disease in cats. Transmission across species lines between dogs and cats is possible. Current

vaccines protect against these strains; in addition, point-of-care ELISAs can detect both FPV and CPV.

Feline Leukemia Virus (FeLV)

Feline leukemia virus (FeLV) remains a significant threat to cats. Infection with FeLV may lead to lifelong persistence of the virus, and causes immunosuppression, degenerative conditions such as anemia, and/or proliferative diseases such as lymphoma and leukemia. Investigations of FeLV infection using molecular detection techniques have identified four stages of infection. In this study, a small % of cats positive by genetic detection were negative by antigen (p27) detection using ELISA. Other studies detecting proviral DNA in whole blood found ~5% were negative by antigen ELISA. It is not know if this is a stage in clearance of the virus, or if the provirus remains. A recent study evaluating risk factors for FeLV infection found that adults, sexually intact males, and outdoor cats were at higher risk for infection.

Vaccines for FeLV were developed many years ago, and are commonly used in veterinary practices. Most are inactivated vaccines with adjuvant. Recently, a recombinant canarypox incorporating the env and gag genes of FeLV has been developed. This vaccine is nonadjuvanted, is administered intradermally, and has been shown to induce comparable immunity to the subcutaneous vaccine. Immunity with FeLV vaccines appears to be nonsterilizing, and in fact, provirus can be found in immunized cats following challenge. The significance of the "latent" virus is not known. As stated in a report by Hoffman-Lehmann and others (2007) vaccines "protect cats from persistent antigenaemia and thus from FeLV-associated fatal disease. They significantly prolong the life expectancy of vaccinated cats. Nonetheless, the search for improved vaccines, which prevent FeLV proviral integration, should continue."

Feline Immunodeficiency Virus

Feline immunodeficiency virus (FIV) also continues to threaten cats worldwide. The risk factors noted above for FeLV also apply to FIV. Infection with FIV is lifelong, thus accurate diagnosis is imperative. Currently, diagnostic assays rely on antibody testing.

FIV isolates are classified into 5 subtypes (A-E) based on genetic sequence of the envelope glycoprotein. Many endemic FIV isolates in Europe, Japan and the US are subtype B, and emerging isolates within this subtype have been documented. A vaccine containing subtypes A and D became available for cats in 2002., and this vaccine has shown efficacy against heterologous subtypes including subtype B. However, other studies have shown less cross protective capabilities. The extreme genetic variation of FIV isolates would seem to indicate that protection against all strains is not feasible. The vaccine is inactivated virus with adjuvant, and is recommended primarily for those cats at high risk, such as outdoor male cats or cats that reside with FIV-infected cats. While protection is afforded, vaccination results in the production of antibodies indistinguishable from that induced by natural infection. Thus, vaccinated cats will test positive with current diagnostic assays. Kittens from vaccinated dams will also possess passively-acquired antibodies.

To circumvent this problem, genetic detection of the virus has been used to diagnose active infection with FIV. However, because of the genetic variation of the virus, false negative results are not uncommon. In addition, false positive results have been found in vaccinated cats. The results from one study by Crawford and others (2005) are shown in this table:
Thus, reliable and accurate detection of FIV infection by molecular assays is difficult. Recently, a report by Levy and others (2008) has shown promising results with an antibody assay able to distinguish vaccinal response from that of natural infection. This discriminant ELISA may prove to be useful for accurate testing of vaccinated cats.

Influenza

The emergence and spread of the H5N1 strains of avian influenza in recent years has caused concern over a future pandemic in the human population. The virus, a particularly virulent and contagious strain, has affected waterfowl and domestic poultry in Asia, Europe, the Middle East and Africa. In addition, it has successfully infected humans in contact with infected birds,

leading to severe disease, and death in over 50% of cases. Thusfar, efficient human-to-human spread has not occurred.

Infection has also occurred in domestic cats and dogs. Seropositive dogs and cats have been found in Thai villages. Natural infection of dogs has occurred from ingestion of infected carcasses. In some cases, systemic disease and death have occurred. Cats also may be infected by consumption of carcasses of infected birds. During an outbreak in Germany among waterfowl, infection of several domestic cats occurred. Infections were fatal, and pneumonia and hepatic necrosis was found. Experimental studies in cats have produced lethal infections, and spread to in-contact cats. Shedding was documented in both respiratory secretions and feces of infected cats. Inoculation studies in dogs have shown susceptibility of dogs to infection with H5N1, and shedding may occur from the nose with no signs of disease. This study also showed receptors for the avian influenza exist in both the upper and lower respiratory tracts of dogs.

Because these animals live in close contact with humans, concern exists over the risk of transmission from these animals. This possibility also brings questions from owners regarding risks to their pets, and themselves. Currently, it is unlikely that cats and dogs play any role in the natural transmission of avian influenza. No direct transmission has been reported, and the level of shedding by these animals appears to be lower than that of birds. However, monitoring of domestic pets during an H5N1 outbreak is warranted.

In 2009, a new reassortant emerged that resulted in a worldwide pandemic. The 2009 pandemic H1N1 as it came to be known infected a number of other species, including cats resulting in significant disease. We can now add seasonal flu to the list of feline pathogens of concern.

Rabies

Rabies virus continues to be a threat to domestic pets worldwide. Recently, it was announced by the CDC that the canine strain of rabies has been eliminated from the US. However, the virus remains present in wildlife in the US, posing a risk for domestic pets, as well as people. Lyssaviruses continue to emerge in other parts of the world, and genetic variants of rabies virus do exist. New variants of rabies virus in North America could occur and pose an emerging threat. Rabies infections in raccoons are of particular concern due to the increased likelihood of raccoon contact with pets as well as people in suburban areas. In addition, importation of dogs poses a risk for introduction of foreign variants. Data indicates an increasing number of unvaccinated puppies are being imported into the US, and since 2004, infection has been documented in at least two imported puppies. Federal regulations are under review to address these risks.

Other viruses to be discussed include feline papillomaviruses, which may be associated with squamous cell carcinoma; the newly recognized feline morbillivirus; norovirus; and bornavirus.

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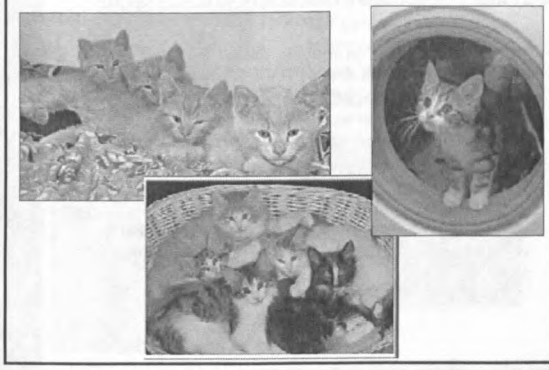
24th Annual Fred Scott Feline Symposium July 2012

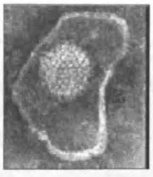
- Melissa Kennedy, DVM, PhD, DACVM
  University of Tennessee
  College of Veterinary Medicine
  Knoxville, Tennessee

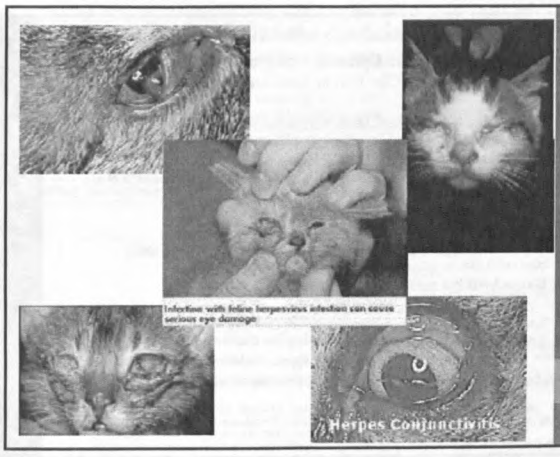
The kitties….update on virus pathogens



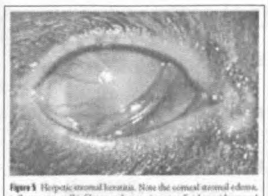
Feline Herpesvirus – the gift that keeps on giving….

- Majority of infections are never cleared.
  - Latency in neural tissue.
  - Recrudesce during stressful episodes - subclinical.
- Signs of URTI.
  - Sneezing, conjunctivitis
  - Ocular and nasal discharge
  - Can cause severe ocular disease, including keratitis and dendritic ulcers.
  - Brief viremia occurs with primary infection, but not recrudescence.





- Stromal keratitis may occur subsequent to FHV-1 infection.
  - Immune-mediated pathogenesis.
  - Infiltration of cornea with inflammatory cells.
  - May lead to blindness.
  - Persistent viral antigen – no, or low level viral replication, but not latency either.
  - Antivirals not effective alone.



From: Maggs, D. J. 2005. Update on Pathogenesis, Diagnosis, and Treatment of FHV-1. Clin. Tech. in Small Anim. Pract. 20:94-101

Diagnostics

- Detection of the virus most useful due to infection rates and vaccination (serology often positive).
  - Virus isolation – not as useful for chronic infections.
  - Antigen detection by IFA – low sensitivity.
  - Molecular detection by PCR – better for chronic infections, but can also detect subclinical, even latent infections.

Detection of virulent feline herpesvirus-1 in the corneas of clinically normal cats

Journal of Feline Medicine and Surgery (2008) **10**, 154–159

Jean Stiles DVM, MS, DACVO[1]*, Roman Pogranichniy DVM, PhD[2]

This study documents the presence of FHV-1 capable of replicating in the corneas of asymptomatic cats. Whether this finding represents latency of FHV-1 in the cat cornea or low level persistent infection is not possible to determine. The latter

Relative sensitivity of polymerase chain reaction assays used for detection of feline herpesvirus type 1 DNA in clinical samples and commercial vaccines.
David J. Maggs, BVSc, and Heather E. Clarke, BS. AJVR, Vol 66, No. 9, Sept 2005

- "....the sensitivity of an assay (ie, the probability that an FHV-1 PCR assay will detect FHV-1 DNA in a sample that contains the virus) *does not necessarily equate to diagnostic sensitivity* (ie, the probability that an FHV-1 PCR assay will detect FHV-1 DNA in subjects with disease attributable to FHV-1).
- Indeed, as the lower limit of viral DNA that a test can detect decreases (ie, test sensitivity increases), the *number of clinically normal animals in which subclinical shedding of low amounts of virus is detected would be expected to increase*. This would be associated with decreased diagnostic sensitivity of that assay."

Treatment

FHV-1 is one viral pathogen for which antivirals are available.

- None currently approved for use in cats.
- Caution before assuming a human drug will work or will be safe.
- Most topicals are virostatic and require frequent application.
- Use with severe, persistent, or recurrent disease, or with corneal involvement.

From: Maggs, D. J. 2005. Update on Pathogenesis, Diagnosis, and Treatment of FHV-1. Clin. Tech. in Small Anim. Pract. 20:94-101

- **Trifluridine** is first choice, but it is irritating when applied.
- **Idoxuridine** is a good choice because of efficacy, cost, and lower irritancy; requires compounding by pharmacist.
- **Cidofovir** (0.5% soln topically) was recently evaluated (Fontenelle et al., AJVR, Vol 69, No. 2, February 2008).
  - Decreased severity of disease; Decreased shedding of virus.
  - Administration 2x/d and for short periods were effective.
- **Acyclovir**, a systemic drug, has poor efficacy for FHV-1and low bioavailability in cats and can suppress BM.
- **Ganciclovir** has been found to inhibit FHV-1 in vitro.

- Recent studies (J Fel Med Surg, 11:40-48, 2009; AJVR 2011 72:85-95) found oral **Famciclovir** to be promising for treatment.
  - Improvement of all parameters – signs, shedding, recovery period.
  - Most required treatment >1mo; improvement was observed in all cases.

Adjunctive therapies....

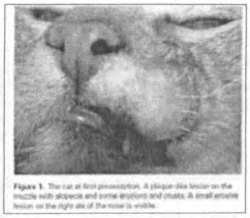
- **Lysine** – antagonizes Arg uptake, which is required for FHV-1 replication.
  - Reduces severity of disease in primary infection.
  - Reduces shedding in recrudescence.
- **Lactoferrin** – iron-binding glycoprotein produced by mucosal epithelial cells of many mammals, incl cats.
  - Inhibits FHV-1 adsorption to and/or penetration into the cell in vitro.
  - Not yet commercially available.
- **Interferon**
  - Both human and feline rIFN have shown efficacy in vitro.
  - rFeIFN has shown efficacy in vivo (topical and oral).
  - Dose-dependent.

Oral supplementation with L-lysine did not prevent upper respiratory infection in a shelter population of cats

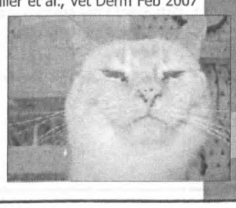
- A study by Rees and Lubinsky (J Fel Med Surg, 10:510-513, 2008) evaluated efficacy of L-lysine as a preventative for URTI in shelter cats.
- Healthy cats/kittens coming into the shelter over a three-month period; only healthy animals included.
- Randomly assigned to treatment (n= 144; oral lysine daily) or non treatment (n=147).
- As the title indicates, no difference was seen between the two groups in terms of URI.
  - Etiology was not determined.
  - Numbers make it likely FHV was involved.
  - Stress of the environment may negate positive effects of lysine treatment.
  - According to the authors: "Time, staffing, and money may be better spent in working toward developing infection control practices, limiting fomite transmission, and general stress reduction."

Feline Herpesvirus Dermatitis

- Ulcerative facial and nasal dermatitis.
- Characterized by eosinophilic infiltrate.
- Can be mistaken for eosinophilic granuloma if inclusions not found.
- Test biopsy by PCR for FHV.



Gutzwiller et al., Vet Derm Feb 2007



Lentigo Simplex
Provided by Rebecca Korven, DVM; Cape Breton Vet Services, Canada

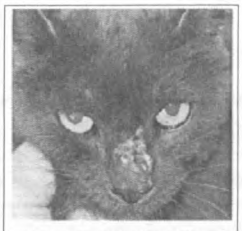


Figure 1. Ulcerative dermatitis of face of cat with feline herpesvirus 1 documented by PCR. This lesion cannot completely spontaneously healed after persisting for at least 7 months. The lesion recidivated but unknown reasons in the same site. The recurrent lesion is depicted in this photograph. Photograph courtesy of Dr Dennis E. Dobbs.

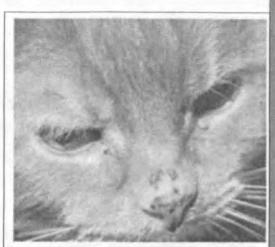
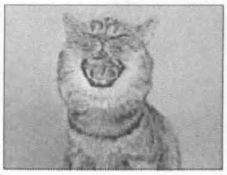


Figure 2. Dermatitis of the nose of a cat with feline herpesvirus 1 documented by PCR. Note ulceration and crusting. Photograph courtesy of Dr Alan C. Mundell.

Hargis A.M., Ginn P.E., Mansell J.E.K.L., Garber R.L., Ulcerative facial and nasal dermatitis and stomatitis in cats associated with feline herpesvirus 1, Vet. Dermatol. (1999)10:267–274.

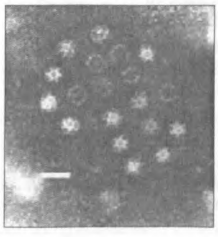
Vaccination

- MLV parenteral and intranasal recommended.
- Prevent disease, not infection, nor the carrier state.



Virulent Systemic Feline Calicivirus (VS FCV)

- First documented case in 2000.
- Cases reported across the US and also in the UK.
- Majority originate in shelters or rescue facilities, introduced into new population.
- Has occurred in exotic felids.



Lethal outbreak of disease associated with feline calicivirus infection in cats

K. P. Coyne, B. R. D. Jones, A. Kipar, J. Chantrey, C. J. Porter, P. J. Barker, S. Dawson, R. M. Gaskell, A. D. Radford The **Veterinary Record**, April 22, 2006

An isolated epizootic of hemorrhagic-like fever in cats caused by a novel and highly virulent strain of feline calicivirus

Veterinary Microbiology 73 (2000) 281–300

N.C. Pedersen[a,*], J.B. Elliott[b], A. Glasgow[a], A. Poland[a], K. Keel[c]

An outbreak of virulent systemic feline calicivirus disease

JAVMA, Vol 224, No. 2, January 15, 2004

Kate F. Hurley, DVM, MPVM; Patricia A. Pesavento, DVM PhD; Niels C. Pedersen, DVM PhD; Amy M. Poland, BS; Erin Wilson, DVM; Janet E. Foley, DVM, PhD

Journal of Zoo and Wildlife Medicine 38(2): 292–299, 2007
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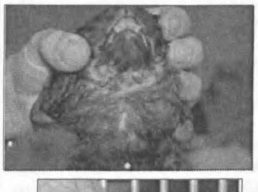
SYSTEMIC CALICIVIRUS EPIDEMIC IN CAPTIVE EXOTIC FELIDS

Tara M. Harrison, D.V.M., M.P.V.M., James Sikarskie, D.V.M., M.S., Dipl. A.C.Z.M., John Kruger, D.V.M., Ph.D., Annabel Wise, D.V.M., Ph.D., Thomas P. Mullaney, D.V.M., Ph.D., Dipl. A.C.V.P., Matti Kiupel, D.V.M., Ph.D., Dipl. A.C.V.P., and Roger K. Maes, D.V.M., Ph.D.



- In addition to characteristic URT and oral lesions:
  - Skin ulceration, esp pawpads, pinnae, and nares.
  - SQ edema.
  - Bronchointerstitial pneumonia.
  - Hepatic, splenic, pancreatic necrosis.
  - Significant mortality, even among vaccinated cats.

- What is responsible for the "new" phenotype?
  - No consistent genetic mutation has been identified – no marker.
  - Change in attachment site?
  - Change in neutralizing epitope?
  - Each variant arises independently, and outbreaks thusfar "burn out".

- Is it really "new"?
- Previous reports as far back as 1970's document systemic involvement associated with FCV infection.

- May involve strains that can replicate to high titer.
  - In a population with some immunity, as in a rescue facility where the virus is circulating, rapid virus replication is selected for.
    - Presence of VN antibodies in the population.
    - Viral replication may thus be limited.
    - Multiple variants may be in circulation – increases diversity.
  - When introduced to a naïve population, rapid high titer replication and systemic spread.
  - Severe disease.

Feline caliciviruses (FCVs) isolated from cats with virulent systemic disease possess *in vitro* phenotypes distinct from those of other FCV isolates

Journal of General Virology (2007), 88, 506–517

Robert J. Ossiboff,[1] Alexander Sheh,[1]† Justine Shotton,[1] Patricia A. Pesavento[2] and John S. L. Parker[1]

Genetic analysis of feline caliciviruses associated with a hemorrhagic-like disease

J Vet Diagn Invest 17:420–429 (2005)

Mohamed Abd-Eldaim, Leon Potgieter,[1] Melissa Kennedy

Characterization of a highly virulent feline calicivirus and attenuation of this virus

Virus Research 122 (2006) 95–108

Sing Rong[a,*], David Slade[a], Kim Floyd-Hawkins[b], David Wheeler[b]

- The analyses of the genome have shown differences among isolates, primarily in the gene encoding the major capsid protein.
- Spreads more easily in tissue culture.
- But no conserved mutation that could be exploited in a specific test for VS FCV.

Is there a specific test for VS FCV?

- Diagnose by same methods as for classic presentation:
  - Virus detection.
    - Virus isolation
    - RT-PCR – most sensitive,
      - But beware! - can detect subclinical infection.
      - False negative results can occur as well.
    - Antigen detection
    - Post mortem – Histopathology, IHC
  - Serology – not as helpful due to infection rates and vaccination.
  - Characterization as VS FCV based on clinical presentation.

Detection of FCV by genetic detection:

- A significant hurdle has been the sequence variation of isolates.
  - High mutation rate.
  - Sequence divergence as high as 38%.
  - Leads to false negative results.
- Work done by Abd-Eldaim et al. (Arch Virol 154:555-560, 2009) identified a highly conserved region in the 5'-end of the genome.
  - Used this information to design a real-time PCR assay for FCV.
  - Uses a hybridization probe (increased specificity)
  - Proved to be both sensitive and specific.

Calicivirus treatment on the horizon?

- In vitro sensitivity to **rFeIFN.**
  - Decreased viral replication.
  - BUT – it varied with the strain.
- Specific **antiviral** treatment.
  - Used small pieces of genetic material matching a portion of the FCV genome.
  - In vitro blockage of replication.
  - In vivo trials showed reduction of virus shedding and faster clinical recovery in severe calicivirus outbreaks.

Vet Res Commun (2008) 32:167–174
DOI 10.1007/s11259-007-9019-5

ORIGINAL ARTICLE

Sensitivity of FCV to recombinant feline interferon (rFeIFN)

Kyoko Ohe · Toshikazu Takahashi · Daisuke Hara · Motonobu Hara

Virus-specific antiviral treatment for controlling severe and fatal outbreaks of feline calicivirus infection

AJVR, Vol 69, No. 1, January 2008

Alvin W Smith, DVM, PhD; Patrick L. Iversen, PhD; Peter D. O'Hanley, MD, PhD, MPH; Douglas E. Skilling, BS; Janet B. Christensen, MSPH; Sherry S. Wagner, DVM, Elizabeth Longley, DVM, Michael A. Stone, MS, DVM; Steve E. Poet, DVM, PhD; David O. Matson, MD, PhD

Significant antigenic variability complicates vaccine efficacy….

- Emergence of antigenically distinct strains has been documented in closed feline population.
- In endemically infected colonies, divergence near 20% reported.
- In addition, endemically infected colonies provide an environment for increasing FCV genetic and thus antigenic diversity, and may lead to the emergence of new strains with varying virulence.

Recombination of *Feline calicivirus* within an endemically infected cat colony

Journal of General Virology (2006), 87, 921–926

K. P. Coyne,[1] F. C. Reed,[2] C. J. Porter,[2] S. Dawson,[1] R. M. Gaskell[2] and A. D. Radford[1]

Evolutionary Mechanisms of Persistence and Diversification of a Calicivirus within Endemically Infected Natural Host Populations[▽]

Karen P. Coyne,[1]* Rosalind M. Gaskell,[2] Susan Dawson,[1] Carol J. Porter,[2] and Alan D. Radford[1]

JOURNAL OF VIROLOGY, Feb. 2007, p. 1961–1971

When evaluating a new FCV vaccine, bear in mind….

- Neutralizing antibodies raised to one strain may not neutralize a heterologous strain.
- Disease phenotype does not segregate with antigenicity.
- Studies evaluating cross-protection demonstrated that *protection against heterologous strains correlated with serum cross-neutralization studies.*
  - Laboratory evaluation of the ability of serum antibodies induced by a particular strain of FCV to neutralize multiple strains will be important in determining which strains to include in a vaccine.

- Strain combination should be based on genetic and antigenic, and in particular, cross-neutralization studies rather than disease phenotype alone.

Is the current VS FCV vaccine recommended?

- Generally speaking, increasing antigenic spectrum of a vaccine is beneficial.
- Data has indicated an increased antigenic spectrum of this vaccine (unpublished).

But…

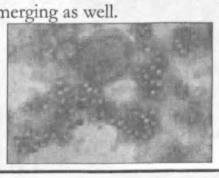
- Killed component with adjuvant.
- The VS FCV outbreaks have been relatively limited.

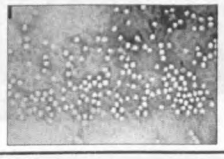
What about the FCV carrier state?

- Significant % remain chronically infected.
  - Prevalence rates of 15-91% reported.
  - Shed virus – not latent as with FHV-1.
  - Excretion primarily from oropharynx.
- Sequential reinfection occurs in populations where FCV is endemic.
- May lead to new variants with change in antigenicity.
  - Divergence of 20% has been documented in strains within a population.
  - Could lead to changes in virulence.

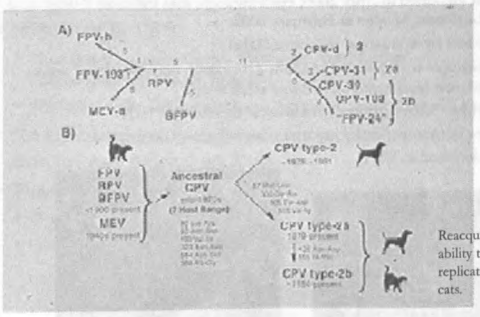
Parvoviruses have a mutation rate similar to that of RNA viruses – high.

- Parvoviruses have a higher mutation rate than most DNA viruses; recombination between different strains also may occur.
- Canine parvovirus 2 originally arose from a virus related to feline parvovirus.
- In the 1980's, 2 new variants emerged – CPV-2a and -2b; CPV-2 has been replaced by these variants; CPV-2c now emerging as well.





Relatively few amino acid changes responsible for changes in host and tissue tropism….



Reacquired ability to replicate in cats.

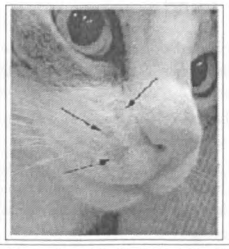
- CPV-2a,2b, and 2c can replicate in cats.
  - Regained feline tropism.
  - Only a few amino acid changes in the major capsid protein gene.
  - May cause typical disease.
  - In Asia, CPV is more prevalent in cats than FPV.
  - Mixed infections can also occur.

Predominance of Canine Parvovirus (CPV) in Unvaccinated Cat Populations and Emergence of New Antigenic Types of CPVs in Cats
Virology 278, 13–19 (2000)
Yasuhiro Ikeda,*,† Masami Mochizuki,† Risako Naito,* Kazuya Nakamura,* Takayuki Miyazawa,* Takeshi Mikami,*,‡ and Eiji Takahashi*,§

Feline Host Range of *Canine parvovirus*: Recent Emergence of New Antigenic Types in Cats
Yasuhiro Ikeda,*† Kazuya Nakamura,† Takayuki Miyazawa,† Yukinobu Tohya,† Eiji Takahashi,‡ and Masami Mochizuki‡
Emerging Infectious Diseases • Vol. 8, No. 4, April 2002

Feline Papillomavirus

- Associated with viral plaques in immunosuppressed cats.
- Also found in some squamous cell sarcomas (cutaneous and oral).
- Viral DNA has also been found in normal skin; and majority of SCC's do not contain papillomavirus in studies done thusfar.
- More research is needed on its possible role in carcinogenesis.



Vet Dermatology 19(6):400-404 December 2008

J Vet Diagn Invest 22:946–949 (2010)

Consistent detection of *Felis domesticus papillomavirus 2* DNA sequences within feline viral plaques

John S. Munday,[1] Jeanine Peters-Kennedy

What about noroviruses?

- Found in a number of animal species, including cattle, swine, mice, lion cub.
- Caliciviruses have been identified in feces of dogs with diarrhea.

Human Noroviruses in Swine and Cattle
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 8, August 2007

Norovirus is a problem for the food service industry

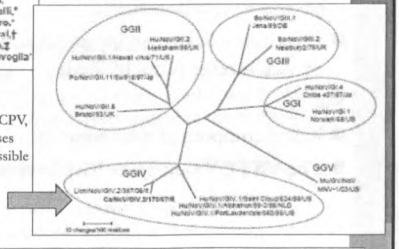
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 7, July 2007

Norovirus in Captive Lion Cub (*Panthera leo*)

Detection and Molecular Characterization of a Canine Norovirus

Vito Martella,[1] Eleonora Lorusso,[1] Niccola Decaro,[1] Gabriella Elia,[1] Arianna Radogna,[1] Maria D'Abramo,[1] Costantina Desario,[1] Alessandra Cavalli,[1] Marialaura Corrente,[1] Michelle Camero,[1] Cinzia A. Germinario,[1] Krisztian Bányai,[2] Barbara Di Martino,[3] Fulvio Marsilio,[3] Leland E. Carmichael,[4] and Canio Buonavoglia[1]

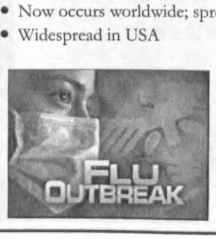
Isolated from dog with diarrhea;the dog also had CPV, so it's not known if it causes disease, nor if it's transmissible to humans.

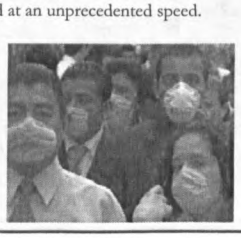


Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 14, No. 8, August 2008

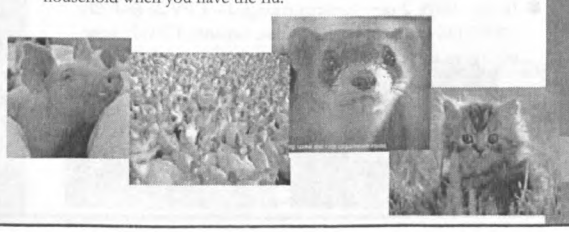
2009 H1N1 (aka Swine Flu)

- First identified in April 2009; epidemiologic data indicates it originated in La Gloria, Mexico in February 2009.
- Distinct from seasonal influenza H1N1
- Quadruple reassortant – contains genes from two lineages of swine virus, one human strain, and one avian strain.
  - HA is ~20% divergent from seasonal flu strains of H1N1
- Now occurs worldwide; spread at an unprecedented speed.
- Widespread in USA





- Likely emerged in humans as a single event from swine (human involvement?).
- Spreads efficiently from person to person; appears to be more transmissible than the seasonal influenza.
- Has also been transmitted to swine, turkeys, ferrets, and several cats.
- Potential exists for spread to other species – thus, use same precautions with pets as with human members of the household when you have the flu.



Influenza A Pandemic (H1N1) 2009 Virus Infection in Domestic Cat

Brett A. Epurzycki, Erin Ekstrand, Albert Jorgens, Jessie Trujillo, Karen Harmon, Leo Koster, Melinda Jenkins-Moore, Mary Killian, Sabrina Swenson, Holly Bender, Ken Waller, Kristina Miles, Tracy Pearce, Kyoung-Jin Yoon, and Peter Nara

Influenza A pandemic (H1N1) 2009 virus continues to rapidly spread worldwide. In 2009, pandemic (H1N1) 2009 infection in a domestic cat from Iowa was diagnosed by a novel PCR assay that distinguishes between Eurasian and North American pandemic (H1N1) 2009 virus matrix genes. Human-to-cat transmission is presumed.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 16, No. 11, November 2010

Experimental Pandemic (H1N1) 2009 Virus Infection of Cats

Judith M.A. van den Brand, Koert J. Stittelaar, Geert van Amerongen, Marco W.G. van de Bildt, Lonneke M.E. Leijten, Thijs Kuiken, and Albert D.M.E. Osterhaus

To demonstrate that pandemic (H1N1) 2009 virus may cause respiratory disease in cats, we intratracheally infected cats. Diffuse alveolar damage developed. Seroconversion of sentinel cats indicated cat-to-cat virus transmission. Unlike in cats infected with highly pathogenic avian influenza virus (H5N1), extrapulmonary lesions did not develop in cats infected with pandemic (H1N1) 2009 virus.

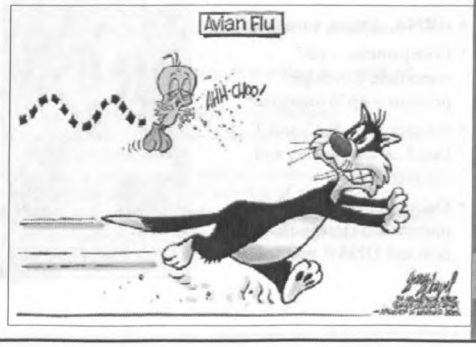
At least one study has shown significant seroprevalence in household pet cats.

Seroprevalence of seasonal and pandemic influenza A viruses in domestic cats

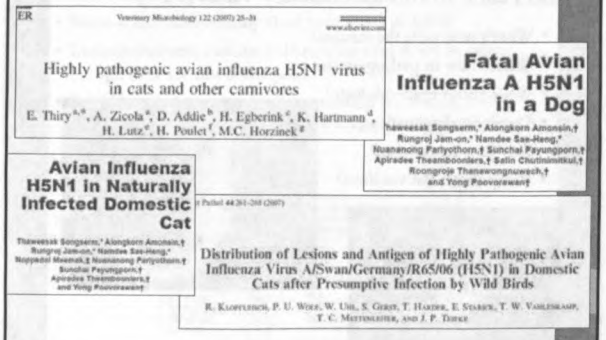
Jonathan A. McCullers • Lee-Ann Van De Velde • Ronald D. Schultz • Cristen G. Mitchell • C. R. Halford • Kelli L. Boyd • Stacey Schultz-Cherry

Arch Virol (2011) 156:117–120

Avian flu – is it a threat to our pets?



It can infect other animals….



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Veterinary Microbiology 122 (2007) 25–31

Highly pathogenic avian influenza H5N1 virus in cats and other carnivores

E. Thiry[a,*], A. Zicola[a], D. Addie[b], H. Egberink[c], K. Hartmann[d], H. Lutz[e], H. Poulet[f], M.C. Horzinek[g]

Fatal Avian Influenza A H5N1 in a Dog

Thaweesak Songserm,* Alongkorn Amonsin,† Rungroj Jam-on,* Namdee Sae-Heng,* Nuanaong Pariyothorn,† Sunchai Payungporn,† Apiradee Theamboonlers,† Salin Chutinimitkul,† Roongroje Thanawongnuwech,† and Yong Poovorawan†

Avian Influenza H5N1 in Naturally Infected Domestic Cat

Thaweesak Songserm,* Alongkorn Amonsin,† Rungroj Jam-on,* Namdee Sae-Heng,* Noppadol Meemak,‡ Nuanaong Pariyothorn,† Sunchai Payungporn,† Apiradee Theamboonlers,† and Yong Poovorawan†

Avian Pathol. 44:261–268 (2007)

Distribution of Lesions and Antigen of Highly Pathogenic Avian Influenza Virus A/Swan/Germany/R65/06 (H5N1) in Domestic Cats after Presumptive Infection by Wild Birds

R. Klopfleisch, P. U. Wolf, W. Uhl, S. Gerst, T. Harder, E. Starick, T. W. Vahlenkamp, T. C. Mettenleiter, and J. P. Teifke

- Cats – inhalation or ingestion from infected birds/meat.
  - Systemic infection; lung liver.
  - Fever, respiratory distress
  - Shed in respiratory, urine, feces of cats.
  - **But** at only 0.1% level of birds.
  - Not believed to be important epidemiologically.
- Dogs – seroconvert.
- Other carnivores have been infected.

What is the current situation with H5N1?

- H5N1 not in USA.
  - "hot spots" remain China, southeast Asia, Indian subcontinent, parts of Africa.
  - Surveillance in US is ongoing – domestic and wild fowl.
- No efficient human-to-human spread, nor spread among hosts other than birds.
- The virus continues to evolve.
  - Drug resistance.
  - Will it be the next pandemic?.....Unknown.

Some good websites…..

- www.pandemicflu.gov
- www.avma.org/public_healthy/influenza/avian
- www.usda.gov
- www.who.int/csr/disease/avian_influenza/

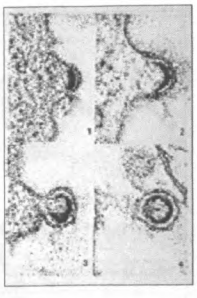
Update on Feline Retroviruses….

Feline Leukemia Virus (FeLV) and Feline Immunodeficiency Virus (FIV)

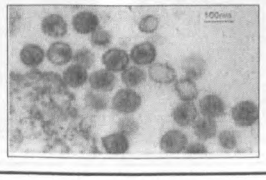
- What's new with the viruses?
- What's new in pathogenesis?
- What about epidemiology?
- Latest on diagnostics…..
- Any new treatments?
- What about the vaccines?

FeLV - Retroviridae, Gammaretrovirus (used to be Oncovirinae)

- ss**RNA**, diploid, enveloped
- Core proteins – p27 important; Envelope proteins – gp70 important.
- Subgroups A, B, C, and T based on antigenicity and cell receptors.
- During replication, **DNA** intermediate integrates into host cell DNA – provirus.



- FeLV A is weakly pathogenic, and is the predominant virus spread cat-to-cat.
- Subgroups B, C, and T arise from A by point mutation, insertions and recombination events.
  - Lead to lymphoma, anemia, and immunodeficiency respectively.



FeLV – the virus and the host response

- Molecular methods have provided insight into FeLV infection.
- **Four possible outcomes** of infection.
  - Abortive – antigen and provirus negative
  - Regressive – antigen negative, transient or low provirus
  - Latent – transient antigen, persistent provirus
  - Progressive – persistent antigen and provirus
- **FeLV-exposed, antigen negative cats represent a spectrum of outcomes**, with some completely eliminating infection, while others maintain low to moderate levels of infected cells.
  - Reactivation could occur in the latter group.

From: *Torres, A. N., C. K. Mathiason, and E. A. Hoover. 2005. Re-examination of feline leukemia virus: host relationships using real-time PCR. Virology 332:272-283.*

- The authors hypothesize:
  - Abortive infections result from effective early host immune response.
  - Regressive infections contain virus infection while retaining a low level of FeLV infected cells.
    - Many may go on to eliminate infection entirely.
  - Latent infections have delayed containment of viral replication resulting in residual provirus.
    - Could reactivate if immune containment wanes.
  - **For the latter two (which are ELISA -), proviral DNA was detected in lymphoid tissue and in circulation, in addition to BM.**
    - **Could impact blood donation.**

R. Hofmann-Lehmann et al. / Vaccine 25 (2007) 5531–5539

Table 1
Description of response categories observed after intrapreputial FeLV challenge of 30 cats of vaccine study 2 and comparison with those described after o antigenaemia, proviral and plasma viral RNA loads, virus isolation from blood and bone marrow

Putative response categories	Antigenaemia	Proviral loads (duration of detectability)	Plasma viral RNA loads[a] (duration of detectability)	Virus isolation blood[b]	Virus from bone marrow[c]
Abortive[d]	Undetectable	Undetectable	Not tested	Not tested	Not tested
Regressive with undetectable antigenaemia[e]	Undetectable	Low to moderate (persistent)[f]	Low to moderate (transient or persistent)	Negative	Negative
Regressive with transient antigenaemia	Transient	Low to moderate (persistent)	Low to moderate (transient or persistent)	Negative or transiently positive	Negative or positive
Latent[g]	Transient	Low to moderate (persistent)	Low to moderate (transient or persistent)	Negative	Positive
Progressive	Persistent	High (persistent)	High (persistent)	Positive	Positive

[a] Quantified in weeks 1–15 after challenge.
[b] Determined in weeks 3, 6, 9, 12 and 15 after challenge.
[c] Determined in week 17 after challenge.
[d] Observed after cronnasal challenge [39] but not after intrapreputial challenge.
[e] Observed after intrapreputial challenge but not after cronnasal challenge [39].
[f] No persistent clearance of provirus observed in any of the cats after intrapreputial challenge throughout an observation period of >3 years.
[g] Defined by absence of antigenaemia but persistence of reactivatable virus in the bone marrow [21,22].
[h] Two cats listed with transient antigenaemia were found to be also latently infected.

What is the importance of the persistence of proviral DNA?

- The clinical relevance of PCR (+) but antigen (-) cats is not clear.
  - Provirus DNA is present in a high % of feline lymphomas.
- **At a minimum, PCR(+) cats should not be used as blood donors.**
- Provirus and viral RNA are detectable within one week of exposure.
  - Occurs with regressive and progressive infections.
  - In progressive infections, virus replicates extensively in many tissues, with virus excretion.
  - With regressive infection, the virus is contained before BM is infected; no viral shedding, and little risk of dz.
- ***PCR is thus more sensitive in detecting FeLV exposure, but a + result doesn't necessarily mean the cat will develop FeLV-associated disease, nor that it is contagious.***

- FeLV is transmitted primarily via saliva.
  - One million viruses/ml of saliva.
  - Viremic cats consistently shed viral RNA in saliva.
  - Latently infected cats have detectable viral RNA in saliva, though they are not contagious.
  - Could be used as a noninvasive method for testing for epidemiologic studies, as well as for very young kittens and debilitated patients.

M. A. Gomes-Keller, et al. JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2006, p. 916–922 Vol. 44, No. 3

TABLE 3. Comparison of different tests for the diagnosis of FeLV, considering the detection of provirus in whole blood as the gold standard[a]

Test[b]	Diagnostic sensitivity (%)	Diagnostic specificity (%)	Accuracy (%)	PPV[c] (%)	NPV[d] (%)
RNA saliva	69.2	99.7	94.4	98.2	93.9
p27 saliva	56.4	94.4	87.4	69.8	90.5
RNA plasma	70.5	100.0	94.8	100.0	94.1
p27 plasma	67.9	99.7	94.2	98.2	93.6

- A recent study found evidence of FeLV in feces.
  - FeLV RNA and DNA found in feces of antigenemic cats by PCR and virus isolation.
  - Naïve cats exposed to these feces seroconverted, but did remain negative for viral antigen or RNA/DNA in the blood.
  - Likely a secondary mode of transmission; however, sharing of litter pans by viremic and susceptible cats could lead to transmission.

Fecal shedding of infectious feline leukemia virus and its nucleic acids: A transmission potential

M.A. Gomes-Keller [a,c], E. Gönczi [a], B. Grenacher [b], R. Tandon [a], R. Hofman-Lehmann [a], H. Lutz [a]

Veterinary Microbiology 134 (2009) 208–217

Prevalence rates in North America....

- A study by Levy et al. JAVMA, Vol 228, No. 3, February 1, 2006
  - Tested 18,038 cats; veterinary clinics and shelters.
  - All ages, lifestyles, and health conditions.
  - Tested over a four-month period; not random.
  - ELISA only.
- Overall seroprevalence ~2.5%.
- Vet clinics > Shelters; Sick > Healthy.
- FeLV and FIV seropositivity highest among adults, males, cats with access to outdoors.
- Cats in all categories were at risk for infection.

- A study by Goldkamp et al. (JAVMA, Vol 232, No. 8, April 15, 2008) found that a high proportion of cats with abscesses or bite wounds were seropositive to either FIV or FeLV.
  - The investigators concluded testing should be done at the time of treatment and 60 days later.

Treatments for FeLV-infected cats….

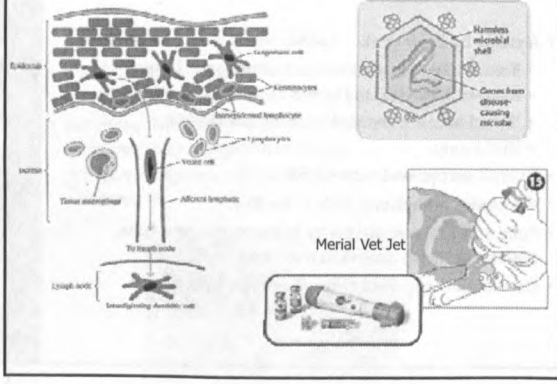
- Use of **Staphylococcus protein A** has shown minimal benefit (McCaw et al., J Am Anim Hosp Assoc 2001;37:356–363).
  - May enhance antibody production, T cell activation and IFN production, stimulate NK cells, and increase removal of immune complexes.
  - No improvement observed in any objective parameters.
- Results with **interferon** have been conflicting.
  - Inhibitory *in vitro*.
  - Some studies have shown improved clinical parameters and survival rates.
  - Others have shown no effect, or even deleterious effects.
  - Human IFN can induce abs against it, making the drug ineffective within a few weeks.

- Antivirals designed for HIV.
  - Some have shown in vitro efficacy, such as AZT (Zidovudine); in vivo success against FeLV has not been as clear.
  - Newer drugs may show more promise.
- Ribavarin inhibits several RNA and DNA viruses – inhibits capping of viral mRNA; but it is ***extremely toxic in cats.***

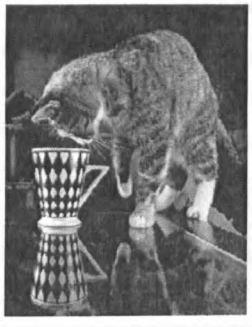
FeLV Vaccination….

- Vaccination with both the recombinant and killed FeLV vaccines leads to protection against antigenemia.
- Molecular assays have shown that after challenge with FeLV, vaccinated cats may become provirus and RNA positive in cells and plasma initially, albeit at lower levels than nonvaccinated cats.
- Thus immunity is not sterilizing.
- However, the vaccines do protect against progressive infections.
- Recommended for all kittens; for adults, it is considered non-core, recommended for cats at risk (e.g. outdoors, contact with known +'s, etc.)

Recombinant intradermal vaccine…

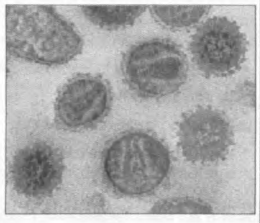


What's new with FIV and its pathogenesis?

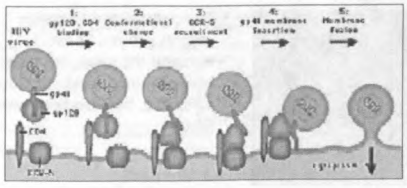


Retroviridae, Lentivirus

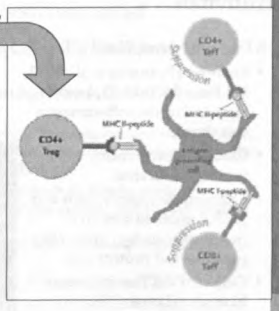
- ss**RNA**, diploid; enveloped.
- Several (A-E) subtypes based on diversity of envelope glycoprotein.
  - Target of immune response.
  - Variations affect cross-protection.
- Replicates in T helper cells (CD4+); also cytotoxic T cells (CD8+), B cells, macrophages, salivary gland epithelia, megakaryocytes; fibroblast and neural cell lines.



- Like HIV, FIV utilizes co-receptors for attachment to target cells.
  - Chemokine receptors.
  - Broader tissue tropism than just CD4+ cells.
  - This receptor usage changes as the infection progresses, such that the broader tissue tropism occurs later.
  - May affect therapeutic and vaccine design.



- FIV infects T regulatory cells, a type of T helper lymphocyte.
  - Function in suppression of other T lymphocytes.
  - A study by A. Mexas et al. (Vet Immunol and Immunopathol, 126:263-278, 2008) found that FIV infection led to **activation** of this **suppressor activity**, and decreased IL-2 production.
- **Contributes** to the lack of viral clearance following infection and the resultant immunodeficiency.



As with most RNA viruses, FIV has a significant mutation rate….

- Emergence of new strains.

Pathogenesis of a Texas feline immunodeficiency virus isolate: An emerging subtype of clade B

Anagha P. Phadke[a,b], Andres de la Concha-Bermejillo[b], Alice M. Wolf[c], Philip R. Andersen[d], Veerabhadran Baladandayuthapani[e], Ellen W. Collisson[b,c]

Veterinary Microbiology 115 (2006) 64–76

- Can lead to changes in pathogenicity and virulence.

Characterization of a Highly Pathogenic Molecular Clone of Feline Immunodeficiency Virus Clade C

Sobela de Rozières,[1] Candace K. Mathiason,[2] Matthew R. Rolston,[1] Udayan Chatterji,[1] Edward A. Hoover,[2] and John H. Elder[1]*

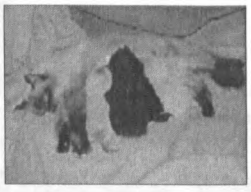
JOURNAL OF VIROLOGY, Sept. 2004, p. 8971–8982

- Genetic divergence within the US fall into one of four clades.
  - Clade B most prevalent.
  - Vaccines may need to be multiclade.

PLoS ONE | www.plosone.org August 2010 | Volume 5 | Issue 8 | e12004

What about FIV transmission?

- Transplacental transmission may occur.
  - Rate of transmission increases as gestation progresses.
  - Often leads to fetal resorption, abortion, stillbirth.
- Transmission at birth and via milk may also occur.
- Transmission rate increases if queen is experiencing the acute infection at the time of gestation or lactation.
- In addition, low maternal CD4 count (<200 cells per ml), longer duration of maternal infection (>15 months), and maternal symptoms of clinical immunodeficiency correlated with increased rates of mother-to-kitten FIV transmission.



- Viral load in newborns is higher than in adults following infection - could affect neonatal thymocyte development and development of tolerance to the virus.
- More casual transmission such as grooming can transmit the virus, not only between queen and offspring, but also between adults.

Anything new in FIV treatment?

- **Lactoferrin**, an iron-binding protein present in secretions, has been shown to have anti-inflammatory and immunomodulating effects in vitro on chronically activated PBMCs from FIV-infected cats.
  - Could improve immune functions of these cells.
  - In vivo studies needed. *J. Vet. Med. Sci.* 70(5): 429–435, 2008
- **Interferon** has shown promise.
  - rHuIFN α was shown to improve the condition and prolong survival despite no change in viral load.

E. Pedretti et al. / Veterinary Immunology and Immunopathology 109 (2006) 245–254

- **rHuG-CSF** to help counter the loss of neutrophils.
  - rHuG-CSF treatment increased neutrophil counts in FIV-infected cats without affecting the infection status of cats.
  - However, antibodies to the cytokine were produced which may cross-neutralize FeG-CSF.
  - Not recommended.

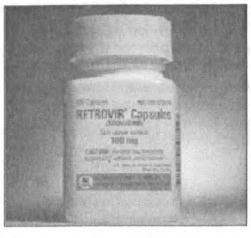
Veterinary Immunology and Immunopathology 108 (2005) 357–371

FIV-infected cats respond to short-term rHuG-CSF treatment which results in anti-G-CSF neutralizing antibody production that inactivates drug activity

K. Phillips [a,1], M. Arai [a,1], T. Tanabe [a], R. Raskin [b], M. Volz [a], E.W. Uhl [c], J.K. Yamamoto [a,*]

Antivirals....

- RTase inhibitors, like AZT.
  - Study by Hartmann et al., 1995, Fel Pract 23(5):16-21, both in vitro and in vivo effectiveness was shown.
  - Clinical improvement, prolonged survival.
  - Other studies have shown that AZT combined with 3TC (nucleoside analog) given after exposure can protect cats.
  - Other HIV RTase inhibitors have also shown ability to inhibit FIV in vitro.
- New inhibitors of protease, integrase, fusion, other targets show promise - HAART.
- Side effects are a concern.



What about vaccinations in FeLV or FIV + cats?

- Generally, inactivated or killed vaccines are recommended.
  - Core vaccines for FeLV- and FIV-infected cats are recommended.
- Concern that vaccination of FIV+ cats could lead to increased viral replication.
  - Activation of Th cells, a primary target cell of FIV.
  - Clinical significance is not known.
- In general, it should be "based on individual risk assessments" (2008 AAFP feline retrovirus management guidelines, J Fel Med Surg, 10:300-316).

What about the FIV vaccine?

- Contains two virus strains - subtype A and D.
- Some studies have shown a relative broad efficacy, with protection against a subtype B.

Dual-subtype vaccine (Fel-O-Vax FIV) protects cats against contact challenge with heterologous subtype B FIV infected cats

Veterinary Microbiology 108 (2005) 155–165

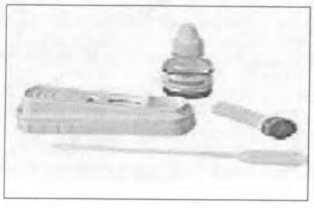
- Other studies have shown limited efficacy of the vaccine.

Veterinary Record (2006) 158, 561-562

Limited efficacy of an inactivated feline immunodeficiency virus vaccine

S. P. Dunham, J. Bruce, S. MacKay, M. Golder, O. Jarrett, J. C. Neil

- Recommended only for high risk cats.
- Complicates testing.
  - Current testing involves antibody detection.
  - Cannot distinguish vaccinal response from natural infection, including maternally derived antibodies.



What about PCR for FIV detection?

- At least one study by Crawford and others has shown that the diagnostic accuracy of FIV-specific PCR assays varies significantly (58-90%).
  - False negative results common – sequence variation and low virus load.
  - False positive results in vaccinated cats.
  - Real-time assay worked the best **overall**.

Table 1—Sensitivity and specificity (95% confidence intervals) for 4 commercial polymerase chain reaction (PCR) assays used for detection of FIV infection in cats.

Status of cats	No. of cats	PCR1	PCR2	PCR3	PCR4
FIV-infected cats (sensitivity)	41	76[a] (60, 88)	83[a] (70, 93)	51[b] (35, 67)	41[b] (26, 59)
Unvaccinated cats (specificity)	42	100[a] (92, 100)	95[a] (87, 99)	81[b] (68, 91)	81[b] (68, 91)
Vaccinated cats (specificity)	41	90[a] (83, 99)	69[b] (49, 86)	44[c] (28, 58)	51[c] (35, 67)

[a-c]Within a row, values with different superscript letters are significantly different ($P < 0.05$).

JAVMA, Vol 226, No. 9, May 1, 2005

Any hope for a test that is sensitive and specific, and can distinguish natural infection from vaccination?

Recently, a new assay with this ability was described…

- Discriminant ELISA, can distinguish vaccinated from infected cats.
  - Utilizes 2 assays, one with whole formalin-treated virus antigen, one using a synthetic peptide corresponding to a portion of the transmembrane region of the Env gp.
    - *This protein is altered in the vaccine due to the formalin inactivation.*
    - *Thus vax but uninfected cats do not have antibodies that recognize the native peptide.*
    - *And cats infected but not vaccinated have lower levels of response to the formalin-treated antigen.*
  - Less than 5% error rate for positive and negative results.
  - Does require both assays, and analysis of results using data plots of ELISA readings in two dimensions (x and y axes); thus it is done only in a reference lab.

Based on these two research publications….

Serological differentiation of FIV-infected cats from dual-subtype feline immunodeficiency virus vaccine (Fel-O-Vax FIV) inoculated cats

Hajime Kusuhara [a,b], Tsutomu Hohdatsu [a,*], Takeshi Seta [a], Kaori Nemoto [a], Kenji Motokawa [b], Tsuyoshi Gemma [b], Rie Watanabe [b], Chengjin Huang [c], Setsuo Arai [b], Hiroyuki Koyama [a]

Veterinary Microbiology 120 (2007) 217–225

Levy et al., 2008. Differentiation of feline immunodeficiency virus vaccination, infection, or vaccination and infection in cats. J Vet Intern Med, 22(2):330-4.

- **BUT, it's not commercially available….**

- Quantitative PCR –
  - Amount of virus in submitted sample is determined.
  - Very good specificity (low false pos rate), approaches 100%.
  - Not as good sensitivity (false neg rate), 76%.

ABSTRACT ID-8
SENSITIVITY AND SPECIFICITY OF QUANTITATIVE PCR AND VIRUS ISOLATION FOR DIAGNOSIS OF FELINE IMMUNODEFICIENCY VIRUS INFECTION. M Ammersbach[1], S Little[2], D Bienzle[1]. [1]University of Guelph, Guelph, ON. [2]Bytown Cat Hospital, Ottawa, ON.

"…detection of antibodies remains the most reliable test for diagnosis of FIV infection, but qPCR may be suitable to rule out infection."
ACVIM 2011

FeLV and FIV diagnostics….

Comparison of six in-house tests for the rapid diagnosis of feline immunodeficiency and feline leukaemia virus infections

K. Hartmann, R. M. Werner, H. Egberink, O. Jarrett

Veterinary Record (2001) **149**, 317-320

TABLE 1: Comparison of six FIV tests used on 800 serum samples with a prevalence of infection of 9·1 per cent

Criterion	Snap	DUO Speed	FASTest	Witness	OnSite	Oni-Step
Invalid tests (%)	1·7	0·3	0·1	12·6	0·1	0·2
Tests difficult to interpret (%)	14·4	8·4	6·8	6·7	8·1	2·6
Sensitivity (%)	86·1	97·3	90·1	95·5	43·1	67·5
Specificity (%)	98·6	98·6	99·0	99·7	97·1	99·2
Positive predictive value (%)	86·1	87·7	90·3	97·0	58·5	91·3
Negative predictive value (%)	98·6	99·7	99·0	99·5	94·8	96·8

With one exception, generally good PPV and NPV were reported.

TABLE 2: Comparison of six four tests used on 800 serum samples with a prevalence of infection of 6·6 per cent

Criterion	Snap	DUO Speed	FASTest	Witness	OnSite	Oni-Step
Invalid tests (%)	1·7	0·3	0·0	13·6	2·7	1·0
Tests difficult to interpret (%)	14·4	4·0	2·4	20·1	14·0	10·7
Sensitivity (%)	93·3	89·6	85·5	66·6	51·8	88·4
Specificity (%)	98·2	98·1	98·2	98·7	95·8	91·8
Positive predictive value (%)	82·9	81·1	81·0	83·5	52·7	50·8
Negative predictive value (%)	99·2	99·0	98·6	96·9	96·3	96·8

Quality of different in-clinic test systems for feline immunodeficiency virus and feline leukaemia virus infection

Katrin Hartmann Prof, Dr Vet Med, Dr Vet Med Habil, Dipl ECVIM-CA[1,*], Pascale Griessmayr Dr Med Vet[2], Bianka Schulz Dr Med Vet[1], Craig E Greene Prof, DVM, MS, Dipl ACVIM[3], Anand N Vidyashankar Assoc Prof[4], Os Jarrett Prof, DVM, BVMS, PhD, MRCVS, FRSE[5], Herman F Egberink DVM, PhD, Assoc Prof[6]

Journal of Feline Medicine and Surgery (2007) 9, 439–445

Table 1. Comparison of seven FIV test systems in

Tests	Witness	Snap Combo Plus	Fastest	Duo Speed	Viracheck FIV	PetChek Plus Anti-FIV	Mapic FIV
Companies	Synbiotics	IDEXX	MegaCor	Bio Veto Test	Synbiotics	IDEXX	Biotech
Countries	USA	USA	Germany	France	USA	USA	USA
Invalid tests (%)	0.4	1.1	0.6	1.1	0.6	0.2	23.1
Tests difficult to interpret (%)	0.8	0.6	0.6	0.8	1.5	0	11.1
Sensitivity (%)	94.5	100	96.4	96.3	92.6	94.5	nd
95% CI (sensitivity)	85.1–98.1	93.1–100	87.7–99.0	87.5–99.0	82.4–97.1	85.1–98.1	nd
Specificity (%)	99.4	99.6	99.2	98.9	99.8	100	nd
95% CI (specificity)	98.5–99.9	98.5–99.9	97.9–99.7	97.6–99.5	98.8–100	99.2–100	nd
Positive predictive value (%)	94.5	94.5	93.0	91.2	98.0	100	nd
Negative predictive value (%)	99.4	100	99.6	99.6	99.2	99.4	nd
n	535	535	535	535	535	535	402

CI = confidence interval; nd = not determined.

Table 2. Comparison of eight FeLV test systems in

Tests	Witness	Snap Combo Plus	Fastest	Duo Speed	Viracheck FeLV	PetChek FeLV		One-Step Mapic FeLV
Companies	Synbiotics	IDEXX	MegaCor	Bio Veto Test	Synbiotics	IDEXX	Biotech	EVL
Countries	USA	USA	Germany	France	USA	USA	USA	Netherlands
Invalid tests (%)	1.3	0.6	0.2	1.9	0.2	0.4	30.4	13.3
Tests difficult to interpret (%)	13.8	0.4	1.3	1.5	1.5	1.4	7.2	8.4
Sensitivity (%)	92.1	92.3	94.7	94.7	94.9	92.1	nd	96.8
95% CI (sensitivity)	79.7–97.3	79.7–97.3	82.7–98.5	87.2–98.5	83.1–98.6	79.2–97.3	nd	83.9–100
Specificity (%)	97.5	97.3	98.8	99.2	98.4	99.6	nd	95.4
95% CI (specificity)	95.7–98.6	95.5–98.4	97.3–99.4	97.9–99.7	96.8–99.2	97.3–99.4	nd	93.2–96.8
Positive predictive value (%)	74.5	73.5	85.7	90.0	82.2	85.4	nd	62.0
Negative predictive value (%)	99.4	99.4	99.6	99.6	99.6	99.4	nd	99.7
n	528	528	528	528	528	528	378	317

CI = confidence interval; nd = not determined.

- Again, most in-clinic tests in general are comparable to the microplate ELISA tests in their performance and can be recommended for use in private practice.
- Confirmation, esp in healthy cats with a different test is recommended.
  - Western blot
  - PCR – qPCR??

What the heck is feline foamy virus??

- Also a Retroviridae member – Spumavirus.
- Relatively widespread.
- Causes productive and persistent infection.
- No clinical signs of disease.
- Wide organ tropism.
- In at least one study, histopathological changes in lungs and kidneys were observed.
  - Mild glomerulonephritis.
  - Moderate interstitial pneumonia.

A.C. German et al. / Veterinary Immunology and Immunopathology 123 (2008) 114–118

- Before use as a vector, more studies needed.

….and Bornavirus??

- Staggering disease identified in cats in Europe, Australia, Japan.
  - Hindlimb paresis, ataxia
  - Tends to be progressive
- Bornavirus identified associated with affected cats.
  - RNA virus; found in many species
  - Meningoencephalitis
- Immune response to the virus contributes to the pathology

Staggering Disease in a Cat:
The First Case of Borna Disease Virus Infection in a Belgian Cat

Hendrik De Bosschere, DVM, PhD
Stefan Roels, DVM, PhD
Emmanuel Vanopdenbosch, DVM, Lic
Luc Bode, PhD
Hans Ludwig, DVM

And Morbillivirus?

- Related to Canine Distemper and Rinderpest Viruses.
- Found in urine of stray cats in Hong Kong using PCR and virus isolation techniques.
- Jury is still out on significance –
  - Associated with tubular interstitial nephritis
  - But numbers were small

Feline morbillivirus, a previously undescribed paramyxovirus associated with tubulointerstitial nephritis in domestic cats

Patrick C. Y. Woo[a,b,c,d,*], Susanna K. P. Lau[a,b,c,d,1], Beatrice H. L. Wong[b], Rachel Y. Fan[b], Annette Y. P. Wong[b], Anna J. X. Zhang[b], Ying Wu[b], Garnet K. Y. Choi[b], Kenneth S. M. Li[b], Janet Hui[b], Ming Wang[e], Bo-Jian Zheng[c,d,e], K. H. Chan[b], and Kwok-Yung Yuen[a,b,c,d,2]

Any questions?

mkenned2@utk.edu

"NASA has made an amazing discovery — our cat really IS the center of the universe!"

"The vet says I need a hobby. I thought eating and sleeping were my hobbies!"

Feline Coronaviruses:
Dissecting out the internal mutations in the viral spike protein that allow macrophage tropism and lead to FIP

Gary R. Whittaker
Professor of Virology
Dept. Microbiology & Immunology
Cornell University College of Veterinary Medicine

Learning Objectives

1) Understanding of the molecular basis of vial pathogenesis for FIP
2) Understanding of virus entry processes
3) Understanding how basic research contributes to clinical medicine

Cornell Veterinarian 1963

SOME IMPORTANT DISORDERS OF CATS*

By JEAN HOLZWORTH
Angell Memorial Animal Hospital
Boston, Massachusetts

A peculiar entity with a definite predilection for cats is *chronic fibrinous peritonitis*, in which the fibrin deposited on the abdominal organs, especially the liver and spleen, gradually organizes into a tough, pale fibrous coating. The liver and spleen may become contracted into barely recognizable forms. Clinical signs are persistent fever, gradual loss of weight and appetite, and enlarging of the abdomen with a more or less clear fluid. The condition is seen most often but not invariably in kittens and young cats, often in several in a household or cattery. Respiratory infections and lavish dosing with various antibiotics appear in many of the histories. To date no causative organism has been isolated or any effective treatment found.

*Presented at the 54th Annual Conference for Veterinarians, Ithaca, N.Y., 10 Jan 1963.

FIP is caused by a coronavirus

feline enteric coronavirus (FECV) - avirulent
feline infectious peritonitis virus (FIPV) - virulent

JOURNAL OF VIROLOGY, Jan. 1989, p. 436–440 Vol. 63, No. 1
0022-538X/89/010436-05$02.00/0

Intrinsic Resistance of Feline Peritoneal Macrophages to Coronavirus Infection Correlates with In Vivo Virulence

CHERYL A. STODDART AND FREDRIC W. SCOTT*
Cornell Feline Health Center and Department of Microbiology, Immunology, and Parasitology, New York State College of Veterinary Medicine, Cornell University, Ithaca, New York 14853-6401

Received 1 July 1988/Accepted 19 September 1988

Cats infected with virulent feline coronavirus strains develop feline infectious peritonitis, an invariably fatal, immunologically mediated disease; avirulent strains cause either clinically inapparent infection or mild enteritis. Four virulent coronavirus isolates and five avirulent isolates were assessed by immunofluorescence and virus titration for their ability to infect and replicate in feline peritoneal macrophages in vitro. The avirulent coronaviruses infected fewer macrophages, produced lower virus titers, were less able to sustain viral replication, and spread less efficiently to other susceptible macrophages than the virulent coronaviruses. Thus, the intrinsic resistance of feline macrophages may play a pivotal role in the outcome of coronavirus infection in vivo.

FECV-1683
FIPV-1146

VIROLOGY 243, 150–157 (1998)
ARTICLE NO. VY988045

Feline Infectious Peritonitis Viruses Arise by Mutation from Endemic Feline Enteric Coronaviruses

Harry Vennema,*,†,1 Amy Poland,* Janet Foley,* and Niels C. Pedersen*,†
Center for Companion Animal Health and the †Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California at Davis, Davis, California 95616

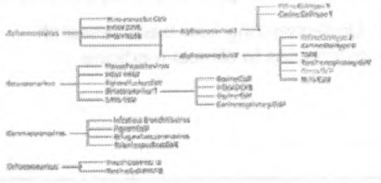
Received June 11, 1997; returned to author for revision July 2, 1997; accepted January 14, 1998

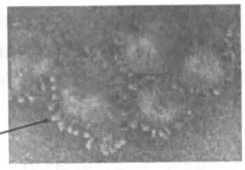
the "internal mutation" hypothesis

Serotype 2 (type 2)
Grows very well in cell culture
A recombinant with canine coronavirus (spike)
Prototype strains = FECV-1683, FIPV-1146
Not common in cats

Serotype 1 (type 1)
Most common in cats
Grows very poorly in cell culture
The 'ancestral' feline coronavirus

Both type 1 and type 2 have FECV and FIPV biotypes



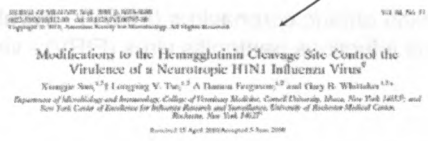


major antigenic determinant
mediates receptor binding
mediates membrane fusion

coronavirus	influenza virus
spike protein (S)	hemagglutinin (HA)

major antigenic determinant
mediates receptor binding
mediates membrane fusion
needs to be activated by a protease

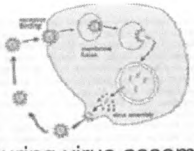
both are RNA viruses,
with high mutation rate



Modifications to the Hemagglutinin Cleavage Site Control the Virulence of a Neurotropic H1N1 Influenza Virus†

many viruses are activated by proteases

many examples of changes in virulence/tropism based on modifications to the cleavage site
(avian influenza, Newcastle disease)



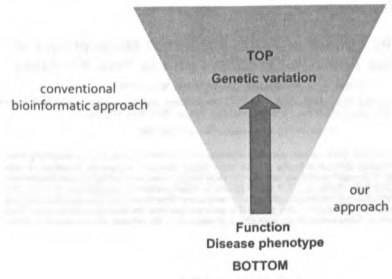
cleavage during virus assembly (*furin*) - paramyxovirus
cleavage of released particles (*trypsin*) - influenza
cleavage during virus entry (*cathepsin*) - Ebola

Our approach:
sequencing studies of type 1 FCoV

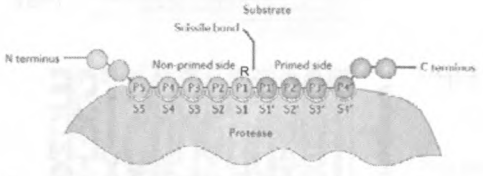
Specifically compare:
fecal samples from FCoV+ healthy cats (FECV)
tissue samples from gold-standard FIP cats

(stage 1)

focus on the spike cleavage site



Protease basics

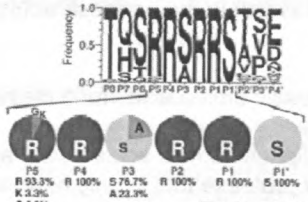


Modified from Nature Reviews Drug Discovery **5**, 785-799 (September 2006)

Fecal samples from healthy cats, wide geographic distribution

n=30

Summary of FECV sequence data



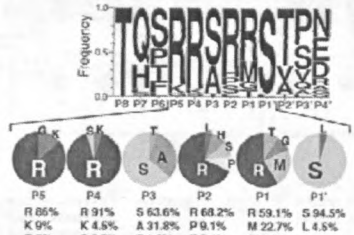
Furin cleavage site

$R_{P5}R_{P4}S/A_{P3}R_{P2}R_{P1}|S_{P1'}$

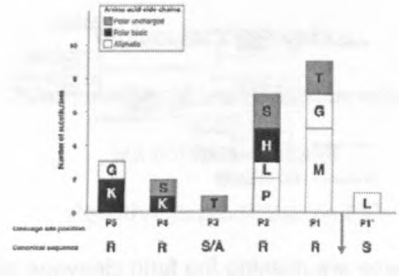
Tissue samples from FIP cats, IHC+ by histopathology

n=22

Summary of FIPV sequence data



Summary of FIPV mutations



FIPV sequencing (stage 2)

more cats, clinical cases
over 100 sequences to date

live cats
(blood, ascites, feces, CSF)

euthanized cats
(tissue)

FECV

n=51

FIPV

n=69

does this site of sampling make a difference?
blood, ascites, feces, tissue type?

Cat 234	Cat 304
sampled in January 2009 (healthy cat)	*sampled in January 2009 (healthy cat)*
NHTHT**RRSRRS**APVAV	NHTHT**RRSRRS**APVAV
sampled in November 2011 (euthanized - FIP)	*sampled in January 2012 (healthy cat)*
NHTHT**RRSRLS**APVAV	NHTHT**RRARRS**APVAV

Overall summary of mutations

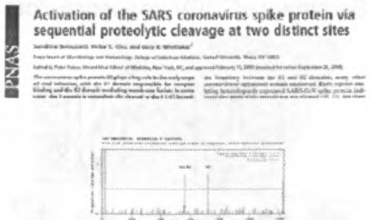
functional switch in the protease activating the virus

loss of basic amino acids/furin cleavability

gain of aliphatic amino acids - cleavage by a different protease that is only expressed in macrophages
- PC1, PC7 or MMPs??

FCoV type 2

these are missing the furin cleavage site



Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites

FCoV-1(FECV)	RRSRRS	KRKYRSAVEDLLF
FCoV2 (FECV)	------	xxxxRSAVEDLLF
SARS	xxxxRx	xxxxRSFIEDLLF
IBV (field isolate)	RRFRRx	xxxxRSFIEDLLF
IBV (pantropic)	RRFRRx	RRFRRSFIEDLLF

Summary of mutations at S2' site

IBV_Bddte LLTTP--------SSRRKRSLIEDLLF
HCoV_NL63 LPRSG--------SRIAGRSALEDLLF
HCoV_229E LPRSG--------SRVAGRSALEDILF
MHV_A59 IGSTCAEDGNGPSAIRGRSAIEDLLF
SARS_CoV DP----------LKPTKRSFIEDLLF

FECV_1683 LPSHN--------SRKRYR|SAIEDLLF

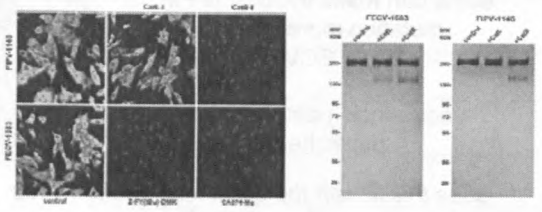
↓

FIPV_1146 LPSHN--------SRKRYGSAIEDLLF
FIPV_DF2 LPSHN--------SRKRYGSAIEDLLF
FIPV #165 LPSHN--------SRKRYGSAIEDLLF
FIPV #168 LPSHN--------SRKRYGSAIEDLLF

R-G mutation at P1

Ferret Enteric CoV CANKHGSCRSTIEDLLF
Ferret Systemic CoV CAKKHGTCGSAIEELLF

Type 2 FCoVs are differentially activated by endosomal proteases



R-G mutation at S2' cleavage site consistent with existing data for FIPV-1146/FECV-1683

Acquisition of Macrophage Tropism during the Pathogenesis of Feline Infectious Peritonitis Is Determined by Mutations in the Feline Coronavirus Spike Protein

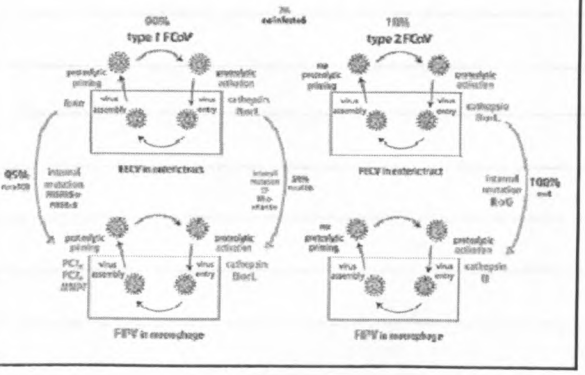
Peter J. M. Rottier,* Kazuya Nakamura,† Pepijn Schellen, Hankefina Volders,‡ and Bert Jan Haijema

Type 1 viruses at the S2' site

FECV

FIPV

Overall summary



What does this all mean?

molecular diagnostics

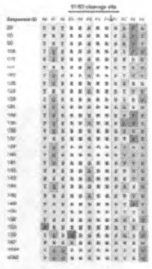
PCR/sequencing of blood, ascites, other fluid (CSF),
but not fecal material

algorithm to predict/score FIP

FIP "outbreaks"

maybe not all FECVs are equal, some can make the critical FIP mutation more readily -"hot" FECVs ??

sequencing data to inform public health?



does this fit with the circulating virulent virus hypothesis?

Genetics and Pathogenesis of Feline Infectious Peritonitis Virus

Meredith A. Brown, Jennifer L. Troyer, Jill Pecon-Slattery, Melody E. Roelke, and Stephen J. O'Brien

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What does this all mean?

therapeutics?

inhibitors of proteases needed for macrophage infection
(unlikely to be a single protease)
PC1, PC7, MMP, cathepsin B?

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The Role of Infectious Agents in Feline Dental and Oral Disease (Part I and II)

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Lectures presented at the 24th Annual Fred Scott Feline Symposium, July 27 – 29, 2012, Ithaca, NY

Learning objectives

1. Review the role that infectious agents play in the pathogenesis of periodontal disease and chronic stomatitis.
2. Review the diagnostic principles and guidelines of these conditions.
3. Review and discuss the possible treatment strategies.

Part I – Periodontal disease[1-17]

Introduction

The pathogenesis or periodontal disease (PD) in humans and animals has been the focus of researchers for several decades. Several disease mechanisms have been investigated; it has been shown that bacteria play a determinant role in PD. The purpose of this lecture is to review and discuss the current level of understanding of the role played by microorganisms in the pathogenesis of PD in cats.

Periodontal disease is recognized among the most common diagnoses of small animals; PD is the most common dental disease. PD can be defined as the inflammation and/or destruction of the attachment apparatus of teeth (periodontium). The periodontium consists of four different tissues: gingiva, alveolar bone, periodontal ligament, and cementum.

Frequent presenting complaints for cats with PD include halitosis, oral discomfort, ptyalism, and difficulty eating, among others. It has been suggested that cats with PD are more painful compared to affected humans and dogs, and as consequence are more likely to develop more severe associated signs, including weight loss and dehydration. However, PD can also be asymptomatic, or its clinical signs may be too subtle for the owner to detect.

The impact of PD is both local and systemic. If left untreated, PD represents a permanent site of inflammation inside the oral cavity. Additionally, PD in cats is often associated with tooth resorption, which is recognized as a painful condition that can exacerbate clinical signs. Other possible local consequences of PD include intra or extraoral draining tracts, pathological mandibular fractures, and oronasal fistulae.

The systemic consequences of PD are not obvious, but may be equally or more important that the local ones; some of them have been extensively documented humans. For example, a clear association exists between cardiovascular disease and PD; it has also been observed that pregnant women with PD are at increased risk of delivering low-weight babies; additionally, diabetic patients with uncontrolled PD require higher doses of insulin. Some of these systemic consequences of PD are likely to occur in cats as well.

Periodontal disease can be tentatively diagnosed based on history and conscious oral examination findings. Oral examination findings indicative of PD include gingival erythema and edema, and in more advanced stages, gingival recession, root and furcation exposure, and tooth mobility and/or loss. The extent and severity of PD can only be documented with periodontal probing and full-mouth radiography under general anesthesia; these two diagnostic steps are a critical part of any routine or advanced periodontal treatment.

In general, PD can be limited to inflammation of the gingiva without destruction of the periodontium; in this case it is referred to as gingivitis and is considered reversible, granted the inciting cause is eliminated or controlled. If left untreated, periodontal tissue destruction may follow; this form of PD is called periodontitis and is considered irreversible. Further classification of PD is based on the severity of the gingivitis (different indices have been described) or periodontitis (based on the amount of attachment loss); the terms mild, moderate and severe are usually used. Similarly, the terms focal, localized, and generalized are added to the final diagnosis to reflect the number or percentage of teeth affected.

The role of microorganisms in the pathogenesis of periodontal disease

A common misconception is that dental calculus is responsible for PD; its presence is frequently but incorrectly used as an indicator of disease. Calculus is simply mineralized plaque, and because of its rough surface it is considered plaque-retentive.

Instead, plaque plays a more critical role in the pathogenesis of PD. Dental plaque is a biofilm that is clinically described as a invisible sticky substance that adheres to the teeth and any other hard surface in the oral cavity, including enamel, dentin, calculus, restorative materials or prosthetics; it is present both supra and subgingivally. Plaque is formed mainly from residues of food, saliva, and millions of bacteria and other microorganisms. It has been shown that the accumulation of plaque on dental surfaces begins within minutes after thorough professional mechanical instrumentation, and that if left undisturbed for several days it will invariably lead to gingivitis.

Formation of plaque goes through a series of events: formation of a dental *pellicle*, *initial colonization* of the tooth surface and *secondary colonization* and *plaque maturation*. The initial event in this process is the deposition of a glycoprotein layer (*pellicle*). The sources are saliva, crevicular fluid, bacteria and debris. Other components of the pellicle include albumin, polysaccharides, lipids, and inorganic components (i.e., phosphorus and

calcium). This layer is attached to these surfaces thanks to electrostatic, Van der Waals and hydrophobic forces.

The *pellicle* provides a perfect substrate to which mainly planktonic Gram-positive facultative microorganisms adhere in a process named *initial colonization*. These early colonizers form physical bonds through adhesins (present in fimbrae) and receptors present in the pellicle layer. As the number of bacteria increases, oxygen levels decrease and allow for *secondary colonization* to begin, including proliferation of Gram-negative bacteria.

Specific and nonspecific plaque hypotheses

The nonspecific plaque hypothesis proposes that PD results from the release of toxins by the bacteria present in plaque as a whole, regardless of which bacterial species are present. One of the thoughts is that the host's immune system is normally capable of neutralizing these toxins, but that once a critical mass of plaque is present, the capabilities of the immune system are overwhelmed and PD ensues. Certain arguments contradict this hypothesis, however. In particular, the fact that PD occurs and progresses in patterns that are not uniform within the oral cavity of an individual, fails to explain how this would occur in the face of an immune system that theoretically acts as a whole.

In contrast the *specific plaque hypothesis* proposes that specific bacteria or groups of bacteria are the cause of PD. Research has made great progress and more than 400 periodontal bacterial species have been identified in both healthy and periodontally diseased individuals.

One of the earliest and most consistent observations regarding the bacteria present in plaque is a shift in its composition, as the site progresses from a healthy state to disease. This shift can be summarized as follows:

1. From gram-positive to gram-negative bacteria.
2. From cocci to rods (and spirochetes in later stages).
3. From non-motile to motile bacteria.
4. From facultative anaerobes to obligate anaerobes.
5. From fermenting to proteolytic bacteria.

Much of what is known today about the microbiology of PD in humans comes from the work of Socransky and collaborators. In 1998, after introducing innovative DNA-based methods for studying periodontal bacteria Socransky *et al.* (1998) grouped bacteria commonly identified in plaque, both in health and disease, into complexes or clusters, in an attempt to describe how within plaque, certain groups of bacteria are often found cohabiting together. Contained in the so-called "red complex" are bacteria that are believed to be pathogenic to the periodontium: *Porphyromonas gingivalis (*previously *Bacteroides gingivalis), Tannerella forsythia* and *Treponema denticola*. The pathogenicity of bacteria has been a matter of debate and their role as causative agents or secondary residents is still controversial. However, evidence supports the idea that certain microorganisms should be considered primary pathogens.

Interestingly, the proposed infectious origin of PD does not fully comply with Koch's postulates which state that in order to consider an infectious agent causative of disease, it must: a) be routinely isolated from diseased individuals; b) be grown in pure culture in the laboratory; c) produce a similar disease when introduced into laboratory animals; and d) be recovered from lesions in a diseased laboratory animal.

The reasons why, based on Koch's postulates, PD does not qualify as an infectious disease are: the inability to culture some of the bacteria associated with PD; there are serious difficulties isolating and culturing sites of true active disease; there is no good animal model for investigating PD.

In an attempt to reconcile Koch's postulates with the possible infectious origin of PD, Socransky proposed that in order to classify as a periodontopathogen, the microorganism responsible must: a) be associated with disease, as evident by increases in the number of organisms at diseased sites; b) be eliminated or decreased in sites that demonstrate clinical resolution of disease with treatment; c) demonstrate a host response, in the form of an alteration in the host cellular or humoral immune response; d) demonstrate virulence factors responsible for enabling the microorganism to cause destruction of the periodontal tissues.

Interestingly, it has been extensively demonstrated that the host's immunological response plays a major role in the pathogenesis of PD. For example, periodontopathogens may be found in healthy individuals. Even though it is accepted that if left undisturbed long enough subgingival plaque will invariably lead to gingivitis, this does not explain why PD progresses to destructive forms in some patients but not others.

It is well known that, during phases of active periodontitis, the host's immunological system releases significant amounts of proteinases, cytokines and prostaglandins, and that these play a more significant role in periodontal tissue breakdown if compared to the enzymes released by the bacteria themselves.

Some researchers have thus argued that the so called periodontopathogens are necessary but not sufficient to induce disease, and that the host's immunological characteristics and presence of other predisposing factors will determine whether attachment loss will occur or not. Therefore, the question of whether or not PD is truly an infectious disease remains open. The following are considered non-immunological risk factors for PD: subgingival calculus, malocclusion, radiation, and habits (i.e. in humans aggressive tooth brushing, smoking). Contrary to common believe, age has not been shown to be predisposing factor for PD.

Microbiology of PD in cats

The periodontal microbiology of cats has been studied and similarities with PD in humans have been identified. Some representative events and studies, and the corresponding findings, are summarized in chronological order:

1. Mallonee *et al.* (1988) studied the subgingival plaque of 32 cats with different stages of PD and reported that the bacterial population tended towards anaerobic Gram-negative rods in diseased sites. The bacterial species most frequently identified was *Bacteroides gingivalis*. One important biochemical difference was found, however; namely, unlike human *B. gingivalis*, the one identified in cats was catalase-positive.
2. *Bacteroides gingivalis* is reclassified as *Porphyromonas gingivalis*.
3. Fournier and Mouton (1993) studied 99 strains composed of *P. gingivalis and P. gingivalis*-like bacteria from humans and other mammalian species including the cats. They performed biochemical tests and confirmed significant differences between human and animal strains; they proposed that human and animal *P. gingivalis* be classified in two different biotypes.
4. Norris and Love (1995) studied the serum response to *Porphyromonas spp.* of 38 cats with PD. They found a positive correlation between serum response to *Porphyromonas spp.* and severity of PD. They also found a positive correlation between the number of *Porphyromonas spp.* isolated from individual sites within the oral cavity and the severity of PD.
5. Norris and Love (1999) used labeled DNA probes against *Porphyromonas spp.* of feline origin in 40 cats with and without PD. Their study suggested that *P. gingivalis*, *P. circumdentaria*, and *P. salivosa* play a role in the pathogenesis of PD in cats.
6. Norris and Love (2000) tested the *In vitro* and *In vivo* susceptibility of *Porphyromonas spp.* to different antibiotics. Their study showed that *P. gingivalis*, *P. circumdentaria*, and *P. salivosa* are susceptible *In vitro* to amoxicillin, amoxycillin-clavulanate, benzyl penicillin, clindamycin, doxycycline, erythromycin and metronidazole. *In vivo* results showed susceptibility to all except amoxycillin-clavulanate.
7. Fournier *et al.* (2001) proposed that, based on biochemical and DNA differences, *P. gingivalis* of animal origin, including that from cats and dogs, be reclassified as a different species called *P. gulae*.
8. In 2006, Pfizer Animal Health introduces the Porphyromonas vaccine for use in dogs, with a conditional license. It is a bacterin containing *P. gulae*, *P. denticanis*, and *P. salivosa*. Testing demonstrated safety but not efficacy; it was withdrawn from the market after clinical studies failed to demonstrate clinical results between vaccinated and non-vaccinated animals.

Clinical applicability of current knowledge

Scientific research has shown that the pathogenesis of PD in cats and humans is very similar and equally complex. Despite all the advances in periodontal microbiology and immunology, simplistic measures are still in place; mechanical means continue to be the best tool to prevent and control PD. The goal is to keep subgingival areas free of plaque; the most effective ways to achieve this are ultrasonic and manual removal of subgingival deposits to halt any ongoing PD; and maintenance measures based on daily tooth brushing.

Many products are commercialized for prevention of PD in animals including specially designed foods, chew toys and treats, water additives, oral antiseptic solutions, and until recently for dogs, the so-called periodontal vaccine. None of these have been shown to fully prevent or help in the treatment of PD; routine professional care, and more importantly, an appropriate home-care regime remain the gold standard.

Different approaches for the prevention and treatment of PD are likely to appear in the future. These will probably include modulation of periodontal flora and of the host's immune response.

Practical recommendations for management of PD

- Implement a diagnostic plan for all PD patients including full-mouth radiography and dental charting.
- Favor mechanical means versus antibiotic intervention for the treatment of PD.
- Emphasize to clients the importance of oral home-care measures.

Part II – Chronic stomatitis[18-23]

Introduction

Chronic stomatitis (CS) is a poorly understood disease that affects cats without any apparent sex, breed or age predilection. Although the etiology of CS remains largely unknown, several potential causes have been proposed including infectious agents. The purpose of this lecture is to review the role of infectious agents in the pathogenesis of CS in cats.

Common presenting complaints for cats with CS include halitosis, salivation, and inability or reluctance to eat. The medical history often includes partial and/or temporary response to periodontal treatment, oral antibiotics, and steroidal and non-steroidal anti-inflammatory medications.

Physical examination findings frequently include poor body condition, dehydration, and poor hair quality due to inability to groom. Extraoral examination findings frequently reveal excessive salivation that may or not contain blood, temporal muscle atrophy, and pain when manipulating the face. Oral examination findings include pain when opening the mouth, ulcerative and sometimes proliferative lesions affecting large areas of gingiva, as well as alveolar and buccal mucosa, usually more severe over the premolar and molar areas; and of the so-called caudal oral mucosa. Other less commonly affected areas include the sublingual mucosa, the dorsum of the root of the tongue, and the lateral walls of the oropharynx. Chronic stomatitis may occur simultaneously with dental disease; concurrent severe periodontitis and tooth resorption are not uncommon.

The condition has received multiple names over the years including: (chronic) gingivostomatitis, caudal mucositis/buccal stomatitis, lymphoplasmacytic stomatitis, among several others. The diagnosis is usually clinical and is based on the medical

history and oral examination findings. A comprehensive dental diagnostic plan is necessary to rule out other dental diseases that can mimic the clinical signs of CS, including severe generalized periodontal disease and generalized tooth resorption. The diagnostic approach must include full-mouth radiographs and dental probing and charting.

A biopsy of the lesions is necessary to rule out the two main differential diagnoses: squamous cell carcinoma and eosinophilic granuloma. Biopsy results usually report ulceration of the epithelium and lymphoplasmacytic infiltrates of the basal layer, hence one of the commonly used names of the condition. Such histopathological finding is consistent with chronic inflammation. Neutrophilic infiltrates are common and are likely due to secondary infection of the lesions. Dysplastic changes representing premalignant lesions are possible; malignant transformation (carcinoma in situ, carcinoma) has been observed anecdotally.

Chronic stomatitis is usually responsive to certain medication; in particular, corticosteroids have been shown to be very effective, providing immediate relief to the patient. However, the effect is short-lived and clinical signs reappear as soon as the effects of the medication wear off. A similar situation occurs with the administration of antibiotics, although the temporary relief of clinical signs is usually not as immediate and dramatic. Non-steroidal anti-inflammatory medications may be of value to alleviate the associated pain but usually have no effect on the lesions. Other drugs that have been used for symptomatic treatment of CS include megestrol acetate, gold salts, and cyclosporine.

Clinical studies have shown that surgical therapy may be of value. One study reported that 60-80% of affected cats that receive near- or full-mouth dental extractions are either significantly improved or "clinically cured"; 13% show significant improvement but still require medical intervention; and approximately 7% do not respond at all. The authors of this study could not explain the reasons why this happens, and hypothesized that CS was a multifactorial disease, likely combining immunological predisposition and bacterial activity. It has been proposed that CO2 laser ablation of the oral lesions may be of value as adjunct treatment of CS; no study has validated this technique, however.

Large epidemiological studies of CS are lacking. However, it has been noted that CS is more prevalent in cats that live in multi-cat households and catteries, favoring the suggestion that CS is of infectious origin. In contrast, a common finding among cats with CS is hypergammaglobulinemia, suggesting that the disease may be of immunological origin.

The possible role of infectious agents in the pathophysiology of CS

Viruses

An association between CS and some of the viruses that frequently infect cats has been suspected for several years. It has been shown that cats with CS may be shedding feline calicivirus (FCV), feline immunodeficiency virus (FIV), feline herpesvirus-1 (FHV-1), or feline leukemia virus (FeLV) in saliva; FCV and FHV-1 have been associated with CS.

Feline calicivirus and FHV-1 are a common cause of upper airway disease in cats; common clinical signs of acutely affected animals include nasal discharge, sneezing, conjunctivitis and ulceration of the tongue. Not all infected cats develop clinical signs, however, and some become latent or subclinical carriers; the prevalence of FCV is significantly higher in multi-cat environments. FHV-1

Vaccination against FCV or FHV-1 does not protect against acute or latent infection, or viral shedding; instead, it decreases the severity of clinical signs if acute infection ensues. In animals infected with FHV-1, the virus persists hiding in nervous tissues and corneas. Corticosteroid administration and stress have been shown to influence and promote viral shedding.

Ulcerative lesions of the tongue and caudal oral mucosa are common during acute infection with FCV; a study in which specific-pathogen-free cats were inoculated with different strains of FCV failed to induce CS, however. Nevertheless, some show that cats with CS are more likely to be chronic shedders of FCV.

A study done by Lommer and Verstraete (2003) showed that cats with CS are also more likely to be shedding FHV-1; in fact, this study showed that simultaneous chronic oral shedding of FCV and FHV-1 in CS-affected cats is common. Using PCR virus detection methods, 25 cats with CS and 24 cats with no CS as a control were tested for FCV and FHV-1 from oral swabs. Results showed that 88% of affected cats were shedding both viruses, versus only 21% from the control group. It was also found that none of the affected cats were negative to both viruses, versus 17% from the control; this difference was found to be statistically significant.

Another study performed by Belgard *et al.* (2010) investigated the presence of several infectious agents in 52 cats with CS, including FCV, FHV-1, FeLV and FIV; using 50 cats as controls. They used molecular antigen detection techniques as well as serology. Their results showed that none of the investigated agents were associated with CS except for FCV. They found that FCV RNA was significantly more common in cats with CS (53.8%) than in controls (14.0%). A significant difference was also found in the prevalence of antibodies to FCV between the cats with CS (78.8%, $p = 0.023$) and controls (58.0%); the authors concluded that FCV is commonly associated with chronic CS in cats. Similar results were obtained by Dowers *et al.* (2010) when using molecular testing to investigate the presence of different infectious agents in a group of 42 cats with CS and comparing to 19 healthy individuals.

Based on a possible viral etiology of CS, a study conducted by Hennet *et al.* (2011) compared the efficacy of daily oral mucosal administration of feline recombinant interferon omega in cats with unresponsive CS. The study failed to show significantly better results when in many parameters recorded compared to a 3-week course of prednisolone using an observation period of 90 days, except for a decrease in pain scores. Interferons are a group of cytokines that help inhibit viral replication; feline interferon omega has been shown to possess antiviral activity against FHV and FCV.

Bacteria

Even though it has been speculated for many years that bacteria may be associated with CS, few studies have investigated this possibility. One bacterial agent that has received much attention in past years is *Bartonella spp.* Studies have shown that experimentally infected cats develop lymphoplasmacytic infiltrates in some tissues. Also, serological testing performed in 728 cats in Switzerland suggested an association with CS. However, later studies using molecular testing, including those conducted by Dowers *et al.* (2010) and Belgard *et al.* (2010), have provided solid evidence that such an association does not exist; it has been suggested that, given the high prevalence of *Bartonella spp.* infections in cats, and an association with CS may not be made based only on serological data.

To investigate the possible pathogenic role of other bacterial species, Dolieslager *et al.* conducted a culture-dependent and culture-independent study of 5 cats with CS, comparing their results with 3 healthy cats. Based on culture results, they found that the predominant species in affected cats was *Pasteurella pneumotropica*, and *P. multocida* in CS cats. The results of culture-independent methods were consistent with these findings; however, based on molecular techniques, *Capnocytophaga canimorsus* was the predominant species in healthy cats. They also found that the oral flora in cats with CS is less diverse that that of healthy cats. According to the authors, the findings suggest that *P. multocida* may play an etiological role in CS.

Clinical applicability of current knowledge

The etiology of CS in cats remains unknown and treatment strategies are few. Medical symptomatic management is generally unrewarding and many of the drugs used are associated with serious side effects. In general, once medical management is no longer effective or becomes contraindicated, surgical options may be pursued. Among the different surgical options, the only one in which outcome has been documented is dental extractions. Only anecdotal evidence exists for other treatment including laser ablation and cyclosporine administration. Immunomodulatory treatments like the use of interferon may prove effective in the future but scientific data is still lacking.

Practical recommendations for management of PD

- A comprehensive diagnostic approach that takes into consideration the medical history, physical examination, and oral examination findings, as well as full-mouth radiography and a biopsy of a representative oral lesion, is necessary for the diagnosis of CS and is recommended before implementing any treatment.
- Many options are available for medical (symptomatic) treatment; to date, the most effective is the use of corticosteroids.
- Because the outcome of surgical management appears to be highly technique-sensitive, and because dental extractions in cats may be difficult, referral is recommended.
- When a diagnosis of CS is made, warn the clients that immediate solutions are not available, and that treatment results can be very frustrating and costly.

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FELINE INFECTIOUS DISEASE OF THE CENTRAL NERVOUS SYSTEM

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Objectives

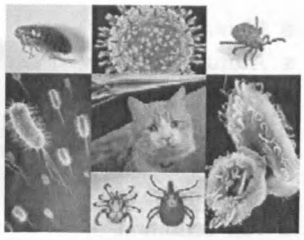
- Prevalence of infectious disease in cats.
- Diagnostic tests available.
  - Infectious disease testing
  - Advanced imaging
- Common treatment options.

Cause	Percentage
Inflammatory/Infectious	**32**
No abnormality detected	18
Degenerative	15
Neoplasia	13
Feline dysautonomia	9
Feline spongiform encephalopathy	8
Congenital	4

Data from Bradshaw JM, Peearson GR, Gruffydd-Jones TJ. A retrospective study of 286 cases of neurological disorders of th cat. J Comp Pathol 2004; 131: 121-20.

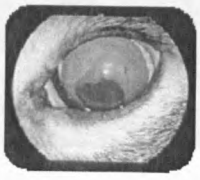
Feline CNS Infectious Disease

- Viral
- Bacterial
- Fungal
- Protozoal
- Parasitic
- Rickettsial



Diagnostics

- History
  - Including vaccination status & travel
- Physical exam
  - Ophthalmic exam
  - Otoscopic exam
- Neurologic exam

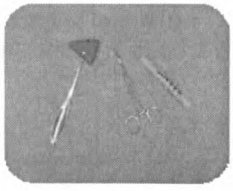


Feline Neurologic Exam

- Difficult!!!!
  - Cats are aliens
  - Different than dogs
- Limited patience
- Need a time out

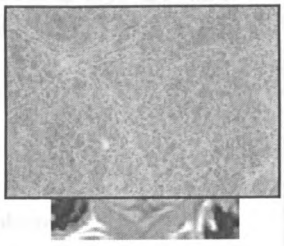
Tools for Performing the Neurologic Examination

- Pleximeter
- Hemostat
- Strong light source
- Cotton tip swab
- Confidence and humility



Neuroanatomic Localization

- Brain
- Spinal cord
- Peripheral nervous system

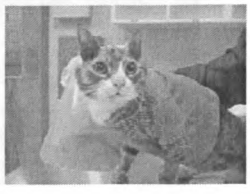


Essential Aspects of the Neurologic Examination in Cats

- Mental status
- Attitude/posture
- Gait
- Cranial nerves
- Proprioception
- Spinal reflexes
- Pain sensation

Mental Status

- Quantitative Assessment
- Alert
- Obtunded
- Stuporous
- Comatose



Attitude and Posture

- Attitude-position of eyes and head with respect to body

- Posture-position of body with respect to gravity

Gait

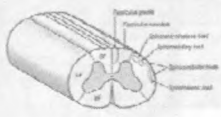
- Lameness
- Ataxia
- Paresis/plegia
- Abnormal movements

Proprioception

- Proprioceptive positioning
- Tactile (vs. visual) placing
- Hopping
- Hemiwalking
- Wheelbarrowing

Proprioceptive Tests: Interpretation

- Conscious vs. unconscious
- In context with other neurologic deficits



Cranial Nerves

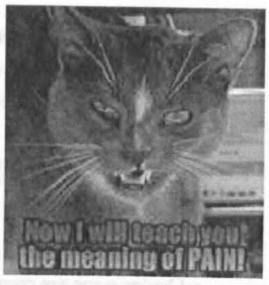
- Palpebral reflex
- Menace response
- PLR's
- Facial sensation
- Muscle symmetry/atrophy
  - Lip droop
  - Pain on palpation

Spinal Reflexes

- Patellar reflex
- Gastrocnemius reflex
- Biceps reflex
- Triceps reflex
- Withdrawal reflex

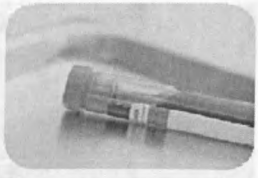
Pain Perception (Nociception)

- Superficial vs. deep pain perception
- Implications of loss of DPP
- Do NOT confuse with withdrawal reflex



Diagnostics Continued

- CBC/Chemistry/FeLV/FIV
- MRI (or CT)
- Cerebrospinal fluid (CSF) analysis



CSF Analysis

Disease	Total Protein	Cell Counts	Predominant Cell Type
Viral	Normal – Markedly Elevated	Normal – Moderate Pleocytosis	Mononuclear
Bacterial	Mildly – Markedly Elevated	Moderate – Marked Pleocytosis	Neutrophilic
Protozoal	Mildly – Markedly Elevated	Moderate Pleocytosis	Mixed
Fungal	Markedly Elevated	Moderate – Marked Pleocytosis	Mixed
Parasitic	Mildly – Markedly Elevated	Mild – Moderate Pleocytosis	Mixed – often eosinophilic

Specific Infectious Disease Tests

- Serology
  - Serum &/or CSF
  - Toxoplasma & Cryptococcus
- PCR
  - FIP, Toxoplasma, & Bartonella

Clinical Signs

- Usually young cats
- Acute onset
- Progressive
- Usually symmetrical
  - FIP & Toxoplasma are usually multifocal
- Rarely specific
  - Wound from cuterebra migration
  - History of pig exposure (Aujeszky's disease)

Feline Viral CNS Diseases

- Feline coronavirus (FCoV)*
- FIV
- FeLV
- Feline panleukemia virus
- Rabies
- Aujeszky's Disease Virus
- Borna disease virus
- Certain arboviruses

Feline Infectious Peritonitis

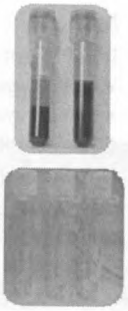
- Pedigree cats <4 years old
- Large breeding colonies
- Kittens from shelters

FIP

- ~10% of will convert to FIP
- 45-50% of all inflammatory cases
  - 15-20% of all neurologic cat cases
- Effusive form
  - Usually systemic (peritonitus/pleuritis)
- Dry form
  - Can be neurologic
  - Overactive humoral immunity
  - Ocular signs are common

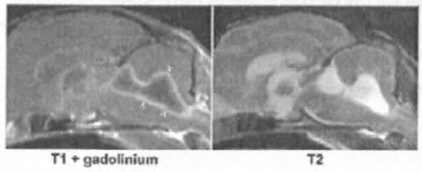
FIP

- Serum
  - Low Albumin:Globulin ratio
  - FCoV
    - Low specificity
  - Alpha-1 acid glycoprotein level
- CSF
  - Elevated total protein
  - Can have elevated cell count (or be normal)



MRI

- Obstructive hydrocephalus
- Contrast enhancement
  - Meningeal
  - Ependymal



FIP

- Usually need post-mortem for definitive dx
  - Perivascular cuffing
  - Meningeal infilatration with mononuclear cells
  - Gliosis
  - Neuronal degeneration
- No treatment

FeLV & FIV?!?

- Indirect nature
  - More vulnerable to 20 infections
  - Lymphoma→ increased risk
- FIV
  - Experimentally yes (20%)
  - Clinically only 1-5% of the time
  - Behavior changes, anisocoria, paresis

Viral non-FIP Encephalitides

- Non-suppurative encephalomyelitis
  - Acute onset of disease
    - Ataxia, nystagmus, seizures, tremors, fever
    - Vomiting &/or diarrhea
- Polioencephalitis
  - Subacute to chronic disease
    - Ataxia, paresis, hyperasthesia, tremors, visual deficits

Feline Bacterial CNS Diseases

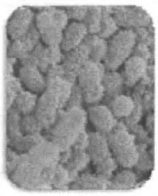
- Pasteurella spp.
- Staphylococcus spp. (most common)
- Other aerobic organisms
- Anaerobic organisms
- Mycobacteria
- Bartonella henselae

Bacterial Meningoencephalitis

- Any age
- Usually history of ear infections
  - But not always
- Bacterial nidus somewhere else
  - Rhinitis
  - Hematogenous spread
- Mature neutrophilia???
  - Some yes, some no.

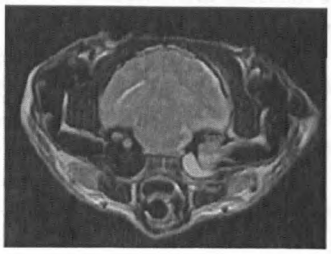
Bacterial Meningoencephalitis

- MRI
- Ideal to get a sample via myringotomy
  - Not always possible
  - Not always diagnostic
- CSF special stains
- Culture blood, urine & CSF
  - False negatives are possible



MRI

- Some need surgical debulking of abscess



Treatment

- Antibiotics for a VERY LONG TIME
  - Ideal from culture & sensitivity
  - Cidal & cross BBB
  - IV for 3 to 5 days
  - Amoxicillin with Sulbactam
  - Enrofloxacin
  - +/- Metronidazole
- 6 to 8 weeks at least
- 40% mortality rate in people

Feline Rickettsial CNS Disease

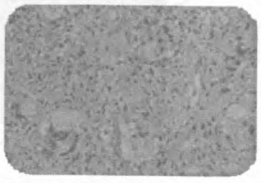
- Ehrlichia spp……..

Feline Fungal CNS Diseases

- **Cryptococcus spp.***
- Histoplasma spp.
- Blastomyces spp.
- Aspergillus spp.
- Dematiaceous fungi

Cryptococcosis

- Saprophytic yeasts
- Soil & pigeon feces
- Inhaled → blood → CNS (usu people)
  - Rhinitis → CNS (usu cats)



Cryptococcosis

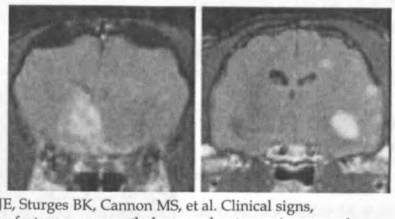
- Clinical signs usually start with upper respiratory tract signs
- +/- local or systemic lymphadenopathy
- Nasal, ocular, & neurologic signs
  - Ataxia, seizures, behavior changes, circling, vestibular signs, tremors, pain, paresis

Cryptococcosis

- Diagnosis:
  - Culture of CSF = definitive
  - Cytology of CSF, tissues, urine, lymph node = high suggestive
    - India ink, new methylene blue, or Gram stain
  - Serology for antigen
    - Serum latex agglutination antigen titer
    - ELISA

Cryptococcosis

- MRI
  - Normal → solitary or multifocal lesions



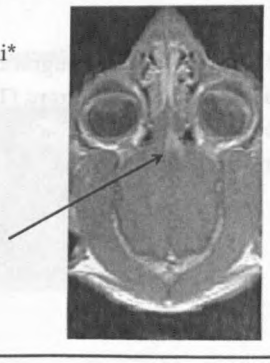
Sykes JE, Sturges BK, Cannon MS, et al. Clinical signs, imaging features, neuropathology, and outcome in cats and dogs with central nervous system cryptococcosis from California. *J Vet Intern Med* 2010;24(6):1427-1438.

Cryptococcosis

- Treatment: minimum of 6 weeks
  - Amphotericin B (IV or SQ) & Flucytosine PO
  - Or Fluconazole or Itraconazole
- Prognosis
  - Very poor
  - MST 13 days in one study
    - If survive > 3 days, then probably ok

Feline Protozoal CNS Disease

- Toxoplasma gondii*

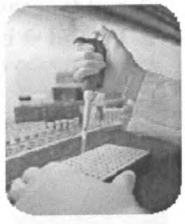


Toxoplasmosis

- Usually adult cats that hunt
  - Can be congenital infection in young cats
- Systemic & ocular signs
- Multifocal CNS signs – 10% of cases
  - Behavior changes, seizures, ataxia, blindness, anisocoria, vestibular, hyperesthesia, paresis
- Lab findings:
  - Anemia
  - Lymphocytosis & neutrophilia

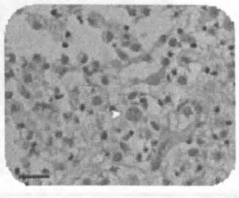
Toxoplasmosis

- Diagnosis
  - Antibody titers
    - IgM elevated = usually recent infection
      - False negatives & false postives
    - IgG elevated = usually represent previous exposure
      - 4-fold increase over 2 to 4 weeks is more suggestive of recent infection
  - Immunohistochemistry & PCR on tissues



Toxoplasmosis

- MRI
  - Non-specific
  - May have solitary lesions of a granuloma
- CSF
  - T gondii IgG or DNA
  - Tachyzoites



Toxoplasmosis

- Interesting….
  - Histologic changes in nearly all cats
  - Only 10% have neurologic signs
- Treatment: at least 4 weeks
  - Clindamycin PO, IM, IV
  - TMS + folic acid supplement
  - Azithromycin (refractory ?)

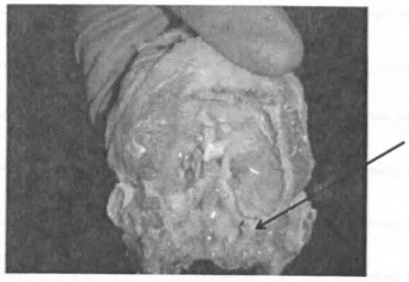
Feline Parasitic CNS Diseases

- Cuterebra larval migration*
- Visceral larva migrans (Toxocara)
- Sarcocystis spp.
- Dirofilaria immitus

Cuterebra

- Signalment
  - Usually mid to late summer
  - Access to outdoors
- Enter through the nose then….
  - Larynx or
  - Brain
- Treatment
  - Ivermectin
  - Enrofloxacin
  - Prednisone

Cuterebra



Take-Home Message

- CNS infectious diseases can look very similar clinically
- Infectious disease testing is therefore important
- Must treat for a very long time
- Most have a very guarded prognosis
- FIP is most common
  - Toxoplasmosis & Cryptococcosis are the second most common → & they are RARE!

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Thank You!

Please ask me any questions you may have…

OTHER FELINE ENCEPAHLITIDIES

Starr Cameron, BVetMed
Cornell University
Neurology/Neurosurgery Resident

Objectives

- Discuss the various congenital intracranial disease processes occurring in the cat.
- Discuss several of the more common acquired intracranial diseases in the cat.
- A better understanding of seizure management in the cat – what's available & what works.

Other Encephalitides

- Congenital
  - Malformations
- Acquired
  - Tumors
  - Vascular events
  - Thiamin deficiency
- Seizure Management
  - Anti-epileptic drugs

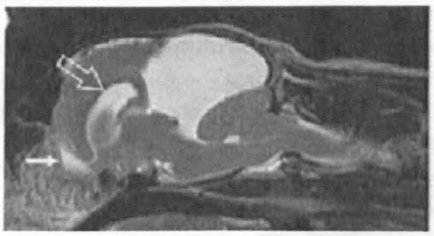
Congenital Malformations

- Intracranial Arachnoid Cyst
- Hydrocephalus
- Cerebellar Hypoplasia

Intracranial Arachnoid Cysts

- Also known as:
  - Quadrigeminal Cistern Cysts
  - Usually found in caudal cranial fossa
- Lack an epithelial lining → are really diverticula
- Primary malformation
  - May develop secondarily to trauma or meningoencephalitis
- All 3 reported were young Persian cats

Intracranial Arachnoid Cyst



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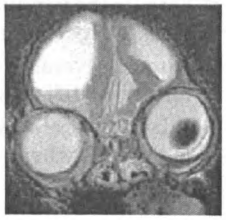
Hydrocephalus

- Obstructive
  - Blockage of CSF flow
  - Insufficient resorption
  - Overproduction
- Non-obstructive
  - Cerebral atrophy
  - Degenerative disease

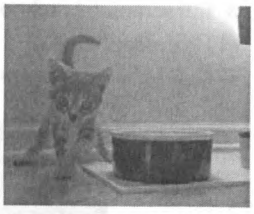


Cerebellar Hypoplasia

- Failed to form appropriately
  - Queen infected during pregnancy
- Primary malformation
- Secondary to infection
  - Feline panleukopenia
- Has been associated with lissencephaly
  - Reduction or absence in number of gyri

Cerebellar Hypoplasia

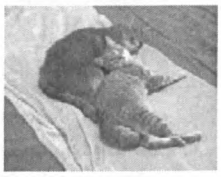
- Cerebellar ataxia
  - Hypermetria
- Wide-based stance
- Head tremor



Picture found on a web article titled:
"10 Reasons to Adopt a Cerebellar Hypoplasia Cat"
www.lifewithcats.com

The 10 reasons to adopt a cerebellar hypoplasia cat

- Non-progressive disease
- Won't jump on counters
- They don't know
- Fun to watch
- Harder to adopt out
- More of a bond
- Awareness of disease
- They are inspiring
- Why not?!? If you have the time & patience.
- Sweeter cats



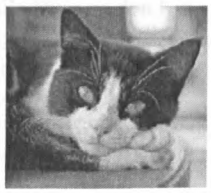
Other Malformations...VERY RARE!

- Intracranial epidural mucocele
- Intracranial teratoma
- Intracranial dermoid cysts

- Neurodegenerative Disorder:
  - Neuronal ceroid-lipofuscinoses
    - 9 month old kitten
    - Progressive signs since birth

Acquired

- Neoplasia
  - Meningiomas
  - Others…
- Vascular Events
- Hepatic encephalopathy
- Thiamin deficiency
- Head trauma

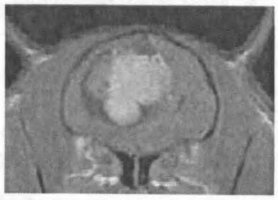


Intracranial Neoplasia

- 61 cats
- Clinical signs
  - 25% seizures
  - Meningiomas (33%)
  - Lymphoma (31%)
    - Significantly younger
    - ~ ½ had generalized dz
  - Astrocytoma (15%)
- 46 cats
- Tumor types
  - Meningiomas (72%)
  - Lymphoma (13%)
  - Glial (8%)

Primary Brain Tumors in Cats

- Signalment: mean age for cats->10 years
- Behavior change most common complaint in cats
- Meningiomas predominate in cats



"Floyd"

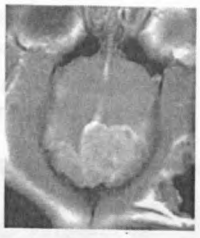
- 9 yr old MC DSH
- Progressive behavior change over 2 mos
- Acting lethargic
- Lately circling and acting more "out of it"

Floyd's Neurologic Examination

- Obtunded mentation
- Blind
- Head turn to left
- Head/neck pain on palpation

Floyd's MR Images

- Large, well-demarcated, uniformly contrast-enhancing mass
- On both sides of falx cerebri-that's not good
- Plan of action?

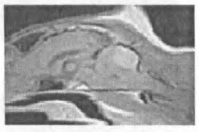


Surgical Removal

- Bilateral craniotomy
- Mass removed
- Recovery uneventful

Intracranial Meningiomas in Cats: Important Features

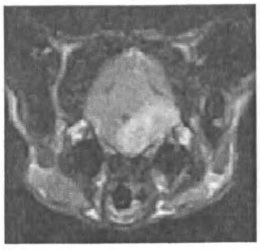
- Most safely removable surgically
- Vast majority of cats do well long-term
- Regrowth-
  - Remove it again, do just as well
- Expect (and treat) post-op anemia
- Recovery fairly rapid
- Continue on anti-epileptic medications



Lymphoma

- Primary or Secondary
- Single or multifocal
- Intra-axial or extra-axial

- Nasal tumors
  - Lymphoma
  - Adenocarcinoma



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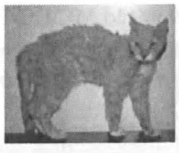
Other Tumors...VERY RARE!!!

- Gliomas
  - Astrocytomas
  - Oligodendrogliomas
- Hemartomas (disorderly overgrowth)
- Cholesterol granulomas
- Metastatic tumors:
  - Lymphoma
  - Hemangiosarcoma

Vascular Events

- Strokes
  - Ischemic
  - Hemorrhagic
- Causes:
  - Hypertension
    - Hyperthyroidism
    - Renal disease
    - Neoplasia
  - Cardiac disease
  - 50% unknown*** (dogs)



Feline Ischemic Encephalopathy

- Due to Cuterebra spp
  - Larval migration
- Cerebral infarction
  - Usually
  - middle cerebral artery
  - Necrosis & atrophy

Hepatic Encephalopathy

- Congenital or acquired
- Failure to remove toxic substances
- Secondary brain atrophy & bilateral changes on MRI
- Treatment
  - Lactulose
  - Metronidazole
    - 7-10mg/kg BID...or we get other problems!

Thiamin Deficiency

- Insufficient ATP production in the brain
  - Dysfunction of Na/K pump
- Secondary neuronal dysfunction
- Bilaterally symmetrical signs

Head Trauma

- ANY NEUROLOGIC SIGNS!!!!
- Mannitol
  - ½ - 1 g/kg over 15 minutes
  - Up to 3 g/kg/day
- Seizure focus
  - Acutely or months later
  - Need anti-seizure meds!
- We do not recommend steroids here.

Feline Seizures

- Frequent occurrence
- Epilepsy common
- Cats often older
- Very few drug choices

Feline Seizures

- The minimal acceptable number of seizures is zero
- We should strive for a higher "standard"
- There are "newer" versions of "new" drugs
- "New" drugs often work well alone
- I LOVE cats

Seizure Disorders in Cats

- Idiopathic epilepsy more common than previously thought
- Very limited drug options
- Extrapolation from dogs or people can be hazardous
- A lot of work to do

Conversations with Clients

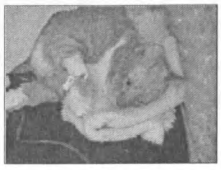
- When to start therapy
- Goals and expectations of therapy
- Anticonvulsant drug choices

Anticonvulsant Drug Choices for Cats

- Phenobarbital
- Levetiracetam
- Zonisamide?
- Others?

Phenobarbital Therapy in Cats

- First-choice drug
- Elimination half-life about 50 hrs
- Starting dose of 2.5 mg/kg BID
- Sedation at high doses
- Liver problems rare

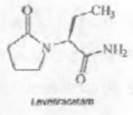


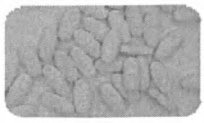
Drugs We Don't Use in Cats

- BROMIDE
  - Asthma-like reaction
  - Doesn't work well
- DIAZEPAM
  - OK to use IV
  - Danger of fatal hepatic necrosis if ADM PO
  - Works well

Levetiracetam

- Very effective anticonvulsant in people and dogs
- Virtually no side effects
- No hepatic metabolism
- No drug-drug interactions
- TID dosing
- Generic form available (Canada)





Oral Levetiracetam in Cats

- Well tolerated
- 20 mg/kg TID dosing
- Levels in therapeutic range for people
- Effective add-on anticonvulsant

Levetiracetam in Cats-Specific Information

- t ½-2.9 hrs
- Mean seizure reduction-68.4% (p=0.002)
- Responders (70%)-mean reduction of 92%
- Non-responder reduction-36%

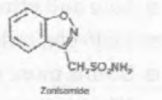
Bailey KS, Dewey CW, Boothe DM ,et al. J Am Vet Med Assoc 232:867, 2008

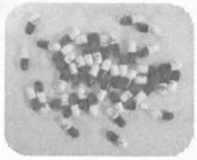
Levetiracetam-Intravenous Use

- IV form available
- Potential use for cluster seizures & status epilepticus
- Synergistic with diazepam in experimental status (rodent model)
- Pharmacokinetics of IV Keppra in dogs
- Good results in cats so far

Zonisamide

- Probably most effective new drug in dogs
- Few side effects
- Cats
  - Little clinical data
- SID dosing in cats
  - AWESOME
  - 10mg/kg PO SID
- Generic form available



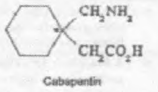


Zonisamide in Cats

- Kinetic data favorable
- Side effects frequent at doses evaluated
- Clinical information limited
- Shows some promise for this species

Gabapentin

- Moderately effective in dogs
- Anecdotal efficacy in cats
- Probably weakest of "new" drugs
- At least TID dosing required
  - 10-20mg/kg PO TID
- Generic form available

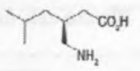


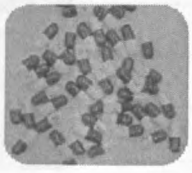
Gabapentin for Cats

- Entirely anecdotal
- Dose recommendations
- Probably safe-no reports of problems
- Maybe not worth investigating further?

Pregabalin

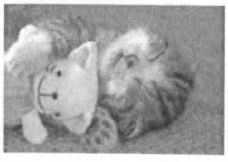
- The next generation of gabapentin
- Main mechanism of action
  - Binding to α2δ subunit of neuronal voltage gated Ca++ channels
- Decreased Ca++ influx at nerve terminals, decreased release of several neurotransmitters





Pregabalin-What We Know

- Safe and effective in dogs
- Half-life in dogs 2X that of gabapentin
- Seems more effective than gabapentin
- Working on cats now
  - 2-4mg/kg PO BID
  - Work up to that dose



Summary of Potential Anticonvulsant Choices for Cats

- Phenobarbital
- Levetiracetam
- Zonisamide
- Gabapentin
- Pregabalin

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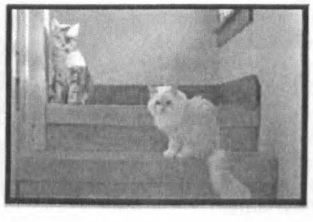
Thank You!

Please ask me any questions you may have...



Those Wonderful Cat Eyes!
What Are They Telling Us?

Ronald C. Riis, MT, DVM, MS, DACVO

Learning Objectives

- Know the ocular expressions of infectious manifestations.
- Know some practice aids in diagnosing ocular lesions.
- Be familiar with laboratory tests to help diagnose the etiology.
- Be aware of ocular ruleouts making your diagnosis.
- Know some of the sequela of early onset disease that may present with age.
- Appreciate how the eye is like the crystal ball of the body.

24th Annual Fred Scott Feline Symposium
July 27-29, 2012

Those Wonderful Cat Eyes!
What Are They Telling Us?

by

Ronald C. Riis, MT, DVM, MS, DACVO

When Those Wonderful Cat Eyes Don't Look So Good (*pun*), They May Have The Following

PART I

Feline Herpes Virus-1 (FHV-1)
Proliferative Keratoconjunctivitis
Corneal Sequestra
Feline Calicivirus (FCV)
Chlamydia psittaci
***Mycoplasma* sp.**
Toxoplasmosis

PART II

Feline Coronavirus (FCOV) → (FIP)
Feline Immunodeficiency Virus (FIV)
Feline Leukemia-Lymphosarcoma (FeLV)
Other Neoplasias/Melanoma Versus Nevus
Mycoses
Retinal Degenerations (Lipemia, Anemia, Diabetes, Retinal Folds, Detachments Secondary to Ethylene Glycol)
Hypertensive Retinopathy
Panleukopenia Virus
Feline Central Retinal Degeneration (FCRD)

P A R T I

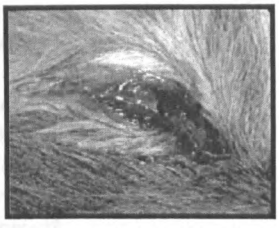
Infectious Feline Diseases

Feline Herpesvirus 1 *(FHV-1)*

Symptoms:

- **Primary infection**
- **Sneezing/coughing**
- **Fever/malaise**
- **Nasal/ocular discharge**

Kitten conjunctivitis and upper respiratory tract disease = FHV-1.

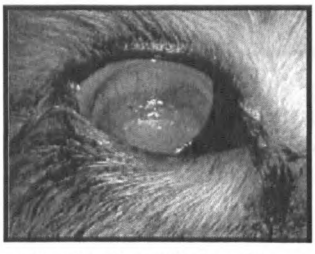


Kitten conjunctivitis with seromucinous discharge = FHV-1.

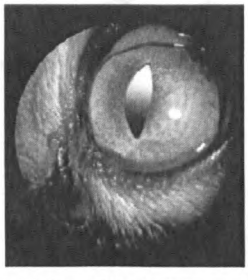
FHV-1

Acute FHV-1: marked keratitis and severe upper respiratory tract disease.

Chronic FHV-1: ulceration and keratitis sequestration, uveitis.



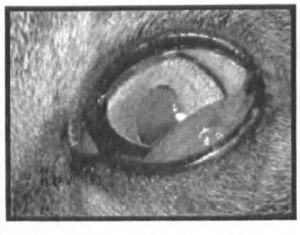
Chronic FHV-1 with keratitis, entropion, and calcific corneal plaque secondary to entropion.



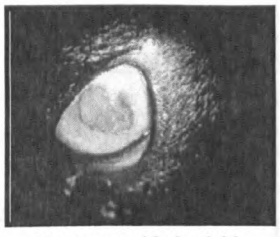
Iritis - FHV-1: Note miosis, iris hyperemia.

FHV-1 Associated Ocular Conditions

- Neonatal Ophthalmia: kittens <1 weeks of age
- Primary Conjunctivitis: hyperemia, blepharospasm, chemosis, and discharge
- Recurrent Conjunctivitis: adults (1-2 years or older) may be stress related
- Keratoconjunctivitis Sicca: persistent mucopurulent exudates, low Schirmer tear test (<5 mm/min), keratitis



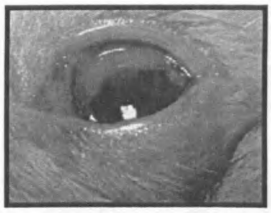
Young cat with conjunctivitis and fluorescein positive ulcer = FHV-1.



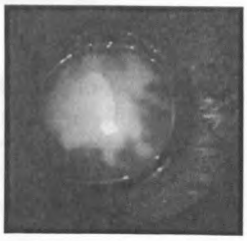
Young cat with dendritic corneal ulcers = FHV-1.

FVH-1 Treatments

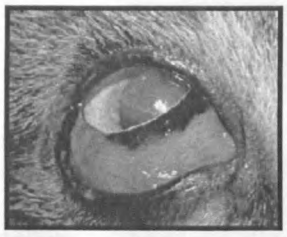
- Primary Infection: respiratory tract may need broad-spectrum antibiotics, subcutaneous fluids, cleansing of ocular and nasal discharge, conjunctivitis: (topical ophthalmic antibiotics, antiviral)
- Recurrent Conjunctivitis: oral lysine (100 mg SID or BID), interferon-α 5-25 IU orally SID
- Corneal Ulcers: debridement and antivirals (trifluridine, idoxuridine, vidarabine, or cidofovir)
- Corneal Sequestra: keratectomy followed by glue or conjunctival or corneoconjunctival graft
- Keratoconjunctivitis Sicca: topical 0.2% cyclosporine A ointment plus antiviral treatment



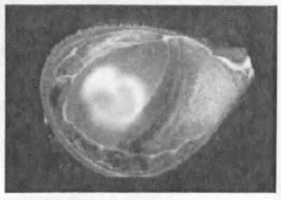
Young cat with conjunctivitis and ulcer = FHV-1.



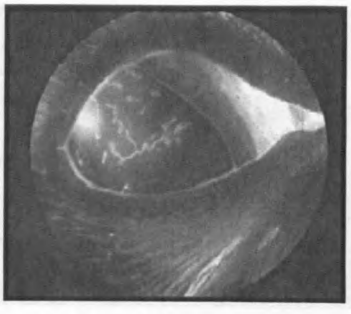
Adult cat with geographic ulcer = FHV-1.



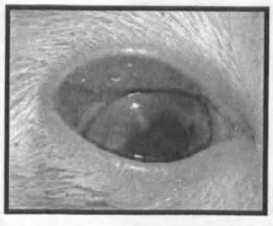
Adult cat with geographic ulcer = FHV-1.



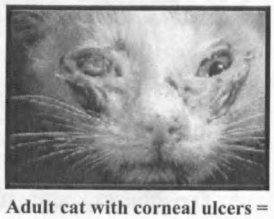
Adult cat with geographic ulcer (black and white) = FHV-1.



Adult cat with dendritic FHV-1 ulcers – black and white.

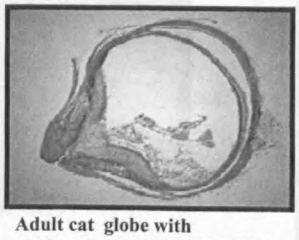


Adult cat with corneal edema and conjunctivitis = FHV-1.



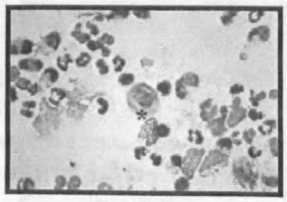
Adult cat with corneal ulcers = FHV-1.

Adult cat with ruptured cornea and prolapsed uveal tract coated with fibrin = FHV-1.

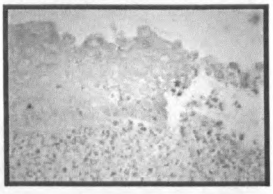


Adult cat globe with perforation of cornea = FHV-1.

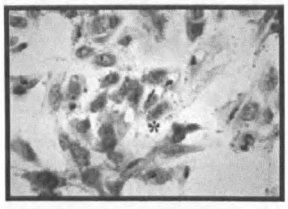
Adult cat cornea positive FA for FHV-1.



Large accumulation of inflammatory cells with cell * intranuclear inclusion.



Pathology of FHV-1 infected cornea * intra-nuclear inclusions



Cell culture of HVl-1 infected cells – note * intranuclear inclusion bodies.

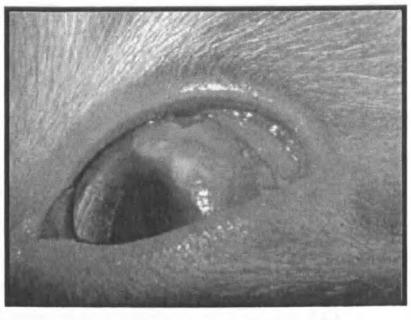
Diagnosis

Diagnosis of proliferative keratoconjunctivitis is from eosinophilic cytology on corneal scraping. CBC may show eosinophilia.

Eosinophilic Keratitis
(Proliferative Keratoconjunctivitis)

Signs:

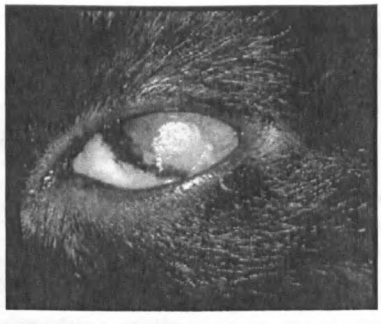
- White-to-pink proliferative irregular mass on corneal surface
- Neovascularization of cornea
- Originates from limbus-nasal or temporal
- May involve adjacent bulbar conjunctiva
- May involve nictitating membranes



Proliferative keratoconjunctivitis.

Treatment

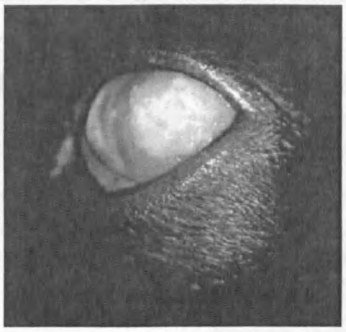
Treat proliferative keratoconjunctivitis with 1% prednisolone acetate drops or 0.1% dexamethasone ointment QID/two weeks, then decrease BID/two weeks, then weekly for one month.



Proliferative keratoconjunctivitis with a "plaque" appearance.

Etiology

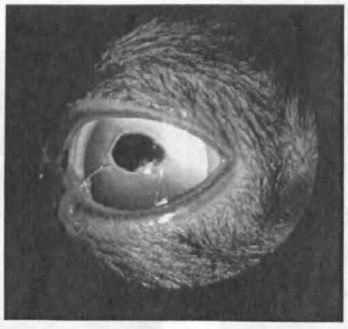
Etiology of proliferative keratoconjunctivitis is unknown. However, 76.3% of the tissue samples from proliferative keratoconjunctivitis were FHV-1 PCR positive. Questionable pathogenesis.



Proliferative keratoconjunctivitis with a "cake frosting" appearance.

Corneal Sequestration

Diagnosed in all feline breeds, highest incidence in Persian, Himalayan, and Burmese.

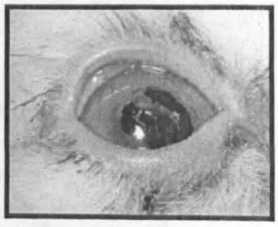


Corneal sequestra.

Corneal Sequestration

Sequestration is a brown-black lesion located centrally or paracentral cornea. The lesion is usually oval. It does not stain positive with fluorescein, but loose edematous epithelium at the periphery may stain positive.

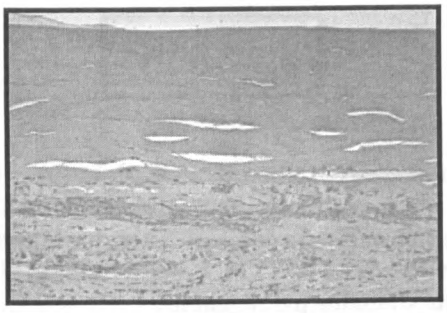
Corneal sequestra – left eye. Note discharge color.



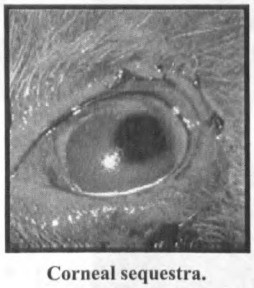
Corneal sequestra – same eye as slide in top left corner.

Histology of Sequestrum

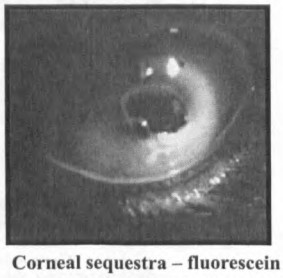
Histology of sequestrum shows degenerative corneal stroma collagen with fibroblasts and variable inflammatory cells.



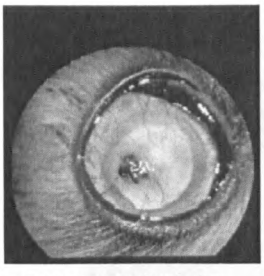
Pathology of sequestrum.



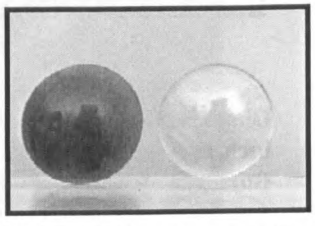
Corneal sequestra.



Corneal sequestra – fluorescein stain negative except around periphery.



Sequestrum stimulating neovascularization



Left contact lens from eye with sequestrum, right contact lens normal.

Etiology

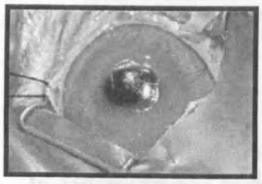
Etiology is unknown but heredity (facial conformation), ocular irritation (entropion, lagophthalmos, microtrauma) and FHV-1 have been suspected.

Treatment

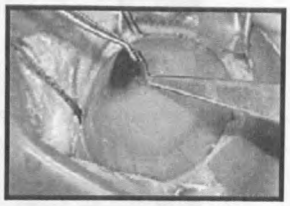
Keratectomy for a superficial sequestra is relatively simple, however, those deep more than half-way through the cornea require a graft or glue.

Treatment

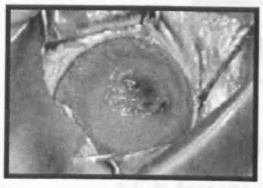
I believe early keratectomy is preferred rather than conservative "wait and see" if it will slough "alternative".



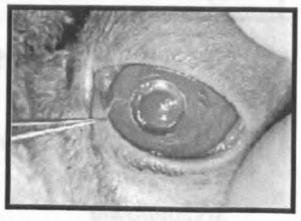
Sequestrum in position for keratectomy.



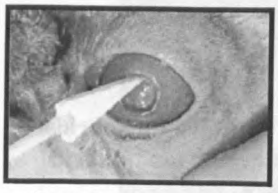
Keratectomy using a Von Graeffe knife.



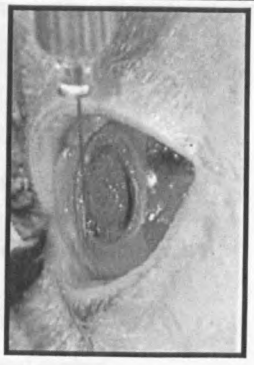
Keratectomized site, incomplete – go deeper.



Deep ulcer - loose epithelium being removed, step 1 for gluing.



Deep ulcer being carefully dried, step 2.



Deep ulcer overcoated with tissue glue (acetylcysteine), step 3 - dry.

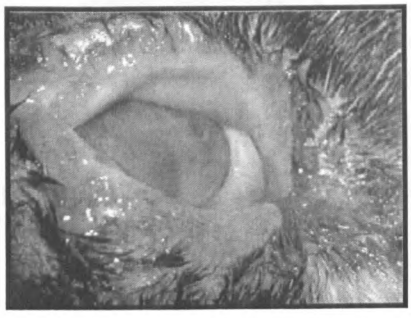
Feline Calicivirus *(FCV)*

Gerriets, W., Joy, N., Huebner-Guthardt, J., Eule, J.: Feline calicivirus: a neglected cause of feline ocular surface infections? Vet. Ophthalmol. 15(3):172-179, 2012.

FCV - kitten with both eyes conjunctivitis (URTD) = upper respiratory tract disease, FCV.

On Study

Ninety-nine cats with ocular surface infection and symptoms or recent history of upper respiratory tract disease.



Young cat with severe erosive conjunctivitis and keratitis = FCV.

Conjunctival samples taken with cytobrush or Schirmer tear test strip for nucleic acid extraction using RT-PCR.

Results

RT-PCR found in 63/99:

- FCV
- FHV-1
- *Chlamydia felis*
- *Mycoplasma*

Results

- 30/63 positive for FCV
- 23/63 positive for *Chlamydia felis*
- 21/63 positive for *Mycoplasma*
- 10/63 positive for FHV-1

Results

The 30 FCV positive:

- 11 positive only for FCV
- 19 positive for FCV plus other agents

Results

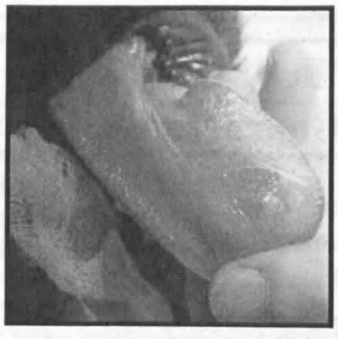
FCV infections highest in age 0-2 months from rescue centers.

Kitten with conjunctivitis secondary to FCV.

Characteristic Findings

FCV lesions

- **Erosive conjunctivitis**
- **Oral ulcers**

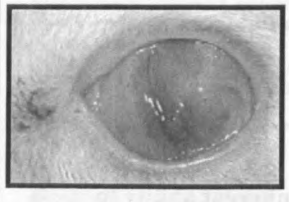


Look for oral mucosal erosions.

Infectious Agents Found

The infectious agents causing upper respiratory tract disease (URTD) and/or ocular lesions are:

- **Feline herpesvirus 1 (FHV-1)**
- **Feline calicivirus (FCV)**
- ***Bordetella bronchiseptica***
- ***Chlamydophila felis***
- ***Mycoplasma felis***



Adult cat with symblepharon secondary to FCV.

Adult cat with symblepharon secondary to FCV.

Think "*any corneal ulceration in a cat is secondary to FHV-1 . . . unless proven otherwise*".

Sixty percent of the conjunctivitis cases in cats is secondary to bacteria or *Chlamydia. Mycoplasma* is seen causing conjunctivitis, rhinosinusitis, and polyarthritis.

FCV accounts for 20-53% of upper respiratory tract disease in cats.

FCV is Typically Characterized By:

- Fever
- Rhinitis
- Oral ulcers
- Chronic stomatitis
- Occasional skin ulcers and pneumonia

Despite Vaccination Against FCV

Infection is still common, especially cats housed in groups (stress)

FCV Genome

FCV genome has an inherent ability to undergo rapid mutation, explaining variation in antigenicity, clinical expression, and repeated outbreaks.

FCV Positive Cats

The ocular symptoms were always coupled with oral ulcers.

Breed Predisposition

Based on breed predisposition, the highest prevalence for ocular lesions and upper respiratory tract disease:

- 83% (52/63) domestic shorthair (ESH)
- 14% (9/63) Persian
- 3% (2/63) British shorthair

FCV Monoinfection

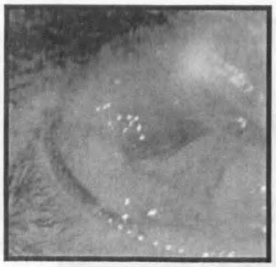
FCV monoinfection was seen more often in females 56% (55/63) than males.

FHV-1 Monoinfection

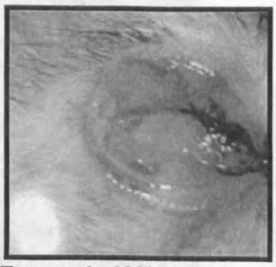
FHV-1 monoinfection was seen equally in both sexes.

FCV Ocular Lesions

- Serous discharge
- Conjunctival chemosis
- Conjunctival hyperemia
- Conjunctival erosions
- Fluorescein positive/Lissamine green positive on conjunctiva
- Fluorescein negative/Lissamine green negative on cornea



Two-month-old kitten with conjunctival erosions stained positive with fluorescein (FCV).



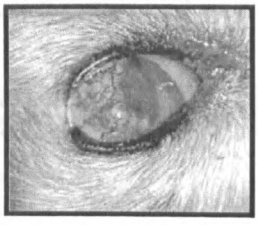
Two-month-old kitten with conjunctival erosions stained positive with Lissamine green (FCV).

FCV Severe Erosive Conjunctivitis Gives Sequela Lesions

Lateral symblepharon secondary to FCV.

Lateral canthus symblepharon – secondary to FCV (blinks with nictitans).

Severe complication of FCV erosive conjunctivitis caused keratoconjunctivitis sicca – zero Schirmer tear test.



Adult cat with lateral symblepharon secondary to FCV.

Please Note

The presence of keratitis and pneumonia and absence of oral ulcers distinguishes FHV-1 infection from FCV infected cats.

All FHV-1 corneal ulcers stained positive with Lissamine green (n=8), but fluorescein stained positive in only 3/8!

Lissamine green from Rose Stone Enterprises, Alt Loma, California ([909] 476-7694).

FCV Infection

Cats once infected with FCV can shed virus for up to 75 days, easily spread infection to other cats in dense populations.

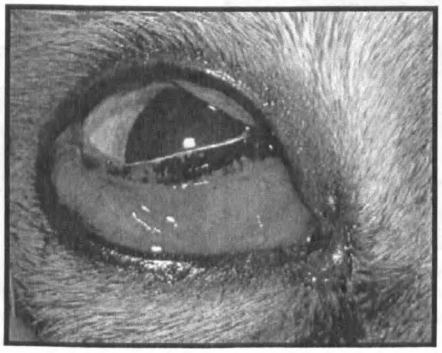
Please Note

FCV can be transmitted through/on cages, bedding, toys, feeding pans, clothing, etc. ∴ practice good hygienic measures.

FCV carriers shed virus continuously ∴ they are mostly always infectious.

Chlamydia psittaci

- Common cause of conjunctivitis
- Chlamydial infections causes a ***marked*** conjunctivitis.

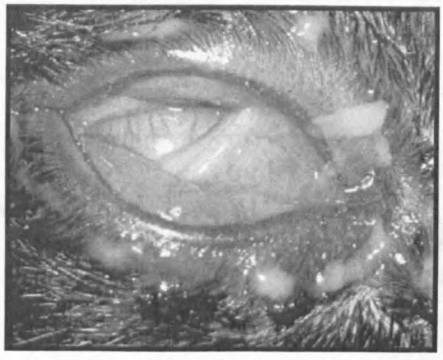


Chlamydia infection causing moderate chemosis.

Cats Infected With *Chlamydia* or *Mycoplasma*

Cats infected solely with *Chlamydia* or *Mycoplasma* displayed:

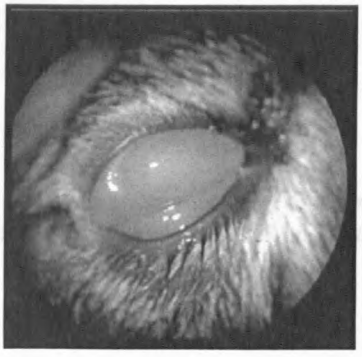
- Mucopurulent-purulent ocular discharge
- Keratitis (neovascularitis)
- Oral ulcers
- Pneumonia
- Lameness



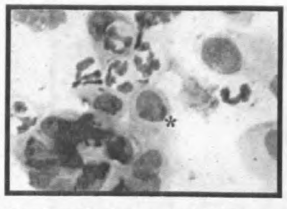
Chlamydia or *Mycoplasma*. Young cat with severe conjunctivitis.

Symptoms of Acute Infection

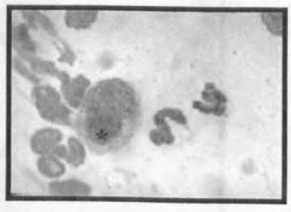
- Conjunctival hyperemia, chemosis, serous discharge, blepharospasm. Mild nasal discharge and sneezing possible. Chronic infections result from untreated cases.
- Diagnosis is by finding characteristic inclusions within the cytoplasm of the conjunctival epithelial cells or positive FA test from scrapings of the conjunctiva.
- Treatment: oral tetracycline, doxycycline, or erythromycin, and topical tetracycline QID for two weeks. Vaccination recommended.



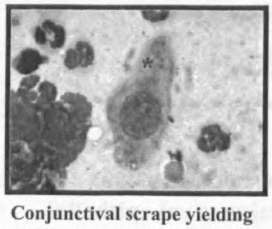
Chlamydia infection causing severe chemosis.



Conjunctival scrape yielding perinuclear * *Chlamydia* inclusions within epithelial cell.



Conjunctival scrape yielding large perinuclear * *Chlamydia* inclusions within epithelial cell.

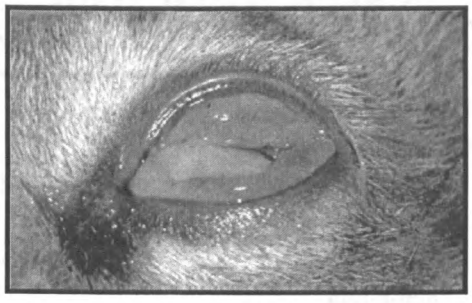


Conjunctival scrape yielding multiple pockets of perinuclear inclusions * confirming *Chlamydia* infection.

FA of *Chlamydia* positive diagnosis.

Mycoplasma sp.

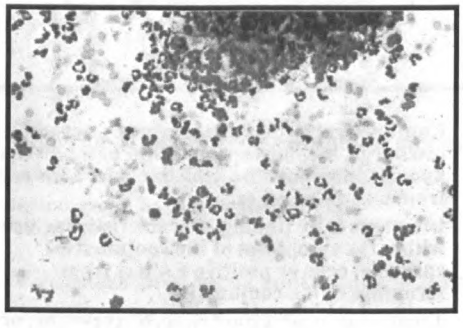
***Mycoplasma felis, M. gatae,* and *M. arginni* have been isolated from both sick and healthy cats.**



***Mycoplasma* conjunctivitis, chemosis, and hyperemia.**

Diagnosis

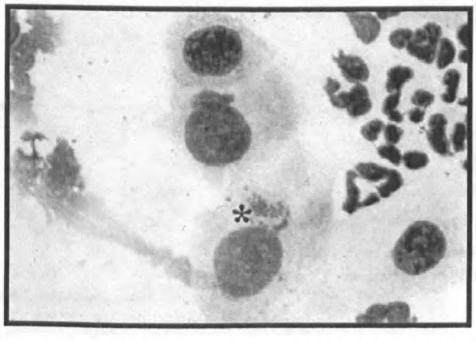
Diagnosis of mycoplasmosis made on cytology and/or culture in special media.



***Mycoplasma* conjunctivitis yielding inflammatory cells.**

Cytology

Characteristic small coccoid inclusions within cytoplasm of conjunctival epithelial cells.



***Mycoplasma* conjunctivitis shows coccoid inclusions * within the cytoplasm of the epithelial cells.**

Treatment

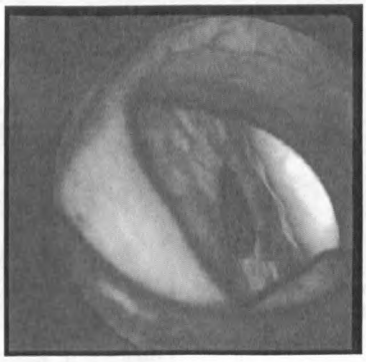
Mycoplasma sp. sensitive to many ophthalmic antibiotics (i.e., triple, terramycin, gentamycin).

Uveitis Associated With Infectious Diseases

- *Toxoplasma gondii*
- Feline immunodeficiency virus (FIV)
- Feline coronavirus (FIP)
- Feline leukemia virus (FeLV)
- Systemic mycoses
- Systemic bacteremias

Toxoplasmosis

Toxoplasma gondii, an intracellular coccidian parasite, uses the domestic cat as the only definitive host and any mammal as the intermediate host.



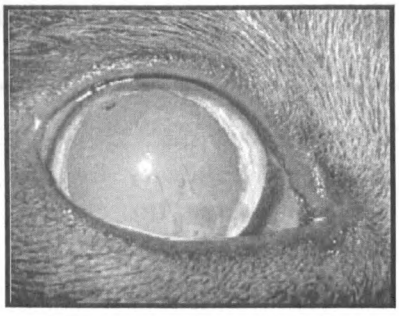
Toxoplasmosis causing nodular iritis.

Clinical Signs

Clinical signs of *Toxoplasma* infection is most commonly seen in cats with chronic secondary *Toxoplasma* recrudescence of encysted organisms

Clinical Signs May Include

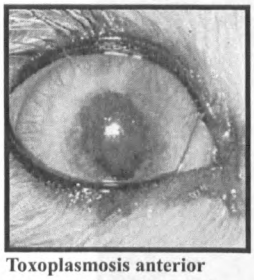
- Pyrexia
- Weight loss
- Diarrhea
- Vomiting
- Uveitis
- Neurological
- Respiratory



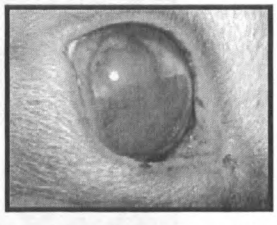
Toxoplasmosis anterior uveitis.

Toxoplasma Ocular Lesions

Ocular lesions to *Toxoplasma* are rare in primary infection, but frequent in secondary infection (anterior uveitis, posterior uveitis, panuveitis, and retinitis).



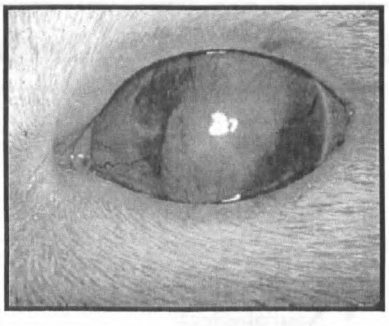
Toxoplasmosis anterior uveitis with posterior iris synechia.



Toxoplasmosis anterior uveitis with large fibrin clot in anterior chamber.

Toxoplasma gondii

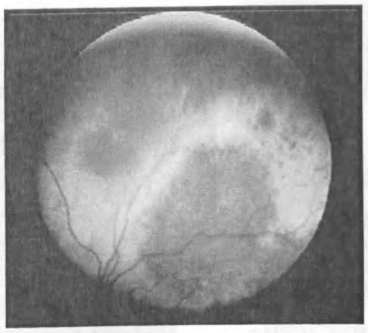
***T. gondii* seropositive cats may show secondary glaucoma or secondary lens luxation most probably due to uveitis**



Toxoplasmosis causing severe uveitis.

Toxoplasma Diagnosis

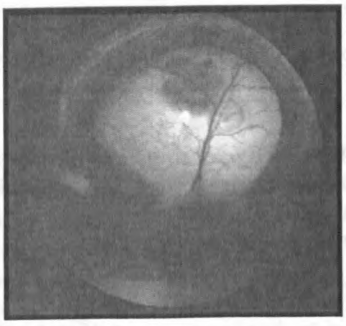
Ideally based on ELISA for detection of *T. gondii* specific IgM, IgG circulating antigens. IgM titers >1:256 and increasing IgG titers are helpful.



Toxoplasmosis retinal granulomas.

Toxoplasma Treatment

- Topical and/or systemic corticosteroids (depending upon site of uveal tract involved).
- Clindamycin HCl: 25 mg/kg/day in divided doses for a minimum for three weeks.



Toxoplasmosis retinal focal granulomas.

P A R T I I

Feline Coronavirus (FCoV)

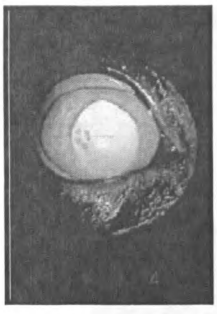
- Feline coronavirus is the cause of feline infectious peritonitis (FIP).
- FIP is one of the most common causes of uveitis in cats.
- FIP is most frequent in young cats than older cats, and more common in pedigree cats kept in multicat households.

FIP Nonophthalmic Signs

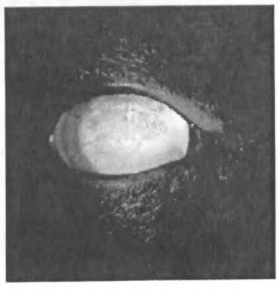
- Lethargy
- Pyrexia
- Inappetence
- Weight loss
- Neurological signs progressive
- Fatal

FIP Ocular Signs

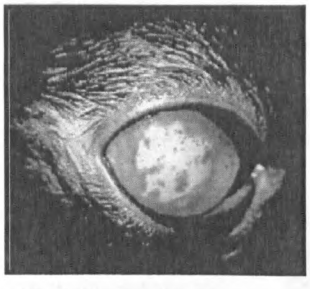
- Uveitis, often both eyes but not symmetrical
- Aqueous flare
- Keratic precipitates
- Hypopyon in anterior chamber
- Vitritis
- Hyphema/iris hemorrhages
- Retinal detachments - focal



FCoV anterior uveitis – note keratic precipitates.



FCoV anterior uveitis – more keratic precipitates.



FCoV anterior uveitis – clumping keratic precipitates.

Pathology of FCoV =FIP ocular inflammation stuck to corneal endothelium, fibrin in anterior chamber.

FIP Diagnosis

- Diagnosis by serology is confusing. IFA (immunofluorescence) is more reliable than ELISA (enzyme-linked immunosorbent assay) kits.
- Clinicopathological results are most helpful in diagnosis: increased total protein, hypergammaglobulinemia, lymphopenia, and coronavirus titer >160.

Feline Uveitis (Clinical Signs)

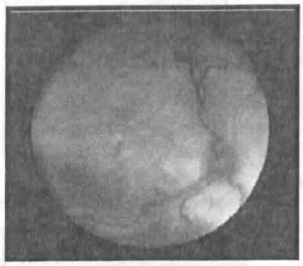
General:
- Painless-to-mildly uncomfortable
- Effect on vision: none to blind

Anterior:
- Inflammation variable
- Aqueous flare, keratic precipitates, hypopyon
- Iris vasculitis, nodules, synechia, color change
- Fibrin/hemorrhage
- Dyscoria/sluggish pupil reaction
- Inflammatory accumulation on anterior lens capsule

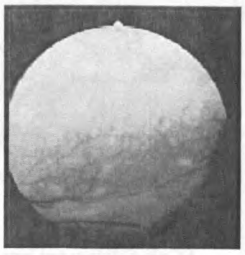
Feline Uveitis (Clinical Signs)

Intermediate:
- Inflammatory accumulation on posterior lens capsule in pars plana and anterior vitreous

Posterior:
- Vitritis (hazy due to inflammation)
- Vitreous opacities
- Chorioretinitis
- Retinal hemorrhage/detachment
- Optic neuritis



FCoV-FIP retinitis, detachment.



FCoV-FIP – retinal exudates best observed in nontapetal fundus

Feline Coronavirus

FCoV titers >1:8 considered antibody positive, a negative titer is significant.

(FIP cats with clinical signs had titers ranging from 1:30->1:2000).

Feline Coronavirus

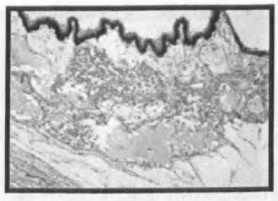
- Titer level is a poor prognosticator of disease!
- Cats with clinical signs of FIP, any positive titer may be significant!
- The majority of FIP confirmed cats have titers >1:100.

Feline Coronavirus

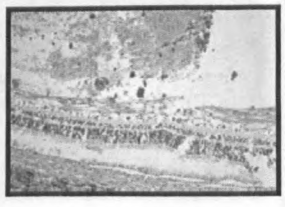
- FCoV test is a kinetics ELISA (KELA) assay.
- Does not differentiate between virulent and avirulent strains.
- PCR for FCoV available

Feline Coronavirus

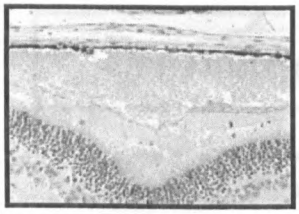
Fecal RT-PCR is available to identify asymptomatic FCoV shedders (2-5 grams of fresh feces submitted in clean-zip lock plastic bag, ship on ice).



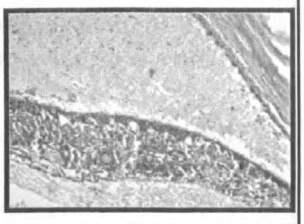
FCoV-FIP pathology showing ciliary body.



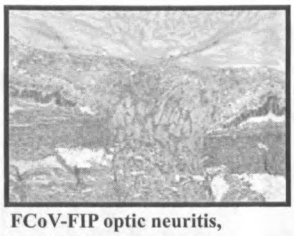
FCoV-FIP pathology showing hemorrhage.



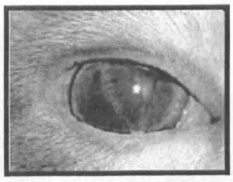
FCoV-FIP focal detachment.



FCoV-FIP retinal inflammation and detachment.

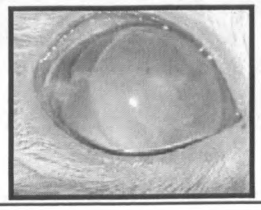


FCoV-FIP optic neuritis, choroiditis, retinitis.



FCoV-FIP iris bombé secondary to fibrin adhesions.

FCoV-FIP luxated lens into anterior chamber secondary uveitis.



Feline Coronavirus

To identify a cat as a chronic carrier shedder, it should be fecal virus positive on multiple tests over an 8-month period.

Feline Coronavirus

A cat with clinical signs consistent with FIP (i.e., uveitis), a FCoV, RT-PCR positive on ocular pericentesis indicates active FIP.

Feline Coronavirus

It is now believed that detection and removal of FCoV infected and shedding cats in a multicat household can decrease risk of FIP within that population.

Feline Immunodeficiency Virus (FIV)

Cats in later stages of FIV infection may develop uveitis due to secondary infection (example: *T. gondii*)

Feline Immunodeficiency Virus (FIV)

FIV most seen in adult, domestic shorthair free-roaming cats, males more commonly than females

Feline Immunodeficiency Virus (FIV)

Rule out FIV in chronic or recurrent uveitis, rarely present with acute uveitis.

Feline Immunodeficiency Virus Signs

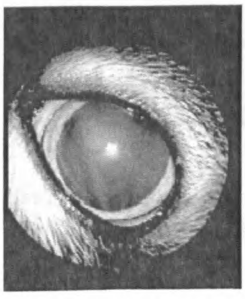
- Edema of cornea
- Aqueous flare
- Keratic precipitates
- Hypopyon
- Irregularity of pupil size
- Iris nodules
- Iris neovascularization
- Synechia formation
- Hyphema

(Many of these signs are similar to FIP and FeLV)

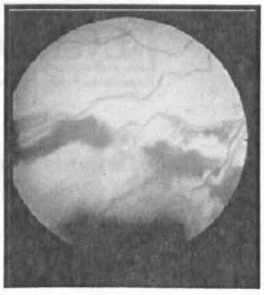
Feline Immunodeficiency Virus

FIV should be considered over other feline viral uveitis diseases when "pars planitis" (intermediate uveitis) is diagnosed.

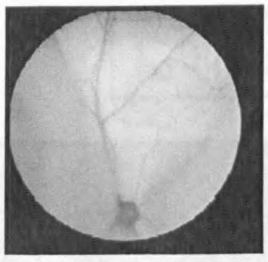
(Pars planitis = inflammatory cells [like snowball opacities] accumulating in anterior vitreous and onto posterior lens capsule).



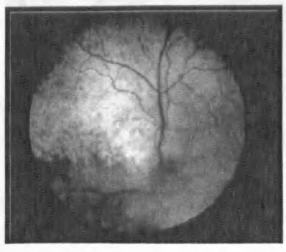
FIV - hemorrhage behind the lens.



FIV - chorioretinitis, detachment.



FIV – bullous retinal detachment.



FIV and toxoplasmosis - hemorrhage, retinal granulomas.

Feline Immunodeficiency Virus

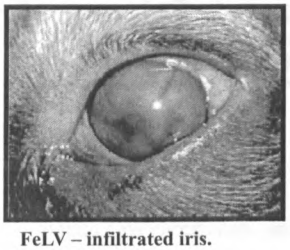
FIV retinal lesions may include:

- Vasculitis
- Focal chorioretinitis
- Hemorrhage
- Detachments
- Opportunistic infections (*T. gondii*)

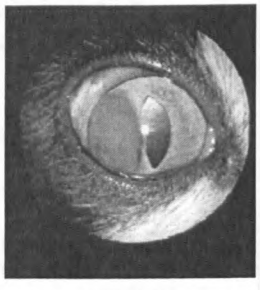
Feline Immunodeficiency Virus

- FIV diagnosis is the positive detection of antibody.
- However, a negative antibody test does not rule out FIV infection.

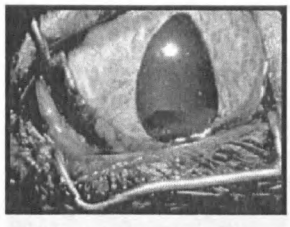
FeLV, Feline Leukemia-Lymphosarcoma



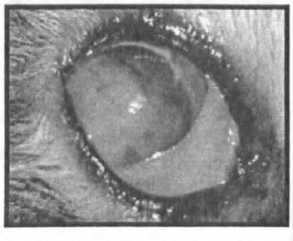
FeLV – infiltrated iris.



FeLV – lymphosarcoma of iris stroma.



FeLV – lymphosarcoma of ciliary body.



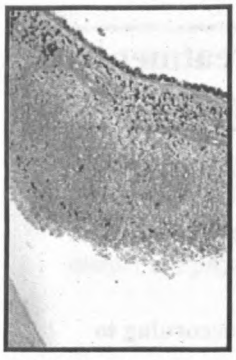
FeLV – lymphosarcoma of globe.

Lymphosarcoma

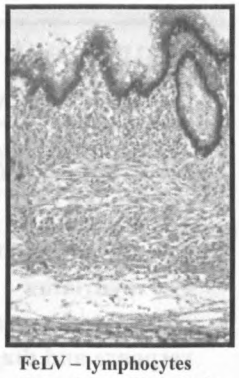
Lymphosarcoma in the cat is the most frequent systemic neoplasia with ocular metastases!

Lymphosarcoma

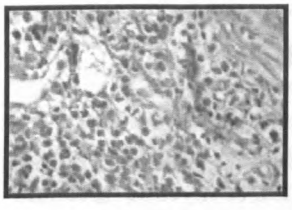
Lymphosarcoma is typically a cause of uveal infiltration, varying from nodular iris lesions to diffuse uveal lesions.



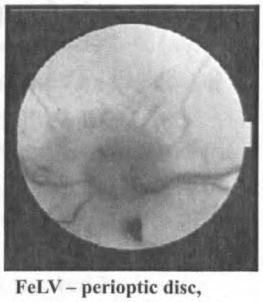
FeLV – lymphocytes throughout the iris.



FeLV – lymphocytes throughout ciliary body.



FeLV – lymphocytic-plasmacytic infiltrates.



FeLV – perioptic disc, lymphocytes with retinal hemorrhage.

Lymphosarcoma

Fewer than one-half of infected cats with lymphosarcoma uveitis test positive for FeLV.

Lymphosarcoma

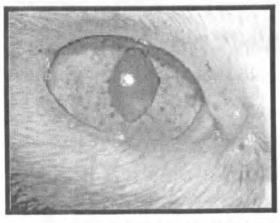
Survival time range from 0 days to 31 months, with a mean of 14 months.

Lymphosarcoma

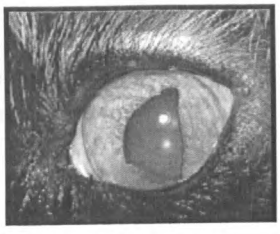
Treatment for lymphosarcoma uveitis should include topical corticosteroids (1% prednisolone acetate) and systemic corticosteroids or other chemotherapeutic agents.

Symptomatic Treatment of Uveitis

- Take sample to help define cause
- Put out the fire!
- Use anti-inflammatory agents
- Use mydriatics
- Re-evaluate treatment according to response and diagnosis



Anterior uveitis with fibrin in anterior chamber.



Mottled iris with a pars planitis (posterior uveitis).

Anti-inflammatory Agents

Topical Choices:

- Prednisolone acetate 1%
- Dexamethasone 0.1%
- Betamethasone sodium phosphate 0.1%

Systemic Choices:

- Prednisolone 1 mg/kg BID (taper in 5-14 days)

Caution!

- Corticosteroids should *not* be used if there is corneal ulceration or mycotic infection.
- Certain latent viral disease can be activated.

Nonsteroidal Anti-inflammatory Agents

Should be used if etiology of the uveitis is unknown or the cornea is ulcerated.

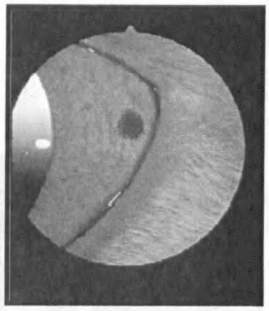
Melanoma Versus Nevus Versus Iris Cyst

Diagnosis

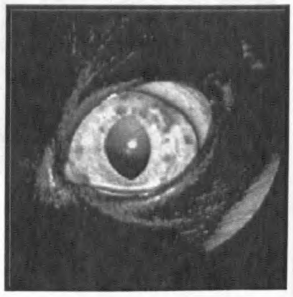
- The diagnosis of melanoma in a cat eye is a "grave" diagnosis!
- If unsure of your diagnosis, take a close-up photograph and follow it with frequent photographs over one month.

- A nevus is flat with sharp borders, very often single. Also called "iris freckle".
- Melanomas are swollen, tumor-like; many distort the pupil.

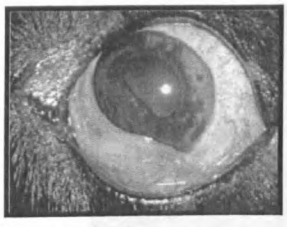
- Iris cyst or ciliary cyst may be black and misdiagnosed as melanoma.
- Diagnose a cyst by transillumination with a bright light. Since the cyst is fluid filled, the light passes through defining only the capsule.
- Large cysts are easily treated by laser.



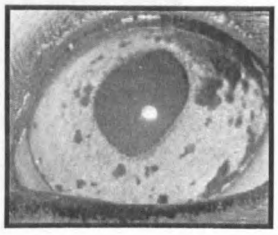
Iris nevus.



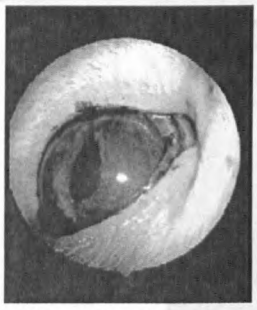
Multiple iris nevi tending to coalesce together



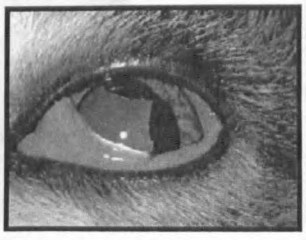
Iris melanoma.



Multiple iris melanomas.

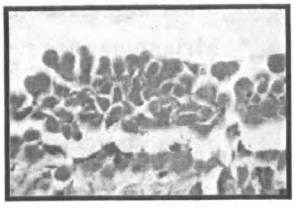


Diffuse iris melanoma.



Ciliary body melanoma.

Ciliary cyst.

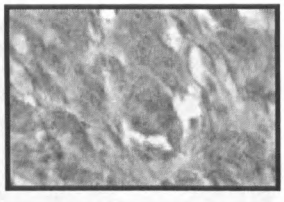


Pathology of iris melanoma.

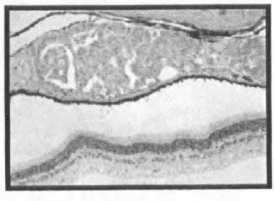
Other Neoplasias

Other neoplasias known to metastasize to the cat eye:

- Adenocarcinoma (from lung, mammary, and uterus)
- Fibrosarcomas
- Squamous cell carcinomas



Pathology of giant cell sarcoma in posterior chamber.



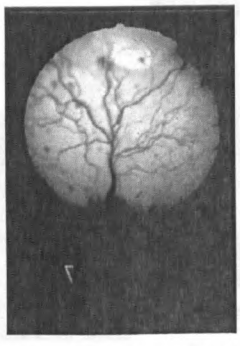
Subretinal adenocarcinoma.

Mycotic Uveitis

Uveitis in cats caused by:

- Cryptococcosis
- Histoplasmosis
- Blastomycosis
- Coccidiomycosis
- Candidiasis

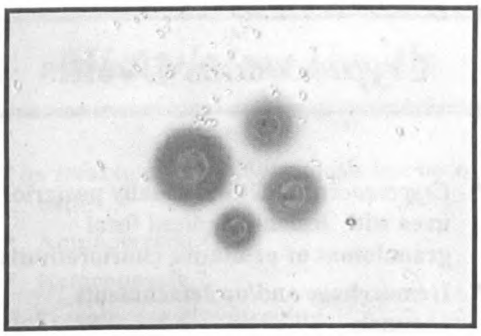
Are rare, but they become a rule out if the infection is systemic and/or FIV is present



Cryptococcus lesions throughout fundus.

Mycotic Uveitis

Mycotic ocular lesions usually are observed in the posterior uveal, vitreal, and retinal area.



Cryptococcus organisms stained with new methylene blue.

Mycotic Uveitis

Mycotic diagnosis is by vitreocentesis submitted for cytology and culture.

Mycotic Uveitis

- Cats of all ages may be infected with no breed or sex predisposition.
- The course of the disease is usually slow.

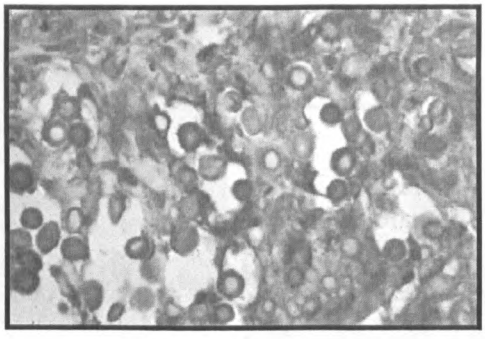
Mycotic Uveitis

Cryptococcus neoformans is the most common systemic mycosis in the cat.

Cryptococcus organisms stained with India ink.

Mycotic Uveitis

Cats with cryptococcosis usually have upper respiratory tract disease, central nervous system, skin, and ocular lesions.



Cryptococcus organisms histology stained with mucicarmine.

Cryptococcus Uveitis

- *Cryptococcus* uveitis is usually posterior uvea with lesions of raised focal granulomas or exudative chorioretinitis.
- Hemorrhage and/or detachments common.

Cryptococcus Uveitis

Cryptococcus treatments have included:

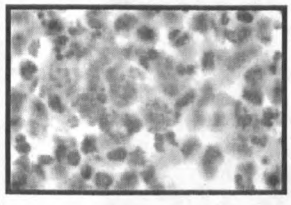
- Itraconazole
- Ketoconazole
- 5-fluorocytosine, triazole, variconazole, or combinations of these

Histoplasma capsulatum Uveitis

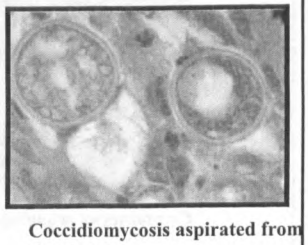
Histoplasma capsulatum in cats can be seen with upper respiratory tract disease because the initial infection is by inhalation.

Histoplasma Uveitis

Histoplasma lesions cause focal granulomatous chorioretinitis and detachments.



Histoplasma aspirated from vitreous.



Coccidiomycosis aspirated from the vitreous.

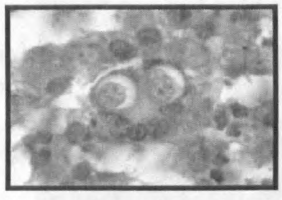
Histoplasma Uveitis

The treatment of histoplasmosis has been with:

- **Amphotericin B**
- **Ketoconazole**

But results are discouraging

***Blastomyces* organism aspirated from vitreous**



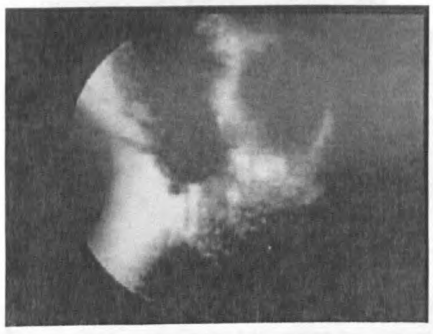
***Blastomyces* organism aspirated from vitreous.**

Blastomyces Uveitis

***Blastomyces dermatitidis* infection is rare in cats, but reports of upper respiratory tract disease, central nervous system, and ocular lesions have been diagnosed.**

Blastomyces Uveitis

***Blastomyces* ocular lesions are usually gray-white choroidal granulomas. Chronic granulomatous uveitis, both anterior and posterior, have been seen. Chronic lesions are dark with pigment, hemorrhage, and inflammation.**



Blastomycosis retinitis.

Bacterial Uveitis

- **Causes are usually not from disseminated bacteria, but rather local trauma.**
- **Hypopyon sometimes indication of sepsis.**

Bacterial Uveitis

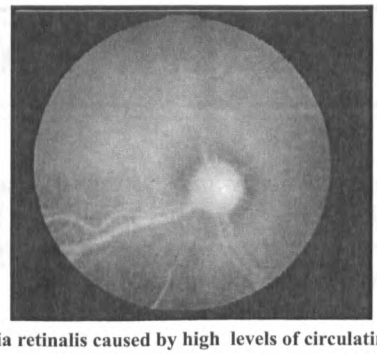
Direct intraocular inoculation of bacteria from a fight is a common cause of cat uveitis.

Bacterial Uveitis

- Symptomatic treatment for the uveitis using topical nonsteroidal anti-inflammatories and antibiotics TID to QID for two weeks is recommended.
- Mydriatic cycloplegics aid in comfort, but cats dislike the taste of atropine ∴ try 1% tropicamide BID.

Lipemia Retinalis

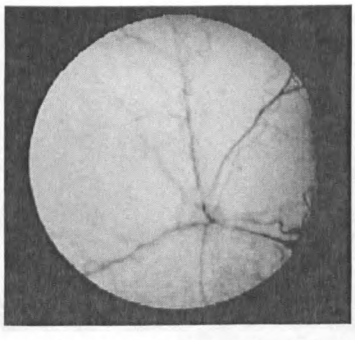
White retinal vascular appearance secondary to high levels of circulating lipoprotein (i.e., increased levels of triglycerides or cholesterol).



Lipemia retinalis caused by high levels of circulating lipoproteins. Note blue color fundus which is normal for a kitten <12 weeks old.

Anemic Retinopathy

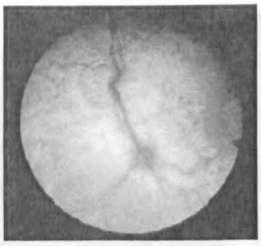
- Pale attenuated vasculature with hemorrhages
- Hemoglobin <5 g/dl
- Check platelet levels
- Rule out FeLV



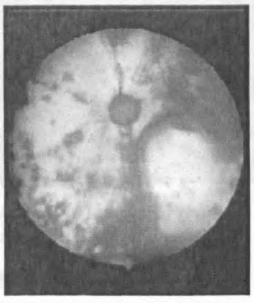
Anemic kitten from heavy flea infestation. Note the blanched vascular character.

Diabetic Retinopathy

- Retinal and vitreal hemorrhage
- Detachments with microaneurysms (rare in cats)



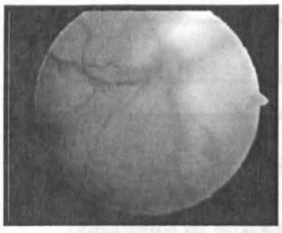
Diabetes in adult cat showing various hemorrhages and focal detachment.



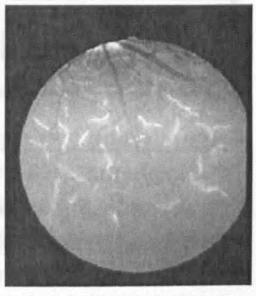
Diabetes in adult cat with larger hemorrhages and detachment.

Retinal Folds/Detachments Rule Outs

- Hypertension
- Hyperviscosity
- Periarteritis nodosa
- Toxoplasmosis
- Cryptococcosis
- Blastomycosis



Severe retinal dysplasia resulting in detachment.

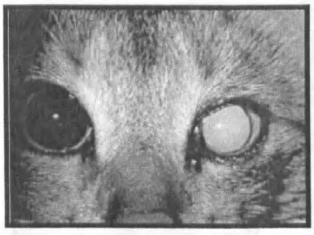


Retinal folds in nontapetum, white linear; some straight, some branching.

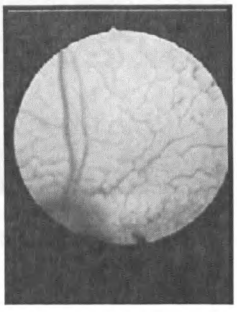
Pathology of retinal folds or retinal dysplasia and detachment.

Retinal Folds/Detachments Rule Outs

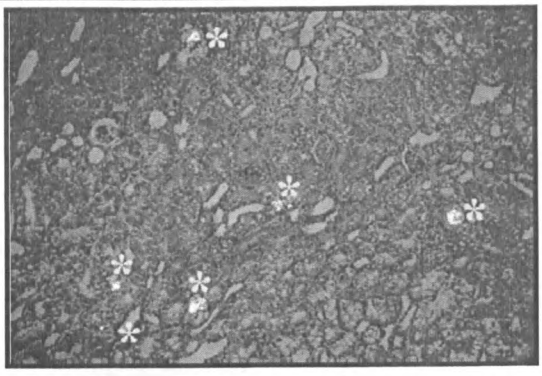
- Histoplasmosis
- Coccidiomycosis
- FIP
- Ethylene glycol toxicity
- Polycythemia
- Neoplasms



Acutely blind cat (widely dilated pupils with no light response).



Acute blindness due to ethylene glycol (antifreeze ingestion).



Kidney biopsy with oxalate crystals * confirming ethylene glycol diagnosis.

Hypertensive Retinopathy

Acute vision loss signs:

- Hyphema
- Secondary glaucoma due to hyphema
- Vitreal hemorrhage
- Retinal vascular tortuosity
- Retinal hemorrhage
- Retinal detachments

Hypertensive Cats

Usually have arterial blood pressure >160 mm Hg

Hypertensive Cats

May Also Have:

- Increased BUN
- Increased creatine
- Cardiomegaly/left ventricular hypertrophy

Hypertensive Cats

- Usually improve on calcium channel blocker
- Amlodipine (0.625 mg/SID)
- Can give with vitamin solution

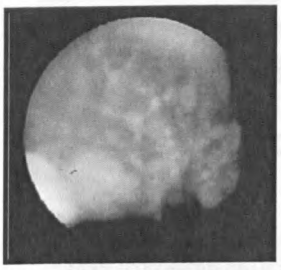
Hypertensive Retinopathy

May be primary or secondary.
Secondary causes include:

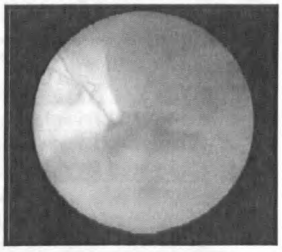
- Renal
- Hyperthyroidism
- Chronic blood dyscrasias
- Diabetes mellitus
- Megestrol acetate
- Corticosteroid usage
- Primary aldosteronism

Hypertensive Retinopathy

- Flat retinal detachments common as early increased blood pressure lesions
- Bullous retinal detachment, usually multiple, as increased blood pressure remains, then total detachment



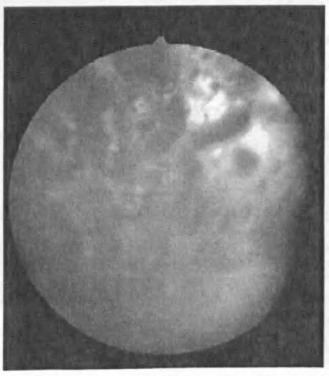
Feline hypertensive retinopathy.



Feline hypertensive retinopathy with detachment.

Hypertensive Retinopathy

- Early cases are more likely to respond favorably to treatment, giving reattachment and vision



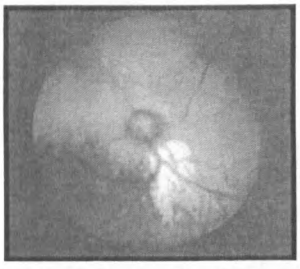
Feline hypertensive retinopathy secondary to polycythemia.

Hypertensive Retinopathy

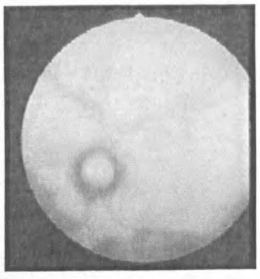
- Hemorrhage from retinal vasculature and iris will lead to hyphema which may turn into glaucoma

Panleukopenia Virus

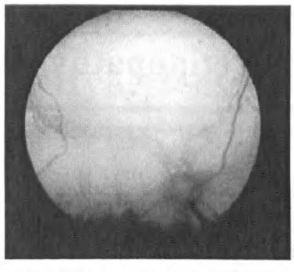
- Kittens infected *in vivo* or just following birth develop retinal dysplasia and cerebellar hypoplasia
- Clinical signs of hypermetria and ataxia as well as visual compromise, even blindness



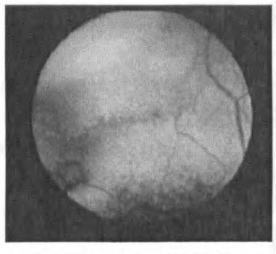
Feline panleukopenia. Note dorsal window of hyper-reflectivity.



Feline panleukopenia. Note color difference dorsal to the disc.



Feline panleukopenia. Note color difference dorsal to the disc.



Feline panleukopenia. Retinal dysplasia diagnosis in an adult cat.

Reported Inherited Retinal Degeneration

- Cone-Rod Dysplasia: Persians (recessive)
- Cone-Rod Dysplasia: Abyssinians (dominant, early onset)
- Cone-Rod Dysplasia: Abyssinians (recessive, later onset)
- Secondary to concurrent administration of ketamine HCl and methyl nitrosourea
- Secondary to prolonged use of enrofloxacin 5 mg/kg SID

Feline Central Retinal Degeneration

FCRD = taurine deficiency

Feline Central Retinal Degeneration

Taurine, a sulfur amino acid, essential to cats but they have a limited ability to synthesize it from cysteine.

Feline Central Retinal Degeneration

Cats need a dietary supplement level of taurine between 500-700 ppm to prevent FCRD.

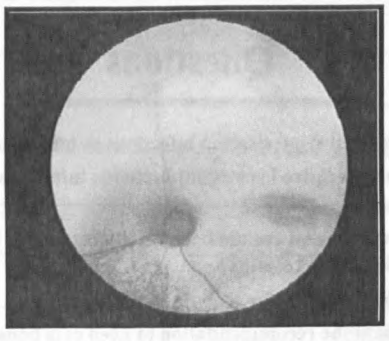
Feline Central Retinal Degeneration

Commercial feline diets contain adequate taurine, thereby decreasing FCRD incidence.

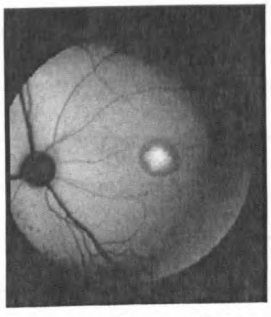
Feline Central Retinal Degeneration

FCRD lesions are pathognomic:

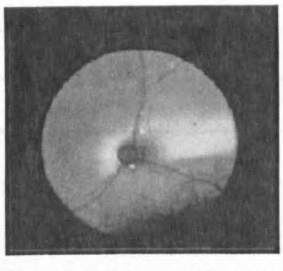
- Stage 1: increased granularity of the area centralis
- Stage 2: ellipsoidal hyper-reflective zone involving the area centralis
- Stage 3: hyper-reflective zone enlarged to include a zone nasally and dorsal
- Stage 4: generalized hyper-reflective fundus with attenuated vasculature



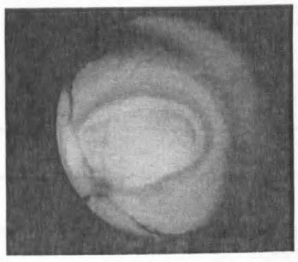
Feline central retinal degeneration (FCRD), earliest stage of increasing granularity of area centralis.



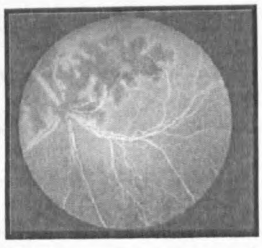
FCRD – Stage I hyper-reflective in area centralis.



FCRD – Stage II hyper-reflectivity expands dorsally.



FCRD - Stage III hyper-reflectivity expands dorsally.



FCRD fluorescein angiogram of Stage III.

Suggested Reading

- *Essentials of Veterinary Ophthalmology* by Kirk N. Gelatt.
- *Veterinary Ophthalmology* by Kirk N. Gelatt.
- *Feline Ophthalmology* by K. C. Barnett and S. M. Crispin.
- *Current Veterinary Therapy edited* by John D. Bonagura.
- *Small Animal Ophthalmology Secrets* by Ronald C. Riis.

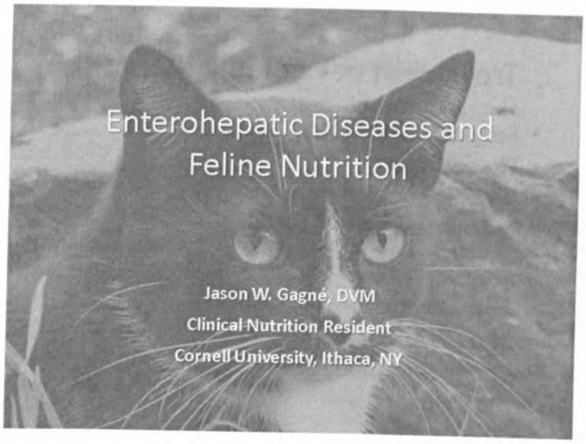
Learning Objects

- Know the ocular expressions of infectious manifestations.
- Know some practice aids in diagnosing ocular lesions.
- Be familiar with laboratory tests to help diagnose the etiology.
- Be aware of ocular ruleouts making your diagnosis.
- Know some of the sequela of early onset disease that may present with age.
- Appreciate how the eye is like the crystal ball of the body.

Questions

- Is corneal sequestration infectious to other cats?
- Is proliferative keratoconjunctivitis infectious to other cats?
- Has megestrol acetate been a good treatment for eosinophilic keratitis?
- Does treatment for toxoplasmosis work?
- Should the recommendation to keep cats house bound be followed?
- How well does a blind cat compensate?

Go within, discovery your invisible higher self, and know God as the love that is within you

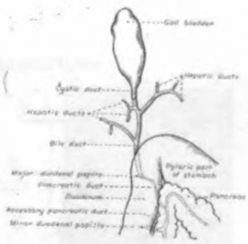


Learning Objectives

- Understand the nutritional approach in terms of diet to be fed in cholangiohepatitis.
- Understand the nutritional approach in terms of diet to be fed in inflammatory bowel disease.
- Understand the supplementation that may be used as an adjunct to nutritional therapy in both of the above conditions.

Inflammatory Liver Disease

- Cholangiohepatitis
  - Acute (suppurative)
    - Histology
    - Bacterial infection
  - Chronic (nonsuppurative)
    - Histology
    - Progression of acute form
    - Biliary cirrhosis



Evans HE. The Digestive Apparatus and Abdomen. In: Miller's Anatomy of the Dog (3rd ed.), WB Saunders, Philadelphia 1993. Hudson LC & Hamilton WP. Atlas of Feline Anatomy for Veterinarians (2nd ed.) 2010.

Conditions associated with Cholangiohepatitis

Inflammatory bowel disease
Chronic bacterial infections within other organs
Pancreatitis
Toxoplasmosis
Anatomic abnormalities of the gallbladder
FIP
FeLV
Cholelithiasis
Extrahepatic bile duct obstruction
Biliary reconstructive surgery
Septicemia
Neoplasia
Liver fluke infestation

Edwards, M. Feline Cholangiohepatitis. *Compendium* 2004;Nov 855-862.

Clinical Presentation

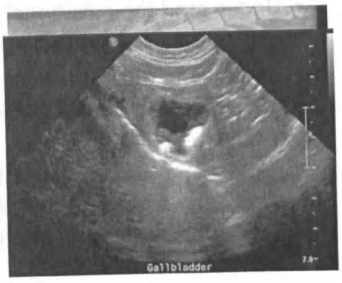
- Signalment
  - Age, gender, breed
- Acute (suppurative):
  - Anorexia
  - Lethargy
  - Pyrexia
  - Abdominal pain
  - Vomiting
  - Icterus
- Chronic (nonsuppurative):
  - Anorexia or polyphagia
  - Weight loss
  - Lethargy
  - Vomiting
  - Diarrhea
  - Icterus

Diagnostic Evaluation

- Complete blood count
- Serum chemistry
- Urinalysis
- Acute (suppurative):
  - Leukocytosis
  - ALT, AST, GGT +/- ALP +/- bilirubin
  - Pre-renal azotemia
  - Electrolyte depletions
  - Bilirubinuria
- Chronic (nonsuppurative):
  - Variable leukogram
  - Mild anemia +/- heinz bodies
  - ALT, AST, GGT +/- ALP +/- bilirubin
  - Hyperglobulinemia
  - Elevated cholesterol
  - Bilirubinuria

Additional Diagnostics

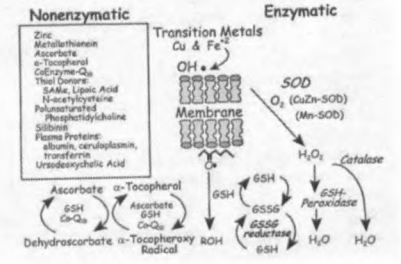
- Coagulation profile
- Thyroid profile
- Spec fPL
- FeLV/FIV
- Toxoplasma titers
- Cobalamin
- Imaging
- Biopsy



Treatment of Cholangiohepatitis

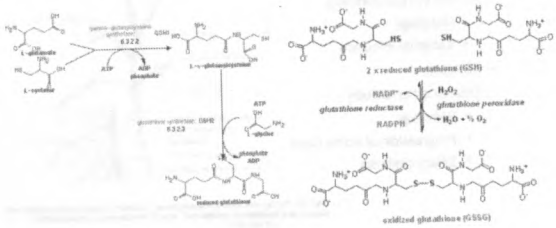
- Surgical intervention
- Fluid support
- Vitamin supplementation
  - B-complex at 1-2 mL/L
  - Vitamin B_{12} – 0.25 – 1.0 mg weekly then monthly
  - Vitamin K – 0.5 – 1.5 mg/kg q12hr x 3 doses
- Antimicrobials
- Immunosuppresants
- Cholorectic medication
- Antioxidants

Antioxidant Mechanisms

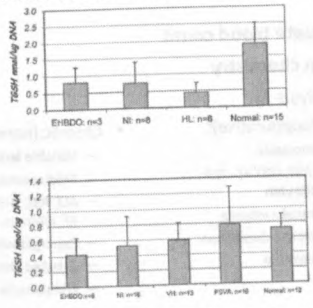


Center, SA. Metabolic, antioxidant, nutraceutical, probiotic, and herbal therapies relating to the management of hepatobiliary disorders. *Vet Clin Small Anim.* 2004; 34:67-172.

Glutathione

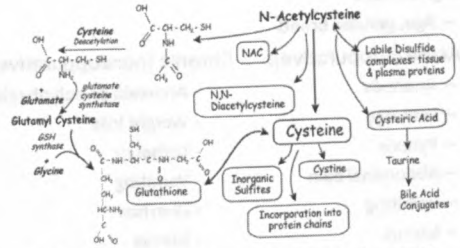


Glutathione Concentration



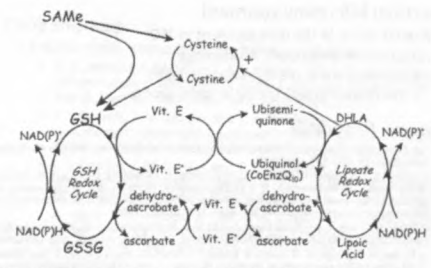
Center SA, Warner KL, Erb HN. Liver glutathione concentrations in dogs and cats with naturally occurring liver disease. *Am J Vet Res*. 200263(8):1187-97.

N-acetylcysteine



Center, SA. Metabolic, antioxidant, nutraceutical, probiotic, and herbal therapies relating to the management of hepatobiliary disorders. *Vet Clin Small Anim.* 2004; 34:67-172.

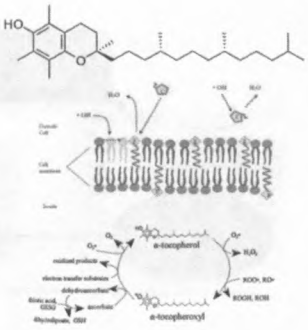
S-adenosylmethionine



Center, SA. Metabolic, antioxidant, nutraceutical, probiotic, and herbal therapies relating to the management of hepatobiliary disorders. *Vet Clin Small Anim.* 2004; 34:67-172.

Vitamin E

- Fat-soluble vitamin
- Tocopherols and tocotrienols
- Synthesized by plants
  - Corn oil - 1.4 mg/10 g
  - Canola oil – 0.8 mg/10 g
  - Vegetable oil – 1.6 mg/10 g
  - Wheat germ oil – 15 mg/10 g
- Dose
  - 10 IU/kg per day
  - α-tocopherol acetate
  - Water soluble



Nutritional Support

- Enteral preferred
  - Nasoesophageal/Nasogastric tube
  - Esophageal tube

Nutritional Support

- Maintenance or maximum calorie/recovery/critical care diet
  - Palatable
  - Calorically dense
  - Easily digestible
  - Ease of preparation
  - Small frequent meals
- Moderate protein 30-40% DM
- Moderate fat 20-30% DM
- Moderate carbohydrate 20-40% DM

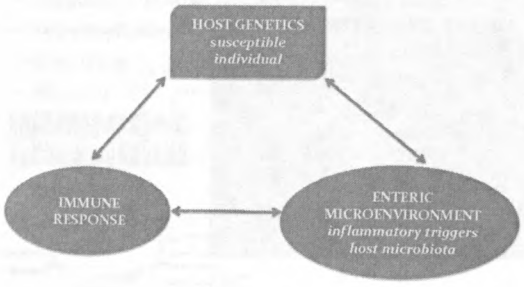
Nutritional Support

- Protein
  - Nitrogen balance
  - Minimize tissue (muscle) catabolism = NH_3
- Hepatic Encephalopathy
  - Minimally start with 3.5 g protein/kg of body weight
  - Reevaluate every 7-14 days and add 0.5 g/kg
  - Excessive Nitrogen
    - Ammonium biurate crystals
    - Monitor CK and BUN
    - Hyperammonemia
  - Minimum 2.5 g protein/kg of body weight

Hepatic Encephalopathy

- Cats require a meat source – arginine
- Avoid red meats = hemoglobin = NH_3
- Avoid aromatic amino acids
  - Phenylalanine, tyrosine, and tryptophan
    - Encephalopathic effects
- Branched chain amino acids
  - Isoleucine, leucine, valine – gluconeogenic
- Soluble fiber
  - Lactulose
- Intestinal microbiome imbalance

Inflammatory Bowel Disease



Inflammatory Bowel Disease

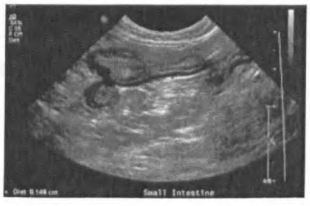
- Intestinal Microenvironment
  - Pivotal factor in the development of IBD
  - Advances in molecular microbiology
    - Fluorescence in situ hybridization (FISH)
    - 16S ribosomal RNA (rRNA) bacterial probes
- Immune Response
  - AA. E. Jergens: Inflammatory bowel disease. Current perspectives. *Vet Clin North Am Small Anim Pract* 29, 501-521, vii (1999)
  - S. Janeczko, D. Atwater, E. Bogel, A. Greiter-Wilke, A. Gerold, M. Baumgart, H. Bender, P. L. McDonough, S. P. McDonough, R. E. Goldstein and K. W. Simpson: The relationship of mucosal bacteria to duodenal histopathology, cytokine mRNA, and clinical disease activity in cats with inflammatory bowel disease. *Vet Microbiol* 128, 178-93 (2008)
  - N. Waly, C. Stokes, T. Gruffydd-Jones and M. Day: Immune cell populations in the duodenal mucosa of cats with inflammatory bowel disease. *J Vet Intern Med* 18, 816-825 (2004)
  - N. N. Van, K. Taglinger, C. R. Helps, S. Tasker, T. J. Gruffydd-Jones and M. J. Day: Measurement of cytokine mRNA expression in intestinal biopsies of cats with inflammatory enteropathy using quantitative real-time RT-PCR. *Vet Immunol Immunopathol* 113, 404-414 (2006)

Clinical Presentation

- Signalment
  - Age, gender, breed
- Anorexia
- Weight loss
- Vomiting
- Diarrhea
- Concurrent inflammatory disease
  - Liver
  - Pancreas

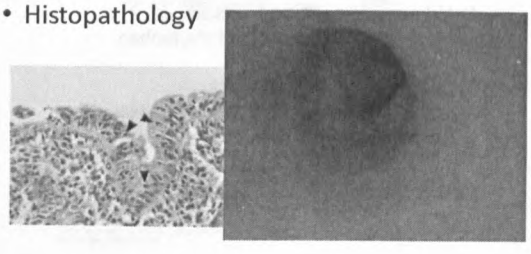
Diagnostic Evaluation

- Complete blood count
- Serum chemistry
- Fecal examination +/ culture
- Spec fPL
- Cobalamin
- Thyroid profile
- Imaging



Diagnostic Evaluation

- Endoscopic biopsy
- Histopathology



Clinical Activity Index

Table 5. The feline chronic enteropathy activity index (FCEAI)

Variable	Assessment
GIT signs	No or yes
Attitude/activity	
Appetite	Scored
Vomiting	0-3*
Diarrhea	
Weight loss	
Endoscopic lesions	0=no; 1=yes
Total protein	0=normal; 1=increased
ALT/ALP	0=normal; 1=increased
Phosphorous	0=normal; 1=decreased

Similar to the CIBDAI, this clinical scoring system incorporates multiple variables including gastrointestinal signs, endoscopic lesions, and select biochemical analytes. Clinical trials indicate that the FCEAI is useful for defining disease activity in cats having either IBD or food-responsive enteropathy. *Range of gastrointestinal signs from not present (0) to severe (3).

Jergens AE, Simpson KW. Inflammatory bowel disease in veterinary medicine. *Front Biosci (Elite Ed).* 2012 Jan 1;4:1404-19.

Treatment

- Drug therapy
  - Prednisolone, metronidazole, tylosin, sulfasalazine
    - A. E. Jergens, F. M. Moore, J. S. Haynes and K. G. Miles: Idiopathic inflammatory bowel disease in dogs and cats: 84 cases (1987-1990). *J Am Vet Med Assoc* 201, 1603-1608 (1992)
    - J. S. Dennis, J. M. Kruger and T. P. Mullaney: Lymphocytic/plasmacytic gastroenteritis in cats: 14 cases (1985-1990). *J Am Vet Med Assoc* 200, 1712-1718 (1992)
    - J. S. Dennis, J. M. Kruger and T. P. Mullaney: Lymphocytic/plasmacytic colitis in cats: 14 cases (1985-1990). *J Am Vet Med Assoc* 202, 313-318 (1993)
    - A. Jergens, J. Crandell, R. Evans, M. Ackermann, K. Miles and C. Wang: A clinical index for disease activity in cats with chronic enteropathy. *J Vet Intern Med* 24, 1027-1033 (2010)
  - Cobalamin
    - 0.25 – 1.0 mg weekly then monthly

Treatment

- Nutritional therapy

Table 6. Nutritional therapy for canine and feline IBD

Clinical Study	Species (No.)	Diet	Primary/Adjunct role	Response
66	Cat (28)	Controlled	Adjunct	50% respond
6	Cat (60)	Controlled	Adjunct	80% respond
96	Dog (6)	Elimination	Primary	70% respond
71	Dog (58)	Elimination	Adjunct	80% respond
8	Dog (65)	Elimination	Primary	50% respond
4	Dog (70)	Elimination	Adjunct	60% respond
94	Dog (54)	Elimination	Adjunct	80% respond
75	Cat (17)	Elimination	Adjunct	100% respond

Jergens AE, Simpson KW. Inflammatory bowel disease in veterinary medicine. *Front Biosci (Elite Ed).* 2012 Jan 1;4:1404-19.

Nutritional Therapy

- Diet characteristics
  - Dietary history
  - Novel or hydrolyzed protein source
  - Digestible carbohydrate
  - Low fat
  - Highly palatable
  - AAFCO approved
- Moderate protein 30-40% DM
- Low fat 20% DM
- Moderate carbohydrate 30-40% DM

Feline Limited Ingredient Diets

- Hill's d/d (pork fat)
  - Rabbit and green pea – rabbit, green peas, fish oil
  - Venison and green peas – venison, green peas, fish oil
  - Duck and green peas – duck, green peas, fish oil
- Royal Canin (coconut oil)
  - Pea and Rabbit – pea, rabbit, vegetable and fish oil
  - Pea and Venison – pea, venison, vegetable and fish oil
  - Pea and Duck – pea, duck, vegetable and fish oil

Feline Limited Ingredient Diets

- Iams (corn oil)
  - Response LB – lamb and barley
- OTC Brands?
  - *J Anim Physiol Anim Nutr (Berl).* 2011 Feb;95(1):90-7.

Does protein hydrolysis help?

- Newer diets are advocating certain molecular weight proteins, less than 10 kD often used.
- Hydrolysis must be nearly complete to do this.
- It may be different for each protein source.
- It is important to restrict the patient to one protein source even if hydrolyzed.
- Limited ingredient vs. Hydrolyzed?

Feline Hydrolyzed Diets

- Hill's z/d (soybean oil)
  - z/d – brewers rice, hydrolyzed chicken and chicken liver
  - z/d Ultra- hydrolyzed chicken liver, corn starch
- Royal Canin HP (chicken fat)
  - Hypoallergenic- brewers rice, hydrolyzed soy protein, vegetable and fish oil
- Purina HA (vegetable oil)
  - Hypoallergenic - rice starch, hydrolyzed soy, canola oil, hydrolyzed chicken liver

Homemade Diets

- Unfortunately a low percentage of cats seem to have antigenic stimulation to other ingredients in the food.
- These cases need homemade diets:
  - The gold standard for food trials
  - Eliminates additives
  - One protein and one carbohydrate source
  - 2:1 volume for cats
  - Not inherently hypoallergenic
  - Labor, cost, acceptance, nutritional imbalance

Modification of Ω6:Ω3

References

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Updates in general anesthesia for the feline patient. General Anesthesia for dental procedures.

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Learning Objectives

1. To discuss factors unique to anesthesia for dental procedures in the feline patient.
2. To analyze strategies that may minimize risks associated with anesthesia for cats during dental surgery
3. To discuss potential complications that are pertinent to anesthesia for dental surgery, including post-anesthesia blindness in cats.

Feline patients requiring dental treatment under general anesthesia can usually be divided into two subpopulations: healthy individuals needing prophylaxis or localized dental procedures, and sick cats, in which their dental disease is only a component of different factors affecting the cat. Our service commonly sees cats (and dogs) that may have renal or heart disease and also require dental procedures. Because the anesthetic management for such patients will dictated, at least in part, by the status of each individual, we will focus this discussion on anesthesia for dental procedures in healthy cats and what may be unique for such interventions.

Healthy cats coming for dental prophylaxis or relatively simple dental surgical procedures are treated in an outpatient basis; there is typically no need for hospitalization and the animals return home the same day of surgery. A thorough physical examination, complete medical history and limited blood work is typically all that is required as part of the anesthesia work-up. Blood work includes packed cell volume, plasma proteins, glucose and urea. Geriatric patients may justify more complex analysis. The value of complex blood work in healthy patients, as a screening tool prior to anesthesia, has been questioned, and it is not clear what advantages this practice may provide. In a recent study (1) in which 1500 healthy dogs were evaluated, an anesthetic protocol was planned for each animal before blood work was completed, and adjustments were made after the results were available. Although minor abnormalities were found in some animals, the anesthetic protocol was adjusted in only 2/1500 dogs.

In order to safely discharge patients after a dental surgical procedure, pets need to be awake, with minimal sedation yet sufficient analgesia, before they can go home. They should also not be nauseated, and have a normal rectal temperature. Short acting or reversible drugs are therefore desirable. Long acting agents, like acepromazine, may result in prolonged recovery from anesthesia. Potent narcotics, such as morphine or hydromorphone, administered for postoperative pain control, may also produce sedation and nausea, preventing a patient to be discharged early. Pre-anesthetic

sedation with a combination of alpha2 agonists (medetomidine, dexmedetomidine) and an opioid, provides sufficient sedation for catheter placement, preoxygenation, and allows for a considerable reduction of general anesthetics needed during the dental procedure. Alpha2 agonists provide an intermediate duration of action, and most of its sedative effects can be reversed with the use of an antagonist (atipamezole). Although the cardiovascular effects of dexmedetomidine are well known, hypertension appears to be less severe in cats than it is in dogs. Bradycardia, however, does occur with frequency. Concomitant administration of atropine with dexmedetomidine is controversial, as it may result in severe hypertension with little improvement in cardiac output and an increase incidence of arrhythmias.

For short procedures, propofol provides a better recovery than the combination of ketamine and diazepam. Propofol also abolishes laryngeal reflexes to a higher extent than ketamine, making intubation easier. This is an important point, since tracheal intubation in cats is associated with a risk of laryngeal or tracheal trauma. Before induction and intubation can occur, oxygen supplementation for at least 3 minutes should be provided. The supplementation of oxygen provides a "reserve" in case of apnea or a difficult intubation, making the procedure safer. In dogs, it has been shown that preoxygenation increases the time of tolerance of apnea (before arterial blood desaturation occurs) from approximately 1 minute to close to 5 minutes (2).

Because of the risk of aspiration pneumonitis, a cuffed tracheal tube should always be placed. Since dental procedures require manipulation of the head and neck, the use of reinforced (or guarded) tracheal tubes may be advantageous. These tubes can be bent without kinking and obstructing. As mentioned before, the risk of laryngeal or tracheal injuries caused by tracheal tubes is higher in cats than in dogs. This may be in part due to the small size of the oral cavity, the fragility of cartilages and the reactive nature of the feline's larynx. Laryngospasm may occur if intubation is attempted before a deep plane of anesthesia is reached. The use of a stylet aids intubation, especially when reinforced tracheal tubes are used. Care must be taken that the stylet does not protrude through the distal end of the tracheal tube and traumatize the airway. The cuff of the tube should be inflated only enough to prevent a leak during positive pressure ventilation; over inflation may produce a tracheal lesion.

During dental procedures, it is common to change positions and recumbencies, so that all dental pieces can be examines. This can however result in tracheal injuries caused by movements of the tracheal tube inside the airway. Tracheal lacerations occur more commonly during dental procedures, and if severe, are evidenced by subcutaneous emphysema, pneumothorax and pneumomediastinum. Some cases may require treatment with oxygen supplementation, and some may even require surgical correction of a defect.

Intraoperative analgesia, if extractions or other invasive procedures are performed, is provided by local anesthesia. Commonly the mandibular nerve can be desensitized for procedures involving the mandible, or the branches of the maxillary nerve – at the level of the infraorbital foramen – can be anesthetized for procedures involving the upper teeth.

Post-operative analgesia and sedation should be tailored so that pets are comfortable yet not deeply sedated. Buprenorphine and/or meloxicam can provide analgesia with minimal to no sedation. More potent narcotics, such as hyromorphone for example, provide reliable analgesia, but also sedation and nausea, which may prevent the patient from having a quick return to normal activities (e.g; ambulation and drinking).

Reports of cats recovering from anesthesia but suffering vision deficits can be found in the literature. This devastating complication has commonly been attributed to cardiovascular depression or hypoxemia, related to anesthesia. In several cases however, vision deficits occurred even after an uneventful anesthesia was performed. A recent retrospective study (3) showed a significant association between the use of a spring-loaded mouth gag and the development of post-anesthesia blindness. Twenty cats developed vision deficits upon recovery from anesthesia; in 17 of them a mouth gag had been used (either for dental or endoscopic procedures). The remainder 3 cats had cardiac arrest during anesthesia, which can explain the development of blindness. We recently conducted a study investigating this complication. In cats, the maxillary artery provides perfusion to a large portion of the brain and the retinas, and it is possible that opening of the mouth by the use of a spring loaded gag may cause a degree of occlusion in these arteries, resulting in hypoperfusion. Magnetic resonance angiography performed in our study showed a decrease in blood flow through the maxillary arteries when the mouth was opened maximally. In addition, electroretinography was also abnormal in some cats after a mouth gag was placed. These findings were sometimes unilateral. Considering the information now available, it is likely prudent to avoid the use of spring-loaded gags that may result in maximal opening of the mouth.

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Controversies with pain management in cats

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Learning Objectives

1. To review common misconceptions and potential complications associated with the use of of locoregional anesthesia in the feline patient

2. To discuss advantages and disadvantages of different types of analgesic therapy in cats under anesthesia

If anesthesiology is a relatively new specialty in veterinary medicine (the American College of Veterinary Anesthesiologists was not funded until 1975), the study and treatment of pain in animals is likely even younger. Postoperative pain in pets was, sadly, not a real preoccupation not too long ago. Furthermore, many of us might have heard as students that some degree of pain probably helped in keeping pets from exercising too much after surgery. Thankfully those days are gone but due to the short life of this specialty, a lot of the current information regarding analgesic therapy is empirical and has moved from one colleague to another based on personal experience, rather than been generated from scientific investigation. Although such information is important and indeed useful, some details might be missed. In this discussion we will briefly examine some common misconceptions about the use and potential complications of intraoperative analgesics in the cat.

Local anesthesia

Local anesthetic techniques have become popular and widely distributed in veterinary medicine. Local anesthesia provides pain relief with, apparently, little complications. From all possible alternatives from treating pain, local anesthesia is the only technique in which pain is actually abolished; administration of systemic analgesics act, through different mechanisms, by modulating the perception or response to pain.

Desensitization of a nerve with a local anesthetic agent interrupts the transmission through that nerve, and the painful stimulus is therefore abated. Nerve blocks are commonly used during dental procedures; they are relatively simple to perform, provide effective analgesia with minimal side effects, allows patients to wake up comfortably after dental surgery without

sedation, nausea or other side effects commonly seen with systemic analgesics, and they are certainly cost-effective. The dose of local anesthetic should not be overlooked.

Local anesthetic overdose during dental blocks does not occur often, but it is always a possibility. Blocks are performed in proximity to not only nerves, but also blood vessels. In addition, gums are generously perfused, and absorption of local anesthetics into systemic circulation occurs. Furthermore, cats are more sensitive than dogs to the depressant effects of local anesthetic agents, and due to the concentration of some commonly used agents, toxic doses can be easily reached. For example, during full mouth surgical procedures, both mandibular and infraorbital nerves might be blocked. If only 0.5ml is administered per injection, a total of 40 mg of lidocaine may be used; more than 10mg/kg for a cat of <4kg. Considering that it has been demonstrated that toxic effects are seen in cats when 11 (±4.5) mg/kg of lidocaine are administered IV, the margin of safety for this example is quite narrow (1). Two cases of local anesthetic intoxication have recently reported in the veterinary literature: in one cat, 20 mg/kg of lidocaine was used for infiltration. This animal presented with "severe lethargy and respiratory distress; erratic, poor-quality pulses with severe hypotension; and pulmonary edema", only 30 minutes after lidocaine administration (2). In a second case, bupivacaine was used during a dental procedure in a cat. Five minutes after 1.16 mg/kg of bupivacaine (0.7 ml) was administered for a mandibular block, severe cardiovascular depression was observed. The authors suspect that since the injection was performed close to neoplastic mass, absorption to systemic circulation might have been excessive (3). Both cats required cardiovascular support.

Dental blocks

Analgesia for dental surgery of the mandibular teeth is commonly administered by performing an inferior alveolar nerve block. The inferior alveolar nerve is desensitized next to the mandibular foramen, on the medial side of the mandible. Anesthesia of this nerve will provide desensitization of any mandibular tooth, rostral lower lip and the rostral intermandibular region. However, when the surgical procedure only involves rostral mandibular teeth, a mental mandibular nerve block might be attempted. In cats, the middle mental foramen is located equidistant between the third premolar tooth (the first tooth after the canine tooth in cats) and the canine tooth, under the lip frenulum, at mid-height of the mandible. These nerves supply the rostral lower lip and the rostral intermandibular region. Local anesthesia of these nerves will result in a "numb" lower lip, without anesthetizing the rostral mandibular teeth. If dental surgery is to be performed in the rostral mandibular teeth, then an inferior alveolar nerve block should be performed. A rostral inferior alveolar block can be performed. In order to desensitize the rostral inferior alveolar nerve, the needle is inserted for a short distance into the middle mental foramen, not always an easy task in cats. The risk of iatrogenic nerve injury, due to the small size of the structures, should be considered before attempting this block.

Epidural anesthesia

Epidural anesthesia is a commonly used technique, for reasons similar to those mentioned above. A variety of abdominal, urologic or traumatologic procedures can be performed aided by epidural anesthesia or analgesia. When local anesthetic agents are used at high enough concentrations, epidural anesthesia is achieved. The administration of either low concentrations of a local anesthetic agent, or an opioid, result in epidural analgesia; pain sensation and responses are blunted. The technique for an epidural injection is relatively simple, however, when performing a lumbosacral epidural, the potential for puncturing the meninges is higher in cats than in dogs. Due to the cat's anatomy, the dural sac extends more caudal than compared with the dog, and it can be accessed at the lumbosacral level. Accidental injection into the cerebrospinal fluid may result in overdosing; doses used for spinal anesthesia are several times smaller than those used for epidural anesthesia. Severe cardiovascular depression may occur after accidental spinal anesthesia overdose, and significant CNS depression may also occur. Care must be taken, when performing an epidural anesthesia in a cat, that no CSF is visible in the hub of the syringe.

An alternative for overcoming this potential complication may be to performe a caudal block, rather than a lumbosacral puncture. Coccygeal epidural anesthesia has been recently described in cats for the treatment of urethral obstruction (4). Although this technique has some limitation, it may be useful for caudal or perineal surgery.

Even when an epidural is performed without complication, some side effects may occur, and these should be anticipated. Morphine has become a popular additive for epidural injection of local anesthetics since it prolongs the duration of analgesia without providing motor blockade. In fact, morphine is often administered as a sole agent by the epidural route in cats, for providing pain relief while allowing ambulation. However, the ability of morphine for causing urinary retention is often overlooked. Urinary retention following epidural administration of morphine in dogs has been reported (5). A recent case involving a cat can also be found (6).

Mixtures of local anesthetics

Local anesthetics are often classified by their onset and duration of action. For example, lidocaine provides quick onset and short duration, while bupivacaine produces a slow onset and long duration of action. A mixture of both agents is commonly used in order to obtain "the best of both worlds", that is, quick onset and longer duration. But one may get "the worst of both worlds" with such practice. Mixtures of lidocaine and bupivacaine have not resulted in these

desirable effects. When a mixture of equal parts of lidocaine and bupivacaine was administered epidurally to cats, onset of action was the same for all 3 groups. Duration of effect however, was longer for the mixture than for lidocaine alone, but significantly shorter than for bupivacaine alone (7). In other words, neither onset nor duration was improved.

Systemic analgesics. Opioids

Similarly to mixing short and long acting local anesthetics, many veterinarians chose to mix short and long acting narcotics. The combination of butorphanol (quick onset and short acting) with buprenorphine (slow onset and long acting) became so popular that the idea generated a scientific study (8). The study showed that a) a mixture of butorphanol and buprenorphine did not have a quicker onset that buprenorphine alone (in fact, it was quicker for buprenorphine alone) and b) that duration of action was not prolonged by the combination of agents when compared with butorphanol alone (but it was longer lasting that compared with buprenorphine, which surprisingly lasted for a shorter time than butorphanol alone). In summary, the combination of drugs did not perform as it was hoped it would.

Systemic analgesics. Lidocaine.

Lidocaine is not only commonly used for local anesthesia, but also infused as a systemic analgesic agent. Other desirable effects, such as anti-inflamation, make lidocaine an appealing adjuvant to general anesthesia. Due to its short duration of action, lidocaine is administered as an infusion to relieve pain and decrease the amount of general anesthetics given. Lidocaine may be infused as a sole adjuvant agent, or in combination with a narcotic and/or ketamine. Balanced anesthesia is therefore performed in order to, not only treat pain, but also for providing a more stable anesthetic from a hemodynamic viewpoint.

Lidocaine was studied in cats (9). Both its ability to decrease inhalational requirements and its cardiovascular effects were examined. At high doses, lidocaine decreased the isoflurane requirements in cats by more than 50%. Despite this improvement in isoflurane requirements, infusions of lidocaine also resulted in a decreased HR, cardiac index and plasma HCO3 concentration. Those effects were not attributed to a decrease in the concentration of isoflurane administered, but to the administration of lidocaine. Cardiovascular depression was such, that the experiment had to be aborted in one individual. The authors concluded, in part, that "Lidocaine administration resulted in decreased oxygen delivery and possibly poor tissue perfusion. In isoflurane-anesthetized cats, lidocaine associated cardiovascular depression can be very severe. Overall, we do not recommend the use of lidocaine for balanced anesthesia in cats."

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Non-Domestic Felidae: Conservation and Medicine

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24th Annual Fred Scott Feline Symposium

July 27-29 2012

Objectives:

- Conservation status of non-domestic Felidae
- Impact of infectious diseases in wild and captive populations
- Efforts and challenges in conservation
- Captive care and husbandry
- Common diseases and management
- Preventive medicine program

From a house to the jungle ...

- "One of the most fascinating aspects of cat biology is that, from the two-pound black footed cat to the five hundred pound tiger, cats of all variations have one common theme. When you have a cat in your house you live with the essence of a tiger." *Felidae Conservation Fund*
- Conservation Medicine: professionals specialized in an area of interest, working together in multidisciplinary approach

www.starling-fitness.com

Carnivores: Common traits

- Developed 4 carnassial teeth:
  - Large fourth upper premolars
  - Large first lower molars
  - Shearing meat
- Elongated canines
- Prominent zygomatic arch for attachment of masseter and temporalis
- Herbivorous species, undeveloped carnassials, reverted to broad and flat molars (crushing veg. matter)

Common traits

- Plantigrade herbivorous sp
- Digitigrade carnivorous sp
- Fused carpal bones
- Ulna and radius prevent rotation
- 4-5 clawed digits - pads
- Undeveloped clavicle
- Anal glands well developed
- Baculum in males
- Offspring born underdeveloped
- Share many infectious and parasitic diseases

Taxonomy

- 97 genera, 247 terrestrial species (36 marine)
- Natural distribution worldwide except in Australia, New Guinea, New Zealand, Antarctica (many Oceanic islands) where introduced
- 2 basic phylogenic divisions: ossified segment in auditory bulla (feliformia)
  - Suborder Caniformia (Canidae, Ursidae, Procyonidae, Mustelidae) --- Pinnipedia
  - Suborder Feliformia (Viverridae, Herpestidae, Hyenidae, Felidae)

Carnivora

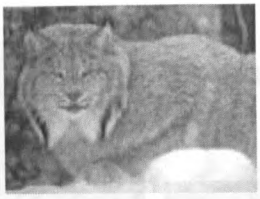
Feliformia (cat-like)

- **Felidae (37 sp. 14 gen.)**
- Prinonodontidae (Asian linsang)
- Nandiniidae (Af. palm civet)
- Viverridae (civets, 35 sp 15 g)
- Herpestidae (mongoose 33sp)
- Eupleridae (malagasy carnivores 8 sp, 7 gen)
- Hyaenidae (4 sp, 4 gen)

Caniformia (dog-like)

- Canidae (37 sp, 7 genera)
- Ursidae (8 sp, 5 genera)
- Ailuridae (Red Panda)
- Mephitidae (skunks, 10sp, 4g)
- Mustelidae (55 sp, 24 genera)
- Procyonidae (19 sp, 6 genera)
- Odobenidae (walrus)
- Otariidae (eared seals, 14 sp 7 genera)
- Phocidae (true seals, 19 sp 9 genera)

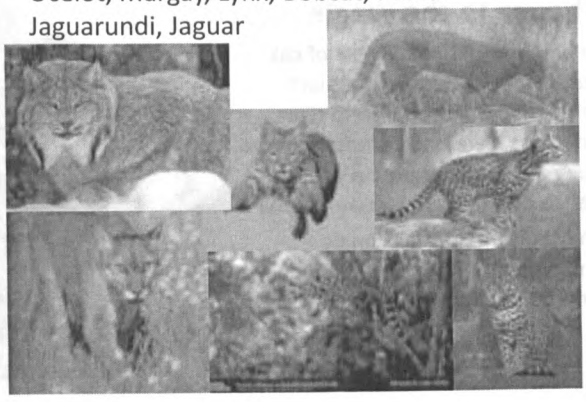
FELIDAE



- 11 genera, 37 species
- I3/3; C1/1; P3/4; M1/1
- Morphology of larynx separates the genera
- Most highly adapted to carnivorous diet
- Same medical care as for domestic cats
- Unable to convert β carotene to vitamin A

Frombearcreek.com

Ocelot, Margay, Lynx, Bobcat, Puma Jaguarundi, Jaguar



FELIDAE

African-Asian Wildcat *Felis silvestris lybica, Felis silvestris ornata*
African Golden Cat *Profelis aurata*
Andean Mountain Cat *Leopardus jacobitus*
Asiatic Golden Cat *Catopuma temminckii*
Bay Cat *Catopuma badia*
Black-footed Cat *Felis nigripes*
Bobcat *Lynx rufus*
Bornean Clouded Leopard *Neofelis diardi*
Canadian Lynx *Lynx canadensis*
Caracal *Caracal caracal*
Cheetah *Acinonyx jubatus*
Chinese Desert Cat *Felis bieti*
Clouded Leopard *Neofelis nebulosa*

Puma *Puma concolor*
Domestic Cat *Felis catus*
Eurasian Lynx *Lynx lynx*
European Wildcat *Felis sylvestris sylvestris*
Fishing Cat *Prionailurus viverrinus*
Flat-headed Cat *Prionailurus planiceps*
Geoffroy's Cat *Leopardus geoffroyi*
Iberian Lynx *Lynx pardinus*
Iriomote Cat *Prionailurus iriomotensis*
Jaguar *Panthera onca*
Jaguarundi *Herpailurus yagouarundi*
Jungle Cat *Felis chaus*
Kodkod *Leopardus guigna*

Leopard Cat *Prionailurus bengalensis*
Leopard *Panthera pardus*
Lion *Panthera leo*
Marbled Cat *Pardofelis marmorata*
Margay *Leopardus wiedii*
Ocelot *Leopardus pardalis*
Oncilla *Leopardus tigrinus*
Pallas's Cat *Felis manul*
Pampas Cat *Leopardus colocolo*
Rusty-spotted Cat *Prionailurus rubiginosus*
Sand Cat *Felis margarita*
Serval *Leptailurus serval*
Snow Leopard *Uncia uncia*
Tiger *Panthera tigris*

Conservation Status of Carnivores
International Union for Conservation of Nature – Red List

FAMILY	TOTAL	EX	EW	CR	EN	VU	NT	LC	DD	% Threatened or Extinct
CARNIVORA										
Alluridae	1	0	0	0	0	1	0	0	0	100.0
Canidae	36	1	0	3	3	0	4	24	1	19.4
Eupleridae	9	1	0	0	1	3	3	1	0	55.6
Felidae	36	0	0	1	6	9	9	11	0	44.4
Herpestidae	34	0	0	0	0	3	1	27	3	8.8
Hyaenidae	4	0	0	0	0	0	2	2	0	0.0
Mephitidae	12	0	0	0	0	1	0	11	0	8.3
Mustelidae	59	1	0	0	7	5	4	36	6	22.0
Nandiniidae	1	0	0	0	0	0	0	1	0	0.0
Odobenidae	1	0	0	0	0	0	0	0	1	0.0
Otariidae	16	1	0	0	4	2	2	7	0	43.8
Phocidae	19	1	0	2	1	1	0	12	2	26.3
Prionodontidae	2	0	0	0	0	0	0	2	0	0.0
Procyonidae	14	0	0	1	0	0	0	10	3	7.1
Ursidae	8	0	0	0	1	5	0	2	0	75.0
Viverridae	33	0	0	1	1	9	2	17	3	33.3

Conservation Status:

International Union for Conservation of Nature – Red List

Extinct	Extinct in the wild	Critically endangered	Endangered	Vulnerable	Near threatened	Least concerned	Data deficient
0	0	1	6	9	9	11	0

FAMILY	TOTAL	% Threatened or Extinct
FELIDAE	**36**	**44.4%**

Convention on International Trade in Endangered Species of Wild Fauna and Flora

- Appendix I lists species that are the most endangered among CITES-listed animals. They are threatened with extinction and CITES prohibits international trade in specimens of these species except when the purpose of the import is not commercial, for instance for scientific research. In these exceptional cases, trade may take place provided it is authorized by the granting of both an import permit and an export permit (or re-export certificate) of the Convention provides for a number of exemptions to this general prohibition.
- Appendix II lists species that are not necessarily now threatened with extinction but that may become so unless trade is closely controlled. It also includes so-called "look-alike species", i.e. species of which the specimens in trade look like those of species listed for conservation reasons. International trade in specimens of Appendix-II species may be authorized by the granting of an export permit or re-export certificate. No import permit is necessary for these species under CITES (although a permit is needed in some countries that have taken stricter measures than CITES requires). Permits or certificates should only be granted if the relevant authorities are satisfied that certain conditions are met, above all that trade will not be detrimental to the survival of the species in the wild. *CITES.ORG*

- Entire group of Felidae is classified in Appendix I or II

Common causes for decline of wild populations of felidae:

- Increased human population, accelerated environmental threats, hunting, encroachment on territory (restricting range and habitats, over exploitation), increased contact with domestic species, loss of prey species, etc.
- Even small events can have devastating consequences
- Health of environment directly affects health of wildlife and humans and is tied to political, economical and cultural well-being of every nation
- Impact of infectious diseases on wild populations: endemic or epidemic events, reservoirs

Factors favoring infectious diseases

- Travel-shrunk international borders
- Encroachment of susceptible hosts into endemic populations
- Increased drug resistance
- Predisposing infection causing immuno-deficiency
- Ecological and epidemiological factors contributing to distribution of infectious disease within population

Diagnostic challenges

- Improved biotechnological techniques and better diagnostic assays → heightened awareness of prevalence of infectious diseases
- Complexity of extrapolation of what is known in domestic animals to related species
- Lack of effective vaccines and therapeutics

Role of infectious diseases in free-ranging carnivores Anim. Conserv. (1999) 2: 241-254

- Literature review: infectious diseases of 34 large (adults >20 kg) terrestrial carnivore species (18 threatened in wild) -> seroprevalence and cases of infection, mortality and population decline
- 52 diseases examined: 44% viral, 31% bacterial and remainder protozoal or fungal
- Many infections endemic in carnivores and/or infected multiple taxonomic families
- Most disease studies consisted of serological surveys for disease antibodies. Widespread antibody detection -> exposure to micro-organisms was common
- Seroprevalence was higher in tropical than temperate areas, and marginally higher for infections known to occur in multiple carnivore groups
- Published descriptions of disease-induced population decline or extinction were rare, most outbreaks presumed to be from direct transmission of rabies or canine distemper virus (CDV)

Morbillivirus infection in a wild Siberian tiger in the Russian Far East. Quigley KS J Wildl Dis 2010 46(4):1252-6.

- First documented case of morbillivirus infection in a wild, free-ranging Siberian tiger (Panthera tigris altaica).
- The tigress entered a small village in the Russian Far East in an ambulatory but stuporous state with no apparent recognition or fear of humans. Her condition progressed rapidly with neurological signs, anorexia, and ultimately death.
- Histologic lesions included vacuolated to malacic white matter in the brain stem, cerebellum, and thalamus, with associated lymphocytic meningoencephalitis. Large, intranuclear, eosinophilic inclusions were within regional astrocytes, and the brain lesions were immunohistochemically positive when stained for canine distemper viral antigen.
- Hematologic and blood chemistry results were consistent with overwhelming systemic infection and starvation.
- The animal also was antibody-positive for canine distemper virus, feline panleukopenia, and feline coronavirus.

Infectious diseases and conservation

- Wild Amur tigers (Panthera tigris altaica, n=44) from the Russian Far East were tested for antibodies to feline leukemia virus, feline corona virus (FCoV), feline immunodeficiency virus, feline parvovirus (FPV), canine distemper virus (CDV), Toxoplasma gondii, and Bartonella henselae. Antibodies to FCoV, CDV, FPV, and T. gondii were detected in 43, 15, 68, and 42% of tigers, respectively. No differences were detected in antibody prevalence estimates between tigers captured as part of a research program and those captured to mitigate human-tiger conflicts.
- Domestic dogs (Canis familiaris) were tested as a potential source for CDV; 16% were vaccinated against CDV and 58% of unvaccinated dogs were antibody positive for CDV. A high percentage of tigers were exposed to potential pathogens that could affect the survival of this species.
- Recommendations: continued monitoring of wild tigers throughout Asia, development of standardized sampling and postmortem examination procedures, and additional research to better understand potential domestic and wild animal sources for these pathogens.

John Goodrich – Siberian tiger project

Canine Distemper

- 1992: CD epidemic among 74 large captive felids (African lion, leopard, jaguar, tiger)
  - 47% became ill (of which 66% with CNS signs), 23% died (only *Panthera*. Pumas showed vague signs only; Members of *Felis* seeemed unaffected)
- 1994: multispecies CD epidemic in Serengeti with 30% of lion population affected (CNS signs, emaciation) – source: unvaccinated dogs transmitting virus to spotted hyenas

Parvovirus

- All members of the family Felidae are susceptible to Feline Panleukopenia virus infection and disease (including lions) – acute enteric disease
- No feline host found to be susceptible to Canine Parvovirus type 2
- Large cats are susceptible to CPV 2a/2b infection and disease (cheetahs, Siberian tigers)
- Note: feline ataxia syndrome documented in one lion cub

Virulent Calicivirus

- Rare reports of FCV infections in felidae (tiger, lion), limited to the respiratory form or seroconversion from natural infection – no severe morbidity or mortality observed
- One report of severe disease caused by virulent calicivirus 4 tiger cubs littermate with mortality:
  - Tongue ulcerations then sloughing. Progression in all cubs to include sloughing of the carpal, tarsal, metacarpal, and metatarsal foot pad epithelium.
  - Oral ulcerations also noted in adult African lions and Amur tigers but not in two adult snow leopards housed in the same building.
- Isolating FCV from tissues: the synovial membrane, foot pad, spleen, tongue, oral cavity, and liver: indicative of systemic calicivirus infection.

J Zoo Wildl Med. 2007 Jun;38(2):292-9.

Feline Leukemia Virus

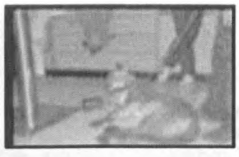
- FeLV does not appear to be endemic in Felidae (free-ranging and captive populations)
- Some species of Felidae do seem to be susceptible to infection (with or without clinical signs) but virus is not maintained in these populations
- Reported to have caused population declines in Fl Florida panthers and Iberian lynx
- Avoid contact with domestic cats

Feline Immunodeficiency Virus

- Seroprevalence varies greatly between species (highest in free-ranging and captive populations on lions) – in captive lions, seroprevalence < 2%
- Virus isolated from lion, Pallas cats, puma- divergent from one another and from the one found in domestic cats (high seroprevalence often without disease)
- Transmission is frequent in captive lion populations and seroconversion has been documented in other species
- Clinical disease: lymphoma, granulocytic leukemia, periodic behavior changes and progressive neurological deterioration, peripheral retinopathy, wasting

Captive Management

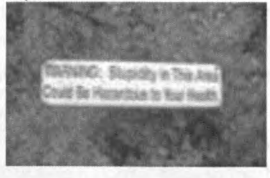
Legal considerations



- Pets:
  - Exotic Pet Law: January 1st 2005
  - Animal acquired before that date may be "grandfathered" if owner obtains permit
- Rabies vector species
- Zoonoses
- Impact on livestock – reintroduction programs

Security

- Protection of people from animals
- Protection of animals from people
- Prevention is crucial !!
- Facility design
  - Construction
  - Barriers
  - Perimeter fences



- Standard operating procedures
- Security team

Safety / Communications

- SOP – trained employees, communications
- Drills – codes: animal escape, human emergency, facility emergency
- Priorities:
  - Public / Personnel safety
  - Safety of the animal collection
  - Prevent/minimize damage to facilities and equipment

Husbandry

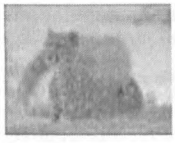
- Buried fences -Escape proof enclosure
- Soft natural ground (sand / dirt / soil)
- Concrete and slippery surfaces lead to:
  - Ulcerated foot pads and worn nails
  - Trauma
  - Osteoarthritis
  - Teeth injuries
  - Neonatal hypothermia
- Electric fencing
- Overhangs

Husbandry

- Safety in height – provide elevated shelf
- Varied activities to avoid abnormal behaviors
  - Environmental enrichment
- Operative conditioning:
  - Shift to facilitate cleaning, observation, minor medical procedures
  - Shift for emergency situation
  - Administration of drugs / vaccines / anesthetic drugs
  - Blood collection

Designing an exhibit

- Identify direct (primary) effects of space restriction: restriction of freedom of movement or possibility of movement in the physiological sense (necessary muscular activity)



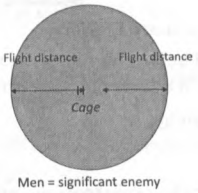
Designing an exhibit

Identify indirect (secondary) effects:

- Lack of diversion and occupation to liberate pent up energy
- No differentiation of space, no free choice of food and of micro-climate
- Impossibility to avoid members of own species or to display anti-social behavior
- Subject to infection and re-infection

Necessary space – Flight distance

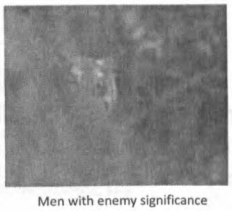
- The animal will not rest until it has put the flight distance between itself and its enemy (man)
- If cage is circular, smallest size:
  - Diameter = minimally twice the flight distance
  - H = home



Men = significant enemy

Necessary space – Flight distance

- The animal will not rest until it has put the flight distance between itself and its enemy (man)
- If cage is circular, smallest size:
  - Diameter = minimally twice the flight distance
  - H = home
- Very difficult to achieve → taming animals to achieve 0 flight distance (or animal is unable to feed)



Men with enemy significance

wildlywise.com

Necessary space

- Tamed animals
  - Will fear less humans
  - Will approach the bars for feeding
  - Will not run away from public
- Opportunities for climbing, cleaning nails, marking territories etc.
- Pool – access to water

Victoria's Open Range Zoo
Lions On The Edge

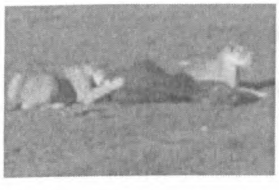
- The goal of the design was to introduce visitors to a *believable, exciting experience* of walking through the bush with lions as part of the *living* landscape.
- The purpose was to help visitors to intuitively appreciate the drama and dilemmas that pastoralists and land managers deal with ... and the successes and failures that they experience ... in trying to maintain a system where lions are an integral part of both the *tourist economy, as well as the natural ecosystem.*

Victoria's
Open Range Zoo

Feeding

- Metabolic and psychological needs
- Social factors
- Feeding patterns (fast days)
- Quality and quantity of food
- Food presentation

Politically correct diet



www.smriti.com/photos
www.nationalgeographic.com

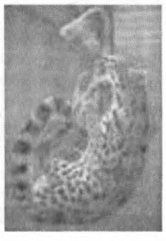
Nutrition:

- Diets in the wild
- Time spent hunting, foraging, eating
- Diets in captivity
  - Safety
  - Appeal
  - Quality

www.eyetide.com

Nutrition

- Diet: mice, quails, commercial meat based diets, cat food, meat
- Chicken necks are unacceptable as sole diet
- Fasting day (value?)
- Monitor for taurine deficiency, obesity



Nutritional problems in captivity

- Palatability of prepared diets
- Malnutrition / under-nutrition
- Obesity
- Metabolic bone disease
- Periodontal disease
- Taurine deficiency
- Thiamin and vitamin A and E deficiencies
- Challenges of environmental enrichment

Hand-rearing

- Passive transfer of immunity
- Find appropriate formula
- Diarrhea / constipation
- Delayed GI emptying
- Hair loss (allergy)
- Cataracts (young wolves, deficiency in arginine)

Preventive medicine

- Proper sanitation
- Monitoring for diseases – quarantine facilities
- Adequate housing and enrichment programs
- Appropriate diet and weight monitoring
- Annual PE, imaging and dentistry
- Routine fecal analysis and deworming

Preventive medicine

- Dentistry
- Routine examination and prophylaxic cleaning
- Evaluate / repair fractured teeth
- Canine extraction in large cats

Preventive medicine

- Vaccination: INACTIVATED vaccine
  - Limited studies
  - Feline panleukopenia, rhinotracheitis, calicivirus (killed virus)
  - Canine distemper (recombinant vaccine canary-pox vectored- Merial)
    - DO NOT use multivalent vaccines
    - DO NOT use attenuated vaccines
  - Rabies (oral, injectable) – adjuvent?
  - Parvovirus inactivated - monovalent
- Check titers if possible

Diseases: viruses

- Canine distemper
- Feline panleukopenia
- Canine parvovirus 2a/2b
- Rabies
- Rhinotracheitis / Calicivirus
- FIV / FeLV
- Viral papillomas: SSC snow leopards

Diseases: Bacterial

- *Salmonella typhimurium*
  - Role of diet?
  - Enteritis and septicemia
- *Clostridium piliforme* (Tyzzer's disease; aka *Bacillus piliformis)*, snow leopard kittens
  - Acute death; diarrhea; enteritis; focal hepatic necrosis
- *Clostridium perfringens* – enteritis

Diseases: Parasites

- *Toxoplasma gondii* – clinically significant with neonatal mortality: Pallas cats, sand cats
- Neospora
- Coccidiosis (Isospora), Giardia, Cryptosporidium
- Roundworms (ascarids)
- Dirofilariosis
- Sarcoptic mange

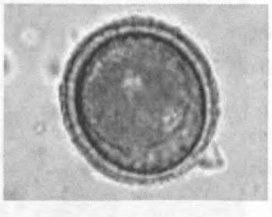
Diseases: Fungal

- *Blastomyces dermatidis*
  - Reported in polar bears, lions, tiger, and cheetah in Tennessee
  - Disease more prevalent in mid-Atlantic, south central U.S. and Ohio-Mississippi River Valley
  - Treatment: Itraconazole

Zoonoses

- Rabies
- Larva migrans
- *Baylisascaris procyon*
- Hydatid cysts
- Cryptococcus
- Giardia
- Sarcoptes

Baylisascaris procyon



Credit: Cornell University

Restraint and Anesthesia

Safety

- Protocols for escape
- Assign one person to oversee entire procedure
- Review procedure before start and assign tasks
- Assign one / two (vet, curator) leaders of procedure
- Keep doors closed during procedure
- Keep dangerous animals enclosed
- Limit number of staff near animal during procedure
- Debrief after procedure, discuss good and bad events
- Vaccination of staff and animals against rabies

Fasting

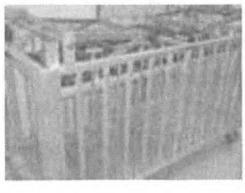
- 12-24 hours for most species
- Less than 4 hours if metabolic rate is high
- Keep water but remove a few hours before induction

Physical restraint or general anesthesia?

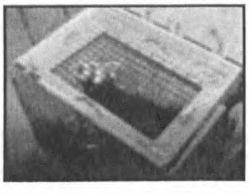
- Is the animal tractable?
- Is the animal trained?
- Do you have access to an animal trained in a squeeze cage?
- Is the animal small enough to capture (net/hand)?
- How large is the enclosure or the cage?

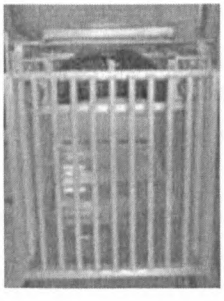
Physical restraint:

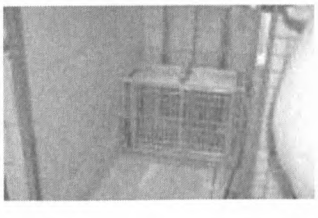
- Physical force /Manual restraint
- Confinement techniques such as chutes and squeeze cages
- Nets
- Snares / tongs



Squeeze cages







Metabolic Scaling

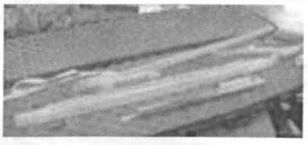
- Estimation of physiological parameters
- Calculation of drug dosages, and treatment frequency

Minimum energy cost:

- MEC= $K(BW_{kg}^{0.75})$
  - K=10 (reptiles)
  - K=70 (placental mammals)
  - K=125 (passerine birds)

Be prepared for the unexpected

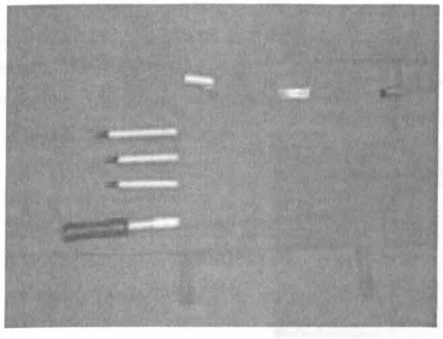
- Close monitoring of the animal
- Equipment and drugs ready to use
  - Antagonist
  - Emergency drug dosages calculated (drawn)
  - Water / ice
  - Oxygen
  - Endotracheal tubes
  - Emergency drugs
  - Fluids
  - Bandage material
  - Surgical pack



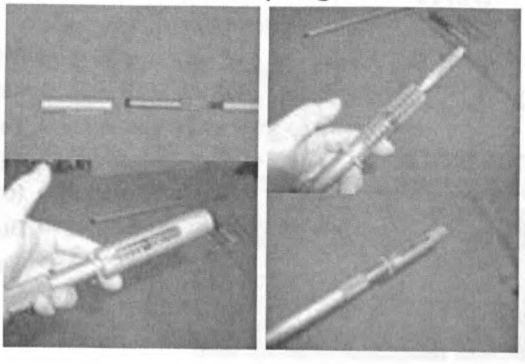
Delivery Systems

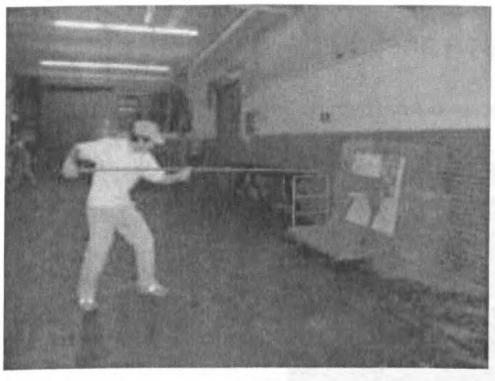
- Oral adminstration
  - Transmucosal absorption
- Hand injection
  - Stationed animal
  - Squeeze cage
  - Net
- Pole syringe
- Darts and projectors

Pole syringe



Pole syringe



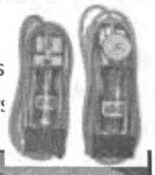


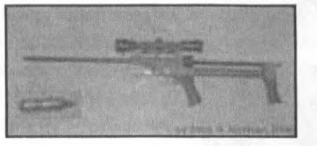
Remote Delivery Systems: Effective Darting Range

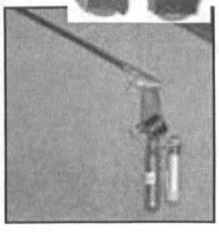
- Blowpipe (1-10 m)
- Pistol
  - Air/gas propelled 1-15 m or 1-30 m
  - Explosive charge propelled 10-30 m
- Rifle
  - Air/gas propelled 2-40 m
  - Explosive charge 10-60 m

Remote drug delivery systems

- Powdered charged projectors
- Carbon dioxide powered projectors
- Compressed air powered projectors

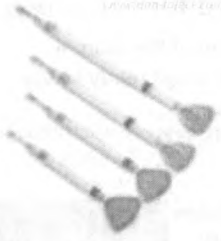






Darts: discharge mechanisms

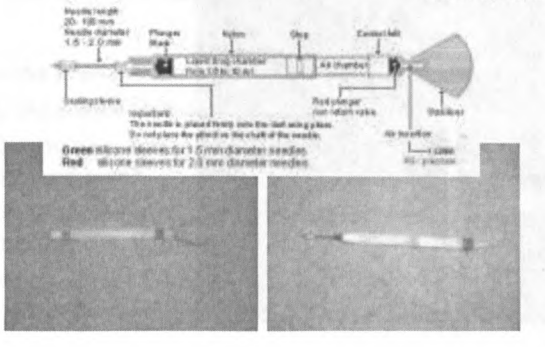
- Explosive
- Air or gas activated
- Spring activated
- Soda acid activated



Cap-Chur Syringes w/Side Port Dropout Needles

Darts

www.dan-inject.com

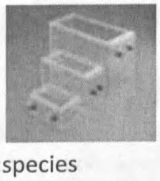


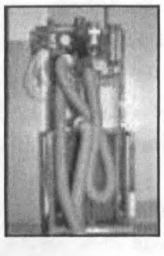
Induction of anesthesia

- Medetomidine – ketamine
- Ketamine – midazolam
- Ketamine - xylazine
- BE VERY CAREFUL IF USING TELAZOL (contraindicated in tigers)
- Butorphanol?
- Butorphanol – medetomidine – midazolam?

Inhalation anesthetics

- Isoflurane
- Sevoflurane
- Desflurane
- Can be used in all species
- Rapid induction and recovery
- Good muscle relaxation





www.paragonmed.com

Inhalation anesthesia

- Used for induction and / or maintenance of anesthesia
- Intubation is recommended
- Provides precise control the depth of anesthesia
- Most drugs will cause cardio-respiratory depression
- Specialized equipment is necessary

Once the animal is unconscious

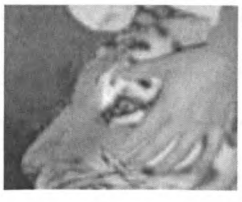
- Approach with caution (usually one veterinarian and a senior animal staff)
- Assess depth of anesthesia
- Secure airway
- Obtain baseline respiratory and heart rates and temperature
- Adjust animal in safe position (may have to be earlier if airway is compromised)

Care of the animal

- Positioning – consider human safety (2 exits)
- Nares should not be covered
- Supplemental oxygen
- Place and secure 1 or 2 intravenous catheters
- Install monitoring equipment
- Administer fluids and drugs
- Procedure

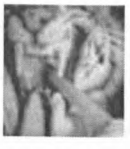
Care of the animal

- Lubricate and protect the eyes against light, wind, trauma
- Monitor, monitor, monitor!!
  - Heart rate (stethoscope / Doppler
  - ECG / oxygen saturation
  - Blood pressure
  - Respiratory rate / blood gas
  - Temperature
  - Depth of anesthesia



Complications of Anesthesia

- Failure of drug delivery
- Improper dosage
- Trauma during induction and recovery
- Unexpected movement or awareness
- Cardiovascular collapse
- Respiratory compromise and arrest
- Regurgitation and aspiration
- Seizures / excitement
- Vomiting



Emergence and Recovery

- Active monitoring
- Reversal – How much? When?
- Intervention
- Must keep recovery area
  - Dark
  - Quiet
  - Ventilated
  - Small
  - Easy to transport
  - Flexible size

References

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- Parvovirus Infections in Wild Carnivores. Steinel, A., *et al.* Journal of Wildlife Diseases. 37 (3): 594-607, 2001.
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  - Updated Vaccination Recommendations for Carnivores
  - Rabies in Wild Carnivores
  - Ageing in Large Cats
- Zoo Animal and Wildlife Immobilization and Anesthesia. West, Heard, Caulkett. 2007

24th ANNUAL FRED SCOTT FELINE SYMPOSIUM

Cornell University

July 2012

A CORNUCOPIA OF CRITTERS: HAVING A (MICROSCOPE) FIELD DAY WITH INFECTIOUS AGENTS

Tracy Stokol BVSc PhD DACVP (Clinical Pathology)
Erica Behling-Kelly DVM PhD DACVP (Clinical Pathology)
Erika Gruber DVM
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The goal of this presentation is to provide:

- A suggested approach for evaluating hematologic and cytologic specimens for the presence of infectious agents
- Tips on recognizing common artifacts and endogenous structures that can mimic infectious agents
- Tips on characteristic features of various infectious agents that can be seen in cats
- Practice identification of infectious agents in digital and real microscopic slides prepared from blood and tissue samples from cats, using a case-based format

Learning objectives

1. After aspirating a cutaneous tissue lesion in a cat, optimally prepare and systematically examine a slide from the aspirate for the presence of infectious agents.
2. While examining the slide, recognize features that may indicate the presence an infectious agent.
3. To select an additional diagnostic test that would be useful for confirming the presence of a suspected infectious agent.

Digital case information and questions

The following 6 slides are presented as digital images that are annotated with questions on cell and structure identification. The original glass slide from each case is also available for viewing on a double-headed microscope in the laboratory. Information on each of the cases is given below, with accompanying questions. Note that these questions are not provided in the annotations that accompany the digital slides. Copies of digital images from cases #2-6 are provided in the DVD.

Case 1: Pleural fluid from a 12 week old female kitten

This smear was presented as a mystery slide case at the Annual Meeting of the American Society of Veterinary Clinical Pathology (ASVCP) in 2007 by Dr. Eric Morrisette from the University of Florida. The digital image can only be viewed in the laboratory and is not available on the DVD.

The kitten presented with respiratory distress of unknown duration. The kitten and its littermates, all of whom lived in a barn, had suffered from a bout of upper respiratory infection 6 weeks prior to presentation. One of the littermates had died, with a necropsy revealing severe upper and lower respiratory tract infection. The kittens had been treated with oral lincomycin and amoxicillin and an erythromycin ophthalmic ointment. Vaccinations were current and FeLV and FIV testing were negative. On examination, the kitten was febrile (102.9°F), severely dehydrated, dyspneic and had increased bronchovesicular sounds. The heart was normal on auscultation. Thoracic radiographs revealed a pleural effusion. On thoracentesis, 60 ml of fluid was obtained, which was submitted for cytologic examination. Cytologic results from the fluid are shown in the table below. The provided image is from a direct (unconcentrated smear) of the fluid.

Test	Result
Color	Red-orange
Clarity	Opaque
Turbidity	Flocculent
Total protein-ref (g/L)	5.8
Total nucleated cell count ($x10^3$/uL)	73.0
Total red blood cell count ($x10^3$/uL)	260.0

1. What is the dominant cell type in the fluid?
2. Is the high RBC count due to blood contamination or hemorrhage?
3. Classify the effusion – exudative, transudative, chylous, hemorrhagic, neoplastic.
4. Is a cause for the effusion evident?

Case 2: Imprints of a colonic biopsy from a 7 month old Persian cat

This slide is provided courtesy of Dr. Christopher Mesher from Phoenix Veterinary Laboratories in Seattle. The digital image is provided with the kind permission of Dr. Mesher.

The cat is one of several in a multi-cat household and was purchased by the owner from a local cattery as a 6 month old kitten. Ever since the owner had gotten the cat, it had persistently soft stool, which was quite smelly. The cat was also observed to defecate frequently and the owner had noticed blood-streaked and mucoid feces in the litterbox. The cat was otherwise eating well and had not lost weight, but the diarrhea was

unresponsive to symptomatic treatment and several drugs, including metronidazole. On physical examination, the cat was bright and alert and no abnormalities were noted on abdominal palpation. An ultrasonographic examination revealed thickened colonic walls and a mild mesenteric lymphadenopathy. A biopsy of the colon was obtained via rectal endoscopy and imprints of the biopsy were submitted for cytologic examination.

1. Is there any evidence of inflammation?
2. What is the infectious agent and it is responsible for the cat's clinical signs?

Case 3: Venous blood smear from a 1.5 year old cat

This smear was presented as a mystery slide case at the Annual Meeting of the American Society of Veterinary Clinical Pathology (ASVCP) in 2005 by Dr. Robin Allison from Oklahoma State University. The digital image is provided with the kind permission of Dr. Allison.

The cat presented to the veterinarian with an acute onset of inability to rise and red urine. The cat had appeared well and had a good appetite the day before presentation. On physical examination, the cat was markedly depressed, icteric with a temperature of 100.6°F, tachycardic (160 beats per minute) and tachypneic (64 shallow breaths per minute). The veterinarian analyzed blood with an IDEXX QBC (results provided during wrap-up). The blood was then sent through regular mail to Oklahoma State University for a parasite check, where it was received 4 days after collection.

1. When examining the digital image (or glass slide), determine if there are any cytopenias present (anemia, leukopenia, thrombocytopenia).
2. If the cat is anemic, does the anemia appear regenerative?
3. Identify the cells/structures/organisms annotated on the slide.
4. What is your diagnosis?

Case 4: Peritoneal fluid from a 13 year old Maine Coon cat

The cat presented with a two month history of weight loss, partial anorexia and lethargy. The owners had noticed an enlarging abdomen in the week prior to presentation. There were two other cats in the household, both of which appeared healthy and one of which did have access to the outdoors. The index case and the other cat were kept indoors. The other two cats were apparently healthy and one of them did access the outdoors. The cat had tested negative for FeLV and FIV and had been treated with antibiotics and dexamethasone with transient improvement. On physical examination, the cat was thin, dehydrated, and recumbent but afebrile. A fluid wave was balloted in the abdomen. Ultrasonographic examination demonstrated an abdominal effusion and irregular large kidneys, but the spleen and liver appeared normal. Abdominocentesis was performed. Cytologic results from the fluid are shown in

the table below. The provided image is from a cytospin (concentrated smear) of fluid diluted 1:1 with saline.

Test	Result
Color	Light yellow
Clarity	Slightly hazy
Turbidity	Viscid
Total protein-ref (g/L)	5.9
Total nucleated cell count ($x10^3$/uL)	2.6
Total red blood cell count ($x10^3$/uL)	5.9

1. After examining the smear, how would you categorize the effusion - exudative, transudative, chylous, hemorrhagic, neoplastic?
2. Is a cause for the effusion evident on the slide?
3. Are any other tests are warranted in this case?

Case 5: Lymph node aspirate from a 4 year old neutered male Domestic Shorthair cat

The cat was referred to the oncology service at Cornell University with a 3 week history of enlarged peripheral lymph nodes, poor appetite and a single transient episode of fever (103.4°F). The cat also had a more recent onset of vomiting and diarrhea. The cat had been treated with amoxicillin and clavulanic acid, followed by enrofloxacin with no response. FeLV and FIV testing were negative. On physical examination the cat was thin and 5% dehydrated but not febrile. The cat had multiple peripheral lymphadenopathy, which was most severe in both mandibular lymph nodes. No abnormalities were detected on abdominal palpation. A hemogram revealed a mild leukocytosis due to a neutrophilia with a mild left shift. There was a concurrent eosinopenia and questionable thrombocytopenia. Mild rouleaux formation was evident in erythrocytes. The cat had a mild decrease in albumin and a moderate increase in globulins and glucose on a biochemistry panel. A urinalysis was performed on urine collected by cystocentesis and showed a urine specific gravity (USG) of 1.015, with marked glucosuria and mild hematuria. The provided image is from an aspirate of the left prescapular lymph node.

1. Is there any evidence of inflammation in the aspirate and, if so, what types of inflammatory cells are present?
2. Is there any evidence of neoplasia?
3. Is there a cause evident in the aspirate which would explain the cat's clinical signs and laboratory abnormalities?

Case 6: Pleural fluid from an unvaccinated intact male barn cat of unknown age

The cat presented with a 2 week history of lethargy and a 3 day history of depression. The cat was normally difficult to handle, but due to his lethargy, he was able to be caught by his owner and was brought into Cornell University for assessment.

On examination, the cat was depressed, underweight, and 6% dehydrated. The cat had marked abdominal respiratory effort and reduced lung sounds on the left with no lung sounds on the right upon auscultation. A pleural effusion was noted on thoracic radiographs. Abdominal ultrasonography showed mild to moderate bowel thickening and mildly enlarged kidneys. A hemogram revealed a moderate leukocytosis due to a neutrophilia with a marked left shift and a monocytosis. There was a concurrent lymphopenia. Neutrophils displayed marked toxic change. A biochemical panel demonstrated decreased concentrations of potassium, calcium, albumin, iron and total iron binding capacity (TIBC), increased concentrations of bilirubin (both direct and indirect) and increased activity of AST. A urinalysis revealed concentrated urine (USG of 1.035) with a mild proteinuria. Numerous sperm were observed in the urine sediment. Fluid was aspirated from the cat's thorax and submitted for cytologic evaluation. Cytologic results from the fluid are shown in the table below. The provided image is from a direct (unconcentrated smear) of the fluid.

Test	Result
Color	Red-brown
Clarity	Opaque
Turbidity	Flocculent
Total protein-ref (g/L)	4.6
Total nucleated cell count ($x10^3$/uL)	ND
Total red blood cell count ($x10^3$/uL)	ND

4. Can you think of a reason why the cell counts were cancelled?
5. What is your estimate for a total nucleated cell count?
6. Is a cause for the effusion evident?

Demonstration cases

The following 6 example or demonstration slides are presented as digital images that are annotated with information on cell and structure identification. We have also provided a sheet with pertinent case information (on the front) and a color image of the infectious agent (on the back). The original glass slide from each case is also available for viewing on a double-headed microscope in the laboratory. We have also provided the digital images from each case, with the exception of Demo/Example 6, on the DVD (the organism in Demo 6 does not scan well).

1. Demonstration/example 1: Smeared imprint of a duodenal biopsy from a cat.
2. Demonstration/example 2: Aspirate from a cutaneous mass in a cat.
3. Demonstration/example 3: Swab of a draining cutaneous lesion in a cat.
4. Demonstration/example 4: Tracheal wash from a cat.
5. Demonstration/example 5: Bone marrow aspirate from a cat.
6. Demonstration/example 6: Blood smear from an anemic cat.

References

1. Canine and feline cytology: A color atlas and interpretation guide, 2nd Ed. Raskin RE and Meyer DJ, eds. Saunders Elsevier, 2010.
2. Diagnostic cytology and hematology of the dog and cat, 3rd Ed. Cowell RL, Tyler RD, Meinkoth JH, DeNicola D, eds. Mosby Elsevier, 2008.
3. O'Neill EJ et al. Pathology in practice. Neutrophilic and histiocytic inflammation with intracellular bacteria (consistent with R equi). JAVMA 2011; 238:1561.
4. Payne PA and Artzer M. The biology and control of Giardia spp and Tritrichomonas foetus . Vet Clin North Am Small Anim Pract 2009; 39:993.
5. Tasker S. Haemotrophic mycoplasmas: What's their real significance in cats? J Feline Med Surg 2010; 12: 369.
6. Lester SJ et al. Cryptococcus: Update and emergence of Cryptococcus gatti. Vet Clin Pathol 2011; 40:14.
7. Elmore SA et al. Toxoplasma gondii: Epidemiology, feline clinical aspects and prevention. Trends Parasitol. 2010; 26:190.
8. Holman PJ, Snowdon KF. Canine hepatozoonosis and babesiosis and feline cytauxzoonosis. Vet Clin North Am Small Anim Pract 2009; 39: 1035.

A cornucopia of critters: Having a (microscope) field day with infectious agents

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Laboratory outline

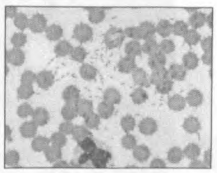
- Introductory information
- Having fun with the virtual microscope: Digital images of 6 cases
- Having fine with a real microscope: Case examples and slides of the digital cases
- Wrap-up/discussion of the 6 cases

General pointers

- Cats are lucky (or smart?): Relatively few infectious agents
- Some agents we cannot diagnose (shucks)
- We ♥ critters!
- We have to tell fact from fiction
  - Good tools
  - Good technique: Collection and examination
  - Extra special stains

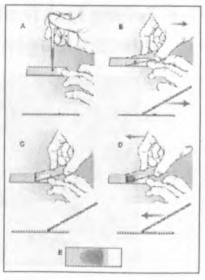
Good tools

- Good quality microscope: Bring on the oil!!
- Good quality slides: Clean clothing fits the bill
- Good quality stain: We ♥ Diff-quik
  - Keep jars clean
  - Its limitations:
    - Black and white
    - Inadequate staining
    - Bacterial overgrowth
  - Its virtues: Viral inclusions! Fungi?



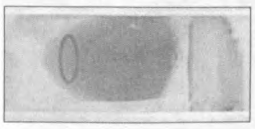
Good hematologic technique

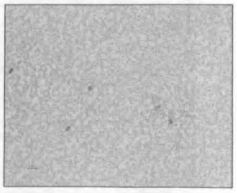
- Fresh is best!!!
- Make blood smear: Wedge
  - Small drop
  - Smooth and steady
  - Even contact
  - Practice makes perfect!!
- Check out our webpage: ahdc.vet.cornell.edu/Sects/ClinPath/sample/test/hema.cfm



Blood: Consistency is key

- Develop a system for slide examination
- Thorough and consistent
- Low power: 10x
  - Find the monolayer



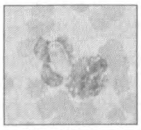


Blood: Consistency is key

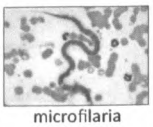
- Develop a system for slide examination
- Thorough and consistent
- Low power: 10x
  - Find the monolayer
- High power: 40x (need a coverslip), oil immersion
  - Finer detail and evidence of infection
  - WBC, RBC, PLT

Blood: Identifying critters

- When to expect?
  - Signalment, history, clinical signs
- When to look?
  - All the time – Expect the unexpected/serendipity
  - The lucky cat
  - Index of suspicion
    - Anemia



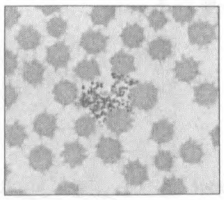
Hepatozoan

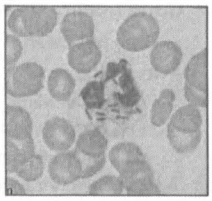


microfilaria

Blood: Identifying critters

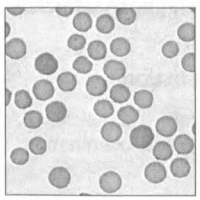
- Telling fact from fiction: Which one is the infectious agent? #1

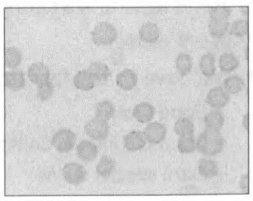




Blood: Identifying critters

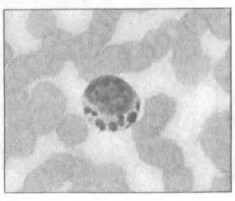
- Telling fact from fiction: Which one is the infectious agent? #2

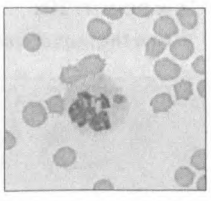




Blood: Identifying critters

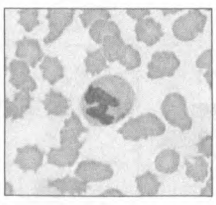
- Telling fact from fact: Which one is the infectious agent? #1

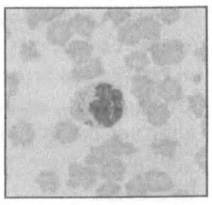




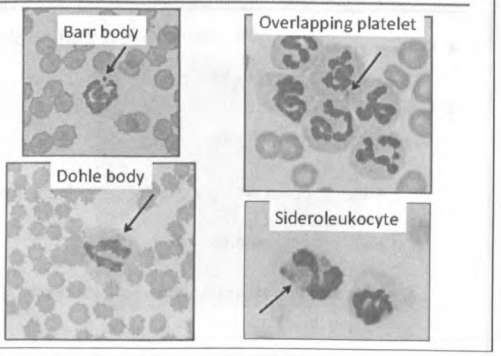
Blood: Identifying critters

- Telling fact from fact: Which one is the infectious agent? #2



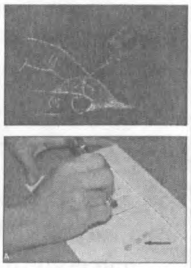


Blood: Things mistaken for bugs



Good cytologic technique

- Collection: Representative
  - Aspiration: 21-22 g needle, 6 ml syringe
  - Non-aspiration: 26 g needle
  - Imprints: Blot tissue first!
- Smear preparation
  - GENTLE squash or wedge
  - Rapidly airdry
  - Check out our website: ahdc/vet.cornell.edu/Sects/ClinPath/test



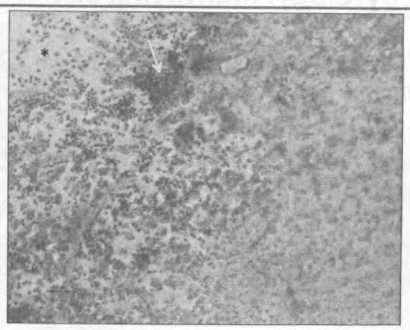
Source: Raskin and Meyer, Atlas of canine and feline cytology, 2001. Fig 1-1

Cytology: Consistency is key

- Develop a system for slide examination
- Thorough and consistent
- Low power: 10x
  - Identify good areas too look at: Well spread and well stained

The best area

OK stain



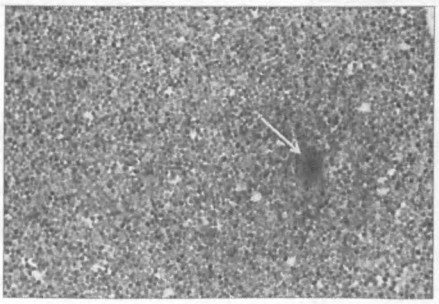
Under-stain

*: Well spread area, yellow arrow: too thick

Cytology: Consistency is key

- Develop a system for slide examination
- Thorough and consistent
- Low power: 10x
  - Identify good areas too look at: Well spread and well stained
  - Identify anything strange and look closer

Case 6 preview



Want a closer look???

Cytology: Consistency is key

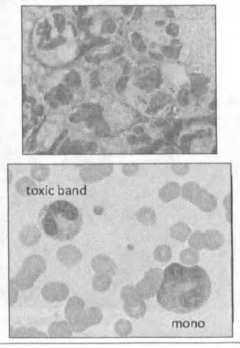
- Develop a system for slide examination
- Thorough and consistent
- Low power: 10x
  - Identify good areas too look at: Well spread and well stained
  - Identify anything strange and look closer
- High power: 40x (need a coverslip), oil immersion (cannot live without)

Cytology: Identifying critters

- When to expect?
  - Signalment, history, clinical signs
- When to look?
  - Inflammation present
    - Neutrophilic
    - Mixed neutrophilic histiocytic (pyogranulomatous)
    - Eosinophilic
    - Histiocytic (granulomatous)
    - Lymphocytic
    - Mixed mononuclear (lymphocytic, histiocytic)

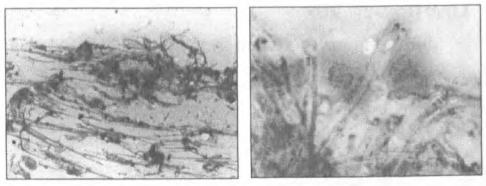
Cytology: Identifying critters

- When to expect?
- When to look?
  - Inflammation present
  - Neutrophils are degenerate
    - Versus toxic?



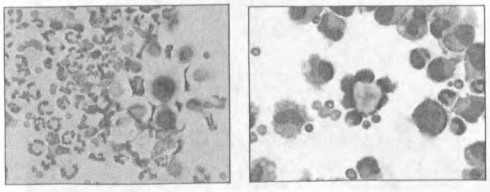
Cytology: Identifying critters

- Telling fact from fiction: Is it really what I think it is????? #1



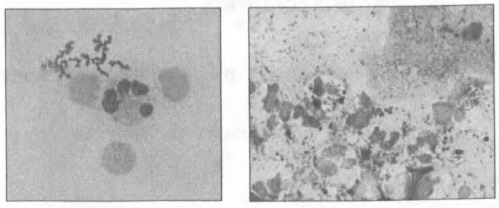
Cytology: Identifying critters

- Telling fact from fiction: #2



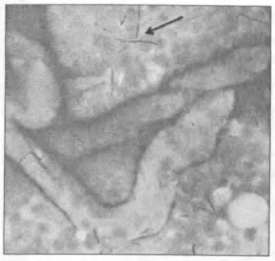
Identifying infectious agents: Cyto

- Telling fact from fiction: #3



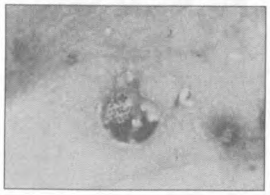
Identifying infectious agents: Cyto

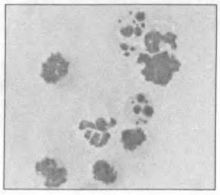
- Telling fact from fiction: #4



Identifying infectious agents: Cyto

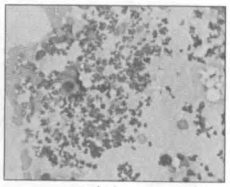
- Telling fact from fact: Which one is the infectious agent?





Identifying bugs: Key points

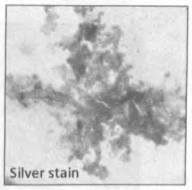
- Is there inflammation/degenerate neutrophils?
- Is it in the plane of focus?
- Is it (relatively) uniform/right color?
- Is it phagocytized?
- Did I put it there?
  - Did it grow with time?
- Does it make sense?
- How do I confirm?



Lubricant

Special (extra) stains

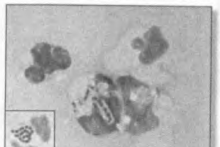
- Gram: Bacteria, fungi ±
- Acid-fast (Ziehl-Neelson or Fite-Faraco): *Mycobacteria*, *Nocardia* ±
- Dye (india ink): Yeast with capsules (*Cryptococcus*)
- Silver stain: Fungi!!
- Other: Machiavello/Jimenez (*chlamydophila*), immuno-cytochemistry (FIPV)



Silver stain

Identifying bacteria

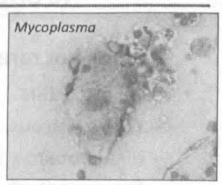
- Shape
  - Cocci: Chains = *Strep*, clusters = *Staph*
  - Rods: Thin, filamentous, bipolar (safety pin), helical, "gulls", fusiform
  - Coccobacilli



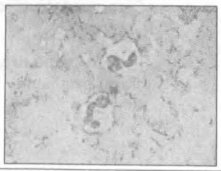
Helicobacter

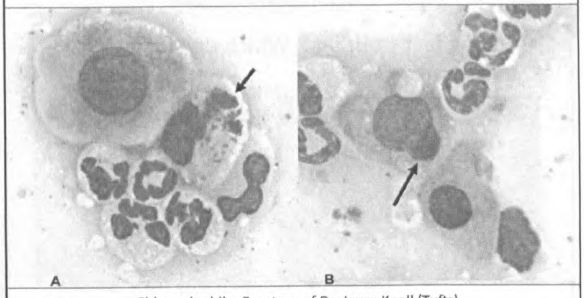
Identifying bacteria

- Shape
  - Cocci: Chains = Strep, clusters = Staph
  - Rods: Thin, filamentous, bipolar (safety pin), helical, "gulls"
  - Coccobacilli
  - Small rings or rods: *Mycoplasma*, *Brucella*
  - Mixed



Mycoplasma

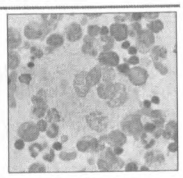




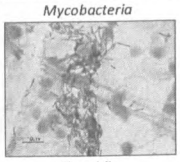
Chlamydophila: Courtesy of Dr. Joyce Knoll (Tufts)

Identifying bacteria

- "Negative" stains: *Mycobacteria*
- Gram staining characteristics
  - Beaded filamentous gram-positive rods: *Nocardia* or *Actinomyces*
  - Large chunky gram positive rods with spores: *Clostridia* or *Bacillus*
  - Weakly gram positive coccobacillii ("chinese letter" shapes): *Rhodococcus*
- Differentiate from other fact or fiction
  - Non-specific phagocytic debris, Döhle bodies, apoptotic nuclei



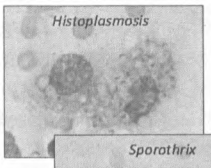
Mycobacteria



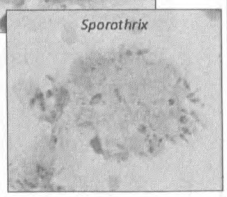
Clostridia

Identifying fungi

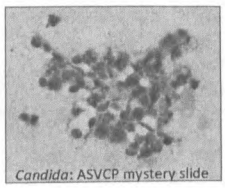
- Form:
  - Yeast: *Cryptococcus*
  - Yeast with "hyphae": *Candida*



Histoplasmosis



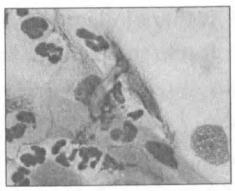
Sporothrix



Candida: ASVCP mystery slide

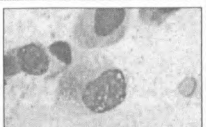
Identifying fungi

- Form:
  - Hyphae: *Aspergillus*

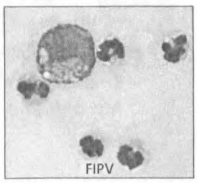


Identifying viruses

- We look but rarely see!
- FIPV: Effusions
  - Yellow, viscous, fibrin clot
  - High protein: > 3.0 g/dL
  - "Transudative" cell count: < 5000/uL
    - Mixture neutrophils and macrophages

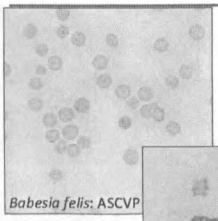


Herpes: Volopich et al 2005



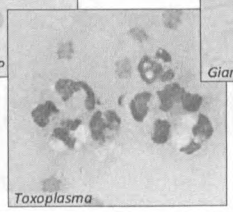
FIPV

Identifying protozoa



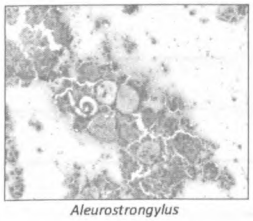
Babesia felis: ASCVP

Giardia

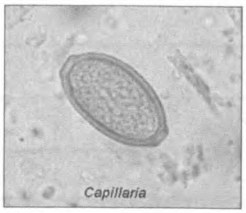


Toxoplasma

Identifying parasites



Aleurostrongylus



Journal Club : A Review of Selected Recent Studies in Feline Cardiology

Bruce G. Kornreich DVM, PhD, DACVIM (Cardiology)

Learning objectives: To review recent publications investigating the diagnosis and treatment of hypertrophic cardiomyopathy in cats.

J Vet Intern Med. 2011 May-Jun;25(3):469-76. doi: 10.1111/j.1939-1676.2011.0705.x. Epub 2011 Mar 21.

Comparison of the effects of ivabradine and atenolol on heart rate and echocardiographic variables of left heart function in healthy cats.

Riesen SC, Schober KE, Cervenec RM, Bonagura JD.

Objectives: To compare the clinical tolerance, heart rate (HR) effects, and effects on cardiac function of the I_f blocker ivabradine and atenolol in lightly sedated healthy cats.

Results: Ivabradine and atenolol were both well tolerated, and both drugs reduced heart rate at the dosages used. HR and rate pressure product (RPP) were not significantly different between treatments. Ivabradine demonstrated more favorable effects on left ventricular systolic and diastolic function and on left atrial performance.

Conclusions: Ivabradine is not inferior to atenolol with respect to tolerance, heart rate reduction, RPP, and left ventricular and left atrial function in lightly sedated healthy cats.

Am J Vet Res. 2012 Feb;73(2):202-12.

Effects of ivabradine on heart rate and left ventricular function in healthy cats and cats with hypertrophic cardiomyopathy.

Riesen SC, Schober KE, Smith DN, Otoni CC, Li X, Bonagura JD.

Objectives: To evaluate the effects of ivabradine on heart rate (HR), LV systolic and diastolic function, and left atrial performance in anesthetized healthy cats and anesthetized cats with subclinical HCM.

Results: Ivabradine reduced HR, RPP, and LV contractile function and increased LV end diastolic pressure, LV end diastolic wall stress, and LV relaxation time constant in cats with HCM. Ivabradine blunted the chronotropic effects of dobutamine, but had no effect on the positive inotropic and lusitropic effects of dobutamine when these compounds were coadministered to cats with HCM. Left atrial performance was not altered by ivabradine in cats with HCM.

Conclusions: Ivabradine significantly affects a number of cardiovascular variables in anesthetized cats with HCM.

J Vet Intern Med. 2011 Sep-Oct;25(5):1044-9. doi: 10.1111/j.1939-1676.2011.0754.x. Epub 2011 Jul 22.

The effect of atenolol on NT-proBNP and troponin in asymptomatic cats with severe left ventricular hypertrophy because of hypertrophic cardiomyopathy: a pilot study.
Jung SW, Kittleson MD.

Objectives: To test the hypothesis that circulating concentrations of NT-proBNP and cTNI are decreased by chronic oral administration of atenolol in cats with subclinical severe HCM and no dynamic LV outflow tract obstruction (LVOTO).

Results: Atenolol did not alter circulating concentrations of either NT-proBNP or cTNI in cats with subclinical severe HCM without LVOTO.

Conclusions: The hypothesis is rejected. Atenolol does not affect the concentrations of these markers of myocardial ischemia and necrosis in this cohort of cats.

Vet Clin Pathol. 2011 Jun;40(2):237-44. doi: 10.1111/j.1939-165X.2011.00305.x. Epub 2011 Mar 24.
Utility of measuring plasma N-terminal pro-brain natriuretic peptide in detecting hypertrophic cardiomyopathy and differentiating grades of severity in cats.
Wess G, Daisenberger P, Mahling M, Hirschberger J, Hartmann K.

Objectives: To evaluate NT-proBNP as a screening test for HCM, to determine a cut-off value for HCM in cats, and to determine whether NT-proBNP concentrations correlate with disease severity on cats with HCM.

Results: NT-proBNP concentrations were significantly higher in cats with mild, moderate, and severe HCM compared with control (non-HCM) cats. NT-pro-BNP concentrations in severely affected cats were higher than those observed in all other groups. No significant difference in NT-proBNP concentrations was found when cats with mild and moderate HCM were compared. An NT-proBNP concentration cut-off value of > pmol/L 49 had a sensitivity of 97.8% and a specificity of 66.7%, a cut-off value of > 100 pmol/L had a sensitivity of 92.4% and a specificity of 93.9%, and a cut-off value of > 150 pmol/L had a sensitivity of 88% and a specificity of 100%.

Conclusions: An NT-proBNP concentration cut-off value of > 100 pmol/L detected even mild HCM in cats. Cats with elevated NT-proBNP should be evaluated by echocardiography.

Cardiac Clinical Decision Making

Bruce Kornreich DVM, PhD, DACVIM (Cardiology)
Cornell University

Learning Objectives:

1) To review cardiovascular parameters that may be altered in feline heart disease.

2) To review therapeutic options for the modification of these parameters as they pertain to the management of heart disease in cats.

3) To apply our understanding of the pathophysiology of feline heart disease and of the modification of cardiovascular parameters in the treatment of feline heart disease to actual clinical cases of heart disease in cats.

In working up clinical cases, I find it helpful to ask a series of questions regarding a number of physiologic parameters for each case. The majority of these questions and their associated parameters are common to all cardiac cases, while a few are more clinically relevant in particular species (i.e. likelihood of thrombosis in cats). Asking these same questions and answering them appropriately for each case provides an organized means of making clinical decisions regarding cardiac cases.

The Questions

1) Does the patient need **preload** modification?

   Preload is roughly defined as the pressure that stretches the ventricle immediately prior to the onset of systole. According to the Frank-Starling Law, an increased preload will result in an increased stroke volume unless the ventricle is stretched beyond the point of optimal actin/myosin overlap, providing a mechanism to synchronize cardiac output with venous return. Decreased preload may result in decreased stroke volume, which may decrease cardiac output unless a compensatory increase in heart rate occurs (CO = SV x HR). Increased preload may cause increased ventricular wall stress with resultant increase in myocardial oxygen demand, which may predispose to arrhythmias or myocardial cell death. Patients that are dehydrated may require an increase in preload via fluid therapy, while patients with volume overload may require a decrease in preload, most commonly achieved by diuretic and/or angiotensin converting enzyme inhibitors (ACEI).

2) Does the patient need **afterload** modification?

   Afterload is roughly defined as the load against which the ventricle must eject its stroke volume. Common causes of increased left ventricular afterload include systemic hypertension (not uncommon in the cat) and fixed aortic stenosis (rare in the cat). An increase in afterload may increase ventricular wall stress, with

subsequent increase in myocardial oxygen demand, which may predispose to arrhythmias or myocardial cell death. Afterload reduction may increase stroke volume and decrease ventricular wall stress and myocardial oxygen consumption. Afterload reduction may be achieved with ACEI, calcium channel blockers, alpha 1 adrenergic receptor blockers, or phosphodiesterase inhibitors.

3) Does the patient need a reduction in **congestion**?

Patients commonly present with clinical signs that are due to congestive failure. Left sided congestive failure results in the development of pulmonary edema, while right sided congestive failure most commonly results in the development of pleural effusion. Pleural effusion may also be seen in cats with apparent left sided congestive failure. Cats that present in respiratory distress (most commonly due to pulmonary edema secondary to left sided congestive failure) are in a tenuous physiologic state and are prone to respiratory and/or cardiac arrest. Reduction in pulmonary congestion is the primary treatment goal in patients with left sided congestive failure. This is most commonly and most effectively achieved by diuretic administration.

4) Does the patient need **inotropic** support?

Inotropic function refers to the ability of the ventricle to generate positive pressure during systole to eject its blood volume. Cats with decreased inotropic function either due to primary dilated cardiomyopathy, chronic volume overload, or long standing hypertrophic cardiomyopathy may benefit from positive inotrope administration. Positive inotropes have historically relied upon increasing intracellular calcium concentration. This increases the likelihood of calcium binding to troponin C, which disinhibits troponin I, allowing cross bridging to occur between actin and myosin (the final event in excitation-contraction coupling). More recently, calcium sensitizers, which increase the affinity of calcium for troponin C, have been developed (i.e. pimobendan). These compounds increase the likelihood of a binding event between calcium and troponin C without incurring the potentially deleterious effects of elevated intracellular calcium. Although not as commonly used in cats as in canine patients, positive inotropes may benefit feline patients with systolic dysfunction.

5) Does the patient need **lusitropic** support?

Lusitropy refers to myocardial relaxation, or the ability of the ventricle to generate negative pressure during diastole to promote ventricular filling. Hypertrophic cardiomyopathy (HCM), which is the most common cardiac disease in cats, is a disease of diastolic, or lusitropic, dysfunction. While calcium channel blockers and beta blockers may improve diastolic function (this is controversial), we most often strive to improve diastolic function by promoting an equalization between myocardial oxygen demand and supply. This can be achieved by controlling heart rate (see below) and by decreasing wall stress (see above).

6) Does the patient need **rhythm** control?

This issue may be roughly divided into two categories. The first, which is a common issue in feline patients, is rate control. Cats with HCM, for example, commonly present with tachycardia (i.e. sinus tachycardia) due to the compensatory mechanisms that strive to maintain cardiac output in the setting of decreased stroke volume (CO = SVx HR). Tachycardia can increase myocardial oxygen demand, which can promote ischemia, arrhythmias, and ultimately myocardial cell death. Control of tachycardia in cats is most commonly achieved by administration of beta blockers, although calcium channel blockers may also be used for this purpose. More recently, antagonists of I_f, such as ivabradine, have been investigated, and are showing promise as another therapeutic alternative for controlling heart rate in cats. Cats in atrial fibrillation most commonly have significant structural heart disease that precludes conversion to normal sinus rhythm. In these cases, ventricular rate control with calcium channel blockers, digoxin, and/or beta blockers is commonly employed. In rare cases, cats may present with bradycardias (i.e. sinus bradycardia, second and third degree AV block), which may decrease cardiac output and cause clinical signs of weakness/collapse. In these cases, although parasympatholytics and/or phosphodiesterase inhibitors may be used to maintain heart rates as high as possible, the definitive therapy is permanent pacemaker implantation. The second category of rhythm disturbances that may require intervention is arrhythmias that may degrade into rhythms that decrease cardiac output (most commonly by increasing heart rate). Ventricular ectopy (i.e. VPCs, VT) may require antiarrhythmic therapy with sodium channel blockers such as lidocaine, although beta blockers are most commonly used chronically. Generally speaking, antiarrhythmics are less commonly used in cats than in dogs.

7) Does the patient need **antithrombotic** medication?

This is an example of an issue that is of greater concern with feline patients. Cat platelets are highly aggregable, and cats with dilated left atria are prone to the formation of intracardiac thrombi, which may embolize systemically. Thromboembolism most commonly occurs at the bifurcation of the abdominal aorta (saddle thrombus), and this is a devastating sequela of HCM that is a poor prognostic indicator. Intracardiac thrombi may be visualized with echocardiography, and spontaneous contrast (smoke like appearance within left atrium/ventricle) may be a harbinger of impending thrombosis. Aspirin and/or clopidogrel therapy may be used to decrease the likelihood of further thrombosis, and the results of a large, ongoing clinical study (FATCAT) carry promise of determining whether aspirin or clopidogrel monotherapy is superior for the prevention of feline thromboembolism. While thrombolytic agents (i.e. streptokinase, urokinase, and tissue plasminogen activator) carry theoretical benefit, the side effects/reperfusion phenomena associated with these agents most commonly precludes their clinical use.

8) Does the patient have **pulmonary hypertension**?

While a rare clinical finding in cats, pulmonary hypertension (PH) may cause clinical signs of dyspnea/tachypnea, lethargy, and weakness or collapse in affected patients. Feline PH has been reported as a sequela of congenital heart defects (i.e. VSD, supravalvular mitral stenosis, PDA), secondary to feline heartworm disease, and also as a presumptive primary syndrome. Treatment of PH in cats is focused toward addressing the primary problem where possible. Phosphodiesterase 5 inhibitors like sildenafil and pimobendan may be administered as a clinical trail for presumptive primary PH in cats, although their efficacy for this application has not, to our knowledge, been verified.