American Association of FELINE PRACTITIONERS®

2014 CONFERENCE

Welcome to the 2014 AAFP Conference!

It gives me great pleasure to welcome you to the 2014 American Association of Feline Practitioner Conference, ***Feline Gastroenterology and Endocrinology.*** With hundreds of feline practitioners in attendance, this conference truly represents the best of feline medicine. I am honored to be able to spend the next few days with you.

Thus far, 2014 has been an exceptional year of accomplishments for the AAFP. We have had many practices renew their Cat Friendly Practice status. The program continues to grow and help us feline practitioners to help our patients and their loved ones even more. The AAFP with AAHA has revised the policy on judicious use of antibiotics. The AAFP and ISFM have produced the guidelines for feline house soiling, as well as a wonderful cat owner brochure. We anticipate that the remainder of the year will be equally as successful. That being said, I would like to thank our members and volunteers for their support and continual efforts that have led the AAFP to be one of the leading associations in the field of feline medicine.

This was a busy summer for AAFP at the annual AVMA meeting. We participated in submitting a revision of the AVMA's mission statement. The AVMA has also revised its policy on the declawing of domestic cats and their policy on Veterinary Dentistry that meets the Cat Friendly Practice (CFP) requirements.

This year's conference is expected to align with the successes of the past year. We are pleased to welcome 14 distinguished speakers to lead the sessions on Feline Gastroenterology and Endocrinology, as well as combined general sessions and three lunch and learn's. The topics will cover a broad range and include interests such as challenges managing endocrine disorders, diarrhea, constipation, liver disorder, pancreatitis, the use of stem cells, and many more. The conference will present you with a unique opportunity to engage with leaders in the field and learn from current data and case studies.

Take this opportunity to advance yourself professionally while enjoying yourself personally. This year's conference has a wide array of activities planned outside of continuing education sessions to keep you engaged and socializing. I strongly encourage you to mingle with your colleagues and use this opportunity to meet new people. Join us for these events which include the Welcome Reception; Exhibitors' Happy Hour Reception; the Fun Run/Walk; and Black, White, and Red Affair Offsite Event. This will include gondola rides at the Indiana State Museum. I look forward to seeing you there!

As AAFP President, I would like to thank the following sponsors on behalf of the AAFP for their support: Boehringer Ingelheim – *Platinum Partnership Sponsor and CFP Sponsor,* Bayer HealthCare – *Diamond Partnership Sponsor and CFP Sponsor,* Merial - *Diamond Partnership Sponsor and CFP Sponsor,* Zoetis – *CFP Sponsor,* Ceva – *CFP Sponsor,* Elanco – *Gold Partnership Sponsor and CFP Sponsor,* Hill's Pet Nutrition – *Silver Partnership Sponsor and CFP Sponsor,* Abbott Animal Health - *Gold Partnership Sponsor,* IDEXX Laboratories – *Silver Partnership Sponsor,* and Nestlé Purina – *Silver Partnership Sponsor.* I'd also like to thank the individual conference sponsors - Dechra Veterinary Products, Merck Animal Health, Nutramax Laboratories, Royal Canin, Wedgewood Pharmacy, and Winn Feline Foundation.



As we look forward, please mark your calendars for next year's conference, which is the World Feline Veterinary Conference, and will take place in San Diego, CA from October 1-4, 2015. The themes of next year's meeting will be *Feline Diagnostic Imaging and Oncology.*

Finally, I would like to welcome you to Indiana. Please enjoy the conference and the city of Indianapolis.

Sincerely,

Marcus G. Brown, DVM
2014 AAFP President

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American Association of Feline Practitioners
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Feline Gastroenterology and Endocrinology

September 18 - 21, 2014 ▪ The JW Marriott ▪ Indianapolis, IN

Pre-conference Day Sessions

THURSDAY, SEPTEMBER 18, 2014

PRE-CONFERENCE SESSIONS
Separate registration required

11:15 – 12:45 pm

Sponsored by BAYER

Food for Thought Luncheon in White River F
Pre-conference registration required

Protecting Cats From the Unexpected: Feline Vector-borne Disease Agents
Dr. Susan E. Little

1:00 – 5:30 pm

ABVP

ABVP/AAFP Seminar & Social in White River E
Included in Pre-conference registration

Sponsored by PURINA

1:00 – 2:00 pm

Update on Feline Infectious Diseases: Agents Associated with Fever
Dr. Michael Lappin

2:00 – 3:00 pm

Update on Feline Infectious Diseases: Upper Respiratory Tract Disease
Dr. Michael Lappin

3:00 – 3:30 pm

Seminar & Social Refreshment Break
Included in Pre-conference registration

Sponsored by PURINA

3:30 – 4:30 pm

Update on Feline Infectious Diseases: Lower Respiratory Tract Disease
Dr. Michael Lappin

4:30 – 5:30 pm

Update on Feline Infectious Causes of Diarrhea in Cats
Dr. Michael Lappin

5:30 – 7:00 pm

WELCOME RECEPTION
All attendees invited

Sponsored by Boehringer Ingelheim

Track Descriptions

Tracks A & B - This conference offers two veterinary concurrent tracks that allow attendees the opportunity to customize their learning experience. Both tracks offer cutting-edge feline research and the latest information in feline medicine. You can choose to follow one track exclusively — or you can jump between tracks, based on your own interests and needs.

Para-professional Track - This track is designed for technicians, practice managers, and other hospital staff who consult with clients.

Feline Gastroenterology and Endocrinology

September 18 - 21, 2014 ▪ The JW Marriott ▪ Indianapolis, IN

Conference Day One

FRIDAY, SEPTEMBER 19, 2014

COMBINED TRACK
White River E & F

BREAKFAST in White River D
Included in your registration
7:00 – 7:45 am

New Data on Chronic Small Bowel Disease in Cats: Don't Accept Vomiting as "Normal"
Dr. Gary Norsworthy
Sponsored by PURINA
7:45 – 10:30 am

NETWORKING REFRESHMENT BREAK in Exhibit Hall
Included in your registration
10:30 – 11:15 am

Diagnosis & Management of Pancreatitis
Dr. Kenneth Simpson
11:15 – 12:05 pm

LUNCH in Exhibit Hall
Included in your registration
Sponsored by Hill's
12:05 – 1:30 pm

12:15 – 1:15 pm **Lunch & Learn: Feline Urethral Obstruction – White River G**
Separate registration required

Winning the Fight Against Hepatic Lipidosis
Dr. Sharon Center
Sponsored by nutramax LABORATORIES VETERINARY SCIENCES, INC.
1:30 – 2:20 pm

AAFP President Remarks, Volunteer Recognition, and Sponsor Acknowledgements
Dr. Marcus Brown
2:20 – 2:25 pm

Are You Comfortable with Feline Constipation?
Dr. Craig Webb
Sponsored by ROYAL CANIN
2:25 – 3:15 pm

NETWORKING REFRESHMENT BREAK in Exhibit Hall
Included in your registration
Sponsored by wedgewood PHARMACY
3:15 – 3:45 pm

TRACK A
White River E

Cholangiohepatitis: Emerging Evidence for Disease Pathomechanisms
Dr. Sharon Center
Sponsored by nutramax LABORATORIES VETERINARY SCIENCES, INC.

Five Unique Feline Hepatic Syndromes
Dr. Sharon Center
4:40 – 5:30 pm

TRACK B
White River F

Is There a Direct Link Between IBD, Cholangitis, & Pancreatitis in Cats?
Dr. Kenneth Simpson
3:45 – 4:35 pm

Diagnosis & Management of Persistent Vomiting
Dr. Kenneth Simpson

EXHIBITORS' HAPPY HOUR RECEPTION in Exhibit Hall
Included in your registration
Sponsored by BAYER
5:30 – 6:30 pm

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Feline Gastroenterology and Endocrinology

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Conference Day Two

SATURDAY, SEPTEMBER 20, 2014

TRACK A *White River E*	TRACK B *White River F*	PARA-PROFESSIONAL *White River D*	
BREAKFAST in Exhibit Hall Included in your registration 7:45 – 8:25 am Cat Friendly Practice Panel: In Our Experience – White River G (Cat Friendly Practice)			7:30 – 8:30 am
Nutraceuticals in Feline Liver Disease *Dr. Sharon Center* Sponsored by nutramax LABORATORIES VETERINARY SCIENCES, INC.	Chronic Diarrhea: What's the Cause? *Dr. Kenneth Simpson*	ICU Boot Camp: What You Should Know on Day One! *Paula Plummer*	8:30 – 9:20 am
Fibropolycystic Feline Liver Disease Syndromes *Dr. Sharon Center*	Managing Cats with Chronic Gastrointestinal Disease *Dr. Kenneth Simpson*	Feline Friendly Handling & Restraint *Paula Plummer*	9:25 – 10:15 am
NETWORKING REFRESHMENT BREAK in Exhibit Hall Included in your registration **AAFP Annual Business Meeting in Room 107**			10:15 – 10:45 am
Stem Cell Therapy in Feline Chronic Enteropathy: In Theory – Bench Top Research *Dr. Craig Webb* Sponsored by WINN FELINE FOUNDATION	Diagnosis & Management of Feline Diabetes Mellitus *Dr. Catharine Scott-Moncrieff* Sponsored by MERCK Animal Health	The Feline Diabetic: Understanding the Disease *Heather Lynch* Sponsored by Abbott Animal Health	10:45 – 11:35 am
Stem Cell Therapy in Feline Chronic Enteropathy: In Practice – Clinical Application *Dr. Craig Webb*	Diabetic Ketoacidosis: Understanding Pathophysiology is Critical to Treatment *Dr. Catharine Scott-Moncrieff*	The Feline Diabetic: Successful Management *Heather Lynch*	11:40 – 12:30 pm
LUNCH in Exhibit Hall Included in your registration 12:15 – 1:15 pm Lunch & Learn: Chronic Kidney Disease – White River G (Sponsored by IDEXX LABORATORIES) Separate registration required 12:50 – 1:20 pm ABVP: How Can it Help Me? – White River E Included in your registration			12:30 – 2:00 pm
Diagnostic Testing for Hyperthyroidism in Cats: More Than Just T4 *Dr. Mark Peterson* Sponsored by Dechra Veterinary Products	Managing the Feline Diabetic: Picking a Protocol *Dr. Audrey Cook* Sponsored by Abbott Animal Health	The Unstable Feline Diabetic Patient *Paula Plummer*	2:00 – 2:50 pm
What's the Best Treatment for Hyperthyroidism? Antithyroid Drugs, Surgery, Diet, or Radioiodine? *Dr. Mark Peterson*	Diabetes: Home Monitoring *Dr. Audrey Cook*	What Every Technician Should Know about Feline Hyperthyroidism *Paula Plummer*	2:55 – 3:45 pm
FUN RUN / FREE TIME Separate registration required			3:45 – 6:30 pm
Offsite Event: A Black, White, and Red Affair Separate registration required Sponsored by Elanco			6:30 – 10:30 pm



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SUNDAY, SEPTEMBER 21, 2014

COMBINED TRACK
White River E & F

BREAKFAST in Exhibit Hall — 7:30 – 8:30 am
Included in your registration
ABVP Breakfast for Diplomates in White River D

Hyperthyroidism & the Kidney: A Strategy to Slow Progression of CKD in Treated Cats — 8:30 – 9:20 am
Dr. Mark Peterson

Feline Hypothyroidism: Much More Common Than You Think! — 9:25 – 10:15 am
Dr. Mark Peterson

Sponsored by Dechra Veterinary Products

NETWORKING REFESHMENT BREAK in Exhibit Hall — 10:15 – 10:45 am
Included in your registration
10:30 am Fun Run Awards Presented in Exhibit Hall

TRACK A
White River E

Nutritional Management of Endocrine Disease in Cats — 10:45 – 11:35 am
Dr. Mark Peterson

Managing Cats with Idopathic Hypercalcemia — 11:40 – 12:30 pm
Dr. Mark Peterson

Sponsored by Dechra Veterinary Products

TRACK B
White River F

Management of Problem Diabetic Patients — 10:45 – 11:35 am
Dr. Catharine Scott-Moncrieff

Role of Concurrent Illness in Insulin Resistant Cats — 11:40 – 12:30 pm
Dr. Catharine Scott-Moncrieff

Sponsored by MERCK Animal Health

LUNCH in Exhibit Hall — 12:30 – 1:45 pm
Included in your registration
12:40 – 1:40 pm Lunch & Learn: Pain Management – White River G
Separate registration required

Sponsored by Abbott Animal Health

Feline Adrenal Disease — 1:45 – 2:35 pm
Dr. Audrey Cook

Hyperaldosteronism — 2:40 – 3:30 pm
Dr. Audrey Cook

Sponsored by Abbott Animal Health

Feline Hypertension Secondary to Endocrinopathies — 1:45 – 2:35 pm
Dr. Catharine Scott-Moncrieff

Diagnosis & Treatment of Feline Acromegaly — 2:40 – 3:30 pm
Dr. Catharine Scott-Moncrieff

Sponsored by MERCK Animal Health

Conclusion of Conference — 3:30 pm

Feline Gastroenterology and Endocrinology

September 18 - 21, 2014 ▪ The JW Marriott ▪ Indianapolis, IN

Distinguished Speakers:

Mark Brady, DVM, DACVECC - *Lunch & Learn*

Sponsored by Hill's

Hill's Pet Nutrition, Inc.

Dr. Mark Brady received his DVM degree from Purdue University in 1995. The following year he completed a small animal internship at Michigan Veterinary Specialists in Southfield, MI. Dr. Brady spent the next eleven years working in the emergency and critical care department at a private specialty referral hospital in Overland Park, KS. He completed his emergency and critical care residency during this time in conjunction with the University of Missouri. Dr. Brady has been with Hill's Pet Nutrition Inc. since 2007 where he is currently the manager of the veterinary consultation service.

Sharon Center, DVM, DACVIM

Sponsored by nutramax LABORATORIES VETERINARY SCIENCES, INC.

James Law Professor of Medicine, Cornell University

Dr. Sharon Center completed her veterinary training at the University of California at Davis, followed by a rotating Internship in Small Animals and an Internal Medicine Residency at Cornell University. She joined the veterinary faculty at Cornell in 1983 and is currently the James Law Professor of Internal Medicine. She co-manages the Internal Medicine Service, provides didactic lectures in the areas of hepatobiliary, hematologic, and urinary disease to 3rd and 4th year veterinary students, trains Small Animal Internal Medicine residents, and conducts focused research in the area of hepatobiliary disease. Current research involves better histopathologic characterization of feline and canine liver disorders, breed related hepatopathies, and identifying toxic and infectious causes of liver injury. She has a long-standing interest in feline metabolism and energy utilization, and in the syndrome of hepatic lipidosis. She has authored numerous research manuscripts, clinical papers, and book chapters regarding liver disease in dogs and cats and often provides national and international lectures on liver disorders. She has received the Norden Teaching Award 2012 and Outstanding Woman Veterinarian by the Association for Women Veterinarians Foundation and was recently named Distinguished Alumni of the College of Veterinary Medicine at the University of California at Davis.

Audrey Cook, BVM&S, MRCVS, DACVIM, DECVIM, DABVP (Feline)

Sponsored by Abbott Animal Health

Associate Professor in Small Animal Internal Medicine, Texas A&M University

Dr. Audrey Cook graduated from the Royal (Dick) School of Veterinary Studies, University of Edinburgh, Scotland, in 1989. The following year, she completed an Internship in Small Animal Medicine and Surgery at North Carolina State University College of Veterinary Medicine and then spent three years at the University of California at Davis College of Veterinary Medicine as a resident in Small Animal Internal Medicine. In 1994, she became a Diplomate in the American College of Veterinary Internal Medicine. In 1996, she achieved Diplomate status in the European College of Veterinary Internal Medicine. From 1997 to 2007, Dr. Cook owned a specialty referral practice in Newport News, VA before joining the faculty at Texas A&M. In 2013, she became a Diplomate of the American Board of Veterinary Practitioners (Feline Practice). She is currently Associate Professor in Small Animal Internal Medicine, with particular interests in endocrinology and gastroenterology.

Robin Downing, DVM, CCVP, CCRP, DAAPM - *Lunch & Learn*

Sponsored by Abbott Animal Health

The Downing Center of Pain Management, Windsor, Colorado

Dr. Robin Downing is Hospital Director of The Downing Center for Animal Pain Management, LLC. She is the recipient of many regional, national, and international awards. Dr. Downing is a Certified Veterinary Pain Practitioner, a Certified Veterinary Acupuncturist, a Certified Canine Rehabilitation Practitioner, a Tui Na practitioner (Chi Institute), and is certified in canine medical massage (CSU) and animal chiropractic (IVCA). She was the third veterinarian to earn the Diplomate credential in the American Academy of Pain Management and the first veterinarian to earn the designation Certified Pain Educator from the American Society of Pain Educators, a second human pain management credential.

Michael Lappin, DVM, PhD, DACVIM

Sponsored by PURINA

Professor of Small Animal Internal Medicine, Colorado State University

After graduating from Oklahoma State University in 1981, Dr. Michael Lappin completed a rotating internship in Small Animal Medicine and Surgery at the University of Georgia. After 2 years in a small animal practice in Los Angeles, he returned to the University of Georgia where he completed a small animal internal medicine residency and a PhD in Parasitology. Dr. Lappin became a Diplomate of the American College of Veterinary Internal Medicine in 1987. He is currently Professor of Small Animal Internal Medicine at the College of Veterinary Medicine and Biomedical Sciences at Colorado State University. Dr. Lappin studies feline infectious and immune-mediated diseases and has written over 250 primary research manuscripts and book chapters. His principal areas of interest are prevention of infectious diseases, the upper respiratory disease complex, infectious causes of fever, infectious causes of diarrhea, and zoonoses of cats. Dr. Lappin is on the editorial board of Feline Medicine and Surgery and Compendium for Continuing Education for the Practicing Veterinarian and is the editor of the textbook, Feline Internal Medicine Secrets. Dr. Lappin has received the Beecham Research Award and the Norden Distinguished Teaching Award. Dr. Lappin is the Kenneth W. Smith Professor in Small Animal Clinical Veterinary Medicine at Colorado State University and is currently the Assistant Department Head for Research. Dr. Lappin is the director of the "Center for Companion Animal Studies." The Center supports clinical research for faculty and students and utilizes only naturally occurring models of disease or research animals that can be adopted. He was selected to receive the European Society of Feline Medicine International Award 2008 for Outstanding Contribution to Feline Medicine, the Winn Feline Research Award in 2009, and was named an Oklahoma State University Distinguished Professor in 2010.

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INDICATION: SIMBADOL is indicated for the control of postoperative pain associated with surgical procedures in cats.

IMPORTANT SIMBADOL (buprenorphine injection) SAFETY INFORMATION

WARNINGS, PRECAUTIONS and CONTRAINDICATIONS: Due to serious human safety and abuse concerns, including physical or psychological dependence, life-threatening respiratory depression and additive CNS depressant effects, read the full prescribing information before using this drug, including the complete Boxed Warning. Not for use in humans. Hospital staff should be trained in the handling of potent opioids and should avoid accidental exposure. For subcutaneous (SQ) injectable use in cats. Opioid excitation has been observed up to 8 hours after anesthetic recovery. Use with caution in cats with impaired hepatic function. SIMBADOL has not been evaluated in breeding, pregnant, or lactating cats, in cats younger than 4 months of age or moribund cats. Do not use in cats with known hypersensitivity to buprenorphine hydrochloride or any of the components of SIMBADOL, or known intolerance to opioids.

ADVERSE REACTIONS: In two controlled field studies, the most frequent adverse reactions with SIMBADOL were hypotension, tachycardia, hypothermia, hyperthermia, hypertension, anorexia, and hyperactivity. Less frequent but serious adverse reactions included two deaths following apnea and two reports of presumptive post-anesthetic cortical blindness. See the full prescribing information for a complete list and additional details of adverse reactions for each field study.

See the Brief Summary of full prescribing information, including the complete Boxed Warning for human safety, on next page.

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Simbadol™ (buprenorphine injection) C-III

1.8 mg/mL

For subcutaneous use in cats

BRIEF SUMMARY: Before using SIMBADOL, please consult the full prescribing information, a summary of which follows.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

HUMAN SAFETY WARNING

Abuse Potential
SIMBADOL contains buprenorphine (1.8 mg/mL), an opioid agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. Buprenorphine has certain opioid properties that in humans may lead to dependence of the morphine type. Abuse of buprenorphine may lead to physical dependence or psychological dependence. The risk of abuse by humans should be considered when storing, administering and disposing of SIMBADOL. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (suicidal depression).

Life-Threatening Respiratory Depression
Respiratory depression, including fatal cases, may occur with abuse of SIMBADOL.

Additive CNS Depressant Effects
SIMBADOL has additive CNS depressant effects when used with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Accidental Exposure
Because of the potential for adverse reactions associated with accidental injection, SIMBADOL should only be administered by veterinarians or veterinary technicians who are trained in the handling of potent opioids.

See Human Safety for detailed information.

INDICATION: SIMBADOL is indicated for the control of postoperative pain associated with surgical procedures in cats.

DOSAGE AND ADMINISTRATION: The dosage of SIMBADOL is 0.24 mg/kg (0.11 mg/lb) administered subcutaneously once daily, for up to 3 days. Administer the first dose approximately 1 hour prior to surgery. Do not dispense SIMBADOL for administration at home by the pet owner (see Human Safety).

CONTRAINDICATIONS: SIMBADOL is contraindicated in cats with known hypersensitivity to buprenorphine hydrochloride or any of the components of SIMBADOL, or known intolerance to opioids.

WARNINGS: For subcutaneous (SQ) injectable use in cats.

Human Safety: **Not for use in humans. Keep out of reach of children.** Because of the potential for adverse reactions, hospital staff should avoid accidental exposure and contact with skin, eyes, oral or other mucous membrane during administration. SIMBADOL contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. SIMBADOL can be abused and is subject to misuse, abuse, addiction and criminal diversion. SIMBADOL should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law. Abuse of SIMBADOL poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances including other opioids and benzodiazepines. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse. Drug abuse is the intentional non-therapeutic use of a prescription drug for its rewarding psychological or physiological effects. Abuse of opioids can occur in the absence of true addiction. Naloxone may not be effective in reversing respiratory depression produced by buprenorphine. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride has also been used as a respiratory stimulant.

PRECAUTIONS: Hyperactivity (opioid excitation) has been observed up to 8 hours after anesthetic recovery (see ADVERSE REACTIONS). Safety has not been evaluated in moribund cats. Use in such cases should be based on the risk-benefit assessment of the veterinarian. Use with caution in cats with impaired hepatic function. The use of SIMBADOL has not been evaluated in breeding, pregnant, or lactating cats, or in cats younger than 4 months of age.

ADVERSE REACTIONS: In two controlled field studies, the following adverse reactions were reported.

Adverse Reactions in Two Field Studies

	SIMBADOL (N = 224)		Control (N = 226)	
Adverse Reaction[a]	**During Surgery[b]**	**After Surgery**	**During Surgery[b]**	**After Surgery**
Hypotension[c]	68 (30.4%)	51 (22.8%)	60 (26.5%)	40 (17.7%)
Tachycardia[d]	55 (24.6%)	73 (32.6%)	30 (13.3%)	44 (19.5%)
Hypothermia (≤98.0°F)	38 (17.0%)	1 (0.4%)	47 (20.8%)	0
Hyperthermia (≥103.0°F)	1 (0.4%)	91 (40.6%)	0	33 (14.6%)
Hypertension[e]	10 (4.5%)	40 (17.9%)	17 (7.5%)	18 (8.0%)
Anorexia	0	40 (17.9%)	0	35 (15.5%)
Hyperactivity	0	26 (11.6%)	0	11 (4.9%)
Reduced SpO_2 (≤90%)	8 (3.6%)	1 (0.4%)	11 (4.9%)	0
Bradycardia (<90 beats/min)	5 (2.2%)	1 (0.4%)	4 (1.8%)	1 (0.4%)
Tachypnea (≥72 breaths/min)	0	5 (2.2%)	1 (0.4%)	6 (2.7%)
Arrhythmia	1 (0.4%)	1 (0.4%)	2 (0.9%)	0
Blindness	0	2 (0.9%)	0	1 (0.4%)
Apnea/Death	1 (0.4%)	1 (0.4%)	0	0
Ataxia	0	1 (0.4%)	0	0
Hyperesthesia	0	1 (0.4%)	0	0

a. Cats may have experienced more than one type or occurrence of an adverse reaction. Cats experiencing the same reaction both during and after surgery are presented in both time periods.
b. During surgery is the time from the administration of the anesthetic induction agent until discontinuation of the gas anesthetic.
c. Hypotension is defined as a mean blood pressure of ≤60 mmHg during surgery and ≤90 mmHg after surgery.
d. Tachycardia is defined as a heart rate of ≥180 beats per minute during surgery and ≥200 beats per minute after surgery.
e. Hypertension is defined as a mean blood pressure of ≥120 mmHg during surgery and ≥160 mmHg after surgery.

To report suspected adverse events, contact Abbott Animal Health at 1-888-299-7416, FDA at 1-888-FDA-VETS or FDA online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

EFFECTIVENESS: The effectiveness of SIMBADOL was demonstrated in two randomized, masked, placebo-controlled, multi-site field studies involving client-owned cats of various breeds. A descriptive, interactive pain assessment system was used by the trained assessor over the 72-hour post-operative period to determine pain control, and treatment success was defined as a cat that completed the 72-hour post-operative period without rescue analgesia. A statistically significant difference ($P \leq 0.005$) in the number of successes in the treatment group over the placebo control group was observed. The results of two field studies demonstrate that SIMBADOL is effective and has an acceptable safety margin for the control of postoperative pain in cats.

HOW SUPPLIED: SIMBADOL (buprenorphine injection) is supplied in a carton containing one 10 mL amber glass vial. Each multidose vial contains 1.8 mg/mL of buprenorphine.

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Distinguished Speakers:

Susan E. Little, DVM, PhD, DACVM-Parasit
Professor & Krull-Ewing Chair in Veterinary Parasitology, Oklahoma State University

Sponsored by Bayer

Dr. Susan Little is Regents Professor of Parasitology and the Krull-Ewing Endowed Chair in Veterinary Parasitology at the Center for Veterinary Health Sciences, Oklahoma State University, where she is active in veterinary parasitology teaching and oversees a research program that focuses on zoonotic parasites and tick-borne diseases. She earned her BS from Cornell University, DVM from Virginia Tech, and PhD in veterinary parasitology from the University of Georgia, and is board certified in veterinary parasitology through the American College of Veterinary Microbiology. She is a past-president of the American Association of Veterinary Parasitologists, co-directs of the National Center for Veterinary Parasitology, and is President-elect of the Companion Animal Parasite Council. Dr. Little has authored more than 100 publications on veterinary and human parasites and tick-borne disease agents. She is also recognized as an outstanding teacher and has been awarded two, Excellence in Teaching Awards from the National Student American Veterinary Medical Association (SAVMA).

Heather Lynch, LVT
Tatum Point Animal Hospital, Phoenix, Arizona

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Ms.Heather Lynch has been the Technical Director for Tatum Point Animal Hospital in Phoenix, AZ since 2009. Prior to this, she spent 14 years as the Supervising Technician in Internal Medicine at the VCA Emergency Animal Hospital and Referral Center in San Diego, CA. Ms. Lynch is a frequent speaker at national veterinary conferences and has authored numerous articles for professional journals. In 2009, she co-authored the pilot study validating the use of Detemir Insulin in dogs. In 2013, she co-authored the Home Monitoring chapter in the Veterinary Clinics of North America Feline Diabetes Volume, edited by Dr. Jacquie Rand.

Gary Norsworthy, DVM, DABVP (Feline)
Alamo Feline Health Center, San Antonio, Texas

Sponsored by Purina

Dr. Gary Norsworthy has been in private practice for over 40 years. Of those 40 years, 25 were spent in small animal practice and 17 were in feline practice. He is the owner of Alamo Feline Health Center in San Antonio, TX. In addition to practice, he lectures frequently on feline diseases and is the editor and major author of six feline textbooks. The most recent being *The Feline Patient, 4th Edition,* which is being or has been translated into Spanish, Portuguese, Japanese, Italian, Chinese, and Korean, and Nursing the Feline Patient, the first American feline textbook for technicians. His practice hosts externs from veterinary schools across North America and internationally. He is a charter Diplomate of the American Board of Veterinary Practitioners in the Feline Practice Category and an Adjunct Professor at the College of Veterinary Medicine, Mississippi State University and the Western University of Health Sciences. He was chosen for the 2009 Practitioners of the Year Award in the Medical Specialist category by the Texas VMA.

Mark Peterson, DVM, DACVIM
Animal Endocrine Clinic, New York, New York

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Dr. Mark Peterson graduated from the University of Minnesota in 1976, moved to New York City for an internship and medical residency at The Animal Medical Center (AMC), and then completed a post-doctoral fellowship in endocrinology and nuclear medicine at The New York Hospital-Cornell Medical Center and the Animal Medical Center. Following his training, Dr. Peterson stayed on as head endocrinologist at the AMC for over 30 years. In 2009, Dr. Peterson opened the Animal Endocrine Clinic in New York City, a specialty referral hospital devoted exclusively to the diagnosis and treatment of dogs and cats with endocrine disease, where he now cares for his endocrine patients. Over the last 35 years, most of Dr. Peterson's clinical and research efforts have been directed toward advancing our understanding of endocrine disorders of the dog and cat, especially hyper- and hypothyroidism, diabetes mellitus, and adrenal disease. He has published more than 500 journal articles, book chapters, and research abstracts. With more than 500 lecture presentations to his credit, Dr. Peterson is a frequent speaker at veterinary colleges and scientific seminars both in the United States and abroad.

Paula Plummer, LVT, VTS (ECC, SAIM)
Veterinary Technician of Feline Internal Medicine, Texas A&M University

Ms. Paula Plummer has been at Texas A&M University since 2007, first working in the Small Animal ICU and then moving to the Feline Internal Medicine service in 2011. She graduated from Murray State College in Tishomingo, OK and has been a registered veterinary technician since 2000. In 2011, she received her veterinary technician specialty in emergency and critical care. Paula has spent most of her career in academia working in critical care or feline internal medicine teaching veterinary students tasks that will help them be better patient advocates when they graduate.

Feline Gastroenterology and Endocrinology

September 18 - 21, 2014 ▪ The JW Marriott ▪ Indianapolis, IN

Distinguished Speakers:

Jane Robertson, DVM, DACVIM - *Lunch & Learn*

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Dr. Jane Robertson received her DVM from the Ontario Veterinary College at the University of Guelph in Canada in 1992. She worked in mixed-animal and small animal practice before completing a small animal internship at the same institution in 1994. Dr. Robertson completed her medicine residency at University of California, Davis, and became a Diplomate of the American College of Veterinary Internal Medicine in 1998. She practiced in a busy referral hospital before joining IDEXX as a Medicine Consultant in 2000. Dr. Robertson is currently Director of Internal Medicine for IDEXX Laboratories. She enjoys speaking about kidney disease, endocrinology, pancreatitis, and the clinical utility of real-time PCR.

Catharine Scott-Moncrieff, VET MB, MA, MS, DACVIM, DECVIM

Sponsored by MERCK Animal Health

Professor of Small Animal Internal Medicine, Purdue University

Dr. Catharine Scott-Moncrieff received her Master of Arts and Vet MB (Veterinary Medicine) degrees from the University of Cambridge in 1985. She completed an internship in small animal medicine and surgery at the University of Saskatchewan, Canada, and a residency and Master of Science degree in internal medicine at Purdue University. In 1989 she joined the faculty of Purdue University, where she is currently Professor of Small Animal Internal Medicine and Director of International Programs. She is a Diplomate of the American College of Veterinary Internal Medicine (small animal), the European College of Veterinary Internal Medicine (companion animal), and has a diploma in Small Animal Medicine from the Royal College of Veterinary Surgeons. She is the author or co-author of over 60 peer reviewed publications, 20 book chapters, and has lectured extensively both nationally and internationally. Her clinical and research interests include clinical endocrinology and immune mediated hematologic disorders.

Kenneth Simpson, BVM&S, PhD, DACVIM, DECVIM

Professor of Small Animal Medicine, Cornell University

Dr. Kenneth Simpson graduated from Edinburgh in 1984 and gained a PhD in Gastroenterology at the University of Leicester in 1988. Dr. Simpson hopped the pond for an internship at the University of Pennsylvania in 1989 and a medicine residency at the Ohio State University in 1991, then hopped back to the UK as a lecturer at the other Royal Veterinary College. He fled the hostile climes of Londinium in 1995 to join the faculty at Cornell University, Ithaca, NY. He is a Diplomate of the American and European Colleges of Veterinary Internal Medicine. He is a recipient of the National Phi Zeta and Pfizer awards for research, the BSAVA Bourgelat Award for outstanding contributions to the field of small animal practice, and the AVMF/AKC Career Achievement Award in Canine Research. He is a past president of the Comparative Gastroenterology Society. His research interests are centered below the diaphragm, with a focus on inflammatory diseases of the GI tract (including the pancreas and liver), host bacterial interactions in health and disease, and culture independent bacteriology.

Craig Webb, DVM, PhD, DACVIM

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Associate Professor & Head of Small Animal Medicine Section, Colorado State University

Dr. Craig Webb is currently an Associate Professor in the Clinical Sciences Department at the Colorado State University Veterinary Teaching Hospital, where he is head of the Small Animal Medicine Section. Dr. Webb received his PhD in Neuroscience prior to completing his DVM degree at the University of Wisconsin-Madison. Dr. Webb completed his internship at Alameda East in Denver, CO, spent a year in private practice, and then went on to complete his Small Animal Residency at Colorado State University where he has been ever since. He is a Diplomate of the American College of Veterinary Internal Medicine and specializes in Clinical Gastroenterology. Along with Drs. David Twedt and Eric Monnet, Dr. Webb is an integral part of CSU CE courses in both Flexible Endoscopy and Laparoscopic Techniques. Dr.Webb presents annually at the ACVIM Convention and lectures throughout the United States and Europe on current topics in Small Animal Veterinary Medicine. Dr. Webb's research interests include stem cell therapy, antioxidants, and figuring out how to best educate veterinary students.

Session Abstracts:

KEY: Ⓐ TRACK A Ⓑ TRACK B Ⓒ COMBINED TRACK

THURSDAY, SEPTEMBER 18, 2014 – Pre-conference Day

11:15 – 12:45 pm **Protecting Cats from the Unexpected: Feline Vector-borne Disease Agents,** *Dr. Susan E. Little*
Although risk is often underestimated, infection of cats with vector-borne disease agents, including heartworm (*Dirofilaria immitis*), bartonellosis (*Bartonella henselae,* other *Bartonella* spp.), and cytauxzoonosis (*Cytauxzoon felis*), is surprisingly common in many areas. Several recent studies have shown that consistent use of parasite control products can prevent transmission of these agents by preventing feeding of arthropod vectors or abrogating infections prior to development of disease. For example, application of imidacloprid/moxidectin heartworm preventive to cats prior to high challenge experimental infection with *D. immitis* prevented development of lung pathology and seroconversion in treated cats; cats wearing acaricidal collars with flumethrin are protected from tick-borne transmission of *C. felis* and development of cytauxzoonosis; and flea control using imidacloprid has been shown to block transmission of *Bartonella* spp. between cats. This presentation will review data from several studies that document the ability of parasite control products to prevent infection with common vector-borne pathogens in cats, thus supporting efforts to help cats live longer, healthier lives.

1:00 – 2:00 pm **Update on Feline Infectious Diseases: Agents Associated with Fever,** *Dr. Michael Lappin*

2:00 – 3:00 pm **Update on Feline Infectious Diseases: Upper Respiratory Tract Disease,** *Dr. Michael Lappin*

3:30 – 4:30 pm **Update on Feline Infectious Diseases: Lower Respiratory Tract Disease,** *Dr. Michael Lappin*

4:30 – 5:30 pm **Update on Feline Infectious Causes of Diarrhea in Cats,** *Dr. Michael Lappin*
In this four lecture series, Dr. Lappin will provide updates on the diagnosis, treatment, and prevention of select feline infectious diseases using a case-based approach. Emphasis will be placed on new clinically relevant information generated in the last 12-18 months and will include infectious agents associated with fever (Bartonella, hemoplasmas, Rickettsia felis, Anaplasma phagocytophilum), upper respiratory tract disease (FHV-1, FCV, Mycoplasma), lower respiratory tract disease (FIP, Toxoplasma, Bordetella), and diarrhea (Giardia, Cryptosporidium, and use of probiotics).

FRIDAY, SEPTEMBER 19, 2014

7:45 – 10:30 am Ⓒ ***New Data on Chronic Small Bowel Disease in Cats: Don't Accept Vomiting as "Normal,"*** *Dr. Gary Norsworthy*
This lecture will address chronic vomiting, chronic diarrhea, and weight loss, all of which occur very commonly in cats and usually originate from disease in the small bowel. The attendee will learn how to recognize cats that need an abdominal ultrasound which usually leads to small bowel, liver, and pancreatic biopsies. Nearly 50% of these cats have chronic enteritis (usually IBD), and nearly 50% have lymphoma. Once the diagnosis if firmly made, the practitioner is in a position to treat both of these diseases. Dr. Norsworthy will reveal his approach to both and give instructions on how to communicate with the client before, during, and after the diagnosis is made. You should leave equipped with the knowledge and documents to diagnose and treat cats with this very common disease. You will find this new knowledge a game-changing event in your professional career.

11:15 – 12:05 pm Ⓒ ***Diagnosis & Management of Pancreatitis,*** *Dr. Kenneth Simpson*
Pancreatitis is increasingly recognized in cats and is often a real challenge to diagnose and manage. Cats are not small dogs and we have to challenge conventional DOGMA and pursue our inner CATMA. In this session we will also discuss - How good are fPL and ultrasounds, feeding in the face of pancreatitis, management of concurrent diseases (triaditis), and why you could consider bacterial infection in severe pancreatitis.

12:15 – 1:15 pm **Lunch & Learn – Feline Urethral Obstruction: New Options, New Solutions to an Old Problem,** *Dr. Mark Brady*
Urethral obstruction (UO) is a potentially life threatening manifestation of feline lower urinary tract disease. This condition is thought to be a sequel to feline idiopathic cystitis, so a review of this pathophysiology will be presented. Recommendations for management of this problem can be cost prohibitive for some clients leading to unwanted outcomes for our patients. The discussion will focus on recently published evidence to provide options in these challenging cases.

1:30 – 2:20 pm Ⓒ ***Winning the Fight Against Hepatic Lipidosis,*** *Dr. Sharon Center*
Complex acquired metabolic deficiencies and dysregulations challenge survival in cats with hepatic lipidosis. This presentation will focus on evidenced-based approaches for hastened recovery from this devastating syndrome.

2:25 – 3:15 pm Ⓒ ***Are You Comfortable with Feline Constipation?,*** *Dr. Craig Webb*
Imagine if our human counterparts were faced with something as seemingly simple as constipation being a terminal disease, and in fact, for too many cats it is. Clinical cases of cats with constipation will be used to highlight important aspects of this condition, and the standard diagnostic work-up will be reviewed. Treatment strategies, both old and perhaps new, will then be presented and discussed. The clinician should walk away from this presentation with a new level of "comfort," or a few new ideas to try when faced with these frequently frustrating cases.

3:45 – 4:35 pm Ⓐ **Cholangiohepatitis: Emerging Evidence for Disease Pathomechanisms,** *Dr. Sharon Center*
Investigation of oxidant injury, inflammatory signaling, and antimicrobial epitopes in feline cholangiohepatitis has broadened our understanding of its pathophysiologic mechanisms. This lecture will provide an overview of new information that better characterizes this complex feline syndrome.

Ⓑ **Is There a Direct Link Between IBD, Cholangitis, & Pancreatitis in Cats?,** *Dr. Kenneth Simpson*
Concurrent inflammation of the intestinal tract, liver, and pancreas is a relatively common occurrence in cats. In this session we will also discuss - is there a common stimulus driving inflammation in the intestinal tract, liver, and pancreas; could it be pathogenic bacteria or an immune-mediated disease; or could it possibly be the resident intestinal microbiota?

4:40 – 5:30 pm Ⓐ **Five Unique Feline Hepatic Syndromes,** *Dr. Sharon Center*
This discussion will provide a synopsis of feline primary copper associated liver disease, cholelithiasis, hepatocellular carcinoma, hepatic amyloidosis, and biliary atresia.

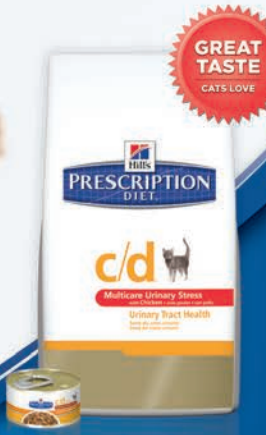
Ⓑ **Diagnosis & Management of Persistent Vomiting,** *Dr. Kenneth Simpson*
A thorough and systematic approach is required to determine the cause of persistent vomiting. An integrated approach based on patient history, physical findings, clinicopathological testing, and diagnostic imaging will be presented. In this session we will also discuss - is Helicobacter a friend or foe, what antiemetic should I use, and when should I default to "Vitamin P?"

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[1]Kruger JM, Lulich JP, Merrils J, et al. *Proceedings.* American College of Veterinary Internal Medicine Forum 2013.

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Session Abstracts:

KEY: A TRACK A · B TRACK B · P PARA-PROFESSIONAL

SATURDAY, SEPTEMBER 20, 2014

7:45 – 8:25 am

Cat Friendly Practice Panel: In Our Experience
Please join us for this panel discussion to learn more about the AAFP Cat Friendly Practice (CFP) Program. This session will be led by approved CFPs who have went through the process. You will hear about creative ideas, implementation tactics, here is what worked for us, and even he helpful tips that you can use in your practice. This is also your opportunity to ask questions and brain-storm ideas. So whether you would like to learn more about being cat-friendly, you are thinking about starting the CFP program, or even if you are already in the process, please grab your breakfast and join us for this discussion and Q&A.

8:30 – 9:20 am

A **Nutraceuticals in Feline Liver Disease,** *Dr. Sharon Center*
Nutraceuticals including antioxidant, hepatoprotectants, antifibrotic, and choleretic agents importantly collaborate with conventional multimodal nutritional, immunomodulatory, and antibacterial treatments in feline liver disease. This discussion will highlight reasoned utility of these adjunctive therapies.

B **Chronic Diarrhea: What's the Cause?,** *Dr. Kenneth Simpson*
A thorough and systematic approach is required to determine the cause of chronic diarrhea. An integrated approach based on patient history, physical findings, clinicopathological test, intestinal function testing, and diagnostic imaging will be presented. In this session we will also discuss - is it parasitic, immune, infectious, or neoplastic, and could diet be the problem?

P **ICU Boot Camp: What You Should Know on Day One!** *Ms. Paula Plummer*
What should technicians know when in the ICU? Your questions will be answered in this session. Some topics that will be covered are proper dosage calculations, CRI calculations, how to handle infectious patients, and how to deal with a burn out.

9:25 – 10:15 am

A **Fibropolycystic Feline Liver Disease Syndromes,** *Dr. Sharon Center*
Fibropolycystic feline liver disorders include a spectrum of developmental disorders typically recognized in mature adult cats but confused with necroinflammatory and cholestatic processes. This presentation will discuss five distinct fibropolycystic manifestations and the confusion surrounding these diagnoses.

B **Managing Cats with Chronic Gastrointestinal Disease,** *Dr. Kenneth Simpson*
This presentation will review the differentiation and management of chronic enteropathies in cats. In this session we will also discuss – how do I manage inflammatory bowel disease and how do I manage lymphoma?

P **Feline Friendly Handling & Restraint,** *Ms. Paula Plummer*
This session will discuss tips on how to make your practice feline friendly with new techniques for feline handling and restraint. There will be demonstration videos so you can see how to handle your patient safely. We will end with discussions on feline body language.

10:45 – 11:35 am

A **Stem Cell Therapy in Feline Chronic Enteropathy: In Theory – Bench Top Research,** *Dr. Craig Webb*
The phrase "stem cells" conjures up a huge array of reactions and opinions, covering the gamut from moral repulsion to medical miracle. From this session, practicing veterinary clinicians will learn to discriminate between the many entries that fall underneath the "stem cell" umbrella, including important and distinct differences between the stem cells that fuel political debate, and those stem cells currently being offered as therapy for a myriad of human and veterinary diseases. The many potentially beneficial properties of mesenchymal stem cells will be covered, giving clinicians the foundation of information to more critically appraise the therapeutic use of this modality, both in theory and in practice.

B **Diagnosis & Management of Feline Diabetes Mellitus,** *Dr. Catharine Scott-Moncrieff*
This lecture will focus on diagnosis and treatment of feline diabetes mellitus. Topics will include insulin choice, diabetic monitoring, and management of diabetes in the presence of concurrent illness. The lecture will also discuss alternative strategies for cases that do not respond well to the initial choice of insulin.

P **The Feline Diabetic: Understanding the Disease,** *Ms. Heather Lynch*
Many strides have been made in our understanding of the diabetic state in cats. This session will focus on increasing understanding of the causes and effects of diabetes in cats, why they are different from diabetic dogs, and give talking points to help technician's better support clients and DVMs when working with diabetic felines. Included in this session is a discussion of the important role annual care plays in the detection, and possibly prevention of this disease.

11:40 – 12:30 pm

A **Stem Cell Therapy in Feline Chronic Enteropathy: In Practice – Clinical Application,** *Dr. Craig Webb*
Clinical cases will be used to highlight the history, diagnosis, and current treatment options commonly used for cats with chronic diarrhea (and/or vomiting). This will include a brief review of the evidence currently available to support these treatment choices (hence, the word "brief"). From there, the design, implementation, and results of a recently completed study using feline-derived mesenchymal stem cells for the treatment of client-owned cats with a chief complaint of chronic enteropathy will be detailed. The session will conclude by considering the stem cell therapy options currently available to the veterinary practitioner, leaving participants with a solid armamentarium when considering this therapeutic tool, or when asked to consider it by their clientele.

B **Diabetic Ketoacidosis: Understanding Pathophysiology is Critical to Treatment,** *Dr. Catharine Scott-Moncrieff*
This presentation will focus on the cause of pathophysiologic derangements associated with diabetic ketoacidosis and how an understanding of the pathophysiology can improve case management.

P **The Feline Diabetic: Successful Management,** *Ms. Heather Lynch*
With good communication and teamwork between the client, the DVM, and the veterinary team, almost all diabetics will be managed successfully. This session will cover the important role the technician can play in the management of diabetic cats, with talking points, common barriers to communication or treatment, and common treatment protocols. Some case examples will also be presented.

12:15 – 1:15 pm

Lunch & Learn – Diagnosis & Management of Feline Chronic Kidney Disease, *Dr. Jane Robertson*
This lecture will focus on the diagnosis and management of cats with chronic kidney disease (CKD). A new renal biomarker, symmetric dimethylarginine (SDMA), that has been shown to increase earlier than creatinine in cats with CKD will be introduced. The International Renal Interest Society's (IRIS) classification system for staging CKD in cats will be reviewed followed by a discussion of appropriate therapy that can slow progression of disease, improve clinical signs, and prolong life.



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Session Abstracts:

KEY: A TRACK A | B TRACK B | P PARA-PROFESSIONAL

SATURDAY, SEPTEMBER 20, 2014 continued

12:50 – 1:20 pm

ABVP: How Can it Help Me?
The American Board of Veterinary Practitioners offers a short informational presentation showing the benefits of getting Board-Certified in Feline Practice. Find out why the 90 Board Certified Feline Practitioners on Planet Earth stand out from the rest!

2:00 – 2:50 pm

A **Diagnostic Testing for Hyperthyroidism in Cats: More Than Just T4,** *Dr. Mark Peterson*
Over the past two decades, many advances have been made in the availability of tests that can be used to diagnose feline hyperthyroidism. However, all of the commonly-used tests have limitations, especially when evaluating cats suffering from non-thyroidal illness. This lecture will focus on an update on the diagnostic approach for the workup of cats with suspected hyperthyroidism. Since definitive diagnosis of this common disorder is not always clear-cut, this review concentrates on protocols used in the work-up of "occult" or problem cases, in which misdiagnosis can be common.

B **Managing the Feline Diabetic: Picking a Protocol,** *Dr. Audrey Cook*
This lecture will review the factors to consider when starting a diabetic cat on insulin, such as frequency of administration, when and what to recheck, dietary considerations, and essential client education issues. The importance of creating a team approach and establishing appropriate expectations will also be discussed.

P **The Unstable Feline Diabetic Patient,** *Ms. Paula Plummer*
Complications with your feline diabetic patient can be commonly seen in an emergency. These complications include diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, and insulin resistance. This session will focus on how to recognize these complications, treatment options available, and an overview of pathophysiology with each complication.

2:55 – 3:45 pm

A **What's the Best Treatment for Hyperthyroidism? Antithyroid Drugs, Surgery, Diet, or Radioiodine?** *Dr. Mark Peterson*
In cats, hyperthyroidism can be treated in four ways — surgical thyroidectomy, radioactive iodine (131-I), chronic administration of an antithyoid drug, or lifelong feeding of an ultra-low iodine diet. Each form of treatment has advantages and disadvantages, which must be considered when formulating the best treatment plan for the individual hyperthyroid cat. The treatment of choice for an individual cat depends on several factors, including the age of the cat, presence of associated cardiovascular diseases, other major medical problems (e.g., chronic kidney disease), availability of a skilled surgeon or radioiodine treatment facility, cost, and owner's preference. This lecture will review the pros and cons of each form of treatment, which should help the practicing feline veterinarian and owners decide which is really the "best" treatment for their cat.

B **Diabetes: Home Monitoring,** *Dr. Audrey Cook*
This lecture will explore the reasons for encouraging home-monitoring of the feline diabetic and the benefits to the patient, client, and hospital. A step-by-step guide on getting started with home monitoring will be provided.

P **What Every Technician Should Know about Feline Hyperthyroidism,** *Ms. Paula Plummer*
Occurrence of hyperthyroidism in feline patients is common. Every technician should understand basic physiology, clinical signs, different diagnostic methods, treatment options, and client education. This session will also include how to find that enlarged thyroid gland and how to understand our feline hyperthyroid patients so we as technicians can be better patient advocates.



Session Abstracts:

KEY: A TRACK A | B TRACK B | C COMBINED TRACK

SUNDAY, SEPTEMBER 21, 2014

8:30 – 9:20 am C ***Hyperthyroidism & the Kidney: A Strategy to Slow Progression of CRD in Treated Cats,*** *Dr. Mark Peterson*
Hyperthyroidism and chronic kidney disease (CKD) are both common disorders in older cats. About a third of hyperthyroid cats will have concurrent chronic kidney disease (CKD), but the CKD is commonly masked and azotemia may not develop until euthyroidism is restored. This lecture will focus on methods to help diagnose masked renal disease, as well as provide treatment strategies designed to prevent or slow the progression of CKD in these hyperthyroid cats.

9:25 – 10:15 am C ***Feline Hypothyroidism: Much More Common Than You Think!*** *Dr. Mark Peterson*
Unlike the situation in dogs, naturally occurring hypothyroidism is extremely rare in cats. Most commonly, feline hypothyroidism is an iatrogenic complication associated with overtreatment of hyperthyroidism. Although early reports suggested that cats were resistant to hypothyroidism and did not require treatment, it is now realized that milder degrees of iatrogenic hypothyroidism are very common and that these cats may benefit from thyroid replacement therapy. This lecture will review the range of thyroid function tests available to aid in diagnosis of feline hypothyroidism and discuss its management.

10:45 – 11:35 am A **Nutritional Management of Endocrine Disease in Cats,** *Dr. Mark Peterson*
When treating cats with endocrine disease, most veterinarians concentrate on the use of medical or surgical treatments that can be used to manage or cure the disease. Dietary issues are frequently ignored or not properly addressed. This is unfortunate, in as much as nutritional support should play an integral role in the successful management of feline endocrine diseases. The lecture will cover the two most common endocrine problems of cats seen in clinical practice (hyperthyroidism and diabetes mellitus) and discuss the way one can integrate nutrition into the management of these common feline diseases. Our goal is to use the cat's diet as a means to support their overall body health and metabolism and, therefore, help manage their underlying endocrine disease.

B **Management of Problem Diabetic Patients,** *Dr. Catharine Scott-Moncrieff*
This lecture will outline an approach to problems of insulin regulation in diabetic cats. The lecture will cover problems such as owner compliance, short duration of insulin action, insulin induced hypoglycemia, and insulin resistance. Case examples will be used to illustrate each problem.

11:40 – 12:30 pm A **Managing Cats with Idiopathic Hypercalcemia,** *Dr. Mark Peterson*
Unexplained (idiopathic) hypercalcemia has been increasingly diagnosed in cats since the disorder was first described in the early 1990s. It is not clear what causes idiopathic ionized hypercalcemia or why it is becoming more prevalent in cats, but it is likely that the diet is playing a role in its pathogenesis. This lecture will review how I manage these cats with a stepwise approach that includes a change of diet therapy, followed by the use of glucocorticoids, bisphosphonates (alendronate), or both.

B **Role of Concurrent Illness in Insulin Resistant Cats,** *Dr. Catharine Scott-Moncrieff*
Management of feline diabetes mellitus is sometimes complicated by underlying diseases that may cause profound insulin resistance. Lack of recognition of underlying disorders that cause insulin resistance results in poor glycemic control and decreases the likelihood of diabetic remission. This lecture will focus on the underlying causes of insulin resistance in cats, with special attention to two endocrinopathies (hyperadrenocorticism and acromegaly) that cause profound insulin resistance.

12:40 – 1:40 pm **Lunch & Learn – What's New in Acute Feline Pain Management: Before, During, and After Surgery,** *Dr. Robin Downing*
Cats have been the "red-headed stepchildren" in the veterinary pain management world. Fortunately, this is changing rapidly as veterinarians are provided with more tools with which to recognize, prevent, and treat acute feline pain. An effective acute pain management plan for feline patients means anticipating when pain will occur, as well as anticipating how intense it may be. Learn how to construct a multi-modal approach that targets specific sites in the body with new (and some not so new) options to provide the broadest protection possible for our feline patients.

1:45 – 2:35 pm A **Feline Adrenal Disease,** *Dr. Audrey Cook*
This lecture will review the clinical manifestations of adrenal disorders in cats, and the diagnostic and therapeutic options currently available. Patient management and prognostic considerations will be discussed for the various types of adrenal problems encountered in cats.

B **Feline Hypertension Secondary to Endocrinopathies,** *Dr. Catharine Scott-Moncrieff*
This lecture will review the endocrine causes of feline hypertension including hyperthyroidism and hyperaldosteronism. Topics include diagnosis of feline hypertension, differential diagnosis of feline hypertension, and management of hypertension.

2:40 – 3:30 pm A **Hyperaldosteronism,** *Dr. Audrey Cook*
In the last few years our understanding of feline hyperaldosteronism has changed substantially. In particular, the impact of hyperaldosteronism in cats with chronic kidney disease has been recognized. This lecture will review the current literature on this complex disorder and its potential impact on geriatric feline patients.

B **Diagnosis & Treatment of Feline Acromegaly,** *Dr. Catharine Scott-Moncrieff*
This lecture will focus on the clinical signs, diagnosis, and treatment of feline acromegaly. Indications for testing, interpretation of diagnostic test results, and approach to management will be discussed using case examples.

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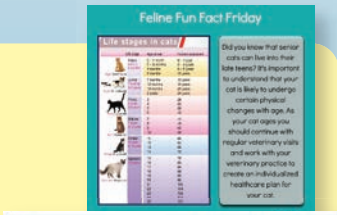
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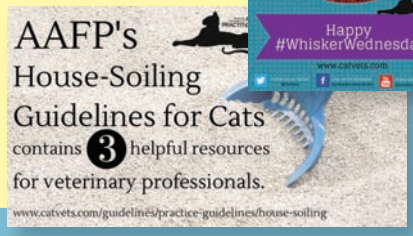




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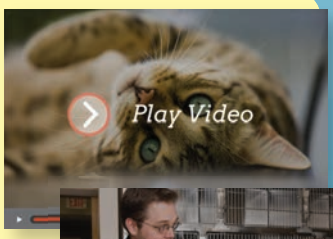
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Food for Thought Luncheon in White River F

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Protecting Cats From the Unexpected: Feline Vector-borne Disease Agents
Dr. Susan E. Little

1:00 – 5:30 pm

ABVP/AAFP Seminar & Social in White River E

Included in Pre-conference registration

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1:00 – 2:00 pm

Update on Feline Infectious Diseases: Agents Associated with Fever
Dr. Michael Lappin

2:00 – 3:00 pm

Update on Feline Infectious Diseases: Upper Respiratory Tract Disease
Dr. Michael Lappin

3:00 – 3:30 pm

Seminar & Social Refreshment Break

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3:30 – 4:30 pm

Update on Feline Infectious Diseases: Lower Respiratory Tract Disease
Dr. Michael Lappin

4:30 – 5:30 pm

Update on Feline Infectious Causes of Diarrhea in Cats
Dr. Michael Lappin

5:30 – 7:00 pm

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Protecting Cats From the Unexpected: Feline Vector-borne Disease Agents

Susan E. Little, DVM, PhD, DACVM-Parasit

Introduction

Although risk is often underestimated, infection of cats with vector-borne disease agents, including heartworm (Dirofilaria immitis), bartonellosis (Bartonella henselae, other Bartonella spp.), and cytauxzoonosis (Cytauxzoon felis), is surprisingly common in many areas. Several recent studies have shown that consistent use of parasite control products can prevent transmission of these agents by preventing feeding of arthropod vectors or abrogating infections prior to development of disease. For example, application of imidacloprid/moxidectin heartworm preventive to cats prior to high challenge experimental infection with D. immitis prevented development of lung pathology and seroconversion in treated cats; cats wearing acaricidal collars with flumethrin are protected from tick-borne transmission of C. felis and development of cytauxzoonosis; and flea control using imidacloprid has been shown to block transmission of Bartonella spp. between cats. This presentation will review data from several studies that document the ability of parasite control products to prevent infection with common vector-borne pathogens in cats and thus support efforts to help cats live longer, healthier lives.

Heartworm Disease in Cats

Feline heartworm infection (*Dirofiliaria immitis*) can induce a severe, potentially fatal disease that in some patients manifests as respiratory distress or sudden death[1]. Infection by third-stage larvae from mosquitoes and subsequent larval molting and migration in the feline host appears to provoke a robust immune response which leads to abridged infections and characteristic histopathologic changes in the lung[2,3]. Estimates for prevalence of feline infection, and thus burden of disease, vary widely depending on both geography and the test used. For example, in areas of the southern United States where ample infected dog reservoir hosts are found, necropsy surveys document that as many as 16% of cats may be infected with adult *D. immitis,* and reports of feline prevalence based on antibody tests, which reveal evidence of both past and current infections, are even higher[2]. However, the rate of infection detected using antigen tests is low, with only approximately 0.9% of cats positive nationwide[4,5].

Recent data suggest that false negative antigen tests may develop commonly in cats with *D. immitis*, particularly early in infection, due to formation of antigen-antibody complexes in feline serum which block antigen, preventing detection. Heat treatment of serum samples prior to conducting the antigen test destroys the antibody, allowing detection. In one study using serum samples collected from cats with necropsy-confirmed *D. immitis* infection, antigen was detected in 0 or 1 of 6 samples depending on the test used, but was identified in 5/6 samples after heat treatment, including samples collected from cats harboring single worm infections[6]. Data presented at a national meeting showed that antigen testing in clinically normal cats changed from 0.5% positive to 5.9% positive after heat treatment of samples[7]. While these data are important and potentially clinically useful in cats in which a heartworm diagnosis is strongly suspected, routine heat treatment of all serum samples prior to testing is not recommended. The antigen tests were not licensed or approved to be used in this way, and heat treatment destroys antibodies, interfering with results on multianalyte tests.

Monthly administration of macrocyclic lactone anthelmintics, including ivermectin, moxidectin, and selamectin, is recommended to prevent heartworm disease in cats. Prior to approval, efficacy of each of these preventives was confirmed using the standard model accepted by FDA in which cats are infected by inoculation of third-stage larvae, treated 30 days later with the preventive, and then evaluated 6-8 months later for the presence of adult worms[8]. In clinical practice, cats are given preventives monthly, ideally throughout the year. The half-life of ivermectin and selamectin are relatively short compared to that of moxidectin[9]. Topical moxidectin/imidacloprid, when administered monthly, has been shown to lead to a steady-state in which sustained plasma levels of moxidectin are present in treated cats throughout the month[10].

Recent research has shown that steady-state levels of moxidectin protect cats from subsequent, repeated challenge infections with *D. immitis* even when additional doses of preventive are not given[11]. In this study, cats were treated monthly with the label approved dose of moxidectin/imidacloprid for 4 months and then repeatedly challenged with 25 third-stage larvae of *D. immitis* at 1 week, 2 weeks, 3 weeks, and 4 weeks after the last treatment day. Because of the presence of steady-state levels of moxidectin adult worms did not develop in any treated cat, even though no heartworm preventive was given after infection. Moreover, treated cats had no evidence of pulmonary damage on histologic examination, and did not develop detectable antibody or antigen on serologic tests. In contrast, the majority of control cats became infected with heartworm, developed pulmonary lesions, and serology revealed the presence of both antibody to and antigen of *D. immitis*[6,11]. Together, these data suggest the steady-state achieved in cats on moxidectin-based heartworm preventive protects them from both *D. immitis* infection and related pathology regardless of when they are infected during the month, and suggests that antibody tests may be useful for revealing recent infections in cats on some heartworm preventives.

Flea-borne Infections

Fleas (*Ctenocephalides felis*) are the most common disease vector feeding on cats throughout much of the world, and are known or strongly suspected to play a role transmitting a number of feline pathogens, including *Bartonella* spp., *Rickettsia* spp., and *Dipylidium caninum*. Flea control has been shown to prevent transmission of bacterial agents. Experimental studies have documented that administration of imidacloprid to cats in a flea infested environment prevents seroconversion to *Bartonella henselae*[12,13]; flea infestations are also associated with *Rickettsia* spp. infection in cats although these infections are considered largely asymptomatic[14]. Fleas are also the primary vector for *D. caninum*, a tapeworm which has been shown to be much more common in cats than previously thought, particularly in cats with a high prevalence of flea infestation. Because *D. caninum* eggs are heavy and shed intermittently in feces, they are rarely detected on fecal examination even in cats with documented intestinal infections. A 2010 survey documented *D. caninum* in 34.5% of cats in central Oklahoma even though all fecal floats were negative[15]. Diagnosis is often made upon owner report of proglottids in the perianal region or in areas of the home frequented by cats. Preventing flea infestations protects cats from infection with *D. caninum* and other flea-transmitted organisms.

Cytauxzoonosis

Cytauxzoon felis is endemic in lone star tick (*Amblyomma americanum*) populations throughout much of the southeastern United States. The range of this tick is expanding, with recent documented reports of established populations in southern Minnesota and southern Ontario, suggesting lone star ticks have successfully established in most of the eastern two-thirds of the country. Lone star ticks and other tick species, including *Dermacentor variabilis* and *Ixodes scapularis*, readily attach to and feed on cats, transmitting disease agents. However, *Cy. felis* is the most important and highly fatal feline tick-borne pathogens in the United States. Infection with *Cy. felis* results in an acute, severe, and often fatal disease that manifests as high fever and respiratory distress[16]. Cats may present moribund; pale mucous membranes, dehydration, and anemia are often present. If initiated early in infection, combination atovaquone / azithromycin therapy has been associated with improved outcomes in cats with clinical cytauxzoonosis although fatalities remain common[17]. Diagnosis can be complicated by the absence of piroplasms on blood smears very early in the course of disease; PCR testing of whole blood can identify some of these infections.

Preventing infection with *Cy. felis* requires diligent attention to tick control. To prevent cytauxzoonosis and other tick-borne diseases, the Companion Animal Parasite Council recommends routine acaricide use for all cats. Acaricides are particularly important for cats with regular outdoor access and in the spring and summer months when tick activity peaks. Recent research documents that flumentrin/imidacloprid collars prevent transmission of *Cy. felis* to cats in experimental studies[18]. Domestic cats have also been shown to harbor *Cy. felis* infections long-term and repeatedly infect ticks, suggesting cats may serve as a reservoir of infection in some areas[19]. Protecting cats from ticks, particularly in areas where *Cy. felis* is known to cycle in nature, also breaks the transmission cycle by decreasing the number of infected ticks present in a given area.

Conclusion

Fleas, ticks, and mosquitoes are more than just an irritation to cats and their owners. Vector-borne infections threaten feline health. Routine use of heartworm preventives protect cats from infection and pathology associated with D. immitis larval migration; depending on the preventive selected, development of a detectable antibody response may also be prevented. Flea and tick control limits infestations on cats and also prevents infection with arthropod associated bacterial, protozoal, and helminth organisms that can cause severe feline disease or pose a zoonotic threat. The Companion Animal Parasite Council's recommendation to protect "every cat, every month, all year long" defends cats from most common arthropod vectors and the infections they transmit, ultimately safeguarding both feline and human health.

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Update on Select Feline Infectious Diseases

Michael Lappin, DVM, PhD, DACVIM

Introduction

In this four lecture series, Dr. Lappin will provide updates on the diagnosis, treatment, and prevention of select feline infectious disease agents using a case-based approach. Emphasis will be placed on new clinically relevant information generated in the last 12-18 months and will include infectious agents associated with fever (*Bartonella* spp., hemoplasmas, *Rickettsia felis*, *Anaplasma phagocytophilum*), upper respiratory tract disease (FHV-1, FCV, *Mycoplasma*), lower respiratory tract disease (FIP, *Toxoplasma* gondii, *Bordetella*), and diarrhea (*Giardia*, *Cryptosporidium*, and use of probiotics).

Select Feline Blood Borne Agenda Associated with Fever

A number of feline blood borne agents have been grown, amplified or have induced serum antibodies in the serum of cats with fever. The purpose of this section of the lectures is to provide an update on the diagnosis and management of fever associated with *Anaplasma phagocytophilum*, *Bartonella* spp, *Ehrlichia* spp., haemoplasmas, and *Rickettsia* spp. infections of cats. Please also see the AAFP Panel report on feline bartonellosis (www.catvets.com) and the ACVIM *Ehrlichia* Consensus Statement (www.acvim.org) for further information.

Anaplasmosis

Cats have shown to be susceptible to *A. phagocytophilum* infection after experimental inoculation. DNA of *A. phagocytophilum* has been amplified from naturally exposed cats in multiple countries including Sweden, Denmark, Switzerland, Poland, Finland, Ireland, and the United States. Cats living in endemic areas are commonly seropositive but a validated serological assay is not available. As in dogs, *A. phagocytophilum* is transmitted by *Ixodes* spp. and so infections of cats are likely to be most common in these areas.

While the pathogenesis of disease associated with *A. phagocytophilum* in cats is unknown, some cats experimentally inoculated with *A. phagocytophilum* developed anti-nuclear antibodies and increased IFN-gamma mRNA suggesting that an immune pathogenesis of disease may contribute to the clinical findings. Fever, anorexia, and lethargy are the most common clinical abnormalities in naturally infected cats. However, in a recent experimental study in my laboratory, cats infected with *A. phagocytophilum* by exposure to wild caught *Ixodes* spp. ticks remained clinically normal over the 70 day study period in spite of being PCR positive for *A. phagocytophilum* DNA in blood for several weeks. Whether or not this agent is associated with chronic recurrent fever in cats is unknown.

Cats with fever in endemic areas can have blood smears examined cytologically but morulae are less commonly detected than in dogs. Some commercial laboratories offer serologic testing or PCR assays to amplify *A. phagocytophilum* DNA from blood. Approximately 30% of cats with proven clinical infections induced by *A. phagocytophilum* are seronegative when first assessed serologically, but most of the proven cases evaluated to date have ultimately seroconverted. We recently showed that SPF cats exposed to wild caught *I. scapularis* will develop PCR positive test results prior to becoming SNAP®4DX® positive for antibodies. Some mountain lions with *A. phagocytophilum* DNA amplified from blood have been serum antibody negative and so a single negative antibody result in an acutely infected cat does not exclude infection. Therefore, cats with suspected anaplasmosis may need convalescent serum samples to prove infection. Alternately, antibody testing could be combined with PCR testing of whole blood in acute cases.

Several antibiotics have been administered to naturally infected cats, but all cats in 2 studies became clinically normal within 24 to 48 hours after initiation of tetracycline or doxycycline administration and recurrence was not reported. While clinically normal, 2 cats were still PCR positive 17 days and 90 days after treatment (of 21 to 30 days duration) which suggests that treatment with tetracyclines for 21 to 30 days may be inadequate for eliminating the organism from the body. In a recent experimental study, bacteremia as determined by PCR assay was limited over several weeks.

Bartonellosis

A number of *Bartonella* spp. including *B. henselae*, *B. clarridgeiae*, *B. koehlerae*, *B. quintana* and *B. bovis* have been cultured or amplified from client-owned cats with fever. Fever following experimental inoculation with *B. henselae* has been documented in a number of studies including a recent study in our laboratory where the CSU-1 strain of *B. henselae* induced significant fever in three of six cats after exposure to infected *C. felis*. None of the six cats administered imidacloprid-moxidectin in that study became infected or febrile. However, not all strains or *Bartonella* spp. induce fever in all cats; for example in the imidacloprid-moxidectin study, cats inoculated with the same strain intravenously failed to develop fever. Whether fever will occur during *Bartonella* spp. infection is likely a complex interaction that is influenced by both host and organism factors.

As *B. henselae*, *B. clarridgeiae*, *B. koehlerae* are transmitted by fleas, bacteremia and antibody positive rates can be very high. For example, serum antibodies were detected in 93% of cats housed in a North Carolina shelter and *Bartonella* spp. DNA was amplified from the blood of > 50% of cats housed in a Alabama shelter. The majority of these cats were thought to be normal which emphasizes that fever from bartonellosis cannot be documented by test results alone. In one study of pair matched cats with or without fever, serum *Bartonella* antibodies detected by ELISA or Western blot immunoassay were not correlated to the presence of fever. In addition, serum antibody test results are negative in between 3 and 15% of bacteremic cats. Thus, if a cat with fever is to be evaluated for *Bartonella* spp. infection the combination of blood culture or PCR assay on blood, and serologic testing will detect the greatest number of cats that are currently or previously infected. Febrile cats that are seronegative and negative for *Bartonella* spp. in blood by culture or *Bartonella* spp. DNA in blood are unlikely to have the organism as the cause of fever.

If fever from bartonellosis is suspected in a cat, administration of doxycycline or a fluoroquinolone is generally effective. The AAFP Panel Report recommended doxycycline at 10 mg/kg, PO, daily for 7 days as the initial therapeutic trial. If a positive response is achieved, continue treatment for 2 weeks past clinical resolution of disease or for a minimum of 28 days. If a poor response is achieved by day 7 or doxycycline is not tolerated and bartonellosis is still considered a valid differential diagnosis, fluoroquinolones are appropriate second choices. In experimental or field studies, administration of enrofloxacin or orbifloxacin have led to rapid resolution of fever in cats with presumed bartonellosis. Azithromycin is now considered contraindicated because of rapid induction of resistance.

Ehrlichiosis

Ehrlichia-like bodies or morulae have been detected in peripheral lymphocytes or monocytes of naturally exposed cats in a number of countries including the United States, Kenya, France, Brazil, and Thailand. One study of cats in North America amplified DNA consistent with *E. canis* from naturally infected cats. However, other studies of cats in endemic areas (Florida and Arizona) have failed to amplify *Ehrlichia* spp. DNA from the blood of cats. In 2 separate experimental studies, we have failed to amplify monocytotropic *Ehrlichia* spp. from blood or detect seroconversion in cats inoculated SQ with different strains of cultured *E. canis* (Lappin and Breitschwerdt, unpublished observations, 2007; Lappin and Little, unpublished observations, 2010). These results indicate the *E. canis*-like DNA amplified from naturally-infected cats may be from a different *Ehrlichia* spp. more infective to cats, not all *E. canis* stains will infect cats, not all cats are susceptible to infection by *E. canis*, or SQ inoculation is not an effective method for infecting cats with *E. canis*. Some cats with suspected clinical ehrlichiosis have seroreacted to E. canis or N. risticii morulae.

Fever is one of the reported clinical abnormalities detected in cats with suspected ehrlichiosis and so testing may be indicated in these cats. However, a validated serological assay is not currently available and some cats with *E. canis*-like DNA in blood were seronegative. In contrast, most *A phagocytophilum* infected cats have strongly positive antibody test results. Positive serologic test results occur in both healthy and clinically ill cats, and so a diagnosis of clinical ehrlichiosis should not be based on serologic test results alone. *Ehrlichia* spp. PCR and gene sequencing can be used to confirm infection and should be considered the tests of choice at this time.

Clinical improvement after therapy with tetracycline, doxycycline, or imidocarb dipropionate was reported for most cats with suspected mononcytopic ehrlichiosis. However, for some cats a positive response to therapy was a criterion for the diagnosis of ehrlichiosis. The current recommendation of the ACVIM Infectious Disease Study Group is to give doxycycline (10 mg/kg PO q24h for 28 days). For cats with treatment failure or those intolerant of doxycycline, imidocarb diproprionate can be administered (5 mg/kg IM or SQ twice, 14 days apart). Salivation and pain at the injection site are the common adverse effects and imidocarb efficacy is in question for the treatment of canine monocytotropic ehrlichiosis.

Hemoplasmosis

Fever has been detected in some cats with infection by *Mycoplasma haemofelis*, *'Candidatus* Mycoplasma haemominutum', or '*Candidatus* M. turicensis'. In multiple studies of experimentally infected cats, *M. haemofelis* is apparently the most pathogenic species. Dual infection with hemoplasmas may potentiate pathogenesis of disease. In one study, cats with chronic *'Candidatus* Mycoplasma haemominutum' infection had more severe anemia and longer duration of anemia when experimentally infected with *M. haemofelis* when compared to cats infected with *M. haemofelis* alone. In one abstract, we reported an association between *M. haemofelis* and fever in cats without anemia. Clinical signs of disease depend on the degree of anemia, the stage of infection, and the immune status of infected cats. Direct transmission may occur with the hemoplasmas and so the agents should be on the differential list for cats with a history of fighting.

Diagnosis of hemoplasmosis is based on demonstration of the organism on the surface of erythrocytes on examination of a thin blood film or by PCR assay results. Organism numbers fluctuate and so blood film examination can be falsely negative up to 50% of the time. The organism may be difficult to find cytologically, particularly in the chronic phase. Thus, PCR assays are the tests of choice due to sensitivity.

Doxycycline is often administered as a flavored suspension (to avoid esophageal strictures) at 10 mg/kg, PO, every 24 hours for a minimum of 7 - 10 days. In cats intolerant of doxycycline, enrofloxacin given at 5 mg/kg, PO, every 24 hours for 14 days was tolerated by cats and is equally effective or more effective than doxycycline. Administration of marbofloxacin or orbifloxacin gives similar results. Azithromycin was not effective for the treatment

of hemoplasmosis in one study. Pradofloxacin (Veraflox®; Bayer Animal Health) is the only drug proven to eliminate *M. haemofelis* infection in experimentally inoculated cats. Most drug protocols have failed to eliminate infection and so at this time there is no clinical utility to repeat PCR testing. The owners should be warned that recurrences may occur but are unusual.

Feline Rickettsiosis

Rickettsia spp. are obligate intracellular gram negative bacteria that are divided into the spotted fever group and the typhus group. Cats can be infected by *Rickettsia felis* and have been shown to have antibodies against *R. rickettsii*. *Rickettsia felis* DNA has been amplified from *C. felis*, *C. canis,* and *Pulex irritans;* these fleas have a worldwide distribution. *Ctenocephalides felis* is a biological vector for *R. felis*; the organism can be transmitted transovarially and transtadially within the flea. Rickettsial infection is suspected to a cause of fever in cats but this has not been well documented. While we have commonly amplified *R. felis* from *C. felis* (67.4% of flea extracts in one study), we have not amplified the organism from the blood of healthy cats or cats with fever. However, in one study of cats with fever we showed *R. felis* and *R. rickettsii* antibody prevalence rates in cats in the USA to be 5.6% and 6.6%, respectively but neither organism was amplified from blood. These results prove that cats are sometimes exposed to spotted fever group organisms but further data are needed to determine significance of diseases associations. Because clinical illness in cats has not been documented, optimal treatment is unknown. However, based on results in dogs, doxycycline or a fluoroquinolone would be logical choices.

Summary

There are other infectious agents of cats that are either blood borne or associated with bacteremia that should be on the differential list for cats with appropriate clinical findings and geographical locale including feline leukemia virus, feline immunodeficiency virus, *Cytauxzoon felis*, *Hepatozoon* spp., *Francisella tularensis*, and *Yersinia pestis*.

Select Upper Respiratory Infections

Viral Diseases

Herpesvirus 1 (rhinotracheitis; FHV-1) and calicivirus (FCV) are the most common viral causes of sneezing and nasal discharge in the cat. If oral ulcers are present, calicivirus is most likely. If corneal ulcers are present, herpesvirus 1 is most likely. FHV-1 has now also been associated with chronic stomatitis, facial dermatitis, and endogenous uveitis. Viral rhinitis with or without secondary bacterial infection can be recurrent. FHV-1 can be documented by direct fluorescent staining of conjunctival scrapings, virus isolation, or polymerase chain reaction. Since FHV-1 DNA can be detected in conjunctival cells of approximately 25% of healthy cats, the positive predictive value of these tests in diseased cats is low. Quantitative PCR may ultimately prove to correlate to the presence or absence of disease. However, in a recent study from our laboratory, neither quantitative nor qualitative results correlated to treatment responses. Currently used PCR assays also detect vaccine strains of FHV-1. RT-PCR assays can be used to amplify the RNA of FCV. However, these assays have the same problems with predictive value as those to detect DNA of FHV-1.

Feline viral rhinitis with or without secondary bacterial infection can be recurrent. There are no consistently effective primary therapies. I generally only use the following therapies if chronic disease is present. Lysine at 250-500 mg, PO, BID may be helpful in some cats and has been shown to be safe but should be given as a dose, not fed with food. Lysine has been shown to be ineffective for prevention of upper respiratory tract infections in 2 separate shelter studies and so should probably not be used for this purpose.

Administration of human alpha 2b interferon at 50 U, PO, daily may help some cats with suspected chronic calicivirus or FHV-1 infection. This can now be formulated for practitioners by prescription at some pharmacies (www.roadrunnerpharmacy.com/) in the USA. Topical administration of alpha interferon in saline to the eyes of cats with conjunctivitis or the nose may aid in the management of some cats. Lysine and alpha interferon are unlikely to lead to a cure, but hopefully will lessen clinical signs of disease. Intranasal administration of modified live, intranasal FHV-1 and FCV vaccines may lessen disease in some chronically infected cats. If there is a positive response to intranasal vaccination in a cat with chronic disease, I will use this form of immunotherapy up to 3 times per year. The intranasal vaccine has been shown to potentiate cell-mediated immunity to FHV-1 better than parenteral vaccination. Intranasal vaccination with a modified live FHV-1/FCV vaccine (Zoetis) induced cross protection to Bordetella bronchiseptica in a recent study suggesting non-specific immune stimulation.

In kittens with acute life-threatening infection, use of alpha interferon at 10,000 U/kg, SQ, daily for up to 2 weeks can be beneficial. Acyclovir is an anti-herpesvirus drug for use in people but can be toxic to cats and so should not be used. Famciclovir is safer and more effective than acyclovir and is now being used for long-term therapy. One dose that has been used is 1/2 tablet of a generic 250 mg tablet (125 mg), PO, q8-12 hr. Depending on the size of the cat, this is about 30 mg/kg. If a cat with suspected FHV-1 infection is not responding and is on less than 40 mg/kg per dose, three times daily, the dose should be increased before assuming therapeutic failure. The drug is safe at up to 90 mg/kg, PO, q8hrs and so the dose should be increased if the initial response is suboptimal and FHV-1 is still suspected. Topical cidofovir (product for humans) can be used for the treatment of FHV-1

conjunctivitis twice daily and was effective in a controlled research project. The drug was easier to administer (twice daily) than idoxuridine or other anti-FHV-1 ocular therapies and does not cause as much irritation. This drug is available in some compounding pharmacies (www.rxfixer.com). However, it is now known that famciclovir is excreted in high levels in the tears for 4 hours after a dose and so topical treatment with anti-FHV-1 drugs may not be needed if famciclovir is prescribed.

Feline leukemia virus and feline immunodeficiency virus can induce immunosuppression predisposing to bacterial rhinitis. However, there is no universally effective treatment. Interferon alpha as described can be tried. In addition, AZT at 5 mg/kg, PO, twice daily can be tolerated and improved clinical parameters in some cats with FIV. Both FIV and FeLV have been associated with nasal lymphoma and so if upper respiratory tract signs occur in retrovirus positive cats, this neoplasm should be excluded.

Bacterial Diseases

Almost all cats with mucopurulent or purulent nasal discharge have a bacterial component to their disease. Primary bacterial disease is rare but may be associated with *Bordetella bronchiseptica*, *Mycoplasma* spp. and *Chlamydia felis*. In one recent Morris Animal Foundation sponsored study, we showed Mycoplasmas to be more common that FHV-1 and were associated with illness. Recently it was shown that *Bartonella* spp. are not causes of rhinitis in cats. Both *B. bronchiseptica* and *Mycoplasma* spp. can be associated with bronchitis in cats. Chlamydiosis in general, is a mild infection resulting only in conjunctivitis. If primary infections are suspected, doxycycline 10 mg/kg, PO, once daily or topical administration of tetracyclines (conjunctivitis) are usually effective. Cats with acute disease only need to be treated for 7 to 10 days. Most cases of bacterial rhinitis are secondary to other diseases including trauma, neoplasia, inflammation induced by viral infection, foreign bodies, inflammatory polyps, and tooth root abscessation. Thus, if routine antibiotic therapy fails, a diagnostic workup should be performed.

My laboratory completed a study of cats with upper respiratory disease complex that had two major objectives; to identify organisms associated with feline rhinitis in a natural setting and to compare the efficacy and safety of pradofloxacin and amoxicillin for the treatment of suspected bacterial rhinitis in cats residing in a humane society in north-central Colorado. Forty humane society cats with suspected bacterial upper respiratory infections were studied. Nasal discharges were collected for performance of infectious disease diagnostic tests prior to random placement into one of three treatment groups. Cats were administered amoxicillin at 22 mg/kg q12hrs, pradofloxacin at 5 mg/kg q24hrs, or pradofloxacin at 10 mg/kg q24hrs; all drugs were administered by mouth. Cats failing to initially respond to either pradofloxacin protocol were crossed to the amoxicillin protocol and cats that failed amoxicillin were crossed to one of the two pradofloxacin protocols.

The organisms most frequently isolated or amplified by polymerase chain reaction assays (PCR) pre-treatment were feline herpesvirus-1 (75%), *Mycoplasma* species (62.5%), *Bordetella* species (47.5%), *Staphylococcus* species (12.5%) and *Streptococcus* species (10.0%).

The initial treatment was amoxicillin for 15 cats, pradofloxacin at 5 mg/kg for 13 cats, and pradofloxacin at 10 mg/kg for 12 cats. Of the amoxicillin-treated cats, clinical signs resolved in 10 cats (66.7%) and five cats were switched to pradofloxacin (10 mg/kg for one cat and 5 mg/kg for four cats) after which clinical signs resolved in four. Of the pradofloxacin-treated cats (5 mg/kg), clinical signs resolved in 10 cats (76.9%) and three cats were switched to amoxicillin after which clinical signs resolved in all three. Of the pradofloxacin-treated cats (10 mg/kg), clinical signs resolved in 11 cats (91.7%) and one cat was switched to amoxicillin after which clinical signs resolved. Overall, 73.7% of amoxicillin-treated cats resolved and 83.3% of pradofloxacin-treated cats resolved. However, differences in response rates between groups were not statistically different ($P = 0.2919$), potentially because of the relatively small sample size. Drug toxicity was not noted and all cats were reported to tolerate the administration of the drug. We concluded in the manuscript that pradofloxacin can be a safe, efficacious therapy for some cats with suspected bacterial upper respiratory infections (Spindel 2008).

In a separate study, our research group collaborated with researchers in the Department of Small Animal Internal Medicine, Veterinary Teaching Hospital, LMU, in Munich, Germany. In that study, we focused primarily on *Chlamydia felis* and *Mycoplasma* spp. with the purpose of finding a potentially effective therapy that could be used rather than doxycycline.

In this placebo-controlled, double-blind clinical trial, 39 cats with signs of bacterial upper respiratory infections or conjunctivitis were entered. The cats were randomly entered into 1 of 2 treatment groups: treated orally with either 5 mg/kg pradofloxacin q24hr or 5 mg/kg doxycycline q12hr for 42 consecutive days. Changes in health status and clinical scores were evaluated. The presence of *C. felis* and *Mycoplasma* spp. DNA was determined by quantitative polymerase chain reaction (PCR) and nested PCR of conjunctival swabs, respectively.

Prior to treatment, DNA of *C. felis* and *Mycoplasma* spp. was amplified from samples from 23 and 20 cats, respectively. Clinical signs improved markedly within the first week for cats of both groups. Complete elimination of *Mycoplasma* spp. DNA was achieved in both groups. During treatment with either drug, *C. felis* DNA copy number declined quickly, all cats administered doxycycline became *C. felis* DNA negative and 4 cats treated with pradofloxacin remained *C. felis* DNA positive.

In this study, it was concluded that both pradofloxacin and doxycycline have good efficacy against *C. felis* and *Mycoplasma* spp., resulting in a marked improvement of clinical signs. The study showed evidence that the

pradofloxacin protocol studied may eliminate *Mycoplasma* spp. infections. However, since *C. felis* DNA was still amplified from samples from some cats after treatment with pradofloxacin, infection might not always be eliminated using this protocol.

Since bacterial rhinitis leads to chondritis and osteomyelitis, antibiotic therapy should be continued for weeks in cats with chronic disease. Drugs with an anaerobic spectrum that also penetrate bone and cartilage well are often effective. Clindamycin or amoxicillin-clavulanate are frequently used. Amoxicillin-clavulanate has the advantage of killing most *Bordetella* isoloates. Clindamycin has the advantage of effective against *Mycoplasma* spp. and the drug can be used once daily for routine bacterial infections in cats. Azithromycin (10 mg/kg, PO, q 24-72 hr) or fluoroquinolones can be used for cats with chronic disease. For cats that are difficult to treat, cephalosporin injections can be considered. However, this drug class is ineffective for *Mycoplasma* spp. and most *Bordetella* isoloates and so should not be a first line therapy unless the cat is impossible to treat orally.

Bronchial Diseases

Bronchial obstruction can develop due to inflammatory infiltrates (eosinophils, neutrophils, or macrophages) or hypertrophy of bronchial tissues. The result is obstructive airway disease. Obstructive airway disease is characterized by increased airway resistance with resultant expiratory dyspnea. There is no clear terminology for the bronchial obstructive diseases in the cat. Bronchitis is inflammation of the airways. Asthma generally implies a reversible bronchoconstriction related to hypertrophy of smooth muscle in airways, hypertrophy of mucous glands, and infiltrates of eosinophils. Asthma in cats is primarily due to Type I hypersensitivity reactions; the etiology is generally undetermined. Cats with bronchitis not due to asthma generally have infiltrates of neutrophils or macrophages as well as hypertrophy of mucous glands, hyperplasia of goblet cells, excessive mucous, and ultimately fibrosis secondary to chronic inflammation. Calicivirus is the most common viral disease of cats leading to acute bronchial disease. *Bordetella bronchiseptica*, *Mycoplasma* spp., and possibly, *Chlamydia felis* are the bacteria capable of inducing bronchial disease. If disease occurs due to *Chlamydia* occurs, it is mild. Heartworm associated respiratory disease can result in bronchitis. Bronchitis may also result from *Aelurostrongylus abstrusus*, *Eucoleus aerophila*, or *Toxocara cati* infestation.

Cats with bronchitis can be of any age; chronic bronchitis usually develops in middle-aged to older cats. There is no obvious breed or gender predilection. Primary presenting complaints include cough, dyspnea, and wheezing. Some cats will have a terminal retch following cough. Physical examination abnormalities include cough, dyspnea, and crackles, and wheezes in the pulmonary tissues. Increased bronchovesicular sounds may be the only abnormality noted on auscultation. If dyspnea occurs, it commonly has a pronounced expiratory component. Open mouth breathing or panting commonly occur during periods of stress.

CBC is generally normal with the exception of eosinophilia in some cats with allergic bronchitis. Thoracic radiographs reveal primarily a bronchial pattern. Overinflation and air trapping is seen in some dyspneic cats with chronic disease. Air bronchograms are commonly seen in cats with bronchitis due to bacterial infection. Cytology of transtracheal wash samples generally reveal increased mucous with the primary cell types being eosinophils, neutrophils, or macrophages. Bacteria may or may not be visualized. Aerobic and *Mycoplasma* culture as well as antibiotic susceptibility testing should be performed regardless of the type of inflammatory cell and whether or not bacteria are seen.

Cats with eosinophilic TTW cytology should be assessed for dirofilariasis using adult antigen detection tests and antibody tests if from endemic areas. Fecal flotation (*Toxocara*), Baermann examination of feces (*Aelurostrongylus*), and fecal sedimentation (*Paragonimus*) should be performed in cats with eosinophilic TTW cytology particularly if indoor-outdoor and from parasite endemic areas.

Non-dyspneic cats are generally treated with broad spectrum antibiotics while awaiting diagnostic test results. I generally use doxycycline initially due to efficacy for the primary bacterial respiratory pathogens and anti-inflammatory effects. I generally do not use oral theophylline (phosphodiesterase inhibitor) or terbutaline (beta 2 agonist) unless necessary. Feline terbutaline pharmacokinetics varies from people; serum levels are extremely high in cats. This drug should be avoided in cats with cardiac disease or disease resulting in hypertension like renal failure and hyperthyroidism. Phosphodiesterase inhibitors often cause anorexia and behavior change in cats. Inhalational albuteral given via inhaler may work more quickly and oral or injectable bronchodilators in cats with dyspnea. Cats with neutrophilic TTW cytologic results and positive bacterial cultures are treated with appropriate antibiotics for 4- 8 weeks depending on radiographic severity of disease and response to therapy. Some cats with acute bronchitis will have the disease resolve and not recur. Most cats with chronic bronchitis will require life-long anti-inflammatory therapy and perhaps, bronchodilator therapy.

If an eosinophilic component is present on TTW cytology, glucocorticoids will likely be required. Oral, repositol, or inhalational glucocorticoids can be administered. I generally attempt oral prednisolone therapy initially. Administration of methylprednisolone acetate every 2-3 weeks adequately controls some cats with asthma or allergic bronchitis. Titrate the dosage of glucocorticoid to the lowest dose required to control clinical signs of disease. Use of inhalational steroids can be very effective and if fluticasone are used, minimal systemic side-effects occur. In dyspneic cats, delivery of glucocorticoids by inhalation may work more quickly than those delivered orally or by injection. Chambers for the delivery of inhalational drugs can be purchased at www.aerokat.com. Use of omega 3

fatty acid supplementation may lessen requirements for glucocorticoids. Since allergic bronchitis can be related to dietary hypersensitivity, a hypoallergenic diet trial should be tried in cats with recurrent or persistent disease. Cats that become refractory to prednisolone will often respond to methylprednisolone, dexamethasone, or triamcinolone. Some cats with allergic bronchitis asthma will have seasonal exacerbations. Removal of potential irritants in the environment including clay litter, cigarette smoke, hairspray, and carpet cleaners should be considered in all cases of bronchial inflammation.

Parasitic Diseases

Parasites leading to cough or dyspnea in cats include *Toxocara cati*, *Toxoplasma gondii*, *Aelurostrongylus abstrusus*, *Eucoleus aerophila*, and *Paragonimus kellicotti*. *Aelurostrongylus abstrusus* has an indirect life cycle with rodents as intermediate hosts; the organism occurs in Colorado. It is difficult to prove respiratory cough due to roundworms; demonstration eggs in the feces of coughing kittens supports a presumptive diagnosis. There is no effective primary treatment for the migrating phase of the parasites.

Diagnosis of the primary respiratory parasites is based on demonstration of the organism in transtracheal aspiration samples, bronchoalveolar lavage samples, or in feces. Most of the agents are intermittent shedders and so fecal examination techniques may have to be repeated multiple times. The Baermann funnel technique will increase the odds of finding larva.

Fecal sedimentation techniques are superior to flotation techniques for demonstration of *Paragonimus kellicotti*. Serologic tests are available to help support a diagnosis of toxoplasmosis. Lungworms generally respond to ivermectin at 0.4 mg/kg, SQ, once. Since eosinophilic pneumonitis occurs with these agents, prednisolone is generally administered at 1.0-2.0 mg/kg, daily, PO concurrently with ivermectin. Fenbendazole is an alternate therapy; 25 mg/kg, PO, daily for 5 days, repeated again in 5 days is often used. Praziquantel can be used for the treatment of *Paragonimus kellicotti*. Clindamycin administered at 10-12 mg/kg, BID, PO for 4 weeks can be effective for the treatment of toxoplasmosis.

Pneumonia

Pneumonia is inflammation of the lung parenchyma; bronchopneumonia is pneumonia that has begun in the terminal bronchioles. Bacterial pneumonia is rarely a primary disease. Occasionally, *Bordetella bronchiseptica* or *Mycoplasma* spp. will induce pneumonia directly due to their adverse effects on mucociliary apparatus function. *Yersinia pestis* can cause pneumonia in infected cats and is directly zoonotic. Febrile cats with cough in the Southwestern states should be handled carefully. *Toxoplasma gondii* causes interstitial pneumonia.

Most cases of bacterial bronchopneumonia are secondary to immunosuppressive diseases or previous inflammatory insults including viral infection, aspiration, and irritant inhalation. Owners should be carefully questioned concerning potential exposure to other animals and clinical signs associated with immunosuppressive diseases or aspiration.

Most cats with bacterial pneumonia will be clinically ill. Common complaints include depression, anorexia, dyspnea, productive, moist cough with a terminal retch, and exercise intolerance. Some cats with bacterial pneumonia will present only with cough. Physical examination findings commonly include fever, crackles and wheezes, and muffled lung sounds in cases with consolidated or abscessed lung lobes. Many cats will have increased tracheal sounds, a tracheal cough, and pharyngeal inflammation due to transport of inflammatory cells up the mucociliary apparatus to the mouth.

The initial diagnostic plan for cats with suspected bacterial pneumonia should include a CBC, biochemical panel, urinalysis, thoracic radiographs, FeLV antigen test, and FIV antibody test. Neutrophilic leukocytosis with or without a left-shift is common but not present in all cases. Monocytosis is common in chronic pneumonia. Assessment of the biochemical panel and urinalysis will often detect underlying immunosuppressive diseases. Thoracic radiographs usually reveal a mixed alveolar, bronchial, and interstitial pattern. Aspiration pneumonia generally has radiographic lesions that are most pronounced in the right middle lung lobe. If interstitial pneumonia is noted, *T. gondii* IgM and IgG serology should be considered, particularly if the cat has a history of hunting or eating raw meat.

Esophageal diseases are commonly evident on evaluation of thoracic radiographs. Laryngeal paralysis commonly predisposes to aspiration pneumonia and is characterized by inspiratory stridor; this disease is rare in cats. Further diagnostic testing for cats with inspiratory stridor includes laryngeal function assessment by visualization under sedation. Intravenous administration of low-doses of ultra-short acting thiobarbiturates will enable examination of laryngeal function. Following documentation of pulmonary disease on thoracic radiographs, a TTW for cytology, aerobic bacterial and *Mycoplasma* culture, and antibiotic susceptibility testing should be performed. PCR assay for *T. gondii* DNA can be performed on the washings or BAL as well. Transthoracic aspiration of consolidated lung lobes should be considered for anaerobic culture and antibiotic susceptibility testing. Bronchoscopy for bronchoalveolar lavage and biopsy is superior to TTW and is sometimes required.

The combination of increased numbers of neutrophils and macrophages on cytologic assessment of secretions obtained by TTW and positive bacterial culture confirms the diagnosis of bacterial pneumonia. Bacterial culture is commonly positive in healthy cats and so the presence of bacteria without inflammatory cells does not

document pneumonia. Treatment consists of airway hydration, antibiotic therapy, physical therapy, expectorants, and bronchodilators.

Following correction of underlying conditions, the most important treatment of bacterial pneumonia is hydration. The mucociliary apparatus functions best in a well-hydrated animal and is essential for the clearance of infection. Affected cats should receive parenteral fluid therapy until able to maintain hydration orally. Airway hydration can be accentuated by nebulization or by placing the animal in a closed bathroom while running hot water through the shower.

Antibiotic therapy should be based on culture and antibiotic susceptibility testing. Septic cats should be treated initially with parenteral antibiotics. Oral antibiotics should be administered for 6-8 weeks or for at least 2 weeks following resolution of radiographic evidence of disease.

Antibiotics can be administered by nebulization. Aminoglycosides are commonly used. Renal toxicity is not a concern since serum levels of aminoglycosides remain low following nebulization. If nebulization is used, 25 mg of gentamycin is generally mixed in 3-4 ml saline. Saline has some mucolytic effects and will aid mucociliary apparatus function. Nebulization is generally administered 3-4 times daily. Mucolytic agents such as acetylcysteine are generally not used during nebulization of cats due to severe bronchoconstriction. If acetylcysteine is used, a topical beta-2 agonist like isoetharine should also be nebulized. Nebulization can be administered through most oxygen cages. Electric air pumps and hand-held nebulizers that give a particle size of 5 microns can be rented from many human home respiratory care companies. There are also veterinary products now available. Nebulization can be performed by attaching the nebulizer to a closed box with holes placed on the opposite side to allow escape of CO_2.

Oxygen therapy is indicated due to acute dyspnea in some cats with bronchopneumonia. If an oxygen cage is not available, oxygen can be administered via nasal tube. Positive end expiratory pressure aids in the treatment of some pulmonary conditions but is not practical in most clinical settings.

Passive physical therapy is indicated for the treatment of bacterial pneumonia. Gentle percussion using a cupped hand is the technique most commonly used but is not tolerated by many cats. Playing with the cat to encourage mild exercise may be beneficial.

Bronchodilator treatment may be of benefit in the treatment of bacterial pneumonia. I generally use this therapy if above treatments are not rapidly resolving the disease. Phosphodiesterase inhibitors improve mucociliary apparatus function and may strengthen muscles of respiration. Bronchodilators can be indirect anti-tussives.

Cats with consolidated lung lobes should be receive antibiotics that penetrate tissue well and have a spectrum against anaerobes. Clindamycin hydrochloride or azithromycin are appropriate choices and also have a *T. gondii* spectrum. I generally combine enrofloxacin with clindamycin for the treatment of consolidated lung lobes. Thoracic radiographs should be reassessed in all cases within 3-4 days post-treatment and then every 2-3 weeks until radiographic evidence of disease has resolved. If the consolidated lung lobes that are not starting to inflate within 7-10 days post-treatment, surgical exploration should be considered, particularly if systemic signs like fever persist.

Management of Infectious GI Disease Agents

There are multiple drugs used in the treatment of gastrointestinal parasitic infections. For all kittens, the strategic deworming recommendations for the control of hookworm and roundworm infections from the Centers for Disease Control and the American Association of Veterinary Parasitologists should be followed by veterinary practitioners. ***http://www.cdc.gov/ncidod/dpd/parasites/ascaris/prevention.htm***

Kittens should be administered an anthelmintic at 3, 5, 7, and 9 weeks of age and then periodically monitored or treated. If the kitten is not presented to the clinic until 6-8 weeks of age, administer the anthelmintic at least 2-3 times, 2-3 weeks apart. Pyrantel pamoate and fenbendazole are usually effective drugs for use in strategic deworming programs and for the treatment of nematodes causing gastrointestinal tract disease. Albendazole is more likely to cause hematologic side-effects than fenbendazole and so should not be used in cats. Even if anthelmintics for hookworms and roundworms are administered, a fecal flotation should be performed to evaluate for other parasites.

Monthly *D. immitis* preventatives can help control or eliminate some nematode infections as well as prevent heartworm infection. Ivemectin at heartworm preventative doses is effective for control of hookworms but not roundworms. Thus, selamectin, milbemycin, or moxidectin should be used in regions where roundworm infections are common. Selamectin and imidocarb-moxidectin have the advantage of controlling fleas as well and so may lessen the potential for *Bartonella* spp., *Rickettsia felis*, and *Haemobartonella* (*Mycoplasma*) spp. infections. In a recent study in our laboratory, administration of imidacloprid-moxidectin monthly blocked flea transmission of *B. henselae* amongst cats. *Dipylidium* and *T. taeniaformis* infestations usually are eliminated by praziquantel or espiprantel; fenbendazole is effective for *Taenia taeniaformis*. Since *Echinococcus multilocularis* can be a significant zoonosis transmitted to cats by carnivorism, hunting cats in endemic areas should be treated up to monthly. Administration of a pyrantel/praziquantel combination may be effective in these cats since praziquantel is approved for the treatment of *Echinococcus* and roundworms are also transmitted by carnivorism.

Withholding food for 24 to 48 hours is indicated in cats with acute vomiting or diarrhea. Highly digestible, bland diets are used most frequently if vomiting and small bowel diarrhea are the primary manifestations of disease. High fiber diets are generally indicated if large bowel diarrhea is occurring. Diarrhea associated with *Giardia* spp.

generally resolves during or after administration of metronidazole. In a recent study, cyst shedding resolved in 26 cats after the administration of metronidazole benzoate at 25 mg/kg, PO, q12hr for 7 days. Metronidazole also helps correct the anaerobic bacterial overgrowth that commonly accompanies giardiasis. If inflammatory changes exist, metronidazole may also be beneficial due to inhibition of lymphocyte function. Central nervous system toxicity occasionally occurs with this drug; it is unlikely if no more than 50 mg/kg, PO, total daily dose is given. Fenbendazole has not been studied extensively for treatment of giardiasis in cats. In one experiment study of cats coinfected with *Giardia* spp. and *Cryptosporidium* spp., four of eight cats treated with fenbendazole at 50 mg/kg, PO, daily for 5 days stopped shedding *Giardia* cysts. The combination product of febantel, pyrantel, and praziquantel has been shown to have anti-*Giardia* activity in dogs. When given at the febantel dose of approximately 56 mg/kg, PO, daily for 5 days, *Giardia* cyst shedding was eliminated in some cats. Metronidazole and fenbendazole can be given concurrently in resistant cases. Albendazole has been evaluated for treatment of giardiasis in a limited number of dogs, but has been associated with neutropenia. Furazolidone (4 mg/kg, PO, q12hr, for 7 days) and paromomycin (appropriate dosing interval for cats is unknown) are other drugs with anti-*Giardia* effects but have not been evaluated extensively in cats. There are no known advantages of using tinidazole or ronidazole compared to metronidazole in cats and ronidazole has a greater risk of CNS toxicity. Previously, the feline *Giardia* spp. vaccine could be attempted as an immunotherapy but the vaccine has been discontinued. In some cats with *Giardia* and diarrhea, administration of a probiotics or addition of fiber to the food and retreating can result in resolution of diarrhea. The primary goal of *Giardia* therapy is to resolve diarrhea. It is unlikely the infection can be eliminated in most cats and reinfection is common. If treatment is to be monitored, a fecal flotation (not antigen assay) could be performed within 14 days of ending therapy.

Multiple drugs have been evaluated for the treatment of cats with *Tritrichomonas foetus* (*T. blagburni*) infections; until recently no drug eliminated infection and diarrhea rarely resolves during the treatment period. Recently ronidazole at 30 mg/kg, PO, q24hr, for 14 days eliminated clinical signs of disease and trophozoites from cats infected with one strain of the organism. Ronidazole is more neurotoxic than metronidazole and so should be used carefully. In another one small study, administration of metronidazole and enrofloxacin lessened diarrhea in kittens but it is unknown if the organisms infecting those cats was *T. foetus*. It is possible that some cats with *T. foetus* have other enteric coinfections and so antihelmintics or drugs with activity against *Giardia* spp., *Cryptosporidium* spp., and enteric bacteria like *Campylobacter* spp. are often prescribed. Paromomycin should be avoided cats with bloody stools because of the potential for being absorbed and inducing renal disease or deafness. In one study, 23 of 26 cats with diarrhea and *T. foetus* infection had complete resolution of diarrhea a median of 9 months after initial diagnosis.

Cryptosporidium spp. associated diarrhea sometimes resolves after administration of tylosin (10-15 mg/kg, PO, BID for at least 14 days) or azithromycin (10 mg/kg, PO, daily for at least 14 days). If the cat is responding to therapy, continue treatment for 1 week past clinical resolution. Some cats may require several weeks of treatment. Nitazoxanide at 10 mg/kg, PO, twice daily for at least 14 days has been effective for controlling *Cryptosporidium* spp. diarrhea, but is a gastric irritant that commonly induces vomiting.

The *Toxoplasma gondii* oocyst shedding period can be shortened by administration of clindamycin, sulfadimethoxine, or ponazuril. *Cystoisospora* spp. generally responds to the administration of sulfadimethoxine or other sulfa-containing drugs. Clindamycin, trimethoprim-sulfa, or ponazuril are also options. Ponazuril and toltrazuril are very safe for kittens and ponazuril can be administered once (50 mg/kg, PO) or twice, two days consecutively (20 mg/kg, PO).

Since many of the gastrointestinal parasites that infect cats are transmitted by carnivorism, cats should not be allowed to hunt or be fed raw meats. Additionally, infection of cats by many feline parasites results from ingestion of contaminated water. Clinical disease in some parasitized cats can be lessened by eliminating stress and providing a quality diet and clean environment.

Clostridium perfringens and bacterial overgrowth generally respond to treatment with tylosin, metronidazole, ampicillin, amoxicillin, or tetracyclines. The drug of choice for campylobacteriosis is erythromycin; however, oral administration of quinolones is often less likely to potentiate vomiting. Salmonellosis should only be treated parenterally due to rapid resistance that occurs following oral administration of antibiotics. Appropriate antibiotics for the empirical treatment of salmonellosis while awaiting susceptibility testing results include chloramphenicol, trimethoprim-sulfa, amoxicillin; quinolones are also effective. *Helicobacter* spp. infections are usually treated with the combination of metronidazole and tetracycline or amoxicillin and metronidazole in dogs. Clarithromycin or azithromycin may be logical choices in cats since the species is often difficult to treat with multiple drugs. Whether to concurrently administer an antacid like famotidine is controversial but seems to lessen vomiting in some cats.

Probiotics can be beneficial in some cases with diarrhea. In a recent double blinded study, all cats in one room of a shelter were fed FortiFlora® and another similar room was fed a placebo for 1 month. After a one week wash out period, the treatment rooms were switched and the study continued for another 1 month. A standardized diet was fed for the duration of the study and a fecal score was determined for every cat housed in the rooms every day. The percentages of cats with diarrhea of >2 days duration over the course of the study were calculated and was shown to be 7.7% for the probiotic group and 20.7% for the placebo group ($p=0.0297$) which was significantly different.

Cats with apparent bacteremia due to enteric bacteria should be treated with parenteral antibiotics with a spectrum against anaerobic and gram negative organisms. The combination of enrofloxacin with a penicillin or first generation cephalosporin is generally effective. Second generation cephalosporins or imipenem are also appropriate choices.

Cats that have hepatic infections and signs of bacteremia should be treated with antibiotics that kill gram positive, gram negative and anaerobic bacteria as discussed before. Non septic hepatic infections generally respond to amoxicillin, amoxicillin-clavulanate, first-generation cephalosporins, or chloramphenicol. Decreasing numbers of enteric flora by oral administration of penicillins, metronidazole, or neomycin can lessen the clinical signs of hepatic encephalopathy.

Panleukopenia virus, feline leukemia virus, feline immunodeficiency virus, and coronaviruses are the most common viral causes of gastrointestinal tract disease in cats. Viral diseases are managed by supportive treatment. Make sure to maintain hydration, correct hypoglycemia, and maintain normal potassium concentrations. Use of jugular catheters is superior to leg veins since blood samples can be drawn and CVP can be measured. Based on results in dogs with parvovirus infection, administration of plasma or serum (1 ml/kg) from your hyperimmune blood donor cat may lessen morbidity in cats with panleukopenia due to passive transfer of immunity. This is effective because parvoviruses induce a viremic state; virus particles are complexed by the antibodies transferred passively. Adminstration of interferon alpha at 10,000 U/kg, SQ, once daily may have anti-viral effects. Antibiotics effective against gram negative and anaerobic bacteria are commonly indicated. Vaccines are available for the prevention of parvovirus, coronaviruses, and feline leukemia virus infection.

Histoplasma capsulatum infection is the most common fungal infection of the gastrointestinal tract of cats in the United States. Treatment with itraconazole can be effective.

Infection of people by feline enteric agents is usually from contact with feces in the environment, by ingestion of contaminated food or water, or by ingestion of undercooked meat (*T. gondii*). Contact with infected cats is an unlikely way for humans to acquire infection. The following guidelines may lessen the risk of transfer of feline enteric zoonotic agents to people.

- Perform a thorough physical examination and zoonoses risk assessment on all new cats.
- Perform a physical examination and fecal examination at least once or twice yearly.
- Take all cats with vomiting or diarrhea to a veterinarian for evaluation.
- Fecal material produced in the home environment should be removed daily, preferably by someone other than an immunocompromised individualUse litterbox liners and periodically lean the litterbox with scalding water and detergent.
- Do not allow cats to drink from the toilet.
- Follow the CDC strategic deworming guidelines.
- Wear gloves when gardening and wash hands thoroughly when finished.
- Filter or boil water from sources in the environment.
- Wash your hands after handling cats.
- Maintain cats within the home environment to lessen exposure to other animals and their feces.
- Feed cats only commercially processed food.
- Do not share food utensils with cats.
- Avoid being licked by cats.
- Control potential transport hosts like flies, rodents, and cockroaches.
- Cook meat for human consumption to 80 C for 15 minutes minimum (medium-well).
- Wear gloves when handling meat and wash hands thoroughly with soap and water when finished.

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NOTES:

Feline Gastroenterology and Endocrinology

2014 CONFERENCE

September 18 - 21, 2014 ▪ The JW Marriott ▪ Indianapolis, IN

Conference Day One

FRIDAY, SEPTEMBER 19, 2014

COMBINED TRACK
White River E & F

BREAKFAST in White River D
Included in your registration — **7:00 – 7:45 am**

New Data on Chronic Small Bowel Disease in Cats: Don't Accept Vomiting as "Normal" — **7:45 – 10:30 am**
Dr. Gary Norsworthy
Sponsored by PURINA

NETWORKING REFRESHMENT BREAK in Exhibit Hall
Included in your registration — **10:30 – 11:15 am**

Diagnosis & Management of Pancreatitis — **11:15 – 12:05 pm**
Dr. Kenneth Simpson

LUNCH in Exhibit Hall
Included in your registration — **12:05 – 1:30 pm**
Sponsored by Hill's
12:15 – 1:15 pm Lunch & Learn: Feline Urethral Obstruction – White River G
Separate registration required

Winning the Fight Against Hepatic Lipidosis — **1:30 – 2:20 pm**
Dr. Sharon Center
Sponsored by Nutramax Laboratories Veterinary Sciences, Inc.

AAFP President Remarks, Volunteer Recognition, and Sponsor Acknowledgements — **2:20 – 2:25 pm**
Dr. Marcus Brown

Are You Comfortable with Feline Constipation? — **2:25 – 3:15 pm**
Dr. Craig Webb
Sponsored by Royal Canin

NETWORKING REFRESHMENT BREAK in Exhibit Hall — **3:15 – 3:45 pm**
Included in your registration
Sponsored by wedgewood pharmacy

TRACK A
White River E

Cholangiohepatitis: Emerging Evidence for Disease Pathomechanisms — **3:45 – 4:35 pm**
Dr. Sharon Center
Sponsored by Nutramax Laboratories Veterinary Sciences, Inc.

Five Unique Feline Hepatic Syndromes — **4:40 – 5:30 pm**
Dr. Sharon Center

TRACK B
White River F

Is There a Direct Link Between IBD, Cholangitis, & Pancreatitis in Cats? — **3:45 – 4:35 pm**
Dr. Kenneth Simpson

Diagnosis & Management of Persistent Vomiting — **4:40 – 5:30 pm**
Dr. Kenneth Simpson

EXHIBITORS' HAPPY HOUR RECEPTION in Exhibit Hall — **5:30 – 6:30 pm**
Included in your registration
Sponsored by Bayer

New Data on Chronic Small Bowel Disease in Cats: Don't Accept Vomiting as "Normal"

Gary Norsworthy, DVM, DABVP (Feline)

A. Overview
    a. Chronic vomiting is very common in cats, but we (veterinarians and owners) have either made excuses for it or accept it as normal using the following excuses:
        i. My cat eats too fast.
        ii. My cat has a nervous stomach.
        iii. It is just hairballs and they are normal.
        iv. "He's just a puker," i.e., it is normal for this cat.
    b. Most chronic vomiting and chronic diarrhea in cats originate in the small bowel, not in the stomach.
    c. Small bowel disease is segmental in over ¾ of cats. Areas of normal and abnormal alternate. It is important to examine the entire bowel to make proper biopsy site choices.
    d. Endoscopic biopsies are a very poor way to diagnose most cases because:
        i. Location: You can access the stomach + 1-2 cm of duodenum OR colon (if you are really proficient with an endoscope. The ileum is very difficult to access, and most cases of lymphoma begin in the ileum.
            1. Small bowel disease may be in any part of the small bowel, and it is usually segmental. In many cats only the jejunum is involved, and it is inaccessible by an endoscope.
        ii. Sample Size: about 1 mm piece of tissue; not full thickness. The pathologist is hindered by getting to only read small fragments of the mucosa.
    e. Chronic small bowel disease is manifested as chronic vomiting, chronic diarrhea, or both.
B. What we are not talking about
    a. Vomiting of whole dry food is not due to eating too fast. Cats typically swallow 80% of the dry food they consume.
    b. Cats that eat grass vomit because grass is irritating to the stomach. They eat it because they like it.
C. Typical history
    a. "My cat has vomited all of its life. The vomiting was occasional for months to years. Then it became 1-2 times per month. Now it is daily. Otherwise, he/she feels good and eats good."
        i. Think small bowel, not stomach.
    b. "My cat has vomited hairballs all of its life. The vomiting was occasional for months to years. Then it became 1-2 times per month. Now it is several times per week. Otherwise, he/she feels good and eats good."
    c. Alternative: "has been losing weight" "losing weight but has a tremendous appetite."
    d. Differential list
        i. Inflammatory bowel disease6
        ii. Neoplasia without mass formation
            1. Small cell lymphoma
            2. Lymphoblastic lymphoma
            3. Mast cell tumor
            4. Note: Mast cell tumor, adenocarcinoma, and lymphoblastic lymphoma can cause chronic small bowel signs, but a mass forms resulting in rapid weight loss and vomiting (partial to full obstruction). The mass is found by palpation, ultrasound, or surgery.
        iii. Food intolerance (less than 10%)
D. Diagnostics
    a. When the clinical picture is presented to me I recommend:
        i. Small intestinal ultrasound looking for thickening of the small bowel wall. Use of a linear probe is highly recommended to get needed detail.
        ii. If the walls are thick (0.28 cm or more), I recommend a full-thickness biopsy of the small bowel via laparotomy.
        iii. Possible exception: food trial first, but 6+ weeks are lost so you must consider the consequences of that. In some cats that is not a problem. In cats losing weight rapidly, that can be disastrous.
    b. Objections to this approach
        i. Cannot do ultrasound.
        ii. What an ultrasound study does:

1. Allow you to document small bowel thickening.
2. Allows the owner to see it.
3. Makes a laparotomy much easier to sell.
4. The laparotomy and biopsies get a diagnosis leading to specific treatment.
5. Pays for the ultrasound machine.

c. Why palpation fails to get a diagnosis
   i. Mild to moderate small bowel thickening is not palpable.
   ii. Heavy cats are hard to palpate.
   iii. Segmental disease occurs.

E. Small bowel biopsy technique
   a. You need a full-thickness sample.
   b. Cut out a wedge beginning on the antemesenteric side of the bowel.
   c. Alternate: 6 mm biopsy punch (***Much better sample than a wedge made with a scalpel.)
   d. Trim away excess mucosa so you suture muscle and serosa to muscle and serosa.
   e. Use simple interrupted through-and-through sutures of 4-0 PDS placed 1 mm apart.
   f. When the bowel is closed, test with a saline injection.
   g. Consider biopsy of the mesenteric lymph node if it is enlarged, but not a part of my current protocol. It is often misleading as LN may be inflammatory with lymphoma in small bowel.

F. Triad disease (concurrent inflammation in the small bowel, liver, and pancreas) is reported to be common in the cat. During this laparotomy, get samples of the pancreas and liver.
   a. Pancreas: Examine both limbs of the pancreas. Biopsy an area that appears grossly abnormal. If there are no abnormal areas (likely), use a 4 mm biopsy punch to take a sample on the edge of the organ to avoid the centrally located exocrine duct; bleeding unlikely.
      i. If bleeding occurs, use a clotting powder (Bleed-X Vet Clotting Powder, DVM Solutions)
      ii. Because this is a very small sample, put it in a separate tube so it does not get lost during tissue processing.
   b. Liver: Cut a wedge of liver with scissors then close with (usually) one 4-0 PDS suture. Choose an area that appears grossly abnormal, but most cats with liver disease have diffuse disease so the location is usually chosen based on accessibility. Do not crush this tissue during the biopsy process or when handling the tissue.

G. Miscellaneous observations and comments
   a. On ultrasound, the wall thickness is not half the diameter of the bowel loop due to the luminal contents.
      i. Measure from the outside of the wall (serosa) to the near edge of the lumen.
   b. Enlargement of the mesenteric lymph node is not diagnostic or prognostic.
      i. A biopsy of the LN will not substitute for a full-thickness biopsy of the small bowel. Sometimes the LN will be inflammatory and the bowel wall neoplastic.
      ii. Biopsy of the LN rarely adds to the diagnosis; it is an optional procedure.
      iii. It is a friable organ; close it with mattress sutures.
      iv. Do not cut the mesenteric artery. Take a superficial biopsy.
   c. Mesenteric LN aspiration
      i. Enlarged mesenteric LNs are often found on ultrasound and often palpable.
      ii. They may be aspirated with or without ultrasound guidance in lieu of surgical biopsy of the small bowel.
      iii. Mesenteric lymph nodes were aspirated in 8 cats during surgery to determine correlation with LN cytology and histopath of the small bowel.
      iv. Expected finding: poor correlation with T-cell (small cell) lymphoma.
         1. 85% of the cats with lymphoma in the study had small cell lymphoma.
      v. Total correlation: 1/8 correct. The two cats with lymphoma did not have lymphoma in the lymph nodes.
      vi. Unexpected findings
         1. 6/8 had either very poor appetite or anorexia for 7-14 days post-op.
            a. Cause not determined but compromise of the mesenteric artery is suspected. Will result in compromised blood flow to the small bowel.
         2. Concerning bleeding in 2/8 cats.
   d. Case Schedule
      i. Day 1: Surgery.
      ii. Day 2: Remove IV and offer food.
      iii. Day 3: Discharge if doing well.
      iv. Day 5-7: Get HP report and call owner. Send the appropriate handout regarding the disease and the treatment protocol.

v. Day 10: Remove sutures; begin treatment.
vi. Modifications for fractious cats
1. Induce with chamber (Wild Child, Veterinary Concepts).
a. Carrier Cover; Leah Palombo, catty1@earthlink.net Cell: 210-288-8380; Office: 210-545-4854
2. Place IV catheter and begin fluids at 100 ml/hr.
3. Give IV fluids through the end of surgery.
4. Before extubation, remove IV catheter and give 150 ml fluids SC.
5. Offer food the next morning.
6. If doing well, discharge that afternoon.

e. Small masses may accompany thickened loops and be very hard to find with palpation or ultrasound. If found, resect them.
f. Take more than one biopsy as the disease is segmental. Often, some samples will be normal and some abnormal. Frequently, there will be enteritis in one or two and lymphoma in the others. This is more evidence that the disease has transformed from IBD to lymphoma.
g. Hairball obstruction
i. Chronic small bowel disease (IBD or lymphoma) can cause reduced small bowel motility.
ii. This results in slower movement of hair through the GI tract.
iii. This results in more vomiting of hairballs or hairball obstruction.
iv. When removing a hairball, biopsy the bowel about 3-4 inches aboral (downstream).
1. Expect to find that the cat has either chronic enteritis or lymphoma.

h. Norsworthy's thoughts regarding hairballs
i. Hairballs can be normal due to normal shedding and the cat's grooming behavior.
ii. However, most chronic cases are a sign of chronic small bowel disease.
iii. Therefore, ultrasound the small bowel.
1. If the US is normal, treat for hairballs – hairball diet, GI lubricants.
a. If the response decreases over time, US the SI again.
2. If the US is abnormal, recommend surgery for small bowel biopsy.
iv. Treating hairballs symptomatically can mask the signs of chronic small bowel disease. Our concern is allowing IBD to transform to lymphoma.

i. Loss of layering of the bowel wall
i. There is a strong correlation with neoplasia.
ii. Occurs most commonly in lymphoblastic lymphoma and when a GI mass occurs.
iii. Cats with GI infiltrative disease (especially small cell lymphoma) have normal layering.

j. The stomach
i. Can be the site of tumors and IBD and can be the source of vomiting.
ii. When doing an ultrasound of the small bowel, look at the stomach also.

k. Transformation
i. There have been multiple publications that support the transformation of IBD to lymphoma.
ii. Evidence is mounting that this happens.
iii. However, it has never been definitely documented in the cat – yet.

l. Acute on Chronic Vomiting
i. Some cats will be presented for multiple vomiting events per day for 2-5 days.
ii. Ask about the vomiting history for the past six months.
iii. Acute on chronic vomiting is common in cats with chronic small bowel disease.
iv. Don't miss the bigger picture by treating an acute event.

H. Histopathology Service
a. J Scot Estep, DVM, DACVP (co-author on the *JAVMA* paper).
b. Texas Veterinary Pathology
c. (830) 237-2955
d. http://texvetpath.com
e. 3-4 small bowel samples: $55; 3-4 small bowel samples + liver + pancreas = $85

I. *JAVMA*, Nov. 15, 2013: Diagnosis of chronic small bowel disease in cats: 100 cases (2008-2012); Norsworthy, Estep, Kiupel, Olson, Gassler.
a. Findings
i. Clinical signs
1. Vomiting only 61%
2. Diarrhea only 11%
3. Vom & Diarr 13%
4. Weight loss* 70%
a. Most with vomiting or diarrhea.

b. Many without vomiting OR diarrhea.

ii. Diagnoses

1. Normal	1%		
2. Chronic enteritis	49%		
3. Adenocarcinoma	1%	|	
4. Mast cell tumor	3%	| --- Neoplasia	50%
5. Lymphoma	46%	|	

a. Large cell 15%

b. Small cell 85%

J. Client Response

a. "Let's go to surgery."

b. Rejection due to:

i. Cat is too sick.

ii. Cat is too old. (Oldest cat we have operated is 19 yrs.)

iii. Cost: Either cannot afford or will not spend this much money on a cat.

iv. Must check with spouse. (Real or excuse?)

v. Disbelief. This is different than they have heard in the past, including from other veterinarians.

vi. Will not spend this much money on *this* cat.

c. Rejection rate 40%.

i. Owner's decision.

ii. My decision or a joint decision.

1. Not a good surgical candidate. Recall that 50% have neoplasia, they are usually over 12 years of age, they have BCS of 1-3/9, and often have concurrent geriatric diseases.

d. If rejection occurs.

i. Caution: too much pressure can cause you to lose a client even though you are convinced that you are recommending the correct course of action for the cat.

ii. Give handout material about chronic small bowel disease. See resources below.

iii. Do a food trial.

1. It might work although the chances of success are about 10%.
2. It keeps the owner focused on the problem for 6 weeks. If the food trial fails, there is a better chance surgery will be reconsidered.

iv. Treat without a diagnosis.

v. Do not bring it up next year. They may reconsider but let them take the initiative.

K. Main messages

a. Chronic vomiting usually originates in the small bowel.

b. A full thickness biopsy is needed for diagnosis.

c. Quit treating these cats for hairballs and get a real diagnosis.

d. Untreated IBD probably has the ability to progress to lymphoma.

L. Anesthesia and Surgery on Geriatric Cats

a. Pre-Anesthetic Workup

i. Good physical examination

ii. Chemistry panel with electrolytes (and TT4)

iii. CBC (or PCV)

iv. Careful cardiac auscultation

v. Single-lead ECG with XX (DVM Solutions; 1-866-373-9627)

b. Anesthetic Induction

i. Isoflurane (or sevoflurane) by face mask

1. In my practice we do this 5-10 times per day

ii. Problems with face mask induction are due to

1. Wrong size mask (Jorgensen; 5.5" diameter).
2. Improper restraint.
3. Lack of cleanliness of the mask (smell of dogs).

c. Medications

i. Pre-op

1. Buprenorphine-SR (120 mcg/kg IM or SC) (www.srvet.net) or buprenorphine mucosal: 0.02 mg/kg IM or SC See Footnote.
2. Antibiotics: Convenia OR Baytril + ampicillin injectables
3. Fluids: IV

ii. Intra-op

1. Atropine PRN for bradycardia (HR <90 bpm)

iii. Post-op
1. Acepromazine for rough recovery
a. Dilute 1:10; 1 mg/kg concentration
b. Give 0.05 mg/# IM or SC

d. Surgical Monitoring
i. Parameters
1. Respiration rate *
2. Heart rate *
3. Temperature *
4. ECG tracing
5. Blood pressure
6. Pulse Ox
7. End Tidal CO2

ii. Equipment
1. VetGard (DVM Solutions; 1-866-373-9627)

e. Temperature Control during Surgery: For Prevention of Hypothermia
i. Warm IV fluids
ii. IV Fluid wrap: Kenna's Kreations; Small (fits 500 ml bag) - $45.00 plus shipping; Large (fits 1000 ml) - $50.00 plus shipping. kenna.mckenney@yahoo.com
iii. Run the IV line between two beanies on its way to the cat.
iv. Surgery table worming pad: ChillBusterVet (ThermoGear, Inc.; 1-503-697-1900)
v. Beanies laterally to the cat. Caution: if too hot will burn the cat's skin.
vi. Booties (for 6-12 month baby) on each foot to prevent heat loss from the pads.
vii. Multiparameter surgical monitor that includes core body temperature. (VetGard; DVMSolutions.com)
viii. Abdominal infusion of 100 ml of warm (100 F) saline for cats with end-surgery temperature below 97 F. Leave in the abdomen at closure. Caution: Some of the fluid will leak through the incision and be blood tinged from the bleeding of the liver biopsy. This is not active hemorrhage so do not re-operate the cat.
ix. Warming pad (ChillBusterVet) in the recovery cage.
x. Note: Extended surgery time will directly contribute to hypothermia. Our laparotomies are 1 hour from induction to extubation with 20 minutes from skin to skin.

f. Body Wall Closure
i. Needs to be secure and fast
ii. Muscle
1. 2-0 PDS
2. Simple interrupted pattern about 1.0 cm apart
3. Simple interrupted (1.5 cm apart) + continuous pattern on top of simple interrupted.

iii. Subcutaneous tissue
1. 4-0 PDS in continuous pattern

iv. Skin
1. 4-0 Braunamid/Polymid
2. Ford interlocking pattern.

g. Recovery
i. Very rapid due to the anesthetic protocol used.
ii. Wrap in warm bath towel
iii. Beanies (if needed) and Chillbuster for warmth OR heating pad below the cage rack
iv. Watch brachycephalic cats for airway obstruction during recovery.

h. Post-op Protocol
i. Continue IV fluids for 24 hours post-op and keep the cat NPO.
ii. Then, offer food and keep the cat another night.
iii. If the cat eats and does not spike a fever, it goes home on the second post-op day (after two nights in the hospital).

M. Advanced Testing
a. Immunophenotyping
i. To differentiate B-cell and T-cell lymphoma.
ii. Options
1. Immunohistochemistry
2. Polymerase Chain Reaction
3. Flow Cytometry

iii. Therapeutic Implications
1. Dogs have significantly better response to therapy if it is B-cell.
2. There is minimal (if any) difference in response for cats.
a. In our study, only 4% of the lymphoma cases were B-cell.
b. Lymphoma caused by the FeLV is B-cell.

b. PARR Testing (PCR for Antigen Receptor Rearrangement); Michigan State University; Dr. Matti Kiupel's lab; he is the creator of this test.
i. Differentiates small cell lymphoma from chronic enteritis.
ii. Performed on "ambiguous" cases; these are defined by Dr. Estep in the *JAVMA* paper.
iii. Definite therapeutic implications on how to treat and outcome.
iv. Your pathologist should determine when this testing is needed; about 10% of the time.

N. Therapy
a. General prognoses
i. Good: food reaction, inflammatory bowel disease, small cell lymphoma, mast cell tumor.
ii. Less Good: lymphoblastic lymphoma
iii. Bad: adenocarcinoma.

b. Food reaction
i. There is a technical difference in food allergy vs. food intolerance, but it is not clinically feasible to make the distinction. This distinction is skirted by using the term 'food reaction.'
ii. The HP will usually state "eosinophilic enteritis."
a. If the HP says that and the cat does not respond to a food trial, eosinophilic enteritis is more difficult to treat than other types. See below.
iii. As a rule, anti-inflammatories are not effective or may be effective for only a few days to weeks.
iv. Food trials based on novel protein diets (rabbit, duck, venison) or hydrolyzed protein diets (HA by Purina or z/d by Hill's).
v. The food trial should go 6+ weeks before deeming it to be a failure. The cats MUST eat one or more of these diets EXCLUSIVELY for the food trial to be valid.

c. "Chronic Enteritis"
i. IBD is a diagnosis of exclusion. Rule outs are needed to justify a diagnosis of IBD. The histopath will be the same for the following. Eliminate each with therapy.
1. Food allergy/intolerance: food trial (see above)
2. GI Parasitism (*Physaloptera* and *Giardia*): fenbendazole
a. The quantity when using liquid Panacur liquid is too great
b. Compounded tabs: 100 mg q24h PO
i. Apotheca Pharmacy, 210-226-1112
3. Dysbiosis (formerly, bacterial overgrowth)
a. Metronidazole
i. Compounded tabs: 50 mg q24h PO
ii. Apotheca Pharmacy, 210-226-1112
b. Probiotic: FortiFlora (Purina) or Proviable (Nutramax)
4. Therapeutic trial schedule
a. Day 1-42+: Food trial
b. Day 1-5: Fenbendazole
c. Day 6-36: Metronidazole + probiotic
d. Recheck at 6+ weeks to assess success or failure.
e. Do not use steroids or do not use them past Day 30.

2. Cobalamin (B12)
1. Testing can be done (GI Lab, Texas A&M) OR treat every cat.
f. 1000 mcg/dose
g. Give SC 2X per week for 6 weeks then
h. Give SC 1X per week for 6 weeks.
2. Advantage of treating all is that vitamin B12 is a good appetite stimulant, which is a plus when changing a cat's diet.

3. Check list for therapeutic trials
1. Hypoallergenic diet
2. Fenbendazole
3. Metronidazole
4. Probiotic
5. Vitamin B12

4. Inflammatory Bowel Disease

1. Diagnosis made by eliminating the above causes of chronic enteritis.
2. Diet: Change to a low-carb, high-protein diet and feed long-term
    a. My preference: EN or DM.
    b. Fancy Feast alternatives: https://dl.dropboxusercontent.com/u/69563616/Fancy%20Feast%20CHO%20DM.doc
3. Cerenia: Can be given PRN to control episodes of vomiting.
4. Immune suppressants
    a. One of more of the following needed to suppress the over-reaction of the immune system. The goal is control not cure; therefore, treatment is needed long-term.
    b. Corticosteroids: prednisolone 0.5 mg/kg q24h PO or Depo-Medrol at 20 mg q30d.
        i. Oral pred preferred; less chance of inducing diabetes.
    c. Alternatives if pred not effective.
        i. Cyclosporine (Atopica): 25 mg q24h PO for 15-30 days then 25 mg q48h PO. May change to prednisolone for long-term control.
        ii. Lomustine (CCNU): 12 mg capsule for cats 5-15 pounds q28d PO.
            1. Monitor for neutropenia.
            2. I use this if the wall thickening is great or there are eosinophils in the inflammation.
            3. Give 2-3 doses with prednisolone or Depo-Medrol then continue with the steroid only.
5. Laser therapy: Artemis by Epica Medical; greg@epicamed.com

5. Lymphoma
    1. Success is remission, not cure. Remission is defined as lack of clinical signs. These cats will stop vomiting, eat well, regain their lost weight, and become very active. The small bowel walls should return to normal or near normal as documented by ultrasound.
    2. Short-term
        a. Vitamin B12: 1000 mcg/dose
            i. SC 2X per week for 6 weeks then SC 1X per week for 6 weeks
            ii. May be given long-term if it increases the appetite and make the cat feel better.
        b. Probiotic (FortiFlora or Proviable) for 30-90 days or long-term.
        c. Vomiting control: Cerenia** or transdermal metoclopramide.
    3. Diet
        a. Low-carb, high-protein diet preferred
            i. EN or DM (Purina)
            ii. Should be fed long-term.
    4. Chemotherapy Options
        a. Prednisolone: 2 mg/kg q12h PO for +7-10 days then reduce slowly to 5-10 mg/cat q24h PO. Least expensive approach with fewest side effects; however, the least effective approach. If given alone for several weeks, the response to other chemo protocols may be reduced significantly.
        b. Modified Wisconsin protocol: 15 treatments in 24 weeks using Modified CHOP) (L-asparaginase, vincristine, cyclophosphamide, chlorambucil, doxorubicin, prednisone); first remission rate 68%; median survival time 225 days. See *The Feline Patient* editions 2, 3, or 4 for specific protocol. The protocol of choice for most veterinary oncologists.
        c. Chlorambucil + prednisolone: Chlorambucil (0.1 mg/kg q24h PO or 6-8 mg/m^2 PO. The tablets should never be split so cats must take 2 mg q24h PO to q3d depending on the weight of the cat; Prednisolone (1-2 mg/kg q24h PO)
        d. Lomustine + prednisolone
            i. Generally not considered a first-line chemotherapy agent. It is usually given as a rescue drug to dying cats so its efficacy is considered poor.
            ii. My treatment of choice for lymphoma and mast cell tumors.
            iii. Lomustine: (CCNU): 10 or 12 mg capsule for cats 7-15 pounds q28d PO*.

iv. Depo-Medrol q4w (or oral pred at 1 mg/kg q24h PO)
v. Monitor for neutropenia. If it occurs, discontinue lomustine until neutrophil count is in the normal range but continue prednisolone. Recheck WBC q14 days. In Norsworthy's experience it occurs about 40% of the time, but all cats were eventually able to get 6 doses or more. Prognosis is usually better in these cats. Alternative: Instead of delaying treatment, reduce the dose to 9 or 6 mg.
vi. Dosing for cats without neutropenia

Body Weight in Kg	Mg of Lomustine
2.0-3.0	6
3.1-4.5	9
4.6-5.9	12
7 or more	15

vii. Other side effects
    1. Focal hair loss
    2. Very slow regrowth of hair from surgery. (Very common)
    3. Focal alopecia; any location. (Uncommon)
    4. Cardiotoxicity? Watch for pleural effusion; it is a grave prognostic sign. (Rare)
viii. Protocol:
    1. Visit 1: CBC + administer lomustine + give Depo-Medrol at the time of stitch removal = 10-14 days post-op.
        a. Also start vitamin B12, probiotic, LCHP diet.
    2. Visits 2-6: Recheck, CBC, & lomustine 4 weeks later.
    3. Visit 6: Repeat ultrasound: measure small bowel wall thickness.
ix. Success is remission, not cure.
    1. Vomiting stops
    2. Good appetite
    3. Weight gain (if weight loss initially)
    4. Good quality of life
    5. Small bowel walls normal or greatly improved.
x. At 6th dose
    1. Explain that discontinuing lomustine will eventually result in relapse. Cats do not respond after relapse occurs. Continuing long term results in greater longevity.
    2. Measure the small bowel wall.
        a. If improved or normal and clinical signs are gone or much improved:
        b. Give 2 more doses at 6 week intervals + Depo-Medrol then continue at 8 week intervals long-term. If decline occurs, revert to 4 or 6 week intervals.
xi. The capsule becomes very sticky when moist.
    1. Use a Pill Popper if needed for clean administration.
    2. Give water with two 2X2 gauze squares (soaked in water) to prevent the capsule from sticking to the esophageal wall and causing an esophageal stricture.
    3. If pill becomes sticky, roll it in Corn Starch.
xii. Sources of lomustine
    1. Local pharmacies or veterinary distributors
        a. CCNU
        b. 10 mg capsules; bottle of 20
        c. ~$200 per bottle/~$10 per capsule
        d. When available
    2. Apotheca Pharmacy, San Antonio, TX
        a. Phone: (210) 226-1112
        b. Fax: (210) 226-1119

c. 6, 9, and 12 mg capsules
d. $8.00 each (either size)

xiii. Treating the fractious cat
1. Induce with isoflurane or sevoflurane using induction chamber (or face mask).
2. Draw blood and perform CBC.
3. Pass a 12 Fr. red rubber catheter into the stomach.
4. Put the contents of a lomustine capsule in 5 ml of water in a 6 cc syringe; shake well. Flush through the stomach tube.
5. Administer Depo-Medrol.
6. Cat will recover in 15 minutes and can be discharged immediately.

5. Treatment without a confirmed diagnosis
a. The cat has the correct clinical signs, especially significant weight loss.
b. The small bowel walls are thickened according to U/S.
i. Or, U/S not available.
c. Owner will not agree to a laparotomy for biopsies OR
d. The cat is not a good candidate for a laparotomy.
e. The odds are 95+% that the cat has either IBD or lymphoma.
f. I prefer to treat for lymphoma because both will respond to the lomustine + steroid protocol.
g. It is ESSENTIAL that you receive informed consent from the owner and document it in your records.

O. Take Home
a. Chronic vomiting is VERY common in cats.
b. It is so common that we have made excuses for it.
c. Therefore, clients usually do not report it.
d. You have to ask about it.
e. Chronic vomiting is not normal.
f. Chronic vomiting originates from the small bowel, not the stomach 98% of the time.
g. Chronic small bowel disease is segmental in most (about ¾) of cats.
h. Proper biopsies need to be made in the proper locations, as determined by full bowel inspection (run the bowel).
i. Proper biopsies need to be full-thickness.
j. You can do it, and you should do it. These do not have to be referral cases.
k. You can treat these cats, and you should treat these cats. They do not have to be referrals.
l. You clients and your bottom line will appreciate it.

P. Vaccinations during chemotherapy
a. No veterinary reference available
b. CDC: Recommendations of the Advisory Committee on Immunization (ACIP): Use of vaccines and Immune Globulins in Persons with Altered Immunocompetence.
i. “Killed or inactivated vaccines do not represent a danger to immunocompromised persons and generally should be administered as recommended for healthy persons.”
ii. “Frequently, the immune response of immunocompromised persons to these vaccine antigens is not as good as that of immunocompetent persons; higher doses or more frequent boosters may be required, although even with these modifications, the immune response may be suboptimal.”
iii. “When cancer therapy or immunosuppressive therapy is being considered, vaccination ideally should precede the initiation of chemotherapy or immunosuppression by greater than or equal to 2 weeks.”
iv. “Vaccination during chemotherapy or radiation therapy should be avoided because antibody responses are suboptimal.”
a. What if long-term (maintenance) chemotherapy is used?
c. Our dilemma
i. Chemotherapy patients will be in our hospitals monthly.
ii. Exposure to respiratory viruses is likely to occur.
iii. FHV-1 is a very poor antigen.
iv. It does not produce sterilizing immunity.
v. Exposure results in infection and illness.
vi. It has the shorted DOI of all of our major vaccines.
d. My Plan

i. Herpesvirus vaccine is the most important because it is the most common hospital pathogen.
ii. Infection in an immunocompromised patient can be deadly.
iii. Ideal: Give FVRCP > 2 weeks before starting and repeat every 6 months.
iv. When boosters are due:
    1. Give FVRCP one week before the next dose: the best compromise of immunocompromise and immune response.
    2. Use a killed product.
    3. Do not give with other vaccines.

Resources: dvm360.com/chronicvomiting

Summary Article
Diagnostic Algorithm
Relevant diagnostic images
Client Handout: Chronic Intestinal Disease in Cats (Downloadable)
Client Handout: Inflammatory Bowel Disease
Client Handout: Lymphoma
Selling the Laparotomy
Performing the Laparotomy
Dr. Norsworthy's experience with lomustine

"Intestinal lymphoma is likely the most underdiagnosed cause of chronic gastrointestinal disease and vomiting in the cat. Of the last 100 full thickness feline intestinal biopsies that I have evaluated, 35 were positive for lymphoma, 60 were positive for some degree of chronic enteritis and 5 were normal. Six cases that were originally diagnosed as IBD were later confirmed as lymphoma within 1 year. All 35 positive cases were from three practices that regularly perform laparotomy-obtained full thickness biopsies.

The likelihood of diagnosing feline intestinal lymphoma is more a measure of the surgeon's willingness to perform full thickness intestinal biopsies than it is the actual incidence of the disease. Twenty to thirty percent of cats with chronic GI disease are likely due to lymphoma. If a veterinarian who regularly sees cats has not made the diagnosis of intestinal lymphoma in the last year, it is probably only because he or she has not performed any full thickness intestinal biopsies."

J Scot Estep, DVM, DACVP
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http://texvetpath.com

Summary: Chronic Vomiting in Cats

- The Great Four Excuses for chronic vomiting are: 1) He eats too fast, 2) She has a sensitive stomach, 3) It's just hairballs, and 4) "He's just a puker," to quote one of my clients. We have accepted these largely because we have not known what to do when the blood panel was normal or when endoscopic biopsies of the stomach were normal.
- Mild to moderate thickening of the small bowel initially usually affects peristalsis and results in hypomotility. This is what initiates chronic vomiting. Moderate to severe thickening results in malabsorption and results in weight loss, often followed by polyphagia.
- The clinical signs of small bowel disease are chronic vomiting, chronic diarrhea, weight loss, or a combination. Note that older cats that do not have diabetes or hyperthyroidism and do not have vomiting or diarrhea but are gradually losing weight should have abdominal ultrasound with emphasis on the small bowel.
- Cats presented for acute vomiting for 2-4 days (often several times per day) should be queried about the presence of chronic vomiting that has preceded the acute episode. Many cats with chronic small bowel disease have episodes of acute vomiting (acute on chronic). If chronic vomiting is present, abdominal ultrasound is indicated.
- When ultrasound is utilized to measure the small bowel wall, one needs to be careful about how 'normal' is defined. The study clearly showed that 0.28 cm or greater justifies surgical biopsies. Some references state that up to 0.32 cm is normal. The study shows that cats with measurements of 0.28 cm or more have a 99% chance of having chronic small bowel disease.
- Over three fourths of the cats in the study had some ultrasound measurements that were normal and others that were abnormal. This represents segmental disease and demands that at least six ultrasound measurements be

made with the expectation that some will be normal. See Figure 2. However, even in the presence of chronic small bowel disease, a few cats will have normal small bowel measurements.

- Surgery can be performed very safely; however, precautions must be taken because many of these cats have body condition scores of 2/9 and 3/9. Fifty percent of them have neoplasia, and most are over 12 years of age. The greatest complication to surgery is hypothermia so several steps should be taken to maintain body temperature.
- Although endoscopy is often used to obtain small bowel samples, it is limited because only a very small portion of the small bowel is accessible and its inability to obtain full thickness biopsy samples. The segmental nature of this disease greatly reduces the sensitivity of endoscopic biopsies.
- The incidence of chronic enteritis (usually inflammatory bowel disease) and neoplasia is almost equal. See Table 1. Over 90% of the cats with intestinal neoplasia have lymphoma.
- There is mounting evidence that some cases of IBD will transform to lymphoma. If we can diagnose cats at the IBD stage, we have a therapeutic chance of preventing progression to lymphoma, saving the owners hundreds, or even thousands, of dollars and prolonging the cats' lives.
- Vomiting of hairballs is not nearly as 'normal' as we have thought. It is usually the result of hypomotility caused by inflammatory or neoplastic chronic small bowel disease.
- A cat diagnosed with hairball obstruction should have small bowel biopsies 4+ cm aboral to the obstruction to find the underlying cause of hypomotility.
- In the study, 25% of the cats taken to surgery were presented for an annual examination. Careful history taking, including proactively asking about vomiting and a comparison of prior and present weights, is an opportunity to identify cats that have not caused alarm in their owners. Failure to motivate your clients to have annual examinations on their cats is a tragic loss to the cat, the owner, and your practice.
- If the pathologist reports chronic enteritis, one must rule out chronic parasitism (especially *Giardia* and *Physaloptera*), dysbiosis (formerly bacterial overgrowth), and food allergy/intolerance. If those are ruled out (by therapeutic trials), the diagnosis becomes inflammatory bowel disease (IBD). Note that it is a diagnosis of exclusion.
- Resist the urge to treat these cats symptomatically: the use of diets for "sensitive stomachs," diets for hairballs, hypoallergenic diets, medications for hairballs, and antiemetics (metoclopramide, ondansetron, maropitant, famotidine, etc.). Although there may be improvement for weeks to months, the symptoms of serious, underlying disease is only being masked.
- However, there will be situations in which laparotomy and biopsy are not feasible, either due to the owner's finances or reluctance or due to the cat's condition. If the cat is stable (no or minimal weight loss), a six week food trial can be performed using a novel protein diet or a hydrolyzed protein diet. If that is not successful, some owners will agree to surgery. Alternatively, a therapeutic trial with a corticosteroid may be considered. However, treatment of a cat with lymphoma with only a corticosteroid may jeopardize the outcome of subsequent chemotherapy.
- If IBD is diagnosed, a high-fiber diet or a low-residue diet plus corticosteroids plus a probiotic plus injectable vitamin B12 should be prescribed. In general the response to treatment is good to excellent. However, it is not curative so long-term treatment is required. If possible, do not give steroids during these therapeutic trials.
- If lymphoma is diagnosed, the Modified Wisconsin Protocol, chlorambucil plus prednisolone, or lomustine plus prednisolone should be used. My preferred approach is the latter. Lomustine is given PO q4w. A CBC is performed at the time of each treatment to monitor for the only significant side-effect, neutropenia. If neutropenia occurs, the next dose of lomustine is delayed until the neutrophil count is normal, generally two weeks. The typical treatment protocol is six doses of lomustine. Some cats require more than six doses. Survival can be increased by extending treatment to long-term but only given lomustine every 6-8 weeks. If a cat comes out of remission, rescue is very difficult with any protocol.

Footnote:

Buprenorphine SR by ZooPharm (www.zoopharm.net)

Key Features of Buprenorphine SR™

- Provides sustained release delivery of Buprenorphine in a fully biodegradable liquid polymer matrix
- Provides a consistent 72-hour release profile with consistent drug absorption
- Provides blood levels greater than 1 nanogram/mL for post-operative analgesia
- Formulation can be injected subcutaneously through a 22-gauge needle

Pharmacokinetics

Buprenorphine is metabolized by the liver, via CYP3A4 (also CYP2C8 seems to be involved) isozymes of the cytochrome P450 enzyme system, into norbuprenorphine (by N-dealkylation). The glucuronidation of buprenorphine is primarily carried out by UGT1A1 and UGT2B7, and that of norbuprenorphine by UGT1A1 and UGT1A3. These

glucuronides are then eliminated mainly through excretion into the bile. The elimination half-life of buprenorphine is 20–73 hours (mean 37). Due to the mainly hepatic elimination, there is no risk of accumulation in patients with renal impairment.[5]

Buprenorphine's main active metabolite, norbuprenorphine, is a μ-opioid, δ-opioid, and nociception receptor full agonist, with a κ-opioid receptor partial agonist. Buprenorphine antagonizes its effects. In an unpublished study, three dogs administered 270 ug/kg subcutaneously had plasma concentrations that rose rapidly reaching average Cmax of 2.14 ng/mL at an average Tmax of 1 hour. Notably average plasma concentration remained over 1.0 ng/mL from under 1 hour to over 72 hours post injection.

A recently published study in the Journal of the American Association for Laboratory Animal Science, tested this sustained-release formulation of buprenorphine in rats for analgesic efficacy and plasma concentration over a 72-h time period. Rats were injected subcutaneously with either 1.2 mg/kg sustained-release formulation (Bup-SR), 0.2 mL/kg buprenorphine HCl (Bup-HCl) and tested in a thermal nociception model or a surgical postoperative pain model. In both models, Buprenorphine-SR showed evidence of providing analgesia for 2 to 3 d, reporting plasma concentrations of buprenorphine remaining over 1 ng/mL for 72 h after a single dose.[6]

A pilot study, conducted in domestic cats was designed to determine if the sustained release Buprenorphine SR™ formulation was equivalent to repeated doses of transmucosal administration of the commercial preparation Buprenex™ over a period of 72 hours. Animals received either a single, subcutaneous injection of Buprenorphine SR at a dose rate of 120 mcg/kg, or a transmucosal dose of buprenorphine HCl [Buprenex™] every 12 hours for 72 hours. Results from analysis of blood samples [obtained at 1, 4, 8, 12, 18, 24, 36, 48 and 72 hours], reported data showing that only the single-dosed Buprenorphine SR cats maintained therapeutic blood levels for 72 hours.[7]

No visible injection site irritations or clinical side effects were reported within both test groups.[7]

5. Moody DE, Fang Lin SN, Weyant DM, Strom SC, Omiecinski CJ. Effect of Rifampin and Nelfinavir on the Metabolism of Methadone and Buprenorphine in Primary Cultures of Human Hepatocytes. Drug Metab Dispos December 2009 37:2323-29.
6. Foley PL, LiangH, Crichlow AR. Evaluation of a sustained release formulation of buprenorphine for analgesia in rats. JAALAS Vol 50, No 2, March 2011, 198–204.
7. Pilot Study: Comparison of sustained release buprenorphine and transmucosal buprenorphine in cats.

NOTES:

Diagnosis & Management of Pancreatitis

Kenneth Simpson, BVM&S, PhD, DACVIM, DECVIM

Introduction

Since its initial description in 1989, feline pancreatitis has emerged as an important and potentially life threatening disease. Despite increased awareness its etiology remains unknown, diagnosis is challenging, and surgical biopsy is often required to confirm a diagnosis and facilitate detection of intercurrent disease. Treatment is generally symptomatic and typically involves aggressive nutritional support. This article reviews the current state of play in the diagnosis and treatment of acute pancreatitis in cats.

Key Points

- The most common clinical findings in cats with acute pancreatitis are lethargy, anorexia, and weight loss.
- A specific cause for pancreatitis is not apparent in the majority of cats
- There is no single test that will accurately diagnose pancreatitis in all affected cats
- Cats with pancreatitis often have inter-current disease involving the liver and small intestines
- Medical treatment is based on maintaining or restoring adequate tissue perfusion, limiting bacterial translocation, inhibiting inflammatory mediators and pancreatic enzymes and providing enteral nutritional support.
- Surgical treatment consists of restoring biliary outflow, removing infected necrotic pancreatic tissue, or coping with sequela such as pseudocysts.
- The prognosis for acute pancreatitis in cats is always considered guarded, and is particularly poor for suppurative pancreatitis
- Feline EPI is typically due to end stage chronic pancreatitis
- Weight loss, subnormal fTLI and low serum cobalamin are very common in feline EPI

Clinical Findings

Signalment and History

Acute pancreatitis has been reported in cats aged from 4wks to eighteen years old. Domestic Short- and Long-hair cats are most commonly affected. Siamese cats have been over-represented in some series. No sex bias has been demonstrated. A small number of cases have been associated with trauma, *Toxoplasma gondii*, pancreatic and liver flukes, FIP, calicivirus (virulent variant) and lypodystrophy. Usually there are no obvious associated factors.

Diagnostic Approach and Differential Diagnosis

Lethargy anorexia and weight loss are the most common presenting complaints.Localizing signs or findings such as vomiting, icterus, diarrhea, abdominal pain, abdominal mass, polyuria or polydipsia should be pursued if present. The duration of clinical signs until presentation varies from less than 3 days to 12 wks.

Where a high index of suspicion for pancreatitis is present ultrasonography and determination of pancreatic markers (e.g. pancreas specific lipase) should initially be employed to help to detect pancreatitic inflammation. However, given the spectrum of inter-current disease in cats with pancreatitis a well performed exploratory laparotomy with biopsy of the pancreas, liver, intestines and mesenteric lymph nodes is often required to generate an accurate diagnosis and enable feeding tube placement.

Laboratory Findings

Hematology

A mild anemia that may be non-regenerative, and leukocytosis, often without a left-shift, are common in cats with pancreatitis. Leukopenia is present in some cats and carries a poorer prognosis.

Serum Biochemistry

Increased ALT, SAP, bilirubin, cholesterol and glucose, and hypokalemia and hypocalcemia (total and ionized) are most frequently observed. Azotemia is variably present.

Hypocalcemia, present in about 50% of cases, is perhaps the most helpful finding for raising the probablility of a diagnosis of pancreatitis. Pancreatitis associated hypocalcemia may be caused by a variety of reasons, such as saponifcation of fat , soft tissue accumulation and changes in PTH homeostasis. The presence of ionized

hypocalcemia (<1mmol/l) carries a poor prognosis. Hypocobalaminemia is present in some cats with pancreatitis and is thought to reflect concurrent intestinal disease, rather than exocrine pancreatic insufficiency.

Urinalysis

Enables azotemia to be characterized as renal or pre-renal. The presence of glucose or ketonuria should prompt consideration of diabetes mellitus.

Pancreas specific enzymes

Classically, elevations in serum amylase and lipase activity have been used as indicators of pancreatic inflammation in dogs. In cats it seems fair to state that total serum amylase and lipase are of no utility for diagnosing acute pancreatitis.

These limitations have stimulated the development of assays for enzymes or "markers"considered pancreatic in origin. Tests for trypsin-like immunoreactivity (TLI), trypsinogen activation peptide (TAP) and pancreas specific lipase have been evaluated in cats.

Feline Trypsin like Immunoreactivity (fTLI)

Immunoreactive trypsin has been shown to be a reliable indicator of pancreatic mass, enabling the reliable detection of feline and canine exocrine pancreatic insufficiency. It is much less useful as an indicator of pancreatic inflammation. It's sensitivity has been reported to be as low as 28%, and cats with fatal acute pancreatitis frequently have values within the normal range. Specificty is better, @ 66-75%. The poor sensitivity, particularly in cats with severe acute pancreatitis strongly suggests down regulation of TLI in the inflamed pancreas, similar to that observed in dogs with pancreatitis. Altered renal clearance in cats with renal failure can impact the specificity, as can the finding of normal pancreatic histology in cats with high TLI and intestinal disease.

Pancreas Specific Lipase Immunoreactivity (fPLI)

Given the limitations of fTLI tests to measure feline pancreas specific immunoreactive lipase have recently been developed. Clinical utility is still being ascertained. However the initial results for fPLI are a lot more promising than fTLI, with sensitivity for pancreatitis reported as 67%, and specificity at 91%. Preliminary evaluation of the the commercial version of the fPLI test, Spec fPL using 5.4 µg/L as the diagnostic cut off, yielded a sensitivity of 79% and the specificity of 82% (Forman et al unpublished observations).

How do I accurately diagnose pancreatitis?

- There is no single non-inasive test that accurately identifies all cats with pancreatitis
- Measurement of serum amylase, lipase and TLI is not reliable for confirming a diagnosis of acute pancreatitis
- Pancreas specific lipase shows promise with a sensitivity estimated at 67% sensitivty , 91% specificity for fPLI. For the Spec fPL assay (a commercialized version of fPLI) using 5.4 µg/L as the diagnostic cut off, yielded a sensitivity of 79% and the specificity of 82%.
- Abdominal ultrasound has a sensitivity of 35-67% and specificity of @73%
- Cats with pancreatitis may have normal fPLI/SpecfPL and ultrasonographic findings
- Pancreatic biopsy enables confirmation and distinction between histological subtypes of pancreatitis, pancreatic hyperplasia and pancreatic cancer
- An exploratory laparotomy enables diagnosis of intercurrent disease in the liver and small intestine.

Diagnostic Imaging

Radiography

Radiographic findings in cats with acute pancreatitis may include loss of serosal detail, increased opacity in the right cranial quadrant of the abdomen, displacement of the duodenum ventrally and/or to the right, dilated hypomotile duodenum and caudal displacement of the transverse large intestine. Although radiographic signs often are absent and non-specific radiography is a logical first choice imaging modality for animals with gastrointestinal signs.

Ultrasonography

Ultrasonographic findings include enlarged, hypoechoic pancreas, cavitary lesions such as abscess or pseudocyst, dilated pancreatic duct, swollen hypomotile duodenum, biliary dilatation and peritoneal fluid. Findings in cats indicate that ultrasound will detect from 35 to 67 % of cats with pancreatitis (confirmed with biopsy), with a specificity of @ 73%. Arecent study using fPL as the gold standard for pancreatitis found that the single ultrasound characteristic with the highest sensitivity was hyperechoic peripancreatic fat at 68%, indicating a moderate probability

that cats with pancreatitis will have this abnormality on ultrasonographic examination. Specificity was >90% for each of increased pancreatic thickness, abnormal pancreatic margin, and hyperechoic peripancreatic fat. The sensitivity and specificity of ultrasound were 84% (and 75%, respectively, in cats with elevated serum fPLI indicative of pancreatitis. These findings reveal that a normal ultrasound does not rule out pancreatitis, and that diseases other than pancreatitis (e.g. pancreatic hyperplasia,pancreatic neoplasia) should be considered when an abnormal pancreas is visualized.

Computed Tomography and MRI

Studies in cats with CT have been disappointing, ranging from a failure to detect the pancreas to no diffrenecs visualized in cats with pancreatitis. A recent study using MRI detected pancreatic abnormalities in cats suspected of pancreatitis, including T1 pre-contrast hypointense and T2 hyperintense pancreatic parenchyma and a dilated pancreatic duct. The MRI findings of the liver were non-specific. Nine of 10 cats had biliary abnormalities, including gall bladder wall thickening, gall bladder wall moderate contrast enhancement and/or gall bladder debris. Eight of 10 cats had histologic evidence of pancreatitis, as well as hepatitis or cholangitis, with one cat diagnosed with hepatic lymphoma. The advantages of MRI/MRCP over sonography was operator independence and lack of interference from bowel gas.

Prognostic Indicators

Severe pancreatitis requires aggressive support and carries a guarded prognosis, whereas mild pancreatitis may respond to short-term symptomatic therapy. The presence of shock or abnormalities such as oliguria, azotaemia, icterus, markedly elevated transaminases, ionized hypocalcaemia (<1mmol/l), hypoglycaemia, hypoproteinaemia, acidosis, leukopenia, falling haematocrit, thrombocytopaenia and DIC should be considered likely indicators of severe pancreatitis in the cat.

Pancreatic Biopsy and Histology

The pancreas can be biopsied surgically or laparoscopically. Current recommendations, based on the patchy distibutionof pancreatic inflammation, suggest taking biopsies from parts that look or feel abnormal,and from the left and right limbs and the body. Histological findings are variable and there is not yet a consensus on their interpretation. In general histopathology is reported according to the predominant features as acute necrotizing (necrosis predominates), acute suppurative (neutrophils predominate) or non-supputative (lymphocytic/plasmacytic inflammation and fibrosis). Whether these histologic types indicate a distinct etiology or some form of progression is unclear. The prognosis for suppurative pancreatitis is poor.

How do I treat pancreatitis?

No studies have critically evaluated treatment modalities in cats with naturally occurring pancreatitis.

Medical therapy:

- maintain or restore adequate pancreatic perfusion
- provide analgesia
- limit bacterial translocation
- inhibit inflammatory mediators and pancreatic enzymes
- provide enteral nutritional support
-

Surgical treatment

- restore biliary outflow
- remove infected necrotic pancreatic tissue
- cope with sequelae such as pseudocysts.

Medical Management

Medical treatment is based on maintaining or restoring adequate tissue perfusion, limiting bacterial translocation and inhibiting inflammatory mediators and pancreatic enzymes; surgical treatment consists principally of restoring biliary outflow, removing infected necrotic pancreatic tissue, or coping with sequela such as pseudocysts. No studies have critically evaluated treatment modalities in cats with naturally occurring pancreatitis.

Ionized hypocalcemia is a common finding in cats with acute pancreatitis and impacts prognosis. However, it is not clear if treatment of hypocalcemia, which is not usually associated with fasiculations, tetany or seizures, will impact outcome.

Plasma (20ml/kg i.v.) or colloids (10-20ml/kg/day i.v.). may be indicated in the presence of hypoproteinemia or shock. Colloids such as dextran 70 and hetastarch may also have antithrombotic effects that help maintain the microcirculation.

Insulin therapy is initiated in diabetic patients. Stress hyperglycemia has to be diffrentiated from diabetes mellitus.

Where vomiting is a persistent problem antiemetics (e.g. maropitant, ondansetron or chlorpromazine) and antacids (e.g. famotidine 0.5-1mg/kg) may be beneficial. It is emerging that maropitant has viseral analgesic properties that may be beneficial in patients with pancreatitis.

Prophylactic broad-spectrum antibiotics (e.g. amoxicillin ± enrofloxacin depending on severity) may be warranted in patients with shock, fever, diabetes mellitus or evidence of breakdowm of the GI barrier. Bacterial translocation has been demonstrated in experimental feline pancreatitis using distinct *E.coli* placed in the colon, and other sites e.g. bile, and colonization was prevented with cefotaxime (50mg/kg TID). A recent study revealed that bacterial infection is present in the pancreas of 35% (11/31) of cats with moderate to severe pancreatitis. The high frequency of infection (71%, 5/7) in acute necrotizing and suppurative pancreatitis may be linked to the poor prognosis associated with this form of pancreatitis. These localization and type of intrapancreatic bacteria suggests translocation of enteric bacteria is a likely source of infection

Analgesia is an important aspect of caring for patients with pancreatitis. It can be provided using injectable opioids such as buprenorphine (0.005-0.01mg/kg SC q6-12hrs) or oxymorphone (0.05-0.1mg/kg cats IM, SC Q 1-3hrs). It may be necessary to administer low dose sedation with acepromazine (0.01mg/kg IM) to patients who become dysphoric after opioids. A transdermal fentanyl patch (Duragesic, Janssen) applied to a clipped clean area of skin provides longer duration of analgesia (25µg/hr patch q118hrs). This author does not use non-steroidal antiinflammtory drugs to provide analgesia to cats with suspected pancreatitis.

Once a diagnosis of pancreatitis is confirmed potentially more specific therapy may be employed. The lack of success with inhibiting the progression of spontaneous pancreatitis has led to increased emphasis on damage limitation; ameliorating the effects of inflammatory mediators or pancreatic enzymes on the patient and maintaining pancreatic perfusion.

Coagulation abnormalities should be pursued and treatment with parenteral vitamin K can be assessed. Where a coagulopathy e.g. DIC, or hypoproteinemia are present, or the patient with pancreatitis is deteriorating, fresh frozen plasma (10-20 ml/kg) may be beneficial in alleviating the coagulopathy, hypoproteinemia and restoring a more normal protease-antiprotease balance. The administration of heparin (75-150 IU/kg TID) may be potentially useful in ameliorating DIC, promoting adequate microcirculation in the pancreas and clearing lipemic serum. In experimental pancreatitis isovolemic rehydration with dextran has also been shown to promote pancreatic microcirculation in dogs. A dopamine infusion (5µg/kg/min) had a protective effect when administered to cats within 12 hrs of induction of experimental pancreatitis . H_1 and H_2- antagonists blocked the progression of edematous to hemorrhagic pancreatitis in experimental cats and may be beneficial in patients .

Oral pancreatic enzyme extracts have been reported to reduce pain in humans with chronic pancreatitis, though this is controversial. The presence of a protease mediated negative feedback system has not been described in cats.

Dietary Management

In contrast to dogs, where vomiting and abdominal pain predominate, pancreatitis in cats is usually associated with anorexia and weight loss. The presence of anorexia and weight loss in cats with pancreatitis may be a significant contributing factor to their poor prognosis. There is growing evidence in people, and animals, that enteral nutrition is superior to parenteral nutrition in the treatment of acute pancreatitis. Good responses (approximately 70% discharge rate) have been observed at referral centers employing esophagostomy or gastrostomy tube feeding of enteral diets (e.g. clinicare) containing approximately 50% calories as fat. In one study 50 /55 cats being fed a liquid enteral diet via an ng tube survived 28 days post-discharge Complications associated with NGT feeding for all cats included: mechanical problems (13%), diarrhea (25%), vomiting following NGT placement (20%) and vomiting following NGT feeding (13%). Mean time to discharge for all cats occurred after 78.6 ± 29.5 hours with an overall weight gain of 0.08 ± 0.52 kg.These results seem consistent with findings in people and experimental dogs that show the major benefits of enteral support in acute pancreatitis are due to reductions in the systemic inflammatory response and the translocation of enteric bacteria rather than a reduction in pancreatic stimulation.

Surgery

Surgery is often necessary to confirm a diagnosis of acute pancreatitis in cats and also enable feeding tube placement. The increased utility of ultrasonography and measurement of markers of pancreatic inflammation (e.g. fPLI) may lead to a reduced dependency on surgery in cats with high fPLI and sonographic abnormalities. However it should be stressed that cats with pancreatitis often have concurrent abnormalities in other organ systems e.g. liver and gut, and biopsy of these organs and the pancreas may be indicated to optimize diagnosis and treatment. Transient euglycemia and reduced insulin requirements were noted after the removal of a pancreatic abscess in one cat suggest that surgical intervention may be beneficial in these cases. Surgery is potentially indicated for infected pancreatic necrosis, abscess drainage, and to investigate and to relieve persistent biliary obstruction. Resection or surgical drainage of pancreatic pseudocysts is not always necessary as these can resolve spontaneously or following percutaneous drainage.

Prognosis

The prognosis for acute pancreatitis in cats must always be considered guarded. Extensive hepatic lipidosis, suppurative pancreatitis, leucopenia and ionized hypocalcemia <1mmol/l are associated with a poor prognosis.

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NOTES:

Winning the Fight Against Hepatic Lipidosis

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Introduction

Hepatic lipidosis (HL) is a *syndrome* that develops secondary to a primary health problem in > 90% of cats, or as a consequence of starvation. You need to find the underlying problem.

Clinical Features

Although cats of any age may be affected, most are middle aged neutered adults (7 [0.5-20] years), with history of over-conditioning (BCS ≥ 4/5), and inappetence (2-7 days; >90%) and usually an ~25% loss of body weight (dehydration & body condition). Weight is primarily lost from peripheral tissues while abdominal fat is conserved. Gastrointestinal signs are most common: vomiting in ~38%, variable diarrhea and/or constipation. Other historical features reflect underlying/primary diseases.[1,3] Jaundice (~70% cats) and non-painful smooth hepatomegaly are notable on physical examination. Severe electrolyte derangements (marked hypokalemia or hypophosphatemia) may provoke profound head/neck ventroflexion. Ptyalism is common and may reflect nausea or hepatic encephalopathy (HE). Severe weakness and recumbency may reflect symptomatic electrolyte disturbances (potassium, phosphate), thiamine (vitamin B_1) deficiency, or a primary disease. Electrolyte disturbances may contribute to gastric and intestinal dysmotility and vomiting that complicate alimentation (usually before electrolyte correction). Ultrasonography discloses diffuse hepatic hyperechogenicity that may over-shadow a primary hepatobiliary disease process.

Clinicopathologic Features

Hematology

Poikilocytosis (~63% initial blood smears) is common. Heinz bodies may suddenly appear and lead to symptomatic anemia and death; may follow oxidant challenge imposed by drug or anesthetic agents or reflect a primary illness (e.g. diabetes mellitus, other liver disorders, hyperthyroidism, pancreatitis).[4] Anemia (~22% cats on presentation) may develop secondary to phlebotomy, hemolysis (Heinz bodies, severe hypophosphatemia) or provoked blood loss (i.e. feeding tube placement). Depending on the decade examined, ~25-40% of FHL cats in the author's hospital have required blood component therapy (whole blood, packed RBCs, or fresh frozen plasma). Leukograms reflect underlying diseases as FHL lacks necroinflammatory features.

Serum Biochemistry

Increased liver enzyme activities (ALP, ~84%; ALT, ~72%; AST ~91%, □GT, 61%), subnormal BUN (~44%) despite initial dehydration (impaired urea cycle function presumed), and hyperbilirubinemia (variable magnitudes) are common . There is no diagnostic value in fractionating bilirubin. Cats with primary necroinflammatory liver disease (e.g. cholangiohepatitis, extrahepatic bile duct occlusion [EHBDO], bile duct carcinoma), pancreatitis or pancreatic adenocarcinoma develop high □GT activity; ~30% of cats have ≥ 3-fold increase in □GT compared to ~60% with ≥ 3-fold increase in ALP. ~18% have a greater fold increase in □GT relative to ALP coordinating with comorbid disorders.[5] This unique feature increases clinical suspicion of underlying conditions. Subnormal albumin ~65% of cats (before fluid therapy) reflects complex influences on albumin (synthesis, turnover) and malnutrition. Hyperglobulinemia is rare and hypoglobulinemia occurs ~18%. Concentration of cholesterol and glucose reflect primary disease processes. Despite diffuse hepatic steatosis, few cats present hypoglycemic (~ 4%) whereas ~53% are hyperglycemic (initially) reflecting either over-conditioning or a feline stress response (~ 3-4% are Diabetics). A subset (~56% cats) develop mild/marked increased creatinine kinase reflecting muscle injury (i.e IV catheter or feeding tube placement, muscle catabolism, recumbency, rhabdomyolysis due to electrolyte depletions [i.e., hypokalemia, hypophosphatemia], or a primary disorder).

Electrolyte Abnormalities

Importantly contribute to morbidity and mortality; hypokalemia increases risk for death.[3] Hypokalemia, hypophosphatemia, and/or hypomagnesemia present in ~31%, ~15%,~ 21% of cats, respectively, or develop after fluid therapy or subsequent to a re-feeding syndrome. Severe hypokalemia and hypophosphatemia increase risk for RBC hemolysis (hypophosphatemia), muscle weakness, enteric atony and vomiting, head/neck ventroflexion, and neurobehavioral changes confused with HE. Anticipated refeeding electrolyte disturbances are now commonly averted by prophylactic IV electrolyte supplementation (KCl, K-phosphate, with frequent monitoring). Lipiduria is common and likely reflects renal tubule lipid vacuolation; a buoyant lipid phase may be observed in centrifuged urine. Renal tubular potassium wasting has been verified in a subset of cats; this may resolve with FHL resolution.

Coagulation Assessments

Coagulopathies are more reliably detected using a test sensitive to Vit. K_1 sufficiency (PIVKA clotting test, Thrombotest, Nycomed).[6] Routine bench PT, APTT, and PIVKA tests were abnormal in ~26%, ~30%, and ~59% of FHL cats. Coagulopathies usually respond to parenteral Vit.K_1 (1.0 mg/kg, IM or SC, @ 12 hour intervals x 3). Routine early Vit. K_1 supplements facilitate uneventful catheter and feeding tube placement and hepatic tissue aspiration. Coagulopathy in > 50% of cats dictates initial venipuncture using peripheral veins that allow pressure assisted hemostasis. Cystocentesis, jugular catheter insertion, urethral catheterization, and feeding tube placement should be delayed until after a Vit. K_1 response interval.

Blood Gas Analyses

Venous blood gas (on presentation) demonstrate metabolic acidosis in ~33%, reduced strong ion difference in ~87%, and increased unmeasured anions in ~82%. Changes are consistent with accumulated ketones and lactate. Cats with spontaneous clinical and experimentally induced FHL demonstrate propensity for hyperglycemia and accumulate plasma ketones within range observed in diabetics (□-OH butyrate from 0.5 to 8.9 mmol/L). Experimental FHL confirmed ketone accumulation as early as 7 days of "self imposed fasting". Ketone concentrations in experimental FHL have been lower than observed in clinical cases because of early rescue strategies. Similar ketosis (~5–7 mmol/L) develops in humans fasted 1-23 days. Longer fasts coordinate with higher ketone concentrations, as seen in FHL.[9] High lactates have only been confirmed in a small number of cats (limited testing).

Liver Function Tests

Serum Bile Acid (BA) tests are redundant in FHL as hepatobiliary jaundice is overt. Fractioned BA (blood & urine) from cats with FHL, EHBDO, and healthy cats disclosed significantly reduced secondary BA concentrations in FHL & EHBDO. Since secondary BA are derived from enteric bacterial dehydroxylation of primary bile acids, findings implicate impaired enterohepatic BA circulation likely linked to canalicular collapse ultrastructurally observed.[14] This reconciles with apparent Vit. K_1 insufficiency. *Blood Ammonia-* concentrations are inconsistently increased in clinical FHL. Experimental FHL demonstrated NH_3-intolerance commensurate with insufficient quantities of essential amino acids implicating compromised urea cycle function. Similar amino acid changes develop in spontaneous FHL.[12,15] Ammonium biurate crystalluria has not been documented in FHL.

Presumptive Diagnosis

Based on signalment, physical and clinical features, abdominal ultrasound and aspiration cytology of liver (after vitamin K_1 [24 hrs]). Cytosolic vacuolation should be evident in > 80% of hepatocytes.

Is Liver Biopsy Necessary for HL Diagnosis?

Liver biopsy is not necessary for presumptive diagnosis of HL; this is usually based on hepatic cytology, finding a diffusely hyperechoic hepatic parenchyma on US, compatible biochemical features, and history of over-conditioning and inappetence. Liver biopsy (or other tissues) is reserved for cats with suspected comorbid conditions requiring definitive histologic diagnosis or cats with recalcitrant HL (rigorous supportive care does not resolve/improve clinicopathologic features within 2-wks). However, cytology can be misleading unless sufficient hepatocytes are sampled (several different areas), and percentage of severely vacuolated cells estimated- you must see > 80% of hepatocytes that are heavily vacuolated with triglyceride (TG) membrane bound vacuoles. It is important to realize that ill cats commonly display hepatic TG vacuolation. Cholangiohepatitis, EHBDO, and some neoplastic disorders are not defined cytologically, similar to inaccuracy of small needle-core biopsies.

Vitamin & Anti-Oxidant Sufficiency

Water Soluble Vitamins

The liver stores and activates many water soluble vitamins required as cofactors for enzymes essential to cell function, intermediary metabolism, and energy production. Cats have an apparent susceptibility for both thiamine and cobalamin depletion. There are few investigations of B vitamin sufficiency in the cat. In ill inappetent cats, depletion of other B vitamin(s) remains possible.

Dose

To thwart potential water soluble vitamin deficiencies, a doubled daily maintenance dose of fortified water soluble vitamins (with thiamine concentration ~50 mg/ml) is recommended; 2 ml/L fluids. Fluids containing B-vitamins should be protected from direct light (tin foil scrunched over the administration set; large black garbage bag over the fluid bag and administration set).

Thiamine (Vitamin B_1)

Thiamine deficiency can induce neurologic signs confused with HE or neurologic injury (Wernicke's Encephalopathy). Cats with suspected B1 deficiency demonstrate central vestibular signs (cerebellar signs), dilated non-responsive pupils, head/neck ventroflexion, abnormal postural reactions, hypothermia, hypotension, and stimuli

induced seizures. Deficiency is deduced if clinical signs remit after thiamine supplementation. Ensuring thiamine adequacy is essential prior to feeding, as thiamine requirements increase with carbohydrate metabolism. Feeding a cat with an uncorrected thiamine deficiency can provoke lactic acidosis and non-reversible neurologic injury (Wernicke's Encephalopathy) confused with HE. We avoid supplementation with injectable thiamine because of rare vasovagal responses and neuromuscular paralysis observed in a few cats and dogs given parenteral (IM) thiamine. Rather, oral tablets are used for supplementation.

Dose

50 to 100 mg PO q12hr x 1-3 days, followed by 50-100 mg/day per cat. Fortified B-vitamin supplements are added to IV fluids to provide a continuous slow and steady thiamine supplement.

Cobalamin (B_{12})

Cats chronically malnourished due to small intestinal disease or pancreatic insufficiency (rare) or maintained on chronic oral antimicrobials may develop B_{12} deficiency. Of 58 sequentially tested cats with HL, low cobalamin was documented in 58%. A subset of these cats given B_{12} before sample collection, had supraphysiologic B_{12} concentrations (>5,000 pg/mL) on measurement. Insufficient B_{12} compromises function of the tricarboxylic acid cycle (mitochondrial toxicity) and complex II of the respiratory chain (methylmalonic acid accumulation) and □-OH butyrate dehydrogenase (resulting in ketosis).[10] Supplemented cyanocobalamin requires cyanide removal and activation by addition of an adenosyl or methyl group synthetic pathways dependent on folate, other B vitamins, and SAMe. It is unknown if B_{12} deficiency is causally linked with HL or reflects antecedent conditions or long term inappetence. The conventional laboratory B_{12} assay cannot distinguish inactive from functional vitamin B_{12}. Baseline and sequential testing are used to tailor chronic B_{12} supplementation.

Dosing

0.25 to 0.5 mg/cat given on first day of hospitalization*, AFTER collection of baseline B_{12} sample*. Baseline and sequential testing allows tailoring of chronic supplements to maintain B_{12} within reference ranges.

Fat Soluble Vitamins- Vitamin K & Vitamin E

This may require supplementation due to enteric malabsorption secondary to reduced enterohepatic bile acid circulation in severe HL likely related to the canalicular collapse observed on transmission electron microscopy. Chronic inappetence also contributes to vitamin depletions. We suspect that cats do not maintain long-term vitamin K stores owing to the frequency of vitamin K responsive coagulopathies observed in HL.

Vitamin K_1

This should be given parenterally as soon as HL is a considered diagnosis (first 12-hrs). This often corrects coagulation abnormalities typical of HL such as prolonged PIVKA clotting time (proteins invoked by vitamin K antagonism) or prolonged Prothrombin time. Parenteral dosing is necessary because enteric uptake of fat soluble vitamins is limited by the reduced bile acid enterohepatic circulation needed to assimilate fat soluble vitamins. Dramatic correction of coagulopathies in HL follow Vitamin K_1 administration, corroborating concern that cats have only marginal stores of this fat soluble vitamin. It is possible that cats have a slow capacity for reactivation of Vitamin K in the Vitamin K epoxidase cycle.

Dosing

0.5 and 1.5 mg/kg Vitamin K_1 is given SC or IM, q12hr x 3 doses, repeating treatment once or twice weekly. *This should never be given IV* because of concern for anaphylactoid reactions. Avoid every day administration of Vitamin K_1 as this will lead to development of Heinz body hemolytic anemia.

Vitamin E (□-tocopherol)

Whether or not vitamin E is insufficient in HL cats is unknown. However, circumstantial evidence suggests it may be subnormal: 1) finding low liver glutathione (GSH) reflecting oxidative utilization of other antioxidants, 2) concurrent presence of low Vitamin K- also a fat soluble vitamin, 3) depletion of vitamin E in similar hepatic disorders (hepatic lipidosis in humans and experimental animal models), and 4) bile acid profiles in HL consistent with impaired enterohepatic bile acid circulation (reduction in secondary bile acids formed in the gut) as occurs in complete major bile duct obstruction. Restitution of vitamin E would importantly restore its function as an important membrane terminator of peroxidative injury and protection against oxidative challenges imposed by cholestasis.

Dosing: Initially use the water soluble form of □-tocopherol: polyethylene glycol alpha tocopherol succinate: 10 U/kg/ PO q24hr.

Thiol Donor Supplementation

Similarities between feline HL and kwashiorkor in children (low protein malnutrition associated with lethal hepatic lipidosis) includes finding low liver GSH concentrations, susceptibility to heinz body hemolytic anemia, cholestatic injury, and suspected subnormal vitamin E concentrations.[11,12] These findings argue for thiol

supplementation. Because liver is the major source of circulating GSH, it is not surprising that subnormal GSH has been confirmed in whole blood in cats with HL.[13] Thiol donors can preserve and replete GSH. Acute critical thiol administration can be given IV as N-acetylcysteine. More chronically thiol supplementation is provided by oral administration of bioavailable SAMe.

N-Acetylcysteine-Crisis Rx

Intravenous N-acetylcysteine (NAC) is initially dosed at 140 mg/kg using a 20% solution diluted 1:4 with saline or 5% dextrose. Thereafter,70 mg/kg IV q6-12hrs. NAC is administered IV through a 0.25 um nonpyrogenic filter over 20-minute interval. Longer infusions may impair urea cycle ammonia detoxification.

SAMe

Once enteral dosing is possible, NAC treatment is converted to enteric coated SAMe tablets (Denosyl-SD4™, Nutramax, Inc.)

Dose

20 mg/kg PO q24hr on an empty stomach. While enteric coating improves bioavailability, administration of tablets can be problematic. Crushing tablets and administering with food reduces SAMe bioavailability (doubling of SAMe dose is recommended in this circumstance). However, it is generally accepted that SAMe tablets should not be crushed. Administration via a feeding tube is strongly contraindicated as the drug may irreparably clog the feeding appliance.

Acute Case Management

Suspect Bleeding Tendencies

A vitamin K_1 responsive coagulopathy is common in HL and should be routinely treated with parenteral vitamin K_1 , as described previously. Provide 0.5-1.5 mg/kg SQ or IM giving 3 doses over 24 hours at q12hr intervals. Do not insert jugular catheters, perform cystocentesis, or place an esophagostomy or gastrostomy-tube *before vitamin K repletion.*

Body Condition Assessment

Assessing lean body mass is essential as this weight should be used to formulate fluid and drug dosing in over-conditioned cats.

Fluid Therapy

Avoid dextrose supplementation (promotes hepatic fat accumulation and hypokalemia due to urine electrolyte wasting). Lactate intolerance may exist: thus avoid lactated ringers. Acetate metabolism may be compromised: thus avoid acetate supplemented fluids. Initially use: 0.9% NaCl, *supplemented with electrolytes and B-vitamins.*

Electrolyte Abnormalities

These are an important cause of patient morbidity and mortality in HL and their management is crucial to case recovery. Hypokalemia, hypophosphatemia, and/or hypomagnesemia are initially identified in 30%, 17%, 28% of cats, respectively. Severe hypokalemia and hypophosphatemia increase risk for hemolysis (hypophosphatemia), and can cause muscle weakness, “silent” gut atony thwarting feeding attempts (vomiting: associated with gastric, intestinal, or esophageal dysmotility or stasis, head/neck ventroflexion, inability to concentrate urine (promotes dehydration and electrolyte losses), and neurobehavioral changes confused with hepatic encephalopathy. Head ventroflexion also may reflect thiamine deficiency. Low potassium and phosphate can develop in response to the **ReFeeding Syndrome**: *see below. Hypokalemia* is the most common electrolyte abnormality in HL and is exacerbated by the Re-Feeding syndrome. *Severe hypophosphatemia* also can develop within 48-hours of feeding with clinical signs developing when phosphate $\leq$ 1.5 mg/dl. Symptomatic hypomagnesmia is uncommon but effects can be profound and confused with hypokalemia and hypophosphatemia. Signs of *Thiamine deficiency* also may appear in unsupplemented patients owing to its involvement in enzymatic reactions involving glucose metabolism.

Re-feeding Syndrome

A potentially lethal condition involving severe electrolyte and fluid shifts invoked by sudden metabolic adaptations in malnourished patients undergoing initial re-feeding (oral, enteral, or parenteral). This should be anticipated in all HL cats. Shifted metabolism promotes insulin release and cell uptake of glucose, phosphate, potassium, magnesium and water, and enhances protein synthesis. Nutritional support intensifies requirements for phosphate, potassium, glucose, water, and increases demand for ATP, 2,3 diphosphoglycerate (2,3 DPG), and creatine kinase (CK). Prodigious decline in potassium and phosphate may occur within 24-48 hours of initial food intake.

Potassium Supplementation

Hypokalemia imparts neuromuscular signs and cardiac arrhythmias when ≤ 2.5 mEq/L (membrane hyperpolarization) and is significantly associated with failure to survive. Initial KCl supplementation is based on the conventional sliding scale (shown below) with the administration rate restricted to < 0.5 mEq/kg/hr.

Serum K concentration parenteral fluid therapy	***Amount KCl per 250 ml***
> 3.5 mEq/L	5 mEq
3.0-3.5 mEq/L	7 mEq
2.5-3.0 mEq/L	10 mEq
2.0-2.5 mEq/L	15 mEq
< 2.0 mEq/L	20 mEq

Never exceed a rate of 0.5 mEq/Kg/hour = cardiotoxic

Judicious titration of potassium supplementation is tailored using twice daily potassium assessments during the first week. It is essential to account for all potassium sources during supplementation (KCl in fluids and K phosphate for management of hypophosphatemia) to avoid iatrogenic hyperkalemia.

Phosphate Supplementation

A CRI of K phosphate: 0.01 to 0.03 mmol/kg/hr is given at initial feeding, but may require upward titration. Phosphate status must be monitored twice daily to avoid over-supplementation; otherwise, K phosphate is slowly tapered over 36 hours after sustained phosphate concentrations have normalized.

Magnesium Supplementation (CAUTION: Rarely needed can have severe side effects)

Acute treatment: IV magnesium using magnesium sulfate (8.13 mEq/g) and magnesium chloride (9.25 mEq/g) salts, (available as 50% solutions) but given as 20% solutions (or lower) in 5% Dextrose and water. *Initial dose:* 0.75 to 1.0 mEq/kg/day administered by CRI for the first day, with lower dose of 0.3 to 0.5 mEq/kg/day given for an additional 2-5 days (slow restitution of magnesium stores occur in true deficiency). Treat overdose with calcium gluconate (IV), 50 mg/kg slow bolus followed by 10 mg/kg/hr CRI.

We rarely intervene with magnesium supplement unless we encounter intractable hypokalemia which may not correct until magnesium is corrected. Hypokalemia in this circumstance appears to be due to the direct effect of low cytosolic magnesium on potassium channels and enhanced renal losses of potassium.

Nutritional Support -
Initial Feeding= Oral or Nasogastric (NG) Feeding.

Use NG if cat objects to oral feeding (salivates, vomits, struggles) to **avoid Feline Food Aversion.** NG tubes (5-8 french) are NOT appropriate for long term feeding (nasopharyngeal discomfort, retroflex with emesis, and require an Elizabethan collar). Yet, some cats have recovered from HL with NG feeding.

Energy Allowance

The quantity of food ingested must provide adequate energy and protein to avoid catabolism; 40-60 kcal of metabolizable energy/kg ideal body weight per day. A balanced feline diet should be used; **protein restriction is strongly contraindicated**. Liquid enteral human formulas lack adequate taurine and arginine/citrulline for cats and must be supplemented.

Esophagostomy (E-Tube) / Gastrostomy (G-Tube) Feeding

Placed after improved hydration and electrolyte status, and vitamin K_1 therapy such that cat can tolerate anesthesia and not have a bleeding crisis. E-Tubes are associated with the fewest critical complications.

E-Tube

10-12 French; avoid highly pliable silicone tubes easily retroflexed. A thoracic radiograph is mandatory after E-tube placement to verify its position cranial to gastroesophageal junction (insertion into stomach increases risk for reflux esophagitis).

G-Tube

Mushroom tipped (not foley catheters) ≥ 20 French permit greater food variety, easier feeding, amenable to trickle feeding approach. Best placed percutaneously with endoscope; biopsies of stomach and duodenum collected if appropriate. Surgically placed G-tubes impose greater risk and suffer more complications. Premature G-tube removal (within 2-3 weeks) may lead to septic peritonitis. This is not the preferred route of feeding in HL.

Feeding Tube Care

Maintain tube hygiene by flushing with tepid water after use, using a minimal volume. Avoid administration of congealing medications through feeding tubes (e.g., SAMe, L-CN). Aspirate G-Tube before feeding to evaluate gastric emptying: >10 ml indicates gastric hypokinesia warranting assessments of electrolytes and tube related problems. The site of any tube insertion should be inspected daily (first 10 days) and any discharge cytologically inspected (is it food or infection ?). Triple antibiotic ointment and a supportive aseptic wrap are recommended. Some cats require an Elizabethan collar to avoid tube mutilation / removal. Bandages concealing G-Tubes should have the tube outline traced on the bandage surface to prevent accidental cutting of the tube during bandage change.

Resolving Tube Occlusions

Use solutions that can digest food: Coca Cola, papaya juice, or pancreatic enzymes. Retain solution for 20-40 minutes then hydropulse with tepid water.

Feeding Regimen

Initial feeding of 15 ml of lukewarm water, 1-time tests the likelihood of emesis /gastric atony (wait for 2-4 hrs before continued feeding). The amount of food allowed is progressively increased over 2-4 days to achieve 250 -400 kcal/day for an average sized cat. Feeding can immediately commence in cats after a nasogastric and E-tube insertion (after recovery from any sedation). Initial feeding is delayed 24-hrs after G-tube placement awaiting return of gastric motility and formation of an initial wound seal around the stoma. Daily food intake is divided into 4 or more meals per day based on physical tolerance. If meal feeding is not tolerated, than trickle feeding is undertaken. Upon initiation of food intake, caution is taken to protect against pathologic electrolyte depletions characteristic of the "Refeeding Syndrome" (see above)

Trickle Feeding

This is accomplished using an infusion pump and a liquefied diet. The daily food intake is given over a 12 to 24 hour “trickle interval”. While trickle feeding is best done using a G-tube, it can also be accomplished with a NG-or E-tube. Re-new food q4-6 hours to avoid bacterial contamination. With G-tube- monitoring of residual volume relfecting gastric hypokinesis should be assessed at q8-12-hrs intervals. If aspirated gastric volume >hourly delivery rate of food, then feeding should be discontinued for several hours, electrolytes revaluated, and other potential causes of gastric hypokinesis investigated. If no complications are detected, the hourly feeding rate is reduced by 20%. A continued trend of high residual gastric volume warrants evaluation of tube position.

Persistent Vomiting

Consider: electrolyte derangements (enteric hypomotility), nausea (hepatic disease or drug therapy), G-tube dysfunction / displacement (pyloric obstruction ?), or E-tube displacement, or underlying primary disease (IBD, pancreatitis). Tube investigation may require contrast radiography or ultrasonography. Changing “meal” feeding to “trickle feeding” eliminates emesis in some cats.

Antiemetics

After ruling out correctable causes of emesis a number of drugs may be tried.

Metoclopramide (Reglan®)

As a constant rate infusion (CRI, 0.01-0.02 mg/kg/hr IV forr 24 hours) in cats trickle fed, or as a bolus dose in cats meal fed (0.2 - 0.4 mg/kg SQ or PO) 20-30-minutes before feeding, 4 doses per day). Metoclopramide is prokinetic and may stimulate gastric and intestinal motility. It also functions as a central antiemetic (perhaps not effective in cats?). The prokinetic effects however, may help thwart emesis. Reduce dose by $\geq$ 50% in renal insufficiency. *Overdose:* results in tremors or frenzied behavior, and may be worsened by concurrent administration of phenothiazine antiemetics (dopamine antagonism). Alternative antiemetics include: *Ondansetron (Zofran®)*, *Dolasetron* (*Anzemet®)* antiemetics with 5 HT_3 receptor antagonist activity (CNS, GI tract) mediating nausea/vomiting via chemoreceptive trigger zone, or *Maropitiant (Cerenia®)*.

Ondansetron Dose: 0.1 to 0.2 mg/kg q 6 to 12 hours up to 0.5 mg/kg q12hrs.

Dolasetron Dose: 0.6-1.0 mg/kg IV or PO q24hrs. No adverse feline effects have yet been identified with these drugs with the suggested dosing regimen. In humans, ondasetron may cause-dizziness and dolasetron may initiate a prolonged PR interval, heart block and bradycardia, with hypokalemia a recognized risk factor. Electrocardiographic changes may initiate a malignant arrhythmia.

Maropitiant (Cerenia®) is a neurokinin-1 (NK-1) receptor antagonist that inhibits substance P binding to NK-1 receptors located in the emetic center, chemoreceptor trigger zone, and enteric plexus of the gut (when stimulated

these sites initiate or lead to emesis). *Dose:* initially recommended at 1 mg/kg IV, SC, or PO q24hr (given once) and then repeated at 36 to 48 hours (has a 13-17 hr $T_{1/2}$).

Butorphanol may provide an antiemetic effect when combined with other antiemetics and given at a low dose of 0.1-0.2 mg/kg SC q12hrs.

Exercise

May stimulate enteric motility; 15-30 minutes free walking in non-stressful environment (no barking dogs) during owner visit and before feeding in meal fed cats.

Appetite Stimulants

Appetite stimulants (e.g. diazepam, clonazepam, cyproheptadine, mirtazapine) *are unreliable* for ensuring adequate energy intake in HL. We prefer feeding tube assisted nutrition.

Diazepam (*dose:* 0.05 to 0.2 mg/kg IV before voluntary food ingestion) requires hepatic biotransformation and imposes risk (albeit low) for idiopathic fulminant hepatic failure; injectable diazepam also may deliver an oxidant challenge (propylene glycol). Idiopathic hepatotoxicity has also been observed with clonazepam and cyproheptadine given as appetite stimulants.

Propofol, was once suggested as an antianorexic in inappetent cats and is strongly contraindicated for this purpose owing to its pro-oxidant, sedative, and potential mitochondrial toxic effects.

Cyproheptadine: 0.2-0.5 mg/kg PO q12hr can provoke unpleasant antiserotonergic effects associated with anxiety, excitability, aggression, and vomiting.

Mirtazapine acts as an appetite stimulant in humans, dogs, and cats and also imparts an anti-nausea effects. Mirtazapine has extensive hepatic metabolism, with desmethylmirtazapine the only pharmacologically active metabolite. Among side effects reported for humans are: drowsiness, dry mouth, constipation, and weight gain, with rare hepatotoxicity. In cats, high doses may lead to hyperexcitability and muscle tremors. *Recommended dosing of mirtazapine* in cats is no greater than 1 mg/kg body weight q24hrs or 1.88 total dose per cat. How many doses may be safely given is undetermined; in one study a 1.88 total dose/cat was given to healthy young cats for 6 consecutive days with no adverse side effects. It has been suggested to reduce customary doses of mirtazapine by 30% in cats with liver disease- but there are no studies regarding this recommendation in veterinary patients.

L-Carnitine (CN) Supplementation

Hepatic CN synthesis may be limited during catabolism, or secondary to hepatic dysfunction. It is also possible that substrates needed for L-CN synthesis are unavailable (lysine, SAMe [methionine]), Fe^{2+}, Vitamin C, succinate, and pyridoxal phosphate [vit. B_6]). Ability to strategically provision CN for hepatic FA oxidation/dispersal and for mobilization of hepatic FA from the liver remains undetermined. It is important to use oral L-CN sources that have proven bioavailability (medical grade: Carnitor® or Quinacarn®). Studies in obese cats confirm that CN can enhance FA oxidation during weight loss, attenuate hepatic TG accumulation, and may facilitate urinary elimination of CN-esterified FA.

Dose: 250-500 mg CN /cat per day using a bioavailable pharmaceutical product.

Amino Acid Supplementation

Taurine

Short-term taurine supplementation (an essential feline amino acid) is recommended based on low plasma taurine concentrations in HL and the obligatory conjugation of bile acids with taurine. Taurine conjugated bile acids undergo both biliary and renal elimination. Serum bile acids are profoundly increased in HL cats – similar to extrahepatic bile duct obstruction in bile acid profile. This likely reflects canalicular collapse, observed on transmission EM study. Prodigious losses in urine with bile acids likely occurs in HL. Taurine also influences other physiologic/metabolic processes important in HL such as membrane calcium flux, membrane stabilization, detoxification reactions, and antioxidant protection.

Dose: 250 mg/day for 7-10 days or longer if a human enteral diet is being fed or if ursodeoxycholate is being used as a therapeutic intervention (we are not sure the latter is appropriate in the HL cat) see below.

Arginine: Supplementation (essential amino acid) is recommended if a human enteral diet or designer diet is fed to ensure adequate arginine for urea cycle function.

Dose: 1 gram/ 8 fl oz can (250 mg/100 kcal) diet.

Ursodeoxycholic Acid (UDCA)?

I do not recommend UDCA in HL: 1) all bile acids impose cytotoxicity in high concentrations (bile acids are extremely high in HL), 2) high bile acids impair hepatic TG egress, 3) there is no evidence that UDCA improves similar disorders (humans, rodents), 4) HL has no necroinflammatory/fibrotic component for which UDCA is helpful, 5) HL recovery is acute, before UDCA may impart benefit, and **6)** cholestasis is associated with canalicular dysfunction and compression which may compromise UDCA utility.

Drugs to Avoid

A number of drugs are specifically contraindicated in HL, including: stanozolol (a 17-alpha alkylated steroid) (enhances hepatic HL); tetracyclines (enhances hepatic HL); drugs imposing oxidative challenge: such as propylene glycol as the carrier in diazepam and etomidate, propylene glycol in semimoist pet foods, propofol (phenol derivative) that has caused hemolysis in severely ill HL cats (despite a publication suggesting that does not occur), onion powder (flavoring), cetacaine and benzocaine (local anesthetics used for tracheal intubation), high dose buprenorphine may impair mitochondrial respiration and ATP formation, sedatives requiring glucuronidation (diazepam, oxazepam) may have a prolonged resident time, and drugs associated with idiopathic hepatic necrosis (benzodiazepines, cyproheptadine). Care must be taken in calculating the appropriate vitamin K dose as too much imparts an oxidant challenge.

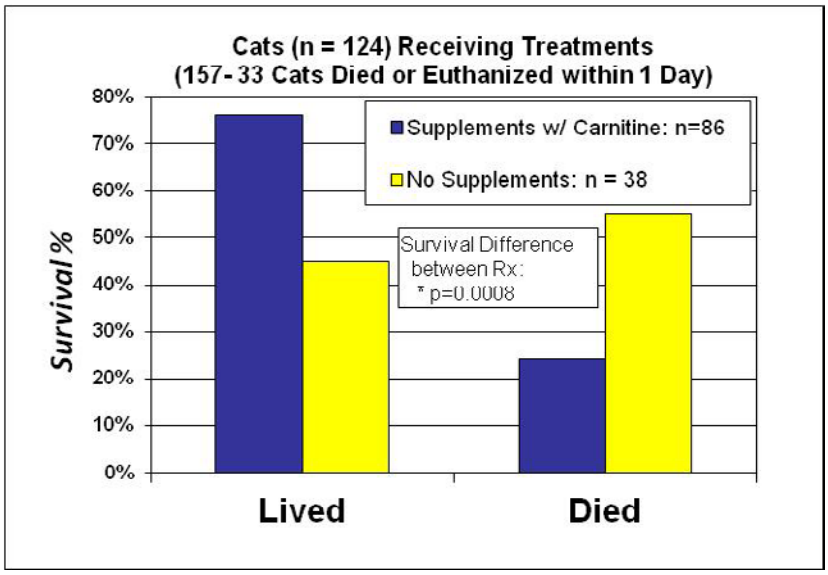
Predicting Recovery

Clinical recovery is demonstrated by gradual reduction in serum enzymes and total bilirubin concentrations. Generally, within 10 days the bilirubin concentration declines by $\geq$ 50% while serum enzyme activity may remain near admission values. Cats successfully recovering require approximately 10 days of hospitalization; those succumbing typically do so within 7 days. Some survivors require protracted hospitalization.

Do Supplements Make a Difference?

Survival statistics-Nutritional support with a premium cat food (e.g. Maximum calorie, a/d) with or without metabolic supplements in cats surviving the initial 96 hours (n=86 supplements, n=36 no supplements) suggests that supplements significantly improve survival.

Data: NYSCVM, Center SA.



Treatment Pearls

1. *Procedures* requiring *sedation/anesthesia* should be delayed until electrolyte and hydration perturbations resolve. The FHL cat is in metabolic crisis with high risk for anesthetic and surgical complications. Vit K_1 treatment and correction of electrolyte and fluid deficits are imperative.
2. *Base fluid & drug dosing on Lean Body Weight in overconditioned cats.*

3. *Fluid Therapy*: avoid dextrose supplementation (may reduce adaptive □-oxidation, worsen electrolyte depletions [in urine], contribute to ketosis), avoid lactate (likely have high lactate already), acetate also may not be appropriate; judiciously supplement KCl and K-phosphate correcting aberrations and in anticipation of a "Refeeding Syndrome".
4. *Avoid drugs & toxins* suspected to promote hepatic steatosis (humans, HL models, cats) include: endotoxin, stanozolol (Winstrol-V;FHL in renal insufficient cats fed a protein restricted diet), tetracyclines, glucocorticoids, bupivacaine & buprenorphine (humans: buprenorphine is a lipophilic protonatable amine metabolically activated and concentrated in mitochondria; may impair respiration and ATP formation), repeated/prolonged propofol anesthesia, drugs with propylene glycol carrier (i.e. etomidate, diazepam), oxidants, drugs with high risk of hepatotoxicity.
5. *Antibiotics-* individualize therapy to primary disease process; endotoxin may be a causal factor in infections (abscess, pyelonephritis, constipation, inflammatory bowel disease, pancreatitis).
6. *Antiemetics:* metoclopramide CRI or mirtazapine (no side effects yet noted in HL cats). Metoclopramide advantageously stimulates enteric motility and may be useful during initial introduction of enteric feeding.
7. *Gastroprotectants:* Are these necessary? Individualize Rx for clinical signs & primary disease process.
8. *Water Soluble Vitamins:* ensure B_{12} adequacy, submit plasma B_{12} test before administering 250-500 ug/cat (SC or IM). *Thiamine:* 100 mg PO BID x 2 days then 50-100 mg PO/day; consider possible vasovagal episode and neuromuscular paralysis with parenteral thiamine injections. Use f*ortified B-Vitamin supplement in IV fluid therapy.*[1] Cover fluid lines to avert photo-degradation of B soluble vitamins.
9. *Vitamin K_1:* 0.5-1.5 mg/kg SQ or IM (not IV) x 3 doses q12hr intervals; irrespective of coagulation tests.
10. *Vitamin E:* 10 iu/kg mixed □-tocopherols, with food as supplemental antioxidant; Vit. E is not synthesized by mammalian cells. May assist in detoxification of cyanide removed from therapeutic B_{12} (cyanocobalamin).
11. *S-Adenosylmethionine (SAMe)-* essential methyl donor and for GSH synthesis; 20-40 mg/kg PO SID has antioxidant effect in liver.[27]
12. *L-Carnitine:* 250-500 mg/cat per day PO, only medical grade or soluble certified L-CN
13. *Feeding:* oral feeding can rescue some cats but food aversion may importantly delay recovery. Preferred feeding route is by E-tube. Initial feeding is by nasogastric intubation using a liquified diet such as CliniCare. An E-tube is inserted after achieving fluid and electrolyte balance, coagulopathy abated with Vit. K_1, when the cat can withstand the stress of sedation/anesthesia.
14. *Avoid protein restricted foods,* rather, use balanced feline diets formulated for critical care patients (i.e. Maximum Calorie, A/d). Allow exercise to stimulate enteric motility.
15. *Do Appetite Stimulants Work in HL?:* probably not, we see many HL cats treated with this approach; potential for hepatotoxicity with some stimulants (i.e. diazepam, oxazepam) although rare.

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NOTES:

Are You Comfortable with Feline Constipation?

Craig Webb, DVM, PhD, DACVIM

Introduction

Constipation is not usually thought of as a terminal disease…unless you are a cat. In that case, constipation, and its potential progression to obstipation and megacolon can eventually result in euthanasia in a tragic number of cases. The list of causes of feline constipation is far longer than the list of cures, or even effective treatments. Gastrointestinal motility is impacted (no pun intended) by a myriad of conditions external to the GI tract as well as within the GI tract itself. To make matters even more complicated – we are, after all, talking about cats – the clinical manifestation of feline constipation can show itself far away from the source, with vomiting be a common clinical presentation.

Clinical Presentation

History and Physical Examination

A bit of constipation, acute in onset and short in duration, can afflict any cat, may not be recognized by the owner, or may not progress to the point where clinical signs motivate the owner to seek out veterinary care. Although diarrhea usually makes itself relatively obvious, whether in the litter box or on the living room floor, the dry, hard feces that makes its way out of a constipated cat may appear quite normal, or at least potentially normal, having likely dried out after-the-fact, especially when coated with litter. The other clinical manifestations of constipation are the ones that more often prompt an owner to seek veterinary care: vomiting, decreased appetite and/or water intake, decreased social interactions, and vocalization when attempting to defecate would all be consistent with feline constipation.

Evaluation of the cat begins with signalment and presenting complaint – which as mentioned, may or may not involve the area or even the "end" of interest. As our profession is becoming more and more aware of the subtleties and complexities of our feline patients, our history-taking is becoming more sophisticated and complete. Onset, duration, progression, other associated clinical signs, history of disease or surgery, medication use and response, a complete dietary history including supplements, probiotics, nutraceuticals, water intake, potential stressors or changes, perceived or known changes in weight or body condition, activity level, normal ambulation and activity/interactions, indoor/outdoor and environmental conditions are all important aspects of the case. Also of particular interest will be a historical assessment of the litter box arrangement (number and actual structure of the box, location, type of litter), litter box behavior if witnessed (ease of entry, any vocalization, straining, number of unproductive attempts) and the character of the stool (a sample would help, keeping in mind that there may be some degree of desiccation with storage). It will be important to try and discern between descriptions of unproductive attempts at defecation and straining to urinate, the two problems may look quite similar to many owners. Again, this is not meant to be an exhaustive list of historical questions as the client's answers may well lead the clinician down important and productive tangents or expansions.

A complete physical examination should be a given for any cat presented for veterinary care. Avoid the temptation to focus on the presumed source of the problem, but instead, examine the patient for every normal aspect of any feline physical exam, and the abnormalities should then make themselves obvious. As with the history taking for feline patients, the appropriate physical examination has become more thorough and complex, including a fundic exam (ex. evidence of granulomatous lesions in FIP cats), hydration status and blood pressure, hair coat and cervical palpation, body weight, body condition score, muscle condition, and of course assessment of both neurologic status and orthopedic condition are no longer the realm of the canine. Obviously a careful examination of the peri-anal area, anal sacs, hip joints, and colonic palpation is critical. It is rare that we perform a rectal examination on a cat that is awake, although some tolerate a lubricated and gentle pinky-finger for assessment of anal tone. With sedation or anesthesia a more complete rectal examination can reveal masses, strictures, or other causes of mechanical obstruction, as well as more complete evaluation of anal sacs.

Many cats appear over-represented for megacolon, due in large part to a condition of sacrocaudal dysgenesis. These cats may demonstrate a number of neurologic or neuromuscular abnormalities, with colonic dysfunction being just one manifestation. Similar circumstances are present in cats with dysautonomia, where the GI tract is just one of many systems impacted by a generalized dysfunction of a portion of the nervous system.

Differentials

A common cause of constipation in the cat is dehydration: secondary to a disease process (CKD, DM, hyperthyroidism); a result of vomiting and/or diarrhea; diuretic drug use; restricted access to water; voluntarily decreased intake (stress, behavioral, environmental); pain (inflammation, trauma, disease within the oral cavity, abdominal disease, colitis, anal sac or rectal disease); decreased mobility or painful ambulation (musculoskeletal); dysfunctional thirst mechanism (CNS disease). Any physical obstruction (tumor or mass, stricture, foreign body,

fracture, intussusception, herniation) or functional obstruction (motility disorder, either secondary to GI inflammation, spinal cord disease, electrolyte imbalance, or primary, such as with megacolon or dysautonomia) will result in constipation. Colonic motility is also negatively impacted by a variety of drugs and medications. Obese cats appear at risk for constipation, probably for multiple reasons.

Pathophysiology and Diagnostics

The progression from constipation to megacolon occurs as normal colonic function is lost. The loss may be secondary to a persistent inability to move stool (obstruction) and includes secondary colonic hypertrophy, but in many cases an actual cause cannot be identified, hence the term, idiopathic megacolon. If there is an identifiable inciting cause for a cat's constipation, such as a pelvic fracture, or metabolic electrolyte abnormality, is appears that time is of the essence and early intervention/correction gives the cat the best prognosis for resolution.

Because the list of differentials for a constipated cat is extensive, the appropriate diagnostic work-up could be equally lengthy and involved. After a complete history and physical examination the obvious starting point is a biochemical profile, CBC, urinalysis, total T4, and abdominal radiographs. Follow-up diagnostic steps will depend largely on the clinical and diagnostic picture that is formed up to this point: colonic contrast with barium or air for suspected stricture; colonoscopy for infiltrative mucosal disease; CT or MRI for suspected neurologic disease; skeletal radiographs for fractures or arthritic conditions, abdominal ultrasound for extra-luminal masses, enlarged lymph nodes, or other systemic diseases, etc.

Non-Specific Therapy

Since dehydration is almost always a component of the presentation with a constipated cat, it is one of the most important aspects of non-specific therapy to be addressed. Depending on how the fluid therapy is going to be administered (IV, Subcutaneous, orally, feeding tube) it also represents an opportunity to address electrolyte balance, with potassium being critical for normal neuromuscular function. Various physical exam parameters are used to estimate percent dehydration, and then a variety of formulas exist to calculate the necessary volume of fluid administration to both correct dehydration and meet maintenance requirements. Different types of fluids are appropriate for rehydration, maintenance, and the make-up and degree of electrolyte balance. Clinicians are referred to the recent Davis et al. publication (JAAHA 2013) for a complete discussion of these various parameters. One of the simplest ways to increase fluid intake by cats is to encourage the feeding of canned foods, which are composed of 70% or more of water.

Specific Therapy

Rehydration is the first priority. Once the cat is well on the way to a normal hydration status, with correction of Electrolytes and acid-base status, steps can be taken to remove the feces from the colon – remembering that early intervention is an important step towards avoiding significant long-term consequences. At Colorado State University, many cases of mild to moderate constipation have been addressed with warm-water retention enemas (2-3 over the course of 12=24 hours, 5-10 ml/kg) followed by gentle manual extraction. In some cases this can be accomplished with gentle"milking" of the initial fecal ball followed by successful voluntary defecation. If not successful, brief general anesthesia and more persistent effort, combined with rectal lubrication and assistance is needed. In the worst cases, sponge forceps have been required.

More recently, manual de-obstipation is avoided if at all possible, and a variety of other interventions should be considered.

Laxatives are a potentially useful tool, and classified as lubricating (mineral oil), emollient (Colace ™, Surfax ™), stimulating (Dulcolax ™) or bulk-forming (cellulose), although most are considered only mildly efficacious, stimulating fluid transport and thereby improving the hydration and passage of feces. At CSU we administer most of these as part of an enema, frequently pre-treating with Cerenia ™**,** instead of attempting to get them into the cat orally.

Cathartics are used to increase colonic motility and generally believed to be more effective than laxatives. Lactulose is the most frequently used cathartic at CSU, and frequently is administered orally.

The reader is referred to Scherk et al. Vet Focus 2013 p.36-37 for an excellent summary table of the available products and dosing instructions, briefly summarized below (adapted from Dr. Susan Little, Atlantic Coast Veterinary Conference 2012).

Pediatric rectal suppositories

- DSS (dioctyl sodium sulfosuccinate, Colace ™)
- Dulcolax ™ (bisacodyl)

Enema solutions [10-12 Fr red rubber catheter]

- Warm tap water (5-10 ml/kg)
- DSS (5-10 ml/cat)
- Mineral oil (5-10 ml/cat, do not administer with DSS)
- Lactulose (5-10 ml/cat); Kristlose (lactulose crystals mixed with food or water)

Fleet (sodium phosphate) is CONTRAINDICATED!

GoLYTELY ™, Colyte ™ Miralax PG3350 (polyethylene glycol); NE tube, 6-10 ml/kg/hr

Most recently, thanks to the efforts of Dr. Anthony Carr, we employ polyethylene glycol (Miralax, PG3350), trickled through an NE tube (6-10 ml/kg/hr). Although it may take up to 12-18 hours (Carr AP & Gaunt MC, ACVIM 2010), the success rate with this minimally invasive protocol makes it well worth the attempt and the patience.

Once the immediate problem has been resolved, follow-up care may include dietary intervention, oral lactulose to effect, and pharmaceutical manipulation.

Dietary fiber is characterized as soluble-easily fermentable and insoluble-poorly fermentable, although sources of fiber are rarely only one or the other, but a combination of both properties. Insoluble fiber adds bulk, distends the colon, and in that way, increases colonic water content and stimulates colonic motility. Soluble fiber is metabolized (fermentable) by colonic bacteria into short-chain fatty acids, a preferred nutrient for gastrointestinal mucosal cells.

Insoluble fiber

- Metamcil (psyllium; 1-4 tsp mixed with food q12-24hr)
- Wheat bran (1-2 tbsp mixed with food q12-24hr)

Canned pumpkin is a popular choice for insoluble fiber and it is not unusual for cats to ingest it voluntarily, but it does not actually provide as much fiber content as either of the other 2 choices. Royal Canin Fiber Response is a psyllium-enriched dry extruded diet that has shown promise as a dietary therapy for constipation in cats (Freiche V et al. ECVIM 2010).

Pharmacologic intervention is best achieved with Cisapride (Propulsid™; 5 mg/cat PO q8-12hr). In a number of cats we have had anecdotal success with ranitidine (DOSE).

Acupuncture can be considered if an experienced clinician is available to administer the treatment. Surgical management of megacolon is beyond the scope of these proceedings.

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NOTES:

Cholangiohepatitis: Emerging Evidence for Disease Pathomechanisms

Sharon Center, DVM, DACVIM

Introduction

Feline CCHS is the most common acquired necroinflammatory liver disease in the domestic cat and should be considered a disease syndrome. Unlike chronic hepatitis in the dog, inflammatory effacement of the limiting plate (marginal hepatocytes abutting the portal triad) usually does not occur without involvement of biliary structures. The anatomic difference between the biliary-pancreatic ductal systems in the cat (common ampulla) versus the dog (separate systems) has long been considered influential in feline CCHS.[1]

First described in the early1980's, feline CCHS commonly coexists with inflammatory processes involving the intestines (inflammatory bowel disease, IBD), pancreas, and kidneys (chronic interstitial nephritis, CIN).[1-6] While reviews and small case series have been reported, descriptions of large cohort studies are lacking.[7-16] A retrospective study completed at Cornell characterized pathologic lesions in a large case series in an effort to further refine the Non-Suppurative syndrome. [17] Included in this discussion will be information derived from that study and from > 250 CCHS cases studied by the author. While there is no case based evidence confirming that Suppurative CCHS precedes Non-Suppurative CCHS, a recent study at Cornell has confirmed expression of bacterial motifs and Pathogen Associated Molecular Patterning (PAMP) responses in tissues of cats with non-suppurative CCHS. Primary disorders promoting bile stasis are often discovered in cats with CCHS irrespective of the nature of the inflammatory infiltrate or whether the syndrome involves bile duct destruction (destructive or sclerosing CCHS; **Table** 1. This association may be historical or contemporary with the initial diagnosis of CCHS.

Table 1:
Examples of Disorders Associated with the Feline Cholangitis / Cholangiohepatitis Syndrome

Suppurative	*Non-Suppurative*
Primary bacterial infection	*Inflammatory bowel disease*
Septicemia	*Primary cholangitis*
Chronic bacterial infections:	*Pancreatitis*
sinusitis	*Extrahepatic bile duct obstruction*
splenic abscess	*Cholelithiasis*
pyelonephritis	*Cholecystitis*
cystitis	*Neoplasia:*
Cholecystitis	*Gallbladder adenocarcinoma*
Cholelithiasis	*Bile duct cystadenoma*
Pancreatitis	*Malformation:*
Inflammatory bowel disease	*Choledochol cyst, biliary dysplasia*
Extrahepatic bile duct obstruction	*Chronic trematode infestation*
Acute trematode infestation	*Chronic bacterial infection*
Toxoplasmosis	*(anywhere in the body)*

Historically, pathologic categorization of CCHS lesions (Suppurative vs Non-Suppurative) have relied on "acute" and "chronic" characterizations. However, descriptive morphology (type of infiltrate) provides advantage over assumed "acute" or "chronic" classifications in stratifying disease subsets. Our recent pathologic study employed routine and special histologic stains, immunophenotyping immunohistochemistry, in situ fluorescent hybridization (FISH) for detection of eubacterial organisms in tissue sections, PCR for detection of eubacterial organisms, and T cell clonality studies (T cell receptor rearrangement) to distinguish Non-Suppurative inflammatory disease from lymphoma.17 Collective data and experience with affected cats (long term clinical and pathologic studies at Cornell) suggest that Feline CCHS should be discriminated into 5 histomorphologic groups. We intentionally include cats with small cell lymphoma in this classification scheme as these cases are particularly problematic to differentiate from Non-Suppurative CCHS. It is likely that neoplastic transformation occurs from the chronic non-suppurative inflammatory syndrome.

Pathologic Categorization of Feline CCHS

Suppurative CCHS
Non-Suppurative CCHS
Group 1: without destructive duct lesions
Group 2: with destructive duct lesions
Group 3: Zone 1 Lymphoproliferative Disease
Group 4: Hepatic small cell Lymphosarcoma

New Investigation of Oxidative Injury, TNF-a, Bacterial Motifs, PAMP Signaling in Feline Cholangiohepatitis: Cornell University 2013-2014

A recently completed a comparative immunohistochemical evaluation of liver samples from 152 cats (40 non-suppurative CCHS; 40 suppurative CCHS with positive bacterial culture of liver or bile, 24 hepatic lymphosarcoma with portal involvement, 20 non-necroinflammatory liver disorders, and liver from 20 healthy cats) investigated for evidence of oxidative injury, bacterial residues (lipoteichoic acid), pathogen-associated-molecular-pattern response (Toll-like receptor-4 expression) indicating LPS (endotoxin) exposure, tumor necrosis-α expression (TNF-α), hepatic iron accumulation, portal myofibrocyte transformation (α-smooth muscle actin[SMA]) and fibrillar collagen deposition (Masson's trichrome stain). Markers of oxidative injury included nitrotyrosine (oxidation of protein tyrosine residues), 4-hydroxy-2-nonenal (fatty acid oxidation product), and 8'-hydroxy2'-deoxyguanosine (DNA oxidation product).

Findings confirm 4-hydroxy-2-nonenal positive hepatocytes and nitrotyrosine positive macrophages in all groups of diseased cats. Staining for 4-hydroxy-2-nonenal was significantly greater in cats with nonsuppurative cholangiohepatitis than cats with lymphosarcoma or other non-necroinflammatory liver disorders. A subset of cats with nonsuppurative CCHS demonstrated positive staining for lipoteichoic acid, with many cats having positive signals for Toll-like receptor-4 implicating LPS exposure. Findings implicate potential involvement of bacterial motifs in ongoing inflammation in cats with nonsuppurative CCHS, similar to the postulated scenario in humans with sclerosing cholangitis. Staining with lipoteichoic acid was more common in cats with suppurative CCHS where it was significantly and positively correlated with bacterial culture of gram positive organisms. Staining of TNF-α and hepatic iron was generally common in cats with liver disease including lymphoma. Cats with CCHS had significantly greater portal staining with α-SMS compared to other groups. Significant positive associations between Toll-like receptor-4, markers of oxidative injury, and accumulation of hepatic iron provides the first evidence that a pathogen-associated-molecular-pattern response may mechanistically contribute to liver injury in feline nonsuppurative CCHS. Findings also document that oxidative injury contributes to the CCHS syndrome, justifying use of antioxidants as a therapeutic intervention. Utility of staining for Lipoteichoic acid as a means of detecting gram + bacterial infection was validated and provides an innovated diagnostic method for confirming infection in some cats. Likewise, staining for Toll-like receptor 4 can implicate infection with gram – organisms. Data support that fibrogenesis is more sensitively detected using α-smooth muscle actin IHC compared to routine staining of fibrillar collagen with Masson's Trichrome. This may assist in differentiating cats with cholangiohepatitis from cats with hepatic lymphosarcoma and provide a more sensitive measure for estimation of fibrosis in sequential liver biopsies used to assess treatment efficacy.

Findings of this recent study will be informatively discussed during the lecture to help rationalize treatment interventions. Observations suggest that antimicrobial treatment in cats with nonsuppurative CCHS should not be dismissed during early stages of disease management or when treatment response is less than expected with an immunomodulatory protocol. Recent studies in humans with primary sclerosing cholangitis (similar histologically to feline non-suppurative cholangitis) report response to metronidazole or vancomycin in some patients resistant to immunomodulation. Our long-term positive experience with combining metronidazole as an arm of immunomodulation in management of chronic nonsuppurative CCHS and the results of this study seemingly support a similar scenario.

Association between feline lymphocytic CCHS and inflammatory bowel disease has been long acknowledged. Disruption of the homeostasis between the host and enteric microbiota can lead to pathologic responses as implicated in inflammatory bowel disease where numerous changes, including reduced diversity of the microbiota can drive pathogenic responses.[48-51] Interaction between the gut immunologic responses and its microbiotia and the hepatobiliary system in the development of liver disease has received increasing attention.[48,49] Influence of vancomycin and metronidazole on gram-positive and anaerobic bacterial populations impacts products and bacteria translocating from the gut into the portal circulation.[48,49] This effects change in the innate immune response through interplay with pattern recognition receptors such as Toll-Like receptors. TLR-4 has a pro-inflammatory cytokine influence, promoting pro-fibrotic states and has known activation by LPS.[52-55] Another Toll-like receptor (TLR-3) attenuates these pro-inflammatory effects through immunoregulatory cytokines (e.g., interleukin-10).[49]

These Notes are Divided into Features & Details for Suppurative & Non-Suppurative Syndromes

Suppurative CCHS:

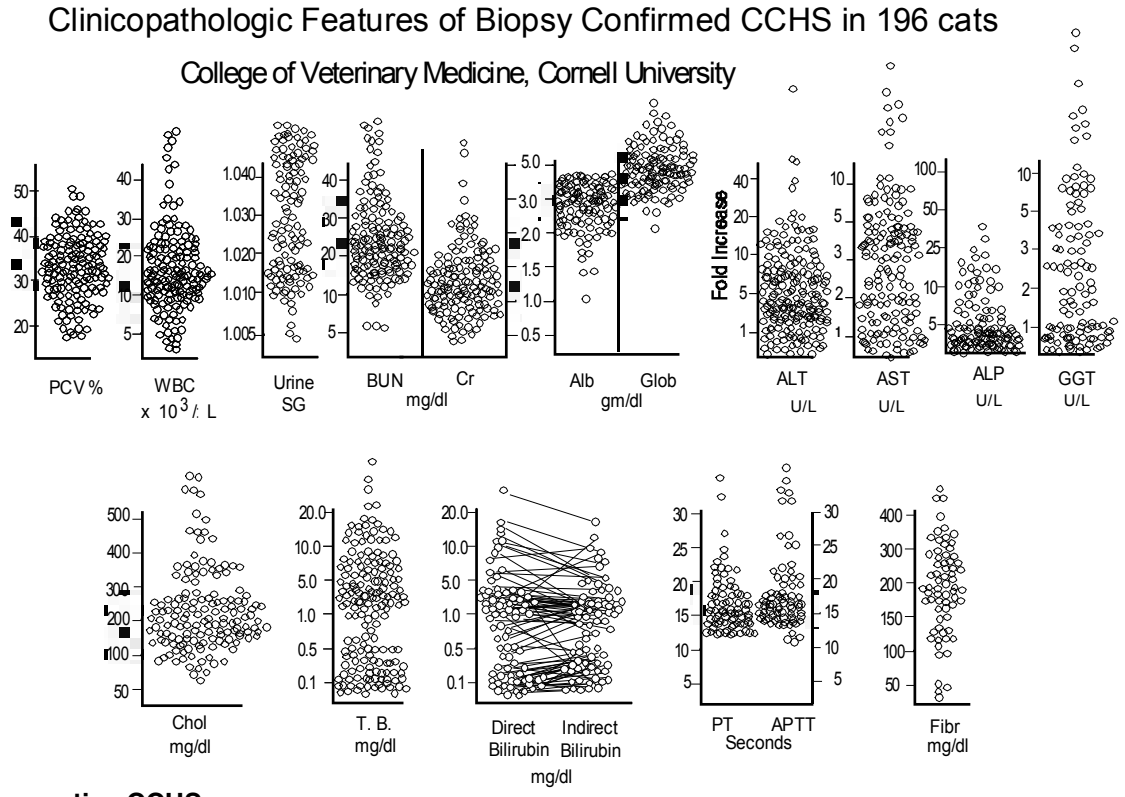
Clinical Presentation

Cats with Suppurative CCHS have a unique clinical presentation that is generally more urgent than cats with Non-Suppurative forms of the CCHS syndrome and will discussed separate from the Non-Suppurative disease categories.

Cats with Suppurative CCHS have a unique clinical presentation that is generally more urgent than cats with Non-Suppurative forms of the CCHS syndrome and will discussed separate from the Non-Suppurative disease categories.

A scatterplot of clinicopathologic features from 196 cats with CCHS is provided in **Figure 1.** Light grey bars on the Y axis indicate normal range values where pertinent. Liver enzymes are shown as fold-increase owing to the change in clinicopathologic chemistry analyzers (4X) in our hospital over the last 30 years.

Figure 1 Summary for Suppurative and Non-Suppurative Feline CCHS



Suppurative CCHS

Suppurative CCHS causes the most overt and urgent clinical illness. Affected cats have a shorter duration of illness before presentation (< 5 days) compared to Non-Suppurative CCHS with young or middle aged adults predominating (age range 3 months to 16 years). In some cats, suppurative CCHS represents an infectious complication (bacterial) to therapeutic immunosuppression (e.g. treatment of Non-Suppurative CCHS with methotrexate, glucocorticoids, chlorambucil or chemotherapy for lymphoma). In these cats, infections may derive from minor irritation at the site of feeding appliances (esophagostomy or gastrostomy tubes), from chronic urinary tract infections, or severe oral disease (as well as other extrahepatic sites of infection).

Clinical Signs

Include pyrexia, lethargy, dehydration, inappetence, vomiting, and variable jaundice. Many cats manifest abdominal pain (tender liver on palpation), and some have palpable hepatomegaly (<50%). Abdominal effusion is uncommon but septic peritonitis has been observed.

Clinicopathologic Features

Typical clinicopathologic features include a leukocytosis, often with a left shift and toxic neutrophils, and increased but highly variable ALT, AST, GGT +/- ALP activities. Variable bilirubin concentrations (some normal) reflect acute disease status. When present, jaundice may reflect inflammation of biliary structures, impeded bile flow, or a sepsis-related hyperbilirubinemia. In cats, bilirubinuria can indicate hyperbilirubinemia in the absence of overt jaundice and thus screening urine with a sensitive method for detecting bilirubin has high utility (e.g. Ictotest). Cats with suppurative CCHS often present dehydrated with pre-renal azotemia and electrolyte depletions. Some of these cats present with classic features of hepatic lipidosis (HL) and marked weight loss. HL can develop subsequent to inappetence, vomiting, and diarrhea reflecting suppurative CCHS or a primary illness preceding the suppurative CCHS. Discovery of high GGT activity helps identify an underlying necroinflammatory process involving hepatobiliary structures or the pancreas in HL cats. This may provide a pivotal “clue” influencing early case management leading to “early” tissue sample acquisition, institution of broad spectrum antimicrobial coverage, and administration of ursodeoxycholic acid (UDCA). At present, cats with HL in the author’s hospital do not undergo tissue biopsy for definitive diagnosis. Rather, HL is diagnosed on the bases of: 1) signalment & history, 2) physical findings, 3) clinicopathologic features, 4) hepatic US findings, AND 5) fine needle hepatic aspiration cytology confirming that > 80% of hepatocytes contain lipid laden vacuoles. UDCA is not routinely recommended for cats with

HL lacking necroinflammatory liver disease by the author. Like all bile acids, UDCA can be toxic to cells in high concentration. Cats with HL have bile acid profiles identical to cats with EHBDO (few secondary bile acids made in the gut) consistent with serious canalicular bile obstruction. The HL cat also develops profoundly increased serum bile acid concentrations (often > 1000 um/L). UDCA must be conjugated with taurine and HL cats are taurine depleted, which increases its retention and may enhance potential toxicity. Furthermore, UDCA is dehydroxylated to lithocholic acid in the distal bowel, and while this bile acid is not well absorbed, it is one of the most toxic bile acids linked to liver injury. Finally, children with a similar fatty liver syndrome are not benefited by administration of UDCA.

Imaging

There are no distinctive ultrasonographic (US) features unique to suppurative CCHS aside from recognition of abnormalities involving large bile ducts, gallbladder (GB), or pancreas (e.g. EHBDO, cholecystitis, choledochitis, pancreatitis), or inflammatory bowel disease (IBD). Co-existent HL complicates US interrogation owing to diffuse hepatic parenchymal hyperechogenicity caused by hepatocellular lipid stores. However, an heterogenous hepatic parenchymal pattern may be notable in some cats reflecting suppurative inflammation. In some cases, small amounts of abdominal effusion may be noted between liver lobes or adjacent to the GB representing an inflammatory effusion or septic exudate. Rarely, abdominal radiographs may disclose mineralized opacities consistent with choleliths or mineralized GB or biliary structures or focal regions suggesting abdominal effusion of peritonitis. In cats with an obstructed common bile duct, the GB silhouette may be prominent. Thoracic radiography may disclose an enlarged sternal lymph node reflecting abdominal inflammation / sepsis.

Definitive Diagnosis

Only histology can confirm a diagnosis of Suppurative CCHS- aspiration cytology and ultrasound examination cannot replace tissue characterization for diagnostic certainty. That said, based on extensive experience with cats with Suppurative CCHS, bacterial infection is typically evident on cytologic specimens of bile and/or tissue aspirates or tissue imprints. Thus, cytologic evaluations (tissues, bile) constitute an essential diagnostic step. Routine histologic assessments usually cannot identify an infectious agent although they clearly identify the suppurative inflammatory reaction. Recent development of FISH (fluorescent in situ hybridization) using universal markers for eubacterial organisms has provided a practical diagnostic capacity for proving the presence of bacterial organisms (at Cornell, this is done in the laboratory of Dr. K. Simpson). However, detection of bacterial agents in cats with suppurative CCHS is typically not difficult and usually does not warrant FISH investigations. Simple aerobic and anaerobic bacterial cultures of liver or biliary tissue AND bile coordinated with cytologic inspection of representative samples will usually disclose involved organisms. Several cytologic smears should be made and stained using modified Wrights-Giemsa (e.g. Diff Quik stain) to detect bacterial organisms. Thereafter, application of a Gram stain to an additional slide will assist in bacterial classification (shape, size, Gram "+" or "-") and detect a polymicrobial infection. This information can promptly guide initial antimicrobial therapy before culture and sensitivity results are available. Since affected cats may not be taken for tissue sampling until after antimicrobial agents have been administered, submitted specimens may culture negative, emphasizing the value of cytologic investigations.

Histology

Histologically, suppurative CCHS is characterized by neutrophilic infiltrates within the adventitia of the portal triad, around and within intrahepatic bile ducts, periductal edema, and hepatocellular cholestasis (canalicular bile plugs). Inflammation may invade adjacent hepatic parenchyma. With chronicity (> several weeks), a circumferential periportal fibrolamellar mantel surrounds and bridges between ducts and biliary epithelium which undergoes proliferative replication (oval cell hyperplasia). Differentiation of "acute" and "chronic" subsets of suppurative CCHS based on cellular infiltrates has confused syndrome characterization. While a mixed lymphoplasmacytic infiltrate combined with neutrophilic or neutrophilic / eosinophilic infiltrates develop in some cats, the cellular infiltrates do not discriminate acute from chronic disease stages. Rather, determination of chronicity must consider: 1) the duration of clinical illness and 2) the extent of tissue remodeling including alterations in biliary structures, the extent of oval cell hyperplasia, and presence of periductal fibrosis semi-quantitatively graded on tissue sections stained with Masson's Trichrome.

What About Routine Use of Cholecystocentesis

Routine sampling of GB bile by US guidance is not advised by the author as it can be associated with bile peritonitis and a severe vasovagal response. Cholecystocentesis should be reserved for cases in which septic inflammation is considered likely and diagnostic strategies will be altered by confirmed bacterial infection. Dull pressure on the GB during cystocentesis can initiate a severe vasovagal response (profound bradycardia, respiratory arrest, death) requiring anticholinergics and cardiopulmonary resuscitation. This response may explain the reported sudden death incidence after tru-cut needle biopsy of the liver in cats;[19] perhaps the GB or large bile ducts were iatrogenically traumatized.

Cultured Organisms

Cultures of liver, bile, or choleliths are reported as positive in 18-25% of feline submissions from several hospital case series (not restricted to Suppurative CCHS). One report described positive cultures in 7/49 (14%) liver and 5/14 (36%) bile samples although the index of suspicion for infection and definitive diagnosis was not clearly detailed.[18] In the author's experience, most cats with Suppurative CCHS will have positive cultures. Both single bacterial (75%-90%) and polymicrobial infections (10%-15%) may be encountered. Gram negative aerobes (E*. coli, Enterococcus, Streptococcus*) are most common. The most common anaerobes include Bacteroides spp and Clostridium spp. Finding *Bacteroides* spp. has special relevance as a sentinel predicting the presence of a polymicrobial infection. Bacteroides can favorably modify the microenvironment encouraging polymicrobial colonization with aerobic bacteria.

Finding bacteria in cats with Suppurative CCHS does not confirm a causal relationship because any form of cholestasis predisposes to infection via obstruction of the normal egress pathway of enteric organisms transiting the entero-biliary pathway. The presence of IBD is thought to be an important variable contributing to hepatobiliary infections. In addition to intestinal translocation through leaky gap junctions associated with IBD, bacteria may ascend the biliary tree secondary to duodenitis or as a result of pressure changes during the act of vomiting that propel enteric bacteria into the common bile duct ampulla. Thus, a history of intermittent vomiting and diarrhea, common in cats with Suppurative CCHS, may coincide with portal bacteremia or reflux of enteric flora into the biliary ampulla. Organisms also may be hematogenously dispersed to the liver from acute or chronic sites of infection elsewhere in the body.

Studies on Helicobacter in Feline Liver & Bile

A role for Helicobacter species has been investigated in humans and cats and at present there is no consistent evidence that Helicobacter is an active participant in feline CCHS. However, a role for Helicobacter as an initiating agent cannot totally be discounted. Below is a synopsis of two studies that investigated Helicobacter in cats with inflammatory liver disease.

In one study, Helicobacter was detected by PCR in bile from 4/15 (26%) cats with Non-Suppurative CCHS, 8/51 (24%) cats with liver disease other than Non-Suppurative CCHS, and 7/12 (58%) cats lacking liver disease.[20] In another study conducted by the same investigator, Helicobacter species in human patients with primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), or other liver disease of known cause (alcoholism, hepatitis B, metabolic liver disease) discovered that ~ 30% of each population was PCR positive, contradicting a causal role for Helicobacter in any specific disorder.[21] Thus, findings in both feline and human patients contradict that Helicobacter is a primary cause or is uniquely associated with inflammatory liver disorders.[20,21]

In another feline study[22] using archived paraffin-embedded liver tissue, Helicobacter sp were detected in 2/32 (6%) cats with CCHS and 1/17 (6%) control cats (non-inflammatory liver disease or healthy cats) by PCR amplification. Positive findings were speciated by sequence confirmation. Using FISH, a single semi-curved bacterium (2-u long) with Helicobacter-like morphology was observed within an intrahepatic bile duct (one cat with Suppurative CCHS). DNA of Helicobacter spp other than H. pylori were confirmed (Suppurative CCHS: H. fennelliae or H cinaedi and H. bilis was amplified from a cat with a portosystemic vascular anomaly). Silver staining (Steiner stain) was uniformly negative in PCR positive cats.

Because discordancy between culture, *in-situ* localization, and positive PCR reports are frequent in experimental and clinical studies of Helicobacter, it is probable that PCR DNA detection reflects enterohepatic circulation of intestinal organisms or bacteria or DNA sojourning the liver rather than true colonization. However, positive reports might also reflect transient tissue colonization and a role for Helicobacter in initiation of Non-Suppurative CCHS.

What about Bartonella?

It is unclear how to be confident that this organism is actively involved in feline CCHS. Experimentally infected cats[23] demonstrated histopathological lesions including peripheral lymph node hyperplasia, splenic follicular hyperplasia, mild lymphocytic cholangitis & pericholangitis, mild lymphocytic hepatitis, lympho-plasmacytic myocarditis and interstitial lymphocytic nephritis. Photomicrographs published in the experimental manuscript were not typical of Non-Suppurative CCHS lesions (very minor). However, experimental studies did implicate Bartonella as a potential pathogen in some cats.[23] Treatment should be considered in a seroreactive or bacteremic individual with disease manifestations that cannot be otherwise explained. However, treatment with doxycycline or enrofloxacin failed to reliably clear Bartonella in experimentally infected cats. Other antimicrobials also have not been proven to "clear" this organism from infected cats. It was demonstrated that immunosuppression may allow this organism to flourish. Thus, Bartonella should not be dismissed in an immuno-modulated CCHS patient where disease activity (enzymes, hyperbilirubinemia) fails to improve with the treatment protocols described in these notes.

Treatment of Suppurative CCHS

Surgical Intervention

May or may not be needed. Medical and surgical interventions should address diagnostic findings as they are discovered. Some cats are surgical candidates necessitating resolution of biliary tree obstruction, cholelith removal, abscess resection, or cholecystectomy. It is essential that antimicrobial therapy be initiated before surgical intervention as this may improve the well documented feline propensity for high perioperative and postoperative morbidity and mortality. However, not all cats with suppurative CCHS require surgical intervention. In those lacking clear indication of duct obstruction, large abscesses, cholelithiasis or cholecystitis, liver and bile aspirates should be used to confirm infection and direct initial antimicrobial treatment.

Before surgical intervention we start cats with suspected biliary obstruction or infection on a trio- of antibiotics that has improved survival and perioperative physiologic responses. We initiated: metronidazole at a reduced dose of 7.5 mg/kg IV q12h, Ticarcillin:25mg/kg q8h, and Enrofloxicin 2.5 mg/kg parenterally q12h. This may influence culture results- but positive bile cultures often are achieved never-the-less. Cytology will disclose infectious organisms that may not grow in culture and allow gram stain to "guess" organism genus. Using in situ FISH will find bacteria but will not speciate unless you specifically suggest what to test for. Using stains to detect Lipoteichoic acid which reflects gram + organisms and Toll-like receptor 4 expression reflecting gram – (LPS) also can indicate bacterial presence.

Fluid Support

Judicious administration of IV fluids is usually needed to correct and maintain hydration and electrolyte status. Water soluble vitamins (1-2 ml/ L) and supplemental potassium chloride (standard sliding scale) should be added to any administered IV fluids.

Nutritional Support

A balanced protein replete feline diet (enteral preferred, maintenance or maximum calorie diet) should be fed. A feeding appliance may be needed (nasogastric or esophageal feeding tube).

Vitamin Supplementation

Water soluble vitamins should be added to any administered IV fluids (1-2 ml/ L).

B_{12} repletion should be ensured by measuring plasma cobalamin concentration (essential for deciding propriety of chronic B_{12} administration unless MMA measurements are available- unlikely due to complex methodology and expensive equipment) and routinely administering a single 250-1000 microgram (0.25-1.0 mg) dose of B_{12}. Measured B_{12} does not consistently correlate with metabolic B_{12} availability based on measurement of methylmalonic acidemia (MMA). Cats may develop low (reference interval) circulating cobalamin concentrations discordant with vitamin sufficiency. Complicating matter is that vitamin supplements erratically increase circulating B_{12} concentrations confusing assessments. B_{12} values < 189 pg/mL measured using the Immulite 1000 system were recently shown to best correlate with metabolic cobalamin insufficiency in a recent study.[45]. Disorders classically associated with subnormal cobalamin include inflammatory bowel disease, enteric (intestinal) lymphoma, cholangiohepatitis and cholangitis, obstructive biliary disease, hepatic lipidosis, pancreatitis, exocrine pancreatic insufficiency, and chronic oral antimicrobial therapy with disturbed enteric biome. Administration of SAMe and Vitamin E along with B_{12} may assist in activation of cyanocobalamin to methylcobalamin or adenosylcobalamin (active forms). To avoid this complication, methylcobalmin can be used. In humans, methylcobalamin is used when functional conversion at the cellular level is suspected (e.g., diabetes mellitus) which in some cases is suspected to correlate an oxidative redox balance. Differences in organ vs plasma distribution of cobalamin also can result in plasma concentration that do not accurately reflect cobalamin metabolic availability (studied in humans with alcoholic hepatitis).

Vitamin K_1: 0.5-1.5 mg/kg SQ q12hrs for 3 doses is usually provided independent of PIVKA analysis based on established needs in jaundiced cats with liver disease, previously published by the author.[23] Treatment is recommended for hyperbilirubinemic cats with liver disease on presentation and in cats that have been inappetent for multiple days.

Antimicrobials

Elimination of cholestatic factors and systemic infections is imperative. Antimicrobials (6-12 wks) are initially selected based on morphology and gram stain characteristics of cytologically identified bacteria (tissue or bile aspiration samples or liver biopsy imprints). Initial recommendations are refined on the basis of culture and sensitivity reports. Combination of enrofloxacin, metronidazole, and ampicillin/sulbactam is often initially administered as noted above (Ticarcillin or Clavamox). Treatment with antimicrobials should be started before surgical interventions and manipulations of the biliary tree because of the risk of endotoxemia and bacteremia. Sepsis greatly compromises perioperative and postoperative survival.

Hydrocholeresis

Ursodeoxycholate (UDCA) and s-adenosylmethionine (SAMe, Denosyl®) play a role in providing hydrocholeresis important for optimizing the mechanical clearance of bacterial pathogens. Bile formation and flow reflects bile acid-dependent and bile acid-independent mechanisms.

UDCA: 15-25 mg/kg PO divided q12hr given with food, increases bile flow through bile acid-dependent mechanisms. It additionally provides beneficial hepatoprotective and antioxidant benefits. If there is evidence suggesting destructive or sclerosing cholangitis- UDCA may be injurious augmenting small duct injury by increasing hydrostatic pressure on obstructed bile ductules. Currently, UDCA is not uniformly recommended for humans with sclerosing cholangitis based on findings in knock-out mouse models of the sclerosing cholangitis lesion.

SAMe: 25-40 mg/kg PO per day can augment bile acid-independent bile formation through its thiol donor status (increases hepatic GSH). Chronic administration of bioavailable SAMe (predominance of S-stereoisomer) to healthy cats (118 days) resulted in significant dilution of GB bile consistent with a hydrocholeretic effect. GSH is broken down at the canalicular membrane into its 3 constituent amino acids tripling its osmotic effect in bile.

Antioxidants

During critical illness, thiol supplementation (thiol is an important antioxidant bond present in GSH and other biologically important antioxidants) is provided by administration of n-acetylcysteine (NAC) and later with SAMe.

n-Acetylcysteine:140 mg/kg initial dose, then 70 mg/kg q8-12hr infused IV over 20 minutes using a 0.25 um filter). SAMe: 25-40 mg/kg when PO administration possible; increases hepatic and RBC GSH concentrations.

Vitamin E (alpha-tocopherol acetate): 10 U/kg/day PO to provide membrane antioxidant protection.

AVOID Lipoic acid- is <u>not recommended</u>. Shown to be lethally toxic to cats in doses easily handled by dogs and humans.[25]

Hepatoprotectants

UDCA, SAMe, Vitamin E, and silibinin (milk thistle) are considered in this capacity. The role of silibinin (milk thistle) remains unclarified. Cats can systemically acquire measurable silibinin from milk thistle-complexed with phosphatidylcholine (Marin™, silibinin with PPC: 2-5 mg/kg). Because silibinin undergoes enterohepatic circulation it likely provides benefit in an inflamed hepatobiliary system. Its use has been complicated historically by administration of poorly available milk thistle extracts in human and animal studies and thus far there is no consensus of benefit in chronic necroinflammatory liver disease in humans except in Hepatitis C where it appears to augment response to ribavirin.

Suppurative CCHS Follow-Up:

1. **Owners should monitor the cat's rectal temperature and appetite closely after discharge.**

2. **Sequential hematologic, biochemical, and urinalysis parameters** should be followed q 1-2 weeks initially and then q 2-4 weeks to confirm improvement and resolution of clinicopathologic features before discontinuing antimicrobials.

3. **If clinical signs or laboratory features FAIL to reasonably improve, consideration should be given to:**
   a. lack of eradication of bacterial organism(s): e.g. hepatic or non-hepatic associated abscess: pyelonephritis,
   splenic abscess, infected choledochal cyst
   b. development of bacterial resistance to the administered antimicrobial
   c. selection of an ineffective antibiotic or owners failure to administer the antibiotic
   d. failure to identify or resolve obstructed bile flow in large or medium sized bile ducts
   e. retention of infected choleliths (nidus of infection)
   f. transformation of Suppurative to Non-Suppurative CCHS
   g. transformation or unidentified underlying hepatic lymphoma
   h. development of Hepatic Lipidosis
   i. "smoldering" pancreatic inflammation or tiny choleliths causing intermittent duct occlusion → pancreatic signs
   j. complicating inflammatory bowel disease not under control.

4. **Diagnostic steps if liver enzymes fail to normalize or hyperbilirubinemia persists:**
   a. Abdominal US: look for abnormalities involving biliary structures, pancreas, gut, or lymphadenopathy.
   b. Aspiration Cytology: look for persistent bacterial infection (bile or liver), hepatic lipidosis or pancreatitis.
   c. Liver biopsy: if none was completed, look for Non-Suppurative CCHS that can justify immunomodulation
   Recheck bacterial cultures before immunomodulation is undertaken
   d. if IBD possible, pursue full thickness gut biopsies as these are more reliably diagnostic compared to endoscopic samples. During exploratory laparotomy, all organs should be inspected, biopsies collected from multiple tissues, bile aspirated, biliary patency evaluated, the biliary tree should be carefully palpated for liths or mass lesions, and lymph nodes inspected and sampled. Common co-existent disorders (**Table 1**) should be considered and investigated.

Non-Suppurative CCHS

Historical Perspective

A ten year retrospective study of liver biopsies (n=175) from cats at one university teaching hospital reported prevalence of inflammatory liver disease of 26% (45/175 cats =4.5 cats/yr).[13-15] Histopathologic description, clinicopathologic characterization, management and survival characteristics of these 45 cats were presented in a series of 3 manuscripts.[13-15] Cats with inflammatory liver disease were stratified into 3 subsets: 1) cats with Suppurative inflammation, and cats with Non-Suppurative inflammation 2) with and 3) without hepatic parenchymal inflammation or necrosis. Cats lacking hepatic parenchymal inflammation were classified as having "lymphocytic portal hepatitis". Cholangiohepatitis was subcategorized as either "acute" or "chronic" according to the predominant inflammatory infiltrate and presence of fibrosis: a large number of neutrophils, fewer lymphocytes, and minimal bile duct hyperplasia and fibrosis were classified as "acute CCHS" while cats with few neutrophils but many lymphocytes and moderate to severe bile duct hyperplasia and fibrosis were classified as "chronic CCHS".

Another investigator[16] described chronic progressive lymphocytic CCHS in 20 cats and used immunophenotyping antibodies to demonstrate histologic features of an immune-mediated disorder.[16] Cases were subdivided based on histologic features into an "active stage" and "chronic stage". The "active stage" was characterized by marked lymphocytic inflammation involving portal tracts and identified inflammation surrounding and infiltrating bile ducts, with occasional extension into periportal hepatic parenchyma ("piecemeal necrosis"). These changes were accompanied by bile duct/ductule proliferation and mild portal-to-portal bridging fibrosis. The "chronic stage" was characterized by prominent monolobular fibrosis and a reduction in intensity of lymphocytic infiltration and extent of bile duct proliferation (presumably "ductopenic" lesions). While the categorical subdivisions could not be immunophenotypically differentiated, the study characterized substantial portal infiltration with lymphocytes bearing CD3 and MHC Class II markers.[16] Findings reported for the first time that T cells infiltrated bile ducts and penetrated the limiting plate of Zone 1, becoming closely associated with individual hepatocytes. Cytotoxic destruction of targeted cholangiocytes was described but "ductopenia" was not characterized. Liver samples from clinically healthy cats demonstrated a scant back ground population of CD3+ T cells residing in sinusoids and portal areas adjacent to

or within bile duct epithelium. These T cells were interpreted to represent enteric inter-epithelial lymphocytes responsible for hepatic immune surveillance. It was hypothesized that these cells may play a pathologic role initiating a primary "anti-ductal" response in lymphocytic CCHS.

The author and colleagues have been investigating the clinical and pathological aspects of CCHS for > 25 years in clinical cases and liver biopsies referred to our hospital and pathology section. The following discussion reflects observations derived from > 250 cats with this syndrome including a detailed study in Veterinary Pathology[17] of liver biopsies from 78 cats with Non-Suppurative CCHS (n=51) or hepatic lymphoma (n= 27). A more recent study has investigated the oxidative injury and molecular signaling molecules in cholangiohepatitis (suppurative, non-suppurative, lymphoma, vs normal cats). Findings in these projects have facilitated rational design of therapeutic recommendations.

Previously published survival statistics in cats with CCHS suggest significantly shorter survival for cats with disease in multiple organ systems; cats with "lymphocytic portal hepatitis" (n=23) had a mean survival of 37 months and those with CCHS (n=15) a mean survival of 29 months.[15] Treatments (i.e. immunomodulation, antioxidant, UDCA, vitamin supplements) were not consistently provided as some study cats were retrospectively identified as having inflammatory liver disease during biopsy review for study inclusion. Thus, the published survival statistics may reflect the natural disease process. The other major study[16] of cats with Non-Suppurative CCHS (n=20) included cases extracted from a pathology archive and included 6 necropsy samples (30%). Thus, part of the spectrum of disease examined represents deceased cats, perhaps at end-stage disease. A more recent publication[46] evaluated cats treated with prednisolone (n=10 [6/1996-10/2000] ; 1 [n=3,] or 2 [n=7] mg/kg daily) or only ursodeoxycholic acid (n=13 [3/2001-9/2008). Median overall survival was 795 days, with overall 50th percentile survival (including 2 cats that received both treatments) of 76%, 51%, and 32%, at 1 , 2, and 3 years, respectively. Survival at the 50th percentile specifically for prednisolone (2 doses used) was: 98%, 78%, and 48% at 1 , 2, and 3 years respectively. Survival at the 50th percentile specifically for Ursodeoxycholate treatment was: 58%, 5%, and 5% for 1, 2, and 3 years, respectively. Survivals are estimated from displayed survival curves in that study.[46]

Our studies clearly show variable liver lobe involvement within cats with Non-Suppurative CCHs and that extent and severity of histologic lesions may not be fully ascertained when only a single liver biopsy is evaluated, especially if needle biopsies are submitted. Needle biopsies are problematic for diagnosis of CCHS because a minimum of 12-15 portal triads must be available with their adjacent acinar units for confident assessment.[27] Single lobe biopsies and scant tissue samples may not be able to detail the full extent of the CCHS lesions leading to a diagnosis of "lymphoplasmacytic hepatitis" and under-appreciation of duct targeted injury. Samples from one liver lobe may display florid duct destruction, inflammation, and hepatitis whereas another lobe may lack inflammation or may lack ducts because of their immunologic elimination. Thus CCHS can be overlooked and ductopenia unrecognized. Comparable observations regarding the unreliability of small needle biopsy specimens have been reported for liver biopsies from humans with a similar disease process (primary sclerosing cholangitis, PSC).[28] Biopsy size becomes even more important when attempting to objectively detect bile duct dropout, fibrosis, and remodeling (see below).

Considerations on Etiopathogenesis of Feline Non-Suppurative CCHS

The remarkable similarity of CCHS and duct destruction to human disorders characterized as "vanishing bile duct syndromes" makes current concepts regarding pathogenesis of these human syndromes relevant to the cat. The most recent work for PSC, an immune-driven acquired "ductopenic" disorder, suggests that biliary epithelial cells mediate their own destruction by exaggerating innate and adaptive immune responses. It is proposed that these may be initiated by bacterial products derived from the gut and associated IBD. "Ductopenia" is considered a final common pathologic outcome reflecting multiple etiologies including autoimmune disorders, adverse effects of medications or toxins, genetic abnormalities, infectious diseases, and neoplastic disorders; (**Tables 2 & 3** below).[29-36] The diagnosis of "ductopenia" is suggested by the clinical features and confirmed by histologic findings. The prognosis and treatment depend on the initiating cause and degree of liver injury.

"Ductopenia" in human pathology refers to the absence of interlobular bile ducts from within the portal tracts.[29-32] This term indicates an absence of a bile duct in close proximity to its parallel hepatic arterial branch within the portal triad. By definition, "ductopenia" or small duct damage exists when there is loss of interlobular bile ducts in >50% of portal tracts in a biopsy deemed "adequate for interpretation".[29,32,33] An adequate biopsy size is 3 cm in length of a 16 gauge tru-cut caliber which generally provide sufficient portal tracts to allow diagnostic accuracy. Diagnostic accuracy declines with specimen size, e.g. needle samples < 2 cm in length.[34,35] At least 11 complete portal tracts are required for accurate semiquantitative assessments, although 20 or more are considered ideal.[34] Diagnostic yield is increased by immunostaining biliary elements (cytokeratin staining of intermediate filaments) in the presence of inflammation because this clarifies the presence and location of ducts and ductular proliferation.[29] Since ductular proliferation may coexist with interlobular duct loss, ductules must be distinguished from bile ducts. The size and location of the biliary elements are integral in this regard. Bile ducts are found parallel to hepatic artery branches of similar size, whereas ductules tend to appear near the limiting plate or within the parenchyma (ductular reaction).[28]

Table 2: **Conditions Associated with Vanishing Bile Duct Cholangitis in Human Beings**[30,31]

Congenital / Developmental Disorders

Atretic
- *Extrahepatic bile duct atresia*
- *Paucity of interlobular bile ducts*
- *Fibrocystic malformations*
  - *Autosomal recessive polycystic kidney dz*
  - *Congenital hepatic fibrosis*
  - *Caroli's disease*
  - *Von Meyenburg complexes*

Syndromic
- *Alagille's syndrome*
- *Williams syndrome*

Nonsyndromic
- *Cystic fibrosis*
- *Alpha-1 antitrypsin deficiency*
- *Trihydroxycoprostanic acidemia*
- *Trisomies 17,18,21*
- *Byler's disease*
- *Niemann-Pick type C*
- *Peroxisomal disease (Zellweger syndrome)*

Idiopathic

Immunologic
- *Primary biliary cirrhosis (PBC)*
- *Immune cholangitis*
- *Primary sclerosing cholangitis (PSC)*
- *Sarcoidosis*
- *Chronic graft versus host disease*
- *Acute hepatic transplant cellular rejection*
- *Chronic hepatic transplant cellular rejection*

Infectious
- *Neonatal exposure to cytomegalovirus, syphilis, reovirus 3, & rubella*
- *Enteric organisms*
- *Viral infections*
  - *Cytomegalovirus*
  - *Reovirus type 3*
  - *Hepatis C virus*
  - *Hepatitis B virus*
  - *Epstein-Barr virus*
- *Cryptosporidium*

Ischemic: hepatic artery damaged

Neoplastic disorders
- *Hodgkin's disease*
- *Histiocytosis X*

Toxins & Drugs *(See Table 3)*

Table 3: ***Drugs Causing Chronic Cholestasis and the Vanishing Bile Duct Syndrome in Humans***[32]

Antibiotics
- *Ampicillin*
- *Amoxicillin/clavulanic acid (Augmentin)*
- *Clindamycin*
- *Erythromycin*
- *Organic arsenicals*
- *Tetracycline*
- *Thiabendazole*
- *Trimethoprim-sulfamethoxazole*
- *Co-trimoxazole*
- *Troleandomycin*

Psychotropics
- *Chlorpromazine*
- *Amitriptyline*
- *Barbiturates*
- *Carbamazepine*
- *Diazepam*
- *Haloperidol*
- *Imipramide*
- *Other phenothiazines e.g. Prochlorperazine*
- *Trifluoperazine (for Alzheimer's psychosis / agitation)*

Androgenic anabolic steroids
- *Methyltestosterone*
- *Norandrostenolone*

Miscellaneous
- *Ajmaline (a class 1a antiarrhythmic agent)*
- *Aprindine*
- *Azathioprine*
- *Carbamazine*
- *Carbutamide (peroxide tooth whitener)*
- *Chlorothiazide*
- *Cimetidine*
- *Cromolyn sodium*
- *Cyamemazine (anxiolytic antipsychotic)*
- *Cyclohexyl propionate (in fragrance & flavor concentrates)*
- *Cyproheptadine*
- *Estradiol (Ethinyl estradiol)*
- *Glibenclamide (sulfonylurea anti-diabetogenic drug)*
- *Glycyrrhizin (Triterpenoid glycoside extracted from liquorice root, antiviral / immunomodulatory effects)*
- *Ibuprofen*
- *Imipramine*
- *Phenylbutazone*
- *Phenytoin*
- *Terbinafine (synthetic allylamine antifungal)*
- *Terfenadine (antihistamine, Seldane, removed from market)*
- *Thiabendazole*
- *Tiopronin (thiol for cystinuria crystalluria)*
- *Tolbutamide, Ticlopidine, Xenalamine (antiviral, now banned)*

Signalment

Affected cats range in age between 2-17 years, with most being middle aged or older. Concurrent infection with FeLV or FIV is uncommon. We find no sex or breed predisposition. Duration of illness ranges between 2 weeks and several years before diagnosis. Most cats have been ill for several months before initial clinical presentation as these cats typically show few clinical signs in the early stages (months to years) of the syndrome. Even with chronicity, clinical signs may remain vague and cyclic. Moderate to marked increases in ALT and AST often initiates the quest for definitive diagnosis.

Clinical Signs

Include cyclic lethargy, weight loss, anorexia or polyphagia, vomiting, diarrhea, and polydipsia. Cyclic signs typically involve inappetence +/- diarrhea, and altered social interactions (increased reclusiveness, apparent apathy) and are followed by spontaneous remissions. Disease activity is apparent on sequential liver enzyme and bilirubin assessments. Vague and inconsistent clinical signs cause owners to question the gravity of their cats illness and often delay definitive diagnosis. Polyphagia may develop in cats with sclerosing cholangitis due to malassimilation associated with inconsistent alimental discharge of bile due to small bile duct occlusion / dysfunction / ductopenia. In these cats, intermittent acholic feces may also be observed. Since CCHS often coexists with IBD, gastrointestinal signs may dominate clinical features. Jaundice may be absent, intermittent, or marked in individual cats depending on the severity of the inflammatory process, tissue remodeling, and secondary illnesses. Rarely, in advanced disease, cats may display signs of hepatic encephalopathy (ptyalism, aggression, and somnolence). These individuals are usually jaundiced and may develop abdominal effusion reflecting intrahepatic portal hypertension secondary to bridging portal fibrosis (biliary cirrhosis); however, this presentation is exceedingly rare. Most cats with Non-Suppurative CCHS have a palpable “normal” or “large” liver size.

Some cats present for HL subsequent to severe cyclic illness. In these, underlying CCHS is initially suspected after discovery of a high GGT (reflects necroinflammatory or proliferative responses of the biliary or pancreatic ductal components). Some cats present primarily for what appears to be pancreatitis, cholelithiasis, or major bile duct occlusion. Involvement of pancreatic ducts occurs in some cats. Ductopenic cats may be mistaken to have major bile duct occlusion (overt jaundiced, high liver enzymes, acholic feces). The common co-existent disorders (**Table 1**) require identification and management along with the CCHS. An increased risk for developing adenocarcinoma / cholangiocarcinoma involving the hepatic ductal or pancreatic ductal system may exist in cats with chronic Non-Suppurative CCHS, similar to the scenario in humans with PSC.[34] A recent study also suggests increase risk cholangiocarcinoma in cats with chronic biliary inflammation associated with fluke infections.[47]

Clinicopathologic Features

Hematology: there are no typical hematologic features with the exception of poikilocytosis, a border line or mild anemia in some cats, and increased numbers of heinz bodies in some cats reflecting reduced GSH status and oxidative stress. The leukogram is variable; toxic neutrophils and a left shift are not typically observed. In a small subset, lymphocytosis due to circulating “activated” lymphocytes is observed.

Biochemical Profile: discloses increased but widely variable ALT, AST, GGT, and ALP activities. Variable bilirubin concentrations (some normal) reflect the severity of lobular involvement, duct destruction, and cyclic disease activity. Cats with advanced sclerosing CCHS with diffuse ductopenia become permanently jaundiced. Cholesterol concentrations may increase in cats with biliary obstruction (ductopenia or major bile duct obstruction due to this disease or cholelithiasis). A stress hyperglycemia may or may not manifest. However, 30% or more of cats with sclerosing CCHS become diabetics when treated with glucocorticoids. It is common enough to warn clients of this eventuality and to closely monitor for glucosuria. Hyperglobulinemia is common usually with normal albumin concentrations. Feline pancreatic lipase may increase in cats with concurrent pancreatitis or severe IBD involving the duodenum. Laboratory features are exaggerated in cats with concurrent hyperthyroidism (enzymes and hyperbilirubinemia). Bilirubinuria is observed before overt hyperbilirubinemia and warrants sensitive scrutiny (i.e. IctoTest). Cats persistently jaundiced secondary to inflammatory obstruction of small and medium sized bile ducts may develop symptomatic coagulopathies responsive to parenteral vitamin K_1 (0.5-1.5 mg/kg SQ or IM, 3 doses given a 12 hour intervals routinely used before liver biopsy). Since some cats have concurrent chronic interstitial nephritis, minor to marked increases in BUN and creatinine may also be encountered. Plasma B_{12} concentrations should be measured as chronic Non-Suppurative CCHS is commonly associated with IBD that can interfere with B_{12} uptake (see above discussion).

Imaging

There are no distinct abdominal US features unique to Non-Suppurative CCHS aside from recognition of abnormalities involving large bile ducts, GB, or pancreas (e.g. EHBDO, cholecystitis, choledochitis, pancreatitis), or IBD. In some cats with acute illness in the cyclic phase, presentation for HL complicates US interpretation because of the diffuse parenchymal hyperechogenicity caused by hepatocellular lipid storage. A heterogenous parenchymal pattern may be notable in some cats with CCHS reflecting hepatic parenchymal inflammation and / or fibrosis.

However, findings overlap with Suppurative CCHS. While a non-uniform or coarse parenchymal pattern may be identified, we have observed many cats with marked histologic lesions that have normal hepatic US findings or only a coarse hepatic echo-texture. Cholelithiasis, GB changes consistent with cholecystitis, and duct thickening consistent with choledochitis also are sometimes discovered and may lead to exploratory surgery and liver biopsy. Lymphadenopathy is unusual and warrants consideration of small cell lymphoma as a complicating lesion (in gut or liver). Thoracic radiography may identify enlargement of a sternal lymph node, reflecting abdominal visceral inflammation or neoplasia.

Definitive Diagnosis- Considerations

1. Cytologic Assessments CANNOT Diagnose Nonsuppurative CCHS. While cytologic assessment of liver aspirates can deduce septic inflammation, cytologic specimens alone are unreliable for detection of non-septic inflammation. Cytologic preparations do not disclose hepatic architectural features needed to establish zonal involvement and confirmation of bile duct involvement. Mixed inflammatory infiltrates may be described in cats without cytologically demonstrable or culturable bacteria, with negative PCR for eubacterial DNA, and negative eubacterial FISH studies[17]

2. Histologic Lesions are NOT Diffusely Distributed Among Liver Lobes: Our study[17] and former work in our laboratory[18] confirm marked differences in disease activity among liver lobes that can compromise diagnostic accuracy when either a single liver lobe is biopsied or small samples are retrieved using tru-cut core instruments. This is consistent with studies of humans with PSC.[27] Best diagnostic samples are surgical wedge or laparoscopic cup-biopsy specimens. However, multiple 14-16g tru-cut needle samples collected under US guidance have successfully harvested enough tissue for confident lesion characterization in some cats. Never-the-less, in consideration of "best practice", it is important to acknowledge that collection of multiple tru-cut biopsies imposes greater risk of iatrogenic complication. Collection of full thickness intestinal and pancreatic samples should also be considered in cats with suspected CCHS. Thus, I prefer open exploration for biopsy collection: multiple liver lobes, bile aspiration, enteric, lymph node, and pancreatic samples.

3. Categorization of Nonsuppurative CCHS is defined into 4 Groups based on based on histologic features, lymphocyte immunophenotyping, and cytokeratin confirmation of small duct status.

Non-Suppurative CCHS
Group 1: without destructive duct lesions
Group 2: with destructive duct lesions
Group 3: Zone 1 Lymphoproliferative Disease
Group 4: Hepatic small cell Lymphosarcoma

Group 1: portal and periportal non-suppurative inflammation sometimes with small populations of neutrophils, associated with oval cell hyperplasia, bile duct hypertrophy and hyperplasia, +/- portal to portal bridging without obvious bile duct immunotargeting. Lymphocytic / lymphoplasmacytic infiltrates efface the limiting plate (region demarcating the beginning of the hepatic parenchyma adjacent to the portal triad). Lesions vary in severity within and between liver lobes and between patients. Individual hepatocyte necrosis may be observed. Cytokeratin staining of biliary epithelium may be necessary to evaluate involvement of bile duct invasion and injury.

Group 2: portal and periportal lymphocytic/ lymphoplasmacytic inflammation (+/- small numbers of neutrophils), evidence of biliary epithelial targeting and duct destruction, and peripheralized biliary hyperplasia, are characteristic. Inflammatory cells follow replicating oval /biliary epithelial cells, chasing bile ducts to the peripheral margins of the portal tract (duct peripheralization). This typically deposits lipogranulomas and removes bile ducts within the original limits of the portal triad. A ductal reaction extends exterior to the limits of the portal triad. Inflammation effaces the limiting plate and intermingles with hepatocytes. Lymphocytic infiltrates may invade major bile ducts, cystic duct, or GB, and may involve the pancreatic ductal system. Occasional lymphoid follicles(B-cell nidus surrounded by T cells) are observed within inflammatory infiltrates that we interpret as evidence of inflammation vs neoplasia. Pancreatic involvement results in periductal inflammation that may lead to duct involution and signs of pancreatitis. Some Group 2 cats have diminished numbers of pancreatic islets, accumulate islet amyloid, and develop clinical diabetes mellitus. This is the group with high risk for diabetes mellitus when treated with glucocorticoids. TCR clonality studies confirm polyclonal T cells in most Group 2 cats, but a few cats in our published study demonstrated clonal expansion consistent with lymphoma in the absence of diagnostic histologic characteristics.

Group 3: characterized by a dense portal lymphocytic or lymphoplasmacytic infiltrate that spills into hepatic sinusoids. Lymphocytes lack microscopic features consistent with a neoplastic population; immunophenotyping usually characterizes a T-cell predominant population. A few of these cats evaluated by TCR gene rearrangement have a polyclonal population. This group may represent clonal expansion and evolving neoplasia.

Some cats in this group are ductopenic due biliary immunotargeting, demonstrate lipogranulomas representing duct elimination, and lymphoid follicular aggregates typical of Group 2 CCHS. Thus, this group may represent a transforming condition between Non-Suppurative CCHS and lymphoma.

Group 4: overtly neoplastic dense lymphoid infiltrates with morphologic features of lymphoid neoplasia, usually spill into adjacent hepatic sinusoids. These are usually have monoclonal TCR-rearrangement. Some of these cats also manifest features displayed by Group 2 CCHS: ductopenia and intra-portal lipogranulomas suggesting progression from an inflammatory to a neoplastic process. This hypothesis has precedence as Hodgkin's disease in human beings is a recognized cause of biliary ductopenia.[36] Two hypothesis explain evolving ductopenia in lymphoma. The first involves cell-mediated immunotargeting initiated as a paraneoplastic response of T lymphocytes against ductal epithelium (e.g. predisposition for developing autoreactive T cells against biliary epithelium). The other proposes that toxic cytokines produced by lymphoma cells directly damage cholangiocytes leading to the ductopenic condition. In humans, eradication of Hodgkins lymphoma improves liver function to the point of normal bilirubin concentrations and prolonged survival supporting that the neoplasia is either directly or indirectly caused ductal injury/inflammation. This form of "vanishing bile duct disease" is reversible although effective chemotherapy is hampered by the hepatobiliary dysfunction (metabolism of chemotherapeutic drugs). Long term remissions have been observed in humans with this form of duct disease and we have similarly observed remarkable responses in some cats with a similar syndrome treated with chemotherapy. Indeed, some of these Group 4 cats have survived for several years with minimal chemotherapeutic intervention (prednisolone and chlorambucil or prednisolone and methotrexate).

Treatment Overview for Nonsuppurative CCHS: This involves multimodal medical support with numerous considerations: think immunomodulatory "cocktail" and broad metabolic / antioxidant support.

1) *Nutritional support:* balanced protein replete feline diet; avoidi protein restricted diets unless hepatic encephalopathy (HE) is obvious (jaundiced cat, portal hypertension, ammonium biurate crystalluria, neurobehavioral signs, ptyalism, post-prandial neurologic events- HE very rare in my experience)

2) *Vitamins-water soluble vitamins:* ensure repletion of thiamine (B_1) and cobalamin (B_{12}). Measure cobalamin to determine whether long term supplementation is appropriate. Initially administer B_{12} 250-1000 micrograms/cat (0.25-1.0 mg/cat) and then decide whether chronic treatment is necessary. If methotrexate is used for immunomodulation, oral folate supplementation at 0.25 mg/kg is recommended for at least 3 days after dose administration.

3) *Vitamins-fat soluble vitamins:*
Vitamin K1: most urgent deficiency in ductopenic cats. Provide parenteral vitamin K_1 before invasive procedures (needle aspirates, liver biopsy, exploratory surgery, placement of feeding tubes). Vitamin K may be urgently needed acutely and for chronic management in cats with sclerosing cholangitis or in cats that have been jaundiced for several days. *Initial dose:* 0.5-1.5 mg/kg given SC x 3 doses at 12 hr intervals. Maintenance dosing should be provided as needed based on PT or PIVKA testing (in ductopenic jaundiced cats, once or 2x weekly usually suffices). Too much vitamin K can cause hemolytic anemia; daily administration is too frequent for chronic management. Ductopenic cats must receive parenteral vitamin K as oral vitamin K will not be absorbed.

Vitamin E: alpha tocopherol acetate should be given orally 10 U/kg per day. In chronically jaundiced cats with ductopenia, a water soluble form of vitamin E may be best: polyethylene glycol alpha tocopherol succinate (TwinLabs distribution) at 10 U/kg per day is recommended. Vitamin E is an important membrane antioxidant, has biologically relevant anti-inflammatory and anti-fibrotic effects.

4) *Antioxidants:* should be provided because reduced hepatic GSH status has been documented in cats with Non-Suppurative CCHS and oxidative mechanisms are central to necroinflammatory disease processes in the hepatobiliary system.[37] Demonstration of Heinz bodies in some of these cats reflects their systemic GSH depletion. Antioxidants should be considered a component of multimodal treatment strategy that also includes: immunomodulatory and anti-inflammatory medications. Only in early mild CCHS does SAMe alone diminish disease activity (histologic basis) shown in our experimental work.

*N-acetylcysteine: (*NAC) as for Suppurative CCHS- 140 mg/kg initial dose, 70 mg/kg thereafter q 8-12 hr infused IV over 20 minutes using a 0.25 um filter. Recommended for critically ill cats requiring intensive supportive care until they can accommodate oral medications (then switch to SAMe)

SAMe: 20-40 mg/kg of a proven bioavailable product with predominance of s-SAMe (chiral molecule) isomer [Denosyl®] SAMe is an important thiol donor and provides numerous benefits advantageous in the management

of chronic necroinflammatory liver disease including: antiinflammatory, immunomodulatory, GSH repletion, facilitates methylation reactions (e.g. formation of l-carnitine, phosphatidylcholine, creatine, DNA, RNA, protein synthesis, detoxification reactions), polyamine synthesis and imparts an antifibrotic influence. Clinical study in healthy cats proved that SAMe can increase intrahepatic GSH stores and can improve redox status in RBCs. SAMe also contributes a hydrocholeretic influence that can assist in mechanically cleansing the biliary tree and facilitating elimination of certain toxins and microbial agents. Higher dose (40-60 mg/kg per day) can effect a choleretic effect. High dose administration was able to control mild Non-Suppurative CCHS lesions in cats (Group 1 CCHS) biopsied before and after SAMe 118 days of SAMe administration.
Vitamin E: see above under fat soluble vitamins.

5) *Ursodeoxycholic Acid (UDCA): IF THERE IS NO DUCT DESTRUCTION*-15-25 mg/kg PO divided BID given with meals to enhance absorption is advised along with supplemental taurine (250 mg/day). UDCA requires taurine conjugation in the cat and chronic dosing of UDCA in a cat that is hyporexic and not consuming a feline balanced diet may become taurine deficient (taurine is an essential amino acid for the cat). UDCA can provide a multitude of disease modifying effects that may mediate cholangiocyte protection. Beneficial effects include: acholeretic effect, anti-apoptosis effect on biliary epithelium and hepatocytes, anti-inflammatory effects, immunomodulation, alteration of an injurious bile acid milieu common in hepatobiliary jaundice, improved cell signaling responces, and several direct and metabolic cytoprotective mechanisms.[38] UDCA is proven to stimulate hepatobiliary secretory capacity, enhancing elimination of toxins and injurious bile acids by increasing expression of transporter proteins involved with the hepatocyte secretory capacity. It also interrupts classic apoptosis pathways by blocking proapoptotic events and through activation of intracellular survival signals. In experimental cholestasis, UDCA can change the bile acid composition in bile rendering it less hydrophobic and injurious; chronic administration saturates the bile pool such that ~60% is UDCA. It has been shown to displace hepatotoxic bile acids from biliary and hepatocellular membranes, and to improve membrane function, integrity and signaling. While a benefit has been shown in humans with certain forms of vanishing bile duct syndromes, there is now concern that UDCA may be detrimental to small damaged ducts.[38] This has been shown in knock-out mouse models of sclerosing cholangitis and inferred based on survival in humans with sclerosing cholangitis. UDCA is NOT considered routine therapy at present for humans with sclerosing cholangitis for this reason- currently we have suspended its use in cats with destructive cholangitis. The previously cited survival data from a study of monotherapy for lymphocytic cholangitis (ref 46) showed significantly shorter survivals in cats treated with UDCA without immunomodulation. This may reflect the lack of immunomodulation rather than worsening disease as there was no untreated control group (even historical).

6) *Antiinflammatory / Immunomodulatory Agents:* varies with the category of Non-Suppurative CCHS, as described below. Immunomodulatory & Antiinflammatory effects are derived from: SAMe, Vitamin E, UDCA, Prednisolone, Metronidazole, Methotrexate, Chlorambucil, and possibly Silibinin. M**ultimodal therapy** is advised with the goal of achieving best disease control with the fewest side effects (especially: lowest glucocorticoid dose)
Prednisolone: 2-4 mg/kg per day ideal body weight PO is prescribed initially and is gradually tapered to 1-2 mg/kg SID or EOD in tolerant cats (tolerance= no hyperglycemia). Prednisone should not be used: as this has low enteric uptake (< 26% of prednisolone) in cats. Dosing of prednisolone should be based on ideal or lean body weight rather than “one size fits all cats” or mg/kg basis as prednisolone does not appear to distribute into adipose tissue. Beware that single dose methylprednisolone acetate (Depomedrol) can impose adrenal suppression > 6 weeks and can jeopardize appropriate adrenal response to stress and/or cyclic disease.

Budesonide: 1-3 mg per day or 3 mg EOD (to avoid compounding) has been suggested for IBD and used in cats with CCHS. The author has only used budesonide in a few cats with CCHS and I have witnessed cats treated with budesonide to develop DM. There is limited experience with budesonide in cats with CCHS and no pharmacokinetic information. The following represents budesonide information for humans, rodents, and dogs. Budensonide is a non-halogenated glucocorticoid absorbed in the small intestine with high first-pass hepatic extraction; is metabolized to 16-□OH-prednisolone and 6-□OH budesonide. Glucocorticoid activity of metabolites (man) are 1% to 10%, but compared with prednisolone, glucocorticoid receptor binding activity is 15-20X higher. Thus it is considered a more potent glucocorticoid compared to prednisolone. Its influence on hepatic inflammation may surpass prednisolone but here is no specific information for cats. In humans with IBD, oral budesonide exerts fewer systemic side effects than conventional corticosteroids. The pharmacodynamic action of budesonide in healthy humans and patients with early-stage primary biliary cirrhosis (a disease similar to feline duct targeting CCHS) seems equal; however, effects on patients with cirrhosis due to PBC were unfavorable. A study evaluating budesonide combined with UDCA in humans with PBC against single agent therapy with UDCA disclosed improved liver histology.

Metronidazole: 7.5 mg/kg PO BID, compounded into gel caps or given as a prepared flavored liquid, is given to allow glucocorticoid dose reduction, to modulate IBD, and to augment beneficial effects of UDCA (see below). We

have not observed chronic problems with neurotoxicity or consequences associated of described in vitro metronidazole genotoxicity.[40] A recent randomized placebo-controlled trial in human beings with primary sclerosing cholangitis (PSC) evaluated the influence of combined UDCA with metronidazole (n=39) vs treatment with UDCA & placebo (n=41).[41] Surprisingly, a significant improvement in liver tests (calculated Mayo Clinic disease status scores), and improved histologic scores were shown with a trend suggesting diminished progression of ductopenia over 36 months (patients were biopsied at the beginning and after 36 months of treatment). The rationale for using metronidazole with UDCA in PSC regards its beneficial effect on intestinal inflammation and reduced permeability of enterocytes to bacterial endotoxins. Metronidazole also has been proposed to inhibit endotoxin-induced tumor necrosis factor-α production, activation of Kupffer cells and portal macrophages, and secretion of chemikines and cytokines by biliary epithelial cells. These effects may attenuate Zone 1 inflammation leading to improved histologic and clinicopathologic features. No influence of metronidazole on UDCA has been demonstrated that would increase its therapeutic benefit.

Methotrexate (MTX): pulsatile therapy given on a single day q7-10 days. Dose: 0.13 mg per dose given 3 times on a single day, using 12 hr intervals once q 7-10 days. This is an antifolate drug with immunomodulatory and anti-inflammatory properties.[42,43] At present, MTX is considered the standard of care for humans with rheumatoid arthritis and has been used for control of an impressive array of non-neoplastic inflammatory disorders including certain forms of liver disease similar to feline CCHS. However, there is great interindividuality in response to MTX in human beings. MTX can have important toxic side effects (hepatic fibrosis, lung fibrosis, bone marrow toxicity, a few others) that can be avoided by co-administration with **folic acid**. However, some scant evidence suggests that high dose folic acid or folinic acid may thwart MTX efficacy**. Currently in humans** the recommendation is: a single dose of 5 mg of folic acid once per week, taken in the morning following the day of methotrexate dosing, if adverse effects still occur, increasing the single dose to 10 mg/week is considered' .Low dose pulsatile once weekly MTX was developed for humans with rheumatoid arthritis to reduce systemic side effects; this strategy has been highly successful and is the basis for the MTX protocol I use in cats. Such low dose intermittent MTX administration allows for cell MTX loading and provides adequate intracellular MTX accumulation to achieve a therapeutic effect. MTX is known to accumulate within lymphocytes, fibroblasts, RBCs, and bile (undergoes enterohepatic recycling). In humans, the 5 mg of folate given the day after MTX administration (once weekly MTX dosing) appears to offset adverse effects. However other recommendations are to provide 1 mg total dose daily for humans on chronic low dose MTX therapy. Some recent work suggests that folic acid administration increases MTX distribution into cells that uptake the drug and polygutaminate it (trap it intracellularly) increasing targeted delivery. The actual dose needed in cats is unknown; we have been supplementing with 0.25 mg/kg once per day x at least 2 doses staring one day following methotrexate administration.

Activity of MTX is complex imparting both anti-inflammatory and immunomodulatory effects by acting at different levels of the inflammatory cascade. Direct inhibitory effects on cell proliferation (lymphocytes) and induction of apoptosis in cells involved in both immune & inflammatory reactions are considered the first step in its therapeutic effects. Specifically, MTX has been shown to: 1) reduce cell proliferation (lymphocytes are a susceptible cell population that polygutaminate MTX , trapping it within the cell), 2) to increase apoptosis of T cells, 3) to increase endogenous adenosine release that beneficially modifies inflammatory cascade signaling, and 4) induces effects that beneficially influence cytokine and humoral responses reducing inflammatory cell trafficking and/or signaling. In man, MTX effects are influenced by genetic variants and specific microenvironmental elements e.g. adenosine availability or glutathione concentrations. MTX is known to suppress TNF□activity, IL-6, and IL-8, to promote transcription of mRNA for an IL-1 receptor antagonist, and to increase secretion of the potent anti-inflammatory cytokine IL-10. The split-dose regimen of 3-equally divided doses given at 12-hr intervals in humans assists with minimizing gastrointestinal effects, headache, and fatigue early after drug ingestion. This is linked to prevention of excessive release of adenosine in the CNS. Since interruption in methylation reactions and methionine biosynthesis (SAMe production) may participate in drug induced hepatotoxicity (lipid accumulation in hepatocytes) co-administration of bioavailable SAMe is recommended**. It is clear that MTX increases risk of infection in human beings on chronic low dose therapy; a similar effect has been documented in CCHS cats treated with low dose MTX by the author.** This likely relates to the fact that MTX has been shown to have significant suppressive effects on neutrophil chemotaxis, even at low doses. MTX also has potential to reduce intracellular GSH, thus altering cellular redox status and decreasing macrophage recruitment and function. Co-administration of SAMe administration may also assist in avoiding this complication.

Chlorambucil: option INSTEAD of MTX described above- 2 mg/cat PO every other day (EOD) or every third day; hemogram monitoring at 2 & 4 weeks, 2 months, and then quarterly for adverse bone marrow effects. Chlorambucil is an alkylating nitrogen mustard derivative used as a chemotherapeutic drug with good efficacy in lymphocyte mediated disorders (small cell lymphoma in cats, immune-mediated disorders). Because cats are intolerant of azathioprine, chlorambucil is used as a surrogate medication in situations where we would use

azathioprine in a dog. Efficacy in some cats with Non-Suppurative CCHS is good. However, some cats with sclerosing CCHS do not respond well to chlorambucil and do better with the pulsatile MTX/folate protocol.

Treatments Specified for Each Diagnostic Group:

Group 1: *Nonsuppurative CCHS without duct immunotargeting*: Initial treatment with appropriate antimicrobials, UDCA, SAMe, vitamin E, water soluble vitamins (B vitamin supplementation), enteral alimentation with a feline formulated maximum calorie diet, and judicious administration of fluids to correct and maintain hydration and to correct electrolyte abnormalities, are essential. As before, broad spectrum antimicrobial coverage (against anaerobic and gram-negative enteric opportunists) is recommended as for suppurative CCHS, until the nature of the disease process is clarified by liver biopsy and culture results. Antimicrobial therapy is thereafter tailored to sensitivity reports of bacteria cultured from hepatobiliary aspirates or biopsies; often nothing is cultured. Long term treatment requires immunomodulation. First line immunosuppressive therapy is prednisolone, initially administered at 2-4 mg/kg lean body mass PO SID with the dose titrated based on treatment response to 5-10 mg/day. Co-administration with metronidazole (7.5 mg/kg PO) may assist with immunomodulation and control of associated IBD. Some clinicians use chlorambucil in these cats (2 mg/cat/day,SID then titrated to EOD). Continued administration of SAMe (40-60 mg/kg/day PO) and vitamin E (10 U/kg/day) are recommended. The role of silibinin (milk thistle) is not resolved; recent studies in humans with PSC suggest that silymarin provides an immunomodulatory and anti-inflammatory benefit but further studies are needed. Presently, UDCA combined with metronidazole or glucocorticoids are the only medications for primary biliary cirrhosis in humans (similar to feline CCHS) that provide an inarguable treatment benefit. Response to treatment in feline Non-Suppurative CCHS usually achieves normalization of bilirubin concentrations but cyclic increases in enzyme activity remain, although the magnitude of enzyme activity is attenuated. Long term survival (>8 years) has been documented with immunomodulatory treatment. Compared to the natural biology of CCHS inferred from one case series[13-15] suggests that treatment improves survival. Some cats with mild lesions may respond well (pathologic lesions resolve) with only high dose oral SAMe treatment (Denosyl®, 40-60 mg/kg PO daily). However, most cats in this group require the treatment regimen described above including a hypoallergenic diet if they also have coexistent IBD.

Group 2: *Sclerosing CCHS with duct immunotargeting* typically do not respond to conventional treatments of only: prednisolone, antioxidants, metronidazole, and require more aggressive immunomodulation. Pulsatile methotrexate (MTX) at 0.13 mg/kg PO q 12 hrs x 3 doses on a single day (total dose = 0.39 mg/cat/day) given once q7–10 days coupled with supplemental folic acid (0.25 mg/kg day for 2 days after MTX dosing) has achieved reasonable disease control. If a cat fails to response after 6-8 wks, increase 0 time dose to 0.26mg and keep other 2 doses at 0.13 mg. MTX can alternatively be given by IV or IM injection with a 50% dose reduction (enhanced bioavailability). Folic acid, 0.25 mg/kg PO daily is concurrently administered to prevent MTX associated hepatotoxicity, as shown in human beings. MTX dosing must be reduced in cats with renal azotemia. Careful inspection for infectious agents before initiating MTX therapy is essential as this drug imposes profound immune-suppression at the dose used (clinical experience). Some cats have developed feeding tube abscesses, hepatic abscesses, pyelonephritis, herpes keratitis, and demodecosis subsequent to MTX immunosuppression. Careful patient monitoring during therapy for complications is essential. Alternatively, chlorambucil is used, dosed at 2 mg/day SID to EOD. Concurrent treatment with the antioxidant SAMe is recommended as a GSH donor and for its antioxidant/apoptotic /anti-inflammatory effects, Vitamin E for its antioxidant, anti-inflammatory and antifibrotic effects, low dose prednisolone and metronidazole to achieve multimodal immunomodulation. Treatment for concurrent inflammatory bowel disease with a hypoallergenic diet, and weekly supplementation with vitamin B_{12} is indicated when appropriate based on measured cobalamin concentrations.

Group 3: *Lymphoproliferative Disease "Masquerading as Lymphocytic CCHS***"** Treatment with chlorambucil has been used at a dose of 2 mg/cat given on alternate days, combined with treatments previously described for CCHS. Some cats have survived for several years with minimal clinical signs and others have progressed to develop lymphoma. In cats with severe gut involvement there may be issues with enteric drug uptake. A few cats in this group in which we have examined oral prednisolone pharmacokinetics have not had a problem with enteric drug absorption.

Group 4: *Small Cell Lymphoma Masquerading as Lymphocytic CCHS*- Treatment with chemotherapy designed for feline lymphoma is recommended. Some cats that have maintained long term remission on the chlorambucil protocol described previously. Judicious administration of nutritional, vitamin, and antioxidant support, as previously described, is advised. These cats may have coexistent intestinal involvement although we also have identified cats in Group 4 with inflammatory bowel disease and cats with overt enteric lymphosarcoma and Group 1 or 2 Non-Suppurative CCHS.

Treatment: What To Expect in Non-Suppurative CCHS ?

1. Warn Clients That This Disorder Spontaneously Cycles

a. Intermittent bouts of hepatic inflammation and associated clinical signs
b. Expect continued low level ☐ liver enzymes BUT usually bilirubin normalizes.
c. Cats with sclerosing CCHS may become diabetics on glucocorticoid therapy

2. Some cats have apparent long term remission to cure.
   a. HOWEVER, Rx withdrawal unlikely→ recrudescence
3. Treatment seemingly diminishes disease activity based on follow up biopsy samples acquired in some of our long term treated clinical cases
4. Cats treated with MTX require high vigilance of detection of acquired infections.
5. Chronic End-Stage Deaths
   a. Biliary cirrhosis
   b. Underlying or associated conditions: gut, pancreas, progression to lymphoma ?
   c. Many cats with CCHS, gut inflammation and pancreatic inflammation ALSO have chronic interstitial nephritis characterized by a lymphoplasmacytic inflammation in the kidney interstitium. May succumb to renal failure.
6. A diagnosis confused with CCHS is Polycystic liver disease in the Himalayan and Persian cat, others.
   a. Progresses to hepatic fibrosis and is commonly misdiagnosed as biliary cirrhosis due to CCHS on liver biopsy.
   b. No therapy is effective.
   c. These may or may not have small renal and pancreatic cysts.

Definitive Diagnosis of CCHS: Rules to Remember!

a. Cannot Reliably Diagnose Non-suppurative CCHS on the basis of Cytology
b. Surgical Wedge or Laparoscopic Cup Biopsies Provide the BEST Diagnostic Samples.
c. Biopsy More Than One Liver Lobe As Involvement Is Variable Among Liver Lobes In CCHS
d. Consider Collecting Biopsy Samples from :
   Intestines (full thickness BETTER than Endoscopic), Pancreas , Lymph Nodes, +/- Kidneys
e. Examine cytologic imprints of bile and tissue samples → look for bacteria & suppurative inflammation.
f. Submit bacterial cultures: bile & tissue & nidus of removed choleliths
   Rare to isolate bacteria from Non-suppurative CCHS …. BUT infection may be a complication due to cholestasis. Without cytology & culture you may overlook a complicating infection.

Brief Summary RX Protocol for Non-Suppurative CCHS.
SA. Center, DVM, DiplACVIM, Cornell University

Underlying Disorders:	Identify and appropriately treat underlying conditions, especially IBD, HL, bile duct occlusion, pancreatitis, acquired pancreatic insufficiency, others.
Nutritional Management:	Do not restrict dietary protein unless overt hepatic encephalopathy. Ensure balanced feline nutritional support. IF HE, use lactulose & low dose metronidazole.
Prednisolone:	2-4 mg/kg lean body weight daily PO Titrate to lowest effective dose; reduce dose q 10 days by 25% based on response Maintenance regimen with 1-2 mg/kg, EOD if possible. Monitor for glucose intolerance / diabetes mellitus esp. if sclerosing CCHS, may require discontinuation of glucocorticoids as an arm of therapy.
Metronidazole:	7.5 mg/kg PO BID (indefinite)
Ursodeoxycholic Acid:	10-15 mg/kg daily PO given with food, divided dose given BID if possible. Supplement taurine if chronic therapy. Currently NOT recommended for cats with destructive or sclerosing cholangitis.
Water Soluble Vitamins:	2-fold normal maintenance dose daily
B_{12}: malabsorption	0.25-1.0 mg IM every 7-28 days as shown based on measured B_{12}, necessary if gut A weekly loading interval may be necessary in depleted cats: follow plasma $B_{12,}$ then monthly vitamin supplementation by parenteral route. Severe IBD, pancreatic insufficiency, enteric lymphoma, disturbed bowel flora are suspected causes. Supplement Vit. E & SAMe to activation.
Vitamin K_1:	5 mg IM (0.5-1.5 mg/kg) every 7 to 28 days based on optimized PT or PIVKA clotting test or observed bleeding tendencies. Too high a dose → hemolytic anemia.
∀-tocopherol (Vitamin E):	10 IU/kg: ∀-tocopherol acetate; if severe ductopenia polyethylene glycol ∀-tocopherol-succinate.
SAMe:	thiol / GSH donor & essential intermediary metabolite, 180 mg/day PO empty stomach Use dog sized tablets (as shown to be effective in our research study).
n-Acetylcysteine:	IV thiol / GSH donor, 140 mg/kg loading, then 70 mg/kg IV BID until enteral route established, then → initiate SAMe administration in place of NAC when PO route possible
Lactulose:	0.25 - 0.5 ml / kg initial dose, titrate to achieve several soft stools / day Only if suspect HE (rare) or to avoid constipation
For cats with biopsy confirmed sclerosing cholangitis: OR Chlorambucil instead see below	
Methotrexate:	Pulse oral therapy q 7 - 10 days based on WBC nadir and tolerance Total daily dose 0.4 mg divided into 3 treatments 0.13 mg at hr 0, 12, and 24hr ONCE per week If fail to respond after 6-8 wks, increase 0 time dose to 0.26. Can use IM in intractable cat: total dose reduced by 50%
Folate:	0.25 mg/kg PO daily. **All cats treated with MTX should receive folate** at least 2 doses starting the day following MTX administration.
For cats with biopsy confirmed sclerosing cholangitis / lymphoproliferative disease / small cell lymphoma	
Chlorambucil:	2 mg per cat SID to EOD as an alterative to MTX. Monitor CBC for hematologic toxicity at 2 & 4 wks, 8 wks, then quarterly.

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NOTES:

Five Unique Feline Hepatic Syndromes

Sharon Center, DVM, DACVIM

Copper Associated Liver Injury: *Primary*

Signalment

Cats with primary copper associated liver injury (PCH) typically present young (≤2 years of age) with no sex or breed predilection with duration of illness ranging from 1-3 wks (most commonly) up to >1 yr. Rarely, we have identified cats as old as 10 yrs based on liver biopsy collected for unexplained ALT activity. We have observed sudden death in severely affected cats before diagnosis of PCH, with patients presenting with extreme ALT and AST increases, vomiting, diarrhea, weakness and collapse. Several cats with PCH had the diagnosis overlooked on initial liver biopsy; in two cats the diagnosis was ascertained on second opinion biopsy review and in one cat diagnosis was ascertained on a second biopsy 9mths later when immunomodulatory drugs failure to modify biochemical abnormalities. Routine application of special stains including Rhodanine for copper detection on all evaluated liver biopsies obviates this diagnostic complication.

Clinical Signs

Include: vomiting (55%0, lethargy (55%), hyporexia, (55%), jaundice (36%), bleeding (27%), weight loss (18%), abdominal effusion (18%), and diarrhea (18%). Seemingly, there is a gradation of severity in copper causing hepatocellular injury and clinical signs, as noted in canine patients. Presentation of one cat was for acute onset of hematemesis, and severe bloody diarrhea. This cat rapidly became recumbent and was obtunded. In another cat present for abrupt onset of clinical signs, severe Heinz body hemolytic anemia with methemoglobinemia was associated with acute renal failure and death. In another cat with severe PCH (copper > 7,000 μg/gm dry weight), abrupt collapse and shock preceded rapid death.

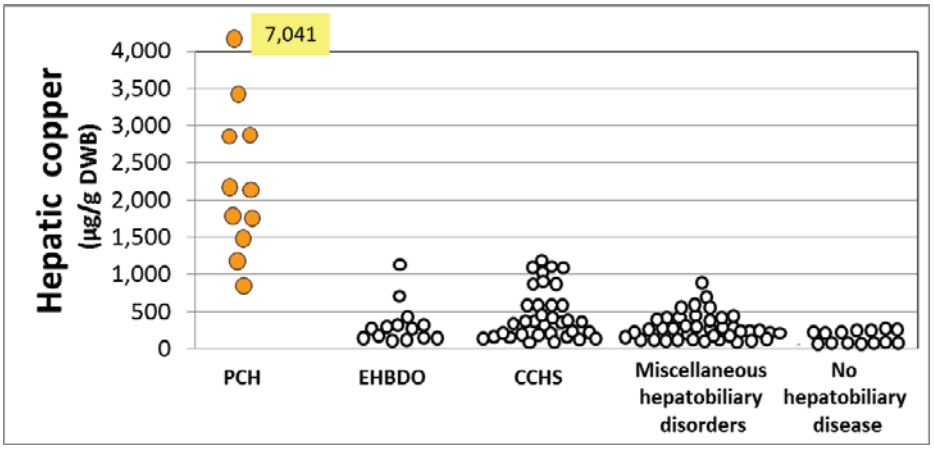
Clinicopathologic Features

Every cat with PCH demonstrates a > 1.7-fold increase in ALT with most also demonstrating increased AST activity that may reflect hepatocellular mitochondrial injury attributable to copper accumulation. However, when signalment, clinical features, clinicopathologic parameters, and ultrasonographic patterns associated with PCH were compared to other common necroinflammatory liver disorders, PCH could not be distinctly recognized without liver biopsy. Acquired Fanconi syndrome has not been documented in cats, as occurs in dogs with severe copper hepatotoxicity.

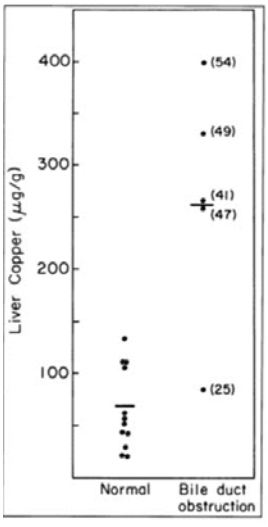
Definitive Diagnosis

Required liver biopsy and staining for copper (rhodanine) and measuring hepatic copper concentration. All cats with PCH have liver copper > 700 ppm DMB (normal reference range < 190 ppm DMB) and distinct distribution of hepatocellular copper granules in the centrilobular region (or more diffusely). Curiously, copper accumulation in PCH is associated with a glycogen-type vacuolar hepatopathy that is uncommon in cats. On gross evaluation the liver may have rounded margins, a nutmeg appearance with coarse mottling and tan discolorations.

Hepatic copper concentration in 11 PCH cats & 80 cats with other liver disorders



Hepatic copper at baseline and then after chronic major bile duct obstruction (days obstructed).



	Copper Hepatopathy	EHBDO	CCHS	Miscellaneous Liver Disorders	Lacking Hepato-biliary Disease	Reference range
n	11	11	30	39	15	
Age	2 (0.5-11)	12.0 (7.0-16)[a]	12.8 (1.9-17)[a]	10 (1.1-16)[a]	6.5 (2-16)[a]	---
Liver Copper Concentration	1,830 (704-7,041)	238 (63-1,004)[b]	320 (40-1,110)[b]	155 (27-791)[b]	101 (23-189)[b]	< 180
PCV (%)	35 (25-42)	33 (25-43)	35 (27-49)	33 (16-45)	40 (33-45)	31-48
WBC (thou/L)	13.5 (5.3-90.4)	15.4 (2.1-27.5)	13.8 (6.5-53.5)	10.0 (2.7-42.0)	9.3 (6.4-18.9)	5.1-16.2
Total Protein (g/dL)	7.9 (6.6-10.4)	7.6 (5.2-9.1)	7.9 (6.2-9.1)	7.0 (4.8-9.3)	7.3 (6.7-7.8)	5.9-7.5
Albumin (g/dL)	3.5 (2.7-4.2)	3.1 (2.3-3.9)	3.5 (2.5-4.4)	3.2 (1.5-3.9)	3.6 (3.0-3.7)	2.8-4.2
BUN (mg/dL)	26 (9-42)	19 (10-33)	25 (12-39)	22 (10-52)	28 (16-35)	16-36
Creatinine (mg/dL)	1.2 (0.5-2.8)	1.3 (0.8-1.7)	1.3 (0.6-2.1)	1.3 (0.4-2.0)	1.4 (1.0-1.8)	0.6-2.0
Glucose (mg/dL)	116 (70-171)	140 (92-600)	117 (78-203)	118 (69-600)	151 (91-472)	64-144
ALT (U/L)	684 (290-1,710)[c]	513 (106-1,426)	455 (48-1,932)[c]	296 (46-3,764)[c]	112 (77-328)[c]	35-176
AST (U/L)	171 (22-9,995)	196 (44-1,371)	162 (21-590)	84 (22-1,060)	62 (29-84)	15-44
ALP (U/L)	132 (1-981)	212 (45-1,247)	214 (22-589)	67 (9-896)	50 (26-75)	13-83
GGT (U/L)	3 (1-11)	8(3-38)[f]	3 (1-27)	3 (0-13)	3 (2-3)	0-2
Total Bilirubin (mg/dL)	2.1 (0.1-10.0)	6.0 (1.0-43.6)[g]	0.8 (0-22.9)	0.5 (0-17.7)	0.1 (0-0.1)[g]	0-0.2
Cholesterol (mg/dL)	183 (76-511)	244 (143-391)[h]	225 (127-571)	174 (47-615)	155 (78-300)	66-317
Urine SG	1.060 (1.036-1.074)	1.021 (1.012-1.045)	1.021 (1.008-1.060)	1.033 (1.004-1.060)	1.047 (1.013-1.060)	> 1.030

All P $\leq$ 0.03 a=0.0003; b=0.0000001; c=0.03; d=0.02;e=0.008; f= 0.0003; g and h= 0.005

Primary hepatocellular neoplasia has been identified in 5/14 PCH cats (4 hepatocellular carcinomas, 1 hepatocellular adenoma). In one case we confirmed profound copper accumulation within neoplastic tissue. Finding primary hepatocellular neoplasia is not unprecedented as humans with Wilson's disease (an important copper storage hepatopathy caused by a gene mutation affecting ATPβ7 that directs formation of a copper transport protein), also have increased risk for hepatocellular carcinoma (dogs seemingly do not). Our studies clarify that cats with cholangiohepatitis and major bile duct obstruction also may accumulate pathologic copper concentrations (> 700 ppm DMB) but the lobular distribution is in the periportal region (zone 1), adjacent to portal inflammatory infiltrates. It is possible that hepatic copper accumulation may complicate treatment response in some cats with feline CCHS. Thus, special staining for copper is recommended for all cats undergoing liver biopsy for suspected feline CCHS.

Treatment

Successful PCH treatment has been achieved using combinations of chelation (d-penicillamine, n=5, 10-15 mg/kg PO q12hr), antioxidants (n=6, s'adenosylmethionine: 20 mg/kg PO q24h, vitamin E: 10-15 u/kg POq24h), low-dose elemental zinc (n=2), and hepatic support or high-protein low-carbohydrate diets suitable for cats with diabetes mellitus. Notably, one chelated cat developed hemolytic anemia which resolved after d-penicillamine withdrawal. Antioxidants used include: Zinc therapy included: 5 mg elemental zinc PO q24hr, increased to q12hrs given 30 minutes before feeding when gastric tolerance was demonstrated. In one cat 8 months of chelation with chelation treatment combined with administration of a generic hepatic support formula (15 mg of silibinin with 30 mg of phosphatidylcholine and 1 mg of elemental zinc PO per day, Prohepatic Liver Support Supplement for Cats and Small Dogs (silybin [15 mg]-phosphatidylcholine [30 mg] complex, grape-seed bioflavanol extract, and zinc chelate [0.95 to 1.3 mg of elemental zinc]), Animal Health Options, Golden, CO). One cat with PCH lived in an environment that was previously a copper mine and we speculate copper contaminated water or food chain led to copper loading. The cat with d-Pen associated hemolysis maintained on low dose zinc, continues to have increased liver enzymes,a low grade anemia, and a coarse nodular liver on abdominal US.

Copper Associated Liver Injury: *Secondary* in the published study of copper associated hepatopathy (Hurwitz BM1, Center SA, Randolph JF, et al: Presumed primary and secondary hepatic copper accumulation in cats. J Am Vet Med Assoc 2014;244(1):68-77) we documented the association between copper accumulation and more primary hepatic disorders in 80 cats (see Table above). Cats can accumulate copper similar to humans secondary to hepatic cholestatic disorders- this does not occur in dogs. One study in cats with experimentally induced major bile duct obstruction clearly demonstrates this phenomenon over a relatively short period of time- shown in the figure above. The most common scenario encountered in clinical practice is in cats with CCHS where copper may variably accumulate adjacent to the inflammatory infiltrates in the periportal region

Cholelithiasis: Symptomatic & Asymptomatic

Cholelithiasis

With advent of routine diagnostic use of abdominal US, antemortem diagnosis of cholelithiasis has increased, particularly in cats. This coordinates with the fact that most choleliths are clinically silent. Choleliths are

more common in middle-aged to older animals and are more commonly recognized within the gallbladder (GB, cholecystoliths). However, choledocholiths within the common bile duct (CBD), and within hepatic and interlobular bile ducts are also recognized. While most choleliths in the CBD initiate from the GB, some choledocholiths seemingly develop within bile ducts as a consequence of bile stasis, inflammation, and/or infection. Some of these are found in cats with congenital malformations (sacculation) of large bile ducts or choledochal cysts (an appendix like outcropping of the CBD). Both of these disorders are forms of Ductal Plate Malformations. Choleliths in dogs and cats differ from those in human beings which are primarily derived from cholesterol crystal precipitaton. Most choleliths in cats contain calcium carbonate and are radiographically visible. However, some are not large enough to be seen on survey radiographs (< 2 mm).

Pigment gallstones are less common in cats and are divided into two categories: "black-pigment" stones composed primarily of bilirubin polymers, and "brown-pigment" stones composed predominantly of calcium bilirubinate.

Black-pigment stones reflect prolonged hyperbilirubinemia; in these bilirubin polymerization occurs after its non-enzymatic deconjugation. These types of stones have been observed in cats with congenital hemolytic anemia caused by pyruvate kinase (PK) deficiency (mutation characterized in Abyssinian and their long-haired morphs: Somalis, Bengal cats, and DSH). See description below of feline PK Hemolytic Anemia.

Brown-pigment stones are frequently associated with bacterial infections in the biliary tree and stasis of bile flow. Bacterial enzymes, such as β-glucuronidase, initiate hydrolysis of bilirubin diglucuronides causing bilirubin deconjugation. Release of unconjugated bilirubin which can precipitate with calcium carbonate, forms calcium bilirubinate. Bacterial phospholipase also can induce breakdown of biliary phospholipids→ free fatty acids and lysophospholipids. Both of these products are water insoluble and increase bile lithogenicity. Accumulation of fatty acids and lysophospholipids also cause biliary epithelial injury and inflammation which increases mucin production (prostaglandin induced) from the injured epithelial cells. This furthers risk for precipitation of calcium salts, fatty acids, bilirubin pigment, and glycoproteins (mucin). Biliary precipitates and micro-calculi promote bacterial colonization providing a substrate for bacterial retention. This further augments calcium bilirubinate aggregation. Mucin production, enhanced by local inflammation and prostaglandin release, entangles calcium bilirubinate and bilirubin polymers into cholelith aggregates that provide an survival niche for bacterial organisms. This process is augmented by GB dysmotility and/or bile stasis.

It is widely recognized that GB distension from any cause stimulates local mucin production and that this contributes to cystic duct occlusion through initiation and perpetuation of biliary sludge; upon dehydration this material becomes inspissated bile. Anything causing cystic duct obstruction can increase mucin production by the inflamed GB epithelium, with exfoliated cells (epithelial, inflammatory) providing a nucleating nidus for stone formation. An alkaline shift of luminal pH explains the increase in calcium carbonate production that leads to mineralization of biliary concretions (calcium carbonate precipitates at a pH > 6.6) and sometimes the GB wall ("Limey Gallblader). It is hypothesized that chronic and/or intermittent cystic duct obstruction and low-grade GB wall inflammation lead to GB epithelium hydrogen secretion dysfunction resulting in the increased GB bile pH. Greater inflammation leads to greater carbonate anion accumulation because of reduced hydrogen influx (Henderson-Hasselbalch equation).

Cholecystitis is lithogenic due to prostaglandin-mediated inflammation that drives local mucin production, hemorrhage, bacterial bilirubin deconjugation, and stasis of bile flow. Thus, it is clear that disease or stasis of bile flow involving the GB, cystic duct, or major bile ducts can lead to cholelithiasis as surely as cholelithiasis can injure these structures leading to bile stasis. Unfortunately, any cause of bile stasis leads to bacterial colonization by bile by enteric opportunists. Thus, complexities increasing risk for cholelithiasis must be individually assessed to determine causal factors that deserve interventional therapy.

In humans, the incidence of left hepatic lithiasis > right hepatic lithiasis and is explained by the anatomical difference in the angle made as these ducts diverge from the common bile duct. The left hepatic duct forms an acute angle at its junction with the common bile duct, promoting bile stasis more quickly in left lobes vs right liver lobes. This has not been investigated in the cat.

Pyruvate Kinase Deficiency and Hemolysis → Bilirubinate Black Stones

Cats predisposed to cholelithiasis due to congenital hemolytic anemia caused by pyruvate kinase deficiency my initially exhibit lethargy, pale mucous membranes, intermittent diarrhea, and inappetence causing weighty loss, with jaundice being rare. Cats develop a prominent to large spleen associated with hematopoiesis, clearance of fragile RBC, and hemosiderosis (macrophage sequestration of iron) and lymphoid hyperplasia. A marked lymphocytosis and hyperglobulinemia may develop. Affected cats demonstrate intermittent mild to moderate, slightly macrocytic-hypochromic anemia with increased osmotic fragility; severe anemia may terminally develop. Liver enzymes (ALT, ALP) may increase from undetermined cause: hemosiderosis observed in such cases usually does not cause hepatic necrosis or enzyme release but microlithiasis and biliary inflammation could explain enzymes as well as development of hepatic lipidosis. Age at diagnosis ranges from young (months) to older cats (5 yrs or more).. Total erythrocyte PK activity is markedly reduced in deficient cats, and all PK-deficient cats have had the same mutation.. Unlike dogs, myelofibrosis and osteopetrosis have not been recognized in cats. *PKLR*, the gene encoding

the regulatory glycolytic enzyme pyruvate kinase (PK) has an autosomal recessive mode of inheritance, has high variability in onset and severity of clinical signs.

Clinical Signs of Cholelithasis

Include vomiting, anorexia, jaundice, fever, and abdominal pain. However, as stated previously, many animals with choleliths remain asymptomatic. Part of the problem is that pain associated with "biliary colic" is referred pain and transient. It may manifest in cats as reclusiveness, inappetence, anxiety, pacing, and altered behavior (including vocalizations). Cholelith movement or impaction within the cystic duct, CBD, especially in the ampulla (fused CBD and pancreatic duct in the cat) or the sphincter of Oddi (at the duodenal papilla), causes intense but intermittent local and referred pain in humans. This discomfort is not exclusively postprandial and pain may localize to the right upper abdominal quadrant, the epigastrium (dermatome of T8/9), radiate to the right scapula or shoulder, or localize to the retrosternal region. How is manifests in cats is unclear. Nausea or vomiting are common in human patients who assume a position of relief or walk to relieve discomfort. Abdominal pain persists for at least 15-30 minutes up to several hours. Pain abates if the cholelith passes into the duodenum or back into a dilated region of the CBD, or an impacted stone in the cystic duct returns to the GB lumen. We believe we have recognized similar discomfort and vague pain in cats symptomatic with cholelithiasis. It is important to consider this problem as a differential diagnosis in cats with vague abdominal pain- when you consider a ureterolith- also consider a cholelith. Biliary sludge or microliths lodging in the distal portion of the CBD (ampulla) in cats may initiate signs considered "idiopathic" pancreatitis, similar to phenomenon described in humans. It is well acknowledged that a large subset of humans with pancreatitis have cholelith associated or induced disease.

Clinicopathologic Features of Cholelithiasis

The hemogram in a cat with cholelithiasis may be normal or reflect inflammation or infection or if the underlying problem is PK associated hemolysis, a regenerative anemia. The chemistry profile may be normal or disclose high cholestatic enzymes or evidence of obstructive jaundice (increased ALP, GGT, ALT, AST, cholesterol, and bilirubin). Thus laboratory features may reflect associated cholecystitis, choledochitis (duct inflammation), or extrahepatic bile duct obstruction (EHBDO) with some cats with intrahepatic small duct lithiasis lacking clinicopathologic abnormalities. Jaundice directly relates to cholelithiasis associated with EHBDO, sepsis, or hemolytic associated choleliths; thus, a large number of animals with US detected cholelithiasis are not hyperbilirubinemic. Comparatively, before common use of US in clinical practice, most animals with antemortem diagnosis of cholelithiasis had EHBDO. Ultrasonography can detect stones $\geq$ 2 mm in diameter in the GB, with more skill and luck needed to recognize small stones lodged in the CBD where enteric gas may interfere with imaging. For animals with small duct cholelithiasis, biopsy and culture of liver tissue is necessary to identify underlying disease and associated bacterial infections. While cholelithiasis may develop secondary to infection, stones also may induce infection- therefore bacterial culture must always be sought in symptomatic animals. Mechanical trauma from choleliths may allow opportunistic organisms transiting the hepato-biliary-enteric circulation to assume residence areas of bile stasis.

Treatment of Symptomatic Cholelithiasis

Suspected Infection

Medical treatment of cholelithiasis in symptomatic patients, particularly those scheduled for surgical interventions, includes coverage with broad spectrum antibiotics considering that enteric opportunists are likely involved. Initially combining: Ticarcillin (25mg/kg IV q8hrs), metronidazole (7.l5 mg/kg IV or PO q 8-12hr2), and enrofloxacin (2.5 mg/kg parenteral or PO q12hrs).

Choleresis

Use of a choleretic regimen may facilitate clearance of biliary aggregates and bacterial organisms if there is no evidence of EHBDO. Treatment with UDCA (15-25 mg/kg/PO divided into two doses / day given with food to increase absorption) and SAMe (Denosyl^{TM}, 20-40 mg/kg/daily PO given on an empty stomach) may have advantage for choledocholiths lodged in small intrahepatic bile ducts. Intrahepatic small duct cholelithiasis (hepatocholelithasis) may reflect chronic inflammatory disease that may benefit from use of these medications. Whether or not there is benefit from administration of dehydrocholate, to increase bicarbonate rich watery bile, has not been evaluated in animals with spontaneous cholelithiasis. However, this is the best bile acid dependent choleretic.

Antioxidants

Alpha tocopherol (vitamin E: 10 U/kg/day) can be safely used for its antioxidant and anti-inflammatory affects without liver biopsy. If the animal is jaundice due to EHBDO, the water soluble form must be used (polyethylene glycol alpha tocopheral succinate, TwinLabs product: **Twinlab** Liqui-**E**). SAMe (Denosyl, 20 mg/kg PO q24hr on an empty stomach) is also advised as symptomatic patients likely have risk for oxidative hepatobiliary injury.

Vitamin K1: if the patient is jaundiced due to EHBDO, the loading protocol is used: 0.5-1.5 mg/kg IM or SQ x 3 doses at 12 hr intervals before surgical intervention.

Surgical Interventions

Surgical intervention is necessary in animals with choleliths associated with cholecystitis, causing cystic duct obstruction, occluding the common bile duct or associated with a Choledochal cyst (one of the Ductal Plate Malformations). Successful treatment of cholecystitis and cystic duct occlusion requires cholecystectomy and lavage of the CBD to remove residual biliary debris to assure duct and sphincter of Oddi patency. It may be possible to remove stones lodged in the CBD by choledochotomy, however, causal factors underlying cholelith formation must be carefully considered. Retaining a diseased or dysmotile GB imposes risk for recurrent lithiasis or necrotizing cholecystitis. Some patients may benefit from placement of a temporary stent through the sphincter of Oddi or a "sphincterotomy" to relive stenosis due to trauma of a stone impaction. While temporary stenting theoretically allows healing of the surgical site while ensuring bile drainage into the duodenum, this procedure is fraught with complications in cats (retrograde infection, suppurative/septic pancreatitis, stent occlusion within a few days). In cases where CBD obstruction is irresolvable, a cholecystenterostomy should be performed (cholecystoduodenostomy, cholecystojejunostomy). These animals require chronic monitoring for episodic septic cholangitis due to risk for retrograde biliary infection with enteric bacteria. Chronic or intermittent administration of antimicrobials may control recurrent infections. Biopsy of biliary structures and liver for histopathologic evaluation is essential at the time of cholelith removal or biliary-enteric anastomosis to determine whether underlying primary inflammatory or neoplastic diseases that provoked cholelith formation. Tissue (liver, bile duct, GB), bile containing particular debris, and cholelith nidus should be submitted for aerobic and anaerobic bacterial cultures. Cytology of tissue and bile imprints and even portions of the cholelith nidus or entangling biliary debris should be assessed for bacterial organisms as this will allow morphologic characterization if cultures do not identify organisms.

Cholecystoduodenostomy and cholecystojejunostomy are the most common cholecystenteric surgical procedures for biliary bypass in cats. Cholecystoduodenostomy is most physiologic allowing bile to mix with duodenal chyme where it can facilitate pancreatic enzyme activity, release, and activation. The anastomotic stoma must be large enough to allow intestinal reflux to exit the GB (or ducts if choledochoenterostomy) and provide a margin of error for contracture of the stoma during healing (can be up to 50%.) In small animals, stoma stricture and retrograde cholangitis are less likely when the stoma is $\geq$ 2.5 cm in diameter at the time of surgery. This seemingly reduces entrapment of intestinal contents in the biliary tree and secondary bacterial cholangitis. Mucosal apposition at the stoma site is important to allow optimal stoma size, early smooth re-epithelialization, and to avoid granulation tissue that can impinge on stoma diameter.

Liver Biopsy Essential

Liver biopsy determines whether immunomodulatory therapy is advisable to control associated liver disease (e.g. chronic non-suppurative hepatitis, feline CCHS syndromes, ductal plate malformations, other).

Cultures

Bile with particulate debris from several regions of the biliary tree if obstruction is lavaged to establish patentcy, cholelith (nidus), liver tissue, and portion of a removed GB should be submitted for aerobic and anaerobic bacterial cultures. Cytology imprints should be made, especially of biliary debris, as this is most likely to demonstrate bacterial organisms associated with the cholestatic syndrome and cholelithiasis. This may be the only sample confirming bacterial infection because pre-treatment with antimicrobials (you should do this to increase patient survival) may reduce positive culture findings.

Feline Hepatocellular Carcinoma / Adenoma

With an estimated prevalence ranging from 1-3% of all feline neoplasms, primary hepatic tumors are uncommon in the domestic cat. Compared to the dog, the cat has a lower risk for hepatocellular carcinoma (HCA) as well as metastatic hepatic neoplasia. Signs associated with feline hepatobiliary tumors are often non-specific. For example, one study of hepatic neoplasia in 21 cats (including two with HCA and 15 with bile duct adenocarcinoma or adenoma) reported common findings of anorexia, lethargy, and weakness. Hepatocellular carcinoma has received far more attention in the dog where it is frequently affiliated with increased liver enzyme activities (particularly serum alanine aminotransferase [ALT] and alkaline phosphatase [ALP]) and an aspartate aminotransferase (AST)-to-ALT ratio <1. Previous studies of malignant primary hepatic neoplasia in cats show a similar association with increased hepatic transaminase activities; however, cats are more likely to demonstrate hyperbilirubinemia because the more common biliary carcinomas commonly cause cholestatic jaundice. Survival statistics for cats undergoing resection of primary malignant liver tumors are dismal, with 60% of cats dying during the immediate post-operative period.[1] However, in the small number of case series reported, most cats suffered from tumor-impaired bile flow (i.e., biliary tree obstruction) thought to impose a substantial negative impact on peri-operative survival because of intractable hypotension.

Signalment

We recently characterized the clinical features of feline HCA (manuscript in press, n=19 cats); median age of 14 (2-21) yrs, with no breed or gender predilection.

Clinical Signs

Many tumors were incidentally discovered as cats presented for one or more co-existent or pre-existent health issues. Feline viral infections were not associated. Common clinical features included weight loss (95%), hyporexia (53%), lethargy (32%), historically increased liver enzyme activities (26%), diarrhea (21%), vomiting (21%), and palpable abdominal mass (21%). Approximately 50% of HCA were recognized antemortem.

Comorbid conditions common in elderly cats obfuscated characterization of which clinical features reflected HCA. Antecedent or concurrent hyperthyroidism was common; most cats had been successfully managed with anti-thyroid drugs, thyroidectomy, or radioiodine before HCA discovery- this may reflect geriatric age.

Clinicopathologic Features

Increased activity of ALT, AST, ALP, and GGT were common (AST in >90%, ALT and ALP > 71%); hyperbilirubinemia was recognized in ~40%. Marked increases in AST and ALT activities in some cats likely reflected necrotic foci histologically recognized within neoplastic tissue. Profoundly prolonged clotting times were observed in two cats with large tumor burdens. Recognizing the small population studied, this observation suggests that HCA may lead to coagulation disorders that should be investigated pre-surgically.

Cytologic interpretation of aspirates or impression smears from tumors in 6 cats was diagnostic for HCA in only 2. Tumors were nearly evenly divided between right and left liver lobes with two cats having HCA in multiple liver lobes.

Physical Characteristics

Tumor dimensions > 4 cm were observed in nearly 50% of cats however, mass lesions were palpable in <25%. Metastatic HCA was not recognized in any cat and massive tumor burden was rare. Despite recurrence of HCA in one cat three years after initial HCA resection (2.6 x 3.6 x 3.4 cm in central liver, 2.7 x 3.5 x 4.2 cm in right caudodorsal liver, ultrasound detection) the cat survived for three more years without clinical illness.

Treatment

This study defines that definitive diagnosis of HCA cannot be reliably deduced from clinical signs, clinicopathologic parameters, cytology, or imaging studies. The tumor is slow to metastasize, expands locally into hepatic parenchyma, and can be effectively palliated by surgical resection. Surgical resection resulted in improved well-being and survivals in 6 cats, ranging from 1 to 6.5 years despite advanced age at initial diagnosis.

Hepatic Amyloidosis

Feline Hepatic Amyloidosis

Advances in the understanding of local and systemic amyloidosis over the last decade have clarified that this syndrome reflects misfolding and aggregation of a pathogenic protein. Formation is complex, reflecting biochemical and /or environmental influences that permit normally soluble proteins to adopt an insoluble folded conformation. In humans, amyloidosis can derive form 27 different parent proteins. Amyloid formation is considered a nucleated self-polymerization reaction or reflects failed editing or disposal processes. Insoluble amyloid fibrils aggregate most commonly in the extracellular space and may be organ specific or systemic. Despite differences in size, tertiary and quaternary structures, and function of the precursor proteins, amyloid fibrils share a common morphology (e.g, cross-β pleated structure, distinctive X-ray diffraction pattern with distinct intensities at 4.7 and 10 A that correspond to intrastrand and stacking distances of the β-sheets). All amyloid fibrils demonstrate apple green birefringence when stained with Congo red and viewed under polarized light (histologically). Although Congo red has long been considered the gold standard for histologic amyloid detection, it is a challenging technique that requires a long staining process and skilled interpretation. Staining for amyloid is not routinely done and thus, hepatic amyloid may be overlooked in cats.

In localized amyloidosis intracellular and/or extracellular amyloid deposits accumulate only in the organ or tissue of precursor protein synthesis. In systemic amyloidosis, the protein precursor is synthesized and secreted at a site distinct from the tissue of deposition. Thus, it is common for multiple organ systems to accumulate amyloid deposits in systemic amyloidosis, explaining the common finding of nonspecific symptoms including fatigue, weakness, loss of appetite, and weight loss.

Primary vs Secondary Amyloidosis

In man the most common precursor amyloid protein is derived from plasma cells (AL, amyloid light chain) and is clinically classified as primary amyloidosis. Secondary amyloidosis often associates with chronic inflammation or infection being commonly derived from characteristic acute phase proteins (entitled SAA). However, it is important

to acknowledge that syndrome characterization is much better understood in humans and experimental animal models compared to cats and dogs.

Systemic Amyloidosis in the Cat:

Is recognized in Oriental Shorthair and Siamese cats as well as cats of other pure and mixed breed ancestry. While most cases demonstrate concurrent deposition amyloid in other tissues, presentation for clinical illness usually involves spontaneous hepatic lobe rupture and critical abdominal hemorrhage. Diffuse hepatic accumulation of amyloid in the space of Disse (potential space for ultrafiltrate formation that surrounds the endothelial vasculature of the hepatic sinusoids) and portal tract leads to hepatomegaly and increased tissue fragility. Trivial trauma can precipitate hepatic lobe and capsule rupture causing critical hemorrhagic effusion.

Signalment

Cats may demonstrate signs of systemic illness anywhere from 8 mths to 7 yrs with one documented case not showing signs of clinical illness until 11 yrs of age. There is no gender predisposition.

Clinical Signs

These are vague, and may include: lethargy, weight loss, fever, stomatitis, diarrhea, and pallor due to anemia. Presentation for acute abdominal hemorrhage associated with a fractured liver lobe is common- see below. Intestinal dilation and dysmotility may associate with inappetence and diarrhea as a result of enteric amyloid accumulation. Vascular dysfunction associated with amyloid deposition leads to bruising but other coagulopathic changes also contribute.

Clinicopathologic Features

Anemia, and mildly increased liver enzymes are common. Some cats become hypothyroid and some develop hypoadrenocorticism secondary to amyloid deposition in thyroid and adrenal glands, respectively. Some cats develop signs of respiratory compromise due to pulmonary amyloid deposition. Splenomegaly and increased numbers of Howell Jolly bodies reflect reduced splenic function associated with amyloid deposition in the spleen. Bone marrow function may also be compromised secondary to amyloid deposition resulting in a non-regenerative anemia and other cytopenias and the increased propensity for infection. Inhibitors of thrombin and Factor X (man, suspected in cats) and deficiency of vitamin K dependent proteins contribute to critical hepatic hemorrhage.

Acute Collapse with Hepatic Hemorrhage

On acute presentation for critical hepatic hemorrhage, cats are tachycardic, in cardiovascular shock, and may develop acute renal failure (amyloid also present in the kidneys). Resuscitation requires prompt blood component therapy, judicious IV fluid administration, perhaps fresh frozen plasma for coagulation factors, and liver lobectomy. At surgery, expanding hematomas and severe blood loss warrant consideration of severe blunt abdominal trauma.mCats surviving critical hepatic hemorrhage have a guarded prognosis as these may succumb to renal failure within 1-2 years.

Definitive Diagnosis

Resuscitation may salvage a cat so close to death that centrilobular hypoxic injury may be a primary pathologic lesion. Amyloid deposition may be overlooked on routine staining with hematoxylin and eosin (H&E). Staining with Congo Red reveals uneven delicate to globular deposition of amyloid throughout the liver.

Treatment

In dogs with systemic amyloidosis, colchicine is the mainstay of therapy and can arrest systemic amyloid deposition in the Shar Pei with “Shar Pei Fever”. I do not know of any cat that has been successfully treated long term after diagnosis of systemic amyloidosis based on clinical signs described herein.

Biliary Atresia

This is a developmental anomaly in cats. These cats are jaundiced early in life, and have increased ALP, ALT, AST, and GGT activities, high normal or increased cholesterol concentration, and increased total serum bile acids. If complete atresia exists, the feces may be pale and soft owing to fat maldigestion and the cats are small. Cats are young < 9 mths at initial presentation. Definitive diagnosis is made on examination of liver biopsy. Affected animals may or may not lack a gallbladder. Liver biopsy discloses a paucity of small and medium sized bile ducts although some large bile ducts may be observed. Tissue staining with cytokeratin 19 immunohistochemistry confirms the lack of bile ducts. There is no treatment for this condition and cats will eventually succumb to the accumulated biliary pigments and liver injury secondary to this form of microscopic mechanical cholestasis.

NOTES:

Is There a Direct Link Between IBD, Cholangitis & Pancreatitis in Cats?

Kenneth Simpson, BVM&S, PhD, DACVIM, DECVIM

Introduction

Concurrent inflammation of the intestinal tract, liver and pancreas is a relatively common occurrence in cats. "Triaditis" is the term that is often used to describe concurrent inflammation of the pancreas, liver and small intestines. Triaditis has been reported in 50-56% of cats diagnosed with pancreatitis (Swift et al 2000, Forman et al 2004) and 32-50% of those with cholangitis / inflammatory liver disease (Table 1) (Weiss et al 1996, Callahan Clark et al 2011, Twedt et al 2014). This paper provides an overview of the causes and treatment of pancreatitis and triaditis in cats, and in depth consideration of the etiopathogenesis of triaditis.

Table 1. Prevalence of concurrent inflammation in the pancreas, liver and intestines

Study	Primary disease	n	Pancreatitis	ILD	IBD	Triaditis
Weiss et al 1996	Cholangitis/ Cholangiohepatitis	18	9/18 (50%)	18/18	15/18 (83%)	7/18 (39%)
Callahan-Clark et al 2011	Cholangitis	44	22/34 (65%) acute 4 chr. active 6 chronic 7 not specified 5	44/44 CNC = 33/44 ANC = 7/44	17/37 (46%)	10/31 (32%) 30/37 nephritis
Marolf et al 2013	Cholangitis	10	8/10 acute 1 chr. active 1 chronic 6	10/10	ND	ND
Twedt et al 2014	Inflammatory Liver Disease	39	15/23 12/15 chronic	39/39	11/24 8/11 LPE 5/24 LSA	7/14 (50%)
Swift et al 2000	Pancreatitis	18	18/18	15/18 (includes lipidosis)	11/18	10/18 (56%)
Forman et al 2004	Pancreatitis	17	17/17	82% 14/17 ILD 3/17 lipidosis	63% 10/16 IBD 3/16 LSA	50%

ILD = inflammatory liver disease and includes reactive hepatopathy in response to pancreatitis, inflammatory bowel disease (IBD) or alimentary lymphoma (LSA). ANC, acute neutrophilic cholangitis; CNC, chronic neutrophilic cholangitis; LPE, "lymphocytic-plasmacytic enyteritis"

The Spectrum of "Triaditis"

A definitive diagnosis of triaditis is based on the histopathological evaluation of each organ. However, the specific conditions that constitute a diagnosis triaditis range from any inflammatory process within these organs, to the combination of chronic pancreatitis, chronic cholangitis/cholangiohepatitis and inflammatory bowel disease. Care must be exercised when drawing conclusions about the prevalence of specific conditions and triaditis as studies performed ante-mortem may select for different subsets of disease and severity vs. those performed post-mortem e.g. severe conditions such as neutrophilic cholangitis or suppurative pancreatitis may be overrepresented in necropsy studies (Callahan Clark et al 2011, Hill and van winkle 1993). The situation is further complicated by differences in the histological classification and evaluation of feline pancreatitis, inflammatory liver disease and inflammatory bowel disease that make it difficult to compare studies, and to correlate specific subtypes of hepatic, intestinal and pancreatic disease with triaditis. For example, the development of standardized criteria for evaluating hepatic and intestinal histopathology makes it difficult to reconcile studies performed before and after adoption of these schemes (Van den Ingh et al 2006, Willard et al 2010). Moreover, the reproducibility of these standardized schemes is problematic (Willard et al 2010).

Diagnosing Triaditis

The diagnostic approach used to establish a diagnosis of pancreatitis and concurrent inflammation of the liver and small intestines i.e. "triaditis" in cats is summarized in Table 2. Clinical findings are variable and include anorexia, weight loss, loss of muscle mass, diarrhea, vomiting, icterus, hepatomegaly, thickened intestines, pancreatic mass, abdominal pain, abdominal effusion, pyrexia, hypothermia, tachypnea, dyspnea and shock.

Hematological and biochemical abnormalities consistent with liver disease (elevated ALT, AST, GGT ALP, bilirubin) (e.g. Center 1986, Callahan Clark 2011), pancreatitis (elevated fPL, fPLI, low calcium) (e.g. Kimmel et al 2001, Fererri 2003, Forman 2004), and inflammatory bowel disease or alimentary lymphoma (subnormal cobalamin, subnormal folate, low albumin) (Kiselow et al 2008, Janeczko et al 2012, Jergens 2010, Worhunsky et al 2014), may be present. Ultrasonographic abnormalities in the pancreas (size, echogenicity, hyperechoic margins, duct system) (Simpson et al 1994, Saunders et al 2002, Williams et al 2013), liver (changes in size/contour, echogeneicty, ducts/biliary system, guided cytology and culture)(Gagne et al1999, Savary-Bataille et al 2003, Callahan Clark 2011), and small intestine (thickness, muscularis hypertrophy) (Daniaux et al 2014) may be detected. The results of clinical evaluation, clinicopathological testing and imaging can provide the clinician with a high index of suspicion for pancreatitis and triaditis, but definitive diagnosis currently requires biopsy and histopathology of each organ.

Table 2: Findings used to establish a diagnosis of triaditis

Diagnostic test	Pancreatitis	Inflammatory liver disease	Inflammatory bowel disease
Clinical examination	Abdominal pain, mass or effusion.	Jaundice, hepatomegaly, hypersalivation	Thickened intestines, mesenteric lymphadenopathy
CBC	Neutrophilia, neutropeneia, thrombocytopenia	Anemia, neutrophilia	Neutrophilia
Biochemistry	Low calcium Low albumin Elevated fPLI / fPL	Elevated AST, ALT, ALP, GGT, bilirubin, globulin	Low cobalamin Less commonly low albumin or folate
Radiographs	Loss of serosal detail, focal mass, duodenal distension, ileus, abdominal effusion, pleural effusion	Hepatomegaly, cholelithiasis	Usually not helpful
Ultrasonography	Increased size, hypoechoic, hyperechoic rim, pancreatic duct dilatation, bdominal effusion	Hyperechoic, hepatomegaly Intrahepatic? Extrahepatic bile duct enlargement, choleliths, biliary sludge, gall bladder wall abnormalities	Wall thickening, muscularis hypertrophy, mesenteric lymphadenopathy
Sonography enabled procedures	Centestis of focal masses: necrosis, infection, neoplasia	Centestis: Liver: cytology for lipidosis, inflammation, infection (bacteria, *Toxoplasma*) Gall bladder: culture and cytology Needle biopsy	Centesis: Reactive lymphadenopathy
Endoscopy	Not useful	Not useful	Abnormal color or texture of mucosa. Biopsy
Laparoscopy	Abnormal size, shape, color, texture, biopsy	Abnormal size, shape, texture, color, biopsy, centesis of gall bladder.	Laparoscopy assisted biopsy
Exploratory lapatrotomy	Gross inspection of pancreas targeted biopsy	Gross inspection of liver, gall bladder and biliary tract. Targeted biopsy, culture of gall bladder	Gross inspection, targeted biopsy, sampling of regional lymph node

Why Triaditis?

The presence of concurrent inflammation in the pancreas, liver and intestines may be due to separate disease processes at each site or could reflect a common stimulus. The potential causes of pancreatitis, inflammatory liver disease and inflammatory bowel disease are summarized in Table 3.

It can be seen from Table 3 that bacterial infection, immune mediated and idiopathic mechanisms are considered potential causes of inflammation in each organ that may participate in the development of triaditis. When considering the potential roles of these inflammatory stimuli and the temporal development of triaditis, several models emerge.

Table 3: Potential cause of feline pancreatitis, inflammatory liver disease and inflammatory bowel disease

Stimulus	Pancreatitis	Inflammatory liver disease	Inflammatory bowel disease
Fluke	Yes; regional sporadic	Yes: regional sporadic	-
Enteric bacteria	Usually considered secondary to pancreatitis with infection via common pancreatic and bile duct, or hematogenous seeding. Bacteria visualized in 35% of 31 cats with moderate-severe pancreatitis (predominantly *Streptococcus* spp., *E. coli)*	• *Escherichia coli, Enterococcus* spp., *Bacteroides spp., Streptococcus* spp., and *Clostridium* spp. cultured from bile or liver of cats with ILD. • Bacteria visualized in 33% of 39 cats with ILD: Predominantly Reactive hepatopathy, neutrophilic cholangitis , Acute hepatitis *Streptococcus* spp *E.coli*, *Clostridium* spp ? • Positive PCR for *Helicobacter* spp DNA in bile and liver of ILD but also in controls. • Suspected that bacteria are an antigenic/immune stimulus for lymphocytic cholangitis	Dysbiosis (increased *Enterobacteriaceae, Streptococus Enterococcus, and Clostridium* spp). Correlates with severity of mucosal abnormalities and cytokine upregulation. Unclear if cause or consequence.
Bartonella	-	Experimental infection	-
Toxoplasma gondii	Mild to severe necrotizing pancreatitis	Heptaocellular necrosis	Granulomatous inflammation Villus atrophy?
Feline Infectious Peritonitis	Virus detected, occasional	Pyogranulomatous hepatitis	Focal pyogramulomatous inflammation
Virulent systemic Calicivirus	Necrotizing pancreatitis	Scattered hepatocyte necrosis	-
Immune-mediated	Lymphocytic-plasmacytic	Lymphocytic cholangitis	“Lymphoplasmacytic enteritis”
Diet	-	-	“Lymphoplasmacytic enteritis”
Trauma	Yes, sporadic	-	-
Organophosphates	Yes, but unlikely with current products	-	-
Acute hypercalcemia	Yes, with experimental hypercalcemia,	-	-
Lipodystrophy	Yes	-	-
Idiosyncratic drug reaction	-	e.g. oral diazepam, methimazole	-
Idiopathic	Yes	Yes	Yes

Acute pancreatitis as the initiating stimulus for triaditis?

Acute inflammation of the pancreas, independent of the initiating trigger, could lead to the development of triaditis through its impact on the intestines and liver. In this scenario pancreatitis induces intestinal inflammation that promotes dysbiosis and the translocation of enteric bacteria across the inflamed intestines to the liver and/or into the pancreaticobiliary duct or pancreas. The combination of pancreatitis, intestinal inflammation and bacterial translocation drives the development of a reactive hepatopathy, neutrophilic cholangitis or hepatitis and septicemia. This possibility is supported by culture-based analyses that have identified predominantly enteric bacteria (e.g. *Escherichia coli, Enterococcus* spp., *Bacteroides spp., Streptococcus* spp., *Clostridium* spp. and *Salmonella* spp.) in liver and bile of cats with cholangitis / cholangiohepatitis (Wagner et al 2007, Brain et al 2006, Twedt et al 2014). Recent studies employing fluorescence in situ hybridization (FISH) have enabled direct visualization of bacteria

(predominantly *E. coli* and *Streptococcus* spp.) in formalin fixed tissue sections from cats with ILD and pancreatitis. Eighty six percent of FISH positive cats with ILD and of 79% of FISH positive cats with pancreatitis had concurrent pancreatic, hepatic, and intestinal inflammation (Twedt et al 2014, Simpson et al 2011). Moreover, studies of experimental feline pancreatitis have clearly demonstrated that *E. coli* can translocate from the intestines into the acutely inflamed pancreas (Widdison et al 1994abc). It seems plausible that the hypoglycemia and poor prognosis associated with suppurative pancreatitis (Hill and Van Winkle 1993) could also be attributable to the presence of bacterial infection and septicemia. This model of triaditis seems most applicable to the subset of cats with moderate to severe pancreatitis and ILD that is categorized as reactive hepatopathy, acute hepatitis, neutrophilic cholangitis and obstructive cholangitis (Twedt et al 2014, Simpson et al 2011).

Intestinal inflammation and autoimmunity as stimuli for triaditis?

In cats with chronic lymphocytic pancreatitis or lymphocytic cholangitis invasive bacteria are rarely visualized (Warren et al 2011, Simpson et al 2011, Twedt et al 2014), and the presence of DNA for *Helicobacter* species, which have been linked to hepatobiliary and pancreatic disease in other species (e.g. Franklin et al 1996), does not correlate with the presence of disease (Otte et al 2012). Hence the combination of lymphocytic (chronic) pancreatitis, lymphocytic or mixed lymphocytic and neutrophilic cholangitis and lymphocytic plasmacytic enteritis may be a consequence of an immune-mediated process rather than active bacterial infection**.** In people and experimental animals autoimmune pancreatitis and cholangitis are recognized as extra-intestinal complications of IBD, with immune attack frequently directed against bile and pancreatic ducts (Navaneethan and Shen 2010, Yanisagawa et al 2011,2014). Immune mediated damage is typically considered a consequence of immune responses against bacteria (that may or may not have established an active infection) that cross-react with host tissues with resultant innocent by-stander immune responses in the intestines, liver and pancreas, or immune attack against host antigens unmasked by tissue damage (Haruta et al 2012). Several experimental studies support the possibility that immune responses to enteric bacteria are related to immune mediated pancreatitis and cholangitis. For example C57BL/6 mice inoculated intraperitoneally (i.p.) with heat-killed *E. coli* weekly for 8weeks, develop marked cellular infiltration and fibrosis of the exocrine pancreas accompanied by a high serum gamma globulin level and the production of autoantibodies against carbonic anhydrase and lactoferrin (Yanisagawa et al 2011). Subsequent studies have identified FliC from *E. coli* as an immunogenic stimulus and higher antibody titers to FliC have been detected in serum of patients with immune mediated pancreatitis (Yanisagawa et al 2014). Expression of host antigens can also shape the immune response. Mucin 1 (MUC1) is overexpressed in an abnormal, hypoglycosylated form on the colonic epithelium in human IBD where it contributes to inflammation. MUC1 is also expressed on pancreatic ductal epithelia. It has recently been shown in mice that MUC1-specific T cells migrate to the colon in mice with IBD and also to the pancreas. This suggests that pancreatitis is an extraintestinal site of IBD, characterized by proinflammatory abnormal expression of MUC1 (Kadayakkara et al 2010).

The immune targeting of bile ducts in cats with lymphocytic cholangitis is similar to that observed in people with primary sclerosing cholangitis (PSC) (Warren et al 2011, Eaton et al 2013, Yimam and Bowlus 2014). PSC is typically characterized by progressive inflammation, fibrosis, and destruction of the intrahepatic and extrahepatic biliary tree, resulting in the development of biliary fibrosis, cirrhosis, and ultimately hepatic failure (Eaton et al 2013, Yimam and Bowlus 2014). PSC is a complex disease that involves host genetics, innate and adaptive immunity and the environment. It is frequently associated with IBD and it has been proposed that immune attack against biliary structures may involve the homing of memory lymphocytes that arise as a consequence of IBD to the liver. The discovery that MAdCAM-1 and CCL25, previously thought to be restricted to the gut, are up-regulated in the liver during inflammatory liver diseases support the concept that common mechanisms may control lymphocyte recruitment to the inflamed liver and gut (Berlin et al 19993, Eaton et al 2013, Yimam and Bowlus 2014, Eksteen et al 2004). MadCAM-1 expression has also been linked to lymphocytic inflammation of islet cells in diabetes (Hanninen et al 1998), but has not been directly linked to immune mediated pancreatitis. A variety of autoantigens have also been implicated in PSC and the recent identification of b-tubulin isotype 5 (TBB5), which has high homology with bacterial cell division protein FtsZ, as an ANCA autoantigen (Terjung et al 2009) suggests that immune responses to translocated bacteria, perhaps facilitated by a leaky gut, may promote inflammation in a susceptible individual (Eaton et al 2013).

While, PSC has often been linked to autoimmune pancreatitis it is increasingly thought that intrahepatic and extrahepatic biliary tract abnormalities with strictures are more often attributable to a particular subvariant of PSC, IgG4-associated cholangitis (Okazaki et al 2011, Zen et al 2011). This disease is associated with increased serum IgG4/IgE levels, abundant infiltration of IgG4 + plasmacytes and lymphocytes, autoantibodies, and steroid responsiveness (Okazaki et al 2011). It is thought that autoantigens, autoantibodies (e.g. to lactoferrin, carbonic anhydrase) and potentially pathogens may drive IgG 4 mediated inflammation but this remains to be determined (Okazaki et al 2011, Zen et al 2011). A number of other organs can be involved including the salivary glands (Sjögren's syndrome), bile duct strictures, lung nodules, autoimmune thyroiditis, and kidney (interstitial nephritis with an IgG4-positive plasma cell infiltrate and IgG4 deposits in the tubular basement membrane). It is noteworthy that nephritis is commonly reported in cats with cholangitis and/or pancreatitis (e.g.Callahan Clarke et al 2011) where it is often considered age related co-morbidity.

Conclusions and Future Directions

Since the recognition of acute pancreatitis in cats (Macy 1989) a broad spectrum of feline pancreatic pathology has been described that is often associated with inflammation in other organ systems, particularly the intestine and liver (triaditis), but also the kidney. While the etiopathogenesis of pancreatitis and its relationship to inflammation in other organ systems is unclear, preliminary studies point to a heterogenous group of conditions with differential involvement of host inflammatory and immune responses and enteric bacteria. Comprehensive, prospective studies that simultaneously evaluate the presence of pre-defined clinical, clinicopathological and histopathological abnormalities, coupled with high resolution evaluation of pancreaticobiliary morphology (e.g. MRI, Marolf et al 2013), immunological profiling (e.g. IgG4, autoantibodies), and screening for bacterial colonization (e.g. culture and culture independent analysis) of a large cohort of cats undergoing surgical biopsy or necropsy are required to gain further insights to guide diagnosis and therapy .

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NOTES:

Diagnosis & Management of Persistent Vomiting

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The clinical importance of vomiting stems from its association with a large and varied group of diseases and the potentially life threatening consequences of vomiting per se (e.g. aspiration pneumonia and fluid and electrolyte depletion). Patient management is directed at detecting and treating the cause and consequences of vomiting. Where the cause is undetermined it is necessary to adopt a rational approach to controlling emesis.

Initiation of Vomiting

Vomiting is a reflex act initiated by stimulating the vomiting center in the medulla. The vomiting center can be stimulated directly, or indirectly via the chemoreceptor trigger zone (CRTZ) situated in the area postrema where the blood brain barrier is accessible to blood borne substances such as toxins or drugs. Neurological input from the vestibular nucleus can also stimulate the CRTZ or the vomiting center. Disease or irritation of the gastrointestinal tract, abdominal organs or peritoneum and cerebral diseases can directly stimulate the vomiting center via visceral receptors and vagal afferents. Once the vomiting center is adequately stimulated a set of visceral events is initiated - these include the sequential inhibition of proximal gastrointestinal motility, a retrograde power contraction in the small intestine and antral relaxation that enables transfer of intestinal contents to the stomach. These events are followed by moderate amplitude contractions in antrum and intestine and shortening of the intra abdominal esophagus. Dilatation of the cardia and lower esophageal sphincter enables transfer of gastric contents to the esophagus during retching and vomiting. Retching often precedes vomiting and is characterized by rhythmic inspiratory movements against a closed glottis. Negative intrathoracic pressure during retching prevents expulsion of esophageal contents. During vomiting the abdominal muscles contract and the intrathoracic and intrabdominal pressures are positive which results in the forceful expulsion of gastric contents from the mouth.

Causes of Vomiting

There are so many potential causes of vomiting that it is often easiest to think in broad terms initially i.e. gastric, intestinal, intra-abdominal non-GIT, metabolic-endocrine, drugs, toxins, dietary, neurologic, infectious diseases and consider more specific causes when vomiting is localized to one of these groups (**Table 1**).

Patient Evaluation and Diagnostic Approach

The initial plan for vomiting animals is to separate those whose problems are acute and self-limiting from those in need of more thorough investigation and treatment. If vomiting is acute and the animal is systemically well, in-depth diagnostic testing is usually not warranted as vomiting frequently resolves on its own or after short-term symptomatic therapy.

If the animal is systemically unwell, has been vomiting for more than a week, or has vomiting associated with hematemesis, bloody diarrhea or abdominal pain a more aggressive work-up is necessary to define the nature of the problem.

Most non-gastrointestinal causes of vomiting, and gastrointestinal causes such as a foreign body or intussusception, are usually detected, or ruled out, by taking a detailed history, performing a thorough physical examination, routine laboratory tests (e.g. CBC, profile, UA, fecal, with evaluation of cobalamin, folate, lipase/PLI, T_4, FeIV, FIV where indicated) and abdominal radiographs. Abdominal ultrasound is useful for detecting pancreatic, hepatic and splenic lesions, GI thickening (focal or diffuse) and sampling masses and parenchymal abnormalities. If these tests are negative or show abnormalities compatible with primary gastric or diffuse intestinal disease, endoscopic examination of the stomach and upper duodenum or contrast radiography are the principal diagnostic options. Endoscopy enables detailed examination and sampling of the gastric and duodenal mucosa with minimal patient discomfort and is generally accepted as the best method of evaluating mucosal abnormalities. Radiographic contrast studies (± fluoroscopy) are generally restricted to examining functional (emptying) disorders of the stomach and the anatomy and patency of the intestinal tract distal to the duodenum. Patients with evidence of focal intestinal disease or concurrent involvement of multiple organs (e.g. liver, pancreas, intestine in cats with triaditis) are often best evaluated surgically.

Overview of Therapy for Vomiting

Patient management should be aimed at detecting, and treating the cause and consequences of vomiting. Parenteral fluid therapy (usually IV) should be tailored to correct volume depletion, and electrolyte and acid base abnormalities. Dietary alteration in patients with acute vomiting is traditionally NPO for 24-48hrs followed by a transition to a bland, carbohydrate rich diet (to facilitate gastric emptying) when vomiting decreases. However, this notion has been challenged by the results of early enteral nutrition in dogs with parvovirus enteropathy, where feeding was associated with decreased duration of hospitalization and reduced intestinal permeability. Modified diets

may be useful in patients with delayed gastric emptying, or chronic gastroenteropathies associated with food intolerance. Gastric protectants (e.g. sucralfate) can be used to bind toxins and protect the GI mucosa where vomiting is associated with gastritis or gastric ulceration. Inhibitors of gastric acid secretion (usually H_2 antagonists) are used to limit gastric erosion/ulceration in patients with gastritis / ulceration and those considered at risk of developing GI ulceration (e.g. shock) or esophagitis. Inhibition of gastric acid may also limit the hypochloremia and alkalosis associated with gastric outflow obstruction. Analgesics may decrease vomiting associated with acute abdominal conditions e.g. buprenorphine for pancreatitis. Antiemetics are indicated in patients with vomiting that is compromising hydration status, affecting electrolyte and acid base balance, and those at high risk for esophagitis or aspiration pneumonia, and those distressed by repeated vomiting. Antibiotics are usually limited to suspected infections, acute abdominal conditions or gastritis associated with Helicobacter infection. Prokinetic agents are used to promote gastric and intestinal motility in patients with a patent GI tract. Surgery is indicated to remove large foreign bodies, treat some causes of pyloric outflow obstruction, and to obtain biopsies of the GI tract and concurrently diseased organs.

Pharmacological Control of Vomiting

The pharmacological control of vomiting involves antagonizing central and peripheral receptors that regulate emesis and stimulating receptors promoting ordered gastrointestinal motility. The receptor subtypes involved in vomiting and examples of drugs that are commonly used in the management of vomiting are summarised in **Figure 1**.

Some antiemetics have more than one mechanism of action e.g. Phenothiazines (e.g. chlorpromazine) are antagonists of a1 and a_2 adrenergic, H_1- and H_2-histaminergic and D_2-dopaminergic receptors; Metoclopramide antagonizes D_2-dopaminergic and $5HT_3$-serotonergic receptors and has cholinergic effects on smooth muscle.

Antiemetics are generally contraindicated in patients with gastrointestinal toxicity where they may limit expulsion of the toxic agent. Antiemtics can effectively mask signs of serious underlying disease hence a clinical response to antiemetics should not preclude a search for the underlying cause of vomiting. Non-selective cholinergic receptor antagonists (other than the M_1 specific antagonist- pirenzipine) e.g. atropine, scopolamine, aminopentamide, isopropamide, may cause ileus, delayed gastric emptying and dry mouth. It is recommended that phenothiazines and the NK_1 antagonist maropitant are not given to hypotensive patients. Phenothiazines may also cause unwanted sedation and decrease the seizure threshold in animals with epilepsy. Maropitant is metabolized by the liver and is heavily protein bound, hence careful monitoring is suggested in patients with liver disease and hypoproteinemia, and maropiatant should not be used for more than 5 consecutive days. Maropitant can prolong the Q-T interval and is contraindicated in bradycardia. Antiemetics with prokinetic activity, such as metoclopramide, are contraindicated where there is a suspicion of intestinal obstruction.

The animal species, and age may also impact selection of antiemetic. Certain antiemetics are not recommended / require caution / are ineffective when used in the cat e.g. the cat is resistant to apomorphine induced vomiting suggesting the D_2-dopaminergic metoclopramide may have less activity than a_2 adrenergic antagonists. Maropitant is currently not licensed for use in dogs <12 wks of age due to dose dependent bone marrow hypoplasia.

Despite the high frequency of antiemetic use in veterinary practice there is a paucity of controlled studies of their efficacy.

The comparative efficacy of commonly used antiemetics against vomiting induced by apomorphine (central stimulus) and ipecac (peripheral stimulus) in laboratory dogs indicates that maropitant, chlorpromazine, and metoclopramide have similar activity against apomorphine induced emesis (all had greater activity than ondansetron), and that ondansetron and maropitant have equal activity against ipecac (both had greater activity than metoclopramide and chlorpromazine). Maropitant has been shown to reduce vomiting induced by xylazine in cats and has an analgesic effect in cats iundergoing ovariohysterectomy.. $5HT_3$ antagonists have been shown to reduce cisplatin and dexmedetomidine-induced emesis in cat, but do not block the effect of xylazine

Clinical trial are lacking in cats. Two recent clinical trials in dogs, one in Europe, the other in the USA have focused on maropitant. In the US study of 275 dogs, 50% of dogs treated with placebo (32/64) versus 22% (41/188) treated with maropitant vomited at some point after treatment. In the European study vomiting was controlled in 97% of dogs receiving maropitant vs. 71% of those receiving intermittent metoclopramide (0.5-1mg/kg /day over 3 doses).

Strategies for Managing Persistent Vomiting

Uremia

Vomiting in uremia is mediated via the effects of uremic toxins on the CRTZ and afferent inputs from the inflamed stomach. Control of vomiting is focused on ameliorating uremia with fluid therapy, antagonizing the effects of uremic toxins on the CRTZ and limiting potential afferent input from the GI tract e.g. uremic / hypergastrinemic gastritis. Recenty studies in cats and dogs have shown that gastric ukceration is rarely associated with uremia. In cats maropitant (1mg/kg SC/24hrs for no more than 5d) or ondansetron (0.5mg/kg BID) are typical first line antiemetics for uremia associated vomiting. H_2 antagonists (e.g. famotidine 0.5-1.0mg/kg SID-BID) and mucosal protectants (sucralfate 0.25-1g PO TID) are frequently prescribed to address concurrent gastritis, though recent studies have questioned the association of uremia with gastric ulcers in dogs and cats. Metoclopramide may not be

an effective centrally acting antiemetic in the cat and its potential impact on renal dopamine receptors should be considered in cats with primary renal disease. Mirtazapine (1.88mg EOD) appears to be an effective appetite stimulant and anti-emetic for cats with CKD and could be a useful adjunct to the nutritional management of these cases.

Gastric Ulceration

Vomiting in patients with suspected acute gastritis or gastric ulceration is managed by providing adequate fluid therapy and limiting afferent input from the inflamed gut by decreasing gastric acid secretion (e.g. H_2 antagonists) and providing mucosal protection (e.g. sucralfate). Where ulceration is severe and vomiting is not adequately controlled antiemetics such as maropitant, ondansetron and phenothiazines may be used.
In patients with severe or persistent ulceration more complete inhibition of gastric acid secretion can be achieved with the H/K ATPase inhibitor - omeprazole (0.7 mg/kg SID PO). This drug may be particularly effective in patients with excessive secretion of gastric acid e.g. gastrinoma. The combination of omeprazole and the long acting somatostatin analog Octreotide (which decreases gastrin release and inhibits gastric acid secretion) effectively reduced vomiting in a dog with gastrinoma (but has not been evaluated in cats to date.

Mast cell tumors may cause vomiting via the central effects of histamine on the CRTZ and the peripheral effects of histamine on gastric acid secretion (with resultant hyperacidity and ulceration). Treatment of mastocytosis with H_1 and H_2 histamine antagonists (e.g. diphenhydramine and famotidine) may reduce the central and peripheral effects of histamine. Corticosteroids are used to decrease tumor size and release of histamine.

Gastritis

The treatment of gastritis is guided by the presence or absence of gastric *Helicobacter*. In cats with chronic vomiting, lymphoid follicular / lymphocytic gastritis, and gastric Helicobacter spp., antibiotics directed against *Helicobacter* have produced positive clinical responses. In an uncontrolled trial of antibiotics in dogs and cats with gastritis and *Helicobacter* spp. infection clinical signs in 90% of 63 dogs and cats responded to treatment with a combination of metronidazole, amoxicillin, and famotidine. 74% of 19 animals re-endoscoped had no evidence of Helicobacter spp. in gastric biopsies. A recent controlled trial of amoxicillin (15mg/kg PO BID x 14d), metronidazole (10mg/kg PO BID 14d) and bismuth ± famotidine in 24 dogs found a similar decrease in vomiting (86.4%) and reduced gastritis scores in dogs that were Helicobacter negative at 6mo. The use of famotidine did not improve resolution of clinical signs or eradication of Helicobacter. Unfortunately, only 43% of dogs were free from Helicobacter at 6 months, which echoes the results of controlled studies in asymptomatic Helicobacter-infected dogs and cats. Another recent study gave metronidazole (11-15mg/kg PO BID), amoxicillin (22mg/kg PO BID) and bismuth subsalicylate (0.22ml/kg PO Q-TID) to 5 Helicobacter infected animals (3 dogs and 2 cats) for 21d, and documented resolution of vomiting and long term eradication of Helicobacter (9-38months) in all animals (15). The author has employed the combination of amoxicillin (20 mg/kg PO BID), clarithromycin (7.5 mg/kg PO BID) and metronidazole (10 mg/kg PO BID) for 14 days to successfully eradicate *Helicobacter pylori* infection in cats. Taken as a whole, these studies suggest that a longer duration of treatment (21d) or the use of antibiotics that can eradicate intracellular *Helicobacter* (clarithromycin) improve eradication, but further studies are required before clear guidelines regarding the treatment of gastric Helicobacter spp. in dogs and cats can be made. The author recommends treating only symptomatic patients that have biopsy-confirmed *Helicobacter* spp. infection and gastritis.

Chronic Gastritis of Unknown Cause

Helicobacter negative lymphocytic plasmacytic gastritis is relatively common in dogs and cats (@ 25to 40% of cases, unpublished observations). The cellular infiltrate varies widely in severity and it may be accompanied by mucosal atrophy or fibrosis, and less commonly hyperplasia. Gastritis may also be accompanied by similar infiltrates in the intestines, particularly in cats (who should also be evaluated for the presence of pancreatic and biliary disease).

Patients with lymphoplasmacytic, Helicobacter-negative, gastritis are initially treated with diet. The diet is often restricted in antigens to which the patient has been previously exposed, such as a lamb-based diet if the patient has previously been fed chicken and beef, or contains hydrolyzed proteins (usually chicken or soy) that may be less allergenic than intact proteins. Many of these diets are also high in carbohydrate and restricted in fat, which facilitates gastric emptying, and may contain other substances such as menhaden fish oil or antioxidants that may alter inflammation. The test diet is fed exclusively for a period of about 2 weeks while vomiting episodes are recorded. If vomiting is improved a challenge with the original diet is required to confirm a diagnosis of food intolerance. The introduction of a specific dietary component to the test diet, such as beef, is required to confirm sensitivity to that component. If vomiting is unresponsive the patient is usually placed on a different diet for 2 more weeks (usually the limit of client tolerance). If there is no response to dietary manipulation the next step is immuno-modulation with prednisolone (1 to 2 mg/kg/day PO, tapered to every other day at the lowest dose that maintains remission over 8 to 12 weeks). Antacids and mucosal protectants are added to the therapeutic regimen if ulcers or erosion are detected at endoscopy or if hematemesis or melena is noted.

If gastritis is unresponsive to antibiotics, diet, prednisolone, and antacids, additional immunosuppression may be indicated. However, it is important to carefully re-evaluate the patient record and histopathology (e.g. is lymphoma a possibility?) before ramping up immunosuppression. Chlorambucil is a safer alternative to azathioprine in cats and has been successfully employed in the management of inflammatory bowel disease and small cell lymphoma (PO 5mg per cat every other day). Prokinetic agents such as cisapride and ranitidine can be used as an adjunct where delayed gastric emptying is present (see below).

Delayed Gastric Emptying

Delayed gastric emptying is caused by outflow obstruction or defective propulsion and is usually suspected by the vomiting of food 8-12hrs after ingestion. Other signs include abdominal discomfort, distention, bloating and intermittent anorexia. Outflow obstruction can be caused by polyps, foreign bodies, tumors, pyloric hypertrophy or stenosis, granulomata and extraluminal masses such as pancreatic tumors. Defective propulsion may result from primary gastric diseases such as gastritis, ulceration, neoplasia, and parasitism or non-gastric disorders such as stress, trauma, peritonitis, pancreatitis, infectious enteritis, electrolyte and metabolic derangements, drugs and surgery. Disordered motility may be involved in the initiation of gastric dilatation volvulus. The finding of hypochloremia, hypokalemia, and metabolic alkalosis, ± aciduria, should raise the suspicion of an upper GI obstruction or less commonly a hypersecretory state such as gastrinoma or mastocytosis.

Radiography is used to investigate vomiting and to confirm delayed gastric emptying (retention of food or fluid >15hrs after a meal, or delayed gastric emptying of liquid barium (30%w/v, 12-16ml/kg via stomach tube : the stomach should empty within 15-60 min in cats and 1-2hrs in dogs), barium meal (normal < 10-15hrs) or barium polyspheres (normal dogs, ten 5mm and thirty 1.5mm spheres: 50% empty by 7.5hrs, 75% by 13.1, 90% by 22.5hrs)). Endoscopy is useful for confirming gastric outflow obstruction and gastric and duodenal causes of decreased propulsion (e.g. ulcers, gastritis). Measurement of gastric pH and serum gastrin may help to determine the cause of gastric ulceration or mucosal abnormalities.

Treatment of gastric emptying disorders is directed at the underlying cause- e.g. surgery for pyloric stenosis or, antacids, mucosal protectants and/or antibiotics for gastritis. In non-obstructive situations gastric emptying can be enhanced by dietary modification to facilitate gastric emptying (small amounts of semi-liquid, protein and fat restricted diets fed at frequent intervals e.g. intestinal diets blended with water and mixed with an equal volume of boiled rice may also be of benefit) and prokinetic agents such as metoclopramide (0.2-0.5mg/kg PO SC TID), cisapride (0.1-0.5mg/kg PO TID) or ranitidine (1-2mg/ kg PO BID) and nizatidine (2.5-5mg/kg PO SID) may be effective. I am not aware of studies evaluating erythromycin as a prokinetic in cats.

Pancreatitis

Vomiting is likely due to direct afferent input to the vomiting center from the inflamed pancreas and adjacent intestines and ileus secondary to inflammation. Analgesia (e.g. buprenorphine 0.01mg/kg SC BID) is used to decrease afferent stimulation of the vomiting center, and may also have direct central effects on emesis. $5HT_3$ receptor antagonists such as ondansetron, and the NK_1 antagonist maropitant are increasingly used, and may offer the additional benefit of decreasing pancreatic or visceral stimulation of emesis.

Motion Sickness

Maropitant (1.0 mg/kg) was effective in preventing motion-induced emesis in cats.

Cancer Chemotherapy

Granisetron (1 mg/kg, i.m TID) day reduced the retching+vomiting response induced by cisplatin on days 1 and 2; dexamethasone (0.01-1 mg/kg, i.m, TID) reduced significantly the retching+vomiting response by 68.8-100.0% ($P<0.05$) and 33.3-100.0% ($P<0.05$) on days 1 and 2, respectively (Rudd et al 2000).

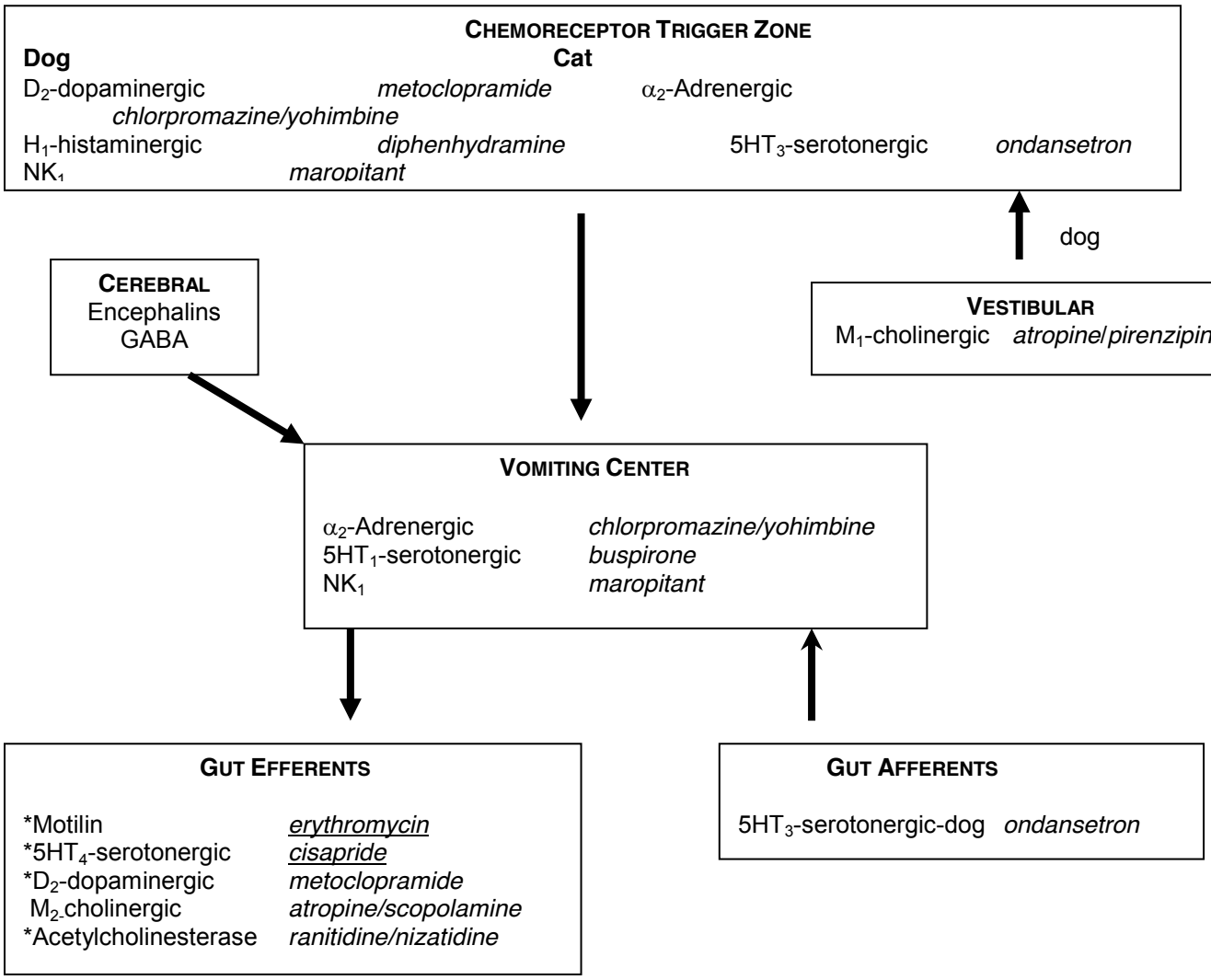
Persistent Vomiting of Undetermined Etiology

Symptomatic fluid support, diet restriction or modification, analgesia and antiemetic therapy to control vomiting are considered where vomiting is frequent or severe enough to cause derangements of fluid, electrolyte and acid base balance. Antiemetic use and selection in patients with unknown causes of vomiting is based on a best guess, least harmful approach taking into consideration the potential contraindications to antiemetic use in general e.g. ingestion of toxic substances, and contraindications for specific agents e.g. age, hypotension, bradycardia.

Table 1. Causes of Vomiting

Gastric	Gastritis, Ulceration, Neoplasia, Outflow obstruction, Foreign bodies, Motility / functional disorders	
Intestinal	Inflammatory Bowel Disease, Neoplasia, Foreign bodies, Intussusception, Enteritis / enteropathy, Functional disorders	
Intra-abdominal	non-GIT	
	Pancreas	Pancreatitis, Pancreatic Neoplasia
	Liver	Hepatitis, Cholangitis, Biliary Obstruction, neoplasia, cysts
	Spleen	Mast cell tumor
	Genitourinary	Nephritis, Pyelonephritis, Nephrolithiasis, Urinary obstruction, Pyomertra,neoplasia
	Peritonitis	
Metabolic / Endocrine	Uremia, Diabetic Ketoacidosis, Hperthyroidism, Hepatic Encephalopathy, Hypercalcaemia, Septicaemia	
Drugs	Intravenous medications, Digoxin, Chemotherapy, Xylazine, NSAID	
Toxins	Lillies, Ethylene Glycol, Lead	
Dietary	Sudden change. Indiscretion, Intolerance, Allergy	
Neurologic	Vestibular disease, Encephalitis, Neoplasia, Raised intra-cranial pressure	
Infectious	feline panleucopenia, virulent calici, FIP, FelV, FIV, salmonellosis, heartworm	

NEUROPHARMACOLOGY OF ANTI-EMETICS AND PROKINETICS



Underlined = receptor agonists, * = prokinetics

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Feline Urethral Obstruction: New Options, New Solutions to an Old Problem

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Introduction

Feline urethral obstruction (FUO) is one of the most common urinary tract emergencies seen in cats.[1] This condition commonly affects young, male cats due to anatomical factors involving their urethral but it has also been reported in female cats. Emergency management of these patients has changed little over the last 20 years. Basic management involves cardiovascular stabilization, fluid resuscitation, management of arrhythmias, correction of acid-base disturbances, and relief of the urinary obstruction. Several risk factors have been proposed for FUO including urolithiasis, urinary tract infections, environmental stress, feline idiopathic cystitis (FIC), and mucus plugs.

Understanding the risk factors and management of FUO provides survival rates >90% when cat owners seek veterinary care for this condition. [2] However, recurrent urethral obstruction post management has been reported to occur in greater than 20% in these cases and euthanasia is an unfortunate outcome to this complication in many situations.[3] This fact has resulted in several studies to assess alternative approaches to manage this condition or assess current treatment recommendations to address whether certain strategies benefit patients.[4,5,6,7] The scope of these proceedings will assess nutritional management of FUO and what impact it may play on some of the common causes of this condition.

Urethral mucus plugs progressing to FUO appears to be the most common cause implicated in the literature for this condition. Studies have reported incident rates from 42%-59% for this problem.[3] Urethral plugs are believed to form when proteinaceous material leaking from an inflamed urinary bladder combines with crystals or crystalline debris. The mineral composition reported for mucus plugs by two separate Urolith Centers has changed little over the last 30 years. Magnesium ammonium phosphate is the primary mineral composition identified in 81.1%-92% of the submitted samples for analysis.[8,9] To the author's knowledge a controlled clinical trial assessing the impact of a therapeutic food to reduce recurrent episodes of FUO in patient's identified with mucus plugs has not been performed. It is unknown what impact if any nutritional management for this problem would have on these at risk patients. However, several studies have been performed assessing the impact of nutritional dissolution of suspected magnesium ammonium phosphate calculi which has been shown to be a highly effective strategy to manage this problem. The results of the most recent study comparing two commercially available dry foods are summarized below. This was a prospective, multicenter, randomized clinical trial. Thirty-seven client-owned, neutered cats with presumed sterile struvite uroliths were randomly assigned to be fed either Hill's® Prescription Diet® s/d® Feline Dissolution dry food or Hill's® Prescription Diet® c/d® Multicare Feline Bladder Health dry food. A thorough diagnostic evaluation was conducted at baseline and each cat was evaluated weekly by physical examination, urinalysis, and abdominal radiography to assess response to treatment. A total of 32 cats (25 female, 7 male) had complete urolith dissolution; mean time (± SD) to observe a 50% reduction in urolith size was 0.69 ± 0.1 weeks in cats fed s/d and 1.75 ± 0.27 weeks in cats fed c/d Multicare.[10] Mean time for complete urolith dissolution was significantly less for cats fed s/d Feline (13.0 ± 2.6 days; range of 6 to 28 days) compared with cats fed c/d Multicare (27.0 ± 2.6 days; range of 7 to 52 days) ($P < 0.002$).[10] At the end of the study, mean ± SD urine pH for cats fed s/d Feline (6.083 ± 0.105) was lower than cats fed c/d Multicare (6.431 ± 0.109) ($P = 0.029$).[10] In 5 cats, uroliths did not dissolve and were subsequently determined to be composed of 100% ammonium urate (n = 4) or 100% calcium oxalate (n=1).[10] Adverse events, including urinary tract obstruction, were not observed in any of the cats during the study.[10] Further studies are required to determine whether a similar strategy implemented in cats presenting with FUO secondary to mucus plugs would benefit from nutritional management to reduce the rate of recurrent urethral obstruction. One could conclude from the above study and length of time to dissolve a calculus for each food that cats documented with mucus plugs would be expected to benefit from a similar nutritional recommendation.

Feline idiopathic cystitis is the next most common cause and has been reported to occur in 29%-42% of the cases.[3] What is currently unknown is whether the development of mucus plugs is an extension of FIC. Some clinicians prefer to classify FIC as nonobstructive or obstructive with the latter often times including the development of a mucus plug in this nomenclature. Recently, environmental stress has been implicated as a trigger for the development of FIC. Although the effects of stress in cats have not been extensively evaluated, recently published evidence shows that stress increases the risk of upper respiratory tract infections[11] and is involved in the pathogenesis of FIC.[12] The importance of providing an enriched environment for cats in domestic settings has recently led to recommendations from the American Association of Feline Practitioners and the International Society of Feline Medicine. They supported a provision of 5 pillars of needs for cats to minimize perceived stressors, and thus stress.[13] The impact of stress in the development of FUO is currently unknown, but a recent study did identify increasing water availability as part of an environment enrichment program as a factor that decreased the risk of recurrent urethral obstruction.[14] The inclusion of nutritional management with multimodal environmental enrichment

appears to be a novel approach to manage patients post urethral obstruction. Recently reported studies in cats describing the effects of nutritional supplements on anxiety and stress-related behaviors are summarized below.

Tryptophan

Tryptophan is an essential amino acid that has multiple metabolic fates. In most species it may be incorporated into proteins, converted to glucose and oxidized for energy, serve as a precursor to partially fulfill the niacin requirement and finally be converted to the neurotransmitter serotonin. Cats are unique from other species in that their ability to convert tryptophan to niacin is negligible and thus they have a requirement for preformed niacin in their diet. Tryptophan is the precursor for serotonin synthesis and requires two enzymes to complete the conversion: the first and rate limiting enzyme is tryptophan hydroxylase, which produces 5-hydroxytryptophan, and the second step involves 5-hydroxytryptophandecarboxylase, resulting in the production of serotonin. Serotonin cannot cross the blood brain barrier so it is important to have an adequate supply of tryptophan to serve as the precursor for its synthesis. Serotonin is an important neurotransmitter that is found in the gastrointestinal (GI) system, platelets and the central nervous system (CNS) of animals. The majority of serotonin is found in the enterochromaffin cells of the GI system and is involved in the regulation of gut motility. Serotonin in the CNS generally is regarded to influence mood, satiety, cognitive and learning ability as well as multiple other physiologic functions. Increased concentrations of serotonin have been associated with a feeling of happiness and decreased anxiety in people and animal models.[15]

A randomized, placebo controlled, double blinded study of 25 multi-cat households was conducted to evaluate the effect of dietary tryptophan supplementation on behavioral signs of anxiety and stress-related disorders. A total of 10 male and 15 female cats were included as part of the study group with one cat representing each household. Cats received a health examination prior to enrollment and at the end of the study. Cats were observed for 10 minutes a day for 5 days a week for 3.5 months by a trained observer. The first 2 weeks of observation were habituation (getting used to the observer), and in the next 4 weeks' observations for baseline prior to intervention were obtained without any supplementation. Starting in week 7, cats were randomly assigned to receive either 12.5 mg/kg body weight of tryptophan or a placebo control with their daily meal and behavioral observations continued for the next 8 weeks. Cats in the tryptophan supplemented group had significantly decreased displays of behavior associated with anxiety and stress [stereotypes (repetitive movements), vocalization, antagonistic (fighting), affiliative, exploring and sustaining behavior] compared with the placebo group ($P<0.05$ for each).[16] The authors concluded that supplementation of cats from multi-cat households with dietary tryptophan may be a beneficial adjunct to decrease signs of stress and anxiety and improve animal welfare.

Hydrolyzed Casozepine (hydrolyzed casein)

Caseins, the major proteins in ruminant milk, may undergo hydrolysis secondary to the effects of trypsin in the digestive tract. This results in production of peptides of varying length that are subject to either further digestion or have biological activity. One such decapeptide, α-casozepine [generally recognized as a safe (GRAS) ingredient] has been associated with significant improvements in alleviation of stress, using models of anxiety in rodents and people.[17] The original mechanism of action was proposed to be through effects on the gamma amino butyric acid (GABA) receptor. The exact mechanism of the anxiolytic effect is unknown and may be mediated through effects on the serotonin, dopamine, or GABA receptor systems.[18] GABA receptors bind GABA and usually are considered to produce inhibitory responses within the CNS. Activation of GABA receptors helps to blunt anxiety signals in the brain. Serotonin has been associated with alleviation of depression and general increases in happiness. Serotonin in the CNS generally is regarded to influence mood, satiety, cognitive and learning ability as well as multiple other physiologic functions. Increased concentrations of serotonin have been associated with a feeling of happiness and decreased anxiety. Dopamine is a member of the catecholamine family and its release is considered a reward signal for the brain. If α-casozepine or smaller peptides from α-S-casein have biologic activity through modulation of any of these systems, it could result in an anxiolytic effect.

A multicentric, randomized, double-blind, placebo controlled trial was conducted to evaluate the efficacy of oral α-casozepine as an anxiolytic in cats. Alpha-casozepine is a 10 amino acid peptide produced by trypsin hydrolysis from ruminant αS-casein milk protein. Cats were evaluated for anxiety by using a validated cat emotional scale. Owners evaluated five behaviors using a scale from 0 to 5; a score of 0 indicated a behavior indicative of high anxiety and 5 was low anxiety. Cats were included in the study if they had a total score of <15 on the evaluation or a score of 0 on any one behavior. There was also a subjective evaluation score performed by owners for an impression of improvement or not. Thirty-four cats (21 female, 13 male) were enrolled in the study and randomly assigned to a placebo or test group. The test group received 15 mg/kg of α-casozepine by mouth once a day. All cats were evaluated 5 times during the study, including an initial hospital visit followed by visits at weeks 4 and 8, and subsequent telephone evaluations at weeks 2 and 6. Three separate categories were tracked at each evaluation: overall score; number of items with a score of 0, and owner's evaluation of change. Positive results for the three categories were defined as: overall objective global score > 16, no behaviors scored as 0, and owner's subjective evaluation score > 6/10. Successful treatment was defined as having attained criterion for both the objective global score and subjective score by week 8. There was no significant difference between the groups at the beginning of the study. By week 8, 59% (10 of 17) of cats in the α-casozepine group and 24% (4 of 17) in the placebo group had responded positively. These results were significantly different by comparison with a chi-square test ($P=0.02$). In

addition, total global score rate of improvement over time, an objective measure, was significantly greater in the α-casozepine group (P=0.003).[19] The authors concluded from the study that it provides evidence for the efficacy of α-casozepine in the management of cats exhibiting anxiety in socially stressful conditions.

Further studies are required to determine whether the inclusion of these novel nutritional supplements would benefit cats presenting with FUO by reducing the rate of recurrent urethral obstruction. However, one could conclude from the above studies when incorporated into a strategy to manage FIC these nutritional supplements could provide a beneficial effect.

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Feline Gastroenterology and Endocrinology

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Conference Day Two

SATURDAY, SEPTEMBER 20, 2014

TRACK A *White River E*	TRACK B *White River F*	PARA-PROFESSIONAL *White River D*	
BREAKFAST in Exhibit Hall Included in your registration 7:45 – 8:25 am Cat Friendly Practice Panel: In Our Experience – White River G			7:30 – 8:30 am
Nutraceuticals in Feline Liver Disease *Dr. Sharon Center* Sponsored by nutramax LABORATORIES VETERINARY SCIENCES, INC.	Chronic Diarrhea: What's the Cause? *Dr. Kenneth Simpson*	ICU Boot Camp: What You Should Know on Day One! *Paula Plummer*	8:30 – 9:20 am
Fibropolycystic Feline Liver Disease Syndromes *Dr. Sharon Center*	Managing Cats with Chronic Gastrointestinal Disease *Dr. Kenneth Simpson*	Feline Friendly Handling & Restraint *Paula Plummer*	9:25 – 10:15 am
NETWORKING REFRESHMENT BREAK in Exhibit Hall Included in your registration AAFP Annual Business Meeting in Room 107			10:15 – 10:45 am
Stem Cell Therapy in Feline Chronic Enteropathy: In Theory – Bench Top Research *Dr. Craig Webb* Sponsored by WINN FELINE FOUNDATION	Diagnosis & Management of Feline Diabetes Mellitus *Dr. Catharine Scott-Moncrieff* Sponsored by MERCK Animal Health	The Feline Diabetic: Understanding the Disease *Heather Lynch* Sponsored by Abbott Animal Health	10:45 – 11:35 am
Stem Cell Therapy in Feline Chronic Enteropathy: In Practice – Clinical Application *Dr. Craig Webb*	Diabetic Ketoacidosis: Understanding Pathophysiology is Critical to Treatment *Dr. Catharine Scott-Moncrieff*	The Feline Diabetic: Successful Management *Heather Lynch*	11:40 – 12:30 pm
LUNCH in Exhibit Hall Included in your registration 12:15 – 1:15 pm Lunch & Learn: Chronic Kidney Disease – White River G Separate registration required Sponsored by IDEXX LABORATORIES 12:50 – 1:20 pm ABVP: How Can it Help Me? – White River E Included in your registration			12:30 – 2:00 pm
Diagnostic Testing for Hyperthyroidism in Cats: More Than Just T4 *Dr. Mark Peterson* Sponsored by Dechra Veterinary Products	Managing the Feline Diabetic: Picking a Protocol *Dr. Audrey Cook* Sponsored by Abbott Animal Health	The Unstable Feline Diabetic Patient *Paula Plummer*	2:00 – 2:50 pm
What's the Best Treatment for Hyperthyroidism? Antithyroid Drugs, Surgery, Diet, or Radioiodine? *Dr. Mark Peterson*	Diabetes: Home Monitoring *Dr. Audrey Cook*	What Every Technician Should Know about Feline Hyperthyroidism *Paula Plummer*	2:55 – 3:45 pm
FUN RUN / FREE TIME Separate registration required			3:45 – 6:30 pm
Offsite Event: A Black, White, and Red Affair Separate registration required Sponsored by Elanco			6:30 – 10:30 pm

Nutraceuticals in Feline Liver Disease

Sharon Center, DVM, DACVIM

L-Carnitine

L-Carnitine (3-hydroxy-4-N-trimethylaminobutyrate; L-CN) is a conditionally essential vitamin-like nutrient involved in intermediary metabolism that plays a crucial role in fat and carbohydrate metabolism. It is most commonly viewed as a facilitator of fatty acid oxidation by virtue of its role in the inter-organelle translocation of fatty acids (FA transfer across the mitochondrial membrane). L-carnitine can be synthesized in vivo or is absorbed preformed through the gastrointestinal tract. Most L-CN is synthesized, primarily in the liver but also in the kidneys of the cat with most distributed to skeletal muscle and heart. A significant amount of absorbed CN is secreted passively into bile, with some undergoing enterohepatic circulation (mostly long-chain acyl-CNs). Biliary elimination of L-CN-FA may provide a mechanism for removing triglyceride from the liver. CN is metabolized in the gastrointestinal tract by bacteria (to trimethyl-lysine & butyrobetaine) in proportion to the amount ingested; extent varies between species. Thus, bioavailability of oral CN, either in pharmacologic amounts or as a dietary supplement, is complexly influenced by both the quantity ingested and the extent of enteric degradation. As such, no supplementary doses are established across species lines. Clinical trials of CN supplementation vs dietary intake in man conclude that dosages approximating 20-50 mg/kg body weight (1-2 g/day for 50-100 kg body weight persons) are safe and physiologic (the higher doses used in extreme circumstances, e.g., maximal exercise of elite athlete's). L-CN dosed at > 50 mg/kg body weight are pharmacologic and used to deplete excessive acids in metabolic acidemia due to in borne errors of FA oxidation. Inconsistent formulations of over-the-counter L-CN complicate its use. One study of 12 CN products provided a mean CN content of 52% of label claim; 5/12 products had unsatisfactory dissolution. Thus, L-CN bioavailability data reflects only pharmaceutical-grade products.

CN & Mitochondrial Function

Protection Against Ammonia Precipitated CNS Encephalopathy: These direct and indirect effects remain controversial. The first derives from increased urea cycle ammonia detoxification (deviation of ketoglutarate to glutamate). The second involves increased tissue acetyl-CN concentrations. Acetyl-L-carnitine hydrochloride, a physiologic metabolite of L-CN, plays an important role in the nervous system as a precursor of acetylcholine and by enhancing acetylcholine release.

L-CN Feline Studies

The relationship between CN and mitochondrial acetyl-CoA/free CoA is the basis for understanding CN dynamics in different metabolic situations. Relationship between acyl-carnitine (A-CN) and free-carnitine (F-CN) (the A-CN/F-CN ratio) defines availability of F-CN, proposed to reflect tissue CN adequacy. In health, ~80% of total-CN exists as F-CN; after feeding, normal AC/FC ~ 0.4. Obese cats at initiation of weight loss have a lower ratio than other species. However, a more favorable ratio is maintained after L-CN supplementation. Achieving a higher AC/FC indicates relatively "limited" F-CN availability and a state of "relative" CN insufficiency. In health, transfer of acyl groups between CN and CoA is near equilibrium. Consequently, metabolic changes or transitions that influence the critical CoA pool also influence the CN pool. Distribution of CN between F-CN and acyl-CN, as well as among different acyl-groups is a useful research and clinical diagnostic parameter for assessing metabolism. However, an in-depth assessment of CN status in biological compartments requires knowledge of the total CN content and relative amounts of different acyl-moieties. Unfortunately, there is no convenient method for applying this parameter to clinical patients as CN assays are expensive and complicated.

Clinical Utility of Supplemental L-Carnitine: 250-500 mg cat per day

Obese Cats Undergoing Weight Loss

Increased cellular CN promotes FA β -oxidation. Experimental *in vitro* (muscle, hepatocytes) and *in vivo* (rodents, pigs, chickens) studies show that increased FA oxidation (in hepatocytes) associates with reduced amino acid catabolism (especially branched-chain amino acids), thought to be orchestrated by feedback inhibition of branched chain keto-dehydrogenase. This effect preserves amino acids for protein synthesis. Collective findings with L-CN supplementation describe advantages that could benefit cats during weight loss and assisted recovery from HL.

Carnitine concentrations in liver and plasma increase in obese humans and cats, and in fasted cats. While high fat diets increase urine carnitine excretion in humans and dogs, we presume a similar change occurs in cats and likely extends to cats with HL although definitive studies have not been conducted. In cats undergoing prolonged fasting, supplemental L-CN reduced plasma FA acid and β-hydroxybutyrate concentrations during fasting and after development of HL. It also protected against ketosis. While supplemental L-CN did not modify liver lipid or protein concentrations, it reduced clinicopathologic indicators of hepatocellular injury and cholestasis (liver enzyme activity)

and significantly reduced plasma ammonia. Providing obese cats undergoing weight loss given 250 mg L-CN per day PO (double blinded study) resulted in higher plasma concentrations of T-CN and percentage of acetyl-L-CN, consistent with enhanced β-oxidation. An isotope labeling study examining the rate of FA-oxidation and change in lean body mass during rapid weight loss in obese cats, with and without supplemental L-CN, confirmed that supplementation maintains the rate of fatty acid oxidation and optimizes lean body mass retention. Both findings are strong arguments for use of L-CN in cats with HL. Weight loss in some obese cats in the described study (body condition score 4-5/5, documented with deuterium dispersal) exceeded 40% over a 16 week interval. Based on collective experimental data (other species and cats) it is possible that certain cats (perhaps those predisposed to HL ?) have limiting L-CN reserves relative to metabolic need. L-CN supplementation would then likely maintain a rate of FA β –oxidation necessary for increasing demands during time of greater fat mobilization from peripheral stores. An "extra" L-CN allowance might also permit greater hepatic-to-systemic circulation FA mobilization and elimination in urine.

L-CN Supplementation in Hepatic Lipidosis and Obese Cats Undergoing Weight Loss: 250 to 500 mg L-CN / cat per day. **NOTE:** L-CN is only one component of metabolic/nutritional support for cats with HL (consult notes under that heading).

Cholestatic Liver Disease

Cholestatic liver disease encompasses a heterogeneous group of abnormalities with the common finding of impaired bile flow. Causes of cholestasis include structural, genetic, immunologic, and inflammatory processes as well as complex metabolic abnormalities associated with sepsis. Proven treatment for these disorders besides mechanical decompression of the obstructed biliary tree, is largely inadequate and unproven except for administration of ursodeoxycholate in selected disorders (human beings). Understanding or at least recognizing the complexities of the cellular and molecular mechanisms leading to liver injury and fibrosis in cholestasis is critical to devising logical interventional strategies. Free radicals importantly contribute to the pathogenesis of cholestatic liver injury. Although the initial insult in certain disorders may be mechanical or immunological, cell injury appears to be exacerbated by direct damage from hydrophobic bile acids. Polymorphonuclear leukocytes, commonly observed to participate in necroinflammatory liver disease, are commonly observed in many conditions considered primarily cholestatic. Hepatocellular copper accumulation, secondary to cholestasis, also is thought to contribute to liver injury and ROS generation through its transition metal status (Haber-Weiss reaction); copper accumulation as a secondary phenomenon occurs in cats but less often in dogs. Clinical evidence in man supporting the role of ROS in cholestasis include 1) finding increased plasma and RBC lipid peroxides, 2) finding reduced activity of Cu, Zn-SOD and catalase in liver tissue; and 3) notable response of children with severe cholestatic liver malformations (biliary atresia) with vitamin E deficiency, to correction vitamin E supplementation. There is much experimental evidence that lipid peroxidation involving mitochondria occurs in the bile duct ligation model of chronic cholestasis. In this test system, the severity of cholestatic injury can be enhanced by feeding of high–lipid, low vitamin E diet and conversely, attenuated by vitamin E supplementation. Accumulation of hydrophobic bile acids (particularly chenodeoxycholic acid, its conjugates, and lithocholic acid) also contributes to hepatocellular injury in cholestasis. The hepatotoxic potential of bile acids, in decreasing order, includes lithocholic acid >deoxycholic acid >chenodeoxycholic acid >cholic acid >ursodeoxycholic acid.

Ursodeoxycholic Acid (UDCA)

This is a non-toxic secondary hydrophilic dihydroxylated bile acid (chemical structure: 3a, 7B-dihydroxy-5B-cholanoic acid) first identified in bile of the Chinese black bear. Secondary bile acids are produced by intestinal bacteria as metabolic by products. UDCA has been shown effective in the non-surgical treatment of cholesterol gallstones in man, and in several forms of inflammatory liver disease. Benefits ascribed to UDCA include: 1)*replacement / displacement of toxic endogenous bile acids* (inhibits absorption of toxic hydrophobic BA in small intestines); 2) *cytoprotection of hepatocytes and biliary epithelium* (competing with toxic bile acids for binding to cell and organelle membranes, maintains cell membrane stability; 3) *antioxidant effects* (suppression of ER and mitochondrial "stress", inhibits hydrophobic bile salt-induced Kupffer cell activation, increases hepatic GSH levels); 4) *regulating immune response* (lowering of serum TNF-a concentrations; immunomodulatory effects in cholestatic liver disease showing similarities with glucocorticoid-mediated immunomodulation via interaction with the glucocorticoid nuclear receptor at the hepatocyte level [suppresses NF-*k*B dependent transcription through interaction with its p65 subunit]), and repression of IFN-gamma induced MHC class II gene expression); 5) *suppression of aberrant expression of major histocompatibility II foci,* 6) *anti-apoptotic effect*, by maintaining mitochondrial membrane stability, inhibiting pro-apoptosis enzymes, activating survival and signal transduction pathways; 7) *hydrocholeresis* (at the canaliculus: bile acid-dependent bile flow) and at the cholangiocyte (non-bile acid-dependent bile flow through HCO_3^- production); and 8) *enhanced biliary elimination of toxins, copper, and microbial organisms.*

Mechanism of Choleresis

Conjugation of UDCA with taurine is necessary for its elimination in bile and induction of choleresis; the mechanism is secretin mediated and involves a tubule-vesicular transport in hepatocytes that is sensitive to colchicine. Studies in humans confirm that dietary taurine supplementation increases the proportion of taurine conjugation in bile. Thus, taurine supplements are recommended for UDCA induced choleresis in humans (specifically, primary biliary cirrhosis [PBC]). Choleresis with dehydrocholic acid (DHCA) is neither related to cholangiocytes nor modulated by secretion and occurs by a non-tubule-vesicular transport mechanism. It is generally considered to be the strongest choleretic. SAMe induces non-bile acid-dependent choleresis through increased hepatocyte glutathione (GSH). GSH is transported across the canalicular membrane is split by GGT into its 3 component amino acids, increases osmotic effect that draws water into bile (thin bile, increased flow).

Clinical Utility of UDCA in Feline Liver Disease: 10-15 mg/kg PO divided q12hr with food WITH taurine supplementation: 250-500 mg per cat/day.

Hepatic Lipidosis (HL)

HL is characterized by severe hepatocellular cholestasis, marked hyperbilirubinemia, total serum bile acid concentrations > 300 uM/L, and development of serum bile acid profiles similar to cats with extrahepatic bile duct obstruction (EHBDO). HL is not considered a necroinflammatory disorder, but rather leads to "hepatic metabolic failure" eventuating in death within 1-2 weeks if nutritional, fluid, electrolyte, and metabolic support are withheld. Observational ultrastructural study (transmission electron microscopy) demonstrated reduction in the number of peroxisomes or microbodies (where long-chain FA are first oxidized), reduced number and abnormally large "unusual" appearing mitochondria, and collapsed canaliculi. Amino acid profiles characterize profound reduction in plasma taurine; taurine is essential for UDCA conjugation. Without conjugation, UDCA will not enter bile. All bile acids are toxic in high concentrations, although UDCA is least noxious (see above). Nevertheless, administration of UDCA contributes to the serum bile acid concentration in the short term whereas disease outcome is determined within 10-15 days before beneficial effects of UDCA (cited above) would be realized. Thus, we do not use UDCA in HL.

Extrahepatic Bile Duct Obstruction (EHBDO)

Do not use UDCA until biliary decompression is accomplished- when it can facilitate bile flow through the biliary tree. Otherwise, it increases pressure in the ductal system and contributes additional bile acid that may contribute to toxic cellular effects.

Suppurative Cholangiohepatitis (CCHS)

UDCA is believed to be beneficial in suppurative CCHS for its hepatoprotective, anti-oxidative, antifibrotic, and choleretic effects. Particularly valuable is restitution of bile flow at canalicular and cholangiolar levels that assist in eliminating bacteria, toxins, bilirubin, and injurious bile acids.

Non-Suppurative CCHS

Here it is important to know if the is a destructive cholangitis or sclerosing cholangitis lesion. In humans with sclerosing cholangitis there is current controversy regarding the propriety of using UDCA because of the associated increased in hydrostatic pressure in small disfigured biliary ductules that escalates their end stage injury. Certainly, most agree that high dose UDCA (20 mg/kg/day) should not be used in these patients and some clinicians avoid use in proven sclerosing cholangitis. So, in feline CCHS, in the absence of destructive duct syndrome, we use UDCA but not in severe destructive cholangitis associated with jaundice.

Primary Copper Associated Hepatopathy: UDCA is used chronically.
Portal Hepatitis: UDCA is used chronically in cats with zone 1 hepatitis.
Ductal Plate Malformations / Polycystic Liver Disease: UDCA likely has no value in these disorders.
Portosystemic Vascular Malformation / Portosystemic Shunt: UDCA likely has no value in this disorder.

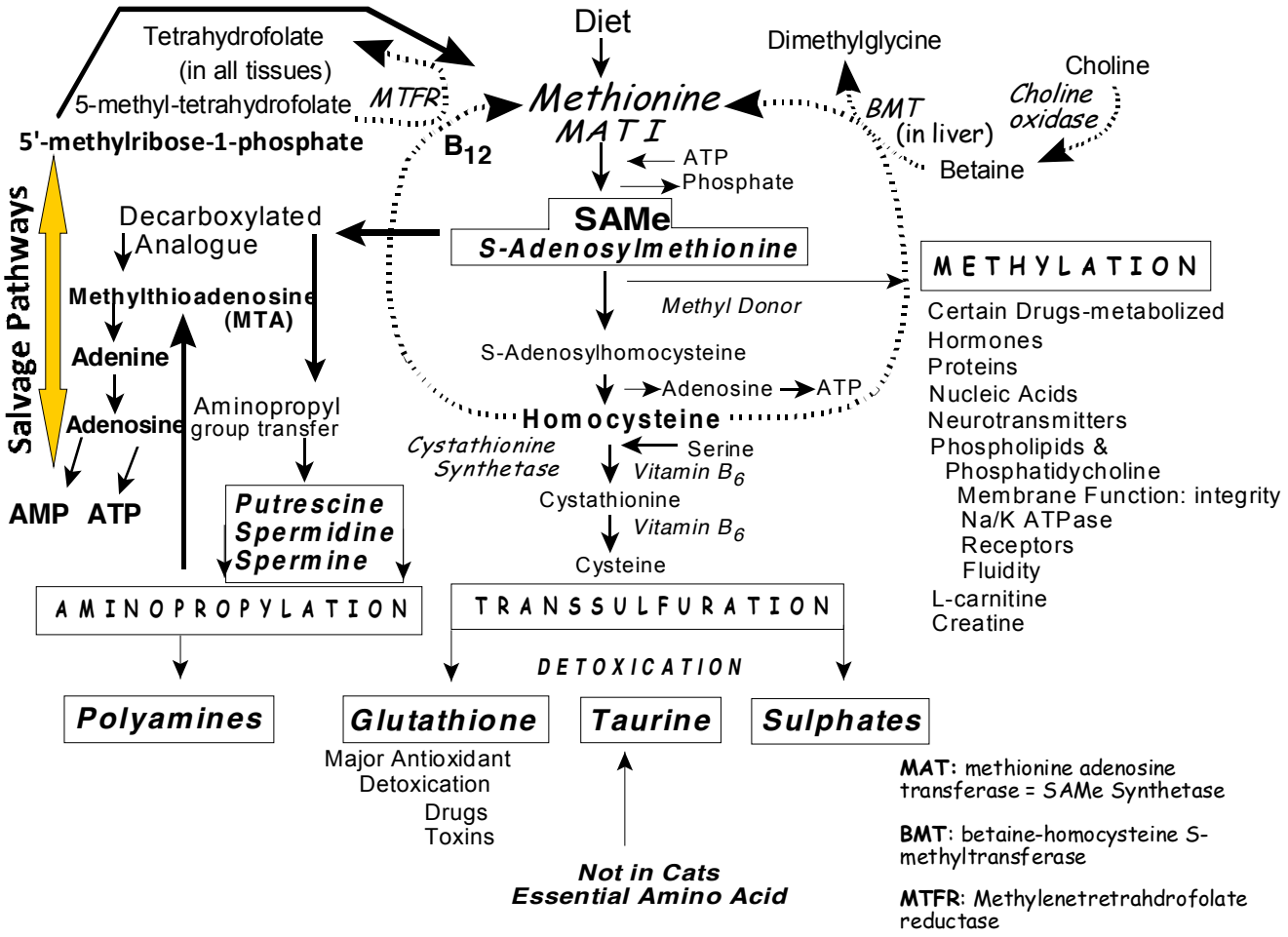
S-Adenosyl-L-Methionine (SAMe)

Plays a complex role in metabolism, functioning as a methyl group donor essential for *transmethylation reactions*, as precursor of *sulphur-containing compounds* (glutathione [GSH] and sulfates used in conjugation/detoxification reactions, and taurine synthesis in species other than the cat [taurine is an essential amino acid for the cat]), and *production of polyamines.* One of the most critical cellular *transmethylation* reactions involves biosynthesis of phospholipids (e.g., membrane essential phosphatidylcholine) important for membrane integrity, fluidity, and signaling. Other important methylation reactions include production of various hormones, neurotransmitters, nucleic acids (DNA, RNA), and proteins, and use in drug metabolism and detoxification reactions. The *polyamine pathway* influences *cell replication / regeneration, DNA synthesis*, and *apoptosis*; these activities influence cell growth, repair, senescence and longevity. An important metabolite in this pathway,

methylthioadenosine (MTA) has recently been shown to play a pivotal role in hepatocyte function gene transcription. MTA is a sulfur containing nucleoside generated from SAMe during synthesis of the polyamines spermine and spermidine, or from spontaneous splitting of SAMe under physiological conditions. Enzyme catalyzed conversion of MTA into adenine and 5-methylthioribose-1-phosphate (MTR1P) is the first and rate-limiting step in purine and methionine salvage pathways. MTR1P is recycled into methionine and adenine, the adenine is used to replenish the AMP and ATP pools. MTA also participates in regulation of diverse cellular functions, for example: regulation of proliferative responses and modulation of inflammatory responses which are effects likely mediated by feedback inhibition on polyamine biosynthesis. Experimental studies have shown MTA to impart significant antiinflammatory and antifibrotic effects in liver injury associated with: bacterial lipopolysaccharide, pro-inflammatory peptides, CCl_4, and diethylnitrosamine, as well as in MDR2 knockout mice (a clinically relevant model of spontaneous chronic liver disease, spanning from peribiliary inflammation and fibrosis to development of hepatocellular carcinoma). MTA is proposed to have an attractive pharmacological profile for the treatment of chronic liver disease- but, at present there is no therapeutic product available.

Because 85% of all transmethylation reactions and as much as 48% of methionine metabolism occurs in the liver, it is no surprise that hepatic SAMe is integrally important to numerous hepatic functions. It is well documented that the transulphuration pathway becomes impaired in chronic liver disease, reflected in delayed methionine clearance (impaired activity of SAMe synthetase in cirrhosis) and dramatic release of sulphurated compounds in response to SAMe administration.

Considering the beneficial effects of MTA explained previously, SAMe can have important benefits in patients with severe liver disease and is considered an hepatoprotective agent. Among documented benefits: preservation of GSH and sulfate synthesis, suppression of TNF-a expression (macrophages, whole liver) including that stimulated by LPS, methyl-donor for methylation reactions imperative for intermediary metabolism and gene function and transcription, L-CN synthesis, detoxification metabolism, membrane function and structure, inactivation of certain p450 cytochromes (e.g., p450 metabolizing alcohol to its toxic product), maintenance of mitochondrial membrane dynamics and proteome, blocking of the initiation and progression of apoptosis, and suppression of sinusoidal collagen synthesis through inhibition of hepatic stellate cell activation, proliferation, adhesion, migration, and invasion. *In vitro* it also induces apoptosis of the myofibroblast phenotype. Mechanistically it interferes with function of TGF-b, an important profibrotic cytokine. SAMe has ameliorated liver injury in animal models associated with galactosamine, acetaminophen, alcohol, endotoxemia, CCl_4, and ischemia-reperfusion injury, and has suppressed progression of hepatic fibrosis in various forms of liver injury. In humans, SAMe is proposed to offer hepatoprotective and antioxidant effects in EHBDO, non-alcoholic steatohepatitis, ischemia-reperfusion injury (hepatic transplantation work), alcoholic liver disease, chronic hepatitis C undergoing treatment, and chronic cholestatic liver disorders (including PBC and cholestasis of pregnancy). SAMe also rectifies development of hepatic lipidosis in Mat1a knockout mice (Mat1a is the enzyme that regulates SAMe synthesis from methionine) fed a choline-deficient diet (these mice are unable to traffic triglycerides into VLDL for release from hepatocytes, similar to suspected issues in feline HL).



Other current or potential applications of SAMe therapy include its use as an antiinflammatory and analgesic in chronic arthritis (human studies), suppression of hepatocellular carcinoma (*in vitro* and animal models) and of mitogens associated with development of colon cancer, correction of lymphocyte responsiveness and activation in chronic alcoholism (humans), as adjunctive treatment for depression in humans non-responsive to mainstream antidepressant drugs, for degenerative neurologic disorders, hepatic chemoprotection with certain chemotherapeutic agents (e.g., dogs given lomustine [CCNU]), and oxidative injury associated with other organ system disorders (e.g., pancreatitis, glomerulonephritis, nephritis, others).

SAMe Induced Choleresis

SAMe induces non-bile acid-dependent choleresis through increased hepatocyte glutathione (GSH) concentrations. GSH is transported across the canalicular membrane is split by GGT into its 3 component amino acids, increases osmotic effect that draws water into bile (thin bile, increased flow).

Clinical Utility in Feline Liver Disease

Oral SAMe is recommended in all forms of feline necroinflammatory or cholestatic liver disease. It may not offer therapeutic value in cats with fibropolycystic liver disorders lacking inflammatory foci or cats with portosystemic vascular malformations/shunts.

Pharmacokinetics

Orally administered SAMe has low bioavailability owing to significant first-pass hepatic extraction and rapid hepatic metabolism. Peak plasma concentrations are achieved 2-7 hours after dosing and decline to baseline by 24 hours. Plasma protein binding is low allowing SAMe to cross the blood-brain barrier, with slow accumulation in CSF. Orally administered SAMe becomes rapidly incorporated within cell membrane phospholipids and enters hepatocytes via paracellular pathways, thereafter influencing intracellular SAMe pathway constituents (including GSH). The exact mechanism whereby SAMe enters the hepatocyte remains unknown. Once within the hepatocyte, SAMe readily crosses into mitochondria, facilitated by a membrane transporter. We studied the oral pharmacokinetics and effect of a stable salt of SAMe (1,4-butanedisulfonate salt, Nutramax Laboratories, Nutramax Laboratories, Inc., Veterinary Sciences Division, Edgewood, MD, USA) in healthy cats and dogs with glucocorticoid induced vacuolar hepatopathy.

SAMe was absorbed, significantly increased plasma SAMe and hepatic and RBC GSH concentrations, and improved redox status in liver and RBCs.

Dose

17-20 mg/kg or higher is advised using enteric coated tablets given on an empty stomach. Choleresis was achieved with 40-60 mg/kg PO (using dog sized tablets) and ample patient hydration.

Hepatic Lipidosis (HL)

The initial thiol supplementation is provided with IV N-acetylcysteine, using a 0.25 uM filter. The initial 140 mg/kg IV dose is administered over 20 min. followed by 70 mg/kg IV q6-8hr until oral SAMe can be initiated. Supplemental SAMe has greater metabolic benefit compared to N-acetylcysteine thiol supplementation.

Toxicity

Adverse effects to SAMe are rare but may include inappetence, vomiting, lethargy, and agitation after initial treatment. Effects may self-resolve, or abate with a reduced dose, gradually increasing back to the therapeutic target. In rodents, a single dose LD50 > 4.6 gm/kg SAMe exits. Chronic studies in rats given 200 mg/kg body weight per day for 104 weeks, dogs given 20 mg/kg PO x 84 days, cats given 40-65 mg/kg for 118 days did not produce any signs of toxicity (blood testing, liver histology).

Milk Thistle

Most popularly cited non-conventional herbal remedy for the treatment of liver disease and hepatotoxicity. The extract is complex comprised of ~7 flavonolignans, and 1 flavonoid (taxifolin). The relative amount of each component varies depending on the botanical source, supplier, and extraction process. Silybin represents ~50%-70% of silymarin extract and is composed of two 1:1 diastereoisomers (silybin A & silybin B). It may additionally also exist as isosilybin, a 1:1 mixture of two diastereoisomeric compounds (isosilybin A & isosilybin B). Concentrations of silybin in the dominant market "pharmaceutical" products containing silymarin in the United States (and other countries) ranges from 20%-40%. Pharmacokinetic studies (rats, humans) demonstrate rapid distribution of silybin in plasma and bile with biliary concentrations of unconjugated and total silybin greatly exceeding plasma concentrations; silybin undergoes numerous glucuronide conjugation reactions that facilitate its entry into bile as well as it's enterohepatic circulation. One unpublished study (poster abstract, ACVIM, 2008, Webb et al) of oral and IV pharmacokinetics of a silibinin-phosphatidylcholine complex demonstrated a 6-7% oral bioavailability and higher achieved plasma concentration (estimated) than reported in dogs given a 4.5x larger mg/kg body weight dose. The greater feline plasma concentrations are speculated to reflect the lower rate of removal by glucuronidation-suggesting lower bile concentrations. While the limiting factors restricting therapeutic use of silybinin are its low water solubility and enteric bioavailability, this has been overcome by development of silibinin-phytosome complexes (silybin with -phosphatidylcholine +/- vitamin E). There are literally hundreds of studies using silybin to treat hepatobiliary disease. However, outcome analyses are difficult to analyze together (for power) owing to study design, lack of rigorous outcome measures, and product variability.

A breadth of silybin efficacies are touted based on numerous small clinical trials, experimental studies using animal disease models, and *in vitro* observations of disease pathomechanisms. Clearly, silybin is the most active component of milk thistle. Claimed benefits include the following attributes: 1) *direct antioxidant activity* (inhibits radical formation, binds some radical species [scavenger function], interferes with membrane lipid peroxidation thereby modulating membrane permeability, and increases intracellular free radical scavengers [thiol substrate donation protects against GSH depletion), 2) *functions as an iron chelator* reducing the transition metal influence on the Haber-Weiss and Fenton reactions, 3) *enhances detoxification* of some toxins (inhibition of certain Phase I detoxification pathways, enhances glucuronidation [Phase II detoxification] of others)- the most notable detoxification effect is against Amanita Death Cap mushroom hepatotoxicity, 4) *antiinflammatory effects* via suppression of NF-kB that controls signal transduction cascades (reduced transcription of genes involved with inflammation), selective inhibition of leukotrienes generated by Kupffer cells (5-lipoxygenase pathway), mast cell stabilization, and inhibition of neutrophil migration, 5) *immunomodulation* (cellular immune parameters) modification of T cell population, reduced antibody-dependent, and lymphocyte cytotoxicity in diseased liver, 6)*antifibrotic* effects (work in laboratory animals suggests silybin reduces myofibrocyte conversion of hepatic stellate cells responsible for hepatic fibrosis which can slow and in some scenarios, reverse fibrosis), 7) *hepatic repair / regeneration* (augments hepatic protein synthesis), specific actions increased synthesis of ribosomal RNA through stimulation of DNA polymerase I and by exerting a steroid-like regulatory action on DNA transcription, and 8) *hepatoprotection* (protecting against genomic injury, decreases activity of tumor promoters [*in vitro* work]), hepatoprotection against Amanita mushroom toxicity (rats, man, dogs, up to 3 days after mushroom ingestion), D-galactosamine, bromobenzene, acetaminophen, ethanol, and carbon tetrachloride (multiple species), ischemia, radiation, and iron associated oxidant injury. Improved survival, liver histology, and clinicopathologic markers have been shown in humans with viral hepatitis, alcoholic and non-alcoholic cirrhosis, and other chronic necroinflammatory liver disorders, as well as in rats with hepatic fibrosis due to major bile duct obstruction. The combined silybin / phosphatidylcholine complex may provide synergistic benefit in

averting fibrosis / inflammation as phosphatidylcholine has recognized influence in suppression of hepatic stellate cell activation to the myofibrocyte phenotype. Silibinin benefits cholestatic liver disease where it has been shown to beneficially alter bile lipid composition (humans, rats) reducing cholesterol and phospholipid concentrations without affecting bile flow or total bile salt concentrations. An improvement in clinical manifestations of psoriasis (man) and a gastroprotective effect on ischemic gastric ulceration have also been shown.

Pharmacokinetics

Since Silymarin is not water soluble and is typically administered as an encapsulated extract, it has low uptake if the phytosome complex described above, is not used which has higher bioavailability. Silybin is a potent inhibitor of human intestinal β-glucuronidase (bacterial) that can block release and reabsorption of free xenobiotics and their glucuronidated metabolites, thwarting their enterohepatic circulation. In chronic liver disease (man) it appears that liver injury influences the bioavailability of different components of silybin metabolism increasing plasma and reducing biliary concentrations.

Dose

Using the silybin-phosphatidylcholine complex (phytosome) form, the only form of silybin that should be prescribed, a 2-5 mg/kg body weight per day dose is safe for cats. Dosage adjustment for certain therapeutic effects are not yet established. For acute hepatotoxicity, the higher dose should be considered.

Toxicity

Animal and human studies indicate that silybin is non-toxic although at doses $\geq$1,500 mg/day in man, a laxative effect is possible secondary to increased bile secretion / flow and increased bile acid elimination. Mild allergic reactions have been reported in man but not in dogs or cats. Because it has possible interference with certain cytochrome p450 enzyme pathways, silybin has potential to influence pharmacokinetics of other drugs – but these interactions are largely unknown. Exactly what enzyme system is affected in each species requires independent investigation that has not yet been undertaken.

NOTES:

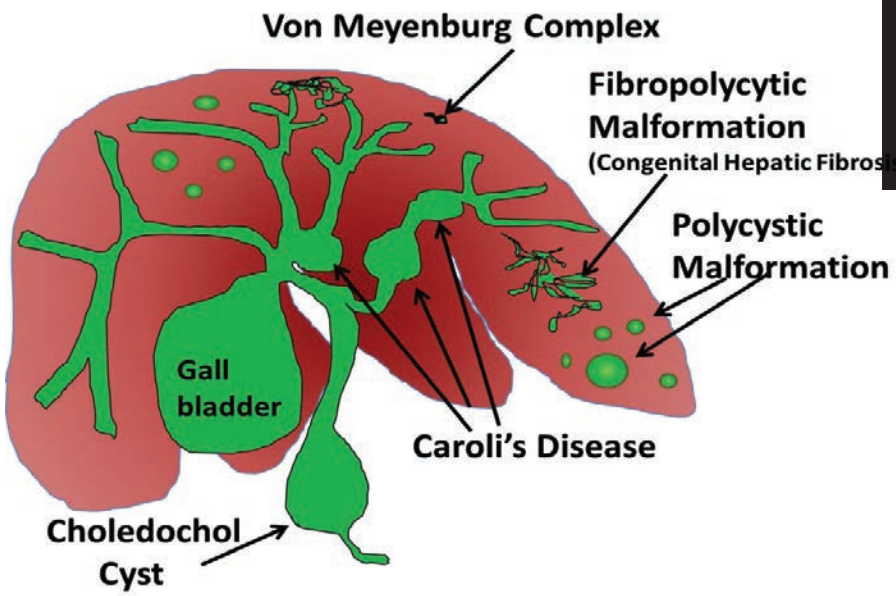
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Fibropolycystic Feline Liver Disease Syndromes

Sharon Center, DVM, DACVIM

A simplified classification scheme divides Cystic Malformations into 6 Groups:

1) simple hepatic cysts,
2) choledochal cysts
3) Caroli's syndrome (Caroli's Dz with congenital hepatic fibrosis)
4) von Meyenburg's complexes
5) congenital hepatic fibrosis
6) polycystic liver disease.



Biliary Cystadenomas

Biliary cystadenomas (variably termed cystadenomas, bile-duct adenomas, cholangiocellular adenomas, cystic cholangiomas or hepatobiliary cytadenomas) are benign "tumors" usually incidentally discovered (no clinical signs, no biochemical abnormalities) in elderly cats during US examinations for other health issues. The possibility exists that these represent developmental anomalies that expand slowly with aging. There is no gender predisposition with mean age of 13.5 ± 3.6 yrs. Cystadenoma may occur in cats as young as 2 yrs. While this lesion is commonly observed in elderly cats at necropsy, it is now more widely encountered antemortem with the extended feline lifespan and increased use of US. Lesions are well-demarcated, unencapsulated, and may be focal discrete or multifocal-complex lesions. Usually they are mutli-loculated with an epithelial lining composed of attenuated or flattened non-ciliated biliary cuboidal/columnar epithelium surrounded, supported, and intersected by a fibrous stroma. Most cystadenomas are histologically benign but lesions have rare potential for malignant transformation (3/143 author observed). Because they may invade adjacent hepatic parenchyma causing compressive atrophy, the most perilous location is within the porta hepatis where they can impose space occupying effects on essential vasculature and bile ducts. Cyst size ranges from < 1 mm-8 cm with tumor mass ranging from 5 mm - 12.5 cm The multi-loculated structure is evident on US evaluation and precludes percutaneous decompression. Cyst contents are anechoic, serous or seromucinous, and rarely hemorrhagic. Some sections may be solid. Cyst fluid lacks of bile components: bilirubin, bile acids, cholesterol. In many patients a biliary cystadenoma is solitary and causes no health related concerns. However, expansion of cystic structures appears to be augmented by development of hyperthyroidism where we have observed cysts to simultaneously enlarge (become palpable).

Clinical Signs

While most cystadenomas do not cause health related concerns, large cysts may cause ambiguous clinical signs: vague abdominal discomfort, inappetence, lethargy, intermittent vomiting, or abdominal fullness/distention.

Treatment

Benign neglect with monitoring or surgical removal. Because of their multilocular structure, surgical excision is the treatment of choice eliminating mechanical compression of vital structures as the tumor expands. However, resection may require liver lobectomy. Dissection from the cystic and common bile duct may be difficult requiring biliary enteric anastomosis. In the most severe scenario, compression of portal vasculature (porta hepatis) can lead to portal hypertension and ascites. Early rather than late resection is a strategy to consider depending on lesion localization and clinical signs. A good prognosis is warranted following complete excision. If complete excision is not

possible, partial resection may delay complications from mechanical invasion of normal tissue. Repeated aspiration, catheter drainage, marsupialization, and partial excision have been used for palliative management. Alcohol ablation also has been used. Mistaken diagnosis of polycystic liver lesions as biliary cystadenomas is seemingly common when only a single biopsy is submitted (see below). It is useful to acquire biopsies from several liver lobes to inspect for other ductal malformations.

Hepatic Fibropolycystic Disorders

Fibropolycystic disorders involving bile ducts and renal tubules are congenital malformations identified in humans and most companion animals, the most notorious being *Polycystic Renal Disease* well documented in cats with Persian ancestry. Hepatic malformations derive from deranged embryonic ductal plate development resulting in cystic lesions associated with intra- or extra-hepatic bile ducts. The ductal plate embryologically evolves as a cylindrical tube surrounding a branch of the portal vein. Biliary ducts are derived by remodeling and partial involution of the cylindrical "plates" with malformations reflecting uneven resorption. There are several different types of malformations and these reflect the time and stage of development during embryogenesis and remodeling that are disturbed (large ducts vs small ducts, intrahepatic vs extrahepatic). The genesis of these malformations are specific gene mutations (many are known for humans, one for the cat) that involve primary cell cilia that orchestrate cell polarity and migration during development. Associated with these ductal plate malformations is excessive deposition of extracellular matrix, hence the nomenclature of "*fibropolycystic disorders*".

Group 1 - Simple Biliary Cysts

Biliary cysts are commonly recognized since incorporation of US in routine diagnostics, as incidental lesions. The overall prevalence of cystic lesions in feline patients remains unknown. Small "benign" cysts are those not involving or closely affiliated with large biliary or vascular structures (common bile duct, gallbladder, hepatic ducts in the porta hepatis) and contain a serous or seromucinous material. They do not communicate with the normal biliary tree and do not contain bile. Simple cysts can usually be disregarded but should be sequentially monitored for change over time.

Clinical Signs

Often a serendipidious discovery during US imaging. Rarely, large cysts compress the stomach causing anorexia, lethargy, omiting or cause uncomfortable abdominal distention.

Treatment

Large "simple" cysts (not multiloculated) can be percutaneously drained to determine their role in causing ambiguous clinical signs (lethargy, apparent abdominal discomfort, inappetence, episodic vomiting). However, these usually rapidly refill because of their secretory epithelium. Large problematic cysts can be surgically resected, marsupialized to the abdominal cavity, multi-fenestrated, or alcoholinized (95% alcohol “rinse”). Alcohol treatment is done under general anesthesia (propofol) with cyst contents slowly aspirated with a 22-23 g spinal needle (maintain needle in position for ethanol infusion). During a single treatment session, two alcohol rinses are completed using 95% ethanol. A volume equivalent to ½ the volume of aspirated cyst fluid is slowly injected into the cyst, left for 3 minutes, then slowly removed. This procedure is repeated with 2% lidocaine added to the alcohol (1 part lidocaine to 10 parts ethanol; 1:10 dilution), letting it dwell for 3 minutes before removal. Tramadol is used postoperatively for pain, as needed. This procedure has also been used for large problematic isolated renal cysts.

Group 2 - Choledochal Cyst

This is a congenital cystic dilation of the bile duct associated with the distal segment of the common bile duct. These may or may not communicate with the normal biliary tree. This adynamic ("appendix" like) diverticulum can act as a "sump" for infection (e.g. seeded by retrograde [up the duct from the duodenum] or hematogenously).

Clinical Sign

May include fever, abdominal pain, and jaundice associated with cyst infection. Signs are insidious in onset and evolve into a syndrome inseparable from septic suppurative cholangitis. Choledochal cysts may be difficult to identify with US because of their close proximity to the bowel and common bile duct (enteric gas may reduce cyst visibility). These may cause suppurative CCHS and are usually identified at exploratory surgery in quest of the cause of biliary tree obstruction. Even then, the anatomical lesion may not be easily understood if there is pericystic fibrosis and adhesions.

Treatment

Resolution of clinical signs requires cyst decompression and optimally extirpation. However marsupialization into the CBD or choledochoenterostomy have been successful in a small number of cases. (author, unpublished information)

Group 3 - Caroli's Disease

This represents ductal plate malformations involving large intrahepatic bile ducts generating macroscopic cystic structures (sacculated large bile ducts) often complicated by cholangitis and cholelithiasis. These lesions may become mineralized such that they are radiographically detected. In humans, these lesions may evolve into a carcinoma. These malformations may coexist with other ductal plate malformations. Caroli's Syndrome is when Caroli's Disease (sacculated large bile ducts) coexists with diffuse fibropolycystic malformations causing congenital hepatic fibrosis.

Clinical Signs

Asymptomatic with increased ALT and AST activity or mineralized bile ducts or asymptomatic cholelithiasis, or signs of suppurative cholangitis or cholelithiasis with: fever, lethargy, inappetence, vomiting, jaundice. Cats with Caroli's syndrome have acquired portosystemic shunts and may develop ascites. Affected cats are predisposed to cholelithiasis and infection in the biliary tree because of bile stasis in sacculated bile ducts.

Treatment

Use of choleretics may assist with reducing further precipitation of calcium carbonate / bilirubinate in forming choleliths. Combined use of bile acid-dependent (ursodeoxycholic acid: 15 mg/kg PO divided q12hr given with food for best bioavailability) and bile acid-independent (SAMe: 40 mg/kg PO q24hr given on an empty stomach for best bioavailability) is advised. SAMe generates glutathione which drives bile flow as it exits the canaliculus and is broken into its 3 amino acid components (glycine, glutamate, cysteine) by GGT and dipeptidases. This results in a 3-fold increase in osmotic pull; this is only realized at higher SAMe dosing as compared to provision of glutathione supplementation. Choleresis with bile acids relates to their critical micellar concentration (CMC) and the best bile acid choleretic is dehydrocholate (Decholin, historically used to treat constipation, CMC ~ 270 mM, but hard to find as an OCT medication currently) whereas ursodeoxycholate CMC is ~ 7 mM- so is much less effective. Neither of these choleretics will dissolve calcium carbonate choleliths but they may help avoid or slow their formation. Chronic ursodeoxycholic acid treatment in cats should be accompanied by supplemental taurine (250-500 mg PO q24hr) as all bile acids require obligatory conjugation with taurine. If the cat is hyporexic it may not consume enough taurine to provide for the obligatory bile acid conjugation. Occasionally animals with Caroli's disease require surgical intervention to remove choleliths in the common duct and distal branches of hepatic ducts, GB, and cystic duct.

Group 4 - von Meyenburg's Complexes

These are intrahepatic malformations of biliary structures intermixed with excessive extracellular matrix, similar to histologic changes observed in Group 5 (see below). However lesions are confined to one or more small areas of liver. It is important to examine liver biopsies from multiple lobes to determine the breadth of this malformation to differentiate Group 4 from Group 5. This malformation does not lead to clinical illness but may be large enough to be imaged as a focal hyperechoic mass by US. There is no treatment.

Group 5 - Congenital Hepatic Fibrosis

These are the most severe ductal plate malformations and involve microscopic malformation of intrahepatic bile ductules and excessive deposition of extracellular matrix (fibrosis) bridging between portal triads and encasing portal triad ductules and vasculature. Islands of hepatocytes are trapped within bridging partitions.

Clinical Signs

This diffuse hepatic lesion leads to portal hypertension, ascites, formation of acquired portosystemic shunts (APSS), and propensity for hepatic encephalopathy in the most severe phenotype. Cats with APSS have profoundly increased total serum bile acids and those developing HE often demonstrated ammonium biurate crystalluria. These cats may be mistaken for cats with congenital portosystemic shunts. Foci of inflammatory infiltrates (mixed lymphoplasmacytic) in portal regions (cholangiohepatitis, cholangitis) also are often observed in biopsy samples and may associate with more anatomically normal portal triads. Ductal malformations are often not evident by US although APSS are identified using color flow doppler. This is one of the few hepatic abnormalities leading to ascites and hepatic encephalopathy in the cat. The lesion is well documented in cats and may occur in ADPKD positive cats-with renal polycystic malformations. It is estimated that ~ 10-15% of affected Persians may demonstrate this lesion. However, the identification of this developmental disorder has not been uniquely attributed only to the Polycystin-1 in affected cats. Variable severities of malformations may exist among liver lobes in a single cat.

Treatment

Cats with cholangitis or cholangiohepatitis are treated according to the form of disease they demonstrate. Often, cats with congenital hepatic fibrosis are prone to suppurative inflammation and recurrent infections because of stasis of bile flow. These require intermittent antibiotic treatment and careful at home monitoring for recrudescent infections. Choleretics are advised for jaundiced cats with recurrent infection. Cats with the severe fibrosing phenotype often require management of ascites and hepatic encephalopathy (HE). HE is, managed with protein

restricted feline diets, lactulose titrated to achieve soft stools, and low dose metronidazole or amoxicillin. Ascites causing discomfort is managed with a sodium restricted feline diets and diuretics (combined: furosemide and spironolactone) and supplemental water soluble vitamins due to losses in dilute urine.

Group 6 - Polycystic Liver Disease

Feline polycystic renal disease is well documented and commonly encountered by feline practitioners. While the phenotypic spectrum is diverse, most cats demonstrate renal rather than biliary malformations. Renal tubular malformations can lead to renal failure in early life or may not progress at all. There are several genetic causes of polycystic renal disease in humans but thus far only a single mutation has been identified in cats (autosomal onset dominant polycystic kidney disease =ADPKD). Genetic testing by restriction fragment length polymorphism (RFLP) or single nucleotide polymorphism (SNP) can be used to ascertain genotype status of breeding founders to reduce syndrome prevalence and to test pet cats suspected of having this disorder. Kidney malformations result in progressive cyst formation and enlargement leading to progressive renal insufficiency due to compressive affects on normal tissue as well as excessive extracellular matrix deposition. Cystic renal lesions are usually US evident by 6 months of age. A subset of cats with this mutation develop *a polycystic liver syndrome* with insidious onset of clinical signs. It is unclear that this genetic defect is the only cause of *polycystic liver syndrome* in cats and it is curious that many cats with polycystic liver disease lack cystic lesions in their kidneys.

Clinical Signs

Feline polycystic liver syndrome is usually diagnosed in young adult animals on the basis of macroscopic cysts identified on US examination. In the early stages there are no clinical signs nor clinicopathologic features. Since this lesion can be associated with dense intersecting portal fibrosis, the same scenario as occurs with the Group 5 malformation (congenital hepatic fibrosis) should be expected (i.e. portal hypertension, APSS, development of hepatic encephalopathy) with the progressive fibrosing phenotype. Foci of inflammatory infiltrates (mixed lymphoplasmacytic) in zone 1 (cholangiohepatitis, cholangitis) are often observed in biopsy samples.

The polycystic liver syndrome may involve few isolated cysts in the liver +/- pancreas +/- kidneys but the most severe phenotype involves too-numerous-to count microscopic cystic structures < 1 mm diameter, too small to be clearly detected by US examination.

Treatment

In some cats, many large hepatic cysts cause profound hepatomegaly and require repeated drainage or marsupialization, or complete or partial surgical resection. These are easy to diagnose with US. Histologic lesions are characterized by dysplastic maldeveloped bile ductules with irregular lumen and flattened epithelium with a fibrolamellar extracellular matrix surrounding and interdigitating between dysplastic structures- similar to the congenital hepatic fibrosis Group 5 lesion**.** There is a paucity of normal hepatic parenchyma in severely affected cats. Extensive connective tissue causes intrahepatic portal hypertension, a firm large liver, development of acquired shunts and propensity for ascites and hepatic encephalopathy. Some cats with this lesion present for related clinical signs after development of hyperthyroidism as elderly cats.

Despite the classification scheme described above, the fibropolycystic liver disorders often do not exist as single entities, but rather as members of a syndrome with broad phenotype severity. All these malformations appear to predispose to cholangitis (suppurative and lymphocytic, some with duct targeting lymphocytic CCHS), many can lead to portal hypertension, or can evolve into space-occupying lesions (cystic structures). The only treatment for diffuse disorders compromising hepatic function is palliation of hepatic encephalopathy with protein restricted diets, lactulose and low dose metronidazole. For these with tense ascites causing discomfort, judicious use of diuretics and dietary sodium restriction is used to mobilize ascites and prevent its reformation. Humans with similar syndromes are treated with organ transplantation.

Treatment Considerations:

1. Associated suppurative cholangitis due to stasis of flow in cystic malformations. Cultures are needed to appropriately target infectious agents with antimicrobials.

2. Cholelithiasis: chronic administration of a choleretic such as SAMe and Ursodeoxycholic Acid may reduce growth of cholelith size. Choleliths form secondary to stasis of bile flow in sacculated areas and are typically composed of calcium carbonate and bilirubinate.

3. Mineralization of the Biliary Tree: secondary to duct “sacculation” & stasis of flow causing precipitation of calcium carbonate associated with focal inflammation (dystrophic mineralization). Mineralization may not be causing an issue and may be misinterpreted as cholelithiasis. Avoid invasive diagnostic sampling unless there is a strong indication of unresponsive infection or progressive obstructing cholelithiasis causing clinical signs of bile duct obstruction or infection needs alleviation.

4. Choledochal Cysts may become infected like acute appendicitis in humans. These malformations may be difficult to diagnose with US imaging- confusing images and cyst is often near the duodenum with gas interference. Treatment requires either cyst marsupialization or removal. Choledochal cysts also may associate with cholelithiasis.

5. Portal hypertension secondary to diffuse fibropolycystic sinusoidal hypertension leads to development of acquired portosystemic shunts, high serum bile acids, abdominal effusion, and hepatic encephalopathy and ammonium biurate crystalluria. Sodium restriction and diuretic treatment are necessary. Antiinflammatory drugs play no role in management unless nonsuppurative cholangiohepatitis also a feature (must be confirmed on liver biopsy). Many cats are erroneously diagnosed with a congenital portosystemic shunt based on clinicopathologic features (ammonium biurate crystalluria, high total serum bile acids).

6. If HE manifests in cats with acquired portosystemic shunting (usually find ammonium biurate crystalluria), use of an appropriate feline diet that is protein restricted, low dose metronidazole or amoxicillin, and lactulose may help ameliorate signs. Diets used are those recommended for cats with congenital portosystemic vascular anomalies.

7. Beware that the severe ductal plate malformation phenotype associated with bridging fibrosis and ductal epithelial proliferation (congenital hepatic fibrosis) may be histologically interpreted as chronic cholangiohepatitis. These animals may demonstrate cyclic increases in ALT and focal cholangitis (bacterial suspected) and some have intrahepatic biliary mineralization. Typically, these do not have increased ALP activity and are not jaundiced.

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Stem Cell Therapy in Feline Chronic Enteropathy: In Theory – Bench Top Research

Craig Webb, DVM, PhD, DACVIM & Tracy Webb, DVM, PhD

Introduction

The field of stem cell biology has expanded rapidly over the last two decades. Stem cells were discovered approximately fifty years ago and are found in all multicellular organisms. A stem cell is generally defined as an unspecialized cell with the capability of dividing and renewing through cell division for extended periods of time and with the capability of giving rise to specialized cell types. Stem cells can be divided into three main categories, embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult (or somatic) stem cells. Adult stem cells can be further divided into hematopoietic (HSCs) and mesenchymal stem cells (MSCs). The stem cell types differ in several ways, particularly in the type of tissue from which they are obtained, the methods used to 'generate' the cells, and the 'potency' of the cells.

Embryonic Stem Cells

Embryonic stem cells (ESCs) are stem cells derived from the inner cell mass of pre-implantation stage embryos (blastocysts). ESCs were first derived from mice in 1981 and from humans in 1998. ESCs require specialized culture conditions to both isolate and maintain cell cultures in an undifferentiated state. ESCs are cultured for months to prove their self-renewal capabilities and are often established as an ESC 'line.' The ESC lines are tested for gene expression and for their ability to differentiate into all three germ layers (i.e. ectoderm, endoderm, and mesoderm). These cells are pluripotent, which means they can generate many cell types.

ESCs have been very controversial since their initial derivation. The Bush administration placed an eight-year ban on ESC research in the United States that was only removed in March of 2009. Additional controversy concerns the pluripotency of ESCs and their tendency to form tumors called teratomas, which is actually used as part of the functional proof of an ESC line. Despite the controversy, significant interest in ESCs has continued not only due to their potential for use in regenerative and restorative therapies but for the ability to use ESCs to study both normal and altered/abnormal development. Such studies may provide the information needed to develop targeted therapeutics for disease treatment as well as prevention.

Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) were developed in 2006 in response to the controversy surrounding ESC research. Unlike ESCs, iPSCs are derived from adult tissue, generally skin. iPSC generation requires cellular reprogramming to 'dedifferentiate' the adult cells. The generated iPSCs are pluripotent and have cell culture requirements similar to ESCs. Unlike most ESCs, iPSCs can be autologous, or patient-specific. Patient-specific iPSCs have great potential to be used for patient-specific disease study, allowing disease modeling to determine patient-specific drug use and dosing as well as potential regenerative therapy through gene correction, tissue differentiation, and transplantation.

Although lacking the ethical concerns associated with ESCs, iPSCs maintain issues concerning their pluripotency. Additional controversy exists over the methods used to create iPSCs. The original iPSCs were generated using viral constructs to deliver reprogramming genes to the adult cells. Other methods using RNAs to produce the necessary proteins have been developed. However, much remains unknown regarding the effects of the reprogramming methods on cell function and behavior. Significant research in iPSCs is ongoing.

Adult Stem Cells

Appropriately named, adult stem cells are derived from adult tissues, which actually include blood, placenta, and fetal tissues. Adult stem cells have been found in almost all tissues types. Adult stem cells remain in specialized 'niches' in adult animals to help maintain their undifferentiated state. Adult stem cells are thought to be used for tissue repair and replacement under normal conditions. Two main types of adult stem cells exist: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). MSCs are also known as mesenchymal stromal cells, multipotent stromal cells, and marrow stromal cells.

HSCs generate the myeloid and lymphoid cell lines. HSCs have been used clinically for bone marrow transplantation for several decades.

MSCs are multipotent cells that can be generated from a multitude of adult tissue types. Although there is no definitive test to determine whether a cell is a MSC, MSCs are spindle-shaped cells that have three defining characteristics: plastic-adherence, self-renewal (limited), and the ability to undergo tri-lineage differentiation (chondrocytes, adipocytes, and osteoblasts) (Dominici et al. 2006). MSCs in general are a heterogeneous population, and the properties attributed to MSCs may result from the interaction between the different cells that make up an MSC culture. Unlike ESCs and iPSCs, MSCs do not require feeder layers for culture and are less controversial. MSCs have been generated from many different species, including the cat. In addition to their potential

use in regenerative therapies, MSCs have been found to be immunologically privileged cells with homing capabilities and immunomodulatory functions. These properties of MSCs have made them of significant interest to both human and veterinary medicine as a therapeutic for several disease processes.

The presence of MSCs in adipose tissue, which is easily accessible and abundant, has expanded the study and use of MSCs. Adipose tissue can be harvested and collagenase-digested into an MSC-containing stromal vascular fraction (SVF). The heterogeneous SVF is sometimes used directly or can be culture-expanded to generate large numbers of MSCs. Culture-expanded MSCs are often described by their passage number, which designates how many times the cells have been harvested and further expanded. For best results, culture-expanded cells are carefully monitored and generally used between passages two and four.

Despite the significant advances in MSC research, controversy and discussion exists over nearly all aspects of the potential clinical application of the cells: tissue source and processing, donor type, necessity of culture, culture conditions, cell passage used, cell numbers, timing of treatment, route of treatment, number of treatments, pre-treatment of cells, etc. Our knowledge of the most advantageous strategies is still very incomplete, and some research suggests that several aspects of cellular therapy may also be disease-specific, species-specific, and even patient-specific.

Feline Stem Cells

Currently, the available literature on feline stem cells is limited. Feline stem cell research is currently ongoing in relation to regenerative/immunologic applications, oncologic applications (cancer stem cells), and reproductive/conservation applications.

Over the past few years, feline ESCs have been generated by several research groups. However, many hurdles exist in the ability to obtain large numbers of oocytes and embryos and then in reliable generation of large numbers of cells and prevention of differentiation of the ESCs for an extended period of time. Research is ongoing in these areas. Feline ESC research is of interest for species conservation issues in addition to disease modeling for use both in feline and human medicine. Potential use of ESCs for clinical regenerative therapy has additional hurdles to overcome associated with immune rejection of the generated tissues (Tecirliouglu and Trounson 2007).

Recently, feline iPSCs have been generated from snow leopard fibroblasts (Verma et al. 2012). As discussed above, the potential use of iPSCs is significant in terms of patient-specific treatment as well as in conservation efforts. The snow leopard iPSCs were generated using retroviral transfection. The need for continued advancement of the field as well as the cost to generate iPSCs will likely keep feline iPSCs in the research arena for a while.

Feline MSCs have already been applied in several clinical research studies. The cells have been successfully generated from bone marrow, adipose tissue, umbilical cord blood, and fetal fluid and membranes. The feline MSCs show appropriate stem cell morphology, plastic adherence, the ability to propagate for several passages (self-renewal) *in vitro*, and multi-lineage differentiation potential when cultured in the appropriate induction medium. The majority of available feline MSC literature has been descriptive, however, and functional data is lacking. MSCs from other species are known to be immunomodulatory and suppress T-cell function *in vitro*. Adipose-derived feline MSCs are similarly capable of suppressing mitogen-induced T-cell proliferation *in vitro* (T. Webb, unpublished data), which has prompted investigation into their use in inflammatory diseases. Of additional importance in their clinical application, adipose-derived feline MSCs can be safely administered to allogeneic recipients without generating a clinically apparent immune response (Quimby et al. 2011, Reinero et al. 2012, Trzil et al. 2012). Allogeneic adipose-derived feline MSCs are currently being used in clinical trials to evaluate their therapeutic effects on several feline disease processes including chronic kidney disease, asthma, and inflammatory bowel disease. Data from a pilot study evaluating intrarenal feline MSC injections in chronic kidney disease found autologous bone marrow- and adipose-derived feline MSC to be safe, and two of the four treated cats saw some improvement in measured parameters (Quimby et al. 2011). Data presented in abstract form from studies using allogeneic adipose-derived feline MSCs in an experimental model of feline asthma additionally demonstrate the safety of repeated intravenous feline MSC injections (Reinero et al. 2012, Trzil et al. 2012)). Some aspects of the asthmatic immune response in feline MSC-treated cats were altered in a sustained fashion in the pilot study (Reinero et al. 2012). Data from a pilot study evaluating allogeneic adipose-derived feline MSCs for treatment of inflammatory bowel disease has shown very positive initial results and is currently ongoing (C. Webb and T. Webb, unpublished data).

Conclusion

The field of stem cell biology covers a diverse group of cells with both regenerative and immunomodulatory activities. Much remains unknown about stem cells and their potential ability to be used to elucidate disease processes as well as treat clinical diseases. Importantly, regulation on stem cell use is not yet standardized and potential clinical use of the cells should be associated with significant and thorough research and understanding.

Suggested Reading

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Stem Cell Therapy in Feline Chronic Enteropathy: In Practice – Clinical Application

Craig Webb, DVM, PhD, DACVIM & Tracy Webb, DVM, PhD

Introduction

Feline Chronic Enteropathies appear to result from a disruption of the normal gastrointestinal mucosal immunity and a loss of tolerance to intestinal antigens. Intestinal inflammation is a common characteristic of these diseases and therapy is aimed at modulating the gastrointestinal immune response and reducing antigenic stimulation. Dietary manipulation and glucocorticoids are the mainstays of therapy for feline chronic enteropathies such as inflammatory bowel disease (IBD), but treatment is challenging and often unsatisfactory.

Mesenchymal stem cells (MSC) have been shown to alter immune responses and reduce inflammation through direct interactions with T-cells, NK cells, neutrophils and dendritic cells, and by increasing regulatory T cells (Tregs). MSC can be generated from adult tissues and do not induce a clinical immune response when delivered to allogeneic recipients. In mouse models of acute colitis, administration of a single injection of adipose-derived MSC has been shown to ameliorate clinical and microscopic signs of colitis, reduce systemic and mucosal pro-inflammatory cytokine production, increase IL-10 secretion, and induce regulatory Tregs in mesenteric lymph nodes Experimental and clinical evidence shows that MSC therapy is safe and induces long-lasting remission in many patients with active severe Crohn's disease that is otherwise refractory to standard treatments. Adipose-derived MSC are currently being used in phase III clinical trials for inflammatory bowel disease in humans.

In Vitro

The immunomodualtory properties of MSC have been extensively characterized *in vitro.* It would appear prior activation by the inflammatory cytokines IFN- γ, TNF- α, and IL-1β is required. This activation results in the MSC production of prostaglandin E2 (PGE2), an immune suppressant that inhibits Tcell mitogenesis and IL-2 production, induces a T helper (Th2) response, and stimulates IL-10 production by macrophages. Activated MSCs also produce IL-6 and HLA-G5, which inhibits the differentiation of monocytes to dendritic cells and suppresses T cell proliferation and cytotoxicity. Perhaps of most relevance, activated MCS decrease the production of inflammatory cytokines IL-12, IFN- γ, and TNF- α by dendritic cells and promote the generation of CD4+CD25+FoxP3+ T regulatory cells (Tregs) and the anti-inflammatory cytokine IL-10. MCS appear to exert their immunomodualtory effects through both direct contact and the production of soluble factors.

Mouse Models

A murine model of IBD (Crohn's disease) is induced by the administration of trinitrobenzene sulfonic acid. Mice are then treated with human adipose-derived mesenchymal stem cells (hASCs). Both the clinical (weight-loss, diarrhea, survival) and histopathological severity of the disease were significantly reduced by this treatment. The therapeutic effect appears to be mediated by an hASC-induced down regulation of the Th1 immune and inflammatory response. Inflammatory cytokine production, including TNF-α, IFN-γ, IL-6, IL-1β, and IL-12 was decreased while levels of the anti-inflammatory cytokine, IL-10, was increased in IBD mice following hASC treatment. Consistent with the hASC cell surface receptor profile, there appeared to be a specific homing of the administered stem cells to inflamed and lymphoid tissue; colonic inflammation led to colonic recruitment of administered stem cells.

The cellular make-up of colonic tissue was shifted from Th1 differentiation and activation to proliferation of IL-10 producing T cells by hASC administration, increasing the number of CD4+CD25+Foxp3+ T cells and down-regulating the Th1 inflammatory response. Similar results were seen with hASC treatment in a dextran sulfate sodium-induced IBD murine model.

Human Models

Twelve patients with Crohn's disease refractory to standard therapy received hematopoietic stem cell transplantation (HSCT) and all 12 achieved remission (CDAI < 150), with no serious or lasting complications. A large percentage of these patients remained in remission and without the need for medication up to 5 years after treatment. In a separate study, 3 patients with severe refractory Crohn's disease received autologous HSCT. Stem cell therapy resulted in long-term remission in all 3 patients, with 1 patient able to discontinue immunosuppressive medications for several years. HSCT therapy requires immune ablation of the patient prior to stem cell transplantation, a significant deterrent to the use of this particular strategy in the veterinary patient population.

Patients with refractory Crohn's disease were treated with bone marrow derived mesenchymal stem cells. Two IV injections, 1-2x10^6 cells/kg, 7 days apart, were administered. The Crohn's disease activity index (CDAI) was monitored and colonoscopies were performed prior to treatment and 6 weeks following stem cell administration. Three of 10 patients showed significant clinical improvement (a decrease in the CDAI) while in 3 other patients the disease progressed and required surgical intervention. Importantly, there were no serious adverse events associated with stem cell injections, supporting the safety and feasibility of this treatment modality.

Fifty patients with either ulcerative colitis or Crohn's disease received IV injection of bone-marrow derived MSC ($1.5x10^8$ cells). A significant decrease in clinical indices of disease and tissue inflammation was seen in treated patients compared to patients who did not receive MCS therapy. Clinical remission was achieved in 40 of patients and the use of corticosteroids was discontinued in 34 patients, while MCS treatment was deemed ineffective in 10 patients.

Stem cell therapy has been used extensively and effectively to ameliorated the pain, diarrhea, hemorrhage, inflammation and fistulization seen in cases of Crohn's disease refractory to established therapies, other fistulizing bowel diseases, and radiation-induced colitis. To date, over 100 human patients with these disorders have taken part in MCS clinical trials and adverse side-effects appear virtually non-existent, even with repeated treatments. The positive response in these patients is attributed to a modulation of the inflammatory lymphocyte subsets from effector T cells to regulatory T cells, stimulation of angiogenesis, and decreasing fibrosis. Administered MCS appear to favor the proliferation of endogenous tissue stem cells through the release of paracrine trophic factors.

Feline Chronic Enteropathies

The most commonly diagnosed Feline Chronic Enteropathy is inflammatory bowel disease. IBD in cats is not subdivided into ulcerative colitis and Crohn's disease, as IBD is in human patients. The cytokine profile in cats with IBD compared to cats with non-IBD GI disease shows an increase in both immunomodulatory cytokines IL-10 and TNF-β as well as the proinflammatory cytokines IL-6, IL-18, TNF-α, and Il-12p40. In a separate study the proinflammatory cytokines IL-1, IL-8, and IL-12 were increased in cats with IBD. Clearly there is significant immune dysregulation in feline IBD, and although the cytokine profile is complex and incompletely understood, it appears consistent with a Th1 response, as seen in humans with Crohn's disease. The trophic properties along with the anti-inflammatory and immunomodulatory effects of MSC administration make it a theoretically beneficial therapeutic modality for the treatment of feline IBD. The early success reported in animal models and clinical trials with human patients suffering from Crohn's disease further suggest that the use of MSC therapy in feline IBD warrants further investigation. Our laboratory has shown that feline adipose-derived MSC (fMSC) can be generated in large quantities to allow for clinical use, and that these fMSC are plastic-adherent, spindle-shaped cells that possess tri-lineage differentiation capabilities and suppress T-cell proliferation in vitro. Allogeneic fMSC have been safely and repeatedly administered to healthy and diseased cats with no notable side effects. We are currently conducting a blinded placebo control study to evaluate the safety, feasibility, and clinical effect of allogeneic fMSC as a treatment for feline IBD.

What's All This Have To Do With My Clients and Their Cats?

Adipose-derived feline mesenchymal stem cells ARE NOT embryonic stem cells, and so a significant barrier to their use (those based on philosophical, religious, and ethical beliefs) has been removed. Any client with a keyboard can quickly immerse themselves in the internet enthusiasm for the "silver bullet" potential of stem cell therapy – and then they come to see you! As summed up by Dr. Dori Borjesson, (Cyranoski 2013), many veterinarians offer stem cell therapies to satisfy demanding customers, so "Clinicians are sucked into giving treatment" even in the absence of research to support such treatment.

It appears that currently there are 2 veterinary companies vying for your stem cell business; Vet-Stem (www.vet-stem.com) which offers Vet-Stem® Regenerative Cell Therapy® and MediVet America, LLC, (www.medivet-america.com) which offers an in-house kit. In either case, the majority of these commercial treatments involve patients with orthopedic and musculoskeletal problems: chronic osteoarthritis, soft tissue injuries of the joints, tendons and ligaments, and fractures, although feline gingivitis, kidney disease, IBD, and pulmonary fibrosis are also reported as targets. Neither website provides any references or cites any research on the use of their product in cats with chronic enteropathies, including IBD.

In both cases the process begins with the harvesting of adipose tissue from the patient to be treated (autologous treatment). Vet-Stem has you ship that adipose tissue to their facility for processing, the company returns the injection-ready product (Vet-Stem® Regernerative Cell Therapy®) within 24 hours, at a cost of approximately $2,000 - $3,500, and with the requirement that the veterinarian has completed the company's accreditation course. MediVet America provides a kit for the in-house processing of adipose tissue, producing an injection-ready product in approximately 4 hours, at cost of about $1,800. Both companies claim to have serviced thousands of pets, although neither provides a specific number for the cats that have received treatment.

MediVet America states that "Adult stem cells are highly concentrated in the fat tissue. At this concentration, it is no longer necessary to culture the stem cells to acquire the necessary cell numbers to make a healing impact. The stem cells are contained within a pool of cells in the fat termed the Stromal Vascular Fraction (SVF). The SVF may impart anti-inflammatory effects, add bioactive peptides, and contribute to reformation and architectural organization. These are benefits lost once stem cells are cultured." The company provides a enzyme system to break down the adipose tissue and a filter and antibiotic wash for sterility of the resultant stromal vascular fraction. A key step appears to be the LED light activation of proliferation, differentiation, and induction prior to the reintroduction into the patient.

MediVet claims that “we have seen positive clinical improvement in 95% of the arthritic cases performed nationwide.”

Vet-Stem processes the adipose tissue within their own facility and returns injection-ready Vet-Stem Regerative Cells (VSRC™) within 24 hours, “a functionally diverse cell population able to communicate with other cells in their local environment.” Bob Harman, Vet-Stem, Inc. CEO is quoted as saying there is “an 80% success rate in imp;rovement of quality of life”. Again, there are no references or cited research on the use of this therapy in cats with chronic enteropathies, including IBD. The website states that Vet-Stem is currently evaluating the use of stem cells for the treatment of IBD, feline CKD, liver disease, immune-mediated diseases, and heart disease. Their website states that cancer, systemic infection, neurologic disorders (including spinal cord injuries), uncontrolled diabetes mellitus, and any organ disease disqualifies a pet for Vet-Stem therapy.

Conclusion

- Stem cell therapy is not currently regulated by the FDA.
- “Stem cell therapy” is actually the injection of a heterogenous population of cells, including mesenchymal stem cells, endothelial progenitor cells, fibroblasts, haematopoietic and immune cells, and others.
- A search of PubMed for studies on MSC therapy in clinical cases of feline diseases produces a single pilot study looking at their use in cats with CKD.
- Stem cells have become the latest in a long line of therapies in veterinary medicine where our use is fast and far out-pacing our understanding.
- Proceed with optimism and hope, but significant contemplation and caution.

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Diagnostic Testing for Hyperthyroidism in Cats: More Than Just T4

Mark Peterson, DVM, DACVIM

Introduction

The diagnosis of hyperthyroidism in cats is primarily based on a constellation of history and clinical signs, and physical examination findings (eg, palpation of thyroid nodule). Since many nonthyroidal diseases can mimic the signs of thyroid disease in cats, a complete database (e.g., CBC, serum chemistry profile, urinalysis) must always be evaluated to help exclude other illness. After reviewing this data, the next step is to then use thyroid function tests to confirm the diagnosis of thyroid dysfunction.

Over the past 2 decades, many advances have been made in the availability of tests that can be used to diagnose feline thyroid disease. However, all of the commonly used tests have limitations, especially when evaluating cats suffering from nonthyroidal illness. Therefore, it remains overwhelmingly clear that we still do not have the perfect thyroid test capable of both confirming the diagnosis of thyroid disease in all affected cats and completely excluding it in cats that do not have thyroid disease.

This overview will review the common thyroid function tests currently recommended to diagnose feline hyperthyroidism. Since definitive diagnosis of these disorders is not always straightforward, I will also concentrate on protocols used in the management of problem cases, in which misdiagnosis is not uncommon.

Diagnosing Cats with Hyperthyroidism: Difficulties in Diagnosis

The diagnosis of hyperthyroidism is usually straightforward, as 90% of hyperthyroid cats will have a serum total T_4 concentration that is clearly high.[1-3] Serum total T_3 is not recommended as a sole screening test for hyperthyroidism because 25-30% of hyperthyroid cats have values that remain within normal, reference range limits (ie, not diagnostic for hyperthyroidism).[2-4]

Practitioners should be aware of the assay techniques being used by their commercial or in-house laboratories. In general, serum T_4 can now be measured by 4 different assay techniques:

1. Radioimmunoassay (RIA), long considered to be the gold standard technique, but the regulations regarding radioactivity has resulted in a search for alternative methods.[5-8]
2. Chemiluminescent enzyme immunoassay (CEIA) (e.g., Immulite®) utilize the same type of antibody testing as RIA, but instead of measuring a radioactive isotope bound to the protein in question, they use a photomultiplier tube that counts light emissions that have also been validated for feline serum.[5,6]
3. Homogenous enzyme immunoassay (EIA) method (DRI® thyroxine assay, Microgenics Corporation) is also now being used by many laboratories. This technique has the advantage for the laboratory of being fully automated, which provides the advantage for the practitioner and patient that results can be available sooner.[7]
4. Enzyme-linked immunosorbent assay (ELISA) test kit[c] for in-house use.[8] It is important to realize that all of these assays can provide serum T4 values that are falsely high or falsely low; no assay will provide perfect test sensitivity and specificity.

Although the correlation of serum T_4 concentrations between all of these assay methods is generally good, any of these different assays can occasionally provide serum T_4 values that are falsely high or falsely low;[3] no assay will provide perfect test sensitivity and specificity 100% of the time. Compared to RIA, CEIA has been shown to provide very similar test results, whereas the ELISA test kit sometimes appears to underestimate the T_4 value. Although most T_4 results correlate well with the cat's thyroid state, in my experience the EIA method shows the highest false-positive results (i.e., falsely high T_4 values) in euthyroid cats.[3] If a high serum T_4 value is found in a cat that lacks clinical signs of hyperthyroidism, especially if no thyroid nodule is palpated, we should never hesitate to repeat the serum T_4 test using a different technique, with RIA or CEIA being preferred in such cases.[2,3]

In cats, difficulties arise in the routine diagnosis of hyperthyroidism in three general scenarios:

1. when a cat is hyperthyroid but the serum T_4 concentration is within normal, reference range limits;
2. when a cat has a palpably enlarged thyroid nodule (s) but does not have other clinical or biochemical evidence of hyperthyroidism; and finally,
3. when a euthyroid cat is screened and is misdiagnosed as hyperthyroid based on a falsely-high serum T_4 (or free T_4) concentration.

Hyperthyroid Cat but Normal Serum T_4 Concentration

Although serum total T_4 is preferable as a screening test for hyperthyroidism, approximately 10% of all hyperthyroid cats (and 40% of cats with early or mild hyperthyroidism) have serum T_4 within the reference range

limits.[1-3] Such T_4 values are usually within the mid- to high-end of the reference range. Thus, finding a single reference range T_4 value does not preclude such a diagnosis.

In general, there are 2 possible reasons why a hyperthyroid cat could have a normal T_4 value. (1) In early or mildly affected cats, serum total T_4 concentrations can fluctuate in and out of the reference range.[9] Such fluctuation of thyroid hormones occurs in all hyperthyroid cats, but the degree of fluctuation is of little diagnostic significance in cats with markedly elevated T_4 concentrations. In early or mildly hyperthyroid cats (no concurrent illnesses), serum total T_4 concentrations will eventually increase into the diagnostic thyrotoxic range upon retesting a few weeks later. (2) Severe non-thyroidal illness is also capable of suppressing serum total T_4 concentrations to below the reference range in euthyroid cats.[1,10,11] Similarly, marginally elevated serum total T_4 concentrations may be suppressed to the mid- to high-end of the reference range in cats with concurrent mild hyperthyroidism and concurrent moderate to severe non-thyroidal disease.[1,2]

If hyperthyroidism is suspected based upon history, clinical signs (weight loss despite a good appetite), and examination findings (tachycardia, palpable thyroid nodule) but the serum T_4 remains within the upper half of the normal range, hyperthyroidism is still possible. There is no definitive approach to diagnose hyperthyroidism in this scenario but we have several options: repeat the T4, measure free T4 or TSH, perform dynamic thyroid function testing, or do thyroid scintigraphy.

Repeat Total T_4

In cats in which overt, manageable underlying disease is identified, such concurrent disease should be managed first, before proceeding with further thyroid testing. Once concurrent disease is resolved, most hyperthyroid cats will develop a clearly high T_4, confirming the diagnosis. On the other hand, in cats without overt underlying disease, simply repeating the serum T_4 concentration in 2 weeks may be diagnostic if the T_4 is fluctuating in and out of the reference range.[9] Again, the veterinarian should never hesitate to repeat the serum T_4 test using a different technique, with RIA or CEIA being preferred in such cats.[2,3]

Thyroid Scintigraphy

Thyroid scintigraphy is a nuclear medicine procedure that produces a visual display of functional thyroid tissue based on the selective uptake of various radionuclides by thyroid tissue.[12-14] Thyroid scintigraphy is able to identify thyroid disease and define the degree of that thyroid disease relatively unaffected by the presence of concurrent nonthyroidal illness. Because thyroid scintigraphy directly visualizes functional thyroid tissue, thyroid imaging can diagnose hyperthyroidism before laboratory tests are abnormal. Thyroid scanning can also prevent misdiagnosis of hyperthyroidism in cats with falsely high serum T_4 values.[13,14]

With thyroid imaging (scintigraphy), hyperthyroid cats usually exhibit increased thyroidal uptake of radioisotope administered, either radioactive iodine (^{123}I or ^{131}I) or technetium-99M as pertechnetate ($^{99m}TcO_4^-$). Percentage uptake or increased thyroid:salivary ratio may be calculated; both are strongly correlated with circulating T_4 concentration and provide a sensitive means of diagnosing hyperthyroidism.[12-14] However, apart from expense and the difficulties in dealing with radioisotopes, few veterinarians have access to the equipment needed to obtain thyroid images or perform thyroid uptake determinations.

Measure Free T_4 Concentration

In cats with mild hyperthyroidism and normal T_4 values, free T_4 concentrations can aid in diagnosis. In support of that, serum free T_4 concentrations measured by equilibrium dialysis were more consistently elevated in hyperthyroid cats (over 98% of cases).[1-3] Although the free T_4 was more sensitive than the total T_4 for diagnosing hyperthyroidism, the test specificity for free T_4 was poor, with up to 20% of sick euthyroid cats having false-positive free T_4 results.[1,15] These sick cats generally have corresponding total T_4 values in the lower half or below the reference range.

Caution is therefore advised in using serum free T_4 measurements by equilibrium dialysis as the sole diagnostic test for hyperthyroidism. It is more reliable if interpreted with a corresponding total T_4 measurement. A T_4 value within the mid- to high-normal reference range combined with a high free T_4 concentration is consistent with hyperthyroidism, whereas a low or low-normal T_4 with a high free T_4 is usually associated with non-thyroidal illness.[1-3] One must always combine these lab results with the cat's clinical features and the presence of a palpable thyroid nodule to make the diagnosis.

To complicate the free T4 assay situation further, unpublished results indicate that the present free T_4 by dialysis assay is not the same assay (originally by Nichols Diagnostics) that was used in all of the published studies evaluating the free T_4 assay in cats with thyroid disease. Nichols Diagnostics sold the distribution rights for the assay a few years ago, and results of a recent study in cats[16] indicate a much higher prevalence of false-positive test results than reported over a decade ago. Therefore, this current assay used to measure free T_4 by dialysis test needs to be reevaluated in a large number of normal, hyperthyroid, and sick cats to verify the accuracy of the assay as a diagnostic test.

In addition, many commercial diagnostic labs (including IDEXX Labs) are now using many other free T_4 assays, most of which do not have the equilibrium dialysis step that we believed was important.[16] At this time, given

the high prevalence of false-positive results, it is unclear how much additional information is truly gained by present free T_4 assays over the use total T_4 estimations alone.

Many veterinarians mistakenly believe that the finding of a high free T_4 in a cat is completely diagnostic for hyperthyroidism. However, since up to 30% of these cats turn out to be euthyroid, it is clear that the free T_4 test can *never* be considered to be a "gold standard" diagnostic test.[13] Use of free T_4 testing can lead to more confusion than clarity in some cats, and can certainly lead to misdiagnosis of hyperthyroidism in euthyroid cats.

Measure Thyroid Stimulating Hormone (Thyrotropin or TSH)

In human patients, measurement of circulating thyroid stimulating hormone (TSH) concentration is usually used as a first-line discriminatory test of thyroid function. A species-specific feline TSH assay has not yet been developed; however, assays for measuring canine TSH (cTSH) are widely available, and it has been suggested that its measurement may provide some diagnostic information in cats with suspected hyperthyroidism.[2,3,17-19] As in people, TSH levels will be suppressed in early stages of hyperthyroidism before T_4 is elevated. However, caution is advised in over interpreting undetectable TSH values in cats, since the current cTSH assay has poor assay sensitivity and cannot accurately measure low TSH values (i.e., the assays cannot distinguish a low-normal TSH concentration from an undetectable value).[2,3]

The current canine assays only detect approximately 35% of recombinant feline TSH,[20] making it difficult to distinguish normal values from the suppressed values expected in cats with hyperthyroidism. At this time, I cannot recommend using routine cTSH determinations to confirm a diagnosis of mild hyperthyroidism in cats. Perhaps the only use for such TSH measurement would be to exclude early or occult hyperthyroidism, i.e., finding a normal rather than suppressed cTSH value. If a normal serum TSH level is measured, a cat is very unlikely to have hyperthyroidism.

Dynamic Thyroid Function Testing

In the majority of hyperthyroid cats with normal total T_4 concentrations, identification of concurrent disease, repeat total T_4 analysis, or simultaneous measurement of free T_4 allows confirmation of the diagnosis. Further diagnostic tests are rarely required. Dynamic thyroid function tests (T_3 Suppression, TRH Stimulation) have been recommended in the past as helpful in confirming a diagnosis of hyperthyroidism.[21] Nowadays, use of these tests are only considered when repeated total T_4 concentration remains within reference range, when the free T_4 concentration is equivocal, or when thyroid scintigraphy is unavailable.

Palpable Thyroid Gland (Goiter) but Not Hyperthyroid

Non-functional enlargement of thyroid glands (goiter) has been recognized since the 1960's but has taken on new significance since functional hyperthyroidism arose as an entity in the late 1970's. Non-functional goiter was 're-recognized' about a decade ago.[22] Many believe that clinical hyperthyroidism has a prodromal period (also called 'subclinical hyperthyroidism' or 'pre-hyperthyroidism').[19] However, it is not clear whether all goiters are indicative that the cat will develop hyperthyroidism. Surgical removal of non-functional goiters has been proposed as a preventative measure, but there is no evidence to support this approach.

Misdiagnosed as Hyperthyroid based on Falsely-High Serum T4 Concentration

A high circulating total T_4 concentration is the biochemical hallmark of hyperthyroidism and is extremely specific for its diagnosis. False positive results (ie, a high T_4 in a cat without hyperthyroidism) are rare but are being seen with increasing frequency, especially with the automated enzyme immunoassays (EIA). However, about 25-30% of cats presenting with borderline-high total T_4 values, sometimes together with high free T_4 concentrations, turn out to be euthyroid.[2,3,13] The reason for this high incidence of misdiagnosis is unclear but may be related to the increasing use of screening T4s as part of the cat's annual "wellness" program.

If a high total T_4 concentration is measured in a cat without the characteristic signs of hyperthyroidism, one should always repeat the cervical palpation and verify the T_4 concentration using a different technique, with RIA or CEIA being preferred in such cats.[2,3] Again, if we have any doubt about the diagnosis, thyroid scintigraphy should be considered.[13,14] It's extremely important to remember that hyperthyroidism is a clinical diagnosis and should never be based on a serum T_4, free T_4, or TSH concentration alone. One MUST combine these lab results with the cat's clinical features and the presence of a palpable thyroid nodule to make the diagnosis.[2,3]

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What's the Best Treatment for Hyperthyroidism? Antithyroid Drugs, Surgery, Diet, or Radioiodine?

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Introduction

Hyperthyroidism can be treated in four ways: medical management with methimazole or carbimazole, nutritional management (low-iodine diet), surgical thyroidectomy, and radioactive iodine (^{131}I).[1-6] Each form of treatment has advantages and disadvantages that should be considered when formulating a treatment plan for the individual hyperthyroid cat.

Medical and nutritional management are considered "reversible" treatments whereas surgical thyroidectomy and ^{131}I are "permanent" or curative treatments.[1,2] Because neither medical nor nutritional management is curative, these treatments cannot be recommended as sole therapy for the rare cases of hyperfunctioning thyroid carcinoma.[5,7 8]

Treatment Considerations: Concurrent Conditions

Chronic Kidney Disease and Hyperthyroidism

Chronic kidney disease (CKD) is very common in older cats so it is not surprising that CKD is found concurrent with hyperthyroidism.[9,10] The increased GFR and reduced muscle mass induced by hyperthyroidism can mask underlying CKD, which may only be revealed once the cat is rendered euthyroid and azotemia is documented.

Because it is not always possible to predict which hyperthyroid cats have underlying CKD, this has led to the recommendation that trial treatment with methimazole (or carbimazole) is routinely performed prior to definitive therapy with radioactive iodine. There are a couple of important implications that result from this recommendation: the first is that if azotemia develops following medical treatment, then it would be best to subsequently leave the hyperthyroidism untreated (or at least under-treat it) to maximize renal function. Second is that if the cat develops azotemia, the client should then be counseled against having definitive therapy for their cat's hyperthyroidism due to a poor long-term prognosis. However, evidence exists to suggest that both these conjectures are misguided.[11,12]

Mild to moderate kidney disease alone should never preclude permanent treatment of hyperthyroidism. Recent research provides evidence that hyperthyroidism may contribute to the development or progression of CKD in cats, suggesting that leaving a hyperthyroid cat untreated (or poorly regulated with methimazole) may be detrimental to long-term kidney function.[12,13] Treating and curing hyperthyroidism may help to both reverse renal damage and preserve the remaining kidney function.

Secondly, in most cats that develop newly diagnosed azotemia following treatment for hyperthyroidism, the degree of CKD is mild (usually IRIS stage 2) and associated with few, if any, clinical signs other than mild polyuria/polydipsia. The survival time of cats that develop azotemia following treatment of hyperthyroidism is not significantly different from those that do not, unless they develop hypothyroidism.[14] This finding may be surprising to practitioners who will tend to assume that the development of azotemia is associated with a worse prognosis. However, CKD is relatively slowly progressive in cats, and only about half of all cats diagnosed with mild CKD will ultimately succumb to the disease, with many dying due to other causes.[15]

In cats that are azotemic prior to treatment for hyperthyroidism, it is generally recommended that they be treated medically initially (and with a gradually escalating dose), so that if their condition deteriorates the anti-thyroid medications can be discontinued and the cat will return to a hyperthyroid state. If the biochemical deterioration is mild following treatment, and the well being of the cat is improved, then permanent treatment for hyperthyroidism (surgery/radioiodine therapy) can be considered. However, in general the survival of cats that have azotemic CKD prior to treatment of hyperthyroidism is poor; in one study, the median survival time for azotemic cats was only 178 days.[16]

Heart Disease and Hyperthyroidism

Cardiac disease associated with hyperthyroidism is mild and reversible in most cats with hyperthyroidism.[1,2,9,17] Murmurs and tachycardia are common but often do not result in clinical signs. On the occasions when cats show more severe cardiac changes such as arrhythmia or congestive heart failure, these should be stabilized before a cat undergoes thyroidectomy or radioiodine therapy.

Hypertension and Hyperthyroidism

Systemic hypertension (generally mild to moderate) develops in approximately 10% of untreated hyperthyroid cats and is generally reversible upon induction of euthyroidism.[19,17,18] Conversely, some cats are normotensive when hyperthyroidism is diagnosed but may become hypertensive after becoming euthyroid. Most of these cats, however, have some degree of concurrent renal disease. If hypertension is severe or persists after treatment of hyperthyroidism, these cats should be managed with amlodipine.

Liver Disease and Hyperthyroidism

Hepatic disease is often suspected in cats with untreated hyperthyroidism because of their high liver enzymes (serum ALT and alkaline phosphatase).[1,2] At the time of diagnosis, it is not always possible to know if increased liver enzymes are due to primary hepatic disease or are secondary to hyperthyroidism. If underlying primary liver disease is expected, especially if the cat is showing signs of apathetic hyperthyroidism (e.g., anorexia, depression, etc.), a treatment trial with methimazole or carbimazole should be considered.

Treatment Considerations: Owner Circumstances and Preferences

Cat owner issues or circumstances, such as cost of therapy, is a major consideration in many instances. Medical or nutritional therapy costs far less initially. However, the cost of ongoing monitoring can exceed that of thyroidectomy or ^{131}I therapy over a period of many months to years. In addition, nutritional therapy may not be practical for owners with multiple cats, especially when the other cats are on prescription diets for other disorders, such as CKD. Some owners find medicating difficult, whereas others are greatly wary of radiation therapy.

Antithyroid Drug Management

Pros and Cons

Chronic management with antithyroid drugs (methimazole or carbimazole) is a practical treatment option for many cats.[1-3,19,20] Medical management requires no special facilities and is readily available. Anesthesia is avoided, as are the surgical complications associated with thyroidectomy**.**

In addition to long-term treatment, medical management is also necessary prior to surgical thyroidectomy to decrease the metabolic and cardiac complications associated with hyperthyroidism. Short-term medical management is often recommended as trial therapy prior to ^{131}I therapy to determine the effect of restoring euthyroidism on renal function.

However, medical management has many disadvantages.[1-3,19,20] This form of treatment is not curative, is highly dependent on owner and cat compliance, and requires regular biochemical monitoring to ensure the efficacy of treatment. Many cats treated on a long-term basis will not be well-controlled, as evidenced by high post-methimazole T_4 values.[3,21] Adverse signs effects, mostly mild but some serious, are relatively common. Most importantly, the thyroid tumor continues to grow and, after many months, may transform from adenoma to thyroid carcinoma in some cats.[22] Long-term medical management is best reserved for cats of advanced age or for those with concurrent diseases, and for when owners refuse either surgery or radioactive iodine.

Surgical Thyroidectomy

Pros and Cons

Thyroidectomy is an extremely effective treatment for hyperthyroidism that is simple, quick, curative and cost effective.[1,2,4,22,23] In practice, it is often considered the treatment of choice particularly if radioactive iodine is unavailable.

However, surgery comes with its own list of disadvantages. First of all, it can sometimes be difficult to differentiate unilateral from bilateral thyroid tumor involvement. If only one thyroid lobe is removed, relapse of hyperthyroidism is common within a few months.

More importantly, thyroidectomy can be associated with significant morbidity and mortality, especially in cats with severe hyperthyroidism. The many potential complications associated with thyroidectomy include iatrogenic hypoparathyroidism, laryngeal nerve damage (most commonly associated with voice change), and Horner's syndrome**.**[1,2,4,22,23]

Temporary hypothyroidism develops in most cats after unilateral thyroidectomy, with serum T_4 and T_3 concentrations falling to subnormal levels for 2 to 3 months. After bilateral thyroidectomy, hypothyroidism will develop within 24 hours if the surgery was successful. Thyroid replacement with L-T_4 is recommended starting on the day of discharge. In these cats, life long replacement therapy is generally recommended. [24]

Radioactive Iodine Treatment

Pros and Cons

Treatment with radioiodine has many advantages over other treatment methods. It avoids inconvenience of daily oral administration of antithyroid drugs as well as the side effects commonly associated with these drugs. Radioiodine also eliminates the risks and perioperative complications associated with anesthesia and surgical thyroidectomy. A single administration of radioiodine restores euthyroidism in most (95%) hyperthyroid cats. The therapy is simple and relatively stress-free for most cats.[1,2,5,26]

There are some downsides of radioiodine treatment, however. Its use requires special radioactive licensing and hospitalization facilities, and extensive compliance with local and state radiation safety laws. Major drawback for most owners is that their cat must be kept hospitalized for a period (3 to 10 days in most treatment centers; but up to a month in some places) and visiting is not allowed.

Treatment complications include failure to restore euthyroidism, iatrogenic hypothyroidism, and relapse of hyperthyroidism. [5,26] Although most hyperthyroid cats treated with radioactive iodine are cured by a single dose,

approximately 5% of cats fail to respond completely and remain hyperthyroid after treatment with radioiodine. In cats that remain hyperthyroid 3 months after initial ^{131}I treatment, retreatment is generally recommended because virtually all cats with persistent hyperthyroidism after the first treatment can be cured by a second treatment, especially if thyroid scintigraphy can be used to restage the disease.[5,27]

A proportion of cats treated with radioiodine will develop permanent, iatrogenic hypothyroidism.[5,25] Most of these cats show few, if any clinical signs for many months and therefore, may be difficult to diagnose clinically. Because hypothyroidism leads to a decrease in the renal blood flow and GFR, development of new azotemia or worsening of the degree of kidney disease is one clue that one should rule out hypothyroidism. Diagnosis of iatrogenic hypothyroidism is based upon the history, clinical signs, development or worsening of azotemia, subnormal serum total T_4 and free T_4 concentrations, high serum cTSH values, and the response to replacement L-T_4 therapy. Life-long L- T_4 supplementation is generally needed (i.e., 0.1-0.2 mg L-thyroxine per day).[25]

Nutritional Management (Iodine Deficient Diet)

The basis for using this diet is that iodine is an essential component of both T_4 and T_3; without sufficient iodine, the thyroid cannot produce excess thyroid hormones.[6] This is an iodine-deficient diet, containing levels below the minimum daily requirement for adult cats.[28]

Use of a low iodine diet takes a few weeks to lower the high T_4 concentrations in cats with hyperthyroidism. This therapy appears to be more effective in cats with only moderate elevations of T_4 than cats with severe hyperthyroidism. It will not effectively suppress high thyroid hormone levels in all cats (see below).

Pros and Cons of Nutritional Management

A major indication for the use of this y/d diet for management of feline hyperthyroidism is in cats that are not candidates for definitive treatment of the underlying thyroid tumor(s) with surgery or radioiodine, which remains the treatments of choice. In addition, nutritional management with y/d food (canned rather than the dry y/d) could be considered in cats whose owners are not able to give oral medication or in cats that develop side effects from methimazole/carbimazole.

Despite some advantages, nutritional management has many disadvantages:

1. First of all, feeding this diet cannot cure hyperthyroidism. Rather, feeding y/d just offers control (withholding fuel for thyroid tumor). The thyroid tumor remains and will continue to grow larger. As now documented in cats with long-standing hyperthyroidism, transformation of adenoma to thyroid carcinoma can occur unless definitive treatment (surgery or radioiodine treatment) is used to cure the disease.
2. The cats fed this diet must not eat any other cat diet, table food, or treats because even tiny amounts of iodine may lead to failure of this diet to effectively control hyperthyroidism.
3. If the diet is stopped, relapse will develop; the cat must eat only this diet for rest of his/her lifetime.
4. The long-term consequences of this iodine deficient diet are not known, especially in normal cats in households that are also fed this diet. For this reason, y/d should not be the only diet fed to normal cats, which can be an issue for owners with multiple cats in the same household.
5. The composition (protein/fat/carbohydrate breakdown) of y/d reveals that it is a high-carbohydrate, relatively low-protein diet. Feeding y/d for long periods is less than an “ideal” diet for an obligate carnivore, especially in an older hyperthyroid cat with severe muscle wasting.[28]
6. Finally, in a recent study of 225 cats treated by feeding this diet, 25% of the cats were still hyperthyroid after 8 weeks of treatment.[6] The majority of these cats had total T_4 concentrations that were within the upper half of the laboratory reference range. These results suggest that dietary management of hyperthyroidism is unlikely to suppress thyroid levels or induce euthyroid to the same extent as permanent therapies or even methimazole.

Bottom Line— What’s The Best Treatment?

When dealing with hyperthyroid cats, treatment is aimed at either removing or destroying the hyperfunctioning thyroid tumor or inhibiting thyroid hormone synthesis and release. Surgical thyroidectomy and radioactive iodine remain the only curative options available. Management of hyperthyroidism with antithyroid drugs or a low-iodine diet are both non-curative since the thyroid tumor is not removed or destroyed, and will continue to grow with time.

Because of these issues, treatment must be tailored to each individual cat, with the following factors taken into consideration when selecting the “best” treatment for that cat.

- Age of cat
- Presence/absence of significant concurrent disease
- Severity of clinical hyperthyroidism
- Size of goiter (thyroid tumor)
- Availability of skilled surgeon

- Access to ^{131}I treatment facility
- Owner/cat compliance for antithyroid drug administration
- Willingness of cat to eat low-iodine diet
- Multicat household/outdoor cat that hunts
- Immediate and long-term costs of each treatment
- Potential complications

In younger cats without concurrent disease, definitive treatment with either surgical thyroidectomy or radioactive iodine to cure the disease is recommended whenever possible. In contrast, long-term medical or nutritional management is best reserved for cats of advanced age or for those with concurrent diseases, and for when owners refuse either surgery or radioactive iodine.

Most cats that we diagnose and treat, however, are neither young nor very old but fall into the intermediate age range (13-16 years). In these cats, we must recommend the best treatment for that individual cat, again based upon cat's age and condition at the time of diagnosis, severity and duration of the hyperthyroid disease, and the presence of severe or life threatening concurrent diseases (e.g., CKD or heart disease).

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Chronic Diarrhea: What's the Cause?

Kenneth Simpson, BVM&S, PhD, DACVIM, DECVIM

Introduction

A thorough and systematic approach is required to determine the cause of chronic diarrhea. An integrated approach based on patient history, physical findings, clinicopathological and intestinal function testing testing, and diagnostic imaging will be presented.

Pathophysiology of Diarrhea

The most frequent clinical sign of intestinal disease is diarrhea - the passage of feces containing excess water, resulting in an increase in the fluidity, volume or frequency of bowel movements. The pathomechanisms in the genesis of diarrhea can be categorised as osmotic, secretory, permeability and motility. Most intestinal disease in dogs and cats involves several patho-mechanisms so attempts to categorise animals presented for the investigation of diarrhea using these criteria are usually redundant. e.g. the accumulation of inflammatory cells within the intestine in response to antigenic challenge and other less well defined stimuli, can exert its effects both directly and indirectly by the production of inflammatory mediators such as prostaglandins and leukotrienes. The net result is abnormal mucosal absorption, secretion, permeability and intestinal motility.

General Approach

Diarrhea which has lasted for 2 or more weeks is considered chronic. The approach to chronic diarrhea is based on the origin of diarrhea - large bowel or small bowel, and the presence of other specific or localising clinical findings. Differentiation is important as the diagnostic and therapeutic approaches to small and large bowel diarrhea are different. Differentiation is made on the basis of information furnished by the owner in response to questions about faecal characteristics, volume and frequency and related signs such as vomiting, weight loss, tenesmus and dyschezia.

Small bowel diarrhea is a consequence of diseases that affect the small intestine or related structures such as the exocrine pancreas.

Causes of Chronic Diarrhea

Infectious	Salmonella, Campylobacter, Giardia, Tritrichomonas, Cryptosporidium, FelV/FIV,FIP
Metabolic	Hyperthyroidism, liver disease, kidney disease
Dietary	Intolerance / allergy
Exocrine pancreatic insufficiency	
Small intestinal disease	
Structural	Partial obstruction- intussusception, foreign object, neoplasia, congenital anomalies
Inflammatory	lymphoplasmacytic, granulomatous (FIP), eosinophilic
Neoplastic	Lymphosarcoma, adenocarcinoma, leiomyoma, fibrosarcoma
Functional	Motility disorders, idiopathic

Patient Evaluation and Diagnostic Approach

Signalment and History

Infectious and parasitic diseases are common in young animals, whereas neoplasia and metabolic disorders are more common in middle aged to older animals. Certain conditions appear more common in certain breeds e.g. IBD in Siamese. Small bowel diarrhea is generally associated with weight loss and large stool volume. Failure to thrive, changes in appetite, borborygmi, flatus, abdominal discomfort, ascites and oedema are also more common with small than large bowel diarrhea.

Physical Examination

Particular attention should be paid to hydration status and examination and palpation of as much of the gastrointestinal tract and abdomen as possible. The thyroid gland should be palpated in cats >6yo. A thorough rectal examination should be performed.

Investigation of Chronic Small Bowel Diarrhea

The approach to patients with chronic small bowel diarrhea who are stable, have no specific localizing clinical findings and are negative for fecal parasites is usually to:

- Rule out endoparasites and pathogenic bacteria — *Fecal*
- Screen for systemic disease — *CBC, profile, UA ± T4, FelV/ FIV*

- Rule out exocrine pancreatic insufficiency — *TLI*
- Rule out partial obstruction — *Palpation, radiographs, ultrasound*
- Evaluate intestinal structure and function — *Biopsy - endoscopic / surgical,cobalamin/folate*

Laboratory Evaluation of Chronic Small Bowel Diarrhea

Fecal Analysis

Giardia (cysts-ZNSO4,IFA, ELISA), Cryptosporidium (IFA), Coccidia, Tritrichomonas fetus (In pouch, PCR), other endoparasites (fecal float). Analysis for Clostridial endospores and endotoxin is fraught with difficulty in interpretation. Culture for Campylobacter and Salmonella in animals with bloody stools, or fever, or chronic undefined diarrhea. Fecal culture cannot be used to diagnose small intestinal bacterial overgrowth which has not ben described in cats!

Hematology

Anemia - Microcytosis (MCV < 42fl cat) may occur secondary to GI blood loss. Macrocytosis (MCV> 53fl): ddx regenerative anemia, hyperthyroidism, FeLV or cbl/ folate deficiency.

Eosinophilia - intestinal parasitism, mast cell tumors, eosinophillic enteritis or hypereosinophilic syndrome. Neutrophilia ± a left shift may be encountered in inflammatory or infectious conditions. Lymphopenia may beassociated with protein losing enteropathies and immunodeficiency.
Lymphocytosis is typical in stressed cats (adrenaline response).

Serum Biochemistry

R/O non-intestinal diseases which cause signs such as weight loss, vomiting and diarrhea that overlap with primary GI disease i.e. hyperthyroidism, kidney disease, renal disease, diabetes mellitus.

Metabolic consequences e.g. hypokalemia, hyponatremia. Mild to moderate increases in liver enzymes such as ALT (up to 500 IU/l) are common in cats with hyperthyroidism and intestinal disease. Serum bile acids - liver dysfunction or shunting in patients with GI signs.

Hypoglycemia with signs of gastrointestinal disease should arouse the suspicion of sepsis, liver disease, hypoadrenocorticism or pancreatic tumor. Hypoalbuminemia + hypoglobulinemia R/0 protein losing enteropathies Hypoalbuminemia with normal or increased globulin concentration has to be distinguished from protein losing nephropathy and liver disease.

Chronic diarrhea associated with hypoalbuminaemia usually requires intestinal biopsy to define the cause. Non-intestinal causes of protein losing enteropathy such as portal hypertension should also be considered. When globulin concentratiouns are normal or elevated renal and hepatic causes should also be pursued.

Protein Losing Enteropathies

Infectious	Panleucopenia, Salmonella,
Structural	Intussusception
Neoplasia	Lymphosarcoma
Inflammation	Lymphoplasmacytic, eosinophilic, granulomatous
Gastrointestinal haemorrhage	Neoplasia, ulceration

Urinalysis

Part of a baseline evaluation to detect or rule out urogenital disorders in patients with signs of intestinal disease. Urate crystalluria may prompt the investigation of hepatic dysfunction as a cause of clinical signs. Urine Prot:creatinine for determining if the kidney is involved in the development of hypoalbuminaemia in patients with intestinal signs.

Serology and hormone assays

T_4,FIV and FeLV

Tests of pancreatic function

Exocrine pancreatic insufficiency is uncommon in cats and is usually associated with chronic diarrhea and polyphagia and a poor haircoat fTLI ≤ 8µg/l.

Pancreatitis can occur concurrently with chronic intestinal disease and cholangitis. Measurement of serum PLI (@sensitivity 67%, and specificity at 91%) and ultrasonography (sensitivity 35 to 67 %, with a specificity of @ 73%) may help to determine the presence of pancreatitis

Radiography

Survey abdominal radiographs are taken in patients with vomiting, but are low yield in patients with chronic diarrhea. Contrast radiography can be useful in evaluating partial obstruction and transit time/ gut length if

ultrasonography is not available. Thoracic radiographs are often warranted in older cats with weight loss to screen for systemic disease.

Ultrasonography

Ultrasound is useful for detecting intestinal lesions such as intussusceptions, masses and foreign bodies, and for assessing intestinal wall thickness. The results of radiography and ultrasound provide a rational basis for selecting endoscopic biopsy (±duodenal juice analysis) or a laparotomy. Normal or diffusely thickened intestines can initially be evaluated endoscopically while focal lesions usually require guided aspiration or laparotomy. Muscularis hypertrophy and mesenteric lymphadenopathy are frequently associated with inflammatory bowel disease and alimentary lymphoma.

Tests of Intestinal Function

When a clinical problem cannot be adequately defined or localised to the small intestine a variety of tests can be used to assess small intestinal function. Intestinal function tests have the potential benefit of allowing an overall assessment of SI function, rather than the small snapshot provided by a biopsy. They should always be critically evaluated in the context of the whole patient.

Cobalamin and folate

The measurement of circulating concentrations of cobalamin and folate may give an indication of the site and cause of intestinal dysfunction. Plasma concentrations of cobalamin and folate are labile and reflect the balance between dietary intake, bacterial utilisation and production, and intestinal absorption and body losses.

The interpretation of circulating cobalamin and folate concentrations with regard to small intestinal disease is only valid if exocrine pancreatic insufficiency, dietary supplementation, parenteral administration have been excluded and attention is paid to dietary vitamin content.

Subnormal concentrations of cobalamin are common in cats with EPI, intestinal, pancreatic or hepatic disease: Forty-nine of 80 serum samples submitted from cats with signs of gastrointestinal disease during the period of January 1996-January 1998 had cobalamin concentrations below the reference range for healthy cats (range 900 - 2,800 pg/ml ; mean ± SD = 1775 ± 535 pg/ml SD ; n=33). Cats with subnormal cobalamin concentrations (mean ± SD = 384 ± 272 pg/ml, range 3 - 883pg/ml) were middle aged or older and were presented for weight loss, diarrhea, vomiting, anorexia and thickened intestines. Definitive diagnoses in 22 cats included inflammatory bowel disease, intestinal lymphoma, cholangiohepatitis or cholangitis, and pancreatic inflammation. Serum concentrations of cobalamin were particularly low in cats with intestinal lymphoma, 3/5 of which also had subnormal serum concentrations of folate (< 9ng/ml). The simultaneous presence of disease in the intestines, pancreas or hepato-biliary system in many cats made it difficult to determine the cause of subnormal cobalamin concentrations. The circulating half-life of parenteral cyanocobalamin was shorter in two cats with IBD (5 days) than in four healthy cats (12.75 days).

The presence of subnormal serum concentrations of cobalamin in 49 of 80 cats evaluated suggests that the measurement of serum cobalamin may be a useful indirect indicator of enteric or pancreatic disease in cats. The rapid depletion of circulating cobalamin in cats indicates that cats may be highly susceptible to cobalamin deficiency. From studies to date it appears that cats with a cobalamin below 200pg/ml consistently have increased MMA and require parenteral cobalamin.

Intestinal Biopsy

Biopsy of the intestine is frequently required to achieve a diagnosis in patients with chronic diarrhea due to malabsorption. In diffuse intestinal diseases and in animals with hypoproteinaemia endoscopy provides a minimally invasive low risk way of obtaining a biopsy. At least seven to 10 endoscopic biopsies should be acquired.

Endoscopic biopsies are restricted to the mucosa and are small, difficult to process and orientate, and can be obtained only from the proximal duodenum and occasionally the distal ileum. Thus surgical biopsies are necessary in patients with focal intestinal lesions and in those whom endoscopic biopsy has not yielded a result. Surgical biopsies should be taken from multiple sites along the small intestine even if the intestine looks grossly normal. A small dermatologic punch aids the surgeon in obtaining full thickness biopsies and biopsy sites are sutured in an appropriate fashion. Extreme care is required where the bowel looks grossly abnormal and in hypoproteinemic patients to ensure leakage does not occur. Precautionary measures such as serosal patch or omental wraps may be employed. Biopsies of mesenteric lymph nodes should also be obtained. Other abdominal organs such as the liver, and pancreas can be grossly examined and biopsied.

The information which can be obtained from intestinal biopsies depends on the expertise of the pathologist. Minimum evaluation should include routine microscopic examination of H&E stained sections. The pathologist should be able to give an indication of villus height and morpholgy, ratio of crypt to villus and the type and degree of cellular infiltrate and intraepithelial lymphocyte count. Recent studies suggest that changes in mucosal architecture are much more significant than subjective alteratons in cellularity. Staining for different lymphocyte sub-types and clonality PCR may be useful in distinguishing IBD and low grade alimentary lymphoma

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Managing Cats with Chronic Gastrointestinal Disease

Kenneth Simpson, BVM&S, PhD

This presentation will focus on the two major chronic enteropathies of cats: inflammatory bowel disease and alimentary lymphoma.

Feline Inflammatory Bowel Disease

Feline inflammatory bowel disease (IBD) is the term applied to a group of poorly understood intestinal disorders that are associated with vomiting, diarrhea and weight loss in cats. Diagnosis is usually based upon subjective analysis of intestinal mucosal biopsies and qualified according to the dominant mucosal infiltrate, typically lymphocytes and plasma cells. However, more objective studies have demonstrated increased expression of MHC class II antigen by leukocytes in the lamina propria and enterocytes, and upregulation of pro-inflammatory and immunoregulatory cytokines, rather than an increase in mucosal cellularity. Abnormalities in mucosal architecture, such as crypt distortion, villous blunting and fusion, and fibrosis have also been described, and have been associated with the severity of clinical signs, and the subjective histological grade of IBD. The cause of feline IBD has not been determined, but it is suspected that IBD in cats, like IBD in people, is a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric microbial, and immunoregulatory factors in genetically susceptible individuals. Genetic susceptibility in people is linked increasingly to defects in innate immunity, exemplified by mutations in the innate immune receptor NOD2/CARD15, that in the presence of the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation. This possibility is supported by studies showing the pivotal importance of the enteric microflora in the development of IBD in rodents with engineered susceptibility and those demonstrating an abnormal mucosa-associated flora, considered to interact most closely with the innate immune system, in people with IBD. Knowledge of genetic susceptibility in cats with IBD is limited, with some studies reporting a predisposition for purebred cats such as Simaese. Culture based studies have shown fewer lumenal microaerophilic bacteria in the duodenal juice of cats with clinical signs of gastrointestinal disease than healthy cats. More recent studies have revealed changes in the intetsinal microflora of cats with chronic gastrointestinal disease, termed dysbiosis. The number of mucosa-associated Enterobacteriaceae was higher in cats with signs of gastrointestinal disease than healthy cats ($P<0.001$). Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture ($P<0.001$) and the density of cellular infiltrates, particularly macrophages ($P<0.002$) and $CD3^{+}$lymphocytes ($P<0.05$). The number of Enterobacteriaceae, *E. Coli*, and *Clostridium* spp. correlated with abnormalities in mucosal architecture (principally atrophy and fusion), upregulation of cytokine mRNA (particularly IL-1, -8 and -12), and the number of clinical signs exhibited by the affected cats. These data establish that the density and composition of the mucosal flora is related to the presence and severity of intestinal inflammation in cats, and suggest that mucosal bacteria are involved in the etiopathogenesis of feline IBD.

A Stepwise Approach to Treating Feline Inflammatory Bowel Disease

How confident am I the cat has IBD?

- Clinical findings
- Clinicopathological tests
- Diagnostic imaging
- Intestinal biopsy

Have I ruled out

Systemic/ metabolic disease
Dietary intolerance/ food allergy
Infectious agents
- Protozoa
  - *Giardia*
  - *Tritrichomonas*
- Pathogenic bacteria
  - Campylobacter / Salmonella
- Viral?

Structural/anatomic abnormalities

- Does the cat have multiple problems or organ systems involved?
- Is the cat deficient in cobalamin or folate?
- Do I need a biopsy?

- **What and how should I biopsy?**
- How do I interpret the biopsy results and integrate gastric and intestinal histopathology?
- Is it IBD or small cell lymphoma?
- What diet should I use?
- When should I use antimicrobials? corticosteriods? chlorambucil?
- How do I manage concurrent disease in the liver and pancreas?
- How do I assess response?

An Overview of Diagnosis and Treatment

Clinical Findings

Vomiting is the most common clinical sign in cats with IBD. Vomitus often contains bile. Other findings include diarrhea, changes in appetite, weight loss and less commonly excessive borborygmi and abdominal discomfort.

The severity of disease ranges from intermittent vomiting in mild cases to intractable small bowel diarrhea, inappettance and weight loss in severe ones. The severity of the disease correlates with the degree of intestinal damage, particularly villus atrophy and fusion

Physical findings range from normal to thickened intestines, mesenteric lymphadenopathy and loss of muscle mass. Ascites or edema are extremely are in cats with IBD.

Routine laboratory testing may reveal mild to moderately elevated liver enzymes as a result of GI barrier dysfunction. However, IBD can be associated with concurrent hepatoibiliary disease and pancreatitis- "triaditis"- so the clinician must consider these disorders (Ultrasonography and fPLI aid detection of intercurrent disease). The presence of hypocalcemia would ring alarm bells for pancreatitis. Hypoalbuminemia is rare. CBC is usually normal. Eosinophilia is encountered in some cats with LP enteritis, and should prompt consideration of parasites or food intolerance/allergy, as well as mastocytosis or hypereosinophilic syndrome. Measurement of serum cobalamin and folate can aid the detection of intestinal disease- low cobalamin concentrations are common in cats with IBD (EPI should be excluded by TLI assay). Cobalamin deficiency can produce identical signs to those associated with IBD. A combination of low folate and conbalamin tends to support a diagnosis of severe IBD or GI lymphoma.

Ultasnographic findings in cast with IBD overlap with those of cats with lymphoma i.e. muscularis hypertrophy and mesenteric lymphadenopathy

Diagnosis

A diagnosis of idiopathic IBD is made by excluding systemic, parasitic, infectious, pancreatic and structural causes of chronic vomiting, weight loss or diarrhea and demonstrating histopathological abnormalities in intestinal biopsies. Keep in mind that IBD may co-exist with hepatobiliary disease and/or pancreatitis.

Treatment

Treatment of IBD is usually a "best guess least harm" approach employing dietary modification, vitamin supplementation, antimicrobial agents and immunosuppression. Treatment is to some extent based on the severity of the disease.

Mild to moderate disease may be associated with dietary sensitivity / intolerance, cobalamin deficiency or antibiotic responsive enteropathy.

A therapeutic dietary trial can be performed with either:1) a highly digestible diet which is gluten-free ,2) a diet limited to a single novel protein source or3) a diet containing protein hydrolysate, to determine if dietary sensitivity or intolerance are present. A response is usually observed within one to two wks. Re-challenge with the original diet is required to demonstrate intolerance.

Cobalamin deficiency is treated with parenteral cobalamin (0.5ml SC q 2-3wks). Folate should be given orally if serum concentrations are low.

A therapeutic trial (21days) with Tylosin (10mg/kg PO TID), metronidazole (15mg/kg PO BID) or oxytetracycline (10-20mg/kg PO TID) can be undertaken to determine if an antibiotic responsive enteropathy is present.

In patients who fail these trials and in those with moderate to severe disease, or hypoproteinaemia, immunosuppressive agents are usually added to achieve a response. Oral prednisolone (1-2mg/kg PO BID) is the initial drug of choice. It is usually administered at an immunosuppressive dose for 2-3 wks and then decreased by 50% every 2-3wks, and continued on an alternate day basis for 2-3 months. If clinical response is poor, chlorambucil (6mg/m2 PO PO EOD (@2mg/5.3kg cat) and prednisone (5mg PO /cat/day) are initiated. Metronidazole (15mg/kg PO BID 10-14d then SID 10-14d) is frequently used in conjunction with corticosteroids to modify the microflora. However metronidazole is a potential mutagen and the author avoids long-term therapy.

Successful treatment is accompanied by a decrease in clinical signs, and an increase in plasma proteins (though low albumin is uncommon in IBD). Once a patient has had 2-3 months remission from signs it may be possible to gradually withdraw immunosuppressive therapy. If signs recur daily medication is continued until signs resolve then

gradually reduced. In patients who respond poorly to therapy or relapse after an initial response lymphoma should be ruled out.

Prognosis

The prognosis for lymphoplasmacytic enteritis is variable and depends on its severity and the preence of concurent disease. Many patients require prolonged treatment with glucocorticoids and diet. As no accurate criteria exist for predicting response it is wise to give a guarded prognosis.

Alimentary lymphoma

The Changing and Variable Phenotype of Feline Alimentary Lymphoma

Lymphomas represent up to ninety percent of hematopoietic tumors in the cat and are one of the most frequently diagnosed tumors of domestic cats. During the feline leukemia virus (FeLV) era of the 1960s through the 1980s, FeLV was the most common cause of up to 70% of cases of lymphoma that were predominantly cranial mediastinal, multicentric, renal and central nervous forms, associated with FeLV antigenemia. However, despite a decline in FeLV-associated lymphoma and contrary to expectations the prevalence of lymphoma has increased in the post-FeLV era, and there has been a change in the frequency of affected anatomic sites and patient demographics. Alimentary lymphoma is now the most common anatomic form and predominantly affects middle age to older cats, in contrast to mediastinal or multicentric lymphoma that typically affect younger cats. This increase in alimentary lymphoma has also been accompanied by a change in immunophenotype, from predominantly high grade B cell to predominantly low grade T cell. In a study of 41 cats with low-grade lymphocytic lymphoma evaluated at the Cornell University Hospital for Animals and South Carolina Veterinary Internal Medicine between 1995-2005, the median age at diagnosis was 13 years 148 (range, 6-17 years) and 40/41 were Domestic Shorthair (n = 33) or Domestic Longhair (n = 7). Lymphoma was confined to the gastrointestinal tract in 68% of cats and eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin by immunohistochemistry, while 8% (3 of 36) were of B-cell origin. A search of our pathology database for feline alimentary lymphoma during the years 2007 to 2011 yielded a total of 136 small cell lymphoma (SCL) and 16 cases of large cell lymphoma (LCL). The immunophenotype of a randomly chosen subset of 33 of the 136 cats with SCL indicated they were all T-cell. Surprisingly, we found that LCL were divided evenly between T- (8/16) and B-cell (7/6), with one tumor considered B&T-cell. This diversity in cell morphology and immunophenotype has potential implications for etiopathogenesis and treatment, and subsequent studies should be stratified on the basis of tumor immunophenotype and cell morphology.

The response to therapy has also changed, with overall median survival time reaching 704 days in low-grade lymphoma versus weeks to months in high-grade large cell lymphoma. Until, recently the large B cell phenotype predominated in Australia and the UK, but small T- cell phenotype has recently emerged. The sequential temporal emergence of low-grade alimentary lymphoma in the USA, Great Britain and Australia echoes the appearance of feline hyperthyroidism and raises the possibility of an underlying environmental or infectious etiology. The factors responsible for the changes in prevalence, immunophenotype and biology of feline alimentary lymphoma are not known.

Clinical Findings

Middle aged and older cats (median 13yrs), predominantly DSH cats are reported. Weight loss, vomiting, chronic small bowel diarrhea and progressive inappettance are common features of GI lymphoma. Physical examination may reveal diffusely thickened or nodular intestines ± mesenteric lymphadenopathy. Hepatosplenomegaly, renomegaly, generalized lymphadenopathy and abdominal mass may also be detected. Acute abdominal pain and shock may be present if intestinal perforation has occurred.

Diagnosis

Routine biochemistry may reveal hypoalbuminemia. Anemia which is either normocytic normochromic non-regenerative or microcytic and hypochromic, and neutrophilia may also be present. Serum concentrations of cobalamin are often very low in cats with GI lymphoma and serum folate concentrations may also be reduced. High PLI concentrations are found in some cats and may indicate concurrent pancreatitis or pancreatic lymphoma. Ultrasound is useful for evaluating intestinal thickness / layering, presence or ansence of mucularis hypertrophy, and detecting mesenteric lymphadenopathy and abnormalities in liver/kidney/spleen and pancreas. However it cannot distinguish lymphoma from IBD. Diagnosis can be made by demonstrating neoplastic lymphocytes in aspirates or biopsies from enlarged intestinal or peripheral lymph nodes, but is more often made by intestinal biopsy. The absence of lymphoma in a fine needle aspirate does not rule it out : there is a high degree of discordance between FNA and biopsy results of LN aspirates from cats with confirmed alimentary lymphoma. Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can also miss submucosal and serosal lesions or yield a diagnosis of “lymphoplasmacytic enteritis”. Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy and circumvent the endoscopy surgery debate.

Treatment and Prognosis

In a recent study of 41 cats with low-grade lymphoma, lymphoma was confined to the gastrointestinal tract in 68% of cats, while 32% had other organ systems affected with or without gastrointestinal involvement. Extra-gastrointestinal sites involved included mesenteric lymph nodes (n = 6), liver (n = 10), spleen (n = 1), and pancreas (n = 1). Some cats had more than 1 site affected. Eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin via immunohistochemistry, while 8% (3 of 36) were of B-cell origin.

Fifty-five per cent of cats achieved a complete response to therapy and 37% achieved a partial response. The majority of cats (n = 31; 76%) received prednisone at a dose of 5 mg, PO, q 12-24 hrs and most (n = 35; 85%) received chlorambucil at a dose of 2 mg, PO, every other day. Eight percent of the cats experienced no response. There was no association between any risk factors and response to therapy. Overall median remission duration was 948 days. Partial response to therapy was associated with shorter remission duration (P = 0.002). Overall median survival time was 704 days. No factors were significantly associated with survival time. Interestingly, 78% of cats tested in this study had hypocobalaminemia, which was associated with short remission duration, but only in the univariable analysis. Thus supplemental cobalamin (0.5ml SC q 2-3wks) and folate should be given as required. Lymphoblastic lymphoma, is much more aggressive than lymphocytic lymphoma, is generally treated with combination chemotherapy, and carries a poor prognosis.

Given the dramatic differences in outcome of lymphocytic vs. lymphoblastic lymphoma is there any way to distinguish these forms of the disease without a biopsy?

In the study of Fondacaro et al clinical signs, physical exam findings and endoscopic localization of disease overlapped in cats with lymphoblastic and lymphocytic lymphoma. Lethargy and the presence of an abdominal mass tended to be more frequent in cats with lymphoblastic lymphoma.

Can I diagnose intestinal lymphoma with an endoscopic biopsy?

Yes and No! Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can miss submucosal and serosal lesions or yield a diagnosis of “lymphoplasmacytic enteritis”. Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy circumventing the endoscopy surgery debacle. Diagnosis also depends on the pathologist! Some pathologists are unwilling to diagnose lymphoma on endoscopic biopsies.

How can I distinguish gastrointestinal lymphoma from inflammatory bowel disease?

The signalment, clinical presentation, physical examination and results of clinical investigation are often very similar in cats with IBD and alimentary lymphoma. Hypoalbuminemia is a rare feature of IBD in cats and it’s presence makes me think of high grade IBD or lymphoma. Intestinal perforation should place lymphoma high up the list. Concurrent renomegaly or splenomegaly should also prompt consideration of lymphoma and aspiration/biopsy. The presence of intestinal thickening, muscularis hypertrophy and mesenteric lymphadenpoathy is consistent with IBD and lymphoma. Moreover, fine needle aspiration of enlarged lymph nodes can yield reactive hyperplasia in cats with GI lymphoma. Endoscopy may reveal marked thickening of the gastric mucosa and increased friability of the intestinal mucosa in cats with lymphoma, but there is an overlap between cats with IBD and alimentary lymphoma. At the present time the accurate distinction of GI lymphoma from IBD relies on histopathological evaluation. This can be relatively straightforward where biopsies are considered adequate in size and number, and unequivocal lymphoblastic cells or a monomorphic population of small lymphocytes are present. However, some biopsies display features of lymphoma and IBD, and others such as endoscopic biopsies do not allow thorough evaluation of all tissue compartments, and make it difficult to distinguish IBD from lymphoma. Immunophenotyping for T and B cell lineage, and PCR to detect clonal expansion of B (feline immunoglobulin heavy chain variable region genes) and T cells (T cell receptor gamma variable region genes) have been developed to aid this process.

What is driving the development of feline alimentary lymphoma?

Low-grade alimentary lymphoma in cats does not appear to be related to FeIV or FIV. There is strong evidence in people that low grade mucosa associated lymphomas develop as a consequence of a genetic predisposition (typically chromosomal translocations that impact mucosal inflammation or apoptosis) and a chronic infections with bacteria and viruses are increasingly associated with lymphoma. In people, infections with *Helicobacter*, *Borrelia*, *Chlamydia* and *Campylobacter* are associated with gastric, cutaneous, periocular and intestinal B cell MALT-lymphomas, respectively. The observation that 8-13% of people with celiac disease develop non-Hodgkin's enteropathy-associated T cell lymphoma is of high relevance to cats with alimentary lymphoma. Lymphomatous transformation in celiac disease is associated with unresolved chronic lymphocytic inflammation, villus blunting, an IL-6 and IL-8 rich cytokine environment, and global shifts in the enteric polymicrobial environment, towards proteobacteria and *E.coli*. We have established that cats with lymphoplasmacytic enteritis have shifts in mucosal Enterobacteriaceae, *E. coli*, and *Clostridium* spp. that correlate with abnormalities in mucosal architecture (principally atrophy and fusion), proinflammatory cytokine upregulation (IL-1, -8 and -12), and clinical severity, that parallel human coeliac disease. In preliminary studies, we found that the mucosal cytokine environment in feline

alimentary lymphoma is dominated by IL-6 upregulation, and have detected invasive bacteria in 14/17 large cell lymphomas (a mix of T and B cell lymphomas) and 6 of 33 small cell lymphomas (T cell) relative to 0/18 controls.
While it is well established that persistent viral infections can drive lymphoma in cats, the relationship of FeLV to alimentary lymphoma in cats is controversial, with discordance between antigenemia (0-38%) and PCR positivity of tissues for viral sequences. It is conceivable that latent FeLV infection drives feline alimentary lymphoma, but this possibility has to be weighed against the falling prevalence of FeLV in the cat population. In people a variety of viruses have been associated with lymphoma including: the γ-herpesvirus Epstein Barr Virus (EBV), which is associated with Hodgkin's lymphoma and various non-Hodgkin's lymphomas, including B-cell lymphoma in immunocompromised patients, Kaposi Sarcoma herpesvirus in individuals with immunosuppressive conditions, Human T-cell Leukemia Virus-I with Adult T-cell leukemia-lymphoma (ATLL), a peripheral T-cell malignancy and Hepatitis C virus (HCV), which has been implicated in the development of some cases of non-Hodgkin lymphoma (NHL). Recent studies have expanded our knowledge of the role that viruses may play in promoting chronic intestinal inflammation, which is a known risk factor for tumorigenesis . A new dimension in understanding the multifactorial basis of chronic inflammatory diseases such as Crohn's disease has emerged from the discovery that a virus trigger (norovirus) is required to observe intestinal abnormalities in IBD susceptible *Atg16l1*HM mice. Mucosal inflammation depended on the presence of the intestinal microbiome and pro-inflammatory cytokines. Thus, variations in a host autophagy gene, exposure to a specific virus and the microbiome can act together to trigger intestinal inflammation in mice that is similar to that in patients with Crohn's disease.

Taken as a whole, the evidence to date supports the possibility that an underlying bacterial or viral infection could be involved in the etiopathogenesis of feline alimentary lymphoma

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Diagnosis & Management of Feline Diabetes Mellitus

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Pathophysiology of Diabetes Mellitus

Diabetes mellitus (DM) is a common endocrine disease in cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition the lack of insulin results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism. Factors that have been identified as predisposing factors in cats include obesity, advancing age and being male.

Two types of DM are recognized in man, and these classifications can be applied to the disease in cats. Type I DM (insulin dependent diabetes mellitus) is due to an absolute deficiency of insulin. Chronic pancreatitis is believed to be a common cause of Type I DM in cats. Other histopathology changes reported include islet specific amyloidosis and beta cell degeneration. Type II DM (non-insulin dependent diabetes) is characterized by an abnormal pattern of insulin secretion in combination with peripheral insulin resistance, and results in a stable reregulation of the blood glucose concentration at a higher concentration. The two types of diabetes are classically distinguished by characteristic responses to challenge by insulin secretagogues such as glucose, glucagon, or arginine. In type I DM, there is a decreased or negligible secretion of insulin compared to normal animals, whereas in Type II DM, total insulin secretion may be normal or increased, although the pattern of secretion may be abnormal and the amount of insulin is insufficient to prevent hyperglycemia. The phenomenon of glucose toxicity complicates interpretation of glucagon tolerance tests in cats however, and the glucagon tolerance test is of little practical utility in clinical practice. Classification of diabetic cats as either insulin dependent or non- insulin dependent is more helpful clinically, recognizing that some cats can transition between the two states. Factors that likely influence the need for exogenous insulin in individual cats include the severity of pancreatic pathology, whether the pancreatic pathology is progressive or static, presence of concurrent disease that results in peripheral insulin resistance, presence of obesity, the caloric content of the diet and the ability of treatment to result in good glycemic control.

Diagnosis

The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss), and documentation of hyperglycemia and glycosuria. In cats the diagnosis may be complicated by stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document persistent hyperglycemia and glycosuria, but also to rule out other diseases that may cause similar clinical signs such as hyperthyroidism and gastrointestinal disease. Measurement of fructosamine concentrations or urine glucose of samples collected in the home environment may allow the clinician to distinguish between stress induced hyperglycemia, and persistent hyperglycemia due to diabetes mellitus. It is however important to remember that other diseases such as hyperthyroidism can also influence the fructosamine concentration. Glucosuria in cats may also be secondary to ketamine anesthesia, chronic renal failure, and post-obstructive diuresis so is not on its own diagnostic for diabetes mellitus. The presence of significant ketonuria and concurrent hyperglycemia is diagnostic for diabetes mellitus in cats.

Because most diabetic cats initially have type II diabetes mellitus, up to 70% of cats may go into diabetic remission if they achieve good glycemic control. Unfortunately, it is difficult to predict which cats are likely to go into diabetic remission. The glucagon tolerance test is not useful in predicting whether or not a cat is likely to go into remission.

Insulin Therapy

Classification of Insulin

It is very important for clinicians prescribing insulin to understand the characteristics of the different products that are commercially available. Insulin may be classified by insulin source, insulin formulation, or duration of action. Not all forms of insulin are currently commercially available and product availability is constantly changing. Insulin formulations that have been available historically include short duration regular insulin (designated R), moderate duration NPH insulin (designated N), moderate duration Lente insulin (designated L), and Long duration PZI insulin. Insulin may be derived from bovine, porcine, or human recombinant sources and the concentration may be either 100 units/ml (human products) or 40 units/ml (veterinary products). A number of human recombinant insulin analogues are also available. The insulin products that are currently available in the US are listed below:

Insulin Products Currently Available Commercially and Used in Cats

Short acting:
Regular insulin (Zinc insulin crystals)
Products: Humulin R [Lilly], Novolin R [NovoNordisk] Both human recombinant.100 U/ml

Moderate acting:
NPH insulin (neutral protamine hagedorn)
Products: (Humulin N [Lilly] , Novolin N [NovoNordisk] Both human recombinant 100 U/ml
Lente insulin (70% Ultralente and 30% Semilente)
Product Vetsulin (Merck) pork 40 U/ml

Long acting:
PZI insulin
Insulin complexed with protamine and zinc.
Product: ProZinc [Boehringer Ingelheim] human recombinant (40 U/ml)
Glargine
Insulin analogue
Products: Lantus [Sanofi-Aventis], human recombinant (100 U/ml)
Detemir
Insulin analogue
Products: Levemir [NovoNordisk], human recombinant (100 U/ml)

There are three insulin products that are appropriate for first line treatment of diabetes mellitus in cats, Protamine zinc insulin, Lente insulin, and Glargine insulin. NPH insulin tends to have a very short duration of action in cats and is not recommended asa first line insulin.

PZI insulin (ProZInc)

There have been two large studies published regarding the use of PZI insulin in cats, one using Beef/pork PZI insulin (PZIVet) and the other using human recombinant PZI insulin (ProZinc). Both studies demonstrated good glycemic control in 85-90% of diabetic cats. Both newly diagnosed cats and cats that had had poor control with other insulin products were included in these studies. In the most recent study of 133 diabetic cats (120 cats with newly diagnosed DM, and 13 cats previously treated cats), PZI insulin was effective in decreasing BG concentration and improving clinical signs in 85% of the cats within 45 days of initiating treatment. All cats were treated with PZI twice daily, and the starting dose was 0.22 – 0.66 U/kg/injection. The mean insulin dose was 0.59 U/kg/injection at the end of the study (day 45). The nadir of the blood glucose occurred at 5-7 hours post injection. Hypoglycemia occurred in 22% of the cats and sometimes occurred even when very low insulin doses were used. For this reason it is recommended that the starting insulin dose should be conservative (1U/cat/injection) with subsequent dose increases made based upon clinical response to treatment and blood glucose curves.

Insulin Glargine (Lantus)

Glargine insulin is a long acting insulin analogue that has also been used for treatment of diabetes mellitus in cats. The pharmacokinetics of insulin glargine is very similar to that of PZI although the time to insulin nadir is longer. In a study of 13 diabetic cats fed a commercial high protein low carbohydrate diet and treated with either once daily Glargine insulin at a dose of 0.5 U/kg once a day or lente insulin (human recombinant) 0.5 U/kg, twice a day, there was a significant improvement in both groups of cats and no difference was detected in glycemic control between the two insulin groups. Of the four cats in remission at the end of the study, 3 had been treated with lente insulin and one with glargine. In a study of 24 newly diagnosed diabetic cats, treated with glargine, PZI, or lente, and fed a low carbohydrate high protein diet, glargine treated cats tended to have lower blood glucose concentrations and fructosamine concentrations than those treated with PZI or Lente. In this study there was a higher rate of diabetic remission rate in the cats treated with Glargine insulin than in the cats treated with PZI or lente insulin.

Pork Lente Insulin (Vetsulin)

Pork Lente insulin has been used successfully in cats in Europe for several years and is now approved by the FDA for use in cats. Vetsulin is pure pork insulin which has an intermediate duration of action, although it has a shorter onset and duration in cats than in dogs. The time from injection to to the BG nadir is 4 hours and the duration of effect (time for BG to return to baseline) is approximately 10 hours, so Lente insulin should be administered twice daily in cats. The starting dose for lente insulin in cats (0.25 -0.5 U/kg/injection) is similar to that of other insulins, and the median dose required for good glycemic control in a group of diabetic cats was 0.5 U/kg. In this same study 7 of 25 cats went into diabetic remission during the 12 months of the study and all the cats that remained diabetic had good or excellent control at the conclusion of the study. In a study of 90 cats with diabetes mellitus, 41 cats were treated with Lente insulin and 23 (53%) went into diabetic remission.

Insulin Treatment for a New Diabetic Patient

The starting dose for insulin in a new feline diabetic patient is 0.25 – 0.5 Unit/kg or 1-3 U/cat. It is recommended that PZI and Glargine insulin are both started at the lower end of this dose. It is difficult to predict in advance which cats will do better with which insulin formulation. Cats should be carefully monitored for occurrence of hypoglycemia, because of the possibility of remission of diabetes mellitus in the cat. A blood glucose curve should be performed 7-14 days after making any change in insulin formulation. Whichever insulin formulation is chosen, twice a day insulin therapy is more likely to result in good glycemic control than one a day therapy. If twice a day treatment is not possible once a day therapy with PZI or Glargine can result in effective control of clinical signs in some cats.

Diabetic Remission

A unique feature of diabetes mellitus in cats is that some diabetic cats become non-insulin dependent after treatment has been initiated. Some 15 to 70% of cats with DM, have been reported to go into spontaneous clinical remission, after initiation of insulin treatment. This is termed diabetic remission. Diabetic remission is typically defined as normoglycemia that persists for greater than 4 weeks without the use of exogenous insulin, although some studies have used a period of 2 weeks. The duration of remission is variable with some cats requiring insulin treatment again within a few weeks to months and other cats remaining in remission for months to years. Factors that have been hypothesized to influence the likelihood of diabetic remission include the duration of diabetes mellitus, whether the cat initially presented in a ketoacidotic crisis, the carbohydrate content of the diet, the type of insulin used for treatment, the breed of cat, the presence of underlying disease, and how closely the blood glucose is maintained within the normal range with insulin treatment. Stimulation tests with secretagogues such as glucagon and arginine have also been investigated to identify cats with residual insulin secretion from the pancreas, however the presence of glucose toxicity in cats complicates interpretation of these tests and they have not proved useful in predicting the likelihood of remission.

Influence of Diet

It has been proposed that low carbohydrate diets increase the chance of diabetic remission in newly diagnosed diabetic cats. A prospective study comparing a low carbohydrate-low fiber diet to a moderate carbohydrate-high fiber diet in 63 diabetic cats showed improvements in glycemic control in both groups, but there was a higher rate of remission of diabetes mellitus in the low carbohydrate-low fiber diet. These findings support the clinical opinion that low carbohydrate diets in conjunction with good glycemic control increase the likelihood of diabetic remission. If diabetic remission occurs in cats it is most commonly in the first few months of treatment.

Influence of Insulin

It has been shown that strict glycemic control is important in achieving diabetic remission and it is clear that diabetic cats can go into remission with any insulin if good glycemic control is achieved. It is currently unclear whether some insulin formulations are more likely to result in remission than others, or whether the critical factor is the glycemic control itself. In a study of 24 newly diagnosed diabetic cats, treated with either glargine, PZI, or lente insulin, and fed a low carbohydrate high protein diet, there was a higher rate of diabetic remission in the cats treated with Glargine insulin than in the cats treated with PZI or lente insulin; however a larger study showed only a small difference in remission rates between cats treated with Glargine insulin versus Lente insulin.

Influence of Clinical Presentation

Although presentation in a diabetic ketoacidotic crisis is believed to be more common in cats with type I than type II diabetes mellitus, suggesting that few cats with DKA should go into remission; a recent study documented that some cats that initially presented with ketoacidosis can go into remission if they achieve adequate glycemic regulation and concurrent illness is resolved.

Other Factors

Other factors that have been documented to increase the likelihood of diabetic remission in cats include short duration of diabetes mellitus (< 180 days), administration of glucocorticoids prior to diagnosis, low insulin dose required to achieve glycemic control, and lack of polyneuropathy. Age, sex, body weight, presence of renal failure, presence of hyperthyroidism, or presence of obesity at diagnosis have not been shown to influence the likelihood of remission. Serum concentrations of glucose, fructosamine, insulin, glucagon, and insulin growth factor I are not different between cats that do and do not achieve remission, but cats achieving remission have a higher glucagon to insulin ratio.

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Diabetic Ketoacidosis: Understanding Pathophysiology is Critical to Treatment

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Pathophysiology of Ketoacidosis

Diabetes mellitus (DM) is a common endocrine disease in cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition the lack of insulin results in increased hepatic gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism.

If a diabetic cat is not treated or receives inadequate insulin therapy, it will eventually develop ketoacidosis. Some apparently previously well-controlled diabetic patients may also become ketoacidotic because of stress, illness, or estrus. The metabolic derangements that occur in DKA are similar but more severe than those that occur in the uncomplicated diabetic. Factors that are thought to predispose to the development of DKA, in addition to lack of insulin, include excess diabetogenic hormones (in particular hyperglucagonemia), fasting, and dehydration. Hyperglucagonemia is currently thought to be primarily responsible for ketonemia. The combination of insulin deficiency and glucagon excess stimulates peripheral lipolysis, resulting in increased plasma fatty acid concentrations. Plasma fatty acids are normally converted to acetyl coenzyme A by the liver which is then converted into triglycerides or shunted into the citric acid cycle for production of protein, glucose or glycogen. In the presence of high glucagon concentrations, fatty acids are converted to acetoacetyl coenzyme A, which in turn is converted to acetoacetic acid. Acetoacetic acid may then be converted to acetone and betahydroxybutyric acid. Ketones are metabolized by many tissues and can serve as a short-term source of energy; however production in excess of utilization results in metabolic acidosis and osmotic diuresis due to ketonuria. Dehydration, electrolyte depletion, vomiting and diarrhea then follow. Pre-renal azotemia and hyperosmolality may be further complications. These derangements are progressive and will eventually result in death if not treated.

Other diabetogenic hormones such as growth hormone and glucocorticoids also predispose to ketoacidosis. The secretion of these hormones may be increased by infection, fasting and other disease states. Dehydration will potentiate the effects of other disease states since this causes a decrease in GFR and a loss of the ability to excrete glucose or hydrogen ions.

Signalment and Clinical Signs of Ketoacidosis

Because DKA is most commonly associated with a new diagnosis of diabetes mellitus, the signalment for cats with DKA is similar to that for other presentations of DM. In a study of 104 newly diagnosed diabetic cats, ketoacidosis was present in 40% of cats. In another study of 42 cats with ketosis or ketoacidosis, diabetes mellitus was newly diagnosed in 26 cats, and previously diagnosed in 16 cats. Historical findings may include a classic prior history for diabetes mellitus, and often a history of recent concurrent illness such as bacterial infection. Studies suggest that concurrent disease is present in up to 93% of cats with diabetic ketoacidosis. The time interval from initial clinical signs of DM to development of DKA is very variable and ranged from 2-52 weeks in one study; however once clinical signs of ketoacidosis begin, severe illness occurs quite rapidly. In a study of ketoacidotic cats, the median time from development of systemic signs to hospitalization was 2 days (range 1-14).

Severe DKA is characterized by fairly rapid onset of lethargy, anorexia, adipsia, vomiting, and diarrhea. Other historical findings may also be present depending on the presence of concurrent disease. Physical examination may reveal depression, dehydration, weakness, tachypnea, abdominal pain and sometimes an odor of acetone on the breath. A thorough physical examination is very important not only to establish severity of ketoacidosis but also because of the high incidence of concurrent diseases in these patients. Concurrent diseases common in ketoacidotic cats include hepatic lipidosis, cholangiohepatitis, chronic renal failure, infection, neoplasia, and pancreatitis. The prognosis for animals with diabetic ketoacidosis often depends upon the severity and appropriate treatment of underlying disease.

Laboratory Abnormalities

The minimum database for a cat with suspected DKA should include a urinalysis and urine culture, CBC (or PCV, total protein, WBC estimate), blood glucose, BUN, creatinine, electrolytes (sodium, potassium, chloride, phosphorus), and total CO2 (+/- blood gas). Other diagnostic testing is dependent on the history and physical examination. The CBC may reveal leukocytosis or hemoconcentration, and the blood glucose may be as high as 1000 mg/dl depending on the severity of the volume depletion and decreased GFR. BUN and creatinine are commonly increased due to pre-renal azotemia or concurrent renal disease. Hyper- or hypo-natremia may occur although hyponatremia is more common due to hyperosmolality (dilutional hyponatremia), and loss of sodium in the urine by osmotic diuresis. Overall body stores of potassium are usually depleted in DKA but the measured serum potassium is usually normal or increased due to metabolic acidosis, lack of insulin, and hyperosmolality, all of which tend to tend to drive potassium extracellularly. Treatment of DKA will drive potassium back into cells and profound

hypokalemia may therefore occur during treatment. Severe hypokalemia may be life threatening and requires immediate treatment. Some diabetic patients may be truly hyperkalemic due to concurrent acute renal failure or Addison's disease. Hypophosphatemia may also occur in DKA and is also exacerbated by insulin therapy. Hypophosphatemia may cause mental confusion, seizures, decreased myocardial contractility, respiratory failure, and hemolytic anemia, and requires immediate treatment. Hypomagnesemia has been reported in cats with diabetes mellitus; however the clinical significance of this finding is unclear at this time. In one study of cats with a variety of disorders, hypomagnesemia was associated with increased morbidity and mortality.

A urinalysis will confirm the presence of glucose and ketones. Urine should also be evaluated for the presence of inflammation and a sample should be submitted for bacterial culture. The specific gravity will allow differentiation of renal from prerenal causes of azotemia, although high concentrations of glucose and ketones in the urine increase the specific gravity.

Serum osmolality may be increased in patients with severe DKA and correlates well with the level of consciousness. Osmolality is not commonly directly measured but can be calculated from the following formula.
Osmolality = 2 (Na+K) + 0.05 (Glucose) + 0.33 (BUN)
(Where Na and K are measured in mEq/l and Glucose and BUN are measured in mg/dl.)

Most patients with DKA is not hyperosmolar because of concurrent hyponatremia, however some individuals do have life threatening hyperosmolality (> 350 mg/dl). Some non-ketotic diabetic patients may also develop severe hyperosmolality.

Hyperosmolar Nonketotic Diabetes Mellitus

This is an unusual complication of DM characterized by severe hyperglycemia, hyperosmolality, and azotemia, with minimal ketosis or acidosis. In these patients the osmolality becomes so high that it results in depressed CNS function. Lethargy, depression, and impaired water consumption then lead to severe vascular volume contraction, and azotemia, which worsens the hyperglycemia and hyperosmolality. The lack of ketonuria is not well understood. Clinically these patients present with severe dehydration, depression, weakness, and shock.

Treatment Healthy Ketoacidotic Patient

In some patients with mild DKA clinical signs are mild or absent and metabolic acidosis is mild. In these cases aggressive therapy is not necessary, however regular rather than long acting insulin should be administered because of its increased potency. Insulin should be administered SC q 8 hours with a meal (1/3 caloric requirements) until ketonuria resolves. At this point longer acting insulin treatment can be initiated.

Treatment of Severe Ketoacidosis

The goals of therapy in DKA are to;

1. Restore water and electrolyte losses
2. Provide insulin and a carbohydrate substrate
3. Correct acidosis
4. Identify and treat precipitating causes and concurrent disease

Fluid Therapy

Fluid therapy should be started as soon as possible after presentation, preferably via a jugular catheter. The fluid rate should be calculated based on an estimate of dehydration, presence of ongoing losses and a maintenance rate that accounts for persistence of osmotic diuresis. In most cases the fluid of choice is normal saline or a balanced replacement solution (Plasmalyte R or Lactated Ringers) with potassium, phosphorus, and dextrose supplementation as necessary. Hydration status should be monitored frequently (q 8 hours) and fluid rate adjusted accordingly. Response to fluid therapy should be assessed by clinical response, and measurement of central venous pressure, bodyweight and urine output. Patients should also be monitored carefully for the development of pulmonary or cerebral edema. The amount of potassium added to the fluids depends upon the serum K concentration; however, the total hourly K administration should not exceed 0.5 mEq/kg body weight (Table 1).

Table 1. Electrolyte Supplementation

Serum Potassium Concentration (mEq/L)	Potasssium Chloride Dose
> 3.5 (maintenance)	0.05–0.1 mEq/kg/H
3–3.5	0.1–0.2 mEq/kg/H
2.5–3	0.2–0.3 mEq/kg/H
2–2.5	0.3–0.4 mEq/kg/H
< 2	0.4–0.5 mEq/kg/H
Serum Phosphorus Concentration (mg/dL)	**Potassium Phosphorus Dose**
2–2.5	0.03 mmol/kg/H
1.5–2	0.06 mmol/kg/H
1–1.5	0.09 mmol/kg/H
< 1	0.12 mmol/kg/H

Phosphorus supplementation (potassium phosphate) is indicated if serum P decreases < 1.5 mg/dl or if clinical signs of hemolysis are detected (Table 1). Addition of potassium phosphate to the fluids does not always prevent development of hypophosphatemia. Hypophosphatemic patients should be monitored for complications of hypophosphatemia such as hemolytic anemia.

Insulin Therapy

Over-aggressive therapy that results in rapid changes in blood glucose, osmolality, potassium or phosphorus concentrations or acid base balance should be avoided. The ideal mode of treatment is to administer small doses of regular insulin, frequently. The aim is to slowly decrease the blood glucose to 150 - 250 mg/dl over about 8 hours. Ketosis can take up to 48 hours to resolve. Low dose insulin therapy accomplishes the goals of therapy without the risks of correcting hyperglycemia too quickly. Insulin may be administered either intramuscularly or intravenously. If using the IM protocol, insulin is administered at an initial loading dose of 0.2 U/kg then at a dose of 0.1 U/kg hourly. The blood glucose should be monitored every hour prior to the next dose of insulin and should ideally decrease by no more than 50 - 100 mg/dl per hour. Once the blood glucose drops to <250 mg/dl the frequency of insulin administration can be decreased to q 4 - 6 hours IM or SC if hydration is adequate (dose 0.1 - 0.4 U/kg with adjustments based on blood glucose). For the IV protocol, insulin should be given at an initial rate of 1.1 U/kg/24 hrs diluted in 250 ml 0.9% saline and administered through a separate line with an infusion or syringe pump at an initial rate of 10 ml//hour (0.05 U/kg/h). The rate is then adjusted based on hourly measurements of blood glucose (see Table 2). Once the blood glucose drops below 250 mg/dl the insulin can then be administered SC as described above. Dextrose (2.5% - 5%) should be added to the fluids to decrease the risk of hypoglycemia, once the blood glucose decreases below 250 mg/dl. Longer acting insulin should not be instituted until the patient is bright and alert, eating, and ketosis has resolved. In one study using an intravenous insulin protocol, ketonuria resolved within 6 –72 hours.

Table 2. CRI Infusion of Insulin Solution

BG Concentration (mg/dL)	IV Hydration Fluids	Rate of Insulin Solution (mL/H)
> 250	0.9% saline	10
200–250	0.9% saline + 2.5% dextrose	7
150–200	0.9% saline + 2.5% dextrose	5
100–150	0.9% saline + 5% dextrose	5
< 100	0.9% saline + 5% dextrose	Discontinue

A protocol using a combination of IM and SC glargine insulin has also been reported to be effective in resolving ketoacidosis in cats.

Bicarbonate Therapy

Specific treatment of metabolic acidosis is usually not necessary since treatment of the underlying cause (ketonemia) will resolve the acidosis and in addition ketones will be metabolized to bicarbonate. Additionally, paradoxical CNS acidosis, metabolic alkalosis, and decreased oxygen delivery to tissues are potential complication of bicarbonate administration. If the serum bicarbonate concentration falls below 10 mEq/l, or the pH is less than 7.0, specific treatment with sodium bicarbonate is necessary since this degree of acidosis causes insulin resistance and can itself be life threatening. Half the calculated dose of bicarbonate (given below) should be added to the fluids and administered over 6 hours. If the acidosis is severe and acutely life-threatening the dose may be administered slowly IV.

Dose bicarbonate (mEq) = body weight (kg) x 0.4 x (12-patients bicarb)

It is important that correction of acidosis is done slowly, since overcompensation or rapid correction may cause metabolic alkalosis, paradoxical cerebral acidosis and a shift to the left of the oxygen dissociation curve, thereby limiting oxygen delivery. Cerebral acidosis results from rapid correction of plasma acidosis with the generation of carbon dioxide. Most of the CO_2 is removed by the lungs but some diffuses across the blood-brain-barrier, recombines with water and generates hydrogen ions in the brain. Clinically these dogs will show progressively worsening of neurologic signs despite therapy.

Identify and Treat Precipitating Factors

If a source of infection is found, appropriate antibiotic therapy is indicated. In cases in which infection is suspected but not proven, antibiotics may be used empirically. Treatment of other concurrent disease states such as pancreatitis and hyperadrenocorticism, must also be initiated as soon as possible so that DKA does not recur. In one study of ketoacidotic cats, ketoacidosis recurred in 42% of the cats that survived the initial episode. Testing for hyperadrenocorticism should be delayed until signs of DKA have resolved and patients are systemically well. If patients do not respond rapidly to treatment of DKA or have clinical signs that suggest additional diseases other than diabetes mellitus, an aggressive search should be made for other concurrent disease. Additional testing that may be indicated in individual patients includes thoracic radiographs to evaluate for congestive heart failure, neoplasia, pneumonia, and dirofilariasis; abdominal radiographs and ultrasound to identifiy pancreatitis, pyometra, or urolithiasis; and blood cultures if septicemia is suspected.

Prognosis

In one study of 114 newly diagnosed diabetic cats the median survival time was 516 days (range 1-3,468 days). Ketoacidosis was diagnosed in 39 cats and presence of ketoacidosis was not associated with survival. Thirty two percent of cats with ketoacidosis survived > 3 years.

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Managing the Feline Diabetic: Picking a Protocol

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Introduction

Diabetes mellitus (DM) is characterized by persistent hyperglycemia, secondary to relative or absolute insulin deficiency. In people, diabetics are classified as Type I (insulin-dependent) or Type II (non-insulin dependent). Type I diabetes is the result of an immune attack on the β islet cells or chronic pancreatic inflammation, whereas Type II diabetes is related to obesity and insulin antagonism. Many feline diabetics share some of the features of Type II diabetic humans.[1]

Starting a feline patient on a treatment plan can be complicated, and several factors need to be considered. These include dietary factors, insulin type and frequency of administration, monitoring methods, concurrent medical disorders, and the likelihood of diabetic remission. Oral hypoglycemic agents are widely regarded as an inappropriate choice for symptomatic diabetics, but may be considered in rare situations. Ultimately, a successful outcome requires careful planning and effective communication with the cat owner. Goals and expectations should be discussed early and a team approach emphasized.

When faced with a new diabetic, I try to decide if the cat is a likely candidate for remission (defined below) as this substantially impacts my initial approach. Remission is most likely to occur within the first 90 days of diagnosis; this is a precious window of time and should be used wisely. If remission is unlikely or a client is not interested /able /willing to head in this direction, my treatment plan is less intense. For those patients, my goals are to simply mitigate the clinical signs of DM with minimal risk of hypoglycemia.

Managing the feline patient with diabetic ketoacidosis is a separate issue, and will not be reviewed in this lecture.

Patient Evaluation

History

Most cats are diagnosed with DM when the owner becomes aware of polyuria and polydipsia. This indicates that the renal threshold for the reclamation of glucose in the proximal convoluted tubule has been exceeded; this varies from cat to cat, but usually occurs when the blood glucose (BG) is about 240-280 mg/dl. Bear in mind that many cats spend some time in a pre-clinical diabetic state, in which BG is above the reference range but the renal threshold has not been exceeded. At the time of diagnosis, some cats have measureable weight loss, although the body condition score is likely to be robust.

As certain drugs are associated with insulin resistance, a thorough review of current medications is essential. If possible, glucocorticoids should be discontinued (tapering may be necessary with chronic use); progestins such as megestrol acetate should also be discontinued.

Dietary history is also key… we need to know the type of diet (dry v canned), amount fed, frequency of feeding (meal v free choice), and the formulation (% protein, fat and carbohydrate). In addition, any specific dietary requirements should be identified (e.g., highly digestible, high fiber, limited antigen, under-saturated to prevent crystalluria, etc.). In multiple cat households, dietary requirements of other cats may limit or complicate the feeding plan for the diabetic patient. Getting a thorough understanding of the current feeding practices, and communicating effectively with all members of the household who are involved in the feeding process is essential.

Physical Examination

A thorough physical examination is necessary, as concurrent disorders need to be identified. Body condition score should be noted, along with an assessment of overall musculature. This information is needed to determine a target body weight for the patient.

Particular attention should be paid to the mouth, teeth, gingiva, etc. Chronic inflammatory diseases can cause substantial insulin resistance and the mouth is a classic site for low grade infection and inflammation. A cat with substantial periodontal disease is less likely to go into remission, unless this issue is effectively and promptly addressed.

Also, carefully evaluate the cat for signs of a peripheral neuropathy. These may be subtle, such as difficulty jumping up or limited ability to 'tip-toe.' It may be necessary to put the cat on the floor to fully assess its ambulation. Evidence of a peripheral neuropathy at the time of diagnosis suggests a prolonged pre-clinical state and associated 'glucose toxicity'. This term is used to describe the effect of sustained hyperglycemia on various tissues. Diabetic neuropathy is a classic example of glucose toxicity. Ironically, another organ markedly impacted by sustained hyperglycemia is the pancreas. The insulin secreting cells in the β islets actually undergo apoptosis (a self-triggered cell death) after just 10 days of experimental hyperglycemia.[2] In cats with spontaneous DM, the exact same process occurs. However, along with apoptosis we also get islet shut-down. Essentially, some cells simply go underground and stop making insulin. If BG is kept below 225 mg/dl, these cells may return to function. If hyperglycemia persists

for long periods (2 months appears to be a key time) then these cells may opt for apoptosis and are lost forever. The concept of glucose toxicity is central to attempts to induce diabetic remission. If we can control BG before all the islet cells die, we may restore insulin secretion.

Laboratory Evaluation

A standard evaluation to establish baseline data and identify concurrent disease should include a CBC, serum biochemical profile with electrolytes, urine analysis and culture, and measurement of total T4. A free T4 should be considered in any cat with a total T4 close to the upper end of the reference range. If the patient's history includes any suggestion of chronic pancreatic or gastrointestinal disease, additional tests (e.g., measurement of feline pancreas-specific lipase immunoreactivity (fPLI), folate and cobalamin) may be warranted.

Client Education: Establishing Goals

A comprehensive and frank discussion regarding the management of DM is necessary to determine each client's goals, expectations, resources and motivation. I try to find out as much as I can about the client's relationship with the cat… Is this a valued member of the family? Who is the primary caretaker for this cat? How much time is spent with the cat? Is the cat easy to handle and medicate in the home environment? I also want to know more about owners' perceptions about DM… How familiar are they with this disease? Have they previously cared for a diabetic pet or family member? How challenging will injections be? Are they likely to master home-monitoring protocols? Also, gather information about daily schedules and routines… Is the cat alone all day? Is a twice daily injection regimen a realistic option? How about travelling, eating out, sleeping in…? These factors will all influence my decision-making at this stage.

As a general rule, my goals with any diabetic patient are a satisfied owner, and an animal with minimal signs of hyperglycemia, no signs of hypoglycemia, an appropriate body weight, and a good quality of life. As every diabetic pet is completely dependent upon the owner for essential care, the owner's perception of the animal's status is crucial. I may have some academic idea of a 'successful' diabetic, but my goals are much less important than the owner's.

If a cat is a likely candidate for achieving remission (defined below), setting out with this goal in mind is a realistic plan. With diligent monitoring in the home environment, over 80% of suitable candidate cats will go into remission within the first 6 months.[3] This is not an option for all cats, and not a realistic prospect for all owners. Clients have to be able to follow specific instructions, test BG diligently, and communicate reliably with the veterinary team.

Is Remission Likely? Identifying Suitable Candidates

The ideal candidate for achieving remission is an obese, sedentary cat, on a high carbohydrate diet, who recently received a long-acting steroid injection! This cat has reversible reasons for insulin resistance, and (as long as this cat does not need long-term steroid therapy) is very likely to go into remission with rapid control of BG, effective weight management, and the introduction of a more appropriate diet.

Poor candidates for remission include cats requiring systemic glucocorticoids to manage chronic diseases such as inflammatory bowel disease or asthma. Patients with any chronic disease are generally poor candidates, as the stress of battling heart disease or chronic kidney disease impacts insulin responsiveness. Patients with a history suggesting chronic pancreatitis are also unlikely to achieve a sustained remission, although the DM may come and go based on the level of pancreatic inflammation (which impacts insulin responsiveness and β cell function).

Dietary influences play a huge role in achieving remission, so a cat with substantial dietary restrictions may not be a good candidate.

Insulin Therapy

Type

The range of available insulin products is extensive, but most specialists recommend starting feline patients on insulin glargine or protamine zinc insulin (PZI).[1] Although there is a lente insulin product currently licensed for cats (Vetsulin), this is not a good first choice. I personally prefer to start with insulin glargine, as it is quite predictable and the cost of the insulin and supplies is reasonable, particularly if clients by the 3 ml vials designed for use with the pen delivery device. Syringes for U100 insulins are less expensive (about half the cost) than those for U40 insulins (about $0.25 each on-line). In a recent study, cats started on insulin glargine were substantially more likely to go into remission than cats started on PZI or lente.[4]

I have had good success with insulin glargine in both meal-fed cats and those on ad-lib feeding plans. Cats have a modest but long post-prandial increase in BG, so and the sustained release of glargine from the subcutaneous tissues often results in very stable BG levels.

Insulin Frequency

The frequency of insulin administration will depend somewhat on the individual cat's response to insulin, but may be influenced by the owner's ability to give insulin twice daily. Even with the long acting insulins such as glargine

and PZI, twice daily therapy is usually preferable and is generally the best starting point. Particularly with glargine, twice daily administration keeps the BG consistently in an acceptable range; this is ideal if remission is the goal. However, if an owner simply cannot commit to twice daily injections, glargine may be given once daily.[5]

Dietary Considerations

In the last 15 years, we have gone through a revolution in our thoughts on diet for feline diabetics. We now know that a high fiber diet is not a good choice, and that we need to feed these cats high protein and high fat diets, with <15% of the calories coming from carbohydrates (so called "Catkins").[6] The impact of these dietary changes is profound; they facilitate effective weight loss and are strongly associated with the induction of remission in these patients.[7]

Current theories suggest that the impact of diet is mediated by the incretins.[9] These are hormones released by specialized enterocytes in response to the arrival of nutrients in the small intestine. The presence of the incretins has been known for many decades, but the actual details have only recently emerged. The incretins essentially provide advanced warning to the liver and pancreas that nutrients are arriving, thereby inhibiting hepatic gluconeogenesis and glycogenolysis, and stimulating the release of insulin from the pancreas before these nutrients actually enter the circulation. In addition, the incretins are trophic for the β cells of the pancreatic islets.

In people, carbohydrates are the most potent trigger for incretin release, followed by fat and then protein. In cats, the pattern for incretin stimulation is different. Protein and fat have the most impact, whereas carbohydrates have minimal effect on incretin production. This is likely the reason why the new "diabetic diets" have such an impact on our feline patients. Just by changing the macro-ingredient composition of the diet, we improve insulin production and responsiveness.

Synthetic incretins (aka incretin analogues) are now licensed for use in people with type II DM. Not only do they improve insulin sensitivity, they actually promote the growth of new islet cells. Patients no longer require exogenous insulin to manage their disease. As an aside, the synthetic incretins hold some promise for use in diabetic cats… If they work in cats as they do in people, we may have an option for treating these patients with an agent that actually restores pancreatic function with minimal/no risk of hypoglycemia.

Oral Hypoglycemic Agents: Pros and Cons

Previous reports regarding the use of oral hypoglycemic agents in cats are not very encouraging, although a small percentage of cats given glipizide may achieve euglycemia or go into remission.[10] I personally do not offer this option unless an owner refuses to administer insulin. It is certainly better than nothing under those circumstances, and provides the owner with time to come to terms with the diagnosis and the prospect of giving injections. Glipizide also gives the cat an opportunity to go into remission if insulin resistant disorders are effectively managed. Having said that, a cat with a strong probability of achieving insulin remission is better served with exogenous insulin. This is most likely to reverse glucose toxicity and encourage remaining islet cells to return to function.

If ketones are present at the time of diagnosis, glipizide is a poor choice as it is unlikely to mitigate hyperglycemic in time to prevent diabetic ketoacidosis. In addition, cats must be monitored for drug-related side effects, including icterus and increased hepatic enzyme activity.

Monitoring

Reasons

Regular assessments are needed to appropriately adjust insulin therapy. In cats on track for remission, early identification of hypoglycemia is essential, to prevent clinical compromise or even death. For other patients, my goals may be more modest, but I still rely on monitoring to direct therapeutic decisions appropriately. In particular, adequate information regarding the BG nadir is needed before an insulin dose can be safely increased.

Blood glucose

Without a doubt, regular direct measurement of BG levels is the best way to manage our diabetic cats. As cats are vulnerable to stress hyperglycemia in the clinic environment, home monitoring is the most reliable option and should be encouraged whenever possible. Most owners can learn to do this and rapidly see the advantages for their cat. (A separate lecture is devoted to Home Monitoring… see schedule for details).

If remission is the goal, home monitoring permits rapid and appropriate adjustment in insulin dose. Various protocols for dose adjustment have been published, in which BG is monitored before insulin is given and at one other time in the day; these values are used to adjust the dose as needed. Careful client education is essential, and the veterinarian must feel comfortable with empowering the owner to make the necessary adjustments in the dose. Due to its pharmacokinetics, insulin glargine is particularly well suited for these protocols.

In long standing diabetic cats or those less likely to undergo remission, at home testing still provides essential information for dose adjustment. In these patients, I encourage the owner to 'curve' the cat once a week initially, and then every 4-6 weeks. If the insulin dose is adjusted, the curve should be repeated within 7 days.

Other Options

Surrogates for determination of BG include measurement of water intake +/or serum fructosamine levels. Although an increase in thirst certainly suggests a period of hyperglycemia, the magnitude of this is unclear. In addition, many cats are substantially hyperglycemic (BG >225 mg/dl) before glycosuria occurs… this makes them vulnerable to complications such as a peripheral neuropathy despite apparently acceptable control.

Measurements of serum fructosamine concentrations provide a helpful 'look-back' at BG levels for the previous 2 weeks. However, an acceptable fructosamine result does not confirm adequate control, particularly in cats on intermediate insulins such as Lente (Vetsulin). Additionally, any concurrent disease which impact albumin homeostasis can confuse fructosamine readings. I think that fructosamine measurements are a poor surrogate for direct assessment of BG status and should be used with caution if dose adjustments are needed.

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Diabetes: Home Monitoring

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Introduction

There are several ways to assess diabetic control, including direct measurement of blood glucose (BG), determination of water intake, detection of urine glucose, and determination of glycosylated proteins, such as fructosamines.[1] Undoubtedly, direct measurements of BG are the most useful option, as they let us know the BG nadir, the BG average over the course of a day, and the duration of effect of the insulin. Traditionally, veterinarians have been reluctant to teach owners to monitor BG levels in their diabetic patients at home, and have required them to bring the cat to the hospital for this process. Many of us trained at a time when glucometers were cumbersome and expensive, requiring direct venipuncture in order to obtain enough blood, and are uncomfortable with having owners do this. However, with modern methods, tiny amounts of blood are needed to reliably measure blood glucose (BG) and this procedure can easily be performed by the owner at home.[2,3]

In this lecture, we will review the reasons to promote home monitoring, how to get owners to adopt this option, how to support them in the early stages, and what to do with the data generated.

Advantages of Home-Monitoring of BG

For the Patient

The effect of stress on cats is enormous…they are generally very disturbed by the process of leaving their home environment and being handled by strangers. Even the most sanguine of cats may have a substantial stress response when transported to the clinic. For diabetic patients, the release of stress hormone (most importantly, cortisol) will impact insulin responsiveness.[1] BG data generated in the hospital is often substantially compromised by this response, and is not a reliable reflection of glycemic events in the home environment. Other activities such as eating are often impacted, which again limits the value of the data collected. Failure to recognize the impact of stress hyperglycemia is a common reason for insulin overdose in cats.

For the Owner

Recent studies have looked at quality of life concerns for the owners of diabetic dogs and cats.[4] One of the most consistent worries is hypoglycemia… many owners are very concerned about this possibility and the thought that their cat may be vulnerable to compromise when the owner is absent. Owners who have learned to monitor BG at home are less anxious about this issue, and are able to recognize hypoglycemia and intervene appropriately if the issue arises.

For many diabetic cats, achieving remission may be a realistic treatment goal. To optimize the chances of remission, owners need to be able to adjust insulin appropriately and promptly. Home monitoring facilitates this process, and permits rapid identification of hypoglycemia as remission occurs.[5]

For the Veterinarian

Home monitoring offers enormous advantages from our perspective. Clients can easily generate the data we need to manage our diabetic patients and spare us having to subject a reluctant cat to the misery of a day in the clinic. We do not need to tie up busy staff members to collect samples, and we can trust the information generated in the home. I am often reluctant to increase an insulin dose based on in-clinic data, as I am worried that stress may have impacted our values. With a home monitored patient, I have confidence in the BG values and feel more comfortable increasing the insulin dose. Plus, I have the owner check the effect of the new dose and let me know if we are on target. In addition, we get much longer periods of observation when owners do a curve at home, as they can start earlier and continue until bedtime. It is rare for us to get more than 10 hours of data when a patient is in the clinic.

Routine in-clinic rechecks are still part of the process, but this is a scheduled appointment during which time the patient is examined, data is reviewed and any appropriate testing (urine culture, fructosamine, etc.,) is performed. I try to get owners to come in every 3-4 months, so that we keep fairly close tabs on these patients. The small loss of revenue previously generated by in-clinic curves is easily replaced by these visits, along with the necessary supplies, food, etc.

One of the other big advantages to this system is that quality time is spent with the owner discussing their pet's needs and current status. Because this is a scheduled recheck appointment and not a drop-off, clients are able to spend time with the veterinarian rather than settle for a quick conversation when the cat is collected. The end of the day is often a busy time in the practice, and there is limited opportunity to meaningful interaction.

Getting Started

I try to plant the idea of home monitoring early on, and present it as the standard way of caring for a diabetic cat. If an owner seems task loaded by learning to give injections, I hold off on talking about home monitoring until they feel comfortable with giving the insulin. As soon as this is mastered, I will bring up the idea of home monitoring. It can be very helpful to suggest YouTube and other internet resources for both administration of insulin and collection of BG readings. The Abbott Animal Health website has excellent videos and step-by-step instructions (www.alphatrakmeter.com)

Educating the entire veterinary team on the benefits of home monitoring may improve client compliance. I am often amazed by the power of an enthusiastic endorsement by one of the front desk staff! Many clients make strong relationships with our support staff and are more likely to ask questions in a less intimidating interaction. Along the same lines, have your most patient and kind technician talk the owner through the steps needed to collect the sample and use the device.

It is advisable to try to collect a sample from the cat yourself, away from the owner, before demonstrating the process. This lets you decide which site(s) is best and gives you some idea about how the cat is likely to respond. Most cats barely notice, but for some, it is helpful to distract them with a toy or a treat.

Devices and Equipment

Glucometer

A veterinary validated glucometer is essential.[6] Most machines use an oxidase reaction to determine BG levels, and have to allow for the amount of blood within erythrocytes. The ratio of glucose in solution versus inside RBCs is species dependent, and the algorithm used by the human devices is incorrect in our species. Typically, the BG reading is an underestimation of the real BG value. This error is less significant as BG rises, but can be substantial when BG is around 100 mg/dl. As the nadir is a key piece of information needed to safely adjust insulin therapy and identify the onset of remission, a reliable reading is essential.

Lancets

For some owners, using a lancet is less daunting than using a needle as there is no risk of going too deep. The depth can be adjusted for thicker skinned patients. However, the noise of the lancet can be upsetting to some cats, in which case a 25g needle may be a better choice.

Location

As a general rule, the pinna is the easiest spot in most cats. If using a small lancet, the marginal ear vein is good site, and can be easily seen with a flashlight. If I am using a needle, I tend to get too much blood if I aim for the vein, so instead I go just medial to this structure. If the ear is unsuccessful, the footpads may be a suitable alternative, although some concern has been expressed about the risk of infection.[7] I sometimes use the side of the pisiform pad as this is less likely to routinely contact litter and other contaminated material.

Preparing the Site

Warming the target site with a heated towel or warmed oats may be helpful, as this dilates the superficial capillaries. The area should be not be moistened, as this will invalidate the results.

How often to monitor

If a cat is a likely candidate for remission, BG must be measured at least twice a day so that the insulin dose can be titrated as necessary. However, for cats with long-standing diabetes, such intensive monitoring is generally unnecessary.

As a starting point, I like to have a blood glucose "curve" performed every 4-6 weeks.[1] If the cat is on insulin glargine, the changes in BG over the course of the day can be modest, so we only need to collect a reading every 4 hours. I ask the owner to start collecting data as soon after they get up in the morning as possible, and then continue until bedtime. As most cats are on twice daily insulin, this gives us an excellent idea of what is happening.

If the insulin dose is increased, the owner should check the BG intermittently over the next few days to look for hypoglycemia and then re-do a curve within a week. As glargine is a long acting insulin, I don't increase the dose again until I have a sound sense of what the new dose is doing; this generally takes about 3 days.

Any time the owner thinks there is a change in the cat's status (e.g., drinking more, sleepier, weak, hungry, etc.,) the curve should be repeated.

What to do with the Data

When I first started home-monitoring, I was reluctant to let owners increase the insulin dose without my input. This made me less anxious as I felt that I had more control. However, as I have become more comfortable with the idea of owners making dose adjustments, I often let owners make changes, using very specific instructions. Most pre-teen diabetic children are able to take charge of their disease and control their insulin pumps… I think that our clients are generally just as able to make good decisions for their cats! No matter how competent the owner is, it is

prudent to provide written instructions with very clear directions about when to decrease a dose and when to call you for advice about a dose increase.

Decide ahead of time how you want to be updated. For many of us, an e-mail is the easiest option as we can respond at our convenience. Make it clear exactly what you want to know… it may be helpful to provide some kind of a form or template that owners can use so that you get all the necessary information (current dose, clinical status, concerns, etc.,) along with the BG data.

Troubleshooting

Problems can occur, usually with collection of the blood sample or with the glucometer. Training one of your technicians to be the 'go-to' person with these issues is helpful, as this person is often better able to sort the issue and it does not take up your time.

If the machine is the problem, make sure it is set up correctly with the correct species code for the test strip and that the appropriate controls have been performed. The control solution should be used regularly, and always when a new box of test strips is opened. Make sure the owner has the correct test strips, and has not been tempted to use a cheaper strip.

If the cat is nervous, try silencing the device; most glucometers beep when the strip pulls up the blood and this can be disturbing.

If the owner has problems getting enough blood, try increasing the lancet depth or switch to a 25g needle. Warming the ear can help if the blood drop is persistently smaller than necessary.

Summary

Home monitoring is now becoming a routine management strategy for our feline diabetics. Moving forward with this option lets you provide better care for your patients and better support of their owners. It really is a win-win proposition.

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ICU Boot Camp: What You Should Know on Day One!

Paula Plummer, LVT, VTS (ECC, SAIM)

Infectious Diseases

Infectious diseases are commonly seen in the ICU. Infectious disease is a disease that can be transmitted by a specific kind of contact. There are many infectious diseases that the feline patient can have. They include; parasite, virus, fungal and bacterial. Written protocols should be in place for infectious disease. Proper personal protective equipment (PPE) should be worn with these patients. It should be mandatory for all personnel to follow that plan. The plan should include what PPE to wear, where to house the patient, how to deal with their wounds (if they have any) and how to clean up after them.

Proper cleaning protocols and adhering to them is a must. The author's place of employment uses bleach to wipe everything down and then use a steam cleaner and allow surfaces to air dry each time after treating a known multi drug resistant (MDR) patient. Everything that the infected patient comes into contact with must be cleaned properly.

If the patient has open wounds, transporting patients around the hospital in a designated carrier will help eliminate contamination. Also don't forget to protect patients from nosocomial infections by keeping all wounds and incisions clean, dry and covered at all times when in the hospital.

The veterinary staff wearing gowns, gloves and booties at all times when in contact with the MDR patients and keeping them in a separate ward are common standard protocols for MDR patients. If the patient is considered critical and needs to be in ICU or a fluid ward, proper precautions are made. Proper PPE is worn at all times, they are kept in a cage that is considered a low traffic area, so at our hospital they are kept in the back of the room with an empty cage between them and another patient, just to help establish a barrier. Separate laundry and trash cans are used with MDR labels on them. The laundry is washed separately and the use of laundry detergent with bleach is necessary to properly disinfect the laundry.

A large draped area is placed on the floor in front of their cage so when they need to come out of the cage for exams, treatments they are placed on the draped area and not the floor. That drape is changed at least every 24 hours. If they have open wounds, a designated area should be used to perform examinations and treatments to not contaminate multiple areas of the hospital. Separate instruments, stethoscopes and thermometers are used and kept for these patients. In the author's place of employment, an infectious patient receives a set of instruments while hospitalized that is used on them and when they leave they are disinfected and sterilized. Then you are not using your stuff to monitor the patient and infecting all of your other patients while on your shift.

Keep visitations with owners to a minimum and the owners have to wear proper PPE when visiting. Separate exam rooms are used for these patients. And doing any procedures with a MDR patient should be done at the end of the day so there is time for proper cleaning protocols to take place and to limit the number of patients being exposed.

These are very serious infections and should not be taken lightly, not only are you protecting the other patients in the hospital but you are protecting yourself. Usually veterinary personnel seek medical advice if they know or think they have been infected by the patient. If you think you have been infected by a MDR patient, seek medical attention, do not hide it. If you are immunosuppressed, it may be a good idea to remove yourself from any high risk situations.

Patient Assessment (The following section is adapted from the author's contribution in writing from the VSPN Notebook ®, A CRASH PLAN) (1)

A - Airway

- Evaluate if the patient has a patent airway
- Is there any type of foreign body or obstruction?
  - Use the "finger sweep" method and/or suction to evaluate an obstruction of the airway
  - Use caution if patient is conscious
  - When an upper airway foreign body is present, it is necessary to perform an emergency tracheotomy

B – Breathing

Is the patient breathing?

- No- intubate immediately and start life saving measures
  - Breathe 8-10 bpm for the patient with 100% oxygen
- Yes- evaluate the patient for dyspnea
  - What are the patient's mucous membrane colors?
    (Refer to C-Circulation for descriptions)
  - What is the patient's pulse oximetry status?
    If below 90%, provide oxygen supplementation.
  - What is the patient's Partial Pressure of Oxygen (PaO2) in the arterial blood?
    An arterial/venous blood gas will need to be drawn and evaluated. Values below reflect normal on an arterial blood gas;
    80-110 mmHg = normal
    >80 mmHg = hypoxic
    >/= 60 = initiate oxygen therapy
    *When oxygen concentration is above 21% (room air) the PaO2 values are different.
    The expected PaO2 should be 5 times the fraction of inspired oxygen (FiO2). For example if the FiO2 is40% then a Pa O2 of 200 mm Hg would be considered normal.

- What is the respiratory rate and pattern?
  - Normal- cat 20-30 rpm. In the hospital it can elevate to 40 rpm.
  - Rapid and shallow- also known as choppy or "dys-synchronous" respiratory pattern- pleural space disease
  - Slow and deep- also known as "Kussmaul" respiration- may indicate metabolic acidosis in patients with diabetic ketoacidosis or renal failure

- Postures and patterns that indicate dyspnea
  - High pitched stridor on inspiration - may indicate an upper airway obstruction, i.e. laryngeal paralysis/edema, foreign body aspiration
  - Head Extension- trying to elongate the airway to maximize each breath.
  - Abducted Elbows- allowing more movement from the chest cavity to maximize each breath.
  - Abdominal Breathing- on expiration abdominal muscles will push the remainder of each breath out if the chest wall is not functioning correctly.
  - Cheyne Stokes- normal or hyperventilation followed by periods of apnea or hypoventilation, indicative of a disorder of the central respiratory center.

- Auscultation-
  - Crackles- suggestive of pneumonia, pulmonary edema, pulmonary contusions or fluid overload
  - Muffled- suggestive of pleural effusion, pneumothorax or hemothorax
  - Wheezes- suggestive of feline bronchitis, obstruction, lower airway disease or feline asthma

C- Circulation/Cardiovascular

- What is the patient's mucous membrane color?
  - Pink- normal
  - Cyanotic (blue) - lack of oxygen
  - Icteric (yellow) - liver disease
  - Red- toxins, shock
  - Pale Pink- hemorrhage or anemia
  - Brown- intravascular hemorrhage or acetaminophen toxicity

- What is the patient's circulation status?
  - What percent is the patient dehydrated?
    - Less than 5%- history of fluid loss but no significant findings on physical exam
    - 5%-7%- oral mucous membranes are dry without panting or tachycardia
    - 7%-10%- mild to moderate degree of decreased skin turgor, dry oral mucous membranes, tachycardia with normal pulses.
    - 10%-12%- moderate to severe degree of decreased skin turgor, dry oral mucous membranes, tachycardia and decreased pulse pressure.

        - 12% or greater- severe degree of decreased skin turgor, dry and pale mucous membranes, tachycardia, severely decreased pulse pressure.

- What is the patient's heart rate and rhythm?
    - Palpate pulses
        - What is the patient's pulse quality, and are they synchronous with the heart rate?
            - Pulses should be synchronous with the heart rate
            - Non-synchronous pulses with heart rate can suggest an arrhythmia or obstruction in circulation
    - Perform non-invasive blood pressure
        - Feline normal (mm Hg) - Systolic 100-160, Diastolic 60-90, MAP 80-120.
    - Perform an electrocardiogram; if any abnormalities are found notify the veterinarian on duty immediately.

- Is the patient presenting with a form of shock?
    - Hypovolemic Shock- most common form of shock - due to fluid loss of any type (hemorrhage, volume loss or third spacing of fluids)
        - Clinical signs of feline shock- Clinical signs of the 1st stage not generally seen. 2nd stage (Early Decompensatory Stage)-bradycardia, hypothermia and hypotension, weak peripheral pulses, pale mucous membranes, weakness and general collapse. The 3rd stage (Late Decompensatory Shock)-pale to cyanotic mucous membranes, bradycardia, severe hypotension, weak pulses, stuporous mentation, organ failure or cardiac arrest.
    - Cardiogenic Shock- seen in any heart failure that impedes cardiac output, characterized by pump failure and increased central venous pressure
        - Pump failure- due to cardiomyopathy arrhythmias and valvular dysfunction
        - Clinical signs include-heart murmurs, jugular distention, collapse, rails or crackles noted on thoracic auscultation, systemic hypotension, tachycardia, increased central venous pressure, increased oxygen needs and decreased cardiac output.
    - Distributive Shock- seen in sepsis, anaphylaxis, neurologic diseases and pharmacologic or toxic reactions
        - Normal phases of hypovolemic shock occur.
    - Traumatic Shock- seen with extensive tissue trauma
        - Can be seen in conjunction with hypovolemic shock

- Is there any arterial bleeding?
    - Note any external wounds
    - Place pressure bandages to any hemorrhaging wounds

- Place a large bore intravenous catheter to administer fluids and necessary medications

- Institute treatment if hypovolemic or traumatic shock is present
    - Shock doses for crystalloid fluids
        - Feline- 45 ml/kg/hr
    - Administration of shock fluids
        - Start with ¼ shock dose over 15 minutes
        - Reassess the patient's heart rate, respiratory rate, mucous membranes, capillary refill time and non-invasive blood pressure
        - If patient is still dehydrated, start the 2nd, ¼ dose over 15 minutes and reassess
        - Repeat until patient is rehydrated or until "shock dose" is complete

CPR

The following recommendations for CPR are adapted from the RECOVER Initiative from AVECC and VECCS. (2) Recognition of a patient in cardio-pulmonary arrest is very important. After recognizing that the patient is not breathing, the first thing to do is to capture an airway. After establishing an airway either by endotracheal intubation or emergency tracheostomy it is important to ventilate for the patient correctly. Ventilate the patient at a rate of 10 breaths/minutes with a tidal volume of 10 ml/kg. The oxygen flow rate should be 150 ml/kg/min

External chest compressions should be started next by placing your hands over the fourth and fifth rib space. Compressions should displace the chest wall by 25-50%. They should be done at a rate of 80-120 times/min. Most cats can be in left or right lateral recumbency. If only one team member is present CPCR can still be done, breathing twice then doing 30 chest compressions and repeat cycle until further help arrives. Internal chest compressions

should be done in specific situations only, such as with a penetrating thoracic trauma or if the patient is in the operating room.

Monitoring the effectiveness of chest compressions during CPR is essential. This can be done by palpation of pulses in the femoral artery or by applying a Doppler monitor to the eye of the patient and listening for blood flow. If femoral pulses are not palpated or noise heard on the Doppler the technique must be adjusted. Repositioning the patient or changing the person doing compressions are the first things to do with inadequate compressions. Remember maintain blood flow and oxygen to the brain and vital organs is the goal in CPR. The most accurate way to monitor the effectiveness of CPR is end tidal carbon dioxide (ETCO2). The capnograph, which monitors the ETCO2, fits between the end of the endotracheal tube and oxygen source. The ETCO2 will be slightly elevated with effective compressions.

Indications for the use of drugs in CPR are, to control life threatening emergencies, increase heart rate, and to improve myocardial oxygenation. Routes of administration vary with each drug. Common routes include, intratracheal (IT), intracardiac (IC), intravenous (IV), and intraosseous (IO).

There are several cardiac rhythms that are common with CPR. They are the following, ventricular asystole, pulseless electrical activity and ventricular fibrillation. Ventricular asystole is characterized by the absence of both mechanical and electrical activity. Treatment is to use epinephrine and atropine. Pulseless electrical activity is without adequate mechanical activity to cause sufficient cardiac output (pulses). It can be caused by insufficient myocardial oxygenation. Treatment includes Naloxone, epinephrine and atropine. Ventricular fibrillation is when chaotic, disorganized ventricular activity is seen.

No perfusion to the body takes place when this arrhythmia occurs. Treatment includes external defibrillation at a dose of 2 joules/kg. If that dose does not convert the rhythm, it can be increased. If fibrillation does not convert the rhythm, then epinephrine is administered.

Defibrillation is more successful when used early in CPR. It eliminates the arrhythmia by sending an electrical current through the heart. This allows the cardiac cells to depolarize and then repolarize all at the same time then ideally the heart will return to normal function. To defibrillate a patient paddles are used and one paddle is placed on each side of the patient's chest over the heart. Gel is placed on the paddles before placing them on the patient. The person holding the paddles must yell "clear" to inform all the other team members of what is happening, then making sure no one is touching the patient, they can discharge the defibrillator. If someone is touching the patient when it is discharged, they WILL be shocked as well. Remember isopropyl alcohol is flammable and metal tables will carry the electrical charge. If the patient is on a metal surface they must be removed before defibrillation occurs. Prolonged life support includes any complications after successful resuscitation. In most cases reoccurrence of cardiopulmonary or respiratory arrest is high with in the first four hours. Cerebral resuscitation is a huge concern due to the lack of blood flow to the brain during CPR. During CPR, hypoxia and ischemia occur which leads to cerebral edema.

Monitoring the patient is critical following CPR. Using an EKG to monitor electrical activity of the heart, SPO2 monitor the oxygen status of the patient and supplying oxygen if necessary. Monitor either invasive or non-invasive blood pressures, and regular physical exams including pupillary light responses, motor function and breathing patterns are done frequently to monitor the patient's cerebral function. Almost always these patients will need oxygen supplementation via an oxygen cage, flow by, or nasal insufflations. The heart will almost always need support in the first 4 hours following successful CPR.

Shift Burn Out

Signs of Burn Out

- Exhaustion - getting 8 hours of sleep in important to keep yourself rested and relaxed. If you work an off shift, such as nights or weekends, it is important to still get appropriate amounts of sleep. Black out curtains, sleeping masks or other sleep aids will help you feel rested and ready for your day at work. Relaxation is important in preventing burn out. Taking time off periodically to rest and restore will prevent burn out.
- Lack of Motivation - If you are dragging yourself into work and thinking you hate your job the entire way there, which is a sign of burn out.
- Complications at home or work - Relationships with the people around you, either at home or work can cause stress in your life. Find someone to talk to, friend, family member, supervisor, that can help you with interpersonal relationships.
- Not Taking Care of Yourself - Each day it is important to eat properly, exercise, rest and take time for yourself.
- Health Problems - Health problems can contribute to burn out if you do not feel you are getting enough rest or the job you are performing causes anxiety or pain in your ever day routine. Don't be afraid to ask for help. Take time for doctor's appointments so you can be healthy and enjoy your life.

Tips to Help Prevent Burn Out

- ✓ Start the day with a relaxing ritual.
- ✓ Do something every day that you love.

- ✓ Adopt healthy eating, exercising, and sleeping habits.
- ✓ Set boundaries.
- ✓ Take a daily break from technology.
- ✓ Nourish your creative side.
- ✓ Learn how to manage stress.

Dosage Calculations

Common Conversions:

- ✓ 1 kg = 2.2 pounds
- ✓ 1gram (g) = 1,000 milligrams (mg)
- ✓ 1 mg = 1,000 micrograms (mcg)
- ✓ 1 Liter (L) = 1,000 milliliters (ml)
- ✓ °F = (°C x 9/5) + 32
  °C = (°F –32) x 5/9
- ✓ mg/ml = % of a solution x 10
- ✓ % of a solution = mg/ml / 10

Common Calculations:

- ✓ Drug calculations:
  - Units needed = weight (kg) x dose
  - Amount needed = dose/concentration of drug
- ✓ whole blood transfusion mL needed
  CAT = patient weight (kg) x 70 x (desired PCV - current PCV) PCV of donor blood
- ✓ RER (Resting Energy Requirement) = 70 x weight (kg) to the 0.75 power
- ✓ MER (Maintenance Energy Requirement) = activity or illness factor x RER
- ✓ Food dosage = kcal required/caloric density of food
- ✓ Common fluid rate is 40 ml/kg/day for patients without fluid deficits
- ✓ Fluid deficit (L) = % dehydration (decimal) x weight (kg) x 1,000 mL
- ✓ drip rate = volume of solution mL x drops/mL = volume in drops/minute (or ggt/min)
  Time (in minutes)
- ✓ mL/hr = volume of solution mL = volume to give per hour
  length of time of infusion in hours
- ✓ CRI Calculations- drug mL/hr x amount of fluid (ml) = amount to add to fluids
  fluid mL/hr
  - Need to know the dose rate of the drug
  - Need to know the patient's body weight
  - Need to know the fluid administration rate
  - Need to know the drug concentration

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2. Special Issue: Reassessment Campaign on Veterinary Resuscitation: Evidence and Knowledge Gap Analysis on Veterinary CPR, JVECC, June 2012, Volume 22 Issue s1, pages S1-S131.

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Feline Friendly Handling & Restraint

Paula Plummer, LVT, VTS (ECC, SAIM)

Fear is the most common cause of aggression in cats at the veterinary practice. Learn to recognize early signs and take steps to reduce or prevent escalation of fear. Reading body language of your feline patient is important to keeping all members of the veterinary team safe. When to know your limits and when to know your patients limits is key to a successful visit to the veterinary clinic for the feline patient.

Feline friendly environment is important for successful feline friendly restraint and handling. If at all possible, handle the feline patient in a dedicated feline area. Choose the feline handling area carefully; a low traffic area is necessary for a successful low stress feline handling experience. High traffic areas can cause stress on the patient causing them to act out in a negative way. Minimize odors by hand washing and cleaning and disinfecting working surfaces between handling each patient. Hand washing, disinfection and wearing gloves will also decrease the work area and patients of contamination of infectious diseases. Consider the use of a synthetic feline facial pheromone analog. Control the room lighting, avoiding intense glaring lights and control the tone and volume of voice by personnel. If at all possible, control the noise level of the work area taking care to avoid any loud, discordant noises. Keep the waiting time of a feline patient to a minimum if at all possible. Some feline patients only become harder to handle the longer they wait, it is important to take note of those patients and begin treatments, sample collecting or examinations in a timely manner.

Safe and appropriate handling of the feline patient may reduce the stress response of the patient. Have staff be proactive in making supplies readily available to perform the exam and obtain lab samples to decrease the amount of time the patient is on the table as well as to avoid the need to handle the patient multiple times. Most cats do not do well with multiple restraints so grouping sample collection, examinations and imaging together can be helpful to reduce stress of the patients. However, some feline patients need to have tasks broken up in sections. Don't hesitate to give your feline patient a break if they need it. It may be the difference between a positive and negative experience for everyone involved.

There are various methods for the safe removal of an anxious/fearful patient from the carrier for the exam. Taking apart the top of the carrier from the bottom of the carrier if the patient will not walk out of the carrier on their own and then covering the patient with a towel to remove them from the bottom portion of the carrier is the least stressful to the patient. Never reach your hands into a carrier to remove a patient. It will put you at risk for a cat bite. We will cover the team approach which includes the use of towels with and without the use of a rigid e-collar for those patients. Scruffing should never be allowed. The medical reasons why scruffing is not allowed is if your feline patient is systemically ill, geriatric or both the scruff of the neck can be pulled off in the event of restraint. Loss of trust with the owner or patient is another reason why scruffing is a poor choice of restraint.

Reducing stress of your feline patient while they are hospitalized can aid in recovery of the feline patient to help them to return home sooner. Common stressors for cats include;

- ✓ Other animals and humans
- ✓ Offensive noises
- ✓ Offensive smells/odors
- ✓ Cages that do not allow hiding
- ✓ Sensory overload from the hospital

Adverse side effects to anxiety in the feline patient can cause the following;

- ✓ Suppression of normal behavior
- ✓ Increase hiding
- ✓ Anorexia
- ✓ Vomiting
- ✓ Diarrhea
- ✓ Constipation/obstipation

Physiological effects of stress in our feline patient can include the following;

- ✓ Hyperglycemia
- ✓ Hypokalemia
- ✓ Increase creatinine
- ✓ Lymphopenia
- ✓ Neutrophilia

- ✓ Hypertension
- ✓ Cardiac murmurs
- ✓ Improper response to drugs

So, if stress in the feline patient can cause all or any of the above then how will we know when our patients are recovering appropriately? If any stress can be removed and some of these abnormal behaviors or physiological effects are reduced we as veterinary professionals, will be able to assess our patient's medical status more correctly. Providing proper cages for hiding, knowing feeding schedules and familiar foods, keeping our canine and feline patients separately are a few ways to reduce some of the stress in our feline patients. In the author's experience, feline patients are more comfortable in the hospital when they have a large enough cage to have some place to hide, room for a litter box, food and a bowl of water. "Hiddy houses" can be made from large plastic containers and decorated or the patient's carrier or even a towel in front of the cage will give feline patients some privacy. Getting to know the patient's personality can also relieve stress. In the author's experience, getting to know my patient's personality will provide better care and learn the eating habits of that patient. Some cats are social eaters, some cats eat at a specific time of day and some cats like to eat privately. If I know eating habits of that patient, then I can be a better patient advocate for them.

Reading body language of our feline patients is very important for successful handling and restraint. Cats communicate through facial features such as ear position, pupil size, whisker position, growling, hissing, as well as tail twitching and body position. An aggressive cat can flatten or pull their ears in a backwards position and adjust their pupil size. They can crouch down or position themselves to strike out or lunge if they feel threatened. It is best to be slow and calm when cats are showing signs of aggression.

When handling aggressive or stressed feline patients, be calm and slow. It is best to handle these cats with a trustworthy team mate. Some feline patients will require sedation to complete an exam, collect proper samples or obtain imaging. The level of sedation required will depend on the procedure being performed and how uncooperative the feline patient is. For example, an extremely "naughty" cat needing an hour long procedure will need a deeper level of sedation than the patient needing venipuncture performed. The level of sedation should be a judgment call made by the veterinarian and veterinary technician as a team.

Sedation Protocols for Feline Patients
(Table Modified from Anesthesia for Veterinary Technicians, Bryant, 2010.) (1)

Drug	Dose	Concentration	Route of Administration	Approximate Duration of Action	Comments
Butorphanol	0.2-.04 mg/kg	10 mg/ml	SQ, IM or IV	45 minutes	IM administration takes 15 minutes to take effect and IV administration takes 2-5 minutes to take effect.
Dexmeditomidine	0.002-0.01 mg/kg	0.5 mg/ml	IM/IV	30-45 minutes	Lower doses to be used in conjunction with other drugs or if giving IV
Ketamine	2-5 mg/kg	100 mg/ml	IM/IV	30-45 minutes	Lower doses to be used in conjunction with other drugs or if giving IV.
Acepromazine	0.025-0.05 mg/kg	10 mg/ml	SQ, IM or IV	30 minutes	Use only if indicated in the patient. Better results are seen when used in conjunction with butorphanol. Decrease dose in older, compromised patients.

*The sedation protocols listed above are the sedatives the author prefers. Other sedation protocols have been used with success.

The American Association of Feline Practitioners (AAFP) has come up with guidelines and a certificate program called The Cat Friendly Practice Program to help you and your clinic become a cat friendly practice. This program is designed to help your practice take the appropriate steps in becoming feline friendly. Your feline patients will be less stressed and the owners will be more compliant to bring their pets in for exams and recommended treatments. This program can be found on the internet at www.catvets.com

Pearls of wisdom to use when handling "naughty" cats is;

- ✓ Be slow and calm
- ✓ Do not get in a hurry
- ✓ Handle these patients with a trustworthy teammate
- ✓ Know your limits
- ✓ Ask for sedation, if necessary

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The Feline Diabetic: Understanding the Disease

Heather Lynch, LVT

Introduction

This lecture is designed to help technicians develop the tools necessary to aid the veterinarian in providing excellent, progressive care for their clients and patients. Diabetes is a fairly commonly diagnosed condition in the cat. Often, successful treatment hinges on gaining owner compliance with the veterinarian's treatment plan. With proper client education and support, most owners will be successful treating their pet. Considering the massive demands on the veterinarian's time daily, having well trained technical staff who can act as a first point of contact for owners of diabetic pets, will result in an improvement in case outcome and client satisfaction. Key in this is the technician having a thorough understanding of the disease process. In the first session, we will discuss the diabetic condition in cats.

Overview of Feline Diabetes Mellitus

Diabetes mellitus is among the most commonly diagnosed diseases in humans in the United States. The Center for Disease Control reported in their 2011 Diabetes Fact Sheet that reports that 25.8 million children and adults (8.9% of the population) in the United States have diabetes, and estimates that 1.9 million cases were diagnosed in the Unites States in 2010 alone[2]. In cats, the incidence is reported has been reported as 1 in 200 (domestic cats). There is some evidence that genetics play a part in the development of diabetes in cats, with Burmese cats, especially in Australia, New Zealand and the UK being overrepresented, and other purebred breeds being underrepresented in comparison with their domestic counterparts.[3] Considering increasing public awareness of this disease in humans, improved understanding on the part of the veterinary profession, and advances in available diagnostic testing, it is possible that the incidence is even higher than this study indicates.

Diabetes is a disease in which the body does not produce or properly use insulin. Insulin is a hormone, produced by the pancreas, which is necessary to allow glucose to pass from the circulating blood into the cells, where glucose is converted into energy needed for daily life.[4] Glucose, a simple sugar, is an important energy source that is needed by all the cells and organs. Glucose is produced from food. In humans, carbohydrates such as fruit, bread pasta and cereals are common sources of glucose. These foods are broken down into sugar in the GI tract, and then absorbed into the bloodstream. Cells need a constant supply of glucose. Humans will generally begin to show symptoms of hypoglycemia within 4 hours if the body is not adequately supplied.[4] As glucose is synthesized by the body from food, the first symptom of hypoglycemia is hunger. When insulin is not present in the body to allow glucose to enter the cells, the glucose simply remains in the circulating bloodstream and exits the body through the kidneys. The kidneys are able to recognize glucose as a vital nutrient, and return it to the circulating blood until the blood level of glucose reaches the "renal threshold". At this level, the kidneys allow the glucose to be excreted into the urine. Without enough insulin to allow the glucose to enter the body's cells, the glucose simply continues to circulate and build up in the blood stream. If the high blood glucose levels (hyperglycemia) is not resolved, a glucose toxicity will develop and the patient will start to show signs of diabetes.

Diabetes mellitus in humans is classified as either Type 1 or Type 2. In veterinary literature, the terms "Insulin-Dependent Diabetes Mellitus (IDDM)", and "Non-Insulin Dependent Diabetes mellitus (NIDDM)" are used interchangeably with the terms "Type 1" and "Type 2" respectively, and physiologically diabetes in cats is similar but not exactly the same as in humans.[1] Type 1 diabetes results from the destruction or loss of beta cells with progressive and eventual complete insulin deficiency these pets will require insulin therapy for the rest of their lives (IDDM). Type 2 diabetes, commonly called "acquired diabetes", is characterized by insulin resistance and/or poor beta cell function. These pets may have increased, decreased or normal insulin secretion when compared with a non-diabetic fasting animal. However, the insulin secretion is insufficient to overcome insulin resistance in the peripheral tissues. In humans and in cats, this type of diabetes may be reversible with lifestyle changes and therapy and insulin may not be required long-term (NIDDM). This type of diabetes is most commonly diagnosed in cats. In one study, 75% of cats were diagnosed with NIDDM or Type 2 diabetes.[5] This accounts for the high remission rate in cats (65-80%), compared to dogs (2%), and also makes classifying diabetes in feline patients difficult as they can initially appear to have NIDDM that progresses to IDDM, or fluctuate back and forth between IDDM and NIDDM as severity of insulin resistance and beta cell function changes over time.[3] Considering the high rate of remission in cats, one theory is that most cats are initially Type 2 (acquired) diabetics, and cats become permanently diabetic when their disease is not recognized early enough to prevent permanent beta cell damage, and/or they have a disease that causes insulin resistance and is not well controlled. There are several theories as to the underlying cause of diabetes in the feline patient, and to date no clear answer has been discovered

Decreased Insulin Sensitivity

The body's insulin sensitivity varies widely in all cats, but is lower in males and in obesity. In one study, a weight gain of 44% over 10 months in cats resulted in a 50% decrease in insulin sensitivity. Acromegaly in cats has also been shown to cause decreased insulin sensitivity. [2] However, while decreased insulin sensitivity puts a patient at increased risk for developing diabetes, a pancreas with normal insulin secretory abilities can increase production to account for the reduced sensitivity. Therefore, insulin resistance itself is a contributor, but not a cause of diabetes.

Glucose Toxicity

Research has shown that the beta cell of the cat rapidly becomes toxic and stops secreting insulin when hyperglycemia is persistent. In one study 6/8 cats required insulin therapy due to reduced or absent beta cell secretion of insulin when hyperglycemia was experimentally induced.[7] Once the hyperglycemia was corrected, the beta cells began secreting insulin again and the diabetic state resolved within 2 weeks. This study suggests that a contributing cause for the development of diabetes in the cat is beta cell injury secondary to persistent hyperglycemia. This may be induced by insulin resistant and inflammatory states such as obesity, or chronic pancreatitis. The data for this study also suggests the reason that cats have such a high remission rate: their beta cells become functional again once the hyperglycemia is resolved. However, it is clear that there is a percentage of cats that, despite achieving glycemic control do not enter remission. It is possible that if hyperglycemia is persistent and uncontrolled for an unknown length of time, the Beta cells become permanently damaged and are no longer able to secrete insulin. It is not known how long the cat has to be hyperglycemic before this occurs, or what percentage of beta cell function has to be lost in order for the cat to be permanently diabetic. Also, the initial development of abnormal hyperglycemia implies that impaired insulin secretion already exists, it is an unlikely primary cause of diabetes, but is likely a reason why aggressive treatment of diabetes is associated with increased remission rates.

Pancreas Associated Diabetes

Chronic inflammation of the pancreas results in fibrosis and inflammatory damage to the exocrine pancreas, and causes damage to the endocrine pancreas. Disorders associated with pancreatitis in cats such as inflammatory bowel disease and cholangiohepatitis are also associated with insulin resistance which also contributes to the development of diabetes. These factors often make cats with pancreatitis associated diabetes more difficult to control.

Remission in Cats

Remission rates in cats started on intensive treatment (aggressive insulin therapy and change to low-carbohydrate diet) within 6 months of diagnosis was 84%, compared with 35% for cats started on the program longer than 6 months after diagnosis. Home blood glucose monitoring was also used in all the studies where remission rates of greater than 80% were reported.[5] The finding of these studies strongly support the aggressive treatment of diabetes in cats, as remission of the diabetic state is possible in most cats. Positive prognostic indicators of remission in diabetic cats include: Steroid use within 6 months before diagnosis, early recognition and institution of therapy, % of body weight loss. The presence of peripheral neuropathy and high cholesterol have been associated with reduced remission rates.[10] It is important to note that remission is not a cure for diabetes and that approximately 27% of cats who go into remission will relapse. Cats with an impaired fasting glucose (119-180 mg/dL) were found to be at a higher risk of relapse.[11]

What about Stress Hyperglycemia?

A study done in 2002 proved that cats develop hyperglycemia as a stress response with blood glucose level increases of as much as 180mg/dL when exposed to stress.[13] The same and subsequent studies as noted above recognized that the stress hyperglycemia generally resolves within 4 hours of the stressful event if the cat is not continually stimulated. Current work suggests that, while stress hyperglycemia exists, simply attributing a high blood glucose to stress may be a missed opportunity to recognize a cat in a "pre-diabetic" state. Therefore, cats with blood glucose readings of >160 mg/dL should be further worked up with follow-up fasting blood glucose readings to differentiate between stress hyperglycemia and "pre-diabetes", as intervention in the "pre-diabetic" phase may result in the cat never requiring insulin supplementation.[12]

Standard Presentation/Clinical Signs

There are four Standard Clinical Signs that are present with both primary presentation and poorly controlled diabetics:[5]

- *Increased Urination*

  Because there is not enough insulin to allow the glucose to enter the cells, the glucose remains in the bloodstream until it enters the kidneys, which recognize the glucose as an essential nutrient and recycles it to the circulating blood for use by the body. However, since the body cannot utilize the glucose without insulin it just remains in the blood stream and continues to be recycled. When the amount of glucose in the blood stream reaches a certain level (called the "renal threshold"), the kidneys filter the "excess" glucose into

the urine and it is passed out of the pet. The rising levels of glucose in the blood and urine result in the body increasing the amount of urine that is produced in an attempt to remove the excess glucose.

- *Increased Thirst*
  As the volume of urine output increases, the pet must drink more and more water in order to avoid dehydration.
- *Increased Appetite*
  Because the body has to utilize energy stores to maintain its normal function, it assumes that the pet has not eaten, and sends signals to the body to find and consume more food. You may notice that your pet is searching or begging for food, or stealing the food from other pets in the house. The problem is, that no matter how much food your pet eats, the lack of insulin prevents the glucose collected from the meals entering the cells, and the pet's body continues to think that it is starving.
- *Weight Loss Despite Increased Appetite*
  Glucose is the main source of energy that is collected from food by the body. It is both used immediately and stored by the cells. When a lack of insulin causes glucose, collected from a meal, to be unable to enter a cell, the cells start using stored energy to continue to function. This results in general weight loss.
- *Other Clinical Signs*
  Dogs and cats with chronic, untreated disease may present with other, more severe clinical signs, such as jaundice, partial to complete anorexia, ataxia or weakness, seizures and lethargy. Dogs may present for acute blindness.

Signalment

Most cats are 8-13 years of age at the time of diagnosis, with peak prevalence at 9-12 years of age. Male cats are affected about three times as frequently as females. Burmese cats in Australia have been documented to have higher risk of DM development than other breeds.[14]

Making the Diagnosis

Thorough veterinary exam and history are absolutely imperative when making a diagnosis of diabetics. For many pets, veterinarians will have a high index of suspicion of the disease before testing, based on history and exam alone. In addition, all pets presented with clinical signs of diabetes should have complete blood and urine testing performed to determine a definitive cause of the clinical signs, and screen for complicating factors. To diagnose diabetes: fasting blood sugar must persistently be greater than 300mg/dl AND the pet must have persistent glucosuria.[1] A study done in 2002 proved that cats specifically will have blood glucose level increases of as much as 180mg/dL when exposed to stress.[4] These findings made the documentation of persistent hyperglycemia and glucosuria more important in diabetes diagnosis. Stress hyperglycemia is present, but less pronounced in dogs.

Common Diagnostic Tests:

- *Blood Glucose*
  This is a direct measurement of the amount of glucose in the circulating blood. Test most often used to screen for diabetes, and test used for at home monitoring protocols. May be collected via capillary blood draw.The results of this test are highly variable depending on the measuring instrument.[15]
- *Urinalysis*
  Primary confirming test to make the diagnosis of Diabetes mellitus by screening for glucosuria. Primary screening test for DKA by screening for ketonuria. Also preliminary screen for presence of Urinary Tract Infection[14]
- *Urine Culture & Sensitivity (MIC)*
  Screening test for a Urinary Tract Infection. Identifies the bacteria and antibiotic most appropriate to treat pet. Low Bacterial counts in urine may yield a negative cytology. Culture is the definitive test.
- *Fructosamine*
  Fructosamine is a protein that is formed in the blood in the presence of glucose and has a half life in the blood of 2-3 weeks. The fructosamine level is generally viewed as a measure of the average blood glucose over the previous 2-3 weeks. Good test to identify how long the pet has been diabetic. Not affected by stress hyperglycemia or any other short term elevations of blood glucose, however it is affected by sample handling and storage.[16] Limitations include limited specificity as to the degree of variation in blood glucose.
- *Blood Glucose Curve*
  Primary and necessary test for longterm evaluation of insulin effectiveness. Blood glucose curves evaluate the insulin efficacy, identify the glucose nadir, time of peak insulin effect, duration of insulin effect,

and severity of fluctuation in blood glucose concentrations in that particular diabetic patient. Changes in insulin dose will usually be determined by this test no matter what other monitoring methods are used.[14]

- *Glycosolated Hemoglobin (GHg)*
  Concentrations of a protein that is bound to hemoglobin in red blood cells, and are a marker of mean glucose concentration during the lifespan of the red blood cell.[4]
- *Serum Insulin Levels*
  The vast majority of dogs with newly diagnosed diabetes have IDDM and serum insulin concentration is in the lower half of normal or undetectable, therefore serum insulin is not a cost-effective diagnostic procedure.[4]
- *Interstitial Glucose Monitoring*
  Fairly new technology in Veterinary Medicine. Involves the temporary implantation of a probe in the subcutaneous tissue of the patient. Probe measures interstitial glucose continuously. Interstitial probes do not replace blood testing completely. Most probes currently on the market still must be calibrated to a blood test several times daily. Due to the cost of the testing units, this testing method is currently used primarily for monitoring on hospitalized patients.[17]

Complications

- *Hypoglycemia*
  Most common diabetic complication in dogs and cats.[4] Can occur suddenly and, if severe and untreated, may cause death quickly after onset.
  - Biochemical (Asymptomatic) Hypoglycemia
    Usually identified on a blood glucose curve, asymptomatic hypoglycemia is usually caused by a mild and chronic insulin overdose Immediate treatment includes the feeding of the pet and/or oral administration of sugar (usually Karo syrup).
  - Clinical (Symptomatic) Hypoglycemia
    Clinical signs include: Lethargy, Collapse, Coma, Partial to complete anorexia, Ataxia or weakness, Seizure. Treatment includes oral administration of sugar (usually Karo Syrup) and/or hospitalization with IV Dextrose administration. Recurrent symptomatic
- *Diabetic Ketoacidosis (DKA)*[14]
  Most common diabetic complication associated with chronic hyperglycemia. Medical emergency that is potentially life-threatening. DKA carries a mortality of less than 5% with adequate and timely treatment[2] DKA results from a shortage of insulin; in response the body switches to burning fatty acids and producing acidic ketone bodies that cause most of the symptoms and complications. DKA may be the first clinical sign of previously undiagnosed diabetes, but it may also occur in known diabetics due to a variety of causes, such as concurrent illness or poor compliance with insulin therapy.
  Clinical signs include: Vomiting, severe weight loss, dehydration, deep gasping breathing, confusion and occasionally coma.DKA in known diabetics is an indication that the current insulin dose is too low.[i]
- *Diabetic Neuropathy*[4]
  Most commonly diagnosed chronic diabetic complication in cats. It can occur suddenly in both newly diabetic cats and those on longterm treatment. Infrequently recognized in dogs. The dogs most commonly affected have been diabetic for a long period of time (5 years or more). It may be first clinical sign in newly diagnosed diabetic of all species. Clinical signs include; weakness, knuckling, abnormal gait, muscle atrophy, depressed limb reflexes, and deficits in postural reaction testing. May or may not resolve once glycemic control is established.
- *Cataract Formation*[4]
  Most commonly diagnosed chronic diabetic complication in dogs. Diabetic dogs that are poorly controlled and have problems with wide fluctuations in the blood glucose concentrations seem especially at risk for rapid development of cataracts. Changes in cellular glucose metabolism cause an influx of water into the lens, leading to swelling and rupture of the lens fibers and the development of cataracts. Rarely diagnosed in cats. May be first clinical sign in newly diagnosed diabetics. Presenting clinical sign is generally sudden progressive loss of vision. Surgical removal of cataracts will often restore sight in the patient once glycemic control is established. There is clinical evidence that dogs, especially newly diagnosed cases, may avoid cataract formation if mean blood glucose is kept under 300mg/dL, and wide fluctuations in blood glucose are avoided.
- *Hypertension*
  In one study, the prevalence of hypertension was 46% in 50 insulin-treated diabetic dogs. Hypertension seems to be associated with duration of diabetes and an increased albumin to creatinine ratio in the urine.[4] The frequency of hypertension in cats caused by diabetes has not been fully evaluated,

however hypertension in a common finding in cats with chronic metabolic disease. Retinal detachment, causing - in most cats – irreversible blindness may be a result of hypertension in all species. Hypertension, for the purposes of this discussion, is defined as: Systolic, diastolic or mean blood pressure greater than 160, 100, and 120 mm/Hg respectively.

- *Severe Long-term Complications*[4]

  The devastating chronic complications experienced in human diabetic patients, (nephropathy, vasculopathy, coronary artery disease), require 10 to 20 years or longer to develop and therefore are uncommon in diabetic cats.

Pre-Diabetic State? Can we detect it?

Prediabetes is a syndrome where the patient has higher than normal blood glucose levels, but not high enough for clinical diabetes to develop. In cats, hyperglycemia causes glucose toxicity of the beta cells with reduction in insulin secretion. "Pre-Diabetic" cats are at a high risk for developing clinical diabetes. With the findings with respect to insulin resistance beta cell glucose toxicity, there is likely to be a period of time where the cat is hyperglycemic, but is not clinically diabetic. Therefore the ideal time to start treatment in a cat is before it becomes overtly diabetic. Identifying this "pre-diabetic" state has proven challenging, especially considering the cat's propensity to develop hyperglycemia rapidly in response to stress. [12] Pilot research into identifying a "pre-diabetic" cat has yielded the following recommendations: Blood glucose should be measured as a screening test (on entry to hospital and any time after eating). Reading up to 160 mg/dL (9 mmol/L) is normal but cats with screening blood glucose 117-162mg/dL need to be retested 3-4hrs later and if not < 117 retested next morning or at home. At home on low carb diet (fasting only necessary if diet > 12% ME carbs ie on moderate-high carb diet) or after overnight hospitalization(fasting if on moderate-high carb diet) > 117 mmg/dL (6.5 mmol/L) is abnormal and > 135 mmg/dL (7.5 mmol/L) is highly predictive of development of diabetes.[12] Cats with fasting blood glucoses of greater than 117mg/dL should be monitored and changes in management, including a switch to a low carb (<12ME carbs) diet should be instituted.[12]

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The Feline Diabetic: Successful Management

Heather Lynch, LVT

Introduction

This workshop is designed to help technicians develop the tools necessary to aid the veterinarian in providing excellent, progressive care for their clients and patients. In the second session, we will discuss treatment, and how to help clients be successful at home.

The Goal of Therapy

The goal of therapy is to establish a durable glycemic control and to avoid complications associated with diabetes. Glycemic control is considered established when clinical signs of diabetes have been resolved, the pet is healthy and interactive in the home, its body weight is stable, the owner is satisfied with the progress of therapy, and if possible, the blood glucose concentrations range between 100 and 200 mg/dL throughout the day.[1] The owner should report that the pet's quality of life is near normal. In newly diagnosed cats, remission of exogenous insulin dependency should also be a goal of therapy.

Basic Treatment Concepts in Cats

The vast majority of cats suffer from acquired diabetes. In one study 84% of cats, who had started treatment within 6 months of onset of diabetes entered remission if the owners were willing to perform home monitoring and aggressive insulin therapy, and change to a low carbohydrate diet. Screen for pancreatitis and other complicating GI diseases. Monitor multiple times yearly.

The Importance of Diet

Diet alone is not responsible for the development of diabetes in cats, nor is it solely responsible for the cat entering remission, however, in most of the remission studies in cats, changing to a high protein diet positively correlated with remission of the diabetic state. Ideally, cats should be fed a diet that is ideally greater than 45% protein and less than 10% carbohydrate (% of Kcal ME) Ideal food is canned diet. As with humans, higher protein diets result in lower postprandial blood glucose, which contributes to better response to insulin at lower doses. Calculate kcal and give owner specific instructions. Meal feed cats as close to 12 hours apart as possible.

Working with Clients to Achieve Treatment Goals

Most of the treatment of a diabetic pet takes place at home; therefore gaining the cooperation of clients with the treatment plan is essential to successful case management. Clear and supportive communication is the Veterinary Team's best tool in achieving client compliance.

Communicating with Clients Effectively

- Be positive: diabetes is a chronic disease with negative effects but that it can be managed and that the pet can have a near normal quality of life at home.
- Be confidant: Understand the pet's condition before you go in to speak with the owner. If you're demonstrating at home monitoring, be sure you can get blood from the pet before you try to demonstrate to the client
- Be realistic: Set realistic expectations for the client about their pet's condition and their treatment protocol. They should understand that there's a learning curve and that it may take a few days to learn how to perform their pet's treatment.
- Be a team: Treating diabetes successfully requires teamwork between the owner and the veterinary staff.
- Be clear: Give the owner clear, written discharges with their treatment protocol and with their follow-up treatment plan.
- Be informative: Provide the client with written educational materials or give them approved internet links to research so that they are getting information that is correct and consistent with the hospital's treatment protocols.

Basic Treatment Tenants that Should be Communicated to Owners

- If pet does not eat: Do not give insulin
- Insulin should be administered as close to 12 hour intervals as possible
- Blood glucoses should be performed prior to insulin and feeding
- Pets exhibiting clinical signs of hypoglycemia, and/or who have blood glucose readings $\leq$ 60mg/dL, should not receive insulin

- Owner should monitor their pets for increase in urine production, increased thirst or appetite and weight loss

Treatment: Understanding Insulin

Exogenous insulin is the cornerstone of treatment for the diabetic. There are many preparations of insulin available. Historically, insulin has been derived from animal sources, but advances in technology has allowed for the development of synthetic (human recombinant) insulins. Other than the source of the insulin, the main differences usually have to with the rate at which it is absorbed from the injection site and onset/duration of action. As of yet, no effective once daily insulin has been developed for cats. All veterinary patients will likely need a minimum of two injections daily.

- Vetsulin (U-40), NPH & NPH 70/30
  Generally not well absorbed in cats.
- Glargine. (U-100)
  Currently most commonly used and studied initial insulin in cats. Long acting basal insulin. Absorption is dependent on pH or tissue at injection site. Shown to have 12 hour duration of action in cats. Has very low incidence of clinical hypoglycemia in cats. Starting dose is 0.25-0.5 IU/Kg
- Detemir. (U-100)
  Long-acting basal insulin. Used once daily in people to avoid wide fluctuations in blood glucose. In cats, it has a similar duration of action and effect as Glargine. Is bound to albumin in the interstium, causing a more predictable release and duration of action than other formations. This insulin may result in improved glycemic control in cats who are poorly responsive to glargine insulin. Starting Dose for cats: 0.25 IU/Kg.
- PROZINC® (U-40)
  Replaces PZI. Little research comparing efficacy to Glargine. Likelly is similar in efficacy and duration to Glargine in cats. U-40 insulin. Starting dose is 0.25-0.5 IU/Kg
- Regular Insulin: (U-100)
  Regular crystalline insulin: Rapidly absorbed after injection, this insulin has a short duration of action (2-6 hrs), and can be administered IV, IM, or SC. Achieving glycemic control requires 3-4 injections daily. In veterinary medicine, regular insulin is typically used to treat diabetic ketoacidosis and life-threatening hyperkalemia.
- Insulin Aspart: (U-100)
  A fast acting insulin analog is a man-made form of human insulin. Fast-acting insulin analogs are considered to act similar to natural secretion of insulin in people without diabetes mellitus. This insulin was approved by the FDA in June 2000. In man, the onset of action is approximately 15 minutes, the peak action is reached in 45–90 minutes, and the duration is 3–5 hours. Use of this insulin in veterinary patients is currently being investigated.

Treatment: Monitoring

Most newly diagnosed diabetic pets who are clinically stable can start treatment at home without hospitalization.

- In-Hospital Monitoring
  - Pet is given a fixed dose of insulin BID at home by owner. Owner returns pet to hospital for blood glucose curve. Serial Fructosamines and blood glucose curves used in concert to adjust insulin doses.
- At-Home Monitoring
  - Current Standard of Care for veterinary patients at University level facilities. Pet started on fixed dose of insulin BID. Owner checks pet's blood glucose at home via capillary blood draw. Owner performed blood glucose curves at home. Insulin is adjusted based on owner's blood glucose log(daily readings), and blood glucose curves.

Capillary Blood Collection

First Step: Get comfortable with capillary blood collection yourself

The most important aspect of developing a home blood glucose monitoring program in your hospital is developing the ability to easily and consistently collect capillary blood samples in all animals. This skill should be developed by the entire staff. The best way to develop this skill throughout your staff is to adopt capillary blood collection as the preferred method of running blood glucoses on all patients in your hospital. One of the first aspects of the collection protocol to decide what blood collection site will work best for the patient. Choice of site depends on the size, temperament and physical characteristics of the dog or cat. There are several sites to choose from and the best site to pick is the one that the animal will best tolerate, and consistently allow for collection of an adequate sample.

- CATS:
  - lateral ear margin
  - Pisiform (wrist) paw pad:

Lancing devices: A lancing device is a spring loaded device that holds the lancet, and when triggered, moves the lancet linearly ahead to prick the skin in a controlled manner. Lancing devices are particularly helpful for clients who feel unable to make the skin prick necessary to collect the capillary sample free hand.

Veterinary vs. Human Glucometers[10]

Clients often ask about using a human glucometer rather than purchasing a veterinary model. I believe the most important point is that clients check blood glucoses at home, regardless of which glucometer they use.

That said, I always strongly encourage clients to try veterinary models for several reasons:

- As was shown in a study in 2009,[2] there are stark differences in accuracy from meter to meter, and generally the veterinary meter, specifically the AlphaTRAK veterinary-specific handheld blood glucose monitor (abbottanimalhealth.com), was far more accurate than most human meters.
- In my experience, the veterinary meters require smaller samples, making it far easier for the owner to consistently collect blood.
- The makers of the veterinary meters provide both educational and technical support for their veterinary customers, whereas the makers of human models do not.

Day to Day Blood Glucose Variability

The primary argument for the use of daily home monitoring is the broad variability in Blood Glucose from day to day in patients. Blood Glucose is influenced by a multitude of physiological and environmental factors that are often outside the control of the owner or the veterinarian. Issues such as stress, inflammatory processes, weather, excitement, fear, insulin resistant diseases, to name just few may result in wide variance in the patient's insulin requirement for that given day. Often the patient's blood glucose level is not obvious without measurement, and owners may give insulin doses that are not appropriate.

Exercise

Changes in exercise can cause sudden and profound changes in daily insulin requirements. Have owner try and maintain a constant amount of exercise at the same time each day. If dog is going to do more than usual exercise, reduce insulin dose, or check blood glucose more frequently.

"Systems" of Home Monitoring

There are multiple ways to implement home blood glucose monitoring. Regardless of what level of monitoring is instituted, there needs to be an understanding that monitoring does not replace regular rechecks with the veterinarian.

Below are the most commonly used protocols:

- "Spot" Check
  - May recognize Hypoglycemia or Hypoglycemia
  - Not enough information to adjust insulin dose
- Home blood glucose curves
  - Reduces "white coat" stress effect
  - Allows for full 12-14 hours curve
  - Works with owner schedule
  - Can be performed on "normal" day with regular routine - more accurate data
- Multiple time daily monitoring
  - Allows for in depth evaluation of the effect of insulin dose on the patient
  - Prevents/allows for immediate recognition of hypoglycemia and extreme hyperglycemia, giving clients and DVMs the opportunity to intervene before the pet become clinical.
  - Allows the veterinarian the data to develop a variable dose insulin chart and institute more aggressive, targeted insulin treatment protocols safely. This protocol creates improved durable glycemic control, increases the chance of remission in the cat and reduces the risk of the development of diabetic complications such as cataracts.
  - In a recently conducted study, glycemic control was improved by 35% in patients on a variable insulin dose chart when compared to a fixed insulin dose. This improvement was documented in all patients, without respect to species, insulin dose, or concurrent disease. Additionally, no patients in this study reported incidences of clinical hypoglycemia or other complications regularly associated with diabetes. The findings of this pilot study suggest that variable insulin dose charts may improve glycemic control and reduce diabetic complications in most diabetic patients.[11]

Developing and Adjusting the Insulin Dose Chart

1. Start patient on standard fixed dose of insulin
2. Institute home blood glucose monitoring 2-4 times daily: Am and Pm, 12 hours apart before feeding and insulin, then ideally 6 hours after am insulin +/- at bedtime.
3. Give insulin at home and monitor for 14 days.
4. Call the office if blood glucose reading is ever less than 60mg/dL, or if owner gets two or more consecutive readings >350 mg/dL. (Adjust dose as necessary if these occur)

Insulin Dosage Chart[10,11]

	Blood Glucose	Eats all food (ounce)	Eats less than ounce
TOO HIGH	>500 (“Hi”)	units	units
	450-500	units	units
	375-449	units	unit
GOOD	300-374	units	unit
IDEAL TARGET RANGE	250-299	units	unit
	200-249	units	unit
NORMAL (non-diabetic)	150-199	units	unit
	*120-149	units	0
LOW	If blood glucose is less than 119, recheck blood glucose one hour after feeding and dose according to chart.		
	*60-119	0	0
	<60	1)Recheck immediately to verify **2) If alert, feed & recheck in 30 min** **3) If weak, give Karo syrup, recheck in 30 min, call hospital**	1)Recheck immediately to verify **2) If alert, feed & recheck in 30 min** **3) If weak, give Karo syrup, recheck in 30 min, call hospital**

5. After 14 days, evaluate blood glucose log and create Variable dose chart as follows:

Dose changes should be made based on pre-insulin glucose concentration or lowest glucose concentrations on the log. Initially, clients should be measuring blood glucose 2 times daily with at least 2-3 "6 hour" post insulin readings weekly.

*ALGORITHM FOR VARIABLE INSULIN DOSE CHART ADJUSTMENT[** 10] (For the veterinarian)*

Parameter used for dosage adjustment	**Initial Dose on Insulin Dosage Chart-Veterinarian Directed**
Step 1: Initial dose and first 3 days	**Try not to increase dose for 1 week**
If the patient received another insulin previously, increase or reduce the starting dose taking this information into account. Glargine has a lower potency than PZI in most cats.	Start at usual insulin starting dose based on patient and insulin choice (usually 0.25 IU/kg of ideal weight BID
Ketonuria or history of Ketones & >300 mg/dL (16.7mmol/L)(after 24-48 hours of treatment)	Start at 0.5 IU/Kg of ideal body weight BID
Step 2 : Post Induction changes	**Change Insulin Dosage Chart Veterinarian Directed**
If nadir (lowest) blood glucose concentration >300mg/dL (16.7mmol/L)	Increase every 3-5 days by 0.5-1.0 IU/cat BID
If nadir (lowest) blood glucose concentration 200-300mg/dL(11-16.7mmol/L)	Increase every 5-7 days by 0.5 IU/cat BID
If nadir (lowest) blood glucose concentration < 200mg/dL(11mmol/L) but peak is > 200mg/dL (11mmol/L)	Increase every 10-14 days by 0.5-1.0 IU/cat BID
If blood glucose is < 80 mg/dL(4.4mmol/L)	Reduce dose by 0.5-01.0 IU/cat BID depending on if patient on low or high dose of insulin
Initally insulin not given if glucose < 150 (8.3 mmol/L)	< 150mg/dL(8.3mmol/L) glucose rechecked 1 hour after feeding if >150mg/dL (8.3mmol/L)insulin given, if < 150mg/dL(8.3mmol/L) glucose recheck in 1 hr, if >150mg/dL(8.3mmol/L) insulin given, if < 150mg/dL(8.3mmol/L) after 2 hours dosage reduced by 0.5-1.0 IU/cat
Step 3: Dosage Maintenance Goal glucose 80-200 mg/dl (4.4-11mmol/L)	**Change Insulin Dosage Chart Veterinarian Directed**
If blood glucose is < 80 mg/dL (4.4mmol/L)	Reduce dose by 0.5-1.0 IU/cat BID
If lowest blood glucose concentration > 200mg/dL(11mmol/L) , **and** your average blood glucose is greater 200-250mg/dL	Increase dose by 0.5-1.0 IU/cat BID depending on dose of insulin and the degree of hyperglycemia
ADDITIONAL STEPS FOR REMISSION GOAL CATS	
Step 4: Dosage Reduction	**Change Insulin Dosage Chart Veterinarian Directed**
Insulin Dosage chart insulin not given if glucose < 110mg/dL(6.1mmol/L)	Insulin dosage chart phases out insulin administration with normoglycemia
When the cat regularly (every day for at least one week), has its lowest blood glucose concentration in the normal range of a healthy cat, and stays under 130-150 mg/dL (7.2-8.3 mmol/L)	Change the insulin dosage chart back to only administer insulin if blood glucose 150mg/dL(8.3mmol/L) or greater
If the nadir glucose concentration is <80 mg/dL(4.4 mmol/L) at least three times on separate days	Reduce dose by 0.5-1.0 IU/cat/BID
If the cat drops below 70 mg/dL(3.9 mmol/L) once	Reduce dose immediately by 0.5-1.0 IU/cat BID or 50%
If peak blood glucose concentration > 200mg/dL (11 mmol/L)	Immediately increase insulin dose to last effective dose
Step 5: Remission Euglycemia for a minimum of 14 days without insulin.	**Change Insulin Dosage Chart Veterinarian Directed**
Insulin Administration stopped (cats remission goal)	**Glucose checked before feeding once a week, if glucose > 180(8.3 mmol/L) restart insulin at last effective dose**

Evaluation of Blood Glucose logs:

Evaluation of blood glucose logs requires only basic mathematics. It is important to note that insulin should never be changed based solely on an overall average blood glucose. The average can be influenced easily by a few outlying very high or very low numbers that may not be representative of the pet's glycemic control. The items generally evaluated are as follows:

1. **Average Blood Glucose:** Take a straight average of all blood glucose numbers performed (ideally is 200-250mg/dL)
2. **Average 12-hour blood glucose**: Separate any blood glucose values performed by the owner at midday, bed-time or 1 hour rechecks and only average values taken at the 12 hours intervals before feeding and insulin. (Ideally should be 200-250 mg/dL). This number is important because it removes any extra high or low numbers (usually the reason for rechecks) from your overall average that might mislead you when looking at overall glycemic control.
3. **Identify how many times the pet's blood glucose has been outside your ideal parameters** (count the "high" and "low" numbers). This gives additional insight into the average, as these numbers can artificially increase or decrease your overall average.
4. **Evaluate insulin dose chart:** Note how each insulin dose affected the blood glucose 12 hours later. This can be done by computer program, "hash marks" on the chart or other method. This step will identify trends in insulin dose effectiveness and will identify specific blood glucose ranges on the chart which require dose adjustment.
5. **Blood Glucose Curve.** If these numbers all appear to be in ideal range, or if the patient appears to be unresponsive to insulin, a 14 hour, at home Blood Glucose Curve should be performed to evaluate insulin performance and duration of action throughout the day prior to recommending that the owner follow the chart longterm, or changing to another insulin due to lack of response.

Developing a Home Monitoring Program in a General Practice

1. **Make a positive recommendation.** In order for the client to be confident in performing blood glucose monitoring at home, the veterinarian has to make a positive recommendation for it at time of diagnosis of diabetes (similar to recommending a urine culture if an infection is suspected). The veterinarian or staff should explain that home monitoring:
    a. Enables the veterinarian to improve their understanding of the day-to-day effect that insulin has on blood glucose
    b. Enables the client to know whether he or she should give insulin or not
    c. Alerts the client to potential emergencies or loss of glycemic control before the pet develops clinical signs.
2. **Be certain you can collect blood from the pet prior to client demonstration.** This is possibly the single most important part of this treatment plan. If you attempt to demonstrate the technique and are unable to draw blood easily, the owner will lose confidence and often decline the plan. In all cases, my suggestion is to:
    a. Discover the best site to collect blood from the animal away from the client, prior to recommending the protocol.Once you have located the best collection site and determined whether the pet is tolerant of the procedure, demonstrate the procedure to the client.
    b. Even if owners have decided not to pursue home monitoring, do not shy away from collecting blood glucose samples in front of them. Oftentimes, if owners see you perform sample collection regularly, they become more amenable to trying it themselves.
3. **Have trained technicians perform a detailed discharge with demonstrations for the owner.** Gives the owner the opportunity to go over the treatment plan and ask any questions they have without placing undue stress on the veterinarian's time:
    a. Include demonstrations of insulin storage, handling and injection
    b. Demonstrate blood collection technique and glucometer use
    c. Ideally have owner perform the techniques during the appointment
4. **Give the client clear, written instructions.** In my experience, compliance failure is often directly linked to the absence of a clear directive from the veterinary team. Written discharge instructions should include:
    a. The treatment plan Specific parameters for clinical signs and blood glucose readings that should prompt the client to contact the office *(For example: Call the office if you obtain 2 readings over 350 mg/dL or any readings under 100 mg/dL)*
    b. The follow-up schedule.
5. **Consider offering rental glucometers at the hospital.** Offering rental glucometers often encourage owners to attempt home blood glucose when they're not obligated to purchase a meter without trying the protocol first.

6. **Be sure the client understands that a learning curve is associated with glucose monitoring.** The protocol should never be portrayed as "simple" or "easy to do." Instead, clients should be prepared for a 7- to 10-day period where they may experience some difficulty in performing glucose monitoring. If clients realize it may take a few days to acclimate, they will feel less frustrated during the learning curve, increasing the likelihood of successful monitoring.
7. **Give the client permission to call or return to the hospital for help.** Ideally have a technician as the primary point of contact and encourage the client to ask for help if they have any issues with the monitoring plan. Have your staff follow up with regular calls to check in on the pet and client to be find out whether they have any questions or concerns.
8. **Charge for staff time appropriately**: It is imperative that the hospital be compensated for the services associated with this protocol. While charging structures will vary between hospitals, basic charges should include:
    a. Interpretation time for the DVM to review and adjust chart (Our protocol is to charge a "Diabetic Quarterly Consult" every 3 months which is ~1.5 times our exam fee)
    b. Technician consultations/demonstrations
    c. Exams and Labwork should be separate from the interpretation charges
9. **Be sure to institute a follow up protocol that creates automatic reminders for the client.** Due to the complexity of the treatment plans, the hospital should be proactive in both follow-up call backs and reminders to help the owner be compliant with the DVM's plan.

Summary

Successful treatment of diabetes hinges on gaining the cooperation and compliance of the pet owner. Supportive, and effective communication and a clear treatment and follow-up plan is integral to achieving this goal. With educated, compliant owners, the trained veterinary team can institute progressive treatment options, and affect excellent case outcomes. This results in substantial improvements in the pet's quality of life, and increased owner satisfaction.

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The Unstable Feline Diabetic Patient

Paula Plummer, LVT, VTS (ECC, SAIM)

So how does the patient get from the uncomplicated diabetic patient to the complicated diabetic? There are many different reasons why a patient could suddenly have a complication of diabetes. The common complications are diabetic ketoacidosis (DKA), insulin resistance, hyperglycemic hyperosmolar syndrome and hypoglycemia.

Getting to the bottom of it will take good history taking skills and a little detective work. Some things to consider are insulin ineffectiveness due to the following:

- ✓ Inactive insulin: Be sure to ask the owners how the insulin was stored. There are some general guidelines for insulin storage and handling. Insulin should never be frozen, used beyond the expiration date or exposed to direct heat or light. Each insulin formulation has specific guidelines and should be included on the product insert.
- ✓ Diluted insulin: Insulin dilution is a popular practice with the very small patients because their dose is tiny and hard to accurately pull up in a syringe do to the volume of the dose. This should not be done unless absolutely necessary and dilution should only be done by a licensed pharmacist.
- ✓ Improper administration technique: ask the owner to show you where on the pet they are administering the insulin dose
- ✓ Improper dose: ask the owner to show you on the appropriate syringe how much insulin they are pulling up
- ✓ Incorrect frequency of dose: always ask the owner what time(s) the insulin is administered, not just how many times daily. There can be a large variance between “twice a day” and 6am and 6pm
- ✓ Impaired insulin absorption: dehydrated patients do not have adequate tissue uptake of drugs injected by the subcutaneous route
- ✓ Once insulin ineffectiveness is ruled out, possible insulin resistance should be considered in the patient. (1)

Insulin resistance is a condition when a normal dose of insulin produces a less than ideal clinical response. Many diseases can cause insulin resistance, some common causes in dogs may include:

- ✓ Hyperadrenocorticism: Cushing’s syndrome is a result of too much circulating cortisol. The effects of cortisol on the metabolism of carbohydrates will decrease the cellular utilization of glucose and increases glucose output from the liver.
- ✓ Exogenous steroids: administration of corticosteroids for the treatment of another disease can result in the same physiological response as a patient with Cushing’s syndrome.
- ✓ Concurrent systemic infections: Diabetics may have underlying renal compromise due to the increase in protein in the urine brought about by elevated blood glucose which can cause urinary tract infections.
- ✓ Hyperthyroidism: The thyroid gland affects the metabolic rate as well as the rate of energy use, and the absorption of nutrients. Hyperthyroidism causing insulin resistance is actually rare in the feline patient. (1)
- ✓ Acromegaly: There has been documentation of elevated growth hormone secretion as well causing insulin resistance in the feline patient.
- ✓ Concurrent systemic illness: It has been proven that pancreatitis, renal disease, liver disease or cardiac disease will cause insulin resistance in the feline patient. (2)

Common diseases that cause insulin resistance in cats include:

- ✓ Acromegaly
- ✓ Exogenous steroids
- ✓ Concurrent infections
- ✓ Hyperthyroidism
- ✓ Concurrent renal, liver or cardiac disease (3)

Diabetic Ketoacidosis

DKA is a result of an improper balance of concentrations of all the hormones insulin, catecholamines, glucagon, cortisol and growth hormone. An insulin deficiency in the body is counter regulated by an excess of the catabolic hormones, especially glucagon. Now there is hyperglycemia present in the body, when the concentration of glucose exceeds 260-310 mg/dl in cats it exceeds the renal threshold, spilling into the urine. (1) Osmotic diuresis is present with significant calorie loss, polyuria and polydipsia. Lipase is activated by the improper insulin: glucose ratio in the body so it then mobilizes adipose. Adipose is stimulated for the primary energy source because of the loss of calories and unavailability of glucose and insulin to the body.

Long chain free fatty acids then transport the fat to the liver. Liver ketone formation is preferred over transformation into triglycerides due to the increase of glucagon. Ketone bodies produced by oxidation of free fatty acids change into acetone and acetoacetate becoming an acid. In a normal body, ketone are then metabolized by tissue to form carbon dioxide and water then used to form bicarbonate. (4) The bicarbonate is then used to help buffer another ketone in the extracellular fluid. In a diabetic body the ketone formation in the liver will exceed the muscle's ability to metabolize the ketone which will cause accumulation in the blood. So then the excessive production of ketone combined with the reduced production of bicarbonate will result in ketonuria and eventually metabolic.

During osmotic dieresis the body will lose not only glucose but sodium, potassium and water in the urine. The body will compensate for all the negatively charged ketone loss in the urine by excreting additional positive charged electrolytes, those include sodium and potassium. More sodium will be lost through the kidney due to lack of insulin in the body. (4) Sodium is the primary extracellular electrolyte that holds water within that space. The regulation of sodium balance in the kidneys and the maintenance of effective circulating volume are closely related. The changes in effective circulating volume are triggered by specific volume receptors in the cardiopulmonary circulation, the carotid sinuses, aortic arch and the kidneys. This activates a series of effectors throughout the body to correct the volume depletion. Most of the receptors will then sense a change in pressure and dilate or constrict to compensate for the change in circulating volume. The receptors that are located in the renal afferent arterioles then activate the renin-angiotensin-aldosterone system (RAAS). (4) The non-renal receptors will help govern the activity of the sympathetic nervous system.

Now total body water is significantly decreased and the patient is hypovolemic and if left long enough untreated in a state of hypovolemic shock. This will lead to prerenal azotemia and a decreased glomerular filtration rate increasing the amount of ketones and glucose in the blood even more and finally resulting in metabolic acidosis. With circulating cortisol and epinephrine in the blood because the body is in a "stressed" state, this will increase the level of glucose in the blood even more, exacerbating the patient's condition. Metabolic acidosis is the result of the exchange of a hydrogen ion for intracellular potassium. Insulin is required to drive potassium back into the cell so with the decreased amount of insulin, potassium will then become extracellular. Most serum chemistry profiles only measure extracellular levels and the total body concentration of potassium is not considered to be decreased.

The most common acid/base abnormality in DKA is metabolic acidosis. It develops because of several different reasons but almost always causes an elevated anion gap. Anion gap is the mathematical difference in measured cations and anions and represents the unmeasured anions. The anion gap is increased in DKA because the concentration of unmeasured anion in the blood is increased due to the production ketoacids and the decrease of bicarbonate concentration. The most important cause for metabolic acidosis in DKA is the production of acidic ketones. Fatty acids that are released can be used for energy in most tissues including the liver but without insulin free fatty acid conversion to triglycerides is impaired. When this process is impaired triglycerides are converted to ketones instead of being oxidized to carbon dioxide. So the liver is then reset to metabolize free fatty acids due to the lack of insulin and increased glucagon to favor ketone production instead of oxidation of fatty acids to carbon dioxide. The other reason for acidosis is the overproduction of lactic acid due to the impaired tissue perfusion from dehydration, shock and reduced renal excretion of hydrogen ions. If the disease has progressed far enough, mixed acid/base disturbances will be seen in the patient. Neurological compromise will lead to depressed respiration (respiratory acidosis) or metabolic alkalosis can be seen with vomiting and diarrhea.

Some clinical signs that the owner may report are, polyuria, polydipsia, lethargy, weakness, hyperventilation, anorexia, vomiting, diarrhea, weight loss, depressed, or coma. (5) Many of these patients have some type of underlying or secondary disease. Other clinical signs include, abdominal pain, neurological abnormalities ranging from depressed mentation to abnormal gait to a coma. Weight loss, muscle wasting, and cataracts can be seen. Some people report a "fruity" odor in the patient's breath due to the overwhelming amount of ketones in the patient. This is not a reliable clinical sign to use for diagnosis.

Initial database for an emergency patient should include blood glucose, PCV/TS, urinalysis, venous or arterial blood gas and a biochemistry panel. Quick analyzers can be purchased to run some of these tests while waiting on full panels. A glucometer will have results in a matter of seconds if your clinic does not own bed side analyzers. Urine glucose and ketone reagent strips are available for fast results while waiting on full urinalysis. A PCV/TS will give information on your patient's dehydration status and can be read in just a few minutes. Some bed side analyzers now have the capabilities to run venous or arterial blood gases for your convenience. The diagnosis of DKA is confirmed by the presence of hyperglycemia, glucosuria, ketonuria, and metabolic acidosis. Other abnormalities can include hyponatremia, hypochloremia, hypokalemia, increased anion gap, and azotemia. (5) Treatment of DKA patient can be tricky and time consuming. Correcting dehydration and electrolyte imbalances should be done first. A large bore peripheral intravenous catheter should be placed immediately. When the patient is stable a long indwelling jugular catheter, which fluids can be administered and blood samples can be drawn from should be considered. Hypoperfusion and dehydration should be replaced immediately with crystalloid fluid boluses and colloid fluids if needed. The typical shock dose of crystalloids is 60 ml/kg/hr in the feline patient. Remember that if your patient has concurrent heart disease, the rate of fluids may need to be tailored to fit that patient. Once hypovolemia is corrected, the fluid rate will need to be adjusted to correct the total fluid deficit.

Monitoring any patient that is receiving intravenous fluids is important. Any acute changes in body weight can be a sign of improper changes in water. Any patient that is losing weight while on fluid therapy is not receiving adequate amounts of fluid. Monitoring blood pressure, heart rate, respiratory rate is essential as well. Central venous pressure can be measured and used as a guide for fluid therapy replacement. Readings under 5 cmH2O are indicators of inadequate fluid replacement. Patients that still have proper renal function, a dehydrated animal will have a urine specific gravity of >1.025. On the other hand fluid overload should be monitored as well. In patients that are experiencing fluid overload or over hydration you will see an increase of nasal discharge, chemosis, increased respiratory rate, pulmonary congestion, crackles, and eventually pulmonary edema will develop.

Knowing which type of fluid to pick off the shelf and why is important. Typically, 0.9% Sodium Chloride is the fluid of choice in the emergency phase of DKA. (6) It is an isotonic fluid and has the highest concentration of sodium compared to other fluid types, which is important to correcting the sodium deficit. Lactated Ringer's Solution should be avoided at this time due to the presence of lactate in the solution. The hepatic metabolic process to make bicarbonate from the lactate is the same process used to metabolize ketones, reducing the liver's ability to correctly metabolize lactate. Poor perfusion will also aide in the retention of lactate because it is negatively charged and in the effort of the body trying to maintain electrical neutrality will dump even more sodium and potassium into the urine to be excreted.

Rehydration alone will improve hyperglycemia, acid/base status and electrolyte imbalances. Supplementation of electrolytes may need to be provided additionally due to the dilution effect of fluid administration. Tissue perfusion will be restored and proper urine production will be restored improving metabolic acidosis. Proper tissue perfusion will also help reduce the amount of lactate in the body helping to reduce the amount of sodium and potassium the body puts in the urine. All of this will help the body to restore normal amounts of electrolytes. (4) Rehydration will also help reduce the concentration of ketones and glucose in the body because of the dilution effect. So as you can see the dilution effect of fluid therapy is important to remember in patients it helps reduce the high concentrations but can reduce them too much. Frequent chemistry panels should be ran on these patients, in the beginning it may be necessary to run chemistry panels every 4 to 6 hours and then as your patient becomes more stable, decreasing the frequency to every 12 hours and eventually to every 24 hours. In the author's experience, a daily chemistry panel is performed until the electrolytes stay within normal ranges; the patient is considered euvolemic and eating on their own.

Regular insulin is suggested in the initial treatment of DKA and is continued until the patient is stable and ketosis has resolved. Therapy is adjusted to reach a blood glucose of 250 – 300 mg/dl in approximately 24 hours. Insulin therapy should begin approximately 2 – 4 hours after fluid therapy. Fluid therapy alone will help decrease the concentration of glucose from dilution effect and urine production in the body. If the glucose is dropped too quickly it can result in cerebral edema and a coma. The maximum drop in blood glucose should not exceed 75 – 100 mg/dl/hr. There are several different recommendations to administration and dosage of regular insulin in the initial treatment of a DKA patient. The advantages of regular insulin are, it can be administered intravenously (IV), intramuscularly (IM), and subcutaneously (SQ), it has a rapid onset of action and a short duration of action.

Intramuscular and especially subcutaneous injection may not be absorbed properly if the patient is hypovolemic. Hourly IM injections of regular insulin can be done successfully if needed. The initial dose would be 0.2 – 0.25 U/kg with follow up doses of 0.1 – 0.2 U/kg hourly. The regular insulin is continued until the patient's ketosis is resolved. When blood glucose drops <250 – 300 mg/dl the hourly dose is decreased by as much as 50%. At that point a 2.5 – 5% dextrose containing solution is started and if the blood glucose drops <100 mg/dl, insulin is temporarily discontinued until it rises above 150 - 200 mg/dl. If the blood glucose drops below 60 mg/dl a 1-2 ml/kg bolus of 25% dextrose should be administered and glucose measurement taken every 30 minutes to 1 hour until rises above 100 mg/dl. Blood glucose measurements are performed every 1 -2 hours until it is continuously in the 250 – 300 mg/dl range. (7)

Regular insulin can be successfully administered IV as well. A popular treatment method is to add the dose of insulin into a 250 ml bag of 0.9 % NaCl to administer it to your patient. The dose of insulin to be added to the 250 ml bag of saline is 1.1 U/kg for the feline patient. This concentration will be started at a rate of 10 ml/hr and infused only with an infusion pump. 50 mls of the solution should be ran through the line and discarded to allow insulin to properly bind to the plastic in the tubing. This will allow for immediate, proper dosing of insulin to the patient. Monitoring the patient is the same as with IM injections of regular insulin that was described above. Once the patient's blood glucose is stable and they are eating, the insulin can be switched to an intermediate acting insulin. (5)

Hyperglycemic Hyperosmolar Syndrome (HHS)

This is an uncommon complication of diabetes in the cat. HHS is diagnosed when the feline patient has hyperglycemia, above 600 mg/dl, hyperosmolality, above 350 mOsm/kg, and dehydration without to ketosis. (5, 8) In HHS it is thought that hepatic glucagon resistance and small amounts of insulin prevents ketosis. It is not known specifically why some feline patients develop HHS instead of DKA as a complication of diabetes mellitus but most patients with HHA have a concurrent illness. (8) Patients can show neurologic clinical signs with this syndrome. Some patients are non-responsive to anticonvulsants and only respond to insulin therapy and rehydration in these

situations. Neurological clinical signs are assumed to occur due to cerebral dehydration secondary to the hyperosmolality. (7) HHS will occur more commonly, with concurrent disease such as, cardiac or renal failure, pancreatitis, sepsis, and/or steroid therapy.

Treatment of HHS and DKA are similar with the goals to correct dehydration restore electrolyte losses and provide adequate insulin to correct any metabolic defects. Correcting dehydration and hyperosmolality with 0.9% NaCl is necessary before starting insulin therapy. If the blood glucose is decreased to rapidly this it will cause a decrease in extracellular fluid osmolality, which will cause cerebral edema. The prognosis of HHS is poor due to the high incidence of serious concurrent disease. (7, 8)

Hypoglycemia

Hypoglycemia can occur with an insulin overdose. This can be avoided by a client education and making sure the client understands how to properly pull up and administrate the correct insulin dose. Clinical signs usually include ataxia, weakness, behavior abnormalities, depression, shaking, seizures, coma, or death. When the clinical signs of hypoglycemia are first recognized owners can offer food or apply Karo ® syrup to the mucous membranes of the patient until veterinary treatment can be performed. One the patient has arrived at the hospital, 50% dextrose can be administered per the request of your veterinarian. When an IV catheter is placed a dilution of 1:4 of 50% dextrose can be administered. This bolus can be repeated as necessary. A CRI of 2.5 % to 5% dextrose should be started to prevent recurrence and continued until the patient can eat. (6)

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NOTES:

What Every Technician Should Know about Feline Hyperthyroidism

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Feline Hyperthyroidism is a common disease seen in feline patients. Every technician should understand pathophysiology of the thyroid gland including how the gland affects the body in a normal and abnormal state. As well as diagnostic and treatment options which will help the technician become a better patient advocate and help educate clients on those options.

Physiology of the Thyroid Gland

The thyroid gland helps regulate many different parts of the body. It is one of many glands in the body that makes up the endocrine system. The thyroid gland is located below the larynx on each side of the trachea and is one of the largest endocrine glands in the body. (1) Secretion of the hormones thyroxine (T4) and triiodothyronine (T3) is the primary function of the thyroid gland. These hormones control the rate of metabolism within the body. When the body secretes too much of the thyroid hormones it is termed “hyperthyroidism” and when the body does not secrete enough of the thyroid hormones it is termed “hypothyroidism”. When the thyroid gland needs to secrete more of the thyroid hormones, the anterior pituitary gland will release thyroid-releasing hormone (TSH). TSH will be secreted to the thyroid gland and in return the thyroid gland releases the hormones. Both T4 and T3 are as equally as important within the body even though T4 is secreted at a much higher rate than T3. T3 is four times more potent and but lasts a shorter amount of time than T4.

Iodine is needed to complete the formation of T4. Only a small amount is needed in the weekly diet. In humans, this was the reason why iodine was added to table salt. (1) When iodides are ingested, they are secreted from the gastrointestinal tract into the blood and then thyroid gland will then transform it into an oxidized state and use them to complete the formation of T4. Once the hormone is released it binds with plasma proteins that are synthesized by the liver. The hormones are then introduced to the tissues of the body slowly. T4 is introduced every 6 days and T3 every day. Once they are introduced to tissue, they will bind again with intracellular proteins.

Calcitonin is the third hormone that is secreted from the thyroid gland. (1) Calcitonin, Vitamin D and the parathyroid hormone (PTH) are all closely intertwined to help control the formation and regulation of calcium and phosphate metabolism as well as bone and teeth formation. Calcium specifically plays a role in this activity by decreasing plasma calcium concentrations and has opposing effects of PTH. (For the purposes of this lecture, specific effects of the PTH will not be discussed.) Increased calcium in the extracellular fluid is the primary stimulus for secretion of calcitonin. It only takes a 10% increase of calcium to cause secretion of calcitonin. (1) The immediate effect of calcitonin is to change the amount of absorbed and deposited calcium, especially in the young animal. The long term effects of calcitonin is to decrease the amount of new osteoclasts being formed.

Functions of the thyroid gland include:

- Increasing metabolic rate in almost every tissue of the body
- Increases the amount and activity of the mitochondria that will cause an increase the rate of formation of adenosine triphosphate (ATP). So in return the body uses more energy
- Effects the Na-K-ATPase which will increase transportation of sodium and potassium ions through cell membranes of tissue in the body. This causes more energy to be used and will increase the core body temperature.
- Growth- promotes growth and development of the brain during fetal life and for the first few years after birth. Growth and maturation can be decreased in the event of not enough of the hormones and vice versa if there is too much of the hormones present.
- Carbohydrate metabolism- stimulation of most aspects of carbohydrate metabolism is effected by thyroid hormone secretion. Rapid glucose uptake of the cells, glycolysis, gluconeogenesis, rate of absorption of the gastrointestinal tract and insulin secretion are all affected by the rate of carbohydrate metabolism in which the thyroid hormones play a role in.
- Fat metabolism- they thyroid gland can alter almost every step of fat metabolism. The lipids will be mobilized rapidly from the fat tissue which will decrease the amount of fat stores in the body and this will affect the free fatty acid concentration in the plasma and cause oxidation of free fatty acids to increase with an increase in thyroid hormone secretion.
- Concentrations of cholesterol, phospholipids and triglycerides will be affected with increased amounts of thyroid hormones. And they will be increased with lesser amounts of thyroid hormones in the body.
- Increased blood flow and cardiac output- because the metabolic rate is increased in the body this will cause the oxygen consumption to increase as well. This will cause vasodilation causing an increase in blood flow peripherally. Vasodilation will occur in the skin to aid in normalization of the increased body temperature. To compensate for the increased blood flow, the body will increase the cardiac output.

- Increased heart rate- The increased heart rate is not only due to the body trying to meet the needs of increased oxygen consumption and cooling the body. The rate at which the heart is beating is increased more than to be expected. It is believed that the increased secretion of thyroid hormone has a direct effect on the excitability of the heart. (1)
- Increased heart strength- Enzymatic activity of the increased flow of thyroid hormone will increase the strength of the heart even if the hormone secretion is only slightly increased. With excessive amounts of hormone in the body the heart will become weak due to long term increased production of protein catabolism.
- Respiratory system- The respiratory system is affected due to the increase rate of oxygen consumption and formation of carbon dioxide. The rate and depth of respiration will be increased with hyperthyroidism.
- Gastrointestinal system- GI motility and rate of secretion of digestive enzymes will be increased to help aid the body in the increased metabolism.
- Central Nervous System- altered amounts of thyroid hormone will affect the patient's ability to think. Hyperthyroidism will cause the patient to be nervous, fidgety or find it hard to sit still. Hypothyroidism will cause the patient to become dull or even lethargic.
- Muscles- a slight increase in hormone secretion the muscles of the body with react with increased reaction time. When the hormone secretion is excessive they will react slowly because the body is in a continuous state of protein catabolism. If decreased, the body will be sluggish to react.

Feline Hyperthyroidism

Feline Hyperthyroidism is the most common endocrinopathy in feline patients over the age of 8 years old. (2) It is a multi-systemic disease resulting in increased production and secretion of the thyroid hormone, T4 and T3 within the body. Typically lateral or bilateral small thyroid masses are palpable on physical examination. The mass causing the disease typically contains an adenoma or adenomatous hyperplasia cells. It is less common for the enlarged lobe to be caused by thyroid carcinoma. (2) There is not a sex related predisposition to the disease. It has been reported that Siamese and Himalayans are at a decreased risk for development of Hyperthyroidism. And domestic long and short hair breed are most commonly affected. (2)

Clinical Signs include the following;

- Weight loss
- Polyphagia
- Hyperactivity
- Increased vocalization
- Hair coat changes
- Polyuria
- Polydipsia
- Vomiting
- Diarrhea
- Behavior changes
- Tachycardia

Clinical signs can be variable and consist of the non-traditional findings listed above if the disease has progressed. The clinical signs of a progressed state could include anorexia, emaciation and severe dehydration.

Upon physical exam, it is important to do a thorough thyroid palpation. Not every patient with hyperthyroidism will have a palpable thyroid in the author's experience. In the author's opinion, a positive enlarged thyroid lobe and a matching history for hyperthyroidism is a positive start to diagnosis of the disease. Techniques for a proper thyroid palpation will be discussed during the lecture hour. Other physical exam findings can include; poor body condition, dull hair coat, dehydration, tachycardia and hyperactivity. In her experience, the author has noted that commonly the hyperthyroid cat will be aggressive, fidgety or vocalizing during examination.

Common abnormalities on a biochemistry panel include increased alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, BUN, creatinine and hyperphosphatemia. On urinalysis the urine specific gravity is typically greater than 1.035. (2)

Diagnosis

Diagnosis of hyperthyroidism can be made on positive palpation of an enlarged node, matching history, clinical signs and documentation of an elevated total T4 on blood work. A total T4 should be ran on serum and can be sent to ay commercial laboratory for evaluation. In cases that the Total T4 levels are not conclusive other testing should be pursued to determine a definitive diagnosis.

A T3 Suppression test can be performed if the serum total T4 is indecisive. This test evaluates the responsiveness of TSH that is secreted by the pituitary gland and if the synthetic T3 that was given suppresses its

secretion. When the synthetic T3 is administered it should suppress pituitary TSH secretion. This would then cause a decrease in the serum T4 concentration in a normal cat. But if the patient has hyperthyroidism it will still have secretion of the thyroid hormone that has is not related to the pituitary gland. So the administration of synthetic T3 will have no effect on the hyperthyroid patient. To perform the test, collect a baseline serum total T4 and T3, the owner will administer 25 mg of sodium liothyronine three times a day for 2 days starting the next morning. The morning of day 3 the last dose of sodium liothyronine will be administered and a final serum T4 and T3 will be collected 2-4 hours after administration of the last dose.

Lastly a radioactive thyroid scan can be done to diagnose an enlarged thyroid lobe and the presence or absence of metastatic cancer. At the author's facility, the scan is performed by injecting 2 millicuries (mCi) of technetium intravenously. After waiting 20 minutes for the technetium to take effect, ventral, left and right lateral images of the thyroid and thoracic regions are acquired. A radiologist will read the scans and determine if I131 is an appropriate treatment for the patient.

Treatment

Treatment options for feline hyperthyroidism include; drug therapy, thyroidectomy and radioactive iodine therapy. The mode of treatment will ultimately be determined by several different factors including; the age and health status of the patient, owner wishes, renal function, cardiac function, the presence or lack of hyperplasia, adenoma or carcinoma, the allowance of the patient to receive oral medications, the availability of I131 treatment and the availability of a surgeon to perform a thyroidectomy.

Initially the patient should be treated with antithyroid drugs to help control the side effects of excessive amounts of the hormone in the body. If surgery was chosen it will help reverse the effects on the body and make that patient a better anesthetic candidate. Oral therapy will also help reverse any cardiac or renal hyperthyroid induced derangements. Renal function abnormalities can be masked in the face of hyperthyroidism so when treated with antithyroid drugs any renal abnormalities will be uncovered and will help aid in final treatment options for the patient.

Antithyroid oral drugs include methimazole, propylthiouracil and carbimazole. Methimazole is the drug of choice for daily oral hyperthyroidism treatment in the feline patient. It can be given orally or placed topically on the pinna of the ear. Typical starting doses of methimazole is 1.25 to 2.5 mg/cat every 12 hours. (3) Methimazole does not block the release of thyroid hormone it blocks the oxidation of iodine once the hormone is released. It typically takes 2 to 4 weeks before T4 concentrations normalize after beginning treatment.Side effects of methimazole include; neutropenia, thrombocytopenia scabbing lesions on the pinna of the ear, hepatotoxicity, anorexia, vomiting, lethargy, renal decompensation and rarely Myasthenia Gravis. Monitoring the CBC, biochemistry panel and serum T4 levels should be done at weeks 2, 4 and 6 initially. (3) If owners choose to give the transdermal methimazole, it is important to educate them on proper administration and the importance of wearing gloves to not allow the medication to absorb into their skin and alter their thyroid levels.

Advantages of I-131 for the treatment of feline hyperthyroidism includes the following: eliminates the difficulty of administering twice a day medication, eliminates the possibility of reactions to anti-thyroid drugs and eliminates the risk of anesthesia during the thyroidectomy. Disadvantages of I-131 treatment includes; the availability of I-131 is limited, it requires knowledge and safety precautions of the radiation therapy, the patient must be hospitalized for a specific period of time to allow the I-131 to be eliminated from the body (the typical hospitalization time is 7 to 10 days), the patient has to be isolated for that period of time without owner visitations, cost, and the patient may not respond properly to a single treatment.

Patient selection for I-131 treatment is very important, the patient must be able to be isolated and unmedicated during the entire duration of hospitalization. If the patient has concurrent medical diseases such as cardiovascular, renal, gastrointestinal, other endocrine or neurological diseases they may be excluded from this particular treatment plan. Pre-radioactive iodine treatment work up should include the following; CBC, biochemistry panel, urinalysis, serum T4, thoracic radiographs, echocardiogram and have been off of methimazole for 7 days. If all requirements are met at that time the patient can have I-131 treatment.

Safety precautions should be followed during hospitalization. They would include the patient being confined to an isolated area of the hospital particularly a nuclear medicine isolation ward, trained personnel should only touch the patient, this team of people should be properly trained on radiation safety and know the proper PPE. Long laboratory coats, disposable plastic gloves and dosimeter monitors are the proper PPE for radiation patients. Every day the radiation level should be monitored and recorded in the patient's chart to ensure the level of radiation is decreasing. In the author's facility, daily readings are performed by trained personnel until a measurement of 2.5 millirem per hour (mr/h) is obtained. Upon discharge owners should keep the cat strictly indoors, limit the amount of contact time with the cat and dispose of the cat waste properly. Children and pregnant women should not come into contact with the patient for two weeks after discharge. Typically I-131 will restore euthyroid in a single dose. The hormone concentrations are normal within two weeks of therapy and typically the patient starts to feel better within days after treatment. However, there are approximately 5% of cats who do not respond appropriately to a single dose and must have a second dose of I-131 to become euthyroid. (3, 4)

Patients that are good surgical candidates are considered a low anesthetic risk, the availability of I-131 is low and the availability of funding is low. (4) Advantages of a thyroidectomy is it is 90% efficacious and/or curative. The

disadvantages of a thyroidectomy include; high initial expense, the risk of hypoparathyroidism, it is nonreversible and the anesthetic risk of the patient. Post operatively patients should be monitored for 7 days for clinical signs of hypocalcemia. Other post-operative complications include; Horner's syndrome, laryngeal paralysis, damage to the laryngeal nerve and permanent hypothyroidism. (4)

Iodine restricted diets are available for hyperthyroid patients. If the patient is put on this diet, it must be fed this diet exclusively, physical exams and rechecking blood work must be done every 6 months for the rest of the patient's life and they must be taken off antithyroid drugs over a course of 2 weeks while the patient is introduced to the iodine-restricted food. (4) Only cats that are diagnosed with hyperthyroidism can eat the iodine restricted diet.

Euthyroid Sick Syndrome

Euthyroid Sick Syndrome is diagnosed in a patient with a nonthyroidal systemic illness with concurrent decreased serum thyroid level. (5) Severe nonthyroidal illness will decrease serum thyroid levels to the low or undetectable range even in patients without concurrent hyperthyroidism. With concurrent systemic illness, patients with serum thyroid levels in the normal to high range should be suspected to have hyperthyroidism. A second serum thyroid level should be checked approximately 1-2 weeks later. (6) If total T4 levels are still suspicious but inconclusive other diagnostic methods for diagnosis of Hyperthyroidism should be pursued.

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NOTES:

Diagnosis and Management of Feline Chronic Kidney Disease

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Introduction

Chronic kidney disease (CKD) is a common disease in cats. The percentage of cats with CKD increases with increasing age with up to 30% of cats over the age of 15 years being affected.[1] CKD occurs over a period of months or years and is an important cause of death in cats.

Etiology

The cause of feline CKD is usually difficult to determine. Damage can occur to any part of the nephron including the glomerulus, tubule, interstitial tissue or vasculature which can result in irreversible damage and loss of function of the nephron. Often, by the time of diagnosis of CKD, the etiology is difficult to determine and histopathology often reveals tubulointerstitial fibrosis. The more common causes of CKD in cats include pyelonephritis, nephrolithiasis, ureteral obstruction with resultant hydronephrosis, tubulointerstitial disease, glomerulonephritis, FIP, and neoplasia. Amyloidosis and polycystic kidney disease are more common in certain breeds.

Clinical Presentation

In cats clinical signs of CKD may not be present in early stages. As the disease progresses cats can present with nonspecific signs including poor body condition, weight loss, decreased appetite, lethargy and dehydration. Polyuria and polydipsia are relatively common. Intermittent vomiting secondary to uremic gastric ulceration may occur. A cat may be asymptomatic until dehydration (potentially due to an unrelated cause) leads to decompensation and an acute presentation.

Physical exam findings in CKD patients reflect the chronic nature of the disease and include poor body condition, unkempt hair coat and small irregular kidneys. Alternatively, the presence of one big kidney and one small kidney may be identified on physical examination resulting from ureteral obstruction of the enlarged kidney. Oral exam may reveal ulcers, uremic breath odor and/or pale mucous membranes. Secondary systemic hypertension may cause retinal hemorrhages, arterial tortuosity or detached retinas.

Diagnosis

A diagnosis of CKD is typically straight forward once the disease is in its later stages and there is clinical suspicion based on history and physical examination findings, azotemia evident on biochemical profile and loss of urine concentrating ability. However, recognition of CKD can be challenging early in the course of disease since clinical signs may be absent, mild or attributed to another concurrent condition and azotemia does not typically develop until approximately 75% loss of nephron function. To add to the confusion, cats often retain some urine concentrating ability until later in the disease process.

BUN (blood urea nitrogen) and serum creatinine concentrations are routinely used biochemical tests to help diagnose kidney disease. BUN can be influenced by several extra-renal factors including dehydration, protein content of the diet, gastrointestinal bleeding and liver insufficiency. Creatinine is a breakdown product of muscle and is a better indicator of glomerular filtration rate (GFR) than BUN, but it can be influenced by a reduction in muscle mass which is not uncommon especially in older cats with CKD. When nonrenal variables have been eliminated, an increase in BUN and/or creatinine above normal indicates that at least 75% of nephrons are not functioning. Clearly, it would be advantageous to be able to identify kidney disease earlier. Performing creatinine measurements routinely during wellness visits can establish a normal baseline for an individual cat. An upward trend in creatinine while it is still within the reference interval can be helpful to identify CKD earlier prior to creatinine increasing above the reference interval.

SDMA (symmetrical dimethylarginine) is a new serum renal biomarker being investigated that shows exciting promise. SDMA has been shown to correlate with GFR and identify the onset and progression of kidney disease. Serum SDMA increases on average 14.6 months and as early as 4 years earlier than serum creatinine in cats with chronic kidney disease, and SDMA can detect kidney disease as early as when there is a 25% reduction in GFR.[2] SDMA increases in older cats as GFR declines and is not influenced by lean body mass;[3] therefore, unlike creatinine, it is a sensitive indicator of renal function in older cats as they lose muscle.[3] Evaluating SDMA along with BUN, creatinine and urine specific gravity will help veterinarians to diagnose kidney disease earlier and with more confidence.

Staging CKD

Historically, CKD has been classified as mild, moderate, or severe, based on laboratory findings and clinical signs. A less arbitrary classification system has been developed by the International Renal Interest Society (IRIS).[4] CKD has to be first diagnosed, and then IRIS staging can be applied. IRIS staging is based initially on fasting plasma creatinine, assessed on at least two occasions in the stable patient (Table 1). The patient is then substaged based on proteinuria and blood pressure (Tables 2 and 3).

Table 1: IRIS Staging System for CKD in Cats

Stage	Renal Azotemia	Creatinine	Comments
1	Nonazotemic	<1.6 mg/dl <140 µmol/L	Confirmed renal disease present: • inadequate urine concentrating ability • decreased GFR confirmed by other testing • abnormal renal palpation, imaging or biopsy • proteinuria of renal origin
2	Mild	1.6-2.8 mg/dl 140-249 µmol/L	Clinical signs usually mild or absent
3	Moderate	2.9-5.0 mg/dl 250-439 µmol/L	Many systemic clinical signs may be present
4	Severe	>5.0 mg/dl >440 µmol/L	Many systemic clinical signs usually present

Table 2: IRIS Substaging by Proteinuia in Cats with CKD

Urine Protein:Creatinine Ratio (UPC)	Substage
<0.2	Non-proteinuric (NP)
0.2-0.4	Borderline proteinuric (BP)
>0.4	Proteinuric (P)

Table 3: IRIS Substaging by Blood Pressue in Cats with CKD

Systolic BP in mm Hg	Diastolic BP in mm Hg	Substage*
<150	<95	Minimal risk (N)
150-159	95-99	Low risk (L)
160-179	100-119	Moderate risk (M)
>180	>120	High risk (H)

*Risk = likelihood that high pressure will further damage the kidney and other end organs.

Prognosis

Several studies have evaluated IRIS stage of CKD based on serum creatinine at the time of diagnosis and found that it is strongly predictive of survival in cats with naturally occurring CKD.[5,6] Results from one study are summarized in the table 4 below. [5]

Despite the fact that the level of proteinuria is relatively low in cats with CKD, the degree of proteinuria has also been independently related to survival in cats with renal failure. One study found that death or euthanasia was 2.9 times more likely in cats with UPC of 0.2-0.4 and 4 times more likely in cats with UPC >0.4 compared to cats with a UPC of <0.2.[6]

Table 4: Survival time by IRIS Stage

IRIS Stage	2b*	3	4
Median survival (days)	1,151	778	103
Range (days)	2 – 3,107	22 – 2,100	1 – 1,920

*2b = Creatinine of 2.3-2.8 mg/dl (203-249 µmol/L)

Long Term Management

It is important to counsel owners on the progressive and irreversible nature of CKD while emphasizing that proper treatment and monitoring can alleviate clinical signs and slow progression. An individualized therapeutic approach should be designed based on the IRIS stage of disease and the individual cat's needs. Key therapies for cats with CKD are listed in table 6.

Maintain Hydration

Most patients with CKD are polyuric and fluid balance is maintained by increased consumption. Avoidance of dehydration is critical in cats with CKD as a decrease in renal perfusion may result in an acute exacerbation of the kidney disease. Fresh clean water should be available at all times and an effort should be made to increase voluntary water consumption. Strategies to encourage increased fluid intake include providing running water sources such as a water fountain or dripping faucet, feeding canned food, adding water to the food if tolerated and offering low sodium beef or chicken broth, clam juice or tuna juice. Subcutaneous fluid therapy administration by the owner may be beneficial to help maintain hydration as CKD progresses. Fluids can be administered every day to every other day as well as on occasions when the cat as at increased risk of becoming dehydrated i.e. when anorexia, vomiting or diarrhea occurs.

Dietary Therapy

Most commercially available kidney diets are protein, phosphorus and sodium restricted; have an increased omega-3: omega-6 polyunsaturated fatty acid ratio and high caloric density, and are alkalizing. Recent studies have confirmed that dietary modification can have a significant impact on the mortality rate of cats with CKD. In one study, cats with CKD that were fed a veterinary renal diet lived considerably longer than cats not eating the renal diet (median survival of 633 versus 264 days).[7] Another study where cats were fed either a maintenance food or a prescription renal diet found that cats fed the renal diet had a reduced number of uremic episodes (0%) compared to cats fed the maintenance diet (26%) and there was also a reduction in renal-related deaths in cats fed the renal diet during the 2 year study.[8]

There is still debate on when is the appropriate time to initiate feeding a renal diet during the progression of CKD in cats. However, most experts believe that a renal diet should be started when the cat is in IRIS stage 2 (i.e. creatinine above 2.0 mg/dl or 175 µmol/L).

There is also an ongoing debate on the how much dietary protein restriction is needed in cats and if protein restricted diets leads to loss of lean body mass, decreased protein synthesis and protein energy wasting. However, there are known benefits to dietary protein restriction including decreases in: production of uremic toxins, tubular hypertrophy, renal acid load, and proteinuria. Levels of protein in renal diets exceed National Research Council (NRC) published requirements and should therefore still contain adequate protein especially if diet contains protein that is of high bioavailability. Finally, increasing dietary protein in the diet of cats with early stages of CKD, who are likely to tolerate higher levels, is tempting and may have advantages (such as palatability), but it must be kept in mind that protein sources also contain phosphorus, and as discussed below management of hyperphosphatemia has direct impact on survival times in cats.

Manage Secondary Gastrointestinal Conditions

Cats with chronic kidney disease (CKD) often experience inappetence, vomiting and weight loss. Treatments that target these secondary gastrointestinal signs are beneficial since poor body condition has been correlated with decreased survival. A recent study[9] evaluating for uremic gastropathy in CKD cats found that gastric ulceration, edema, and vascular fibrinoid change were not observed. Fibrosis and mineralization were the most significant gastric lesions. These results put into question the need for treating cats with CKD with gastric protectants such as sucralfate. Therefore, the investigator postulated that medical management of gastrointestinal symptoms with anti-emetic and anti-nausea drugs may therefore be more appropriate.

These investigators then studied the effects of two drugs in cats with CKD. They evaluated whether the drug controlled vomiting, impacted appetite and resulted in increased activity levels or weight gain. Miropitant citrate (Cerenia®) was demonstrated to palliate vomiting associated with chronic kidney disease; however, it did not appear to significantly improve appetite or result in weight gain in cats with stage II and III CKD.[10] Mirtazapine administration on the other hand not only resulted in a significant decrease in vomiting but cats also had an increased activity level and appetite and gained significant weight.[11]

Manage Hyperphosphatemia

Managing hyperphosphatemia in cats with CKD is an important component of therapy and has been linked to survival time. For cats with CKD, for every 1.0 increase in phosphorus there is an 11.8% increase in risk of death; median time until uremic crisis or death of cats with serum phosphate >2.8-4.7 mg/dL is >500

days, with phosphate >4.7-6.8 mg/dL is 450 days, and with phosphate >6.8 mg/dL is 50 days.[12]

Dietary phosphate restriction prevents hyperphosphatemia in early stages of CKD. The addition of intestinal phosphate binders (see table 6 for available phosphate binders and recommended dosages) should be considered when serum phosphorus rises despite dietary restriction. IRIS treatment guidelines suggest it is ideal to maintain serum phosphate concentrations between 2.7-4.6 mg/dL; however as IRIS stage increases more realistic post-treatment targets for serum phosphate concentrations are listed in the table below. After initiating phosphate binders, monitor serum calcium and phosphate concentrations every 4-6 weeks until stable and then every 12 weeks.

Table 5: Target serum phosphate concentration by IRIS stage

IRIS Stage	1	2	3	4
Target serum phosphate conc.	2.7 – 4.6 mg/dL 0.9-1.5 mmol/L	2.7 – 4.6 mg/dL 0.9-1.5 mmol/L	2.7-5.0 mg/dL 0.9-1.6 mmol/L	2.7-6.0 mg/dL 0.9-1.9 mmol/L

Potassium Supplementation

Approximately 20% to 30% of cats with CRF are hypokalemic.[13] Total body potassium depletion is likely to be even higher. Hypokalemia can cause generalized muscle weakness and may contribute to the progression of CKD. The goal of potassium supplementation is to maintain serum potassium concentrations above 4.0 mEq/L (4.0 mmol/L).

Manage Proteinuria

Based on the recommendations made in the 2004 ACVIM consensus statement on proteinuria[14] and the IRIS treatment guidelines[4], the intervention points for proteinuria differ according to the stage of CKD. In a nonazotemic animal (stage 1 and early stage 2) the number of filtering nephrons through which protein can be lost is high. Thus borderline and low level proteinuria (UPC <2.0) are investigated and monitored closely whereas at Stages 2-4 treatment is recommended in cats when UPC is >0.4.

Treatment consists of feeding a low protein diet and an angiotensin-converting enzyme inhibitor (ACEIs). Benazapril has been shown to be safe and effective in reducing proteinuria in cats with CKD.[15]

Manage Hypertension

The blood pressure needed to prevent renal disease progression is unknown.Goal recommended by IRIS is to reduce blood pressure (BP) to a systolic pressure < 160 mm Hg to minimize the risk of extra-renal end organ damage (CNS, retinal, cardiac problems/damage). Management includes dietary sodium restriction and initiation of therapy with a calcium channel blocker such as amlodipine.[4]

Manage Anemia

As CKD progresses, renal production of erythropoietin becomes inadequate and many cats become progressively anemic. The anemia contributes to the lethargy and poor appetite seen in these cats. In addition, uremic gastric ulceration may result in gastrointestinal blood loss if severe. The cat should be treated with gastrointestinal protectants and iron supplementation if GI blood loss is suspected prior to considering initiating therapy with an erythropoietic agent. Two erythropoietic agents are available: recombinant human erythropoietin (r-HuEPO) and darbepoetin. Treatment with an erythropoietic agent should be considered only if the patient is symptomatic and the anemia is severe (packed cell volume [PCV] <20%). Iron supplementation should be administered concurrently. Approximately 25% to 30% of cats develop antibodies against r-HuEPO which results in a sudden severe nonregenerative anemia. Darbepoetin is a biosynthetic erythropoietic agent that is less antigenic with fewer cats (<5%) developing antibodies and subsequent anemia; therefore if affordable, it is preferred treatment over r-HUEPO.

Calcitriol Therapy

Renal secondary hyperparathyroidism occurs when the parathyroid glands secrete excessive PTH as a result of CKD. This is due to several factors, including phosphorus retention and impaired ability of the kidneys to synthesize calcitriol. Despite the belief that PTH is a uremic toxin, the clinical benefits of PTH reduction have not been conclusively documented in cats. Serum phosphorus concentration must be reduced to ≤6 mg/dl (1.9 mmol/L) before initiation of calcitriol therapy. Calcium containing phosphorus binders should be avoided. After initiation of therapy the optimum maintenance dose should be determined based on frequent evaluation of calcium, phosphorus, and plasma PTH concentrations.

Monitoring

Recheck visits should be scheduled and frequency of these visits should be individualized along with therapy. Close attention should be paid to the patient history, including attitude, appetite and activity level. A physical examination, including a fundic examination, should be performed with particular attention to hydration, body weight and condition including muscle mass. Blood pressure should be evaluated and serial laboratory evaluation, including chemistry panel, complete blood count and urinalysis (including UPC), and urine culture, should be considered at scheduled visits.

Table 6: Key Therapies for Cats with CKD

Therapy	Dose	Frequency	Route	Indications
Renal diet	Achieve and maintain ideal body weight	Ad libitum or meal feed 2 to 3 times daily	PO	Slow progression, prolong survival, control hyperphosphatemia
SQ fluid therapy	75–150 ml/cat	q 24–48h	SQ	Maintain hydration
Cyproheptadine	2 mg/cat	BID	PO	Stimulate appetite
Mirtazapine	1/4 of 15-mg tablet or 1.88 mg (compounded)	Every 3rd day Every other day	PO	Stimulate appetite Antiemetic
Miropitant citrate (Cerenia®)	4 mg (1/4 of 16-mg tablet)	Once daily	PO	Antiemetic
Aluminum hydroxide (Ampohjel®) Aluminum carbonate	30–90 mg/kg/day (can go higher)	Dose divided and given with meals	PO	Hyperphosphatemia
Lanthanum carbonate (Fosrenal®, Renalzin®)	200 mg	TID with meal	PO	Hyperphosphatemia
Calcium carbonate and magnesium carbonate (Pronefra®)	0.25 ml/kg	BID with meal	PO	Hyperphosphatemia
Sevelamer hydrochloride (Renalgel®)	200 mg	TID with meal	PO	Hyperphosphatemia
Chitosan and calcium carbonate (Epakitin®)	1 gm/5 kg	BID with meal	PO	Hyperphosphatemia
Potassium gluconate	2 mEq/4.5 kg	BID with food	PO	Hypokalemia
Potassium citrate	40–60 mg/kg	BID or TID with food	PO	Hypokalemia Metabolic acidosis
Sodium bicarbonate	8–12 mg/kg	BID to TID	PO	Metabolic acidosis
Amlodipine	0.625 mg in cats <4 kg; 1.25 mg in cats >4 kg	q 24 hr	PO	Hypertension
r-HuEPO	100 U/kg	3 X weekly*	SQ	Anemia
Darbopoetin (Aranesp®)	0.5-1.0 µg/kg	Weekly*	SQ	Anemia
Iron dextran	50 mg	q 3 – 4 weeks	IM	Iron supplementation
Ferrous sulfate	50-100 mg	Once daily	PO	Iron supplementation
Benazepril	0.5 – 1 mg/kg	SID	PO	Proteinuria, hypertension
Calcitriol	2.5-3.5 ng/kg	SID	PO	Prevent or treat renal 2° hyperparathyroidism

*Decrease dosing interval once target hematocrit has been achieved.

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NOTES:

Feline Gastroenterology and Endocrinology

2014 CONFERENCE

September 18 - 21, 2014 ▪ The JW Marriott ▪ Indianapolis, IN

Conference Day Three

SUNDAY, SEPTEMBER 21, 2014

COMBINED TRACK
White River E & F

BREAKFAST in Exhibit Hall — 7:30 – 8:30 am
Included in your registration
ABVP Breakfast for Diplomates in White River D

Hyperthyroidism & the Kidney: A Strategy to Slow Progression of CKD in Treated Cats — 8:30 – 9:20 am
Dr. Mark Peterson

Feline Hypothyroidism: Much More Common Than You Think! — 9:25 – 10:15 am
Dr. Mark Peterson

Sponsored by Dechra Veterinary Products

NETWORKING REFESHMENT BREAK in Exhibit Hall — 10:15 – 10:45 am
Included in your registration
10:30 am Fun Run Awards Presented in Exhibit Hall

TRACK A
White River E

Nutritional Management of Endocrine Disease in Cats — 10:45 – 11:35 am
Dr. Mark Peterson

Managing Cats with Idopathic Hypercalcemia — 11:40 – 12:30 pm
Dr. Mark Peterson

Sponsored by Dechra Veterinary Products

TRACK B
White River F

Management of Problem Diabetic Patients — 10:45 – 11:35 am
Dr. Catharine Scott-Moncrieff

Role of Concurrent Illness in Insulin Resistant Cats — 11:40 – 12:30 pm
Dr. Catharine Scott-Moncrieff

Sponsored by MERCK Animal Health

LUNCH in Exhibit Hall — 12:30 – 1:45 pm
Included in your registration
12:40 – 1:40 pm Lunch & Learn: Pain Management – White River G
Separate registration required

Sponsored by Abbott Animal Health

Feline Adrenal Disease — 1:45 – 2:35 pm
Dr. Audrey Cook

Hyperaldosteronism — 2:40 – 3:30 pm
Dr. Audrey Cook

Sponsored by Abbott Animal Health

Feline Hypertension Secondary to Endocrinopathies — 1:45 – 2:35 pm
Dr. Catharine Scott-Moncrieff

Diagnosis & Treatment of Feline Acromegaly — 2:40 – 3:30 pm
Dr. Catharine Scott-Moncrieff

Sponsored by MERCK Animal Health

Conclusion of Conference — 3:30 pm

Hyperthyroidism & the Kidney: A Strategy to Slow Progression of CKD in Treated Cats

Mark Peterson, DVM, DACVIM

Introduction

Hyperthyroidism and chronic kidney disease (CKD) are both common disorders in older cats. Therefore, it should not be surprising that both disorders frequently develop together in the same cat. The prevalence of concurrent renal disease in cats with hyperthyroidism is estimated to be approximately 30-40%.[1-3]

Hyperthyroidism tends to "artificially" increase the renal blood flow (RBF), as well as the glomerular filtration rate (GFR).[1-7] When the GFR is increased in a hyperthyroid cat with underlying CKD, it can mask renal insufficiency; serum concentrations of urea nitrogen and creatinine may be normal despite mild to moderate kidney disease. Decreased muscle mass, a common feature of hyperthyroidism, also contributes to the lowered serum creatinine level in these cats (since creatinine is derived from muscle tissue).[1,3]

Successful treatment of hyperthyroidism restores the high serum T_4 concentration to normal and, in cats without CKD, also returns the high GFR back to normal values. In cats with CKD, however, the GFR will fall to the low-normal or subnormal levels expected with moderate renal dysfunction.[1-7] Therefore, this decrease in GFR can result in the apparent worsening of the serum kidney function tests or the development of renal disease.[1-7] It is important to remember, however, that treating the hyperthyroidism itself does not cause the CKD in these cats. The renal disease was already present before treatment but was masked by the hyperdynamic state of the hyperthyroidism.[1-3]

Physiological Interactions Between Thyroid Hormone and the Kidney

Hyperthyroidism results in increased renal blood flow (RBF) and GFR due to both pre-renal and renal effects.[1-3,8] Among the pre-renal factors, thyroid hormones increase the cardiac output by positive chronotropic and inotropic effects, as well as a reduction in systemic vascular resistance by dilating the arterioles of the peripheral circulation.[1-3] This indirectly contributes to an increase in RBF. There is an increased endothelial production of nitric oxide in the renal cortex and medulla by induction of nitric oxide synthase, directly by the thyroid hormones and indirectly by high arterial pressure related endothelial shear stress.[9] This is accompanied by a reduction in renal vasoconstrictor endothelin.[10] Thus, an increased intrarenal vasodilatation and decreased vasoconstriction ensues, contributing to a net increase in RBF.

The GFR increases by about 25% among hyperthyroid cats.[1-7] This increase in GFR results in part from the increase in RBF, but activation of the renin-angiotensin-aldosterone system and increased β-adrenergic activity play a role.[1-3,8,11] Overall, this results in afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction, leading to increased filtration pressure and glomerular hyperfiltration. This adds to the magnitude of increase in GFR over-and-above that contributed by the increase in RBF alone.

These systemic hemodynamic factors (i.e., increased cardiac output, decreased systemic vascular resistance) combined with intrarenal vasodilation lead to increases in RBF, GFR, and glomerular hydrostatic pressure. Thyroid hormones also influence renal tubular function, including electrolyte handling.[1-3,8,11] With time, hyperthyroidism can lead to renal changes including glomerular hypertension, glomerulosclerosis, proteinuria, and hyperplasia and hypertrophy of the renal tubules.[1-3]

Hyperthyroidism Itself Contribute to Chronic Kidney Disease (CKD) in Cats

The prevalence of CKD in general feline population has been reported to be 7.7% in cats >10 years of age and 15.3% in cats >15 years of age.[2,3] In contrast, the prevalence of CKD in hyperthyroid cats has been estimated to be as high as 30-40%.[1,2] This much higher-than-expected prevalence of CKD supports the supposition that untreated thyrotoxic state is initiating or worsening the CKD in these hyperthyroid cats. If that is true, one may want to always try to correct the cat's hyperthyroidism, even in cats with azotemia and known pre-existing CKD.

Recent research provides further evidence that hyperthyroidism may contribute to the development or progression of CKD in cats. First of all, a number of recent reports indicate that many untreated hyperthyroid cats develop proteinuria, which resolves within 4 weeks of successful treatment.[12-14] This proteinuria, which reverses after treatment, could be a reflection of glomerular hypertension and hyperfiltration, changes in tubular protein handling, or a change in the structure of the glomerular barrier. Whatever the cause of the proteinuria, no treatment is generally needed other than treatment of the hyperthyroid state itself. The proteinuria will resolve after correction of the hyperthyroid state.

Secondly, cats with untreated hyperthyroidism have high levels of retinol binding protein (RBP), a urinary marker for tubular dysfunction or damage.[12,15] This high urinary RBP excretion may reflect tubular damage or dysfunction resulting from the thyroid-induced hypertrophy and hyperplasia of the tubular cells. After treatment, these high urinary RBP levels fall in cats without azotemia but may remain slightly high in cats with pre-existing CKD. This too suggests that hyperthyroidism can cause reversible renal dysfunction; however, the renal tubular changes

may become irreversible with time as CKD progresses.

Thirdly, many cats with untreated hyperthyroidism have high values for urinary N-acetyl-b-D-glucosaminidase (NAG), a lysosomal glycosidase found primarily in epithelial cells of the proximal convoluted tubule.[16] Like RBP, NAG is a specific marker of active proximal tubular damage. After treatment, these high urinary NAG levels decrease, again suggesting that these renal changes can be reversed, at least in cats without pre-existing CKD. Overall, these studies all suggest that leaving a hyperthyroid cat untreated (or poorly regulated with methimazole) may be detrimental to long-term kidney function. Treating and curing hyperthyroidism may help to both reverse renal damage and preserve remaining kidney function.

Predicting Which Cats Have Concurrent (Masked) CKD

Predicting which untreated hyperthyroid cats have clinically significant underlying CKD is difficult.[1,2,17] In the absence of methods for accurately measuring GFR in veterinary practice, serum urea nitrogen and creatinine concentrations, urine specific gravity, and UPC should be carefully evaluated in individual cases. If any parameter is abnormal, then renal failure may become apparent upon resolution of the hyperthyroid state.

Because of these difficulties, trial therapy using methimazole has been recommended as a test of renal function.[18,19] If deterioration in renal function does not occur after medical normalization of the T_4 values, then a more definitive therapeutic option for hyperthyroidism may be selected. Except for advanced CKD, the necessity of this approach is questionable, given that treatment for the hyperthyroidism would still be recommended in most cats.[20,21] In support of that reasoning, the survival of cats that develop azotemia is no different to those that remain non-azotemic after treatment of hyperthyroidism.[3,22,23]

In most hyperthyroid cats that manifest overt renal disease after antithyroid drug treatment, permanent treatments with surgery or radioiodine can be given once the concurrent renal disease is stabilized with proper treatment (subcutaneous fluids, dietary therapy). It is important to realize that the decline in GFR following initial treatment of hyperthyroidism is not progressive with long-term euthyroidism; once serum T_4 concentrations have fallen into the normal range, the GFR tends to stabilize at that new rate.[7]

Iatrogenic Hypothyroidism Contributes to CKD in Cats

Iatrogenic hypothyroidism can develop during therapy with antithyroid drugs,[23-26] after surgical thyroidectomy,[24,27] or after treatment with radioiodine (^{131}I).[28-31] Although early reports suggested that clinical signs associated with iatrogenic hypothyroidism in cats were uncommon and that most cats did not require treatment, it is now realized that milder degrees of iatrogenic hypothyroidism are relatively common and that these cats may benefit from thyroid replacement therapy (especially if concurrent CKD is present).[3,23,32,34] Cats with severe or overt iatrogenic hypothyroidism can easily be confirmed by finding low serum T_4 and T_3 concentrations in conjunction with high serum TSH values, as measured by the cTSH assay.[23,24,26,32,34]

However, based on recent studies, it is not uncommon for high serum TSH to also develop in cats treated for hyperthyroidism despite maintenance of completely normal concentrations of T_4, free T_4, or both.[26,32,34] In a recent study, high serum TSH values developed in over a third of hyperthyroid cats treated with methimazole.[26] However, 17% of these cats had a high TSH value despite low-normal T_4 and completely normal free T_4 concentrations. We have seen similar findings in cats treated with radioiodine, i.e., a subgroup of cats with low-normal T_4 values (<1.5 µg/dl) will develop high cTSH levels, suggestive of mild or partial hypothyroidism.[32,34] These cats remain totally asymptomatic and show no clinical signs suggestive of hypothyroidism (e.g., lethargy, hair loss), although some may develop azotemia.

Do these cats with low-normal T_4 values but high TSH concentrations really have mild degrees of hypothyroidism? Is this a form of "biochemical" subclinical hypothyroidism, as reported in man? [35,36] Should the methimazole dosage (or normal ^{131}I dose) be reduced or should they be treated with levothyroxine despite their normal circulating thyroid hormone values? Or are these serum TSH values falsely high, simply representing a TSH laboratory artifact? At this time, the answers to these questions remain unknown. However, our current studies do suggest that these cats may indeed have a form of subclinical hypothyroidism.

If These Treated Cats Do Not Show Any Clinical Signs of Hypothyroidism, Why is Any of This Important?

In recent studies by Williams *et al*,[3,13,23,37] cats with "overt" iatrogenic hypothyroidism were more likely to develop azotemia in the 6 months after treatment than cats that remained euthyroid. Hypothyroid cats with azotemia also had shorter survival times than nonazotemic cats, whereas no difference in survival between euthyroid cats with or without azotemia could be detected.[23]

Overall, these findings suggest that the development of iatrogenic hypothyroidism contributes to the development of newly detected azotemia, at least in cats with mild underlying CKD that has been masked by the hyperthyroid state. More importantly, the hypothyroidism may shorten survival after treatment of hyperthyroidism.[3,13,23,37]

Recommendations for Monitoring and Treating Hypothyroidism

Whatever treatment option for hyperthyroidism is considered, we now believe it is extremely important to try to avoid iatrogenic hypothyroidism, as it may have its own detrimental effects on GFR. Hypothyroidism in both humans and dogs has been showed to reduce GFR,[8,11,38] and it is likely that similar changes occur in cats that develop iatrogenic hypothyroidism. In cats with normal renal function, such a fall in GFR may not be clinically important; however, hypothyroid cats with underlying CKD may develop moderate to severe azotemia, which is generally progressive.

If a cat with post-treatment azotemia develops a low to low-normal T_4 concentration (T_4<1.5 µg/dl), a serum TSH level should be measured to help exclude overt or subclinical hypothyroidism. If iatrogenic hypothyroidism is diagnosed based on the finding of a high TSH concentration, the methimazole dosage should be reduced. If the cat has been treated with surgery or radioiodine, then treatment with L-T_4 should be considered.[2,18,32,34] Although once daily administration (0.1 mg) may be adequate in some cats, most cats respond better to twice daily treatment (0.075 mg, BID) given on an empty stomach. The dosage should be adjusted based on post-pill serum T_4 and cTSH determinations.[32,34] Most cats treated will show improvement in their azotemia as the hypothyroidism resolves and euthyroidism is restored.[23,32,33]

Progression of CKD in Treated Cats That Maintain Euthyroidism

In most cats that develop post-treatment azotemia, the CKD is not that severe or life threatening, especially if euthyroidism is maintained (i.e., serum T_4 kept at 1.5-3.0 µg/dl). In euthyroid cats, it is unusual to see a jump of more than one IRIS stage after treatment.[14] In other words, hyperthyroid cats with IRIS Stage I-II CKD may develop overt azotemia after treatment, but one would not expect those cats' CKD to advance to more than IRIS Stage II-III after treatment.

In addition, the decline in GFR after successful treatment of a cat's hyperthyroidism is not very progressive. Rather, the fall in GFR is detectable within 1 month but then remains stable at this level for months thereafter.[1,2,7] The rise in serum urea nitrogen and creatinine values in cats with CKD follow the decrease in GFR, so that azotemia, when it does occur, would be expected to develop within 1-3 months of treatment but remain relatively stable over many months.[7,21] However, if overt or subclinical hypothyroidism develops in these cats, treatment with L-T_4 can help raise the cat's GFR and may result in lowered serum renal values.

Using L-T4 Supplementation in Cats with Pre-Existing CKD After Radioiodine or Surgical Thyroidectomy

Managing cats that present with concurrent hyperthyroidism and overt azotemia are more problematic. Again, treatment of the hyperthyroid state will lead to a rise in serum creatinine values, but this worsening in azotemia will be related to the magnitude of the suppression of circulating T_4 and T3 concentrations.

Occasionally cats with pre-existing chronic kidney disease will demonstrate overt deterioration in kidney function following the initiation of therapy for hyperthyroidism leading to a potentially life-limiting uremia. It is my firm belief that the majority of these cases are caused by periods of iatrogenic hypothyroidism that contribute to further decline in renal function. Therefore, it is of critical importance to avoid even temporary hypothyroidism in this subgroup of cats with overt CKD (serum creatinine ≥ 2.0 mg/dl), in order to maintain RBF and GFR as much as possible. Iatrogenic hypothyroidism has been shown to both worsen azotemia and shorten the life expectancy in cats with pre-existing CKD.[2,23]

Following radioiodine therapy or surgical thyroidectomy, a transient period of iatrogenic hypothyroidism is very common.[39] This period of hypothyroidism develops in the period following the radiation-induced death (or surgical removal) of the adenomatous thyroid tissue responsible for the hyperthyroidism but before regeneration of any suppressed normal thyroid tissue is possible. The duration of this iatrogenic hypothyroidism is usually a few weeks and may be completely clinically silent. However, depending on the degree of suppression or damage to normal thyroid tissues, this transient period may be clinically detected.

In most treated cats that have relatively normal renal function, this period of temporary hypothyroidism is not clinically significant and resolves without any intervention. Therefore, unless cats with normal renal function demonstrate other overt symptoms of this transient hypothyroidism (e.g., anemia, lethargy), thyroid hormone (e.g., L-T_4) supplementation is generally avoided. However, cats with preexisting renal dysfunction may show a clinically significant worsening azotemia during this period of iatrogenic hypothyroidism. As a result, thyroid hormone supplementation in these cats with iatrogenic hypothyroidism and overt CKD may be indicated.

To avoid iatrogenic hypothyroidism when treating hyperthyroid cats with concurrent CKD, we have adapted a therapeutic protocol that ensures resolution of the cat's thyrotoxicosis while avoiding even transient hypothyroidism. This therapeutic approach involves the use of customized radioiodine therapy doses (as low as possible), followed by supplementation with oral L-T_4 that is initiated at discharge from the hospitalization required for radioiodine therapy.[40]

Preliminary evaluation of cats with stage 2-3 IRIS chronic kidney disease and pretreatment serum creatinine levels of 2.0-3.5 mg/dl treated with customized doses of radioiodine ranging between 1-5 mCi and discharged on oral L-T_4 (0.075-0.1 mg q12-24h) confirmed the avoidance of iatrogenic hypothyroidism and minimal associated worsening in azotemia.[39,40] In these cats the supplementation with physiologic levels of thyroxine on discharge from the hospitalization needed for radioiodine therapy ensures that the incremental decrease in GFR that accompanies

resolution of thyrotoxicosis will not be accompanied by additional renal injury caused by iatrogenic hypothyroidism.

Most cats with concurrent CKD and hyperthyroidism will also benefit from the initiation of other standard therapies including subcutaneous fluids, dietary phosphorus restriction, phosphate binders, potassium gluconate, antihypertensive therapy (as indicated by confirmation of hypertension), benazepril (as indicated by confirmation of proteinuria), and supplemental B- vitamin administration.

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Feline Hypothyroidism: Much More Common Than You Think!

Mark Peterson, DVM, DACVIM

Introduction

In cats, as in other species, hypothyroidism is the clinical syndrome that results from the chronic deficient secretion of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3).[1-4] Unlike the situation in dogs, in which primary hypothyroidism is common, naturally occurring hypothyroidism is extremely rare in the adult cat, with only 3 documented cases reported.[5-7] Most commonly, feline hypothyroidism is an iatrogenic complication associated with overtreatment of hyperthyroidism. Spontaneous hypothyroidism, when it does develop in cats, is seen most commonly as a congenital form in dwarf kittens.[1-4]

Diagnosing Cats with Hypothyroidism: Pitfalls

Diagnosing feline hypothyroidism can be challenging, regardless of its etiology. This syndrome rarely develops spontaneously, especially in the adult cat. Most commonly, feline hypothyroidism is iatrogenic, secondary to overtreatment of hyperthyroidism. A presumptive diagnosis is based on a combination of the history, clinical signs, physical examination findings, and routine laboratory tests.[1-4]

Although early reports suggested that clinical signs associated with severe iatrogenic hypothyroidism in cats were uncommon and that most cats did not require treatment, it is now realized that milder degrees of iatrogenic hypothyroidism are relatively common and that these cats may benefit from thyroid replacement therapy. Many of these cats with mild or subclinical hypothyroidism fail to develop any overt clinical features that are noticeable to either the owner or veterinarian.

However, a number of factors can make the diagnosis of hypothyroidism difficult to confirm. First, concurrent diseases can result in an "euthyroid sick syndrome," characterized by falsely-low serum thyroid hormone concentrations.[8,9] Second, one should expect weight gain and a decreasing activity level after successfully treating a cat with hyperthyroidism. Therefore, the clinical signs of iatrogenic hypothyroidism and the expected return to a euthyroid status can overlap. Finally, many cats develop a marked transient decrease in total T_4, within the first month of therapy with ^{131}I. This transient hypothyroid state is followed by a return to euthyroidism over the next 3 to 6 months as the remaining normal thyroid tissue recovers and starts to function once again.[10,11]

In most cats, we recommend waiting 3 months before making a definitive diagnosis of iatrogenic hypothyroidism after ^{131}I treatment, especially if the cat is not presenting with typical clinical features of hypothyroidism. However, the veterinarian should diagnose or exclude hypothyroidism as soon as possible in cats with renal disease because hypothyroidism, treatment for hyperthyroidism, and chronic renal disease all lower the glomerular filtration rate (GFR).[12,13] The combined effect of these 3 factors can lead to severe azotemia or even total renal failure. Treating the hypothyroidism can raise the GFR to an acceptable level.[14,15]

Diagnostic Tests for Hypothyroidism in Cats

Serum T_4 Concentration

By definition, cats with hypothyroidism should have deficient thyroid hormone secretion.[1,2] Therefore, finding a low serum T_4 concentration is key in diagnosing feline hypothyroidism. However, it is possible for a cat with mild or subclinical hypothyroidism cat to maintain a *borderline* serum T_4 concentration in the low end of the reference range (e.g., 0.8-1.5 µg/dl; 10-20 nmol/L).[16,17]

While important in establishing a diagnosis, a subnormal T_4 concentration alone is not definitive for hypothyroidism. First of all, the serum T_4 concentration may be falsely low or borderline-low as a result of assay error. If a low serum T_4 value is found in a cat that lacks clinical signs of hypothyroidism, especially if there is no history of treatment for hyperthyroidism or obvious nonthyroidal illness, one should never hesitate to repeat the serum T_4 test using a different technique, with RIA or CEIA being the preferred assay techniques in such cases.[16,18]

Secondly, the serum T_4 concentration can also be low in cats with nonthyroidal illness.[8,9,19] In general, the severity of the illness correlates inversely with the serum T_4 concentration (i.e., sicker cats have lower serum T_4 concentrations). Because multiple diseases and other factors can falsely lower the serum T_4 concentration in cats, the veterinarian must first rule out nonthyroidal disease before considering a diagnosis of hypothyroidism.

Cats with suspected hypothyroidism and a low T_4 concentration still require additional testing before the veterinarian can make a definitive diagnosis. Further tests such as serum free T_4 concentration, cTSH concentration, or thyroid scintigraphy are indicated to confirm the disease.

Serum T_3 Concentration

In most cats with hypothyroidism, serum total T_3 concentrations are low to subnormal, correlating fairly well with the low T_4 values. This is in contrast to the situation in dogs with hypothyroidism, in which serum T_3 generally remains within the reference range limits.[20] As thyroid function abates, it appears that cats cannot compensate —as

dogs and humans initially do— by increasing the thyroidal secretion of T_3 so circulating concentrations fall. Like total T_4, however, T_3 concentrations can also be suppressed in euthyroid cats suffering from a variety of nonthyroidal illnesses.[1,2,19]

Serum Free T_4 Concentration

Free T_4 is the non-protein bound fraction of circulating T_4 that can enter cells, producing the biologic effect of thyroid hormone and regulating the pituitary feedback mechanism. Free T_4 accounts for less than 1% of circulating T_4. Because only the free T_4 is biologically active, measuring free T_4 should be (theoretically) a more sensitive test for diagnosing hypothyroidism. In addition, nonthyroidal illness influences free T_4 less than it influences the total T_4.[19,21] Therefore, free T_4 should be better at distinguishing a euthyroid cat with nonthyroidal disease from a hypothyroid cat.

Although measuring free T_4 concentration by equilibrium dialysis is generally a more accurate stand-alone test than total T_4 concentration, free T_4 is far from perfect for confirming feline hypothyroidism for the following reasons:

1) The performance and accuracy of the current free T4 assays is variable, and false-positive and false-negative test results are not uncommon.
2) Like total T4, it is possible for a cat with mild or subclinical hypothyroidism cat to maintain a *borderline* serum FT_4 concentration in the lower end of the reference range (e.g., 0.7-1.5 ng/dl; 10-20 pmol/L).
3) Moderate to severe nonthyroidal illness can falsely lower the free T_4 concentration, although to a lesser degree than seen with total T_4.[19]
4) Up to 20% of cats with non-thyroidal disease develop a falsely high free T_4 concentration, further confusing the interpretation.[2,19,21]

Serum TSH Concentration

In dogs with hypothyroidism, a high serum TSH concentration confirms that the disease is primary (located within the thyroid gland). A specific assay for feline TSH is not yet available, but the commercially available cTSH assay cross-reacts with feline TSH enough to enable its use as a diagnostic test for hypothyroid cats. In two of the reported adult cats with spontaneous hypothyroidism, the serum TSH concentration was high when measured with the cTSH assay.[6,7] Similarly, many cats with iatrogenic hypothyroidism will also develop high serum TSH concentration as measured by the cTSH assay.[16,17,22]

Normal cats and cats with nonthyroidal illness generally maintain normal values for serum TSH. Therefore, the finding of a low total or free T_4 in combination with a high TSH concentration greatly improves the diagnostic sensitivity for hypothyroidism.

Serum Thyroid Hormone Panels (T4, free T4, T3, TSH)

Differentiating hypothyroid from euthyroid cats can be challenging and may require evaluation of more than a single thyroid function test. The use of thyroid panels, which include serum total T_4, free T_4, total T_3, and cTSH, are now commonly offered by many commercial laboratories. Evaluation of these thyroid panels that measure multiple thyroid hormones can be very helpful in improving diagnostic sensitivity for hypothyroidism.

Although complete thyroid panels are helpful in diagnosis of hypothyroidism, discordant results are very common. For example, as noted above, it is not uncommon to see high cTSH concentrations with completely normal T_4 and free T_4 values in cats that have been treated for hyperthyroidism. Most of those cats are not clinical for hypothyroidism and it is unclear what the clinical significance of the high TSH concentration really is in this subgroup of cats. In general, however, if serum TSH is clearly high and all 3 thyroid hormones (total T_4, free T_4, or T_3) are low to low-normal, that can be considered diagnostic for hypothyroidism.

Thyroid Scintigraphy

Thyroid scintigraphy is considered the best imaging technique for dogs with suspected hypothyroidism because it can distinguish between hypothyroid dogs and dogs with a falsely low serum T_4 concentration.[23,24] In hypothyroid dogs, thyroid imaging typically reveals decreased or even absent radionuclide uptake (thyroid gland is not visible on the scan). In contrast, dogs with a falsely low serum thyroid hormone concentration secondary to illness or drug therapy will have a normal thyroid image.

Thyroid scintigraphy is also a powerful tool for diagnosing adult hypothyroid cats (both spontaneous and iatrogenic). As in hypothyroid dogs, thyroid imaging shows minimal to no uptake of the radionuclide.[6,16.17] Unfortunately, apart from expense and the difficulties in dealing with radioisotopes, few veterinarians have access to the equipment needed to obtain thyroid images or perform thyroid uptake determinations.

Recommended Diagnostic Protocol for Cats with Suspected Iatrogenic Hypothyroidism

After treatment of cats with ^{131}I, surgical thyroidectomy, or methimazole, I recommend monitoring the cats with a complete physical examination, as well as routine laboratory testing (e.g., CBC, serum chemistry panel, complete urinalysis) and total T_4 determinations. No matter what treatment is chosen, the ideal post-treatment serum T_4 concentration is a value in the mid-normal range, i.e., if the T_4 reference range is listed as 0.8-4.0 µg/dl (10-50

nmol/L), my goal is to maintain the T_4 values between 1.5-3.0 µg/dl (20-40 nmol/L). Recent research indicates that both mild hyper- and hypothyroidism are deleterious to kidney function and may worsen already present chronic kidney disease.[13,25,26]

If a low to low-normal serum total T_4 (<1.5 µg/dl; <20 nmol/L) is found during treatment with antithyroid drug therapy, the daily dosage should be reduced and the cat rechecked in a month. If a low to low-normal serum total T_4 develops after therapy with surgery or radioiodine, however, a complete thyroid panel is recommended. As in dogs and human patients with hypothyroidism, the finding of a high serum TSH concentration, together with low serum thyroid hormone values (i.e., total T_4, free T_4, and T_3), is consistent with *overt* primary hypothyroidism. Cats with nonthyroidal illness (such as CKD) commonly have low serum total and free T_4 concentrations, but these sick cats generally maintain normal values for serum TSH, which helps exclude iatrogenic hypothyroidism.

If, after treatment, the serum T_4 remains normal but falls into the low-normal range, a complete thyroid profile is needed to rule out mild or subclinical hypothyroidism. This is especially important to do in cats that develop post-treatment azotemia or show marked worsening of existing CKD. Even if the serum thyroid values remain in the low-normal range, the finding of a high serum TSH concentration is consistent with a diagnosis of subclinical hypothyroidism and thyroid hormone replacement may be considered.

In most cats, we recommend waiting at least 3 months after ^{131}I or thyroidectomy before embarking on a workup for permanent iatrogenic hypothyroidism, especially if the cat is not presenting with the clinical features of hypothyroidism. However, the veterinarian should diagnose or exclude hypothyroidism as soon as possible in cats with renal disease inasmuch as hypothyroidism, treatment for hyperthyroidism, and chronic renal disease all lower the GFR. The combined effect of these three factors can lead to severe azotemia or even total renal failure. In hypothyroid cats with concurrent CKD, instituting T_4 replacement therapy and increasing serum thyroid hormone concentrations back into the reference range may help raise the GFR to an acceptable level and reduce azotemia.[15,17]

Treating Cats with Hypothyroidism

If hypothyroidism is diagnosed in a cat treated with methimazole, the daily dosage should be lowered. On the other hand, if overt hypothyroidism developed after treatment of cats with ^{131}I or surgical thyroidectomy, it's likely that the hypothyroid state is permanent and treatment with thyroid hormone supplementation should be considered. Likewise, if spontaneous hypothyroidism develops, treatment with thyroid hormone must be instituted.

Deciding Which Cats Should be Treated or Just Monitored

If overt hypothyroidism is present (low serum concentrations of total T4, free T4, and T3, together with high levels of TSH), treatment should be instituted. On the other hand, if subclinical hypothyroidism is present (i.e., normal serum concentrations of total T4, free T4, and T3, together with high TSH), then I based the decision about whether to supplement or "wait and see" based on presence and degree of azotemia.

Choice of Thyroid Hormone Preparation

All cats with permanent, overt hypothyroidism require chronic thyroid hormone replacement therapy. A variety of thyroid hormone preparations are available, including synthetic sodium levothyroxine (L-T4), synthetic sodium liothyronine (L-T3), or natural thyroid hormone preparations (desiccated thyroid).[27]

Supplementation with L-T4 is the treatment of choice for most species, as T4 is the principal secretory product of the thyroid gland and is the physiological "prohormone" for T3, the most potent or biologically-active thyroid hormone.[28] Therefore, normalizing circulating concentrations of T4 and T3 in cats with hypothyroidism can be best achieved by administration of L-T4, which ends up replacing T3 as well as T4. However, some cats that do not respond adequately to replacement with L-T4 alone will benefit with the addition of L-T3; this is especially true if serum T3 concentrations remain low on L-T4 supplementation.

Many L-T4 products (both brand name and generic) are available, although none are currently marketed for cats. Most of these are made available as tablets, but an oral solution (Leventa, Merck Animal Health; 100 µg/ml) is marketed for use in dogs.[29] This liquid formulation is preferred over L-T4 tablets by many owners since the small volume formulation of the L-T4 solution may be easier to administer or hide in the cat's food.

Dose of Thyroid Hormone Replacement

Pharmacokinetic studies of oral L-T_4 in young, clinically normal cats indicate that L-T_4 is rapidly cleared from the circulation with an average half-life of only 5.5 hours (range, 3.0-10.7 hours). In that study, the time to reach peak L-T_4 concentrations occurred shortly after administration (i.e., 1.5-3.0 hours) and reached peak plasma concentrations of 57 nmol/L (4.4 µg/dl).[30] Based on those results in normal cats, an oral L-T_4 dosage of 100 µg/cat, given once daily, was suggested.

In contrast to young, clinically normal cats, our clinical studies of cats with iatrogenic hypothyroidism treated with the same oral liquid formulation of L-T4 (i.e., Leventa) demonstrate that it may difficult to achieve high-enough post-treatment serum T4 values in many of these senior or geriatric cats, even after administration of Leventa doses higher than the 100 µg/day.[17] Although the reason for this is not clear, it is well known that many factors can interfere

with L-T4 absorption, including gastrointestinal disease, oral medications (e.g., calcium carbonate, aluminum hydroxide), and food, including high-fiber diets.[31-34] Senior and geriatric cats may have a reduced ability to absorb nutrients from the gastrointestinal tract,[35] which could also play a role in this apparent L-T4 malabsorption.

Because of this poor apparent absorption of L-T4 in many of our senior or geriatric cats, coupled with the short plasma half-life of T4 in cats, we recommend that one initiate supplementation with twice daily administration of 75 µg of L-T4 (either as solution or tablet), given on an empty stomach, if possible.[17] If the owner cannot administer the L-T4 twice a day, once daily administration (100-150 µg, PO) can be attempted, but this regime will not result in adequate thyroid replacement in most older cats with iatrogenic hypothyroidism.

Timing of Feeding and Thyroid Replacement Dosing

Simultaneous administration of L-T4 with food can markedly delay and inhibit the absorption of the drug in both humans[31-33] and dogs,[35] and this likely also occurs in cats. In one study of dogs, giving the L-T4 with food decreased its absorption by about 45%.61 The standard of care for human patients requiring L-T4 is to administer the drug on an empty stomach, generally an hour before meals.

Food, as well as some commonly used medications (e.g., phosphate binders),[34] also appear to impair L-T4 absorption in cats. All balanced commercial cat foods have added minerals (e.g., calcium), which may bind to L-T4 to form an insoluble or nonabsorbable complex and reduce its absorption. To ensure optimal absorption and consistent serum thyroid hormone concentrations, L-T4 is best given by mouth at least 1 hour before or 3 hours after feeding (and administration of other medications).

Depending on lifestyle, not all cat owners can easily follow these recommendations concerning the timing between the L-T4 dose and feeding. However, it is always important to standardize the time in which the L-T4 dose is given in relation to feeding. Once a protocol is established, it should be used for each dosing period, especially on the day of thyroid hormone monitoring (see below).

If the L-T4 must be given in food because of difficulties in directly administering the L-T4 into the cat's mouth, the owners can place the liquid solution or crushed tablet into a small amount of a favorite food (e.g., chicken or beef baby food works well for many cats) and then feed the main meal an hour later. Again, it is important for owners to be consistent in the amount of favorite food fed, as well as the timing between the L-T4 dose and main meal, to avoid marked variations in L-T4 absorption from day to day.

Post-Pill Monitoring and Thyroid Hormone Testing

Timing for serum thyroid monitoring: Hypothyroid cats receiving L-T4 supplementation should demonstrate an increase in circulating total T4 and T3 values, which peak at only a few hours after treatment and then progressively decline until the next dose.[30] In order to identify "peak" serum thyroid concentrations, it is therefore essential that post-treatment samples be collected approximately 4 hours after administration of the morning L-T4 dose.

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Nutritional Management of Endocrine Disease in Cats

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Introduction

When treating cats with endocrine disease, most of us concentrate on the latest or best drug that can be used to cure or manage the disease. However, it is also important to realize that proper nutritional support also plays an integral role in management of these diseases. Whenever considering feline nutrition, it is paramount to remember that cats are strict carnivores that rely on nutrients in animal tissues to meet their specific and unique nutritional requirements. In their natural habitat, cats consume small prey high in protein (50-70%) with moderate amounts of fat (30-50%) but very minimal amounts of carbohydrates (1-2%).[1,2] Evolution has shaped the cat's core metabolism to adapt to this carnivorous diet of animal tissues over a period of millions of years, so it is not very "natural" for cats to eat many of the commercial diets that contain moderate to high amounts of carbohydrates (35-50%) and a much lower amount of protein, especially animal protein.

In this review, I will cover the two most common endocrine problems of cats seen in clinical practice (i.e., hyperthyroidism and diabetes) and discuss the way I integrate nutrition into the management of these common feline diseases. We want to use the cat's diet to support their overall body and metabolism and therefore best manage their underlying endocrine disease.

Hyperthyroidism in Cats

Hyperthyroidism is the most common endocrine disorder of cats, and is one of the most common medical problems seen in small animal practice. Surprisingly, despite the fact that nutritional factors and cat food has been proposed to have a role in the etiopathogenesis of this disease, there are only limited published recommendations about what to feed these cats. The question, *"What's the best diet to feed my hyperthyroid cat?"* is an extremely common one that we all get from concerned cat owners.

The Many Metabolic Problems Facing the Hyperthyroid Cat

When secreted in excess, thyroid hormones have profound metabolic effects on the whole body, and dysfunction of multiple organ systems (CNS, cardiac, gastrointestinal, hepatic, and renal) is common in hyperthyroid cats.[3-5]

Weight Loss and Muscle Wasting

Weight loss, despite a normal to increased appetite, is the classic and most common signs seen in cats with hyperthyroidism. These cats lose weight because their hyperthyroidism accelerates their metabolic rate and body's energy expenditure; they are burning up their food calories faster than they can consume their daily meals.

It's important to realize that hyperthyroidism is a catabolic state. The progressive weight loss and muscle wasting that is so characteristic of feline disease is caused by increased protein catabolism leading to a negative nitrogen balance. When hyperthyroid cats first lose weight, the case can usually be first noticed as a loss of muscle mass in the cat's lumbar paravertebral area. Despite this loss of muscle mass, most mildly hyperthyroid cats retain their "belly" during the initial stages of their thyroid disease and may even have a higher than ideal body condition score. With time, severe muscle wasting, emaciation, cachexia, and death from starvation can occur if the cat's hyperthyroidism is left untreated.[3-5,6] In hyperthyroidism, the cat's body consumes its own muscle tissue to get the protein it needs to sustain its life.

Even with treatment of hyperthyroidism, recovery of muscle mass and function may be prolonged, lasting several weeks to months. This is especially true if these cats are not provided with enough dietary protein to rebuild and maintain their lost muscle mass.

Hyperglycemia, Glucose Intolerance, Insulin Resistance, and Overt Diabetes

Hyperthyroid cats commonly develop profound changes in glucose and insulin metabolism. Mild to moderate hyperglycemia is common in hyperthyroid cats, which is generally attributed to a "stress" reaction. However, the underlying metabolic changes are actually much more complicated: hyperthyroidism frequently causes moderate to severe "endogenous" insulin resistance, as demonstrated by high resting serum insulin concentrations and an exaggerated insulin response during an IV glucose tolerance test.[7,8] This insulin resistance is associated with a decreased glucose clearance (impaired glucose tolerance), which is indicative of a prediabetic state.

Occasionally, an untreated hyperthyroid cat will develop overt diabetes mellitus.[9,10] Many of these diabetic cats will develop moderate resistance to the injected insulin, with poor diabetic control.[9,11] Surprisingly, the insulin resistance and prediabetic state so common in hyperthyroid cats does not always improve and may even worsen despite successful treatment of hyperthyroidism.[8] This indicates that hyperthyroid cats may have long-lasting alterations of glucose tolerance and insulin secretion that cannot always be reversed by treatment. In accord with

that, some of these hyperthyroid cats (not diabetic at diagnosis) will go on to develop overt diabetes in the months after treatment of hyperthyroidism. Most cats that develop diabetes after the hyperthyroid state has been corrected have become overweight or obese, which may also contribute to the development of their diabetes.

Hyperphosphatemia, Secondary Hyperparathyroidism and Chronic Kidney Disease

Hyperthyroidism and chronic kidney disease (CKD) are both common disorders in older cats. Therefore, it should not be surprising that both disorders frequently develop together in the same cat. The prevalence of CKD in the geriatric cat population has variably been reported as 7.7% of cats over 10 years of age,[12] 15.3% of geriatric cats over 15 years of age,[13] and 30% of geriatric cats over 15 years of age.[14] By comparison the prevalence of chronic kidney disease in hyperthyroid cats (average age of 12-13 years) has been reported as 30-40%.[15-17] The higher than expected prevalence of chronic kidney disease in hyperthyroid cats suggests that thyrotoxicosis may actually contribute to the development or progression of CKD in cats.

Hyperthyroidism could be damaging the feline kidney by several mechanisms. In the hyperthyroid state, volume expansion occurs secondary to activation of the renin-angiotensin-aldosterone system. There is also sympathetic activation, leading to an increase in the heart rate. Both of these alterations tend to increase the renal blood flow (RBF) and the glomerular filtration rate (GFR), and could lead to glomerular hypertension.[15-17] When the GFR is increased in a hyperthyroid cat with underlying CKD, it can mask renal insufficiency; serum concentrations of urea nitrogen and creatinine may be normal despite mild to moderate kidney disease. Decreased muscle mass, which is a common feature of hyperthyroidism, also contributes to the lowered serum creatinine concentration in these cats (since creatinine is derived from muscle tissue).[1-3]

Successful treatment of hyperthyroidism restores the high serum T4 concentration to normal and, in cats without CKD, also returns the high GFR back to euthyroid values. In cats with CKD, however, the GFR will fall to the low-normal or subnormal levels expected with moderate renal dysfunction. Therefore, this decrease in GFR can result in the worsening of the serum kidney function tests or the development of renal disease. Although the CKD was present before treatment, the CKD was masked by the hyperdynamic state of the hyperthyroidism.[15-17]

In addition to the hyperthyroid-induced increase in renal hemodynamics, hyperthyroid cats may also develop a number of metabolic disturbances that may contribute to progression of renal disease. Between a third to half of hyperthyroid cats will develop hyperphosphatemia,[18,19] and about 60% of hyperthyroid cats have high plasma concentrations of parathyroid hormone (PTH).[17,18,20] This combination of hyperphosphatemia and high PTH concentrations is consistent with secondary renal hyperparathyroidism, which could indicate the presence of underlying kidney disease in these cats. Since PTH is regarded as a uremic toxin in itself, such hyperthyroid-associated elevations in plasma PTH concentrations could be one mechanism of renal damage leading to increased morbidity and mortality in cats with hyperthyroidism.

Sarcopenia of Aging

In addition to loss of muscle mass from the catabolic effects of thyroid hormone excess, cats also tend to lose muscle mass as they age, independent of their thyroid status. This phenomenon, referred to as sarcopenia of aging, is also common in elderly human beings.[21] The term age-related sarcopenia is derived from Greek (meaning "poverty of flesh") and is characterized by a degenerative loss of skeletal muscle mass and strength, as well as increased muscle fatigability.[22,23]

In adult cats, maintenance energy requirements decrease by about 3% per year up until the age of 11 years, and then actually start to increase again.[24] This contributes to a tendency of senior cats to lose muscle mass if their energy needs are not met. Lean body mass of aging cats drops dramatically after 12 years of age, and by age 15, cats may have a mean lean tissue mass that is a third less than cats aged 7 years or less.[25,26] Body fat also tends to progressively decrease in cats after the age of 12 years; this combination of reduced lean mass and body fat contributes to weight loss experienced by many elderly cats.

The ability to digest protein is also compromised in many geriatric cats. After the age of 14 years, one-fifth of geriatric cats have reduced ability to digest protein.[24-26] Reduced protein digestibility in geriatric cats seems to occur in parallel with reduction of lean tissue and it might predispose them to negative nitrogen balance. Although moderation of calorie intake might be suitable for some mature cats, it does not appear to match the needs of most geriatric cats.

Recent studies of both adult and senior cats indicate that the daily protein requirements of adult cats needed to maintain lean body mass (≈5 g/kg body weight) is considerably higher than that currently recommended for adult maintenance by either AAFCO or NRC guidelines.[27,28] Feeding a higher-protein, highly digestible, energy-dense diet to senior and geriatric cats may prevent or slow their decline in body weight and lean body tissue associated with aging.[24,29] Limiting protein intake in geriatric cats, at a time when lean tissue has been lost, will only hasten the progression of muscle wasting.

Because over 95% of all cats with hyperthyroidism will be older than 10 years of age,[1-3] almost all hyperthyroid cats can be considered to be a senior or geriatric.[30] Therefore, sarcopenia of aging will contribute to the loss of lean body mass induced by the catabolic effect of chronic hyperthyroidism, even after the cat's hyperthyroid state has been successfully treated.

Diet Recommendations for Hyperthyroid Cats

High Dietary Protein

Obligate carnivores, such as the cat, are unique in their need for large amounts of dietary protein (specifically, dispensable nitrogen) that separates them from omnivores and herbivore species.[1,2] This absolute requirement for dietary protein intake in cats is critically important when formulating a diet for hyperthyroid cats, in which protein catabolism and muscle wasting is universally present. Protein is the primary macronutrient responsible for maintenance of muscle mass. Restoring and preserving any remaining muscle tissue in cats treated for hyperthyroidism depends upon the cat consuming a diet with sufficient amounts of high-quality protein (40-60% calories as protein).

This recommendation for higher amounts of dietary protein does not change once euthyroidism has been restored. The dogma that all older cats should be fed reduced energy "senior" diets must be questioned based on what is now known about the increasing energy requirements and nutritional needs of older cats.[24-29] In most geriatric cats, logic dictates the use of highly digestible, energy-dense food to mitigate the decline in body weight and lean body tissue and to avoid protein: calorie malnutrition. Reducing protein intake in geriatric cats, at a time when lean tissue has been lost, is contraindicated. Geriatric cats seem to have nutritional requirements closer to kittens than to mature adult cats. Remember that when deprived of protein, carnivores will continue to break down muscle tissue to create the energy they need.[1,2] By feeding only high-quality protein diets, we will help restore the cat's muscle mass and improve strength and agility.

Low Dietary Carbohydrates

Since most of these cats also have subclinical diabetes —as evidenced by their mild hyperglycemia, glucose intolerance, and insulin resistance— feeding a low carbohydrate diet (<10% of total calories) also is strongly recommended.[6,31,32] Feeding a low carbohydrate diet will lessen postprandial hyperglycemia, improve insulin sensitivity, reduce the need for exogenous insulin, and help stabilize glucose metabolism in these cats.[32-34] This may prevent the development of overt diabetes and control long-term obesity in these cats after successful control of the hyperthyroidism.

It is important to remember that low carbohydrate diets must contain moderate to high amounts of fat (e.g., if we feed 10% of calories as carbohydrate and 40% of calories as protein, the remaining 50% of calories must come from fat). For the underweight hyperthyroid cat, this caloric density of fat can be advantageous. However, after the hyperthyroidism is controlled, one must monitor caloric intake, body weight and BCS to ensure the cat does not become overweight or obese, which will also predispose the euthyroid to diabetes.

Check out this website (www.catinfo.org), which gives you a breakdown of the nutritional composition of the various prescription and over-the-counter diets (click on link entitled "Protein/Fat/Carbs Chart" on the right side-bar of home page). It turns out that many of the over-the-counter canned diets have an acceptable composition of protein and carbohydrates. However, the composition of almost all dry cat diets are much too high in carbohydrates and most are too low in protein content. That is why I believe it's best to limit the amount of dry food that is fed to hyperthyroid cats, or even better, not feed dry food at all.

Lower Dietary Phosphate

If concurrent CKD is documented, either before or after treatment of hyperthyroidism, mild to moderate reduction of dietary phosphate is recommended, depending on the severity of the CKD. Secondary renal hyperparathyroidism may contribute to the progression of CKD in cats, and the feeding of phosphate-restricted diets to cats with CKD can reduce PTH concentrations in cats with CKD and improve survival time.

We determine the severity of the cat's CKD by use of the International Renal Interest Society (IRIS) staging system, which is based on the plasma creatinine concentration (i.e., Stage 1 <1.6 mg/dL; Stage 2 = 1.6 to 2.8 mg/dL; Stage 3 = 2.9 to 5.0 mg/dL; and Stage 4 > 5 mg/dL).[33]

The phosphate content in adult feline maintenance diets can encompass a wide, ranging from diets that contain phosphate levels just above the AAFCO minimum (125 mg/100 kcal) to levels well above 500 mg/100 kcal. In cats with mild CKD (IRIS stage 1 or 2), we recommend feeding a diet containing a phosphate content in the lower end of this range (e.g., 125 to 250 mg of phosphate per 100 kcal), adjusted as needed to maintain serum phosphate concentrations to within the International Renal Interest Society target range for cats with CKD (i.e., 2.5-4.5 mg/dl).[34] In some cats, dietary phosphate may need to be further restricted to < 125 mg/100 kcal to achieve the target serum phosphate concentrations. Again, because we would ideally select a lower phosphate diet that also contains higher amounts of protein and lower amounts of carbohydrates, most over-the-counter (OTC) diets will not meet all of these criteria. To obtain information concerning the phosphate concentrations of cat foods, one should refer to the company's product guide or call the pet food company for specific product information.

For cats with more advanced CKD (IRIS stage 3-4), phosphate restriction to levels below the AAFCO minimum may be indicated.[35] For this purpose, feeding a phosphate-restricted diet (<125 mg per 100 kcal) is recommended. This can most easily be accomplished by feeding a prescription kidney diet; however, none of these commercial kidney diets will meet our other recommendations for higher protein (>40% ME; >12 g/100kcal) and

lower carbohydrates (<15% ME; <4.5 g/100 kcal) levels in these older cats. Alternatively, a high protein, lower carbohydrate diet can be formulated that is also relatively low is phosphorus.

If a low-phosphate diet cannot be fed or serum phosphate concentrations remain above 4.5 mg/dl, the use of phosphate binders is started. Aluminum hydroxide (100 mg/kg/day) is commonly used and can be mixed with canned or dry food.

Diabetes Mellitus

Evolutionary events shaped the cat's core metabolism such that their systems are uniquely set up to metabolize a diet which is high in moisture, high in protein, and very low in carbohydrates. Because this is the diet they have relied upon for tens of thousands of years, they do not have the ability to process carbohydrates very efficiently.[1,2] This becomes extremely important when selecting a diet for cats with diabetes (see below).

Normal Glucose Metabolism and Postprandial Glycemia in Cats

So what are these specific feline adaptive mechanisms that have developed to meet the requirements of a carnivorous diet? First, a cat's gluconeogenic pathway provides an almost continuous source of carbon skeletons for glucose or energy production.[1,2] Secondly, glucokinase concentrations are markedly reduced or absent, whereas hexokinase activity is increased. This is in marked contrast to the liver of omnivores (dogs, man), which contains both glycolytic enzymes that act to catalyze the phosphorylation of glucose during glycolysis. In addition, cats have reduced disaccharide activity in the small intestine, reduced and delayed insulin secretion, and delayed gastric emptying.

As a result of these differences, plasma glucose clearance rates are longer in cats compared to dogs or humans after feeding a moderate to high carbohydrate meal — in other words, even normal cats have much more prolonged postprandial period of hyperglycemia than might be expected. In healthy humans and dogs, postprandial hyperglycemia normally persists for 2 to 5 hours. In contrast, a recent study of healthy cats found that both serum glucose and insulin concentrations remained significantly increased for a median time of 12 hours following ingestion of a moderate carbohydrate meal (25% ME), and that both glucose and insulin concentrations remained above baseline values for 24 hours in approximately 20% of the cats.[36] Most feline diets contain ever higher amounts of carbohydrate and therefore would be expected to result in more severe postprandial hyperglycemia and a longer time to return to baseline.

The Many Metabolic Problems Facing the Diabetic Cat

Diabetes mellitus can be associated with profound metabolic effects on the whole body, leading to hyperglycemia, ketosis, hyperlipidemia, azotemia, and electrolyte imbalances. Dysfunction of multiple organ systems (pancreatic, hepatic, renal, and peripheral nervous system) is common in cats with diabetes mellitus.[37] Like hyperthyroidism, uncontrolled diabetes is a catabolic condition, so while obesity predisposes the cat to becoming diabetic, loss of weight —especially loss of lean body mass— is common in cats with diabetes.

Hyperglycemia, Insulin Resistance, Decreased Insulin Secretion, Glucose Toxicity

Based on clinical characteristics and islet pathology, approximately 90% of diabetic cats appear to have type 2 diabetes mellitus, which results from a combination of impaired insulin secretion, insulin resistance, and amyloid deposition in the pancreatic islets. Insulin resistance is a hallmark of type 2 diabetes. Diabetic cats are, on average, six times less sensitive to insulin than are healthy cats.[37] Weight gain and obesity, not uncommon in cats with diabetes, has a particularly profound effect on insulin resistance.

Loss of beta cell function is another hallmark of type 2 diabetes mellitus.[37] The mechanisms of beta cell failure are still debated, but intracellular amyloid oligomers are a likely contributor in early stages. Insulin resistance and glucose toxicity further contributes to beta-cell damage and maintenance of the diabetic state. Glucose toxicity describes the phenomenon of suppression of insulin secretion from beta cells secondary to prolonged hyperglycemia. Glucose toxicity is dose-dependent, with greater suppression occurring with more severe hyperglycemia. Suppression of insulin secretion by glucose toxicity is initially reversible but eventually results in the irreversible loss of beta cells.[38.39] This explains why cats with poorly controlled diabetes for longer than 6 months will have a reduced probability of remission, even after good glycemic control is achieved.[37]

Weight Loss or Gain, Obesity, Muscle Wasting

At time of diabetes diagnosis, weight loss is reported in about 70% of cats. However, cats are more often overweight or obese (40%) than of normal weight or underweight.[37] Muscle wasting and poor muscle condition scores are detected in about half of cats with diabetes.

Sarcopenia of Aging

Epidemiologic studies in cats consistently show diabetes to be a disease of older cats. Like cats with hyperthyroidism, the typical diabetic cat is a senior, with about 70% older than 10 years of age at time of diagnosis.[37]

Therefore, since most of these cats are older, they are also prone to develop sarcopenia of aging, as discussed above.

In human patients, Type 2 diabetes is associated with an increased risk of concurrent sarcopenia.[40,41] In addition, because skeletal muscle is a primary site for insulin-mediated glucose uptake and deposition, sarcopenia (and especially sarcopenic obesity) may promote insulin resistance, predisposing to the development of type 2 diabetes and making diabetes more resistant to control.[40,41]

We do not know if the loss of muscle mass alone (sarcopenia) or combined with weight gain (sarcopenic obesity) —both commonly seen in cats with diabetes —also contributes to the insulin resistance and hyperglycemia associated with the feline disorder. However, it seems reasonable to assume that sarcopenia and sarcopenic obesity may indeed do so in cats, as it does in man.

Nutritional Strategies and Recommendations for Diabetic Cats

Low Dietary Carbohydrates

As recommended in recent diabetes management guidelines,[31] most practicing veterinarians who specialize in feline medicine agree that feeding a low-carbohydrate diet is a mainstay in the treatment of diabetes mellitus, especially if remission of the diabetic state is the goal. In accord with that, there is strong clinical and research evidence that a diet containing low concentrations of carbohydrate (e.g., carbohydrates <12% of calories) is an effective means for achieving our nutritional goals for cats with diabetes.[31,32,42] In diabetic cats treated with an intensive insulin regime, decreasing carbohydrate content to even lower levels (e.g., <6% of calories) may help increase the rate of remission. Feeding a high protein, low carbohydrate diet will improve insulin sensitivity, help stabilize glucose metabolism, and can reduce or eliminate the need for exogenous insulin in many cats. The likely mechanism for these observations is relatively simple —decreasing dietary carbohydrate load reduces the postprandial blood glucose elevation, which in diabetic cats can be prolonged, sometimes lasting for over 12 hours.[36,43]

If a change in feeding to a low-carbohydrate diet is made in a diabetic cat already stabilized on insulin, it is extremely important to realize that this will result in a lowered daily insulin requirement — often significantly.[37] If not closely monitored—ideally with home glucose testing— severe hypoglycemia can develop in these cats. Therefore, when changing from a higher-carbohydrate to a low-carbohydrate diet, we recommend initially reducing the insulin dose by 30% to 50% to help avoid hypoglycemia.

If the diabetic cat goes into remission (no more insulin needed to maintain euglycemia), we recommend maintaining the low-carbohydrate diet for life to help prevent relapse of the diabetic state.

High Dietary Protein

Because diabetes is a catabolic state, loss of muscle mass is common in cats with diabetes, even if their body condition score indicates overweight or obesity. In these cats, it is essential that we feed a diet containing adequate amounts of protein to ensure maintenance of lean body mass in the face of this catabolic diabetic state. Feeding a higher protein diet might also help restore some of the lost muscle mass in these cats, once insulin therapy is instituted. In addition, higher protein diets will help prevent the hepatic lipidosis from developing during induction of weight loss (needed in many diabetic cats), and are essential to increasing metabolism to help promote fat burning and normal insulin function.[32]

Protein is the primary macronutrient responsible for maintenance of muscle mass.[23] Restoring and preserving remaining muscle tissue in diabetic cats, an obligate carnivore, depends upon the cat consuming a diet with sufficient amounts of high-quality protein (>40% of calories).[31] This higher than average protein level also helps restore and maintain lost muscle mass, since many diabetic cats will develop “sarcopenia” as they age.

Although it is important to implement a low-carbohydrate/high protein diet in the management of most cats with diabetes as soon as possible, there are circumstances where this should be delayed or may be inappropriate. For example, in cats with advanced (IRIS stage 3-4) CKD requiring phosphorus restriction and a reduction in dietary protein, high-protein/low-carbohydrate diabetic diets may not be appropriate. In cats with earlier stages of CKD, phosphorus should be restricted, if possible using other methods than changing to a protein-restricted diet (higher in carbohydrate), because this will likely reduce the probability of remission. In cats with later stages of CKD or in those cats in which remission is unlikely, use of a prescription kidney diet is recommended. It is important to remember that over-the-counter low carbohydrate cat foods may have substantially higher phosphate levels than some of the veterinary prescription diets designed for diabetes. Therefore, one must obtain the nutrient profile of the specific product to determine if the product meets the desired nutrient goals for that individual patient.

It is important to remember that low carbohydrate diets contain moderate to high amounts of fat (e.g., if we feed 12% of calories as carbohydrate and 45% of calories as protein, the remaining 43% of calories must come from fat). For the underweight diabetic cat, this caloric density of fat can be advantageous. However, in the overweight diabetic cat or in the controlled normal weight diabetic, one must monitor caloric intake, body weight, and BCS to ensure the cat does not become overweight or obese, which will also worsen insulin resistance and may lead to relapse of diabetes in those cats placed into remission.

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Managing Cats with Idiopathic Hypercalcemia

Mark Peterson, DVM, DACVIM

Introduction

Over the last two decades, a syndrome of idiopathic hypercalcemia in cats has emerged and appears to be increasing in frequency.[1-3] Although the cause of idiopathic hypercalcemia remains elusive, this is now considered the most common type of hypercalcemia in cats.

Cats with idiopathic hypercalcemia range in age from <1 year to up to 20 years.[1-6] There is no obvious breed or sex predilection, but longhaired cats appear to be overrepresented. About half of affected cats show no clinical signs at diagnosis. Signs reported in the other cats include weight loss, anorexia, or gastrointestinal complains. Most cats with idiopathic hypercalcemia are not azotemic at initial diagnosis, but many develop azotemia at a later date as the disease progresses. Uroliths (often oxalates) are observed in 10% to 15% of affected cats.

Diagnosis of Idiopathic Hypercalcemia

There are many potential causes of hypercalcemia in the cat. A differential diagnostic list ensures that all possibilities for the development of hypercalcemia have been considered. Hypercalcemia may be parathyroid-independent, or parathyroid-dependent (primary hyperparathyroidism). In parathyroid-independent hypercalcemia, the elevation of circulating ionized calcium concentrations results in suppression of parathyroid hormone (PTH) production.

The most common diagnoses in cats with persistent elevations in ionized calcium are idiopathic hypercalcemia and malignancy-associated. Renal failure will often be accompanied by elevations in serum total calcium values, but ionized calcium is rarely elevated in this condition. Hypervitaminosis D can also produce severe hypercalcemia in cats, so a dietary and supplement history should always be collected.

In many cases the diagnosis will be obvious upon analysis of history and physical examination. In others, the cause may not be obvious, and further work-up including hematology, serum biochemistry, body cavity imaging, cytology, and histopathology will be necessary.

The magnitude of elevation of serum total calcium concentration cannot be used to make a diagnosis, as there is considerable overlap in the degree of hypercalcemia in cats with idiopathic hypercalcemia or other conditions. Cats with idiopathic hypercalcemia may present with mild increases in total calcium concentration (11-12 mg/dL), whereas others may have values >15 mg/dL.

The serum concentrations of both total and ionized calcium are high in cats with idiopathic hypercalcemia, whereas serum PTH concentrations are low-normal to low.[3-6] When measured, serum magnesium and 25(OH)-vitamin D concentrations remain normal. Serum concentrations of PTH-related polypeptide, secreted by some malignant tumors, are not detectable in these cats.

A diagnosis of idiopathic hypercalcemia is made when all other causes of parathyroid-independent hypercalcemia are excluded. Though idiopathic hypercalcemia is the most frequent diagnosis in cats with hypercalcemia, it is an exceedingly uncommon finding in dogs following adequate diagnostic workup.

Treatment of Idiopathic Hypercalcemia

In almost all affected cats, hypercalcemia is slowly progressive and relatively longstanding. Clinical signs are usually relatively mild, at least initially. Therefore, most cats can be treated as outpatients with either dietary therapy, alone or in combination with drug therapy.[6]

Dietary Therapy

I generally start with diet modification as a first-line treatment. No matter what type of diet is chosen, it is best to feed a wet-only diet to promote urinary dilution and lessen the chance for calcium oxalate stones.

There are a number of different dietary factors that may influence the calcium absorption, including the amount of dietary fiber, as well as concentrations of calcium, vitamin D, vitamin A, and vitamin K_2. To this end, we have five different types of cat food diets that have been recommended and may help lower calcium in cats with idiopathic hypercalcemia.

1) *High fiber diets*: (e.g., Purina OM Overweight Management, Royal Canin Gastrointestinal Fiber Response HF, Iams Intestinal Plus Low-Residue, Hill's w/d) will restore normocalcemia in some cats with idiopathic hypercalcemia and calcium oxalate urolithiasis.[7] The effects of fiber on intestinal absorption are complex and depend on the type and amount of fiber in the diet, as well as the interactions with other nutrients in the diet. However, these "high fiber diets" are usually supplemented with extra calcium, and therefore calcium content does not explain why these diets are sometimes successful in treating idiopathic hypercalcemia.

2) *Prescription kidney diets*: (e.g., Purina NF Kidney Function, Royal Canin Renal LP Modified, Iams Renal Plus, Hill's k/d) also may result in normocalcemia in some cats with idiopathic hypercalcemia. Most renal diets are less acidifying than maintenance or high fiber diets and are low in both calcium and phosphorus. The decreased consumption of calcium leads to a decrease in the amount of calcium absorbed, and the effects of alkalinization may decrease the release of calcium from bone. In one study in man, acidogenic diets lead to an increase in PTH secretion, leading to calcium release from bone and increased urinary calcium excretion.[8]

Remember, however that veterinary renal diets are also restricted in phosphorus, which may lead to increased calcitriol (active vitamin D) synthesis by the kidney; the action of this increased serum calcitriol could offset the advantage of the decreased calcium absorption in cats with idiopathic hypercalcemia. Because these diets are lower in protein, renal diets are not my first choice — with time, many cats with idiopathic hypercalcemia will become muscle wasted on these diets.

3) *"Stone" diets:* Diets developed to prevent calcium oxalate urolithiasis (e.g., Royal Canin Urinary SO, Purina UR Urinary St/Ox, Iams Urinary-O Plus Moderate pH/O, Hill's c/d) may be beneficial in the treatment of cats with idiopathic hypercalcemia. These diets are restricted in calcium and have less urinary acidification (neutral pH urine production). Some are also restricted in oxalic acid and sodium, and have increased moisture in the canned formulation.

4) *Calcium-restricted, home-prepared diets* can also be used to help lower the serum calcium concentrations in these cats with idiopathic hypercalcemia.[9] These diets must be specially formulated for the hypercalcemic cat, as none of the currently available, commercial cat food diets are calcium restricted. Use of a formulated, home-prepared diet also allows one to restrict the diet's vitamin D content. Ideally, this diet should be formulated with the help of a veterinary nutritionist (e.g., www.balanceit.com).

5) *Natural species-appropriate diets:* Finally, there is some anecdotal evidence that feeding a more "natural" low carbohydrate, higher protein/fat canned or raw diet may help normalize serum calcium concentrations in some of these cats, particularly those with a mild form of idiopathic hypercalcemia.[10,11] Studies of cats fed "natural, species-appropriate diets" have not been reported to determine if these diets would be efficacious in controlling hypercalcemia. However, such studies seem warranted, especially since dietary recommendations generally fail to fully normalize the hyperkalemia in these cats.

When such a natural diet is chosen, ideally we would select one that contains lower amounts of calcium (e.g., 1.5-2.0 g/1000 kcaL) and vitamin D (125-250 IU/1000 kcal). However, we must call the pet food company to obtain this information.

Unfortunately, in most cats with idiopathic hypercalcemia, dietary therapy will be of minimal long-term benefit, but this management is very unlikely to be harmful. In addition, because many cats with idiopathic hypercalcemia do not show clinical signs for months to years, it is appropriate to try dietary therapy as the first line of therapy at least in cats with mild ionized hypercalcemia.

Glucocorticoid Therapy

If normocalcemia has not been restored after a dietary feeding trial of 6 to 8 weeks, treatment with glucocorticosteroids should be considered.[3,5,6] Administration of glucocorticoids can decrease serum calcium concentration by decreased intestinal absorption of calcium, decreased renal tubular calcium reabsorption, and decreased skeletal mobilization of calcium.

Cats usually do not exhibit serious side effects from glucocorticosteroid treatment, as do dogs (e.g., polyuria, polydipsia). Prednisolone is given orally at 5 mg/cat/day for one month before re-evaluation. If the serum ionized calcium concentration is normal, this dose is continued for several months. If the ionized calcium value is still increased, the dose is increased to 10 mg/cat/day. Some cats may require as much as 15 to 20 mg prednisolone/day to restore normocalcemia. Approximately 50% of cats with idiopathic hypercalcemia become normocalcemic with 5 or 10 mg prednisone/day, but some may require increasing doses to remain normocalcemic over time.[3,5,6] One disadvantage of prednisolone is that approximately a third of cats will develop secondary diabetes, especially with long-term, high-dose steroid therapy.[12] When dietary modification and treatment with prednisolone have been unsuccessful, treatment with oral bisphosphonates such as alendronate can be considered.

Bisphosphonate Therapy

Recently, I have been bypassing prednisolone completely and going right to oral alendronate, starting at 10 mg orally per week.[3,5,6,13] This drug is a bisphosphonate, which acts to lower calcium by reducing the number and action of osteoclasts.[14] Compared to glucocorticoids, alendronate is more successful in lowering calcium concentration without the diabetogenic effects.

It is extremely important to administer alendronate after a 12-hour fast (or longer), as food significantly reduces drug absorption.[15] Because the medication may cause esophagitis, we give 6-ml of water orally immediately

after administration of the drug to enhance its passage to the stomach. The cat's fast should be continued for at least 2 hours after alendronate administration.

Serum ionized calcium levels should be checked at 2 weeks, 1 month, 2-3 months, and then every 4-6 months as long as the ionized calcium concentration remains within normal limits.[5,6]

Most cats seem to have at least a partial calcium-lowering response to alendronate. The drug dose can be raised to up to 30-40 mg per week, as needed. In the future, oral bisphosphonates will likely replace prednisolone as the drug of choice for treatment of idiopathic hypercalcemia in cats.

Combined Glucocorticoid/ Bisphosphonate Therapy

In resistance cats, use of both prednisolone and alendronate can be used together. Again, it is of utmost importance to give the alendronate after an overnight fast; if this is not done, none of the drug will likely be absorbed into the bloodstream.

Miscellaneous Treatments

Fluid therapy is used as an adjunct treatment in cats with idiopathic hypercalcemia, especially those that have developed renal failure. The administration of subcutaneous fluids on a daily or every other day basis may help expand the extracellular fluid, and promote calciuresis. Diuretics such as furosemide have been used effectively to decrease serum ionized calcium concentrations during acute rescue protocols for hypercalcemia, usually in combination with IV fluids. Little is known about the effects of chronic furosemide administration regarding calcium status and the development of dehydration. It is a concern that cats receiving chronic diuretics will undergo diuresis but will not increase their water intake, leading to dehydration.

A calcimimetics (cinacalcet; brand name Sensipar) is a new class of drug to be considered as a potential therapy for hypercalcemia that has emerged in human medicine over the last decade.[16,17] Calcimimetics interact with the calcium receptor directly, and have been proven effective in lowering ionized calcium, phosphorus, and PTH concentrations in human patients. The potential future use of calcimimetics in the treatment of idiopathic hypercalcemia is an interesting possibility, but the high cost of these agents is a limiting factor for long-term treatment of our cats.

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Feline Adrenal Disease

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Introduction

Adrenal gland disorders present some unique challenges to the feline practitioner, as the clinical manifestations may be subtle and establishing a diagnosis can be difficult. A specific knowledge of feline adrenal gland physiology is essential, along with an understanding of test methodologies. In this field (as in so many!), feline-specific protocols are necessary and care must be taken when interpreting test results.

Review of Anatomy and Physiology

The adrenal glands are small structures, located cranio-medial to each kidney. The outer layer of the gland, immediately below the capsule, is the cortex. This is the site of steroid hormone production, with three functional layers. The zona glomerulosa produces aldosterone, the zona fasciculate produces glucocorticoids, and the inner cortical layer secretes sex hormones. Below the cortex in the center of the adrenal gland is the medulla, site of catecholamine synthesis and release.

The three layers of the adrenal cortex are anatomically similar, but functionally distinct. This is due to variable enzyme expression within the cortical cells and the presence of specific cell-surface receptors. Aldosterone synthesis is primarily determined by angiotensin activity but is also directly triggered by hyperkalemia, whilst glucocorticoid production is driven by adrenocorticotrophic hormone (ACTH) from the anterior pituitary. There is some overlap, with for example, receptors to ACTH present on both the zona glomerulosa and zona fasciculata.

Hypoadrenocorticism (HOC)

Etiology

Feline Addison's disease is a rare endocrinopathy and the etiology is not well understood. It seems likely that immune-mediated destruction of the adrenal cortex may occur in some patients, although this has not been well proven. Other reasons for cortical failure might include bilateral invasion by neoplastic tissue such as lymphoma, infection, or thrombosis.[1,2] In other species, two forms of HOC have been described: "classic", in which all adrenal cortical function is lost, and "atypical", characterized by failure of glucocorticoid production with preservation of aldosterone synthesis (aka glucocorticoid-deficient HOC). These two forms of HOC have not been well described in cats, but it is likely that both occur. Although iatrogenic HOC can occur in cats, this is suggested by the history and is not discussed here.

Signalment

The age range for cats reported in the literature is wide, ranging from 1.5 to 14 years, although most are middle aged.[3] Breed and gender predispositions are not described.

Presentation and Laboratory Findings

The clinical signs of HOC include those due to hypocortisolemia (i.e., anorexia, vomiting, lethargy) and those due to hypoaldosteronism (i.e., weakness, dehydration).[3] Classic laboratory findings include azotemia, hyponatremia and hyperkalemia. Urine is poorly concentrated, with a specific gravity <1.030.[1,3,4] Affected cats may have a relative polycythemia due to dehydration or anemia due to inhibited erythopoiesis +/or gastrointestinal hemorrhage. White cell patterns are not as well defined in cats with HOC compared to dogs, with variable lymphocyte and eosinophil counts reported. However, a lymphocytosis in a sick cat should raise an index of suspicion for HOC.[1]

Differential Diagnoses

The clinical manifestations of hypocortisolemia mimic those of cats with primary gastrointestinal disease, pancreatitis, or other systemic disorders. In patients with selective glucocorticoid deficiency, the serum biochemical profile may be normal. In classic HOC patients, the history and laboratory findings may initially suggest renal disease (azotemia, poorly concentrated urine, hyperkalemia, acidosis). Although cats with acute or severe renal failure can be hyponatremia and hyperkalemic, this combination of electrolyte changes should immediately prompt a consideration of HOC, particularly if the cat is still making urine and the serum creatinine is <5 mg/dl.

Establishing a Diagnosis

Dynamic testing of adrenal cortical function is necessary to confirm a diagnosis of HOC.[1,3] Baseline cortisol concentrations are expected to be low (< 2 µg/dl); it is reasonable to exclude a diagnosis of HOC if the baseline cortisol is below this level, although there is limited published data to support this assumption. Bear in mind too, that many exogenous glucocorticoids are measured by current 'cortisol' assays; if a cat is given prednisolone prior to sampling, the reported 'cortisol' concentration will actually be the prednisolone. Conversely, administration of a non-

measured glucocorticoid such as dexamethasone will drive down endogenous cortisol levels for at least 8 hours (and probably substantially longer), resulting in a suspicious baseline cortisol measurement.

The ACTH stimulation test is the only way to establish a diagnosis of HOC. The protocol is different from that used in dogs and the results may be misleading if canine protocols are used. In cats, the peak response to exogenous ACTH is faster and seems to fade away more rapidly, so samples must be collected sooner and more often.

Ideally, synthetic ACTH (Cortrosyn/Cosyntropin) should be used for the ACTH stim test. Although so-called 'low dose' protocols have been validated for canine patients, they have not been examined in cats, and are probably an imprudent choice in this species. Instead, 125 µg of aqueous corticotrophin should be administered IM or IV after collection of a baseline sample, with subsequent blood samples collected at 30 and 60 minutes. Compounded ACTH gels are less reliable and should be avoided.

In most cats (including all cats with typical HOC), the baseline cortisol will be <1 µg/dl, with essentially no response to exogenous ACTH (both post-cortisols <2 µg/dl). In patients with atypical HOC due to failure of endogenous ACTH release (i.e., a primary pituitary lesion) a blunted response may be noted.

Treatment: Acute Crisis

Acute treatment of HOC requires aggressive fluid support and management of electrolyte disorders. Ideally, steroids should be withheld until an ACTH stimulation test is performed. In a crisis, dexamethasone at 0.5 mg/kg may be given prior to the ACTH stim test, as this is not measured by the serum cortisol assay and a single dose will not impact the response to exogenous ACTH.

Hyperkalemia is the most crucial immediate issue in most patients.[5] Fluid therapy should be started immediately, using an appropriate replacement fluid. As a general rule, 0.9% NaCl is the fluid of choice for a hyperkalemic patient, as it is the only potassium-free replacement fluid available. However, the sodium content of 0.9% NaCl is the highest, at 154 mEq/L. If the serum sodium concentrations are markedly low (i.e., <130 mEq/L), administration of 0.9% NaCl can result in a rapid rise in serum sodium levels, with subsequent central pontine myelinolysis. This becomes apparent 1-2 days later and is reversible and generally fatal. If the sodium is <130 mEq/L, give a fluid with a sodium concentration within 10 mEq of the patient. For example, a cat with a sodium of 125 mEq/L can receive LRS (which as 130 mEq/L of sodium). A cat with a sodium of 115 mEq/L needs a fluid with no more than 125 mEq/L of sodium. This will need to be made, using a mixture of 0.9% NaCl (812 mls) and sterile water (188 mls of water). The target is to move the sodium upwards at ≤0.5 mEq/L/hour.

Fluid therapy should be aggressive… these cats are often very dehydrated and have a large 'space' for fluid administration. Half of the 'shock' dose should be given in the first hour (i.e., 30 ml/kg) followed by an appropriate volume replacement plan.[5]

Dextrose is also very helpful in hyperkalemic cats, as it triggers the release of insulin which drives both glucose and potassium into the cells. A dose of 0.25 m/kg of 50% dextrose can be given as an immediate bolus, followed by a constant infusion of 2.5 or 5% (50 mls of 50% dextrose added to 1 liter gives a 2.5% concentration). Although administration of exogenous insulin may speed up the intracellular transport of potassium, there is a substantial risk of iatrogenic hypoglycemia.

Beta-agonists (such as terbutaline and albuterol) also move potassium in to the cells, and can be very effective in these cases. The dose of terbutaline is 0.01 mg/kg IM, and the effect is evident quickly and often lasts for several hours. Albuterol can be given by an inhaler if terbutaline is not available.

Calcium gluconate protects the heart from the effects of hyperkalemia, but does not lower serum potassium levels. It must be given by CRI and careful monitoring of the ECG is needed. This author rarely uses this in cats.

Additional supportive care (warming devices, anti-emetics, proton pump inhibitors) should be provided as appropriate. It seems as though cats take a bit longer to improve than their canine counterparts, so clients should be counselled that several days of supportive care may be necessary.[3]

Treatment: Chronic Management

Long term care requires supplementation of glucocorticoids with oral prednisolone (0.5-2 mg/cat/day) and mineralocorticoid replacement with desoxycorticosterone pivalate (DOCP) at 2.2 mg/kg IM or SQ every 25 days, or fludrocortisone at 0.1 mg/cat every day (titrated upwards as necessary). Serum electrolytes should be monitored regularly until the appropriate dose of mineralocorticoid replacement is determined.

Hyperadrenocorticism (HAC)

Although we usually associate hyperadrenocorticism (HAC) with hypercortisolemia, this term applies to any patient with excessive secretion of any of the adrenocortical hormones. Hypercortisolemia (Cushing's syndrome) is certainly the most common manifestation of HAC in cats, but over secretion of aldosterone (Conn's syndrome) or sex hormones can also occur.

Cushing's syndrome: Hypercortisolemia

Etiology

Spontaneous Cushing's syndrome (CS) can be the result of hypersecretion of ACTH by a pituitary tumor (PDH; true Cushing's disease) or inappropriate secretion of cortisol by an adrenocortical tumor (AT). Spontaneous CS due to other causes (such as ectopic ACTH secretion) have not been described in the cat.

Signalment

In a recent study describing 30 cats with CS, the median age was 13 yrs, with a range of 4-17.6 years.[6] There was no apparent gender or breed predisposition.

Presentation and Laboratory Findings

The clinical signs of hypercortisolemia *per se* in cats are different to those seen in dogs and the disorder is often more difficult to recognize in this species. Most cats present for evaluation of unregulated diabetes mellitus (DM; reported in 90% of cats in the recent case series) or because of dermatologic issues.[6] Unless concurrent DM or renal compromise is present, affected cats are not always polydipsic and polyuric. Appetite tends to be robust, but we do not see the ravenous hunger reported in the majority of dogs (unless concurrent DM is present). Other 'classic' Cushingoid signs such as panting are less common in cats than dogs.

The physical examination may be subtly abnormal, with abdominal distension and hepatomegaly. Rear limb musculature may be poor, with stretching of the plantar ligaments. Cats do not usually manifest dramatic trunkal alopecia, but the hair coat on the ventrum is often sparse and hair regrowth after shaving is negligible. One of the most dramatic physical manifestations of feline Cushing's is skin fragility; affected cats often present with large areas of raw tissue as the result of tearing of the dermis. This can occur during routine grooming or handling by the owner.

Laboratory changes which support a diagnosis of hypercortisolemia include hyperglycemia (with or without overt DM), hypertriglyceridemia and hypercholesterolemia.[6] Unlike dogs with CS, serum alkaline phosphatase (ALP) activity may be normal as cats do not have the steroid-induced isoenzyme. However, concurrent DM may trigger an increase in ALP activity in affected cats. The complete blood count is often unremarkable, and generally lacks the classic 'stress leukogram' we expect to see in dogs. The urine may be poorly concentrated (although this measurement may be impacted by concurrent DM) or remain >1.030. The rest of the urine analysis may be unremarkable, or proteinuria, pyuria and bacturia may be noted. Glucosuria may be present if the renal threshold is exceeded. As occult urinary tract infection is commonly associated with DM and CS, a urine culture should always be performed.

Hypertension is variably reported in cats with CS. Routine measurement of systolic blood pressure is warranted even in the absence of overt end-organ damage (such as retinal detachment),

Differential Diagnoses

Other reasons for insulin resistance should be considered, e.g., occult infection, chronic pancreatitis and acromegaly.

Establishing a Diagnosis

A dexamethasone suppression test (DST) is the optimal way to confirm CS in the cat. The dose of dexamethasone used in the feline low dose DST is 10 times higher than the canine dose, at 0.1 mg/kg IV. A serum sample should be collected immediately prior to dexamethasone administration, and then at 4 and 8 hours. Cats with HAC will not suppress cortisol production at the 8 hour time point. Transient suppression (i.e., suppression at the 4 hour time point) supports PDH; failure to suppress at 4 hours does not differentiate between PDH or AT. Suppression is generally defined as a cortisol concentration <1.4 µg /dl or <50% of baseline.

The ACTH stimulation test is not reliable in cats with CS, with a recent reported sensitivity of only 56%.[6] It appears to be substantially less reliable in cats with AT.

An abdominal ultrasound examination is an integral part of the work up in most cats. Although the majority of affected cats have PDH, the likelihood of an AT is higher in cats than dogs. A reliable ultrasound examination will permit the measurement of both adrenal glands, with assessment of vascular invasion and metastatic involvement in cats with AT. A three-view thoracic radiographic study is warranted in any cat with an AT.

If the US findings are equivocal, measurement of endogenous ACTH concentration is warranted. Cats with AT have very low levels, whilst those with PDH have levels within the upper end of the reference range or increased.

Treatment

Treatment of feline Cushing's is challenging.[7] Cats with an operable AT are best managed with adrenalectomy. Peri-operative care of these patients is difficult, as many are diabetic and very poor surgical candidates. Complications such as thrombosis, infection and wound dehiscence are possible. Glucocorticoid supplementation will be necessary in the post-operative period, but should be tapered as quickly as possible.

A number of different medical treatments have been described in the last ten years, but patient responses seem to be unpredictable. Mitotane (Lysodren) appears to be much less effective in cats than in dogs, and is not

recommended. Trilostane (Vetoryl) has been efficacious in some cats, at a starting dose of 10 mg by mouth once daily, adjusted based on the results of ACTH stimulation tests.[8] Improvement in glycemic control is expected, but diabetic remission seems unlikely in affected cats.

In people with PDH, removal of the mass is the treatment of choice. Transphenoidal hypophysectomy has been pioneered by a group in the Netherlands, and has been performed in small number of cats by a group in LA, with generally good outcomes.[9] However, this procedure is technically challenging and is not routinely available. Radiation of the pituitary gland is expensive but often beneficial.[7] Concurrent medical management or adrenalectomy are needed however, as radiation alone is usually insufficient to control the HAC.

Sex-hormone Secreting Adrenal Tumors

Although most functional feline adrenocortical tumors secrete cortisol or aldosterone, other hormones (either sex hormones or cortisol precursors) may be produced instead.[10,11] These are uncommon, but several cases have been reported. The clinical signs are variable; some cats have a Cushingoid presentation (if progesterone excess occurs), whilst others may show behavioral changes such as aggression or urine spraying (if testosterone is secreted).

In a male cat, testosterone secretion is suggested by finding of spines on the penis. In a female cat, estrogen exposure may be supported by findings on vaginal cytology. Diagnosis is based on measurement of sex hormones (University of Tennessee) before and after exogenous ACTH administration, and the findings on ultrasonography. If the tumor is secreting a precursor to cortisol, cortisol levels may be suppressed with an 'Addisonian' result.

Removal of the tumor is the best therapeutic approach. Trilostane may be considered, depending on the hormonal pathway affected.

Hyperaldosteronism (Conn's Syndrome)

This topic will be discussed in detail during a separate lecture. See program for details.

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Hyperaldosteronism

Audrey Cook, BVM&S, MRCVS, DACVIM-SAIM, DECVIM-CA, DABVP (Feline)

Background

Aldosterone is a steroid hormone, secreted by the zona glomerulosa of the adrenal cortex. It is responsible for retention of sodium by the distal convoluted tubule of the nephron, along with the excretion of potassium and hydrogen ions. Reclamation of sodium from the filtrate pulls water back into the vascular space, thereby increasing the extracellular fluid volume and systemic blood pressure. Adequate amounts of aldosterone are essential for management of an effective circulating volume, and production is stimulated primarily by angiotensin II. Hyperkalemia also directly triggers the release of aldosterone by the adrenal cortex. Release is inhibited by the natriuretic peptides, and is decreased by hypokalemia.[1,2]

Introduction

Primary hyperaldosteronism (PHA) was first described in people in 1955, and is often referred to as Conn's syndrome, after the physician who reported it. This disorder is defined as the inappropriate release of aldosterone by one or both adrenal glands, and is now regarded as the most common cause of endocrine hypertension in human patients. Affected individuals have persistent hypertension, with variable hypokalemia. Interestingly, hypokalemia is currently reported in the minority of affected people, and is regarded as a late-stage manifestation of the disorder. Various underlying causes are described, including neoplasia of one or both adrenal glands, or bilateral adrenal hyperplasia. Until recently, this condition was thought to be rare in cats, with only sporadic cases reported, and was primarily associated with a functional adrenocortical tumor. However, recent studies suggest that PHA may be more prevalent than originally thought, and may be associated with substantial morbidity in geriatric feline patients. Specifically, PHA associated with bilateral hyperplasia of the zona glomerulosa has been associated with chronic kidney disease (CKD) in this species.[1,2] Some authorities have now suggested that PHA may be the most common adrenocortical disorder in cats.[2] Patients may be overlooked, as the hypertension and hypokalemia are attributed to CKD, where as in fact, the CKD may be the consequence of PHA.[3]

Clinical Presentation

Signalment, History, Physical Examination

Most cats with PHA are >10 years of age. In a recent report of 10 cats with PHA due to a unilateral adrenal mass, the median age was 12.3 years, with a range of 9-15 years.[4] No breed or gender predispositions have been established in feline patients.

Most cats present with signs related to systemic hypertension, hypokalemia or both. Signs associated with hypertension include vision loss or acute neurological compromise. Hypokalemia will result in weakness, collapse, and cervical ventroflexion. This may be episodic, but is generally associated with serum potassium levels of 2.5 mEq/L or less. Affected cats have poor muscle tone and are often unable to stand unaided. Polyuria and polydipsia are also commonly reported.

Physical examination may suggest a myopathy, with variable weakness and poor muscle tone. A plantigrade stance may be noted in cats with mild hypokalemia. In patients with severe hypertension, ocular lesions are routinely noted, including hyphema, mydriasis, anisocoria, retinal hemorrhage or detachment.

Hypertension may be an incidental finding during a geriatric wellness examination; if an obvious cause is not apparent, PHA should be considered, even if the serum potassium levels are within the reference range.

Routine Laboratory Findings

Hypokalemia may be noted; this may be marked or borderline. A normal serum potassium concentration does not exclude the possibility of PHA. Serum sodium levels are often normal, as the excess sodium is accompanied by water. A metabolic alkalosis may be noted, due to exchange of sodium for hydrogen ions in the distal nephron. Creatinine kinase (CK) may be elevated, due to the hypokalemic myopathy. Evidence of renal compromise may be noted, with increases in serum creatinine, and urea nitrogen. Interestingly, serum phosphorus concentrations may be borderline low or well within the normal range, despite the accompanying azotemia. This finding is strongly suggestive of PHA and likely reflects excessive secretion of parathyroid hormone.

Urine is often poorly concentrated; this is due to a combination of hypertension, chronic kidney disease and hypokalemia (low potassium causes a secondary nephrogenic diabetes insipidus). Proteinuria may be noted, and should be quantified by measurement of the urine protein:creatinine ratio.

The complete blood count may reveal anemia, reflecting chronic disease +/- impaired erythropoietin secretion in those cats with concurrent CKD.

Imaging

Abdominal ultrasonography should be performed in any cat with a clinical suspicion of PHA. PHA is traditionally associated with a unilateral adrenal mass, although a small number of cats with bilateral tumors have been described. However, bilateral hyperplasia has been reported in some feline patients, which may not be easily detected during abdominal ultrasonography.[3] Simply finding an adrenal mass is not sufficient to establish a diagnosis of PHA however, as the lesion may be non-function, or secreting catecholamines (a pheochromocytoma), cortisol, or sex hormones. Cats with tumors secreting both progesterone and aldosterone have been reported, with a confusing constellation of clinical signs!

Thoracic radiographs should also be considered. These may identify metastatic lesions, or evidence of cardiomegaly.

Differential Diagnosis

Other causes of systemic hypertension and weakness should be considered. Differentials for hypertension include hyperthyroidism, chronic kidney disease and hyperadrenocorticism. There are several causes of weakness, including cardiac disease, primary neurologic disorders, anemia, thiamine deficiency, myasthenia gravis, and toxoplasmosis. Hypokalemia is noted with numerous conditions, including diabetes mellitus, renal failure, liver and gastrointestinal disease.

Diagnosis

Aldosterone Concentrations

The first step in establishing a diagnosis of PHA is measurement of circulating aldosterone concentrations. These can be determined by many veterinary reference laboratories. In human patients, confounding factors such as salt intake, concurrent anti-hypertensive medications and body position are carefully controlled. It is unclear if these factors also impact aldosterone measurements in cats, but is seems likely that they would. Aldosterone levels should be interpreted in light of the concurrent potassium status, as hypokalemia should suppress aldosterone release by the zona glomerulosa. In one report, aldosterone levels in some affected cats were in the high normal range despite hypokalemia; these patients were still thought to have PHA.

Plasma Renin Activity and Aldosterone: Renin Ratio

Concurrent determination of plasma renin activity is ideal, as this helps to differentiate PHA (low renin) from secondary hyperaldosteronism (increased renin). Unfortunately, this assay is not consistently available for feline patients. In people, the aldosterone:renin ratio (ARR) is a primary screening test for PHA, with a high value strongly supportive of the diagnosis. The ARR is usually very high in cats with an adrenocortical tumor, as renin release is totally inhibited, but may be less dramatic in cats with nodular hyperplasia, in which some renin activity may be present.[2] If available this test is widely regarded as the gold standard for establishing a diagnosis of PHA.

Urine Aldosterone: Creatinine Ratio (UACR)

This test has recently been proposed as a suitable screening test for PHA in cats. It is superior to simply measuring aldosterone in serum or plasma, as it reflects events over several hours and not just one time point.[5] However, the reference range is quiet wide, and the test may lack sensitivity when used alone.[2]

Fludrocortisone Suppression Test

The idea behind this test is similar to that behind the dexamethasone suppression test, namely that administration of an exogenous aldosterone analogue will suppress aldosterone release in a normal individual. Failure to suppress suggests autonomous/inappropriate secretion and would support a diagnosis of PHA.[5,6] There is limited information on this test in cats with PHA, but it is certainly promising. The protocol is as follows:

1. Determine baseline UACR
2. Administer fludrocortisone for 4 days (0.05 mg/kg twice daily PO)
3. Determine UACR

Failure to suppress aldosterone production indicated PHA

Management

Hypokalemia

Hypokalemia is a medical emergency and should be treated immediately. Cats can become acutely compromised with cardiac arrhythmias and compromised ventilation when serum potassium levels are low.[7] Even if the patient is substantially dehydrated, it is more important initially to manage the hypokalemia than replace fluid losses. Bear in mind that even modest amounts of un-supplemented fluid therapy may markedly exacerbate hypokalemia and result in death. The best way to provide potassium supplementation is by an infusion of KCl; this can be caustic to the vein if given undiluted, but is well tolerated if diluted with >4 parts D5W. The maximum rate of administration of parenteral potassium ('K-max") is 0.5 mEq/kg/hr; this author does not recommend exceeding this rate. For example, if the cat weighs 3.5 kg, the maximum rate for infusion of KCl is 0.5 x 3.5 = 1.75 mEq/hr. Oral

potassium supplementation can be started concurrently, and repeated every 4-6 hours until serum levels are back in the reference range. Fluid losses can be cautiously replaced over 24 hours using an appropriate replacement fluid such as LRS.

Chronic medical management includes oral potassium supplementation, along with the administration of spironolactone (starting at 2mg/kg twice daily). This agent is an aldosterone receptor antagonist, so it directly inhibits the action of the hormone on the distal convoluted tubules.

Hypertension

Prompt control of systemic hypertension is essential to protect the retina, central nervous system and kidney from further damage. Amlodipine is often a good first choice, with minimal risk of side effects and a rapid onset of action. Angiotensin-converting enzyme inhibitors (e.g., enalapril) are unlikely to be helpful, as renin is suppressed.

Surgical

In cats with a non-metastatic unilateral adrenal mass, adrenalectomy is the treatment of choice. The reported outcomes are fairly positive, although a high level of surgical expertise and careful post-operative management is needed.[4]

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Management of Problem Diabetic Patients

Catharine Scott-Moncrieff, VET MB, MA, MS, DACVIM, DECVIM

Pathophysiology of DM

Diabetes mellitus (DM) is a common endocrine disease in cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition the lack of insulin results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism. Factors that have been identified as predisposing factors in cats include obesity, advancing age and being male. Two types of DM are recognized in man, and these classifications can be applied to the disease in cats. Type I DM (insulin dependent diabetes mellitus) is due to an absolute deficiency of insulin. This form of diabetes is characterized by minimal secretory response to β-cell secretagogues such as glucagon. Type II DM (non- insulin dependent diabetes) is characterized by abnormal insulin secretion and peripheral insulin resistance, and results in a stable reregulation of the blood glucose concentration at a higher concentration. This type of DM is common in the diabetic cat. The two types of diabetes are classically distinguished by characteristic responses to challenge by insulin secretagogues such as glucose, glucagon, or arginine. In type I DM, there is a decreased or negligible secretion of insulin compared to normal animals, whereas in Type II DM, total insulin secretion may be normal or increased, although the pattern of secretion may be abnormal. The insulin concentration is still insufficient however, to prevent hyperglycemia. The phenomenon of glucose toxicity complicates interpretation of glucagon tolerance tests in cats, and the glucagon tolerance test is of little practical utility in clinical practice.

Diagnosis

The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss), and documentation of hyperglycemia and glycosuria. In cats the diagnosis may be complicated by the occurrence of marked stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document persistent hyperglycemia and glucosuria, but also to rule out other diseases that may cause similar clinical signs. Measurement of fructosamine concentrations or urine glucose of samples collected in the home environment may allow the clinician to distinguish between stress induced hyperglycemia (and resultant glycosuria) and persistent hyperglycemia due to diabetes mellitus. lucosuria may also occur secondary to ketamine anesthesia, chronic renal failure, and post-obstructive diuresis so is not on its own diagnostic for diabetes mellitus. The presence of significant ketonuria together with hyperglycemia, is diagnostic for diabetes mellitus in and cats.

Clinical diabetes mellitus in cats may be transient or intermittent. Fifteen to 70% of cats with DM have been reported to go into spontaneous clinical remission, with good glycemic control. Unfortunately, the glucagon tolerance test is not useful in predicting whether or not a cat is likely to go into remission.

Poor Response to Insulin

Clinical signs suggestive of inappropriate response to insulin therapy include recurrence or persistence of clinical signs of DM, disorientation or seizures due to hypoglycemia, an insulin dose higher than 6U/dose in the cat, or recurrent ketoacidosis. Adequate assessment of the cause of the problem requires performing a blood glucose curve. Measurement of glycosylated hemoglobin or fructosamine may also be helpful. Once this data has been evaluated, appropriate changes in treatment or further diagnostic testing can then be instituted. In cats receiving twice daily insulin, most glucose curves can be performed during working hours (8am to 6pm). Common problems that may lead to a poor response to insulin include problems with owner administration, inappropriate insulin dose or formulation, insulin induced hypoglycemia, rapid metabolism of insulin, and insulin resistance. It is important to take into consideration the level of stress of the patient while in the hospital when interpreting the results of blood glucose curves. It is also important to appreciate that blood glucose curves show significant day to day variability. Other factors such as clinical signs, results of urine blood glucose measurements at home, serum fructosamine concentrations, and changes in physical examination (especially body weight), should be taken into account when interpreting the results of a blood glucose curve.

Problems with Owner Administration

Diagnosis of problems of owner administration of insulin may be detected either by a thorough history or by administration of insulin from a new bottle in the clinic by a clinician or veterinary technician, followed by a repeated blood glucose curve. Care should be taken to monitor the patient carefully in this setting however, because severe hypoglycemia can result if the insulin dose has been escalated due to problems with administration. If hypoglycemia

does occur, the dose of administered insulin should be decreased by 25-75 % depending upon the severity of hypoglycemia and a blood glucose curve repeated after 7 days of the new dose.

Inappropriate Insulin Dose or Formulation

In most cases this diagnosis can be made easily by evaluation of the blood glucose curve. Most cats require insulin administration twice daily for good glycemic control, so this is the first change to consider if once a day therapy is being used.

Insulin Induced Hypoglycemia

Insulin induced hypoglycemia) occurs when excessive amounts of insulin are administered. When the blood glucose concentration drops below 65 mg/dl in response to insulin, compensatory mechanisms drive the blood glucose back into the normal range. These mechanisms include increased glycogenolysis and gluconeogenesis by the liver, and release of catecholamines, glucagon, cortisol, and growth hormone which oppose the action of insulin. As the blood glucose returns toward normal however, there is not enough insulin present to oppose and dampen these the effect of these hormone increases, and hyperglycemia may result. Hyperglycemia may persist for hours to days following a hypoglycemic event. Since a spot-check blood glucose or urine measurement performed in the afternoon in such a case may reveal hyperglycemia and glycosuria, increases in insulin dosage based on these measurements may worsen the situation. The diagnosis of insulin induced hypoglycemia is made by performing a serial blood glucose curve (samples q 2 hours). The condition is treated by decreasing the insulin dose by 25 – 75 % followed by reevaluation of a serial glucose curve 3 - 5 days later.

Rapid Metabolism of Insulin

Rapid metabolism of insulin refers to a situation when the effect of insulin does not last as long as is necessary to control hyperglycemia for the majority of the treatment period. In most diabetic dogs and cats, twice daily insulin administration is necessary for ideal glycemic control. In some cases however the duration of effect may be only 5 - 8 hours. This may mean that hyperglycemia is present for a significant proportion of the day, even when twice daily administration is instituted. In most cases clinical signs of hyperglycemia are not present and no change to therapy is necessary. In some cases an insulin preparation with a longer duration may be necessary. Alternatively three times a day insulin treatment can be considered.

Insulin Resistance

There are many varied causes of true insulin resistance, however most commonly it occurs due to the effect of excessive concentrations of hormones that oppose insulin. In many cases this is due to the presence of concurrent disease (see table).

In insulin resistance cats, persistent hyperglycemia occurs despite the administration of >6 U per cat. Insulin resistance may be caused by a large number of factors.

Both endogenous and exogenous glucocorticoids are an important cause of insulin resistance in cats.

Glucocorticoids cause insulin resistance by a number of mechanisms including increased hepatic gluconeogenesis, decreased tissue utilization of glucose, and decreased cellular receptor affinity for insulin. Care should be taken when treating hyperadrenocorticism because the insulin requirement will decrease dramatically as endogenous glucocorticoid secretion decreases. Excessive growth hormone secretion and insulin resistance may also occur due to the presence of a growth hormone secreting pituitary neoplasm. Excessive growth hormone secretion due to a growth hormone secreting pituitary tumor is called acromegaly. Treatment for acromegaly relies on treatment of the pituitary neoplasm. Exogenous administration of progestagens may also result in insulin resistance in cats. Rarely adrenal tumors in cats may secrete progesterone and other hormones synthesized by the adrenal gland.

Insulin resistance may also occur due to hyperglucagonemia in cases of bacterial infection, trauma, congestive heart failure, azotemia, and glucagon secreting tumors. The resistance resolves once the underlying problem is corrected. Severe renal failure results in insulin resistance due to increased glucagon concentrations, defective transport of insulin into cells, and acidosis. Acidosis decreases receptor affinity for insulin and results in derangements of intracellular glycolysis. Other causes of insulin resistance in the cat include obesity, pancreatitis, and hyperthyroidism. Subcutaneous breakdown of insulin, insulin antibody formation, and post-receptor defects (abnormality of signal transduction with-in the cell) are possible additional causes of insulin resistance but have not been well defined in the cat**.**

Insulin Resistance in Cats (*most common)

- Drug administration (progestagens/corticosteroids)*
- Infection (urinary tract/oral cavity/sepsis)*
- Hyperthyroidism*
- Impaired insulin absorption (Ultralente insulin)
- Acromegaly*

- Pancreatitis*
- Renal disease*
- Hepatic disease
- Cardiac insufficiency
- Hyperlipidemia
- Neoplasia
- Severe obesity*
- Anti-insulin antibody excess
- Exocrine pancreatic insufficiency
- Hyperadrenocorticism

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Role of Concurrent Illness in Insulin Resistant Cats

Catharine Scott-Moncrieff, VET MB, MA, MS, DACVIM, DECVIM

Introduction

Diabetes mellitus is a common endocrinopathy in cats. Management of feline diabetes mellitus is sometimes complicated by underlying diseases that may cause profound insulin resistance. Lack of recognition of underlying disorders that cause insulin resistance results in poor glycemic control and decreases the likelihood of diabetic remission. This lecture will focus on the underlying causes of insulin resistance in cats, with special attention to two endocrinopathies (hyperadrenocorticism and acromegaly) that cause profound insulin resistance. While relatively uncommon these disorders are important causes of insulin resistance and yet diagnosis is often not straight forward.

Insulin Therapy in Diabetic Cats

It is very important for clinicians prescribing insulin to understand the various forms of insulin available for treatment of diabetic cats. Insulin may be classified by insulin source, insulin formulation, or duration of action of insulin. Insulin may be derived from bovine, porcine, or human recombinant sources and the concentration may be either 100 units/ml (insulin formulated for humans) or 40 units/ml (insulin's formulated for animals). A number of human recombinant insulin analogues are also available. Insulin products that are suitable for use in cats include PZI, Glargine and Lente insulins. NPH insulin may also be used in the cat although it tends to have a very short duration of action. The starting dose for insulin in cats is 0.25 0.5 U/kg or 1-3 U/cat.

Poor Response to Insulin

Clinical signs suggestive of inappropriate response to insulin therapy in cats include recurrence or persistence of clinical signs of DM despite insulin therapy, disorientation or seizures due to hypoglycemia, an insulin dose higher than 6U/dose, or recurrent ketoacidosis. Adequate assessment of the cause of the problem requires performing a blood glucose curve which will allow the clinician to distinguish between the different causes of a poor response to insulin. Blood glucose curves can be done in the hospital or at home by the owner. Common problems that may lead to a poor response to insulin include problems with owner administration, inappropriate insulin dose or formulation, insulin induced hypoglycemia, rapid metabolism of insulin, and insulin resistance. Measurement of glycosylated hemoglobin or fructosamine may also be helpful in some cases. Once this data has been evaluated, appropriate changes in treatment or further diagnostic testing can then be instituted.

In cats receiving twice daily insulin, most glucose curves can be performed during working hours (8am to 6pm). It is important to take into consideration the level of stress of the patient while in the hospital when interpreting the results of blood glucose curves. It is also important to appreciate that blood glucose curves show significant day to day variability. Other factors such as clinical signs, results of urine blood glucose measurements at home, serum fructosamine concentrations, and changes in physical examination (especially body weight), presence or resolution of diabetic neuropathy, should be taken into account when interpreting the results of a blood glucose curve.

Insulin Resistance

There are many causes of true insulin resistance, however most commonly insulin resistance occurs due to the effect of excessive concentrations of other hormones that oppose insulin. In many cases this is due to the presence of concurrent illness. In cats with insulin resistance persistent hyperglycemia occurs despite the administration of >6 U per dose per cat. Insulin resistance may be caused by a large number of factors.

Progestagens (exogenous or endogenous) may be a cause of profound insulin resistance in cats. Excessive growth hormone secretion and insulin resistance may also occur due to the presence of a growth hormone secreting pituitary neoplasm (acromegaly). Both endogenous and exogenous glucocorticoids are an important cause of insulin resistance in the cat. Glucocorticoids cause insulin resistance by a number of mechanisms including increased hepatic gluconeogenesis, decreased tissue utilization of glucose, and decreased cellular receptor affinity for insulin. Insulin resistant diabetes mellitus is a complication in 80% of cats with hyperadrenocorticism.

Insulin resistance may also occur due to hyperglucagonemia in cases of bacterial infection, trauma, congestive heart failure, azotemia, and glucagon secreting tumors. Severe renal failure results in insulin resistance due to increased glucagon concentrations, defective transport of insulin into cells, and acidosis. Acidosis decreases receptor affinity for insulin and results in derangements of intracellular glycolysis. Other possible causes of insulin resistance in the cat include obesity, pancreatitis, pheochromocytoma, subcutaneous breakdown of insulin, insulin antibody formation, and post-receptor defects (abnormality of signal transduction within cells).

Causes of Insulin Resistance in Cats
Drug administration (progestagens/corticosteroids)*
Infection (urinary tract/oral cavity/sepsis)*
Hyperthyroidism*
Impaired insulin absorption (Ultralente insulin)
Acromegaly*
Pancreatitis*
Renal disease*
Hepatic disease
Cardiac insufficiency
Hyperlipidemia
Neoplasia
Severe obesity*
Anti-insulin antibody excess
Exocrine pancreatic insufficiency
Hyperadrenocorticism

Approach to Insulin Resistance in Cats

The majority of causes of true insulin resistance in cats can be identified by evaluation of historical findings, physical examination, minimum data base (CBC, biochemical profile, urinalysis, total T4) and by performance of a small number of readily available tests such as urine culture, thoracic radiographs, and abdominal ultrasound. If no diagnosis can be made using these results, further tests to evaluate for pancreatitis, gastrointestinal disease, hyperadrenocorticism and acromegaly should be considered. Both hyperadrenocorticism and acromegaly are caused by a functional adenoma of the pituitary (pars distalis). In a study of 16 cats with insulin resistance and suspected acromegaly or pituitary dependent hyperadrenocorticism, CT revealed a mass in the region of the pituitary gland in all 16 cats. CT or MRI of 8 cats with well-controlled DM was normal. Diagnosis relies on a combination of specific endocrine testing and diagnostic imaging (ultrasound, CT, MRI). Because testing is expensive it is important to use appropriate clinical parameters to determine which cases are appropriate for further endocrine testing and which underlying disorder is most likely. The decision to pursue either of these diagnoses and if so, which one, should be made by evaluation of the history, physical examination, and minimum data base since these disorders typically have unique clinical features in addition to the common finding of insulin resistance.

Comparison of clinical features of feline hyperadrenocorticism and acromegaly		
	Acromegaly	**Hyperadrenocorticism**
Age	median 10 years of age, range 4-17 years	median 10 years of age, range 5-16 years
Sex	90% male	60% female
Body weight	Usually weight gain or stable weight but may also be loss of weight due to poorly regulated DM	Weight loss is typical
Skin	No skin hair coat changes	Unkempt hair coat, alopecia, dermal and epidermal atrophy, cutaneous lacerations
Adrenal size	Normal to increased	Usually increased (either unilateral or bilateral)
Body size	Often larger cats affected but cats may also be normal size	Body size is normal
Muscle mass	Normal muscle mass	Muscle atrophy common
Abdominal and thoracic organs	Renomegaly Hepatomegaly cardiomegaly	Normal except for adrenals
Joints	Arthopathy	Normal
Predisposition to infection	Slightly predisposed due to DM	Marked increase in urinary, respiratory infections and abscesses due to both HAC and DM

Acromegaly

Pathophysiology

Acromegaly is a syndrome in cats caused by excess secretion of growth hormone from a pituitary adenoma. Excess growth hormone (GH) secretion results in increased secretion of Insulin growth factor I (IGF-1) from the liver and peripheral tissues. Cats with acromegaly have profound insulin resistance and overgrowth of soft tissues, membranous bone and viscera. The anabolic effects of IGF-1 result in proliferation of bone, cartilage, and soft tissues, with organomegaly. The excess growth hormone secretion causes insulin resistance, carbohydrate intolerance, hyperglycemia and diabetes mellitus. Growth hormone is believed to cause a post receptor defect in insulin action at the level of the peripheral tissues. Feline acromegaly is believed to be a rare condition in cats, although recent studies suggest that it may be a more common cause of insulin resistance in diabetic cats than has been previously recognized. In one study in which diabetic cats were screened for acromegaly by measurement of Insulin growth factor I (IGF-1), 32% had increased IGF-1 concentrations and acromegaly was confirmed in 10% of these cats.

Signalment and Clinical Signs

Most cats with acromegaly are middle-aged or older (median 10 years of age, range 4-17 years) and 90% are male (intact or castrated). Clinical signs in cats with overt acromegaly include polyuria, polydipsia, polyphagia (due to insulin resistant diabetes mellitus), large body size, weight gain despite poor glycemic control, and enlargement of the head and extremities. Median insulin dose in a group of 17 cats with acromegaly was 10 U q 12 hours (range 2-35 U). Physical examination may reveal abdominal organomegaly, inferior prognathia, cataracts, clubbed paws, broad facial features, cardiac murmurs or arrhythmias, respiratory stridor, lameness, peripheral neuropathy, and central neurologic signs attributable to an enlarging pituitary mass. Cardiomegaly and renomegaly may be evident on imaging studies. Although weight loss due to poorly regulated diabetes mellitus may occur initially, a key finding in acromegalic cats is weight gain or a stable weight (lack of weight loss) in a diabetic cat with other indications of poor glycemic control such as polyuria, polydipsia, and polyphagia. Median bodyweight in a report of 19 acromegalic cats was 6 kg (range 4-9 kg). Although acromegalic cats tend to gain weight rather than lose weight as the disease progresses, in the study discussed above, the body weights of the acromegalic cats were not significantly different than the bodyweights of well controlled or poorly controlled diabetic cats without acromegaly.

Acromegaly is a slowly progressive insidious disease. Clinicians are beginning to recognize that some cats with acromegaly do not have the classic signs of weight gain and soft tissue enlargement at the time of diagnosis. It is likely that currently only the most severely affected acromegalic cats are diagnosed. In a recent study some acromegalic cats were phenotypically indistinguishable from normal cats and in other cats the changes were subtle and not obvious to the owners. Acromegaly should be considered in the differential diagnosis for any cat with insulin resistance especially if their body weight is stable to increasing, regardless of whether or not the more typical features of soft tissue enlargement are present. Some clinicians have even recommended evaluation for acromegaly in any cats that does not go into diabetic remission with appropriate diet and insulin therapy.

Diagnosis

A tentative diagnosis of acromegaly is based on the presence of consistent clinical signs, together with measurement of growth hormone and IGF-1 concentrations. Assays for both IGF-1 and GH have been validated in the cat although until recently the GH assay has not been available in the US. Measurement of IGF-1 is a good screening test for acromegaly. The assay has been reported to have a specificity of 92% and sensitivity of 84%. Some poorly controlled diabetic cats have elevations in IGF-1 concentrations but in most cases these increases are not as high as in those cats with documented acromegaly. Occasional diabetic cats with no evidence of acromegaly have more substantial increases in IGF-1 so imaging of the brain should be performed to confirm the diagnosis. Most cats with acromegaly have increased serum GH concentration although the short half-life and episodic secretion of GH may explain why GH is normal in some cases of acromegaly. A tentative diagnosis of acromegaly based on measurement of GH or IGF-1, should be confirmed by either contrast enhanced CT or MRI of the brain to document the presence of a pituitary mass. In one case of confirmed acromegaly, acidophil proliferation within the pituitary gland did not result in a detectable mass on CT or MRI. Thus even negative MRI findings do not preclude a diagnosis of acromegaly.

Treatment

Treatment modalities that have been evaluated for acromegaly in cats include radiation therapy, hypophysectomy, and medical therapy with either the somatostatin analog octreotide or L-deprenyl. Radiation therapy has been reported to result in improvement of neurologic signs in cats with pituitary tumors, and to result in decreased insulin requirements or diabetic remission in cats with acromegaly. Unfortunately the cost and availability of radiation therapy often limit access to treatment. Hypophysectomy although feasible in cats, is not routinely performed in the US and although it has been evaluated in cats with hyperadrenocorticism it has not been extensively evaluated in acromegaly. Neither octreotide nor L-deprenyl have been effective in amelioration of clinical signs of acromegaly in cats. In those cases in which treatment of the tumor is not possible due to financial or

logistical concerns, long-term control of clinical signs of diabetes mellitus may be achieved using high doses of insulin. Because of the profound insulin resistance associated with acromegaly hypoglycemic complications using this approach are unusual. Survival times of 4-42 months (median 20 months) were reported in 14 cats with acromegaly. Only two of these cats were treated with radiation therapy. Cause of death is most commonly due to renal failure and/or congestive heart failure.

Hyperadrenocorticism

Hyperadrenocorticism (HAC) is another rare endocrine disease of cats associated with insulin resistance. Eighty percent of cats with hyperadrenocorticism are diabetic at the time of diagnosis of hyperadrenocorticism. Hyperadrenocorticism in cats is caused by either a functional pituitary tumor (PDH) or a functional tumor of the adrenal cortex.

Signalment and Clinical Signs

Cats with hyperadrenocorticism are middle aged to older (median 10 years of age, range 5-16 years) and females are slightly over-represented. Clinical signs of hyperadrenocorticism in cats include signs of insulin resistant diabetes mellitus (polyuria, polydipsia, polyphagia, weight loss, and peripheral neuropathy), lethargy, abdominal enlargement or pot-bellied appearance, muscle atrophy, unkempt hair coat, bilaterally symmetrical alopecia, cutaneous fragility, and recurrent abscess formation. Cats with hyperadrenocorticism are also predisposed to bacterial infection so clinical signs of urinary tract infection, pyoderma and respiratory tract infection may also be observed. In addition to the findings already discussed above, the physical examination may reveal hepatomegaly, seborrhea, and cutaneous lacerations. Skin fragility may be so severe that tearing of the skin occurs during routine grooming of the hair coat by the cat. Virilization has been reported in cats with sex-hormone secreting adrenal carcinomas, and concurrent hyperaldosteronism has also been reported.

Diagnosis

The results of a CBC, biochemical panel, and urinalysis are typically consistent with those of diabetes mellitus. Increased alkaline phosphatase, alanine transferase, hypercholesterolemia, hyperglycemia, and low BUN are common. Cats do not have a steroid induced isoenzyme of alkaline phosphatase, so changes in this enzyme are less prominent than seen in dogs, and occur secondary to poorly regulated DM. Endocrine tests that may be useful in substantiating a diagnosis of feline hyperadrenocorticism include the ACTH stimulation test, the low dose dexamethasone suppression test, and the cortisol:creatinine ratio. The urine cortisol:creatinine ratio is a useful screening test for hyperadrenocorticism. Urine for measurement of the C:Cr ratio should be collected at home to minimize the influence of stress. A normal value makes a diagnosis of hyperadrenocorticism unlikely. Increased values occur in cats with Cushing's, however increases may also occur in cats with other concurrent illness so additional testing should be used for confirmation. The low dose dexamethasone suppression test is considered to be the test of choice for diagnosis of feline HAC and is performed using a higher dose of dexamethasone (0.1 mg/kg IV) than in the dog. A base-line blood sample is collected, and additional samples are collected at 4 and 8 hours after dexamethasone administration. Cortisol concentration will be suppressed (<1.5 □g/dl) at 8 hours in normal cats but not in cats with HAC. A few cats with HAC will suppress normally on the LDDS. If the index of suspicion for HAC is high a second test using the lower dose of dexamethasone (0.01 mg/kg) can be performed but interpretation is difficult because some normal cats will fail to suppress at this dose. The ACTH stimulation test is not a particularly sensitive test in cats because it is only abnormal in 50-60% of cats but it is useful in cases in which dexamethasone suppression testing is difficult to interpret and in cats with suspected iatrogenic HAC. The ACTH stimulation test is performed using a dose of 125 □g of Cortrosyn administered either IV or IM. Samples should be collected at baseline, and at 30 and 60 minutes after administration of ACTH. A post ACTH cortisol of >15 □g/dl at either 30 or 60 minutes after administration is consistent with a diagnosis of HAC.

Some adrenal carcinomas in cats have been associated with high circulating concentrations of other adrenal hormones such as androstenedione, progesterone, 17 hydroxy progesterone estradiol and testosterone. Cortisol concentrations in these cases are typically low with little response to ACTH stimulation. A sex hormone secreting tumor should be suspected in cats with clinical signs of hyperadrenocorticism, an adrenal mass on ultrasound and low cortisol response to ACTH. Confirmation is by a sex hormone profile with hormones measured before and after ACTH stimulation testing.

Differentiation Testing

Either the high dose dexamethasone suppression test, endogenous ACTH stimulation or diagnostic imaging are necessary to differentiate pituitary dependent from adrenal dependant hyperadrenocorticism in cats. Eighty five percent of cats with HAC have the pituitary dependent form of the disease, while 15% are diagnosed with functional adrenocortical tumors. Adrenocortical carcinoma should be suspected in cats with sex hormone secreting adrenal tumors.

Treatment

Treatment options for cats with HAC depend upon whether the disease is pituitary dependent or adrenal dependent. Adrenalectomy is the treatment of choice in cats with adrenal tumors. In cats with PDH, the best outcome has also been reported with bilateral adrenalectomy. Medical treatment is difficult because no drug has been reported to be consistently effective in treatment of HAC in cats. Drugs that have been used with varying success include trilostane, mitotane, metyrapone, and aminoglutethimide. Trilostane treatment has shown the most promising results in treatment of feline HAC but not all cats respond. Other options in cats with PDH include hypophysectomy or radiation therapy of the pituitary tumor.

Summary

Insulin resistance in cats occurs most commonly due to concurrent illness. Feline acromegaly and feline hyperadrenocorticism are important causes of insulin resistance in cats. Although these disorders are rare, they are likely currently under diagnosed. Recent advances allow definitive treatment that may improve quality of life and long-term survival. Although the hallmark of both diseases is insulin resistance, other clinical features allow the clinician to distinguish the two disorders. It is important to be familiar with the clinical signs of both acromegaly and hyperadrenocorticism, so that early recognition can lead to early intervention. In addition if the clinician is familiar with the distinct clinical signs, then testing can be reserved for those cats that truly fit the clinical picture.

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Feline Hypertension Secondary to Endocrinopathies

Catharine Scott-Moncrieff, VET MB, MA, MS, DACVIM, DECVIM

Introduction

Hypertension is a common problem in geriatric cats. Causes of hypertension in cats include chronic renal failure (CKD), hyperthyroidism, and adrenal disorders (hyperadrenocorticism and hyperaldosteronism). Pheochromocytoma can also cause systemic hypertension but is very rare in cats.

Diagnosis of Hypertension

In clinical practice systolic blood pressure is routinely measured using either Doppler ultrasonography or oscillometry. Blood pressure measurement should be performed with a careful and consistent technique ideally in an unstressed patient. Normal SYSTOLIC blood pressure in cats is typically less than 150 mmHg. The table below shows the classification of blood pressure based on risk of target organ damage (TOD) (Brown 2007). Target organ damage associated with hypertension includes signs of hypertensive retinopathy such as sub retinal edema or hemorrhage, retinal detachment, hyphema and tortuous blood vessels; signs of increased intracranial pressure such as obtundation, mental dullness, focal facial seizures and photophobia; and signs of hypertensive cardiac hypertrophy such as a new heart murmur of gallop rhythm. The systolic blood pressure can be affected by the technique used to measure the blood pressure, and the pressure may be increased by the so called “white coat” effect. Blood pressure greater than 180 mmHg is usually clinically relevant in cats. Blood pressure that is consistently > 160 mmHg may also warrant treatment.

	Systolic	Diastolic
Category I: Minimal risk of TOD	**< 150 mmHg**	**< 95 mm Hg**
Category I: Mild risk of TOD	**150-159 mmHg**	**95-99 mm Hg**
Category I: Moderate risk of TOD	**160-179 mmHg**	**100-119 mm Hg**
Category I: Severe risk of TOD	**> 180 mmHg**	**>120 mm Hg**

In cats with suspected hypertension blood pressure should be measured prior to any other intervention. In cats with hypertension with evidence of TOD treatment should be initiated immediately. If there is no evidence of TOD the blood pressure measurement should be repeated to confirm hypertension prior to starting treatment.

Endocrine Causes of Hypertension

The two main endocrine disorders associated with hypertension in cats are hyperthyroidism, and adrenal dysfunction. The blood pressure should be routinely evaluated in cats with these disorders. Conversely these disorders should be considered in cats with unexplained hypertension. Chronic kidney disease is common in geriatric cats and is commonly a concurrent disease with other endocrine disorders. It is important to make sure that adequate investigation is performed in cats with CKD and hypertension to establish whether other endocrine disorders could be contributing to the hypertension. Although hypertension is common in humans with acromegaly it is does not appear to be common in feline acromegaly.

Hypertension in Feline Hyperthyroidism

Hyperthyroidism is a syndrome caused by the excessive production and secretion of the thyroid hormones T_3 and T_4 by an autonomous thyroid gland. Feline hyperthyroidism was first reported in 1979 and since then it has become a common disease in cats. Common clinical manifestations of hyperthyroidism include weight loss, diarrhea, vomition, polyphagia, polyuria, polydipsia, muscle weakness, poor hair coat, and hyperactivity. Anorexia and lethargy are also seen in a smaller subset of patients. Findings on physical examination in addition to the clinical signs noted above may include tachycardia, heart murmur, signs of cardiac failure, cardiac arrhythmias, dehydration, and a palpable thyroid nodule. A combination of the above findings is highly suggestive of hyperthyroidism; however other disorders common in older cats such as renal failure, congestive heart failure, gastrointestinal disease and diabetes mellitus may mimic some or this entire constellation of clinical signs.

The diagnosis of feline hyperthyroidism is made by documentation of an increased total thyroxine concentration in cats with appropriate clinical signs. In some cats with mild disease or other concurrent illness other tests such as the free T4, T3 suppression test, and nuclear scintigraphy may be required.

Thoracic radiographs in hyperthyroid cats may reveal cardiomegaly (due to hypertrophic cardiomyopathy), pleural effusion, pulmonary edema, or pericardial effusion. Thoracic radiographs may also identify evidence of concurrent disease such primary or metastatic neoplasia. Echocardiography is indicated in hyperthyroid cats with evidence of more severe cardiac disease as demonstrated by significant cardiomegaly, pulmonary edema, pleural effusion, or cardiac arrhythmias. Echocardiography will often show evidence of mild hypertrophic cardiomyopathy in cats with no other signs of heart failure, however in this circumstance the only treatment that is usually required is control of the hyperthyroid state. Most cardiac changes resolve after treatment of the underlying disorder; however some severe cardiomyopathies do not resolve after treatment and require continued therapy. An electrocardiographic evaluation is important if cardiac arrhythmias are detected on physical examination. The most common abnormalities are sinus tachycardia and increased amplitude of the R wave (lead II).

The earliest studies investigating the prevalence of hypertension in feline hyperthyroidism reported the prevalence of hypertension to be as high as 87% (Kobayashi et al. 1990). Subsequent studies have shown much lower prevalence rates of between 5% and 20% in cats with hyperthyroidism (Stepien et al. 2003, Syme and Elliott 2003). This likely reflects that cats with hyperthyroidism are now less severely affected that previously. This finding might also reflect use of more conservative cut-offs for hypertension, and better understanding of the white coat effect in feline hyperthyroidism. Stepien et al. showed that cats with hyperthyroidism exhibit a pronounced “white coat effect” which should be taken into consideration when evaluating blood pressure in hyperthyroid cats. Interestingly a recent report found that approximately 20-25% of cats that were normotensive prior to treatment of hyperthyroidism became hypertensive several months (median 5 months) after treatment of hyperthyroidism (Syme 2003). Whether this is due to a decline in renal function after treatment or other undetermined mechanism is unclear. Post-treatment hypertension was not limited to cats that became azotemic after therapy and no differences were detected between cats that developed hypertension and those that did not in regard to RAAS activation (Syme 2007). It is therefore important that blood pressure be monitored carefully for the development of post-treatment hypertension.

Whether there is a causal relationship between hyperthyroidism and hypertension in cats has not been proven. Both disorders are common in geriatric patients and the pathogenesis of hypertension in hyperthyroidism has not been clearly defined. Systolic hypertension is likely due to increased cardiac output but the effects are somewhat mitigated by a decrease in systemic vascular resistance. Activation of the renin-angiotensin-aldosterone system is not associated with development of hypertension in hyperthyroid cats. If hyperthyroidism is a significant primary cause of hypertension in cats, it may not be as common a cause as previously believed. In one study, only 5 of 30 cats with hypertension were diagnosed with hyperthyroidism (Elliott et al 2001). In a study of cats with hypertensive retinopathy, only 5 of 69 cats were hyperthyroid (Maggio et al. 2000). Conversely, another study found no evidence of ocular changes consistent with hypertensive damage in cats with hyperthyroidism (van der Woerdt and Peterson 2000). What is clear is that when hypertension is diagnosed in hyperthyroid cats, they should be treated with anti-hypertensive drugs in addition to treatment of hyperthyroidism.

Treatment of Hypertension in Hyperthyroid Cats

While the diagnosis of hypertension in cats with hyperthyroidism may sometimes be difficult, once the diagnosis is established, the need for treatment is clear. Persistent hypertension damages the kidneys (Brown et al. 2007), and the co-morbid condition of hyperthyroidism and renal failure is well-documented in cats. Drugs used to treat hypertension in cats fall into 3 categories: angiotensin-converting enzyme (ACE) inhibitors, calcium-channel antagonists, and beta adrenergic antagonists. Drugs commonly used to treat hypertension in cats are shown in the Table below. Atenolol is commonly used to treat tachycardia in hyperthyroid cats but studies suggest that it is not particularly effective in controlling blood pressure. Most clinicians recommend starting with amlodipine and adding an ACE inhibitor in cats with concurrent proteinuria or those in which the hypertension remains uncontrolled.

Drugs Used to Treat Hypertension in Cats

Drug	Dosage	Notes
Amlodipine	**0.625 mg/cat q 12-24 hrs**	**Calcium channel antagonist Useful for severe hypertension Decreases proteinuria Well-tolerated**
Atenolol	**3.125-6.25 mg/cat Every 12 hours**	**Selective Beta-1 antagonist Controls tachycardia Limited use for hypertension**
Benazapril	**0.5 mg/kg Every 12-24 hours**	**ACE Inhibitor Not as effective as amlodipine Decreases proteinuria Delays progression of renal disease Well-tolerated**

Enalapril	**0.5 mg/kg Every 12-24 hours**	**ACE Inhibitor** **Not as effective as amlodipine** **No negative effects on kidneys** **Well-tolerated**

Hypercortisolism

A small percentage of cats with hypercortisolism have hypertension. In one study three of 16 cats with spontaneous hyperadrenocorticism were diagnosed with hypertension (Valentin 2014). Hypertension in these cats may be due to the mineralocorticoid effects of high circulating cortisol concentrations.

Hyperaldosteronism

Primary hyperaldosteronism (Conn's syndrome) is a disorder of middle-aged to geriatric cats due to autonomous secretion of aldosterone from the adrenal gland. Excess aldosterone concentrations result in hypertension due to both increased plasma volume and increased peripheral resistance. The disorder is considered rare in cats but it is likely an underdiagnosed disorder because the hypertension and hypokalemia that are the hallmarks of this disorder may also occur in cats with CKD. Primary hyperaldosteronism should be suspected in any cat with hypertension and hypokalemia, especially if the hypertension or hypokalemia are relatively refractory to treatment. Causes of hyperaldosteronism include a mineralocorticoid secreting adrenal tumor (carcinomas are more common than adenomas) or idiopathic bilateral nodular hyperplasia of the zona glomerulosa. The most prominent clinical signs of hyperaldosteronism in cats include signs of TOD due to hypertension, and polymyopathy due to hypokalemia. Other clinical signs may include skin fragility in cats with concurrent hypersecretion of progesterone, inappetance, polyuria, polydipsia, and weight loss. Laboratory abnormalities may include hypokalemia, azotemia, increased creatine kinase activity. Diagnosis of hyperaldosteronism is made by documentation of increased aldosterone and decreased renin concentrations which results in an increased aldosterone to renin ratio. Other diagnostic testing used to support the diagnosis includes measurement of an aldosterone:creatinine ratio, abdominal ultrasound that may demonstrate the presence of unilateral or bilateral adrenomegaly or the presence of an adrenal mass, or use of a fludrocortisone suppression test. The final diagnosis relies on histopathology of the adrenal gland.

Treatment of Hypertension in Hyperaldosteronism

If hyperaldosteronism is due to an adrenal tumor adrenalectomy is the treatment of choice. In cats in which adrenalectomy is not possible due to bilateral tumors or bilateral nodular hyperplasia, presence of metastatic disease, or financial limitations, medical management using the mineralocorticoid receptor inhibitor spironolactone together with potassium supplementation and treatment of hypertension with amlodipine.

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Diagnosis & Treatment of Feline Acromegaly

Catharine Scott-Moncrieff, VET MB, MA, MS, DACVIM, DECVIM

Introduction

Diabetes mellitus is a common endocrinopathy in cats. Management of feline diabetes mellitus is sometimes complicated by underlying diseases that may cause profound insulin resistance. Lack of recognition of underlying disorders that cause insulin resistance results in poor glycemic control and decreases the likelihood of diabetic remission. Acromegaly is a rare but likely under-diagnosed cause of insulin resistance in cats. While relatively uncommon this disorder is an important cause of insulin resistance.

Diagnostic Approach to Insulin Resistance in Cats

The majority of causes of true insulin resistance in cats can be identified by evaluation of historical findings, physical examination, minimum data base (CBC, biochemical profile, urinalysis, total T4) and by performance of a small number of readily available tests such as urine culture, thoracic radiographs, and abdominal ultrasound. If no diagnosis can be made at this point the clinician is faced with the question of whether to initiate diagnostic tests for less common disorders such as hyperadrenocorticism and acromegaly. Both these disorders are caused by a functional adenoma of the pituitary (pars distalis). In a study of 16 cats with insulin resistance and suspected acromegaly or pituitary dependent hyperadrenocorticism, CT revealed a mass in the region of the pituitary gland in all 16 cats. CT or MRI of 8 cats with well-controlled DM was normal. Diagnosis of acromegaly and feline Cushing's disease relies on a combination of specific endocrine testing and diagnostic imaging (ultrasound, CT, MRI). Because testing is expensive it is important to use appropriate clinical parameters to determine which cases are appropriate for testing and which underlying disorder is most likely. The decision to pursue either of these diagnoses and if so, which one, should be made by evaluation of the history, physical examination, and minimum data base since these disorders typically have unique clinical features in addition to the common finding of insulin resistance.

Acromegaly

Pathophysiology

Acromegaly is a syndrome in cats caused by excess secretion of growth hormone from a pituitary adenoma. Excess growth hormone (GH) secretion results in increased secretion of Insulin growth factor I (IGF-1) from the liver and peripheral tissues. Cats with acromegaly have profound insulin resistance and overgrowth of soft tissues, membranous bone and viscera. The anabolic effects of IGF-1 result in proliferation of bone, cartilage, and soft tissues, with organomegaly. The excess growth hormone secretion causes insulin resistance, carbohydrate intolerance, hyperglycemia and diabetes mellitus. Growth hormone is believed to cause a post receptor defect in insulin action at the level of the peripheral tissues. Feline acromegaly is believed to be a rare condition in cats, although recent studies suggest that it may be a more common cause of insulin resistance in diabetic cats than has been previously recognized. In one study in which diabetic cats were screened for acromegaly by measurement of Insulin growth factor I (IGF-1), 32% had increased IGF-1 concentrations and acromegaly was confirmed in 10% of these cats.

Signalment and Clinical Signs

Most cats with acromegaly are middle-aged or older (median 10 years of age, range 4-17 years) and 90% are male (intact or castrated). Clinical signs in cats with overt acromegaly include polyuria, polydipsia, polyphagia (due to insulin resistant diabetes mellitus), large body size, weight gain despite poor glycemic control, and enlargement of the head and extremities. Median insulin dose in a group of 17 cats with acromegaly was 10 U q 12 hours (range 2-35 U). Physical examination may reveal abdominal organomegaly, inferior prognathia, cataracts, clubbed paws, broad facial features, cardiac murmurs or arrhythmias, respiratory stridor, lameness, peripheral neuropathy, and central neurologic signs attributable to an enlarging pituitary mass. Cardiomegaly and renomegaly may be evident on imaging studies. Although weight loss due to poorly regulated diabetes mellitus may occur initially, a key finding in acromegalic cats is weight gain or a stable weight (lack of weight loss) in a diabetic cat with other indications of poor glycemic control such as polyuria, polydipsia, and polyphagia. Median bodyweight in a report of 19 acromegalic cats was 6 kg (range 4-9 kg). Although acromegalic cats tend to gain weight rather than lose weight as the disease progresses, in the study discussed above, the body weights of the acromegalic cats were not significantly different than the bodyweights of well controlled or poorly controlled diabetic cats without acromegaly.

Acromegaly is a slowly progressive insidious disease. It is now recognized that many cats with acromegaly do not have the classic signs of weight gain and soft tissue enlargement at the time of diagnosis. Rather, the first clinical signs are usually the result of diabetes mellitus due to insulin resistance. For this reason acromegaly is likely currently underdiagnosed. In one study some acromegalic cats were phenotypically indistinguishable from normal cats and in other cats the changes were subtle and not obvious to the owners. Acromegaly should be considered in

the differential diagnosis for any cat with insulin resistance especially if their body weight is stable to increasing, regardless of whether or not the more typical features of soft tissue enlargement are present. Some clinicians have even recommended evaluation for acromegaly in any cat that does not go into diabetic remission with appropriate diet and insulin therapy.

Diagnosis

A tentative diagnosis of acromegaly is based on the presence of consistent clinical signs, together with measurement of increased growth hormone and IGF-1 concentrations. Assays for both IGF-1 and GH have been validated in the cat although an assay for feline GH is not currently commercially available in the US. Measurement of IGF-1 is a good screening test for acromegaly. The assay has been reported to have a specificity of 92% and sensitivity of 84%. Some newly diagnosed diabetic cats have elevations in IGF-1 concentrations but these increases are not typically as high as in those cats with documented acromegaly. Occasional diabetic cats with no evidence of acromegaly have more substantial increases in IGF-1 so imaging of the brain should be performed to confirm the diagnosis. Most cats with acromegaly have increased serum GH concentration although the short half-life and episodic secretion of GH may explain why GH is normal in some cases of acromegaly. The assay for GH is not widely available. A tentative diagnosis of acromegaly based on measurement of GH or IGF-1, should be confirmed by either contrast enhanced CT or MRI of the brain to document the presence of a pituitary mass. In one case of confirmed acromegaly, acidophil proliferation within the pituitary gland did not result in a detectable mass on CT or MRI. Thus even negative MRI findings do not preclude a diagnosis of acromegaly.

Treatment

Treatment modalities that have been evaluated for acromegaly in cats include radiation therapy, hypophysectomy, and medical therapy with either the somatostatin analog octreotide or L-deprenyl. Radiation therapy has been reported to result in improvement of neurologic signs in cats with pituitary tumors, and to result in decreased insulin requirements or diabetic remission in cats with acromegaly. Unfortunately the cost and availability of radiation therapy often limit access to treatment. Hypophysectomy although feasible in cats, is not widely available and has not been extensively evaluated in acromegaly. Neither octreotide nor L-deprenyl has been effective in amelioration of clinical signs of acromegaly in cats. In those cases in which treatment of the tumor is not possible due to financial or logistical concerns, long-term control of clinical signs of diabetes mellitus may be achieved using high doses of insulin. Because of the profound insulin resistance associated with acromegaly hypoglycemic complications using this approach are unusual. Survival times of 4-42 months (median 20 months) were reported in 14 cats with acromegaly. Only two of these cats were treated with radiation therapy. Cause of death is most commonly due to renal failure and/or congestive heart failure.

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What's New in Acute Feline Pain Management: Before, During, & After Surgery

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Many thanks to Peter Hellyer, DVM, MS, DACVA, founding President of the International Veterinary Academy of Pain Management and my pain management mentor.

Our moral imperative is to advocate on behalf of beings that cannot advocate for themselves. When we are creating acute pain management strategies, it is useful to think of it as "building a pyramid". Acute pain may be planned (surgery) or unplanned (trauma), and it varies in severity, which dictates the intensity of our pain management strategy. Acute pain patients may ALSO be dealing with chronic/maladaptive pain. A multi-modal approach provides us the opportunity to create a rational plan based on specific targets.

For surgery patients, this is our greatest opportunity to make a difference. The best pain management strategy begins long before the surgical insult, and it can decrease the need for induction agents, inhalant agents, and post-op pain medications. There is greater comfort for the patient, and good pain management sets the stage for optimal healing. Targeted therapy means making rational choices about the areas of the nervous system we need to address and how to get there. We need to prevent an unrelenting afferent barrage of nociceptive signals which leads to peripheral and central sensitization and "windup". General anaesthesia only causes unconsciousness, it does NOT provide analgesia. Without proper intervention (e.g. pre-emptive analgesia), the pain experience upon awakening will be WORSE for the patient than otherwise.

Interestingly, appropriate pain management before, during, and after surgery is NOT just about the drugs! It turns out that COLD is a very bad thing when you are a vulnerable kitty getting ready to undergo the rigors of anaesthesia and surgery. Dr. Sheilah Robertson has done some elegant research to let us know that "the big chill", as she calls it, really undermines our patients' comfort during the anaesthesia/surgery experience.

One of the most important times for body heat to be lost is actually between delivering the pre-meds and induction (if you don't believe me, start measuring rectal temperature when the pre-meds are delivered and then again at induction). Our practice routinely witnessed a 2 – 3 degree drop in temperature in that time once we actually measured it. It is time to invest in a towel warmer for your practice! For a very small investment, you can change the lives of kitties in your care. We pre-spray a little Feli-Way® facial pheromone on the towels before they go in the warmer to make them especially feline-friendly. Once the pre-meds are delivered, the cat goes back into its clinic bedroom with a warm towel on the bottom and another warm towel over the front of the cage. This really preserves their body warmth.

During surgery, be sure to sustain warmth as well. This allows the cat to metabolize anaesthesia drugs more effectively, clearing them more quickly. It facilitates a smoother anaesthetic recovery. Either circulating warm water or warm air works well. DO NOT use electric heating pads as these can cause full thickness (and sometimes fatal) burns. Once the procedure is over, reach for the towel warmer again to wrap the cat in a toasty terrycloth bunting. Emerging from general anaesthesia is a much more enjoyable experience when you are warm and toasty.

It is already difficult enough for cats to maintain appropriate body temperature. Let's not set them up for failure!

Pre-op, combine a sedative and an opioid (e.g. hydromorphone & acepromazine). Acepromazine potentiates the effects of the opioid (but ace is NOT analgesic - - this is important!) Sidebar - - consider carefully the use of anticholinergics - - we no longer use them pre-op. Butorphanol has NO PLACE in a perioperative protocol. As a pre-med, the analgesic effects are GONE just in time for the first stroke of the scalpel. It diminishes effectiveness of any subsequent delivery of pure mu opiate, and it is expensive (by comparison) to "real" analgesics. It is still in use due to complacency - - not a good excuse.

When you deliver your pre-meds, go ahead, shave the catheter site, apply EMLA and cover the area with a bio-occlusive dressing covered by Vetwrap. This creates topical anaesthesia at the catheter insertion site. The bio-occlusive dressing is absolutely essential. While ALL patients appreciate this particular pain relief, cats especially appreciate this extra attention to comfort!

Immediately pre-op, position your patient to have an optimal surgical experience, with minimal pain and optimal healing. At induction, take 5 – 10 minutes to help your patient with pre-oxygenation @ 4 – 6 L/min via mask while you are placing the IV catheter. Remove the Vetwrap and the bio-occlusive dressing, then prepare the catheter site as usual. Once induced, the last pre-op step is local anaesthesia infusion. Place your local anaesthetic BEFORE the surgery begins. Infusing local after a surgery/after an incision is made is precisely like locking the barn door after the horse is gone. Depending upon the nature of the procedure, local may be best administered via epidural, intra-articular injection, specific nerve block, etc.

Continuous Rate Infusion (CRI) is "continuous" rather than "constant." In fact, drug flow can be changed with the patient's needs. This is an extremely effective way to manage pain intra- and post-op. It dramatically reduces

inhalant concentration/need. CRI is really the only place for ketamine any more (not induction). One drug, one fluid bag (50 – 100ml), one IV pump - - this is the level of precision dosing that our feline patients need and deserve.

For intra-op pain relief, the pre-meds need long enough duration to cover surgery time. For longer procedures, consider epidural and/or CRI techniques. Good surgical techniques assist with pain management by minimizing trauma to tissues. Don't forget to keep your patient warm!

Post-op pain strategies should continue CRI's if they are in place. Titrate the dose over time as patient recovers and gains strength. Do not stop CRIs abruptly. Begin NSAIDs at this time (post-op) if appropriate for the patient. Regularly assess your patient and revise the pain plan accordingly. Opioids post-op can be pulse-dosed for patients who do not need/receive CRIs.

It is here in the post-operative period that cats have been underserved. Give the patient the benefit of the doubt when assessing for pain because pain is easier to prevent than to reverse. NSAIDs alone are not as effective as NSAIDs combined with an opioid. The therapeutic AND side-effects of opioids are generally dose-dependent, so don't be afraid to let the patient sleep post-op provided they have stable vital signs. We can reduce potential adverse side effects by choosing drugs and doses to meet the patient's needs.

We have used injectable buprenorphine in cats IV or transmucosally with an onset of @ 30 minutes and a duration of @ 6 – 12 hours depending upon the dose and the level of pain. The doses quoted in the literature vary from 0.03 – 0.05 mg/kg. One downside of using the standard preparations of buprenorphine is the need for fairly frequent follow-up dosing. One newcomer to the perioperative pain "pharmamentarium" serves this enormous unmet need in cats. A new buprenorphine formulation provides 24 hours of pain relief with a single SQ injection. his complements the chosen NSAID. When cats are hospitalized, we want to stress them as little as possible, and one way we can accomplish that goal is to choose medications that only require once per day dosing. Our feline-friendly NSAIDs are dosed once per day. This new buprenorphine formulation is likewise delivered once per day, and can be delivered about one hour before surgery to provide a trans-operative pain relief profile, as well as twice more for three full days of enhanced feline comfort.

The compounded buprenorphine SR from ZooPharm® is labeled for SQ use, but do we have any absorption data (not yet…these are important data that veterinarians should demand…)?

Once the patient is ready to depart the hospital, transition to oral meds for going home. When using NSAIDs, choose according to the best fit for the patient. Determine how long the patient will benefit from their use. If you decide to use meloxicam, be sure to precision dose. There is no compelling anti-inflammatory evidence to demonstrate that delivering the NSAID BEFORE the anaesthetic event provides a superior outcome, but we certainly increase the risk of complications.

Tramadol is a synthetic molecule that IN HUMANS affects mu receptors, serotonin pathways, and norepinephrine pathways. We now know that dogs do NOT metabolize this drug to make the mu-active metabolite. Suddenly we understand that tramadol does NOT provide relief to anything other than minor pain. We do NOT know anything substantive about tramadol in cats, and at this moment, I cannot in good conscious recommend it.

Gabapentin seems to have a role in post-operative pain. It affects the α-2-δ ligand of the calcium channel in the dorsal horn of the spinal cord - - post-op it can help prevent central sensitization. It decreases consumption of morphine & improves functional recovery in humans with total knee arthroplasty (Pain Res Manage 2009;14(3):217-222). Compared with placebo, perioperative administration of gabapentin produced significantly better postoperative analgesia (Reg Anesth Pain Med 2006;31:237-247). Sedation is the dose-limiting side effect, and it exhibits non-linear pharmacokinetics, so dose escalation for really painful patients in more aggressive than with other drugs. So far there has been only one study done in veterinary medicine to evaluate gabapentin post-op. The patients were canine amputees, and the drug failed quite predictably due to a very low dose that was chosen - - opioids will also fail if the dose is too small. Clinically, in "big pain" cases, gabapentin improves outcomes in pain scores and function – both short and mid-term at a dose range of 5 – 20 mg/kg PO BID – TID. You will see effects within 24 hours, and consistent effects within 3 – 5 days. We typically dose for 2 – 3 weeks following a "big" procedure.

Remember physical medicine options to enhance pain management post-operatively. We can use these techniques immediately post-op as well as at home when appropriate. General nursing care includes keeping the patient warm, turning them regularly, keeping the bladder empty, keeping them clean of soiling. Cryotherapy over the surgery site will decrease pain and swelling. Acupuncture/acupressure, therapeutic LASER, and medical massage techniques also can help with post-operative pain.

Build your "pain management pyramid" based on several factors:

- The anticipated pain resulting from the procedure
- Routine castration < routine OHE or cryptorchid castration < toe amputation < large tumor removal < total ear ablation < limb amputation or other orthopedic procedure
- Give the patient the benefit of the doubt
- Layer your modalities to meet the patient's needs both immediately post-op and as recovery proceeds

Building the pain management pyramid:

- Pre-op medication, induction agents, and inhalant will not change much. These form the foundational level of the pain management pyramid
- Next layer - - local anaesthesia
    - Local blocks
    - Regional blocks
    - Epidural infusion
- Next layer - - CRI
- Next layer - - post-op choices
    - Post-op pain meds (short & mid-term)
    - Buprenorphine (consider new q 24hr formulation) – 1st layer
    - NSAID (in appropriate) – 1st layer
    - CRI continuation if needed – 2nd layer
    - Gabapentin – 2nd layer
- Physical medicine options – 3rd layer

For "big pain" procedures, make a detailed plan for reassessments and revisions of the pain management plan. Titrate doses down over time as the patient recovers and becomes more functional. Disassemble the pain management pyramid as it is assembled - - one layer at a time.

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